OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED | **Application Identifier**

5. APPLICANT INFORMATION **Organizational DUNS*:** 0636907050000

Legal Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: Office of Sponsored Programs
Division:
Street1*: 1720 2nd Ave South, AB1170
Street2:
City*: BIRMINGHAM
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111

Person to be contacted on matters involving this application
Prefix: First Name*: Randall Middle Name: Last Name*: Fields Suffix:
Position/Title: Grants and Contracts Officer
Street1*: 1720 2nd Ave. South, AB 1170
Street2:
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 205-934-6932 Fax Number: 205-975-5977 Email: refields@uab.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1636005396A6

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients

12. PROPOSED PROJECT
Start Date* Ending Date*
09/01/2018 08/31/2023

13. CONGRESSIONAL DISTRICTS OF APPLICANT
AL-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Jennifer Middle Name: S Last Name*: Guimbellot Suffix:
Position/Title: Assistant Professor
Organization Name*: The University of Alabama at Birmingham
Department: School of Medicine
Division: Peds - Pulmonary
Street1*: 1600 7th Ave South, ACC 620
Street2:
City*: BIRMINGHAM
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940005
Phone Number*: (205) 934-6066 Fax Number: (205) 934-7593 Email*: GUIM@UAB.EDU

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$865,080.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$865,080.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Melinda Middle Name: T Last Name*: Cotten Suffix:
Position/Title*: Assistant VP for Sponsored Programs
Organization Name*: The University of Alabama at Birmingham
Department: Office of Sponsored Programs
Division:
Street1*: 1720 2nd Ave. South, AB 1170
Street2:
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 205-934-5266 Fax Number: 205-975-5977 Email*: osp@uab.edu

Signature of Authorized Representative*
Randall Fields

Date Signed*
10/09/2017

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_letter.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The University of Alabama at Birmingham
Duns Number:	0636907050000
Street1*:	1600 6th Ave. South,ACC 620
Street2:	
City*:	Birmingham
County:	
State*:	AL: Alabama
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	352940111
Project/Performance Site Congressional District*:	AL-007

Additional Location(s) File Name:

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number 00005960

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Abstract.pdf
8. Project Narrative*	Project_narrative.pdf
9. Bibliography & References Cited	bibliography_and_references_cited.pdf
10.Facilities & Other Resources	Facilities_and_Other_Resources.pdf
11.Equipment	Equipment.pdf

Cystic fibrosis (CF) is an autosomal recessive disorder caused by dysfunction of the CF Transmembrane Conductance Regulator (CFTR) channel. The care of patients with CF has rapidly evolved with the development of CFTR modulators, novel pharmaceuticals that address the basic CF defect and restore CFTR function. Despite the success of one of these, the potentiator ivacaftor, there is still pronounced variance in drug efficacy, as measured in individuals' phenotypic response to therapy and their *in vitro* cellular response when assessed with cell-based biomarkers. Ivacaftor is metabolized by cytochrome P450 (CYP3A enzymes), which are responsible for both hepatic and tissue-specific metabolism, including in airway epithelia. Genetic variation in these enzymes cause altered activity, resulting in variation in efficacy in many drugs. The preliminary data demonstrate CYP3A SNPs may be associated with drug efficacy, and the ability to detect ivacaftor metabolism in vitro in an individualized, cell-based format the applicant personally developed. To maximize efficacy of ivacaftor, and thus, any therapy including it, it is essential to understand pharmacogenetics and effect of variability of CYP3A enzyme activity on the metabolism of ivacaftor. The Specific Aims are: 1) to determine frequencies of genetic variants (single nucleotide polymorphisms) of these enzymes in the CF population and measure association with clinical efficacy; 2) measure intracellular concentrations of ivacaftor using mass spectrometry and quantitate the effect of altering concentrations of the drug on CFTR activity in a novel in vitro biomarker, using fluid transport as a surrogate endpoint; and 3) conduct a pilot study in people to determine population pharmacokinetics of ivacaftor in plasma and the intracellular space, and measure the effect on CFTR activity and in vivo drug response. Ivacaftor is a significant component of many combination therapies, so understanding its variation in metabolism and impact on efficacy as monotherapy is the first key step to understanding pharmacogenetics in complex combinations, and will set the stage for an independent career focused on precision-directed therapeutics in CF.

The applicant has dedicated her professional life to becoming a physician-scientist, studying pediatric pulmonology in general and cystic fibrosis in particular. To achieve this, she accepted a faculty position at the University of Alabama at Birmingham, where a supportive research environment in the Department of Pediatrics and School of Medicine, as well as the Gregory Fleming James Cystic Fibrosis Research Center, has made career advancement and approach to independence possible. To accomplish the goals of this research, the candidate has assembled a mentoring team with decades of experience in clinical trials, pharmacology, genetics, statistics, pharmacogenetics, and drug metabolism to advise and guide her during her career development. She also proposes to undertake formal training in pharmacology, advanced statistics, clinical trial conduct, and genetics to complement her prior medical and graduate studies and acquire the relevant skills to transition to independence.

CFTR modulators are a novel class of therapeutic compounds, and this research will contribute significantly to the understanding of the metabolism of these compounds in patients with cystic fibrosis to optimize therapy and usher in an era of precision therapeutics. The findings will enhance efficacy of CFTR modulator therapy for all patients with cystic fibrosis and help expand these novel therapies to all patients who might benefit from them. The knowledge gained in metabolism enzyme pharmacogenomics also has important implications for other diseases, including chronic obstructive pulmonary disease and asthma.

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FACILITIES AND OTHER RESOURCES

All facilities and resources necessary to conduct the experiments described in this research proposal are already available in the laboratories of Dr. Guimbellot, Dr. Rowe, and the UAB CF Research Center on MCLM 7th floor.

Laboratory Facilities

Dr. Guimbellot has 530 sq. ft. of laboratory space in the McCallum Basic Health Science Building and has access to Dr. Steven Rowe's laboratory which includes 1370 sq.ft. of laboratory space, which is in close proximity in the same building. In addition, she has access to the UAB Cystic Fibrosis Research Center, directed by her mentor Dr. Rowe, with over 13,000 sq.ft. of research space on the 7th floor of McCallum Basic Health Sciences Building. Major capabilities relevant to this proposal include cell culture facilities including dedicated labs for primary human airway cell culture and multiple core facilities provided by the NIH P30 and CFF RDP cores, including the Clinical and Translational Core (Core C) Co-directed by Dr. Rowe. Major resources within the Center support assays of CFTR and protein biology, including iodide efflux studies and Ussing chamber studies of cell monolayers and intact airway tissues. The lab is also fully equipped for protein biochemistry studies including: Western blotting, protein isolation, and ELISA and other colorimetric assays. Dr. Rowe's laboratory also has all equipment necessary to conduct RNA isolation, real time and digital RT-PCR for precise and absolute mRNA quantitation, protein purification and isolation, and Western blotting.

Wet laboratory of the primary Mentor

Dr. Rowe has approximately 1370 sq. ft. of contiguous laboratory space in the McCallum Basic Health Science Building (MCLM 714, 725, 725A, 735, 736) and is also assigned multiple rooms within the CF Research Center (MCLM 791 for Ussing chamber studies, MCLM 789 for optical coherence tomography studies and other live tissue imaging, and MCLM 776 for high throughput screening using equivalent current/transepithelial conductance measurements). Major resources within his laboratory support assays of CFTR activity, including nasal potential differnece, iodide efflux studies, and Ussing chamber studies of cell monolayers and intact airway tissues. This includes a new 18-chamber Ussing chamber apparatus with electronic data analysis (Physiologic Instruments) capable of monitoring cells or excised tissues. We also have a 24-channel conductance/equivalent current assay custom designed by R. Bridges (Rosalind-Franklin University) that is joined with an automated robot controlled assay head (Precise Automation) for high throughput evaluation of ion transport activity in cell monolayers. Laboratories are fully equipped for protein biochemistry, Western blotting, and ELISA and mRNA analysis by qPCR. Dr. Rowe directs the Clinical and Translational Core with the NIH P30. Capabilities of the core include primary human airway cell culture (including lung and sinus origin) and conduct of clinical studies using CFTR related endpoints. Complementing this resource, Dr. Rowe is also Co-PI of the CFF Translational Therapeutics Development Network site, which specializes in CF related clinical trials, and he is the PI of the Center for CFTR Detection, which provides evaluation and analysis of a variety of potential difference measurements (e.g. nasal, lung) in humans throughout the world, quality assurance regarding these outcome measures, and training for operators throughout the TDN network.

Children's Hospital of Alabama

Dr. Guimbellot has access to clinical research facilities at UAB and in the Child Health Research Unit (CHRU), a facility affiliated with the UAB Center for Clinical and Translational Science (A. Reddy and S.M. Rowe, Co-Directors). Together they direct clinical research facilities at UAB and for the CHRU. Dr. Rowe employs 4 research coordinators and a research technician to operate this unit, and it is nationally recognized for its research excellence in respiratory diseases. This facility includes an ancillary physician's office in proximity to the clinic, 4 patient examination rooms, and a nasal potential difference laboratory (2 setups, each capable of electronic and conventional data capture). This facility also houses a specimen processing lab (refrigerated centrifuge, microscope, hemocytometer, -80^{o}C freezers, pipettes, etc.). Further, the team operates a third potential difference apparatus dedicated and optimized for the measurement of Potential Difference at other anatomic locations such as the lower airway (LAPD). Each Potential Difference Apparatus includes 4/30 PowerLab Analog-Digital Converter (AD Instruments), Human grade bioamplifier (CWE), Isolation headstage (CWE), Laptop Personal Computer with Windows XP or better (Dell), KCl calomel electrodes, 60 mL Perfusion pumps (3 for LAPD rig, 5 for each NPD setup), and requisite tubing and disposables. Each of the 4 patient examination rooms are dedicated for research subjects and are fully-equipped for patient care (stethoscopes, illuminating rhinoscopes and otoscopes, patient tables, computers, open office space, etc.). Specialized

equipment for CFTR clinical science are housed in the CHRU, including two sweat iontophoresis devices (each compatible with the Macroduct collection system), two sweat evaporimeters (Cyberderm RG), a carbon monoxide monitor, an Lung Clearance Index measurement device (EcoMedics) for use by the nitrogen washout technique, nasal and exhaled nitric oxide measurement (EcoMedics), two spirometers with calibration equipment (NSpire), an EKG machine, a Code cart, and general laboratory supplies. Medications and solutions used during the nasal and lower airway PD's are stored and provided through the Children's Hospital research pharmacy, which is experienced with ivacaftor administration to adults and children. The facility has a large body of experience conducting PK and PK/PD studies in CF patients, as proposed in Dr. Guimbellot's application.

UAB Pediatric Pharmacology Laboratory and Comprehensive Cancer Center Pharmacometrics Core

The UAB Clinical Pharmacology Laboratory and Division of Clinical Pharmacology is located on the second floor in room 258 of Volker Hall. The enclosed space consists of approximately 1700 sq. ft.; room 270 has 620 sq. ft., room 275 has 593 sq. ft. and room 280 has 287 sq. ft. The laboratory also has 200 sq. ft. of adjacent shared equipment space. The UAB Comprehensive Cancer Center PK/PD Core Laboratory is located on the first floor of Volker Hall and directly below the Clinical Pharmacology Laboratory and Division of Clinical Pharmacology. The Laboratory operates under GLP conditions, has been CLIA certified since May 2002, and undergoes regular inspections by the state agency. We also participate in bi-annual proficiency testing rounds which are organized through the Office of HIV/AIDS Network Coordination. All of our assays used for ACTG studies are reviewed and approved by the Network. Each laboratory personnel has undergone HIPAA training in addition to specialized training to handle infectious substances. We currently have an LC/MS/MS assay that simultaneously quantitates 6 commonly used antiretrovirals, another that measures tenofovir, emtricitabine and their intracellular anabolites simultaneously, a method for nevirapine and maraviroc, and FDA-approved methods for raltegravir and dolutegravir. Other non-standard assays include measuring these drugs in various matrices, such as urine, CSF, genital secretions, breast milk, and tissue biopsies. The Laboratory has also developed methods to quantitate protein-free drug concentrations using equilibrium dialysis and LC/MS/MS. Other assays include acyclovir, ganciclovir, CMX001 and cidofovir, pleconaril, azithromycin, enfuvirtide, elvitegravir, cobicistat and oseltamivir. Drug assays in the PK/PD core include ABT-888, an orally bioavailable poly(ADP-ribose) polymerase (PARP) inhibitor, simultaneous measurement of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), VX770, metformin and a simultaneous method to quantitate estradiol, estrone, estriol and estetrol. Methods in development include MLN8237, dabigatran, prednisolone 21-acetate, and latanoprost. Individual pharmacokinetic data analyses and modeling is conducted on a Dell Latitude E6410 laptop computer with a docking station. This system runs Office Professional 2007 using the Windows 7 64 bit operating system. In addition, we have the necessary data analysis resources including: a Dell Optiplex 980, two Optiplex 780 systems, and a Precision T3500; all Pentium III, IV, or dual processing, four additional laptop computers, an HP Color LaserJet 4600dn printer, and LaserJet 4100tn, 4050tn, and 2200dt printers are also available. All lab personnel have internet access, and all necessary software, including the ADAPT 5 Package of Pharmacokinetic and Pharmacodynamic Modeling Programs, NONMEM (nonlinear mixed effect modeling) integrated with PDx-POP and S-Plus, the Pharsight package of Phoenix 6.4, and R software. Additional computer software resources available include: Microsoft Office 2010 (Word, Excel, PowerPoint, Access); Intel Visual Fortran Compiler Professional Edition 11.1.070 Update 8 for Windows and Intel Math Kernel Library 10.2 Update 7 for Windows; GraphPad Prism 5.0, and Adobe Acrobat 10.0.

Operating room facilities

Children's Hospital of Alabama operating suites consist of 12 rooms with 3 minor procedures rooms. OR suites measure 42,000 square feet. In calendar year 2010, TCHA performed 13,946 cases consisting of dental, ENT, GI, plastic, GYN, Neurosurgery, Oral, Ortho, pulmonary, hematology and general surgery. Since September 2011, the hospital has performed 6,428 One-Day Surgeries and had 3,893 inpatient cases composed of 904,000 minutes of operating time. OR facilities include 2 rooms specialized for pediatric bronchoscopy under general anesthesia.

Cystic Fibrosis Research Center

The CF Research Center at UAB is an accredited center for both adult and pediatric patients and is a designated University-wide Interdisciplinary Research Center. We have close to 500 patients in our center, of which 95% are enrolled in the CF Registry. We are able to use the CF Registry as a recruiting tool under UAB IRB approval X000509005 entitled "Cystic Fibrosis Center for Care, Teaching and Research." Our Center is a

leading enroller in CF clinical trials through our performance in the CF Therapeutics Development Network (ranked No. 2 of 54 sites for enrollment, controlled for study complexity).

Clinical Research Support Program (CRSP)
Dr. Guimbellot has access to the CRSP for regulatory and research coordinator support for her clinical studies. The CRSP has a pool of trained and certified research nurses and coordinators to assist with all aspects of conducting clinical studies, including data management, subject recruitment, regulatory adherence, and other issues. Dr. Guimbellot has an established relationship with the program and the research coordinators are already familiar with her protocols and studies.

Pediatric Research Office (PRO)
Dr. Guimbellot is supported by the PRO through her appointment in the Department of Pediatrics. The PRO provides assistance to investigators conducting pediatric research at Children's of Alabama. It provides pre-award and post-award support for funded investigators as well as those seeking funding or training. The Office's activities are well-integrated with other research and training efforts across the university. Office personnel provide special expertise in the pre-award stage with the completion of forms for the Office of Sponsored Programs and navigation of their systems. They also provide help identifying funding and training opportunities and with the planning and editing of applications, including editorial assistance. They ensure that guidelines are followed appropriately and provide assistance with informatics and with statistical planning and analysis.

Patch clamp analysis of ion channel electrophysiology
Whole-cell and patch clamp current recordings can be conducted in membrane preparations from cell lines and tissues using Leica DM IRB inverted microscope (Leica Microsystems, Heidelberg, Germany) and Axopatch 200B patch clamp amplifier (Axon Instruments, Molecular Devices, USA) with voltage commands and data acquisition controlled by Clampex software (pClamp 10, Axon Instruments) with digitization capabilities (Digidata 1440A interface, Axon Instruments). We also have Clampfit software (pClamp 10) available for analysis.

MAJOR EQUIPMENT:

All equipment necessary to conduct the experiments described in this research proposal are already available in the laboratories of Dr. Guimbellot, Dr. Rowe, and the UAB CF Research Center on MCLM 7th floor, or in indicated core facilities.

Laboratory equipment
Major equipment available in the Guimbellot laboratory includes a tissue culture laboratory with a biological safety cabinet, water-jacketed CO2 incubator, table top centrifuge, radial shaker, freezer, refrigerator, water baths, microcentrifuge, and fume hood. Further, the Guimbellot laboratory has all equipment necessary to conduct protein purification, isolation and Western blotting; and RNA and DNA isolation. This includes protein electrophoresis gel setups and power supply, and requisite pipettes and other disposables.

Microscopy
Dr. Guimbellot has a fluorescent microscope located in her laboratory: Nikon TS2 inverted microscope with CFI60 optical system and LED illumination, including brightfield phase-contrast, with CFI60 Flan Fluor phase contrast objectives (4x, 10x, 20x, and 40x) and fluorescent capability, LED units for fluorescent imaging at 385 nm, 470 nm, 560 nm, including filters. System includes a Nikon DS-Fi3 color camera, NIS-Elements basic research package for acquisition and analysis for 4D imaging, imaging workstation, and monitor. The system also includes an OKOlab H301-mini incubation chamber with temperature, humidity, and CO2 control, including perfusion channels, specimen holder for standard microscope slides and 35mm dishes, for live-cell fluorescent or brightfield microscopy. She also has access to the High Resolution Imaging Facility (HRIF; Shelby Building Rooms 130-136), which includes a Zeiss LSM 710 laser confocal microscope, digital fluorescence and light microscopy (Nikon Diaphot, Nikon SMZ-U stereo/dissection scope, Nikon Eclipse TE-2000U inverted high resolution digital microscope system, Olympus IX-70 Inverted Epifluorescence digital microscope system) and confocal laser microscopy (Nikon A1 high speed laser confocal spectral imaging, Nikon A1R high speed resonance multi photon live tissue imaging system, Leica SP2 confocal laser scanning microscope). A FEI Tecnai F20 FEG transmission electron microscope is also available to investigators. Dr. Guimbellot's laboratory is experienced with this equipment, and may utilize this core resource on a fee-for-service basis.

Additional Equipment:
The Guimbellot laboratory has 2 office computers (HP desktop) and 1 laptop computer (HP), each of which operate Microsoft Windows and are equipped with Microsoft Office, GraphPad Prism, and ImageJ. The laboratory has two laser printers (HP LaserJet Pro) and access to Department of Pediatrics color printers. Dr. Guimbellot and her staff have access to the Rowe laboratory and additional computers and software including SPSS and SAS. Dr. Guimbellot has an office in MCLM approximately 64 sq.ft. and an ancillary office at Children's hospital (64 sq. ft.). The office and laboratory are equipped with four locked filing cabinets for retention of laboratory and subject records.

NOTE: Dr. Guimbellot also has full access to the laboratory of her primary research mentor, Dr. Steven Rowe, located one floor below her own in the same building.

UAB Cystic Fibrosis Research Center and Rowe laboratory tissue culture and common equipment
Dr. Guimbellot has access to the full resources in the Rowe (mentor) laboratory and the UAB CF Research Center (CFRC; 7th Floor, MCLM) including a Tissue Culture laboratory (136 sq. ft.) containing several biological safety cabinets and 4 CO_2 incubators. The main laboratory and 2 additional laboratories contain a Beckman medium speed centrifuge, radial shaker, upright incubators, freezer, refrigerator-freezer, -70°C freezer, balances, water baths, and microfuge. Capabilities include membrane protein purification and biochemistry, DNA sequencing, isolation of proteins synthesized in bacteria or insect cells, protein (acrylamide) and DNA (agarose) electrophoresis, protein digestion, molecular cloning, DNA preparations, gene transfer to eukaryotic cells, Western blotting, histochemistry, surface biotinylation, immunocytochemistry, and RNA isolation and PCR. Major equipment available in the Rowe laboratory supports assays of CFTR activity, including nasal potential difference (NPD) studies, iodide efflux studies, and Ussing chamber studies of cell monolayers and intact airway tissues. The Rowe laboratory has all equipment necessary to conduct RNA isolation, RT-PCR, protein purification and

isolation, and Western blotting. This includes protein agarose gel setups and power supply, DNA and RNA agarose gel equipment and power supplies, and requisite pipettes and other disposables.
The CF Research Center also includes digital confocal microscope for fluorescence-based immunocytochemistry (MCLM 696–698) with a real-time microscope video unit. The Center also houses an QuantStudio 3 Real-time PCR system and the ABI Prism 7000 RNA detection System allowing for the performance of real-time RT-PCR on cell lines and primary airway cell samples; 2 patch clamp rigs with air tables; mechanical pipette manipulators; inverted microscopes; perfusion chambers; accompanying software for single-channel and whole-cell analysis; and a Nagarishi pipette puller. Other core equipment housed within the UAB CF Research Center available to the investigative team includes 3 Beckman ultracentrifuges complete with rotors (L8-60M, TL-100 and XL-90); a Tricarb 2000-CA scintillation counter; 2 cold rooms; 2 Revco -80°C and American Scientific –70°C freezers; 4 tissue culture incubators dedicated to growth of primary airway cells; 2 Nikon upright microscopes; 4 liquid nitrogen cell storage containers; tissue culture water baths; 4 tissue culture hoods; a Forma Scientifica incubated shaker; 3 Perkin Elmer thermocyclers; and a Beckman DU-64 spectrophotometer, in addition to the equipment detailed above. A laboratory dedicated to the growth and procurement of primary airway cells includes 3 CO_2 incubators, a dedicated tissue culture hood, and a polarized light microscope with imaging capabilities.

Heflin Center for Genomic Science. A University-wide Interdisciplinary Research Center, the Heflin Center has the Genomics Core Laboratory (located in the building adjacent to the Rowe and Guimbellot laboratories) has the capability of performing standard fluorescent and Next-Generation Sequencing (NGS), high and low throughput custom genotyping from 1 SNP to more than 5 million SNPs, whole genome linkage and association studies, targeted and whole genome gene expression, and targeted and whole genome assays. This includes ABI 3730xl Genetic Analyzer, Illumina NextSeq500 Next Generation Sequencing (NGS) instrument, among other equipment. SNaPshot® Multiplex System for targeted genotyping is also available.

UAB Pediatric Pharmacology Laboratory and Comprehensive Cancer Center Pharmacometrics Core. The Laboratory has all the equipment necessary to develop novel drug assays and simultaneously quantitate multiple analytes: Shimadzu XR (UFLC) system coupled to an ABSciex 5000 triple quadrupole mass spectrometer (Analyst 1.6.2 software) with freestanding nitrogen generator and air compressor; Shimadzu XR UFLC system coupled to an ABSciex 5500 triple quadrupole mass spectrometer (Analyst 1.6.2 software) with freestanding nitrogen generator and air compressor; Shimadzu XR UFLC system coupled to an ABSciex 5500 QTrap triple quadrupole mass spectrometer (Analyst 1.6.2 software) with freestanding nitrogen generator and air compressor; Sciex Exion UPLC (1300bar) system coupled to a Qtrap 6500+ triple quadrupole mass spectrometer (Analyst 1.6.3 software) with freestanding nitrogen generator and air compressor; stand-alone Waters Acuity Ultra Performance Liquid Chromatography (UPLC) system running empower II software; each quantitation system is coupled with a Dell or IBM computing system and a printer. Routine laboratory equipment also includes: three Eppendorf 5702 centrifuges; Fisher Scientific Marathon centrifuge 16KM; Eppendorf 5424 microcentrifuge; HARRIS -80°C Freezer; Forma Scientific -20°C freezer; Two Caliper TurboVap LVs; Hand-held UV lamp; IKA Vibrax VBR shaker with attachments; Fisher Scientific Isotemp 37°C incubator; Eppendorf 5430 centrifuge with 30x2mL rotor and 2x96 well plate rotor; Fisher Scientific Centrific centrifuge; two SANYO -80°C Freezers; Forma Scientific -80°C Freezer; Standard refrigerator/freezer; Thermo Scientific Genesis 10 UV-Vis spectrophotometer; four Vortex Genie 2 vortex mixers with attachments; IKA MTS shaker with attachments; Boekel Shake N Bake hybridization oven; Fisher Scientific sonicator; Milli-Q Advantage A10 water purification system; One NuAire Biological Safety Cabinet; Two Justrite Chemical storage cabinets; Mettler Toledo MX5 microbalance; two Fisher balances; Fisher- Hematology/Chemistry tumbling mixer; two Thermolyne Nuova stirring hotplates;two Accumet basic AP15 pH meters; two tissue homogenizers (Fisher Scientific pestle grinder, Next Advantage bullet blender).

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Jennifer Middle Name S Last Name*: Guimbellot Suffix:

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Division: Peds - Pulmonary
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Zip / Postal Code*: 352940005

Phone Number*: (205) 934-6066 Fax Number: (205) 934-7593

E-Mail*: GUIM@UAB.EDU

Credential, e.g., agency login: GUIM01

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD,PHD,BS Degree Year: 2008

Attach Biographical Sketch*: File Name: 10-11-2017.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Steven Middle Name Mark Last Name*: Rowe Suffix:

Position/Title*: Professor
Organization Name*: The University of Alabama at Birmingham
Department: School of Medicine
Division: Pulmonary Allergy Critical Car
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E-Mail*: srowe@peds.uab.edu

Credential, e.g., agency login: rowe02

Project Role*: Other (Specify) Other Project Role Category: Mentor

Degree Type: MD,BA,MSPH Degree Year: 1998, 1994, 2005

Attach Biographical Sketch*: File Name: Rowe_biosketch.pdf

Attach Current & Pending Support: File Name: ROWE_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: DAVID Middle Name W Last Name*: KIMBERLIN Suffix:

Position/Title*: Professor
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Department: School of Medicine
Division: Peds - Infectious Diseases
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Phone Number*: (205) 934-5316 Fax Number: (205) 934-8559

E-Mail*: PEDPLLL@UABDPO.DPO.UAB.EDU

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Project Role*: Other (Specify) Other Project Role Category: Co-Mentor

Degree Type: MD,BS Degree Year: 1989

Attach Biographical Sketch*: File Name: Kimberlin_biosketch.pdf

Attach Current & Pending Support: File Name: KIMBERLIN_OS.pdf

PROFILE - Senior/Key Person

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Division: Clinical Pharmacology
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E-Mail*: eacosta@uab.edu

Credential, e.g., agency login: eacosta

Project Role*: Other (Specify) Other Project Role Category: Co-Mentor

Degree Type: PharmD Degree Year: 1992

Attach Biographical Sketch*: File Name: Acosta_biosketch.pdf

Attach Current & Pending Support: File Name: ACOSTA_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Hemant Middle Name K. Last Name*: Tiwari Suffix:

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Department: School of Public Health
Division: Biostatistics
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E-Mail*: htiwari@uab.edu

Credential, e.g., agency login: htiwari

Project Role*: Other (Specify) Other Project Role Category: Co-Mentor

Degree Type: PHD Degree Year: 1986

Attach Biographical Sketch*: File Name: Tiwari_biosketch.pdf

Attach Current & Pending Support: File Name: TIWARI_OS.pdf

PROFILE - Senior/Key Person

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E-Mail*: caban@uab.edu

Credential, e.g., agency login: chichiaban

Project Role*: Other (Specify) Other Project Role Category: Co-Mentor

Degree Type: PHD,MS,BS Degree Year: 1995,1988,1985

Attach Biographical Sketch*: File Name: Aban_biosketch.pdf

Attach Current & Pending Support: File Name: ABAN_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Emily Middle Name E Last Name*: Scott Suffix:

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Country*: USA: UNITED STATES
Zip / Postal Code*: 481090000

Phone Number*: 7347643530 Fax Number:

E-Mail*: scottee@umich.edu

Credential, e.g., agency login: eescott

Project Role*: Other (Specify) Other Project Role Category: Advisor

Degree Type: PHD,BS Degree Year: 1998, 1992

Attach Biographical Sketch*: File Name: Scott_biosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: NITA Middle Name A Last Name*: LIMDI Suffix:

Position/Title*: Professor
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E-Mail*: nlimdi@uab.edu

Credential, e.g., agency login: nlimdi

Project Role*: Other (Specify) Other Project Role Category: Advisor

Degree Type: PharmD,PHD,MS,BS Degree Year: 1994, 2008, 2005,1993

Attach Biographical Sketch*: File Name: Limdi_biosketch.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Guimbellot, Jennifer S.

eRA COMMONS USER NAME (credential, e.g., agency login): GUIM01

POSITION TITLE: Assistant Professor of Pediatrics

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Mississippi State Univ., Starkville, MS (*summa cum laude)*	B.S.	05/2000	Biochemistry, Molecular Biology
University of Alabama at Birmingham	M.D./Ph.D.	12/2008	Genetics
New York-Presbyterian Morgan Stanley Children's Hospital, New York, NY	N/A	06/2012	General pediatrics internship/residency
University of North Carolina at Chapel Hill	N/A	06/2015	Pediatric pulmonary fellowship

A. Personal Statement

My research career goal is to develop personalized therapeutic strategies for children with cystic fibrosis (CF), incorporating pharmacometrics and cell-culture based predictive tools. I optimize cell-culture based tools to understand the use of CF Transmembrane conductance Regulator (CFTR) modulators on a personalized basis and to study pathophysiology in CF. As a fellow, I initiated projects in the effect of airway colonization by bacteria on CFTR trafficking as well as epidemiologic evaluation on the effects of chronic bacterial colonization of patients with tracheostomy. During this time, I significantly changed my research direction due to a serendipitous finding in nasal epithelial culture, resulting in the development of a novel cell-culture based three-dimensional model for assessing CFTR function. Because of this change, my productivity slowed while I developed the new model; thus, I did not publish findings as a fellow. One publication from my original research project is currently under review, while a second, regarding the new models, is in press. A third publication (a review on CFTR modulators), biomarkers, and predictive models, is in press in the journal Pediatric Pulmonology. The change in direction has resulted in a new career path leading directly to the further development of primary cell culture models and pharmacometric analysis for application to precision medicine in cystic fibrosis. I currently have three additional first-author manuscripts in preparation, detailing the mass spectrometry methods of quantifying modulators in human specimens; the development of sweat gland primary cell models; and a clinical observational trial of ivacaftor in non-G551D patients. I have developed expertise in three-dimensional modeling, airway epithelial biology, modulator therapy, biochemical and electrophysiological techniques, and clinical studies of cystic fibrosis, making me uniquely suited to complete the proposed project. As a graduate student and fellow, I received extensive training in both basic science and clinical skills including cell-culture model development; primary human epithelial culture; correction of mutant CFTR proteins by small molecule compounds; CFTR biochemistry, trafficking, and electrophysiology; microscopy; human subjects (including the recruitment of children and their families); and animal studies. My expertise in genetics, cell biology, and biochemistry is broad and encompasses many relevant skills to bring this project to fruition. My career development and training plan includes studies in pharmacology and pharmacogenetics; advanced clinical study design such as personalized medicine trials; and additional professional development skills, all selected to maximize the success of this project and enable my transition to an independent investigator.

B. Positions and Honors

Positions and Employment

2009 Adjunct Faculty, Department of Biology, Millsaps College, Jackson, MS
2015-2016 Instructor, Department of Pediatrics, University of Alabama at Birmingham
2016 Assistant Professor, Department of Pediatrics, University of Alabama at Birmingham

Board Certification

2013	American Board of Pediatrics, General Pediatrics
2016	American Board of Pediatrics, Pulmonology

Other Experience and Professional Memberships

2005-	American Physician Scientists Association
2009-	American Academy of Pediatrics
2013-	American Thoracic Society

Honors

1999	Barry M. Goldwater Scholar
2005	Genetics Award, National Student Research Forum, UTMB, Galveston, Texas
2005	Best Poster Award, MSTP, University of Alabama, Birmingham
2006	American Society of Human Genetics Annual Meeting Travel Award
2006	European Respiratory Society 4th Lung Science Conference Travel Award
2007 & 2006	Outstanding Graduate Student (Doctoral), Department of Genetics, University of Alabama at Birmingham
2013	Johnny Carson Award for Best Overall Research, Department of Pediatrics Evening of Scholarship, University of North Carolina at Chapel Hill
2014	American Thoracic Society, Assembly on Pediatrics Abstract Scholarship

C. Contributions to Science

1. My laboratory has a focus on three-dimensional model development to be used as *in vitro* biomarkers. I developed novel three-dimensional cell culture models from the nasal epithelial airway using a non-invasive biopsy and designed new assays to isolate and evaluate CFTR channel activity and fluid transport. The first of these models results in rapid development of spherical airway models with a simple measurement outcome that correlates with small changes in CFTR activity, and may represent an *in vitro* biomarker for determining cystic fibrosis patient responses to modulator drugs.
    a. **Guimbellot JS,** Sharma J, Rowe SM. "Toward Inclusive Therapy with CFTR Modulators: Progress and Challenges." Pediatric Pulmonology. 2017. In press.
    b. **Guimbellot JS,** Leach JM, Chaudhry, IG, Quinney NL, Boyles, SE, Chua, M, Aban, I, Jaspers, I, Gentzsch, M. "Nasospheroids permit novel measurements of CFTR-dependent fluid transport." JCI Insight. 2017. In press.

2. As a clinical fellow, I initiated an epidemiologic study and subsequently recruited a co-fellow, evaluating the effects of chronic bacterial colonization on the clinical outcomes of pediatric patients with tracheostomies, showing a significant increase on medical utilization with increased admissions and length of stay for those patients with chronic Gram-negative rod infection, the first showing a correlation between such infection and clinical outcomes in patients with tracheostomy tubes regardless of ventilator dependence. *A manuscript to Pediatric Pulmonology has been submitted for peer review describing the results of this research, for which I am a co-first author. To assist in the review, this is included below.*
    a. Sanders CD*, **Guimbellot JS*,** Muhlebach, MS, Lin, F-C, Gilligan P, Esther, CR. "Tracheostomy in children: epidemiology and clinical outcomes." Pediatric Pulmonology. 2017. Revision submitted. *Co-first authors.

3. During my graduate career, I discovered that CFTR is negatively impacted by hypoxemia, a phenomenon with relevance to acquired CFTR dysfunction, the first finding to suggest that individuals with normal CFTR genes may develop illnesses similar to cystic fibrosis, such as chronic obstructive pulmonary disease. During my thesis work I also presented the first evidence that microRNAs are differentially regulated in epithelial cells by hypoxemia.
    a. **Guimbellot JS**, Fortenberry JA, Siegal GP, Moore B, Wen H, Venglarik C, Chen YF, Oparil S, Sorscher EJ, Hong JS. Role of Oxygen in Cystic Fibrosis Transmembrane Conductance Regulator Expression and Function. Am J Respir Cell Mol Biol. 2008 May 12. PMCID: PMC2574524

b. **Guimbellot JS**, Erickson SW, Mehta T, Wen H, Page GP, Sorscher EJ, Hong JS. Correlation of microRNA levels during hypoxia with predicted target mRNAs through genome-wide microarray analysis. BMC Med Genomics. 2009 Mar 25;2:15. PMCID: PMC2667434

4. During my graduate career, I was a contributing author to a seminal publication proving that normal endogenous CFTR protein is efficiently processed. Prior to this publication, it was thought that a large portion of normal, endogenous protein was degraded due to studies in cell models.
   a. Varga K, Jurkuvenaite A, Wakefield J, Hong JS, **Guimbellot JS**, Venglarik CJ, Niraj A, Mazur M, Sorscher EJ, Collawn JF, Bebok Z. Efficient intracellular processing of the endogenous cystic fibrosis transmembrane conductance regulator in epithelial cell lines. J Biol Chem. 2004 May 21;279(21):22578-84. PMID 15066992

5. As a research technician, I contributed to the understanding of different EWS/FLI fusion proteins in Ewing's sarcoma by assisting with the development of cellular models and fusion proteins.
   a. Zwerner JP, **Guimbellot J**, May WA.EWS/FLI function varies in different cellular backgrounds. Exp Cell Res. 2003 Nov 1;290(2):414-9. PMID 14567998

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1hqx7zl0EXf/bibliography/40344656/public/?sort=date&direction=ascending

D. Additional Information: Research Support

Ongoing Research Support

Cystic Fibrosis Foundation — Guimbellot (PI) — 04/01/17 – 03/31/19
Pilot and Feasibility Award
This pilot award will evaluate a two-phase cell-culture based biomarkers for prediction of modulator efficacy and distinction of subtle levels of CFTR activation using three-dimensional cell culture models and micro-optical coherence tomography for outcome measures of mucociliary clearance, fluid transport, and ciliary beat frequency.
Role: PI

Kaul Pediatrics Research Institute — Guimbellot (PI) — 02/01/16 – 01//31/18
Development of Personalized Approaches to CFTR Modulator
This award provides funding for human nasal epithelial-derived three-dimensional sphere cultures for personalized medicine in cystic fibrosis using size change imaged by confocal microscopy as a surrogate for fluid transport.
Role: PI

UAB Department of Pediatrics — Guimbellot (PI) — 08/01/15 – present
Research start-up package
The goal of this support is to provide funding for laboratory equipment and supplies to grow a new investigator research program in personalized medicine for children with cystic fibrosis.
Role: PI

Completed Research Support

NIH/NHLBI 1 R43 HL134056-01 — Prabhakar pandian (PI) — 08/15/16 – 07/31/17
Title: A Predictive In Vitro Model for Screening Personalized Responses to CFTR-directed Therapeutics
The purpose of this project was to develop a novel microfluidics-based platform of epithelial and endothelial co-culture for testing of CFTR modulator efficacy.
Role: Co- Investigator

Cystic Fibrosis Foundation GUIMBE14DO — Guimbellot (PI) — 07/01/14 – 06/30/15
Third year Cystic Fibrosis Foundation Clinical Fellowship Grant
The goal of this grant was to provide advanced clinical and research training for pediatric pulmonology fellowship.

Role: PI

NC Trans. & Clinical Sciences Inst. 2KR541401 Guimbellot (PI) 04/01/14 – 04/01/15
Variation in response to correctors in F508del homozygotes.
The goal of this grant was to develop the use of nasal epithelial culture for use in studies of CFTR trafficking and correction.
Role: PI

Cystic Fibrosis Foundation GUIMBE12B0 Guimbellot (PI) 07/01/12 – 06/30/14
First and second year Cystic Fibrosis Foundation Clinical Fellowship Grant
The goal of this grant was to provide clinical training and research support for pediatric pulmonology fellowship.
Role: PI

Children's Promise, XMRSA, UNC-Chapel Hill Guimbellot (PI) 07/01/13 – 06/30/14
Epidemiology of tracheostomy infections
The goal of this project was to evaluate retrospective and prospective cultures from tracheostomies from pediatric patients to understand the evolution of infection and colonization and to inform ways to reduce new infections by quality improvement.
Role: PI

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Rowe, Stephen Mark

eRA COMMONS USER NAME (credential, e.g., agency login): ROWE02

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Virginia	B.A.	05/1994	Interdisplinary
Vanderbilt University	M.D.	05/1998	Medicine
University of Alabama at Birmingham	MSPH	05/2005	Biostatistics

A. Personal Statement

As an academic physician scientist, I have pioneered personalized therapeutics for CF, made cutting-edge discoveries in airway disease biology and ciliary dynamics, and conducted translational research in CF, COPD, and other airway diseases. As detailed below and in my letter of support, my scientific and career development experience make me well suited to serve as Jennifer's primary research mentor. I maintain a robust translational research laboratory program that includes both human-oriented clinical studies and fundamental research of substantive breadth and impact, ranging from cell based drug discovery to animal modeling to Phase 3 clinical trials. I am an expert regarding the mechanistic features underlying cystic fibrosis and the role of the cystic fibrosis transmembrane conductance regulator (CFTR) towards regulating mucociliary clearance. I was co-Chair of the CF Foundation's Mucociliary Clearance Consortium for seven years (since its inception) and am facile with several complementary methods to measure mucus clearance. I am an expert in the measures of epithelial function, the growth and procurement of primary human airway cells required for the experiments, and I co-invented μOCT imaging technology that can be used to evaluate mucociliary transport and airway epithelial functional microanatomy in real time at the cellular level *in vitro* and *in vivo*. I also have significant experience and training in the design and conduct of clinical trials testing new therapeutic agents intended to address the basic CF defect and resulting abnormalities in mucus clearance; led academic-industry partnerships in this regard, spoke on the topic with Dr. Francis Collins at the Keynote Plenary Session during the North American CF Meetings; and discussed new developments in CF clinical approaches in the Plenary Session of the North American CF Meetings 3 years later. My previous record of training of post-doctoral fellows and junior faculty (including those who have achieved NIH K-level funding or similar career development awards from the CF Foundation, American Lung Association and FAMRI, and have been promoted to faculty at UAB and elsewhere, including an individual promoted to CF Center Director), provide strong evidence of my mentoring capacity for Dr. Guimbellot. My record of training medical students, fellows, and faculty has also been highlighted by UAB, as I was a recent recipient of the prestigious Dean's Excellence Award in mentoring.

Rowe SM, Miller S, Sorscher EJ. "Mechanisms of Disease: Cystic Fibrosis." *New England Journal of Medicine,* 2005; 352: 1992-2001.

1. **Rowe SM,** Hoover W, Solomon GM, Sorscher EJ. "Cystic Fibrosis." IN: *Murray & Nadel's Textbook of Respiratory Medicine,* (6th) edition. Philadelphia, PA: Elsevier Saunders; 2016: Chap 47.
2. Snelgrove RJ, Jackson PL, Hardison MT, Noerager BD, Gaggar A, Shastry S, **Rowe SM**, Shim YM, Hussell T, Blalock JE. "A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation". *Science* Oct1;330(6000);90-4, 2010. PMC3072752
3. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, Griese M, McKone E, Wainwright C, Konstan M, Moss R, Ratjen F, Sermet-Gaudelus I, **Rowe SM**, Dong Q, Rodriguez S, Yen K, Ordoñez C,

Elborn JS on behalf of the VX08-770-102 Study Group. "A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *N Engl J Med* 2011 Nov 3;365(18):1663-72. PMC3230303

B. Positions and Honors

Positions and Employment

1998-01 Intern and Resident, Combined Internal Medicine and Pediatrics, UAB
2001-02 Chief Resident, Combined Internal Medicine and Pediatrics, UAB
2002-05 Fellow, Combined Pulmonary and Critical Care Medicine and Pediatric Pulmonology, UAB.
2006- Assistant Professor, Pulmonary, Allergy, and Critical Care Medicine, Pediatric Pulmonology, UAB
2006-14 Director, Cystic Fibrosis Transition Clinic, Children's Hospital, UAB
2006-08 Associate Director, National CF-Therapeutics Development Network Center for CFTR Detection
2007-16 Co-Chair, International Mucociliary Clearance Research Consortium, Cystic Fibrosis Foundation
2008-16 Director, Center for CFTR Detection, CFF Therapeutics Development Network
2009- Special Consultant for Translational Science, Cystic Fibrosis Foundation
2011-14 Associate Professor with Tenure, UAB
2014- Professor with Tenure, Department of Medicine, Pediatrics, and Cell Developmental and Integrative Biology, UAB
2015- Director, Gregory Fleming James Cystic Fibrosis Research Center; Nancy & Eugene Gwaltney Chair for Medical Research

Awards and Honors

2009 Plenary Session Keynote Address, North American Cystic Fibrosis Conference. **Rowe SM and Collins F**. "Two Decades of CFTR Research: From Gene Discovery to Therapeutic Target", Minneapolis, MN
2006- Ad hoc reviewer for Journals including *Nature*, *New England Journal of Medicine, JAMA, JCI, Science Translational Medicine,* and *American Journal of Respiratory and Critical Care Medicine;* Editorial board for *JCI Insight, AJP Lung* and *Journal of CF*
2012 Plenary Session, Keynote Speaker, North American CF Conference. "Correcting the Basic Defect: A Vision for the Future", Rowe SM and Skach W.
2012 Inducted to the *Southern Society of Clinical Investigation*
2014 Dean's Award for Excellence in Mentorship
2014 Inducted to the *American Society of Clinical Investigation*
2015 Max Cooper Award for Excellence in Research
2017 Inducted, Faculty *AOA*, University of Alabama at Birmingham
2017 Visiting Pulmonary Scholar. University of North Carolina at Chapel Hill, Duke, University, EPA, and National Institutes of Environmental Health Sciences
2017 Visiting Professor, NHLBI, NIH, Bethesda, Maryland
2017 Thomas Hazinski Memorial Lecture, Vanderbilt University, Nashville, TN

C. Contributions to Science

1. I discovered that COPD patients exhibit 'acquired CFTR dysfunction' through a pathway that causes delayed mucociliary clearance and confers chronic bronchitis. I also made the surprising discovery that acquired CFTR dysfunction is a systemic phenomenon, which could explain why smokers have an increased incidence of pancreatitis, infertility, and diabetes mellitus (systemic manifestations of COPD in which CFTR plays has a causative role). After establishing the preclinical basis of this novel mechanism, I now lead an investigator-initiated IND study to evaluate ivacaftor in patients with chronic bronchitis. These results could alter the paradigm for COPD treatment.
    a. Raju SV, Jackson PL, Courville CA, McNicholas CM, Sloane PA, Sabbatini G, Tidwell S, Tang LP, Liu B, Fortenberry JA, Jones CW, Boydston JA, Clancy JP, Bowen L, Accurso FJ, Blalock JE, Dransfield MT, **Rowe SM**. "Cigarette Smoke Induces Systemic Defects in Cystic Fibrosis Transmembrane Conductance (CFTR) Regulator Ion Transport." *Am J Respir Crit Care Med,* 2013;188(11):1321-30. PMC3919073.
    b. Raju SV, Lin VY, Liu L, McNicholas CM, Karki S, Sloane PA, Tang LP, Jackson PL, Wang W, Wilson L, Macon KJ, Mazur M, Kappes J, DeLucas LJ, Barnes S, Kirk K, Tearney GT, **Rowe SM**. "The CFTR potentiator ivacaftor augments mucociliary clearance abrogating acute and chronic CFTR inhibition by cigarette smoke." *Am J Respir Cell Mol Biol.* 2017 Jan;56(1):99-108. PMC5248967

c. Solomon GM, Dransfield MT, **Rowe SM**. "Pilot Evaluation of the CFTR Potentiator Ivacaftor for the Treatment of Chronic Bronchitis." *Lancet Respir Med*. 2016 Jun;4(6):e32-2.PMC4916910

d. S. Raju SV, Kim H, Byzek S, Tang LP, Trombley J, Jackson PL, Rasmussen L, Wells JM, Falk Libby E, Dohm E, Winter L, Samuel S, Zinn K, Blalock JE, Schoeb T, Dransfield MT, **Rowe SM**. "A ferret model of COPD-related chronic bronchitis." *JCI Insight* 2016 Sep 22;1(15)e87536. PMC5033751

2. I co-invented an imaging technique (one-micron resolution optical coherence tomography) that captures 3D imaging in real-time at the cellular level. The technique is highly sensitive to the epithelial function of airway tissues and can provide simultaneous and non-invasive measurements of airway surface liquid depth, ciliary beat frequency, mucociliary transport, mucus viscosity and cilia coordination, providing a first-in-kind measures of functional epithelial anatomy. The technology is unprecedented, and is significantly advancing our understanding of airway disease pathogenesis.
   a. Liu L, Chu KK, Houser GH, Diephuis BJ, Li Y, Wilsterman EJ, Shastry S, Dierksen G, Birket SE, Mazur M, Byan-Parker S, Grizzle WE, Sorscher EJ, **Rowe SM***, Tearney GJ*. Method for Quantitative Study of Airway Functional Microanatomy using Micro-Optical Coherence Tomography. PLoS One 8(1):e54473, 2013. Epub 2013 Jan 23. PMC3553101
   b. Birket SE*, Chu KK*, Liu L, Houser GH, Diephuis BJ, Wilsterman EJ, Dierksen G, Mazur M, Shastry S, Li Y, Watson JD, Smith AT, Schuster BS, Hanes J, Grizzle WE, Sorscher EJ, Tearney GJ*, **Rowe SM***. "A Functional Anatomic Defect of the CF Airway." *Am J Respir Crit Care Med*. 2014;190(4):421-32. *Note: Authors contributed equally to this manuscript. Please also see accompanying editorial. PMC4214131
   c. Birket SE, Chu KK, Houser GH, Liu L, Fernandez CM, Solomon GM, Lin V, Shastry S, Mazur M, Sloane P, Hanes J, Grizzle WE, Sorscher EJ, Tearney GJ, **Rowe SM**. "Combination therapy with cystic fibrosis transmembrane conductance regulator modulators augment the airway functional microanatomy." *Am J Physiol Lung Cell Mol Physiol* 2016 Mar 11. PMC4896103.
   d. Solomon GM, Francis R, Chu K, Birket SE, Gabriel G, Trombley JE, Lemke KL, Klena N, Turner B, Tearney GJ, Lo CW, **Rowe SM**. Assessment of ciliary phenotype in primary ciliary dyskinesia by micro-optical coherence tomograph. *JCI Insight* 2017 Mar 9;2(5):e91702. PMC5333960
3. I am a respected international authority with regard to the design and conduct of clinical trials targeting the basic CF defect, and his contributions have provided a roadmap to the cure of CF. For example, I played a key role in the clinical development of ivacaftor, a novel CFTR potentiator, and established in vivo endpoints of CFTR function. The results firmly established CFTR as a therapeutic target in CF, and I have directed large academic-led multicenter studies of mechanism of action to further characterize the approach.
   a. Accurso FJ, **Rowe SM**, Clancy JP, Boyle MP, Dunitz J, Durie PR, Sagel SD, Hornick DB, Konstan MW, Donaldson SH, Moss RB, Pilewski JM, Rubenstein R, Uluer AZ, Aitken ML, Freedman SD, Rose LM, Mayer-Hamblett N, Dong Q, Zha J, Stone AJ, Olson ER, Ordonez CL, Campbell PW, Ashlock MA, Ramsey BW. "Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation". *N Engl J Med* Nov 18:363(21):1991-2003, 2010. Epub 2011 PMC3148255
   b. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, Griese M, McKone E, Wainwright C, Konstan M, Moss R, Ratjen F, Sermet-Gaudelus I, **Rowe SM**, Dong Q, Rodriguez S, Yen K, Ordoñez C, Elborn JS on behalf of the VX08-770-102 Study Group. "A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *N Engl J Med* 2011 Nov 3;365(18):1663-72. PMC3230303
   c. **Rowe SM**, Heltshe SL, Gonska T, Donaldson S, Borowitz D, Gelfond D, Sagel S, Khan U, Mayer-Hamblett N, Van Dalfsen J, Joseloff E, Ramsey B, on behalf of the GOAL investigators. "Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis. *Am J Respir Crit Care Med*. 2014;190(2):175-184. Please see accompanying editorial. PMC4226057
   d. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, Flume PA, Konstan MW, McColley SA, McCoy K, McKone EF, Munck A, Ratjen F, **Rowe SM**, Waltz D, Boyle MP; TRAFFIC and TRANSPORT Study Groups.Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med*. 2015 Jul 16;373(3):220-31. Epub 2015 May 17 PMC4764353

4. I have advanced both the molecular and clinical understanding of suppression of premature termination codons, representing an exciting strategy for treatment of cystic fibrosis and other genetic diseases caused by nonsense mutations.
    a. Xue X, Mutyam V, Tang LP, Biswas S, Du M, Jackson LA, Dai Y, Belakhov V, Shalev M, Chen F, Schacht J, Bridges RT, Baasov T, Hong J, *Bedwell DM, ***Rowe SM**. "Synthetic Aminoglycosides Efficiently Suppress CFTR Nonsense Mutations and Are Enhanced by Ivacaftor." *Amer J Resp Cell Mol Biol* 2014 Apr;50(4):805-16. Epub 2013 Nov 19. PMC4068923
    b. Kerem E*, Konstan M*, De Boeck K, Accurso F, Sermet-Gaudelus I, Wilschanski M, Elborn JS, Melotti P, Bronsveld I, Fajac I, Malfroot A, Rosenbluth D, Walker P, McColley S, Knoop C, Quattrucci S, Rietchel E, Zeitlin P, Barth J, Elfring G, Welch E, Spiegel R, Peltz SW, Ajayi T, **Rowe SM**, for the Cystic Fibrosis Ataluren Study Group. "Ataluren for the treatment of nonsense mutation cystic fibrosis: a randomized, double-blind, placebo-controlled phase 3 trial." *Lancet Respir Med*. 2014 Jul;2(7):539-47. Epub 2014 May 15. *Note: Authors contributed equally to this manuscript. PMC4154311
    c. Mutyam V, Du M, Xue X, White EL, Bostwick JR, Rasmussen L, Liu B, Mazur M, Hong JS, Falk Libby E, Liang F, Shang H, Mense M, Suto MJ, Bedwell DM, **Rowe SM**. "Discovery of Clinically Approved Agents that Promote Nonsense Mutations". *Am J Respir Crit Care Med* 2016 Nov 1;194(9):1092-1103. (PMCID: PMC5114449) Editor's choice in *Science Translational Medicine* 11 May 2016:Vol. 8, Issue 338, pp. 338ec74. Featured as editor's choice in *Science Translational Medicine* 11 May 2016:Vol. 8, Issue 338, pp. 338ec74. See accompanying editorial by I. Sermet-Gaudelus and O. Namy, "New Pharmacological Approaches to Treat Patients with Cystic Fibrosis with Nonsense Mutations." *Am J Respir Crit Care Med*. 2016 Nov 1;194(9):1042-1044.
    d. Roy B, Friesen WJ, Tomizawa Y, Leszyk JD, Zhuo J, Johnson B, Dakka J, Trotta CR, Xue X, Mutyam V, Keeling KM, Mobley JA, **Rowe SM**, Bedwell DM, Welch EM, Jacobson A. Ataluren stimulates ribosomal selection of near-cognate tRNAs to promote nonsense suppression. *Proc Natl Acad Sci* 2016 Nov 1;113(44):12508-12513. PMC5098639

Complete List of Published Work in MyBibliography (over 95 peer reviewed publications):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1-YI6Ybqp2kA/bibliography/47290266/public/?sort=date&direction=ascending

D. Additional Information: Research Support

Ongoing Research Support

P30 DK072482 05/01/2012 – 04/30/2018
NIH/NIDDK
UAB CF Research and Translation Core Center
This P30 provides 3 Scientific Cores (i.e. Animal Models Core, Single Channel Analysis Facility, and Clinical Core) to CF investigators at UAB and collaborating sites to improve understanding of the most basic underpinnings of cystic fibrosis pathogenesis and the ways this information can be aggressively applied to experimental therapeutics. Two Pilot and Feasibility projects are also supported through the P30.
Role: Program Director; Director of Core C: Clinical and Translational Core

R35 HL135816 (Rowe) 12/01/16 – 11/30/23
NIH/NHLBI
Translational Program in CFTR-Related Airway Diseases
This program supports investigation into diseases of mucociliary clearance, including their molecular mechanism, clinical phenotype, and precision medicine approaches to intervene.
Role: Principal Investigator

R464-CR11 (Rowe) 07/01/15 - 06/30/19
Cystic Fibrosis Foundation
Research Development Program (ROWE15R0)
The major goals of this project are to 1) support basic research core capabilities including construction of cell lines, immunolocalization, conductance, SPQ based functional analysis, as well as recombinant adenoviral vectors and other biochemical and functional endpoints for CF scientists and their projects on our campus, 2) provide resources for Pilot/Feasibility Studies, postdoctoral fellows and graduate students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.
Role: Program Director

U54TR001368 (Kimberly) 08/18/2015 – 03/31/19
NIH/NCATS
UAB Center for Clinical and Translational Science (CCTS)
The UAB CCTS will enhance human health by driving scientific discovery and dialogue across the bench, bedside and community continuum. The CCTS support this overall mission in a highly integrative network of relationships. Success in creating such an environment is dependent upon success in achieving five strategic priorities: 1) enhancing research infrastructure; 2) promoting investigator education, training and development; 3) accelerating discovery across the T1 interface; 4) expanding value-added partnerships; and 5) building sustainability.
Role: Co-Director of Pediatric CCTS

ROWE15R0 (Rowe) 07/01/2015 - 6/30/2019
Cystic Fibrosis Foundation
Research Development Program – Component II
The goals of this project are to 1) support core facilities for RT-PCR, immunolocalization, conductance, SPQ based functional analysis, recombinant adenoviral vectors, and other biochemical and functional endpoints for CF scientists and their projects, 2) provide resources for Pilot/Feasibility Studies, fellows and students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.
Role: Program Director; Co-Director, Core A.

GOAL11K1 (Rowe) 09/01/2011 – 12/31/2020
Cystic Fibrosis Foundation
G551D Observational Study (GOAL-OB-11)
Purpose is to conduct a multi-center observational study evaluating the effects of Ivacaftor in CF patients with the G551D mutation. Dr. Rowe supervises the multi-center component of four outcome based sub-studies.
Role: Principal Investigator of national multicenter trial

ROWE14Y0 (Rowe) 01/01/14 – 12/31/17
Cystic Fibrosis Foundation Therapeutics
UAB Cystic Fibrosis Translational Development Center
The main goals of this project are to provide funding and infrastructure for support of Phase I and Phase II clinical trials in Cystic Fibrosis patients through the Therapeutic Development Network.
Role: Principal Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Kimberlin, David Westin

eRA COMMONS USER NAME (credential, e.g., agency login): DKIMBERLIN

POSITION TITLE: Professor of Pediatrics

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Vanderbilt University (*summa cum laude*)	B.S.	1981-1985	Molecular Biology
University of Texas Southwestern Medical School	M.D.	1985-1989	Medicine
University of Texas Southwestern Medical School	Intern/Res	1989-1992	Pediatrics
University of Texas Southwestern Medical School	Fellowship	1992-1994	Infectious Diseases
University of Alabama at Birmingham	Fellowship	1994-1996	Virology

A. Personal Statement

I am very well suited to assist in the success of Dr. Guimbellot as she establishes her independent academic career. I have 23 years of experience in Phase I, II, and III clinical trials conducted by the NIAID Collaborative Antiviral Study Group (CASG). As Co-PI on the CASG contract, I oversaw all pediatric studies conducted by the CASG from 1996 to 2010. I now am PI on the CASG's six BAA contracts for our ongoing studies, including two awarded in July 2016 to assess the benefit of antiviral therapy in babies born with asymptomatic congenital cytomegalovirus infection and the ideal diagnostic modalities to establish the presence of neonatal herpes simplex virus disease. The CASG is an international collaboration of approximately 37 academic medical centers in the United States, the United Kingdom, and Peru; in the past, we also have had sites in Canada, Mexico, and Sweden. The scientific accomplishments of the CASG are documented in Section C, below. I will bring to bear in my career mentorship of Dr. Guimbellot not only the clinical trials expertise that I have amassed through my leadership of the CASG in its studies of neonatal herpes simplex virus infection and congenital cytomegalovirus disease, but also my experience in the education and training of pediatric subspecialty fellows. From 2001 to 2014, I served as Director of Subspecialty (Fellowship) Education for the University of Alabama at Birmingham Department of Pediatrics. During this time, I directed the education of over 200 fellows who completed subspecialty pediatric training at UAB. I currently am Vice Chair for Clinical and Translational Research for the UAB Department of Pediatrics. I also am Editor of the American Academy of Pediatrics (AAP) Red Book: Report of the committee on Infectious Diseases, and am Past-President of the Pediatric Infectious Diseases Society, which is the world's largest organization of professionals dedicated to the treatment, control and eradication of infectious diseases affecting children. All of these prior and current roles prepare me very well to mentor Dr. Guimbellot's career development. **I commit to being available to mentor Dr. Guimbellot as she establishes her independent academic career in the field of cystic fibrosis research. The full scope of my mentorship is outlined in my statement.**

B. Positions and Honors

Positions and Employment

1989-1990 Pediatric Intern, Children's Medical Center of Dallas, University of Texas Southwestern Medical School, Dallas, Texas

1990-1992 Pediatric Resident, Children's Medical Center of Dallas, University of Texas Southwestern Medical School, Dallas, Texas

1992-1994 Fellow, Division of Infectious Disease, Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, Texas

1994-1996 Fellow, Division of Clinical Virology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
1996-2002 Assistant Professor, Division of Clinical Virology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
2002-2007 Associate Professor with tenure, Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
2007-present Professor with tenure, Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama

Other Experience

1999-present Scientist, Center for Outcomes and Effectiveness Research and Education, University of Alabama at Birmingham, Birmingham, Alabama
1999-present Associate Scientist, Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, Alabama
2001-2007 Associate Director, University of Alabama General Clinical Research Center (GCRC), Birmingham, Alabama
2007-2008 Interim Director, University of Alabama General Clinical Research Center (GCRC), Birmingham, Alabama
2001-2014 Director of Subspecialty Medical Education, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
2014-present Vice Chair for Clinical and Translational Research, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama

Professional Memberships

American Academy of Pediatrics
Pediatric Infectious Diseases Society
Infectious Diseases Society of America
Society for Pediatric Research
International Society for Antiviral Research

C. Contribution to Science

CASG studies that I have developed, implemented, and analyzed have defined the the standard of care in the United States for the treatment of 1) congenital cytomegalovirus (CMV) disease, 2) neonatal herpes simplex virus infection (HSV), and 3) infantile influenza.

1. **With respect to CMV**, we initially determined that six weeks of antiviral therapy using intravenous ganciclovir improved audiologic outcomes in neonates with symptomatic congenital CMV involving the central nervous system. We then conducted a pharmacokinetic/pharmacodynamic study of oral valganciclovir to determine what dose of oral valganciclovir provides the same systemic exposure to ganciclovir as does valganciclovir. This was followed by our most recent study comparing six weeks and six months of oral valganciclovir, in which we demonstrated improved audiologic and developmental outcomes with the longer-term treatment duration. This treatment is now recommended by the American Academy of Pediatrics as the standard of care for babies with symptomatic congenital CMV disease throughout the United States. Cumulatively, CASG studies that I have developed, implemented, and overseen have led to successful supplemental NDAs that have resulted in approval of: 1) a pediatric indication from the U.S. Food and Drug Administration (FDA) for valganciclovir down to 1 month of age (April 2015); 2) a new pediatric indication from the European Medicinal Agency (EMA) for valganciclovir (Fall 2014); 3) a new valganciclovir formulation (tutti-frutti flavored Valcyte for Oral Solution) from the U.S. FDA (August 2009); and 4) patent extension for valganciclovir in the European Union (Fall 2014). CASG data have been incorporated in the valganciclovir drug label. Additionally, data from the CASG's Phase I/II pharmacokinetic/ pharmacodynamic study of valganciclovir, its 6 week versus 6 month Phase III study of valganciclovir, and three earlier CASG studies of ganciclovir [a Phase II study of intravenous ganciclovir, a Phase III study of intravenous ganciclovir, and a long-term follow-up study of adolescents treated as neonates with intravenous ganciclovir] have been incorporated into the Valcyte Investigator's Brochure.

a. **Kimberlin DW**, Lin C-Y, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Kiell

JM, Soong SJ, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: Effect of ganciclovir on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: A randomized, controlled trial. J. Pediatr. 2003;143:16-25. PMID 12915819

b. Acosta EP, Brundage RC, King JR, Griffin J, Cloud GA, Whitley RJ, **Kimberlin DW**, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid formulation of valganciclovir. Clin. Pharmacol. Therapeut. 2007;81:867-872. PMID 17392728
c. **Kimberlin DW**, Acosta EP, Sánchez PJ, Sood S, Agrawal V, Homans J, Jacobs RF, Lang D, Romero JR, Griffin J, Cloud GA, Lakeman FD, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: A pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital CMV disease. J. Infect. Dis. 2008;197:836-845 PMID 18279073.
d. **Kimberlin DW**, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels M, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR, Sood SK, Whitworth MS, Abzug MJ, Caserta MT, Fowler S, Lujan-Zilbermann J, Storch GA, DeBiasi RL, Han J-Y, Palmer A, Weiner LB, Bocchini JA, Dennehy PH, Finn A, Griffiths P, Gutierrez K, Halasa N, Homans J, Shane A, Sharland M, Simonsen K, Vanchiere JA, Woods CR, Sabo DL, Aban I, Kuo H, James SH, Prichard MN, Griffin J, Giles G, Acosta EP, Whitley RJ, for the NIAID Collaborative Antiviral Study Group (CASG). Valganciclovir for symptomatic congenital cytomegalovirus disease. N. Engl. J. Med. 2015;372(10):933-943. PMC4401811

2. <u>With respect to neonatal HSV disease</u>, the studies that I have developed, overseen, and analyzed have defined the standard of care nationally for the management of this lifethreatening disease. This includes determining that polymerase chain reaction (PCR) to the cerebrospinal fluid of babies with neonatal HSV CNS disease could supplant the need for a brain biopsy in these patients. We then determined that mortality and morbidity outcomes are improved with the use of higher dose intravenous acyclovir. Most recently we proved that oral acyclovir suppressive therapy administered for six months following neonatal HSV disease improves both neurologic (for CNS disease classification) and cutaneous (in all neonatal HSV disease classifications) morbidity. This has critically important implications in our understanding of the pathogenesis of this disease, since the only way that suppressive therapy could improve neurodevelopmental outcomes is if there is subclinical reactivation of virus occurring "silently" in the brain following treatment of the initial acute disease. <u>As with congenital CMV, the dose and duration of parenteral acyclovir established by our CASG studies and the use of oral acyclovir suppressive therapy are now recommended by the American Academy of Pediatrics as the standard of care for babies with neonatal HSV disease throughout the United States.</u> We also have proven that suppressive antiviral treatment of pregnant women does not prevent the transmission of HSV to the baby at delivery, with the subsequent development of neonatal herpes. I also analyzed and published the pharmacokinetic analyses of valacyclovir in children.

a. **Kimberlin DW**, Lakeman FD, Arvin AM, Prober CG, Corey L, Powell DA, Burchett SK, Jacobs RF, Starr SE, Whitley RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. J. Infect. Dis. 1996;174:1162-1167. PMID 8940204
b. **Kimberlin DW**, Lin C-Y, Jacobs RF, Powell DA, Corey L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, Murguía de Sierra T, Weller S, Soong S-J, Kiell J, Lakeman FD, Whitley RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 2001;108:230-238. PMID 11483782
c. **Kimberlin DW**, Lin C-Y, Jacobs RF, Powell DA, Frenkel L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, Murguía de Sierra T, Soong S-J, Kiell J, Lakeman FD, Whitley RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. The natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001;108:223-229. PMID 11483781
d. **Kimberlin DW**, Whitley RJ, Wan W, Powell DA; Storch G, Ahmed A, Palmer A, Sánchez PJ, Jacobs RJ, Bradley JS, Robinson JL, Shelton M, Dennehy PH, Leach C, Rathore M, Abughali N, Wright P, Frenkel LM, Brady RC, Van Dyke R, Weiner LB, Guzman-Cottrill J, McCarthy CA, Griffin J, Jester P, Parker M, Lakeman FD, Kuo H, Lee CH, Cloud GA, for the NIAID Collaborative Antiviral Study Group: Oral

acyclovir suppression and neurodevelopment after neonatal herpes. N. Engl. J. Med. 2011;365(14):1284-1292. PMC3250992

3. With respect to infantile influenza, I developed, oversaw, and analyzed the CASG study of oseltamivir in infants under one year of age that resulted in the U.S. Food and Drug Administration lowering the labeled indication for treatment with this antiviral drug to two weeks of age. Importantly, the data from this study also were the basis for the DHHS Emergency Use Authorization during the 2009 H1N1 pandemic, and were the sole data used to guide treatment of infants with pandemic influenza around the world. As with congenital CMV and neonatal HSV, the dose of oral oseltamivir established by our CASG studies is now recommended by the American Academy of Pediatrics and the Centers for Disease Control and Prevention as the standard of care for neonates and infants with influenza infection throughout the United States.

a. **Kimberlin DW**, Shalabi M, Abzug MJ, Lang D, Jacobs RF, Storch G, Bradley JS, Wade K, Ramilo O, Romero JR, Shelton M, Leach C, Guzman-Cottrill J, Robinson J, Abughali N, Englund J, Griffin J, Jester P, Cloud GA, Whitley RJ, for the NIAID Collaborative Antiviral Study Group: Safety of Oseltamivir Compared With the Adamantanes in Children Less Than 12 Months of Age. Pediatr. Infect. Dis. J. 2010;29:195-198 PMC3703844
b. Acosta EP, Jester P, Gal P, Wimmer J, Wade J, Whitley RJ, **Kimberlin DW**, for the NIAID Collaborative Antiviral Study Group: Oseltamivir dosing for influenza infection in premature neonates. J. Infect. Dis. 2010;202(4):563-566. PMC2904429
c. **Kimberlin DW**, Acosta EP, Prichard MN, Sánchez PJ, Ampofo K, Lang D, Ashouri N, Vanchiere JA, Abzug MJ, Abughali N, Caserta MT, Englund JA, Sood SK, Spigarelli MG, Bradley JS, Lew J, Michaels MG, Wan W, Cloud G, Jester P, Lakeman FD, Whitley RJ, for the NIAID Collaborative Antiviral Study Group: Oseltamivir pharmacokinetics, dosing, and resistance among children aged < 2 years with influenza. J. Infect. Dis. 2013;207:709-720. PMC3563309
d. Kamal MA, Acosta EP, **Kimberlin DW**, Gibiansky L, Jester P, Niranjan V, Rath B, Clinch B, Sánchez PJ, Ampofo K, Whitley R, Rayner CR: The posology of oseltamivir in infants with influenza infection using a population pharmacokinetic approach. Clin. Pharmacol. Therapeut. 2014;96(3):380-389. PMID 24865390

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/16oVh0raPCNka/bibliography/43799096/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

HHSN272201600017C (Kimberlin, PI) 07/01/16-06/30/21
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: A Phase II, Single-Stage, Single-Arm Investigation of Oral Valganciclovir Therapy in Infants with Asymptomatic Congenital Cytomegalovirus Infection
This contract evaluates the antiviral treatment of infants who are congenitally infected with cytomegalovirus and are asymptomatic at delivery

HHSN272201600018C (Kimberlin, PI) 07/01/16-06/30/21
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: Burden of Neonatal Herpes Simplex Virus Infections in the United States: Disease Incidence, Adequacy of Diagnostic Assessment, Disease Outcome, and Societal Costs; and Prevalence, Frequency, and Incidence of Neonatal Herpes Simplex Virus Infections in Peru
This contract evaluates the incidence of neonatal herpes simplex virus infections in the Unites States and Peru

HHSN272201100034C (Kimberlin, MPI) 09/28/11-09/27/20
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: Adaptive sequential study evaluating prevention of neonatal HSV: Detection of maternal shedding at delivery followed by preemptive antiviral therapy in exposed neonates

This contract evaluates a novel diagnostic tool for detection of herpes simplex virus in the genital tract of pregnant and nonpregnant women.

HHSN272201100035C (Kimberlin, MPI) 09/28/11-09/27/20
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: A Phase II 6 weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss
This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.

HHSN272201100037C (Kimberlin, MPI) 09/28/11-09/27/19
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: A pharmacokinetic/pharmacodynamic and resistance evaluation of intravenous ganciclovir in premature infants
This contract evaluates antiviral drug dosing in extremely premature infants with congenital or postnatal cytomegalovirus disease.

HHSN272201100038C (Kimberlin, MPI) 09/28/11-09/27/20
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: An Observational Study of Acyclovir Pharmacokinetics, Viral Population Kinetics, and Potential Biomarkers of Disease Severity in Neonatal Herpes Simplex Virus Infections
This contract evaluates viral and drug kinetics in neonates with herpes simplex virus disease, and compares new diagnostic modalities to established tests.

HHSN2722013000231 (Edwards, PI) 09/16/13-09/15/23
NIH-NIAID
Vaccine and Treatment Evaluation Units (VTEU)
The purpose of this contract is to evaluate vaccines and therapeutic agents through the NIAID VTEU network. UAB serves as a site under Vanderbilt University's prime contract. As studies are identified, developed, and performed within the VTEU network, I serve as the Site PI for those pediatric studies conducted at UAB with assignment of appropriate effort to the subcontract. No task orders have been issued to date.
Role: Site PI

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Acosta, Edward P.

eRA COMMONS USER NAME (credential, e.g., agency login): eacosta

POSITION TITLE: Professor and Director, Division of Clinical Pharmacology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Minnesota-Duluth, Duluth, MN	BS	05/1988	Biology
University of Minnesota, Minneapolis, MN	BS	12/1991	Pharmacy
University of Minnesota, Minneapolis, MN	PHMD	06/1992	Clinical Pharmacy
University of Minnesota, Minneapolis, MN	Postdoctoral Fellow	06/1994	Pharmacometrics

A. Personal Statement

The primary focus of my research program is to apply pharmacometric methods to understand the translational and clinical pharmacology of drugs in pediatric and adult patients. Our focus has traditionally been on antiviral drugs, but we have expanded our capabilities to include drug classes in multiple disease states, including antivirals, antiretrovirals, cystic fibrosis, chemotherapy, antiparasitics, antipsychotics, hormones, and others. I direct the UAB Comprehensive Cancer Center Pharmacometrics Laboratory and Pediatric Pharmacometrics Laboratory (PPL), which currently has the capability to quantitate over 100 different compounds and metabolites from multiple matrices. My program uses mass spectrometry to develop novel assay methods under GLP regulations to support innovative study designs, several of which have subsequently led to new or supplemental pediatric indications. In addition to quantitative pharmacology, my program has the expertise to conduct noncompartmental pharmacokinetic analyses and to apply complex state-of-the-art individual and population pharmacokinetic, pharmacodynamic, and drug-disease models to concentration-time and -response data. My role in this proposal will be as a co-mentor and a key part of the advisory committee to ensure the training and research plan is completed as described; specifically, I will advise Dr. Guimbellot on pharmacometric training and analyses that are described in the proposal by meeting with her at least quarterly.

B. Positions and Honors

Positions and Employment

1986 - 1988 Research Assistant, University of Minnesota-Duluth Medical School, Duluth, MN
1992 - 1994 Post-Doctoral Fellowship in Antiviral Pharmacometrics, University of Minnesota
1994 - 1997 Research Associate, University of Minnesota
1997 - 1999 Assistant Professor (Research), University of Minnesota
1999 - 2002 Assistant Professor (Research), University of Alabama at Birmingham
2002 - 2004 Assistant Professor , University of Alabama at Birmingham
2004 - 2008 Associate Professor, University of Alabama at Birmingham
2008 - Professor (with tenure), University of Alabama at Birmingham
2011 - Director, Division of Clinical Pharmacology, University of Alabama at Birmingham School of Medicine
2012 - Director, Comprehensive Cancer Center Pharmacometrics Core, University of Alabama at Birmingham School of Medicine

Other Experience and Professional Memberships

1995 -	Member, American Society of Clinical Pharmacology and Therapeutics
1995 -	Member, American Society for Microbiology
2004 - 2006	Chair, Pediatric Pharmacology Committee , Pediatric AIDS Clinical Trials Group
2007 – 2011	Member, AIDS Drug Development and Therapeutics Study Section, NIH
2009 - 2011	Chair, AIDS Drug Development and Therapeutics Study Section, NIH
2010	Chair, ZRG1 AARR-J (02) M, HIV Pathogenesis, Therapy and NeuroAIDS Study Section, NIH
2012	Chair, Next Generation PrEP II Special Emphasis Panel (RFA-AI-11-023), NIH
2012	Reviewer, AIDS-Associated Opportunistic Infections and Cancer (AOIC) Study Section, NIH
2013	Reviewer, ZRG1 AARR-K (04) Special Emphasis Panel, NIH

Honors

1993	Miles Pharmaceuticals Research Fellowship Award in Infectious Disease
1994	American Society for Microbiology Fellow Travel Grant Award
1995	American Society for Microbiology Fellow Travel Grant Award
2007	Journal of Chromatography Most Cited Author Award, Journal of Chromatography

C. Contributions to Science

1. **Pediatric Registrational Studies.** Historically, pediatric clinical pharmacology has not received the attention it needs, and pediatric drug indications are still lacking. The advent of the Best Pharmaceuticals for Children Act (BPCA) helped bring pediatric clinical pharmacology to the forefront but much work is still needed. The PPL has been involved with pediatric labeling trials since 2007 and our efforts have assisted in attaining 2 new indications and one supplemental indication for antiretroviral therapy thus far. We have also been integrally involved with multiple Collaborative Antiviral Study Group (CASG) trials which have also led to pediatric indications. Based on the need for advanced pediatric clinical pharmacology indication trials, the PPL has evolved into a fully-functional Good Laboratory Practices (GLP) facility capable of supporting new labels and label changes under of FDA guidance. We also have extensive experience in trial development, contracts and budgetary matters, study completion reports, and filing documents. Our long-term goal is to maintain our GLP status and expand our capacities in terms of different drugs and disease states where pediatric indications are needed.
    a. Nachman S, Zheng N, Acosta EP, Teppler H, Homony B, et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-infected children aged 2 through 18 years. *Clin Infect Dis* 2014;58:413-22. PubMed PMID: 24145879; PubMed Central PMCID: PMC3890333.
    b. Viani RO, Alvero C, Fenton T, Acosta EP, Hazra R, O'Gara E, Steimers D, Min S, Wiznia A, on behalf of the P1093 study team. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatric Infectious Disease Journal* 2015;34:1207-1213. PMC4604048.
    c. Nachman S, Alvero C, Acosta EP, Teppler H, Homony B, Graham B, Fenton T, Xu X, Rizk ML, Spector SA, Lisa M. Frenkel LM, Worrell C, Handelsman E, Wiznia A. Pharmacokinetics and 48-week safety and efficacy of raltegravir for oral suspension in human immunodeficiency virus type-1-infected children 4 weeks to 2 years of age. *Journal of the Pediatric Infectious Diseases Society* 2015; 1-8. PMC4681385.
    d. Kimberlin DW, Acosta EP, Prichard MN, Sánchez PJ, Ampofo K, Lang D, Ashouri N, Vanchiere JA, Abzug MJ, Abughali N, Caserta MT, Englund JA, Sood SK, Spigarelli M, Bradley JS, Lew J, Michaels MG, Wan W, Cloud G, Jester P, Lakeman FD, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Oseltamivir pharmacokinetics, dosing, and resistance in children from birth to two years of age with influenza (Editor's Choice). *Journal of Infectious Diseases*, 2013;207:709-20. PMC3563309.

2. **Pharmacometrics and Drug-Disease Pharmacology.** Pharmacometrics encompasses many aspects traditionally considered in clinical pharmacology, including drug assay development and validation and pharmacokinetic/pharmacodynamic analyses. More recently, linking these analyses to disease biomarkers or outcomes allows more precise definitions of drug dosing and target drug exposure to maximize efficacy and minimize toxicity. My laboratory continues to use state-of-the-art pharmacometric methodologies to delineate drug pharmacokinetics, link these parameters to biomarker

outcome measures, and perform predictive simulations to identify target exposures and increase the probability of successful treatment responses.

a. Wang K, D'Argenio DZ, Acosta EP, Sheth AN, Delille C, et al. Integrated population pharmacokinetic/viral dynamic modelling of lopinavir/ritonavir in HIV-1 treatment-naïve patients. *Clin Pharmacokinet*. 2014 Apr;53(4):361-71. PMC3962720.
b. Kamal MA, Acosta EP, Kimberlin DW, Gibiansky L, Jester P, et al. The posology of oseltamivir in infants with influenza infection using a population pharmacokinetic approach. *Clin Pharmacol Ther*. 2014 Sep;96(3):380-9. PMID: 24865390.
c. Rizk ML, Du L, Bennetto-Hood C, Wenning L, Teppler H, Homony B, Graham B, Fry C, Nachman S, Wiznia A, Worrell C, Smith B, Acosta EP. Population pharmacokinetic analysis of raltegravir pediatric formulations in HIV-infected children 4 weeks to 18 years of age. *Journal of Clinical Pharmacology* 2015;55:748-56. PMC4572519.
d. Sutton AL, Acosta EP, Larson KB, Kerstner-Wood CD, Tita AT, Biggio JR. Perinatal pharmacokinetics of azithromycin for cesarean prophylaxis. *American Journal of Obstetrics & Gynecology* 2015;212:812.e1-6. PMC4612366.

3. **Bioanalytical Pharmacology**. Mass spectrometry has become the standard in drug quantitation technologies. It provides highly accurate and precise measurements of drug quantity in multiple clinically relevant matrices. My laboratory utilizes mass spectrometry to develop new bioanalytical procedures that are meticulously quality controlled, CLIA compliant, and have been proven to pass even the most stringent reviews by FDA inspectors by following FDA Good Laboratory Practice (GLP) Regulations and Laboratory Standard Operating Procedures (SOPs). We have supported many different types of studies, including animal studies, and apply the same stringent measures to each method developed.
    a. Bennetto-Hood C, Tabolt G, Savina P, Acosta EP. A sensitive HPLC-MS/MS method for the determination of dolutegravir in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2014 Jan 15;945-946:225-32. PMC4229012.
    b. Long MC, Bennetto-Hood C, Acosta EP. A Sensitive HPLC-MS-MS method for the determination of raltegravir in human plasma, *J Chromatogr B Analyt Technol Biomed Life Sci.* 2008;867:165-71. PMID: 18430616.
    c. Bennetto-Hood C, King JR, Long MC, Acosta EP. Development of a sensitive and specific liquid chromatography/mass spectrometry method for the determination of tenofovir in human plasma. *Rapid Communications in Mass Spectrometry* 2007;21:2087-94. PMID: 17546653.
    d. Bennetto-Hood C, Bryson YJ, Stek A, King JR, Mirochnick M, Acosta EP. Zidovudine, lamivudine and nelfinavir concentrations in amniotic fluid and maternal serum. *HIV Clinical Trials* 2009;10:41-7. PMID: 19362995.

4. **Translational Pharmacology and Clinical Therapeutics**. Translational pharmacology bridges the gap between basic science and clinical therapeutics. My laboratory has helped develop and conduct a multitude of studies *in vitro*, *in silico*, animal, and in pediatric and adult patients that serve to bridge this gap. One of our foci has been to better define therapeutic drug concentration targets, in lieu of adequate Phase II dosing evidence, needed in patients to optimize long-term clinical outcomes. My laboratory has also played a key role in various Phase I-III trials in pediatrics and adults which have led to new or supplemental pediatric indications as well as changes in treatment guidelines. Our long-term goals are to understand the heterogeneity in drug pharmacokinetics, better define therapeutic targets and account for these targets in patients, and by applying these multi-faceted approaches, ultimately improve clinical outcomes for patients.
    a. Haas DW, Ribaudo H, Kim RB, Tierney C, Wilkinson GR, Clifford D, Gulick R, Hulgan T, Acosta EP. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004;18:2391-2400. PMID: 16392089.
    b. Shen L, Peterson S, Sedaghat AR, McMahon MA, Callender M, Zhang H, Zhou Y, Pitt E, Anderson KS, Acosta EP, Siliciano RF. Dose-response curve slope sets class-specific limits on inhibitory potential of anti-HIV drugs. *Nature Medicine* 2008;14:762-66. PMC2743464.
    c. Gulick RM, Ribaudo HJ, Shikuma CM, Lustgarten S, Squires KE, Meyer III WA, Acosta EP, Schackman BR, Pilcher CD, Murphy RL, Maher WE, Witt MD, Reichman RC, Snyder S, Klingman KL, Kuritzkes DR, for the ACTG A5095 Protocol Team. Triple nucleoside analogue vs.

efavirenz-containing regimens for the initial treatment of HIV-1 infection: AIDS Clinical Trials Group (ACTG) Study A5095. *New England Journal of Medicine* 2004; 350:1850-61. PMID: 15115831.

d. Acosta EP, Grigsby PL, Buckoreelall K, James AM, Long MC, Duffy LB, Waites KB, Novy MJ. Transplacental transfer of azithromycin and its application for eradicating intraamniotic ureaplasma infection in a primate model. *Journal of Infectious Diseases* 2014;209:898-904. PMC3935474.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/edward.acosta.1/bibliography/41144491/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance
Ongoing Research Support

UM1-AI68636-07, NIH/NIAID 06/01/2012 – 11/30/2017
AIDS Clinical Trials Group (ACTG) Pharmacology Specialty Laboratory (PSL)
The primary objectives of the PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of adult patients with HIV-infection participating in Adult AIDS Clinical Trials Group (ACTG) studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments.
Role: Subaward PI

UM1-AI068632, NIH/UCLA 06/29/2006 – 11/30/2017
International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) Pharmacology Specialty Laboratory
The primary objectives of the IMPAACT PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of pediatric patients and pregnant women with HIV-infection participating in IMPAACT studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments in these populations.
Role: Subaward PI

ING112578, Merck/JHU 01/01/2014 – 12/31/2017
A Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of GSK 1349572, a novel integrase inhibitor, in combination regimens in HIV-1 Infected Infants, Children, and Adolescents (P1093)
The primary objective is to determine safe and effective dose of dolutegravir for children ranging from 4 weeks to 18 years of age in order to obtain additional pediatric approvals.
Role: Subaward PI

MK-0518-080, Merck/JHU 01/01/2014 – 12/31/2017
A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1 Exposed Neonates at High Risk of Acquiring HIV-1 Infection (P1110)
The primary objective is to determine safe and effective neonatal raltegravir dose from birth through 6 weeks of age in order to obtain a supplemental indication.
Role: Subaward PI

R44AI080335, NIAID/Actuated Medical Inc. 04/01/2016 – 03/31/2018
Portable Transdermal Acoustic Patch for Delivery of Large Molecules to Improve HIV Patient Medication Regime Compliance by Elimination of Side-Effects, Including Injection Site Reactions
The primary objective is to assess the extent of T20 absorption delivered via transdermal administration.
Role: Subaward PI

R01AI20790-01A1, NIAID/Vanderbilt University Medical Center 08/12/2016 – 07/31/2018
Predictors of Treatment Toxicity, Failure, and Relapse in HIV-Related Tuberculosis
The purpose of this project is to analyze concentration-time data generated by Vanderbilt to develop a population PK model in support of Aims 1 and 2.
Role: Subaward PI

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Tiwari, Hemant K.

eRA COMMONS USER NAME (credential, e.g., agency login): htiwari

POSITION TITLE: Professor and Head of the Section on Statistical Genetics

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Kanpur, Kanpur, UP, India	B.Sc.	08/1976	Math, Physics, Statistics
Indian Institute of Technology, Kanpur, UP, India	M.Sc.	08/1978	Mathematics
University of Notre Dame, Indiana	M.S.	12/1983	Mathematics
University of Notre Dame, Indiana	Ph.D.	08/1986	Mathematics
LSU Medical Center, New Orleans, Louisiana	Post-Doc	06/1995	Statistical Genetics
Case Western Reserve University, Cleveland, Ohio	Post-Doc	06/1996	Statistical Genetics

A. Personal Statement

I have extensive experience in both developing statistical methods and their application to biomedical research. My current research interests include Genetic Linkage Analysis, Disequilibrium Mapping, Genome-Wide Association Studies, Copy number variations (CNVs) Structural variations (SV), Epigenetics, Pharmacogenetics/Pharmacogenomics, Gene expression, Exome sequencing, Pathway and network analysis, Bioinformatics, Metabolomics, and Population Genetics. I have published several methodological and applied papers on CNVs. I was lead statistician from UAB to perform data analyses in a Genome-wide Association to conduct a multi-stage GWAS in HyperGEN: Genetics of Left Ventricular Hypertrophy study and is currently an investigator in the recently renewed HyperGEN grant to perform 1200 exome sequences (R01HL055673; Arnett)). I am MPI of the recently funded project on "*Epigenome modification by a dietary pattern rich in polyunsaturated fatty acid*s" to investigate epigenomic biomarkers and biological mechanisms underlying the protective role of the Yup'ik (Alaska Native) traditional diet, rich in n-3 polyunsaturated fatty acids. Also, I am sub-contract PI on the "*Stroke Investigative Research & Educational Network (SIREN)"* to investigate genomic and environmental factors predisposing to stroke. I possess deep expertise in statistical genetics software programs, bioinformatics, and developing new methods for genomics data. In addition, I am interested in developing methods for next gen sequencing technology including Structural variations, Exome sequencing, genome-wide methylation, microbiome, metabolome, and transcriptome data types and integration of different data domains. In addition, I am a PI of funded educational programs, R25, to deliver national short courses in statistical genetics/genomics and short courses on Next-Generation Sequencing Technology and Statistical Methods and co-PI on "UAB Metabolomics Workshop: From Design To Decision". I am a PI of NHLBI funded pre-doctoral T32 training program in biostatistics (T32HL79888) and also director of the post-doctoral T32 training program in the statistical genetics (T32HL072757).

I have unique expertise in computational, mathematical and applied research having PhD in mathematics, teaching and doing research in theoretical statistics, and collaborations with biomedical community. I have extensive experience in statistical genetics, bioinformatics, and training pre-doctoral, post-doctoral and junior faculty members**.** Currently, I am mentoring Dr. Aslibekyan (K01 Awardee) and co-mentoring Dr. Hidalgo (K01 Awardee) in Epidemiology Department. With my extensive experience in statistical genetics, bioinformatics, and training pre-doctoral, post-doctoral and junior faculty members, I am well qualified and highly enthusiastic to advise Dr. Guimbellot in her proposed research project "*Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients*"**. Specifically, I will meet with her at least quarterly to review identification of variants in CYP3A enzymes in her population, calculate allele frequencies, and determine associations with clinical and in vitro study results.**

B. Positions and Honors

Positions and Employment

1986 - 1988	Visiting Assistant Professor of Mathematics, University of Notre Dame, Indiana
1988 - 1990	Visiting Assistant Professor of mathematics, Loyola University of Chicago, Chicago, Illinois
1990 - 1993	Asst. Prof. of Mathematics and Computer Science, University of Maine, Fort Kent, Maine
1993 - 1995	Post-Doc, LSU Medical Center, New Orleans, LA
1995 - 1996	Post-doc, Case Western Reserve University, Cleveland, OH
1996 - 1999	Senior Instructor, Department of Epi and Biostatistics, CWRU, Cleveland, Ohio
1999 - 2001	Asst. Prof., Department of Epi and Biostatistics, CWRU, Cleveland, Ohio
2002 - 2006	Assistant Professor, Section on Statistical Genetics, Department Biostatistics, & Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama
2006 - 2011	Associate Professor, Section on Statistical Genetics, Department Biostatistics, University of Alabama at Birmingham, Birmingham, Alabama
2010 -	William “Student: Sealy Gosset Professor in Biostatistics in the School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama
2011- 2015	Professor and Head of Section on Statistical Genetics, UAB

Other Experience

2002 – 2006	Charter Member of NAME Study Section (formally known as ECDA), CSR,NIH
2010 – 2013	Member of CIDR Study Section NIH/NHGRI

Honors

1993-1995	NIH Postdoctoral Fellowship, Louisiana State University Medical School
1995	NIH Postdoctoral fellowship, Case Western Reserve University
2010	Graduate Dean’s Excellence in Mentoring Award, School of Public Health, UAB

A. Contribution to Science

1. **Statistical Genetics Methods Development**. Due to my training in mathematics, I have always been interested in developing optimal statistical methods for the analyses of the data produced by current genomic technologies. We have always taken lead in developing methods comparing existing methods to determine optimal method or develop a new optimal method with respect to validity and power. Examples of the some of the publications is given below.
    a. Wineinger NE, **Tiwari HK**. The impact of errors in copy number variation detection algorithms on association results. PLoS One. 2012;7(4):e32396. doi:10.1371/journal.pone.0032396. Epub 2012 Apr 16. PMC3327691.
    b. Wineinger NE, Pajewski NM, **Tiwari HK**. A Method to Assess Linkage Disequilibrium between CNVs and SNPs Inside Copy Number Variable Regions. Front Genet. 2011 Apr 25;2:17. doi: 10.3389/fgene.2011.00017. eCollection 2011. PMC3109359.
    c. Waite LL, Weaver B, Day K, Li X, Roberts K, Gibson AW, Edberg JC, Kimberly RP, Absher DM, **Tiwari HK**. Estimation of Cell-Type Composition Including T and B Cell Subtypes for Whole Blood Methylation Microarray Data. *Front Genet*. 2016 Feb 18;7:23. doi: 10.3389/fgene.2016.00023. eCollection 2016. PMC4757643
    d. Mallick H, **Tiwari HK**. EM Adaptive LASSO-A Multilocus Modeling Strategy for Detecting SNPs Associated with Zero-inflated Count Phenotypes. Front Genet. 2016 Mar 30;7:32. eCollection 2016. PMC4811966
2. **Population Genetics.** I published very first paper on population genetics to start my career in statistical genetics. I have taught courses in population genetics, bioinformatics, and molecular evolution. He had developed a course in population genetics pertaining to gene discovery in diseases or traits while at Case Western Reserve University. Here are few examples of publications using population genetics methodology.

a. Knight A, Batzer MA, Stoneking M, **Tiwari HK**, Scheer WD, Herrera RJ, Deininger PL (1996): DNA Sequences of Alu Elements Indicate a Recent, Single Origin for Modern Humans. *Proc Nat Acad Sci* USA 93:4360-4364. PMC39542

b. Makowsky R, Yan Q, Wiener HW, Sandel M, Aissani B, **Tiwari HK**, Shrestha S. The utility of mitochondrial and Y chromosome phylogenetic data to improve correction for population stratification. Front Genet. 2012;3:301. doi: 10.3389/fgene.2012.00301. Epub 2012 Dec 21. PMC3527715

c. Vaughan LK, Divers J, Padilla M, Redden DT, **Tiwari HK**, Pomp D, Allison DB. The use of plasmodes as a supplement to simulations: A simple example evaluating individual admixture estimation methodologies. Computational Statistics and Data Analysis. 2009. 53(5):1755-1766. PMC2678733

d. Hill AE, Plyler ZE, **Tiwari H**, Patki A, Tully JP, McAtee CW, Moseley LA, Sorscher EJ. Longevity and plasticity of CFTR provide an argument for noncanonical SNP organization in hominid DNA. PLoS One. 2014 Oct 28;9(10):e109186. doi: 10.1371/journal.pone.0109186. eCollection 2014. PMC4211684

3. **Collaborative Research.** I have had extensive record of productive collaborations in searching for genes for obesity, cardiovascular diseases, Rheumatoid Arthritis, SLE, Stroke, and Multiple Sclerosis, to name few. I have served as a lead statistical geneticist in several collaborative projects. My role has been as collaborative scientist to design the study and if funded use most optimal method of analysis. I always test a method through simulations for validity and power before using it for the analysis. Some of the long collaborations have been very productive and have resulted in several papers. Below are few examples of my recent collaborative publications.

   a. Vaughan LK, Wiener HW, Aslibekyan S, Allison DB, Havel PJ, Stanhope KL, O'Brien DM, Hopkins SE, Lemas DJ, Boyer BB, **Tiwari HK**. Linkage and association analysis of obesity traits reveals novel loci and interactions with dietary n-3 fatty acids in an Alaska Native (Yup'ik) population. Metabolism. 2015 Jun;64(6):689-97. doi: 10.1016/j.metabol.2015.02.008. Epub 2015 Mar 5. PMC4408244.

   b. Benza RL, Gomberg-Maitland M, Demarco T, Frost AE, Torbicki A, Langleben D, Pulido T, Correa-Jaque P, Passineau MJ, Wiener HW, Tamari M, Hirota T, Kubo M, **Tiwari HK**. Endothelin-1 Pathway Polymorphisms and Outcomes in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2015 Dec 1;192(11):1345-54. doi: 10.1164/rccm.201501-0196OC. PMC4731699.

   c. Aslibekyan S, Vaughan LK, Wiener HW, Hidalgo BA, Lemas DJ, O'Brien DM, Hopkins SE, Stanhope KL, Havel PJ, Thummel KE, Boyer BB, **Tiwari HK**. Linkage and association analysis of circulating vitamin D and parathyroid hormone identifies novel loci in Alaska Native Yup'ik people. Genes Nutr. 2016 Aug 2;11:23. doi: 10.1186/s12263-016-0538-y. eCollection 2016. PMC4971612

   d. Day K, Waite LL, Alonso A, Irvin MR, Zhi D, Thibeault KS, Aslibekyan S, Hidalgo B, Borecki IB, Ordovas JM, Arnett DK, **Tiwari HK**, Absher DM. Heritable DNA Methylation in CD4+ Cells among Complex Families Displays Genetic and Non-Genetic Effects. PLoS One. 2016 Oct 28;11(10):e0165488. doi: 10.1371/journal.pone.0165488. PMC5085095. DOI: 10.1371/journal.pone.0165488

4. **Reviews of current topics.** Reviews are most time consuming manuscripts to write, but they provide all the information in one place and are great service to scientific community. Of course, they require vast knowledge of the topic in question and an author's ability to summarize the large body of work by others in succinct form. Thus, reviews are also very important as methodological work. Here we provide few examples of recent reviews.

   a. Akinyemi RO, Owolabi MO, Oyeniyi T, Ovbiagele B, Arnett DK, **Tiwari HK**, Walker R, Ogunniyi A, Kalaria RN; SIREN group of H3Africa Consortium. Neurogenomics in Africa: Perspectives, progress, possibilities and priorities. J Neurol Sci. 2016 Jul 15;366:213-23. doi: 10.1016/j.jns.2016.05.006. Epub 2016 May 6. Review. PMC4920548

b. Barnes S, Benton HP, Casazza K, Cooper SJ, Cui X, Du X, Engler J, Kabarowski JH, Li S, Pathmasiri W, Prasain JK, Renfrow MB, **Tiwari HK**. Training in metabolomics research. I. Designing the experiment, collecting and extracting samples and generating metabolomics data. J Mass Spectrom. 2016 Jul;51(7):461-75. doi: 10.1002/jms.3782. PMID: 27434804.

c. Barnes S, Benton HP, Casazza K, Cooper SJ, Cui X, Du X, Engler J, Kabarowski JH, Li S, Pathmasiri W, Prasain JK, Renfrow MB, **Tiwari HK**. Training in metabolomics research. II. Processing and statistical analysis of metabolomics data, metabolite identification, pathway analysis, applications of metabolomics and its future. J Mass Spectrom. 2016 Aug;51(8):535-548. doi: 10.1002/jms.3780. PMID: 28239968

d. Singh KK, Choudhury AR, **Tiwari HK**. Numtogenesis as a Mechanism for Development of Cancer. Semin Cancer Biol. 2017 May 13. pii: S1044-579X(17)30126-8. doi: 10.1016/j.semcancer.2017.05.003. [Epub ahead of print] Review. PMID: 28511886

I have published more than 100 peer-reviewed papers including methodological work, collaborative work, and review work. A complete listing can be found in my bibliography at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1bq3yXt-b-tAd/bibliography/47568868/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

R01DK104347-01A1 (Boyer, Tiwari and Absher (multi-PIs)) 09/20/16 – 07/31/20
NIH/NIDDK
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The overall goal of the proposed research is to identify epigenomic biomarkers and biological mechanisms underlying the protective role of the Yup'ik (Alaska Native) traditional diet, rich in n-3 polyunsaturated fatty acids from marine mammals and fish and is associated with protection from type 2 diabetes (T2D).
Role: Principal investigator

R25HG006110 (Tiwari) 04/01/11 – 01/31/18
NIH/NHGRI
Short Course on Next-Generation Sequencing Technology and Statistical Methods
To offer an annual short course focused on technological and statistical approaches pertaining to next-generation sequencing applied to complex human disorders and quantitative traits.
Role: Principal investigator

R25GM093044 (Tiwari) 08/01/10 – 05/31/18
NIH/NIGMS
Short Course on Statistical Genetics and Genomics
To offer an annual statistical genetics short course to be focused on applying advanced quantitative approaches to the search for genes that predispose complex human disorders and quantitative traits.
Role: Principal investigator

R01AR064820-04 (Brown) 07/01/14 – 06/30/19
NIH/NIAMS
Association of genetic and autoantibody signatures with SLE clinical course
The purpose of this study is to characterize complex interactions between variation in DNA sequence and autoantibody profiles with the rate of progression and severity of lupus-associated nephritis and severe organ damage, which are more common among ethnic minorities. The knowledge gained from this study may help us to lower the risk of lupus-related clinical manifestations and to manage and treat it more effectively.
Role: Co-Investigator

R01HL091357-07 (Arnett) 08/01/15 – 07/31/19
NIH/NHLBI
Genomewide Association Study of Lipid Response to Fenofibrate and Dietary Fat
This study aims to identify genetic variants that influence fat and cholesterol's response to diet and drugs.

Role: Co-investigator

R01HL129907-02 (Ambalavanan) 09/15/15 –06/30/18
NIH/NHLBI
STOP BPD
Bronchopulmonary dysplasia (BPD) is a common respiratory disorder in very preterm infants, characterized by impaired lung development, and associated with long-term respiratory complications. In this study, we will evaluate 300 extremely preterm infants to determine alterations in gene expression, protein amounts, or microbial flora in the airway that are associated with resilience (resistance to development of severe BPD, even when considered to be at high risk due to clinical risk factors) or predisposition (higher rate of developing severe BPD even if not initially considered at high risk)
Role: Co-Investigator

Completed Research Support

U54HG007479-01 (Owolabi) 08/01/15-07/31/16
NIH/NHGRI
Stroke Investigative Research & Educational Network(SIREN)
As a key aspect of the Stroke Investigative Research and Education Network (SIREN), the overall goals of the Systematic Investigation of Blacks with Stroke (SIBS) Genomics project are to evaluate the premier genetic risk factors for stroke in black Africans, and through training and mentoring build sustainable cardiovascular genomics expertise/capacity in Sub-Saharan Africa.
Role: Sub-contract PI from UAB with University of Ibadan, Nigeria

R25GM103798-05 (Barnes) 09/18/12 –08/31/17
NIH/NIGMS
UAB Metabolomics workshop: From decision to design
To offer an annual 4 day metabolomics workshop to prepare investigators to advance the use of metabolomics in translational research and to direct highly interdisciplinary teams or collaborations in metabolomic studies.
Role: Co-Principal investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Aban Inmaculada

eRA COMMONS USER NAME (credential, e.g., agency login): chichiaban

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of the Philippines at Diliman, Philippines, Quezon City	BS	10/1985	Statistics
Bowling Green State University, Bowling Green, OH	MS	05/1988	Applied Statistics
Bowling Green State University, Bowling Green, OH	PHD	08/1995	Mathematics

A. Personal Statement

I am currently Professor in the Department of Biostatistics at UAB and a member of the Pediatric Research Office providing biostatistical expertise and analysis at all stages of project development. In this role I am working with Dr. Jennifer Guimbellot to apply human subjects biostatistics approaches to translational studies in personalized medicine for cystic fibrosis. For this application my role will be to serve in an advisory capacity to aid in Dr. Guimbellot's understanding of the application of biostatistics and help her in the design of human subjects studies as well as data analysis and modeling. I have considerable experience in clinical trial studies and statistical methodology research in the past 13 years. I have been involved with the Collaborative Antiviral Study Group (CASG) since 2009 in charge of providing Biostatistical expertise and data coordination and management. Currently, CASG leads 5 studies funded by NIH/DMID where I am the Director of the Data Coordinating Center and Protocol Biostatistician. I am a co-investigator in two randomized clinical trials studies on exercise/training – one funded by NICHD and another by DOD. I am also currently working as a Biostatistician on a Phase 1 clinical trial on Glioblastoma Multiforme funded by NCI. I was the Deputy Director of the Data Coordinating Center of an international multicenter Phase 3 (surgical) trial funded by NINDS on myasthenia gravis (PI: Dr. Cutter). I was the PI of the Biostatistics Core of a NHLBI-sponsored SCCOR program on Heart Failure which involved 2 randomized phase 2 clinical trials. I also provide advice in experimental design and statistical data analyses to pediatric investigators through UAB Pediatrics Research Office. My areas of interest in statistical methods research are in the clinical trials, dose-finding designs, analyses of count data, survival analysis, analysis and modeling of spatio-temporal data from structural magnetic resonance imaging, developing methods of inference for heavy tailed distribution, and developing methods for goodness of fit and model diagnostics. I have been a member of Data Safety Monitoring Board for several clinical studies and currently a member of the NIAMS AMSC Clinical Trial Review Committee. Previously I was a member of the Institute of Medicine Committee on the Review of the Safety of Vaccines and also an ad-hoc member of several study sections and special emphasis panel NHLBI, NIDDK, and NINDS.

B. Positions and Honors

Positions and Employment

1985 - 1986 Instructor, University of the Philippines, Quezon City
1986 - 1988 Teaching Assistant, Department of Applied Statistics and Operations Research, Bowling Green State University, Bowling Green, OH
1988 - 1990 Statistician, Intel-Philippines, Makati

1991 - 1995	Teaching/Research Assistant, Department of Mathematics, Bowling Green State University, Bowling Green, OH
1995 - 2001	Assistant Professor, Department of Mathematics, University of Nevada, Reno, Reno, NV
2001 - 2004	Associate Professor(with tenure), Department of Mathematics and Statistics, University of Nevada Reno,, Reno, NV
2004 - 2008	Assistant Professor, Department of Biostatistics, University of Alabama at Birmingham,, Birmingham, AL
2008 - 2014	Associate Professor(with tenure), Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL
2014 -	Professor, Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL

Other Experience and Professional Memberships

- Member, American Statistical Association
- Member, ENAR
- Member, Society for Clinical Trials

Honors

1985	Cum Laude, University of the Philippines at Diliman
2007	Best Paper Award (Statistics Research), Science Unbound Foundation
2010	UAB President's Award for Excellence in Teaching, University of Alabama at Birmingham

C. Contributions to Science

1. Pediatric Research: Since 2008, I have supported pediatric infectious disease research. In 2015, I became Biostatistician in the Pediatrics Research Office of UAB.
    a. Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR, Sood SK, Whitworth MS, Abzug MJ, Caserta MT, Fowler S, Lujan-Zilbermann J, Storch GA, DeBiasi RL, Han JY, Palmer A, Weiner LB, Bocchini JA, Dennehy PH, Finn A, Griffiths PD, Luck S, Gutierrez K, Halasa N, Homans J, Shane AL, Sharland M, Simonsen K, Vanchiere JA, Woods CR, Sabo DL, Aban I, Kuo H, James SH, Prichard MN, Griffin J, Giles D, Acosta EP, Whitley RJ. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015 Mar 5;372(10):933-43. PMC4401811.
    b. Lebensburger JD, Palabindela P, Howard TH, Feig DI, Aban I, Askenazi DJ. Pediatr Nephrol. 2016 Aug;31(8):1363-8. doi: 10.1007/s00467-016-3370-0. Epub 2016 Mar 24. Prevalence of acute kidney injury during pediatric admissions for acute chest syndrome. PMID: 27011218
    c. Hough-Telford C, Kimberlin DW, Aban I, Hitchcock WP, Almquist J, Kratz R, O'Connor KG. Vaccine Delays, Refusals, and Patient Dismissals: A Survey of Pediatricians.Pediatrics. 2016 Aug 29. pii: e20162127. [Epub ahead of print] PMID: 27573091
2. Clinical Trials: Since 2004, I have been involved in the design, conduct, management and analysis of clinical trials in the areas of neurology (myasthenia gravis, multiple sclerosis), cardiology (cardiac dysfunction and disease), and infectious disease.
    a. Aban IB, Wolfe GI, Cutter GR, Kaminski HJ, Jaretzki A 3rd, Minisman G, Conwit R, Newsom-Davis J. The MGTX experience: challenges in planning and executing an international, multicenter clinical trial. J Neuroimmunol. 2008 Sep 15;201-202:80-4. PMC2654214.
    b. Ahmed MI, Aban I, Lloyd SG, Gupta H, Howard G, Inusah S, Peri K, Robinson J, Smith P, McGiffin DC, Schiros CG, Denney T Jr, Dell'Italia LJ. A randomized controlled phase IIb trial of beta(1)-receptor blockade for chronic degenerative mitral regurgitation. J Am Coll Cardiol. 2012 Aug 28;60(9):833-8. PMC3914413.
    c. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, Ströbel P, Mazia C, Oger J, Cea JG, Heckmann JM, Evoli A, Nix W, Ciafaloni E, Antonini G, Witoonpanich R, King JO, Beydoun SR, Chalk CH, Barboi AC, Amato AA, Shaibani AI, Katirji B, Lecky BR, Buckley C, Vincent A, Dias-Tosta E, Yoshikawa H, Waddington-Cruz M, Pulley MT, Rivner MH, Kostera-Pruszczyk A, Pascuzzi RM, Jackson CE, Garcia Ramos GS, Verschuuren JJ, Massey JM,

Kissel JT, Werneck LC, Benatar M, Barohn RJ, Tandan R, Mozaffar T, Conwit R, Odenkirchen J, Sonett JR, Jaretzki A 3rd, Newsom-Davis J, Cutter GR; MGTX Study Group.Randomized Trial of Thymectomy in Myasthenia Gravis.N Engl J Med. 2016 Aug 11;375(6):511-22. doi: 10.1056/NEJMoa1602489

3. Statistical Methodology: Over the last 20 years, I have conducted statistical methodological research in the areas of survival analysis, heavy-tailed distribution, pool screening, spatiotemporal modeling of imaging data, and more recently Continuous Reassessment Method (CRM) for phase 1 clinical trial studies.
    a. Aban I, Meerschaert M, Panorska A. Parameter Estimation for the Truncated Pareto Distribution. Journal of the American Statistical Association. 2006; 101:270-277.
    b. George B, Aban I. Selecting a separable parametric spatiotemporal covariance structure for longitudinal imaging data. Stat Med. 2015 Jan 15;34(1):145-61. PMC4262538.
    c. Salter A, O'Quigley J, Cutter GR, Aban IB. Two-group time-to-event continual reassessment method using likelihood estimation. Contemp Clin Trials. 2015 Nov;45(Pt B):340-5. doi: 10.1016/j.cct.2015.09.016. Epub 2015 Sep 25. PMID: 26409251
    d. Salter A, Morgan C, Aban IB. Implementation of a two-group likelihood time-to-event continual reassessment method using SAS. Comput Methods Programs Biomed. 2015 Jun 16. pii: S0169-2607(15)00155-8. doi: 10.1016/j.cmpb.2015.06.001. [Epub ahead of print] PMID: 26122068
4. Cardiology Research: Since 2005, I have been actively collaborating with researchers in the area of cardiology -- basic science, clinical trials, epidemiological studies, and cardiac imaging.
    a. Ryan TD, Rothstein EC, Aban I, Tallaj JA, Husain A, Lucchesi PA, Dell'Italia LJ. Left ventricular eccentric remodeling and matrix loss are mediated by bradykinin and precede cardiomyocyte elongation in rats with volume overload. J Am Coll Cardiol. 2007 Feb 20;49(7):811-21. PubMed PMID: 17306712.
    b. Schiros CG, Dell'Italia LJ, Gladden JD, Clark D 3rd, Aban I, Gupta H, Lloyd SG, McGiffin DC, Perry G, Denney TS Jr, Ahmed MI. Magnetic resonance imaging with 3-dimensional analysis of left ventricular remodeling in isolated mitral regurgitation: implications beyond dimensions. Circulation. 2012 May 15;125(19):2334-42. PMC3939018.
    c. Zheng J, Wei CC, Hase N, Shi K, Killingsworth CR, Litovsky SH, Powell PC, Kobayashi T, Ferrario CM, Rab A, Aban I, Collawn JF, Dell'Italia LJ. Chymase mediates injury and mitochondrial damage in cardiomyocytes during acute ischemia/reperfusion in the dog. PLoS One. 2014;9(4):e94732. PMC3986229.
    d. Ahmed MI, Guichard JL, Rajasekaran NS, Ahmad S, Mariappan N, Litovsky S, Gupta H, Lloyd SG, Denney TS, Powell PC, Aban I, Collawn JF, Davies JE, McGiffin DC, Dell'Italia LJ. Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function. J Thorac Cardiovasc Surg. 2016 Jun 25. pii: S0022-5223(16)30647-X. doi: 10.1016/j.jtcvs.2016.06.017. [Epub ahead of print]
5. Other collaborative research: In the past 20 years, I have also been involved in research in the areas of psychology, nutrition, diabetes and geriatrics. In 2015, I became involved in a clinical trial regarding an exercise intervention for osteoarthritis patients undergoing joint anthroplasty.
    a. Batten SV, Follette VM, Aban IB. Experimental avoidance and high-risk sexual behavior in survivors of child sexual abuse. J Child Sex Abus. 2001;10(2):101-20. PMID: 15154403.
    b. Baltazar JC, Ancheta CA, Aban IB, Fernando RE, Baquilod MM. Prevalence and correlates of diabetes mellitus and impaired glucose tolerance among adults in Luzon, Philippines. Diabetes Res Clin Pract. 2004 May;64(2):107-15. PMID: 15063603.
    c. St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks. Am J Clin Nutr. 2007 Jun;85(6):1503-10. PMC3666855.
    d. Kvale E, Ekundayo OJ, Zhang Y, Akhter S, Aban I, Love TE, Ritchie C, Ahmed A. History of cancer and mortality in community-dwelling older adults. Cancer Epidemiol. 2011 Feb;35(1):30-6. PMC3062071.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HD084124, NIH/NICHD
Bamman, M (PI)
Overcoming TWEAK signaling to fully restore muscle mass and mobility function after total joint arthroplasty
The goals of the study are: (1) to determine the effects Progressive resistance exercise training (PRT) vs. usual care after elective THA/TKA on muscle mass, muscle performance, and mobility function; (2) to determine whether MuIS status modifies the effects of 16 wk PRT or usual care after THA/TKA; and (3) to determine whether MuIS status modifies the effects of 16 wk PRT or usual care after THA/TKA.
Role: Co-Investigator

2014/01/01-2017/12/31
000506687, Veterans Administration
Dell'Italia, Louis (PI)
IPA-The Chymase Angiotensin (1-2) Axis in Heart Disease
The Chymase Angiotensin (1-12) Axis in Heart Disease
This study focus on the intracrine synthesis of Ang II produced via a chymase mediated cleavage of Ang-(1-12).
Role: Co-Investigator

2010/09/01-2017/09/31
5U01NS042685-06 , NIH/NINDS
Cutter, Gary (PI)
Thymectomy in Non-Thymomatous Myasthenia Gravis Patients on Prednisone
This multinational clinical trial aims to assess the utility of thymectomy in treating nonthymomatous Myasthenia Gravis patients comparing surgery plus medications versus medications alone.
Role: Deputy Director of the Data Coordinating Center /Senior Biostatistician
Role: Co-Investigator

2011/10/01-2017/09/30
BAA-NIAID-DMID-NIHAI2010101, NIH/NIAID
Kimberlin, David (PI)
A Phase II 6 Weeks Oral Valganciclovir versus Placebo in Infants with Congenital CMV Infection and Hearing Loss
The major goals of this project are to determine if a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss, to define the systemic exposure to ganciclovir, describe the safety and tolerability of valganciclovir syrup in children of this age and to define the pharmacokinetics of ganciclovir when valganciclovir is administered to children of these ages.
Role: Director of the Data Coordinating Center / Protocol Biostatistician
Role: KP

2011/10/01-2017/09/30
BAA-NIAID-DMID-, NIH/NIAID
Kimberlin, David (PI)
Evaluation of the Pharmacokinetics and Pharmacodynamics of Ganciclovir in Premature Infants Receiving Treatment for Cytomegalovirus Infection
The major goals of this project are to define the pharmacokinetics of ganciclovir in premature infants, to assess changes in quantitative viral DNA in whole blood as a function of drug pharmacokinetics, to assess clearance of CMV in urine (by culture) as a function of drug pharmacokinetics, to assess development of neutropenia as a function of drug pharmacokinetics and to determine the potential for the development of resistance to ganciclovir as a function of pharmacokinetics, dose, age, and duration of therapy.
Role: Director of the Data Coordinating Center / Protocol Biostatistician
Role: KP

2011/10/01-2017/09/30
BAA-NIAID-DMID-NIHAI2010101, NIH/NIAID
Kimberlin, David (PI)
An Observational Study Of Acyclovir Pharmacokinetics, Viral Population Kinetics, And Potential Biomarkers Of Disease Severity In Neonatal Herpes Simplex Virus Infections.
The major goal of this project to describe the population pharmacokinetics of high-dose parenteral acyclovir (60 mg/kg/day) in neonates with virologically confirmed neonatal HSV disease.
Role: Director/ Protocol Biostatistician, Data Coordinating Center
Role: KP

2011/10/01-2017/09/30
BAA-NIAID-DMID-NIHAI2010101, NIH.NIAID
Kimberlin, David (PI)
Identification of Herpes Simplex Virus (HSV) Shedding in the Female Genital Tract of Pregnant and Nonpregnant Women by the XPERT HSV 1/2 Assay, Routine PCR, and Culture
The major goals of this project are to evaluate the sensitivity and specificity of the GeneXpert real-time PCR test for detecting herpes simplex virus (HSV) DNA in the genital tract of women in active labor or in sexually transmitted infections (STI) clinics. Additionally this study will determine rates of neonatal HSV disease, attempt to quantify HSV viral load in the genital tract of women shedding the virus who are in active labor and assess the type of maternal infection (first-episode primary, first-episode non-primary, recurrent) among women shedding HSV during active labor.
Role: Director of the Data Coordinating Center / Protocol Biostatistician
Role: KP

2011/10/01-2017/09/30
BAA-NIAID-DMID-NIHAI2010101 , NIH/NIAID
Gnann, John (PI)
Natural History of Infection Caused by BK Virus (and other Opportunistic Viral Pathogens) in Renal and Renal-Pancreas Transplant Recipients
Targeted Clinical Research to Address Select Viral Infections-Safety, Tolerability and Pharmacokinetic Properties of CMX001 in Renal Transplant Recipients with BK Viremia T
he primary objective is to define the natural history of BK viremia. In order to understand the natural history of infection, we will measure the time (days post-transplant) to the development of BK viremia and its correlation with progression to end-organ disease (BKVN or BK hemorrhagic cystitis). Data from this prospective monitoring will allow for the identification of the types of high-risk patients who might benefit from future studies of therapeutic interventions for BKV infection (when effective therapy becomes available). This will be accomplished by serial quantitative BK DNA measurements in blood (plasma), assayed by polymerase chain reaction (PCR).
Role: Director of the Data Coordinating Center / Protocol Biostatistician
Role: KP

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Scott, Emily Elizabeth

eRA COMMONS USER NAME (credential, e.g., agency login): EESCOTT

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Texas at Galveston, Galveston, TX	B.S.	12/1992	Marine Biology
Rice University, Houston, TX	Ph.D.	05/1998	Biochemistry, Cell Biology
Rice University, Houston, TX	Postdoctoral	06/1999	Biochemistry, Cell Biology
University of Texas Medical Branch, Galveston, TX	Postdoctoral	04/2004	Pharmacology, Toxicology

A. Personal Statement

The focus of my research career is to characterize cytochrome P450 (CYP) structure/function relationships to understand and manipulate the metabolism of drugs and key endogenous molecules toward the prevention and treatment of multiple disease states. I have the expertise and experience to successfully undertake membrane P450 structure/function studies. My Ph.D. training focused on heme protein structure/function, followed by NRSA-funded postdoctoral training in cytochrome P450 enzymes. As postdoctoral fellow I determined some of the early X-ray structures of membrane cytochrome P450 enzymes (CYP2B4). In my independent career I have studied the structure and function of human cytochrome P450 enzymes with key roles in drug metabolism, procarcinogen activation, and steroidogenesis. My laboratory is perhaps best known for structures of human membrane P450 enzymes CYP1A1, CYP2A6, CYP2A13, CYP2E1, and CYP17A1. Most of these were the first structures available of each of these membrane proteins. Building on this knowledge, we have recently significantly diversified the range of membrane P450 enzymes we generate and probe with respect to function and structure (crystallography and NMR). Of particular relevance to this proposal, we now routinely express and purify high-quality human CYP3A4 and CYP3A7. Although we have not yet published our work with CYP3A enzymes, we have successfully crystallized CYP3A4 with a novel ligand of interest for another study and crystallization of CYP3A7 is underway. This initial investment and our expertise in the broader area of membrane P450 structure determination puts us in a good position to contribute to the proposed work. In addition, our structural studies are always integrated with functional analysis to facilitate both comparisons between and detailed understanding of the respective capabilities of each enzyme. Potentially relevant to this proposal, we have established both high-throughput and more detailed lower throughput assays to characterize CYP3A metabolism of various substrates and/or their inhibitory effects. The recombinant CYP3A4 or CYP3A7 enzymes, P450 reductase, and cytochrome b_5 we are already producing are also available for enzyme assays and/or site-directed mutagenesis experiments of key mutations. Overall, as evidenced by a productive research track record, broad structural expertise, a solid series of publications, and multiple awards, I have had the good fortune to make key contributions to the cytochrome P450 structure/function field to date and am well positioned to serve as an advisor and collaborator to Dr. Guimbellot. The current proposal invests this accumulated expertise in understanding contributions of CYP3A variability to ivacaftor metabolism. This is an opportunity to better understand potential issues with the metabolism of a drug that CF patients take for decades and certainly in combination with other drugs that modulate CYP3A enzyme function.

B. Positions and Honors

Positions and Employment

2004 – 2010 Assistant Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS
2007 – present Affiliate Faculty, Department of Molecular Biosciences, University of Kansas, Lawrence, KS
2008 – present Courtesy Faculty, Department of Chemistry, University of Kansas, Lawrence, KS
2010 – 2015 Associate Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS
2013 Visiting Scholar, Laboratory of Dr. Tom Pochapsky, Dept. of Chemistry, Brandeis University, Waltham, MA
2015 – 2016 Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS
2016 – present Professor, Departments of Medicinal Chemistry and Pharmacology and the Biophysics Program, University of Michigan, Ann Arbor, MI

(Selected) Other Positions

2006 – 2009 Councilor, Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics
2009 – 2012 Secretary/Treasurer (Elect, Current, Past), Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics
2011 National Institutes of Health, Ad hoc reviewer for study sections: Molecular Structure and Function A (MSFA) and Xenobiotic and Nutrient Disposition and Action (XNDA)
2012 – 2016 National Institutes of Health, Regular member, Molecular Structure and Function Study A (MSFA) Section
2014 – 2017 Chair (Elect, Current, Past), Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics

(Selected) Honors and Awards

1996 – 1998 NIH Predoctoral Fellowship, Houston Area Molecular Biophysics Training Grant
2000 – 2003 NIH National Research Service Award (NRSA) Individual Postdoctoral Fellowship
2003 Best Postdoctoral Scientist Presentation, Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics Annual Meeting
2009 James R. Gillette Drug Metabolism Best Paper, *Drug Metabolism and Disposition*
2011 Early Career Achievement Award, Drug Metabolism Division, The American Society of Pharmacology and Experimental Therapeutics
2012 James R. Gillette North American New Investigator Award, The International Society for the Study of Xenobiotics
2015 MERIT Award, National Institute of General Medical Science, National Institutes of Health

C. Contribution to Science

1. **Determination of some of the earliest membrane cytochrome P450 structures and establishing the unexpected flexibility of the membrane P450 conformational changes related to ligand access.** All mammalian cytochrome P450 enzymes are membrane proteins. Difficulties in expression, detergent extraction, purification, and stabilization precluded crystallization and structure determination until 2000. Shortly thereafter as a postdoctoral fellow I initiated efforts to determine the first structure of a CYP2B enzyme, by engineering protein constructs; by developing and adapting expression and purification methods that maintained protein structure, function, and solubility; and by simultaneously learning and establishing crystallography as a new technique in my PI's laboratory. This work resulted in CYP2B4 structures showing CYP2B4 in both a closed conformation (typical of structures up to that time) and an unprecedented open conformation that enabled substrate access from the protein surface to the buried active site. The availability of this open conformation dramatically changed the way the field thought about P450 enzyme conformations and numerous subsequent publications and structures are interpreted with discussion of the substrate access channel. All subsequent CYP2B structures in the PDB (15 structures of CYP2B4 and 7 structures of CYP2B6) have their origins in the initial constructs and protocols my work established at that time. The main papers establishing this work have been cited more than 750 times:

a. Scott E.E., Spatzenegger M., and Halpert J.R. (2001) A truncation of 2B subfamily cytochromes P450 yields increased expression levels, increased solubility, and decreased aggregation while retaining function. ***Arch. Biochem. Biophys.*** 395:57-68.
b. Scott E.E., He Y.A., Wester M.R., White M.A., Chin C.C., Halpert J.R., Johnson E.F., and Stout C.D. (2003) An open conformation of mammalian cytochrome P450 2B4 at 1.6 Å resolution, ***Proc. Nat. Acad. Sci. U.S.A.*** 100:13196-13201.
c. Scott E.E., White M.A., He Y.A., Johnson E.F., Stout C.D., and Halpert J.R. (2004) Structure of mammalian cytochrome P450 2B4 complexed with 4-(4-chlorophenyl)imidazole at 1.9 Å resolution: Insight into the range of P450 conformations and coordination of redox partner binding. ***J. Biol. Chem.*** 279:27294-27301.
d. A movie made using these structures has been frequently requested and used to illustrate and teach about P450 conformational changes: **http://tinyurl.com/2B4-movie**

2. **Structure/function studies of 2A enzymes.** Early work in my own lab yielded the first structure of human CYP2A13, a lung enzyme responsible for the critical step in the conversion of nicotine into a human carcinogen. Subsequent series of structures of both active human CYP2A enzymes, CYP2A13 and hepatic CYP2A6, bound to common and selective ligands, in concert with site-directed mutagenesis and enzymatic analysis, identified key features of responsible for differential metabolism of nicotine and other substrates. This was accompanied by inhibitor analysis and high-throughput screening and medicinal chemistry developing selective CYP2A13 inhibitors intended to serve as chemopreventative compounds in human smokers.
    a. Smith, B.D., Sanders, J.L., Porubsky, P.R., Lushington, G.H., Stout, C.D., and Scott, E.E. (2007) Structure of the human lung cytochrome P450 2A13. ***J. Biol. Chem.*** 282:17306-17313.
    b. DeVore, N.M., Smith, B.D., Wang, J.L., Lushington, G.H., and Scott, E.E. (2009) Key residues controlling binding of diverse ligands to human cytochrome P450 2A Enzymes. ***Drug Metab. Dispos.*** 37:1319-1327. PMC2683692. ***Selected paper of the year in Drug Metabolism and Disposition***
    c. DeVore, N.M. and Scott, E.E. (2012) Nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) binding and access channel in human cytochrome P450 2A6 and 2A13 enzymes. ***J. Biol. Chem.*** 287:26576-26585. PMC3410998.
    d. Blake, L.C., Roy, A., Neul, D., Schoenen, F.J., Aubé, J. and Scott, E.E. (2013) Benzylmorpholine analogs as selective inhibitors of lung cytochrome P450 2A13 for the chemoprevention of lung cancer in tobacco users. ***Pharm. Res.*** 30: 2290-2302. PMC3781598. ***Patent approved***

3. **Structure/function studies of 2E1 enzymes.** No structures were available for human CYP2E1, which is responsible for the metabolism of many low molecular weight molecules such as ethanol and carcinogens. CYP2E1 hydroxylates fatty acids at the ω-1 position. How this enzyme accommodates both types of ligand scaffolds was unknown. Our first structure of CYP2E1 with low molecular weight ligands revealed a small enclosed active site, but subsequent structures with fatty acid analogs revealed a very different active site. Finally, a structure with the drug pilocarpine revealed yet a third significantly different active site topography. Such structures are important because they underscore the difficulty of *in silico* docking studies successfully predicting binding and drug metabolism, even when structures are known.
    a. Porubsky, P.R., Meneely, K.M., and Scott, E.E. (2008) Structures of human cytochrome P450 2E1: Insights into the binding of inhibitors and both small molecular weight and fatty acid substrates. ***J. Biol. Chem.*** 283:33698-33707. PMC2586265.
    b. Porubsky, P.R., Battaile, K.P., and Scott, E.E. (2010) Human cytochrome P450 2E1 structures with fatty acid analogs reveal unexpected binding mode ***J. Biol. Chem.*** 285:22282-22290. PMC2903405.
    c. DeVore, N.M., Meneely, K.M., Bart, A.G., Stephens, E.S., Battaile, K.P., and Scott, E.E. (2012) Structural comparison of cytochromes P450 2A6, 2A13, and 2E1 with pilocarpine. ***FEBS J.*** 279:1621-1631. PMC3572744.

4. **Structure/function studies of steroidogenic cytochrome P450 enzymes.** Cytochrome P450 enzymes largely dominate human steroidogenesis. CYP17A1, a key enzyme in the production of androgenic sex

steroids, has become a new target for prostate cancer treatment. Our initial contribution to this field was to determine the first structure of CYP17A1, revealing how that inhibitors then in human clinical trials bind very differently than the proposed orientation parallel to the heme. These structures have suggested several ways by which for these clinical inhibitors could be improved to reduce side effects that limit the clinical regimen. In collaboration with a synthetic chemist, we iteratively perform structure-based drug design, inhibition analysis, and structure determination with the goal of developing advanced compounds that selectively inhibit the lyase activity of CYP17A1 without negatively impacting other aspects of steroidogenesis that cause substantial side effects. We have also determined an underlying basis for the intriguing bifunctional hydroxylase and lyase chemistry of this enzyme that lies at the heart of selective drug design.

a. DeVore, N.M. and Scott, E.E. (2012) Structures of cytochrome P450 17A1 with prostate cancer drugs abiraterone and TOK-001. ***Nature*** 482:116-119. PMC3271139.
b. Petrunak, E.M., DeVore, N.M., Porubsky, P.R., and Scott, E.E. (2014) Structures of human steroidogenic cytochrome P450 17A1 with substrates. ***J. Biol. Chem.*** 289: 32952-32964. PMC4239641.

5. **Establishing solution NMR as a viable technique for probing membrane P450 enzymes and interactions with NADPH-cytochrome P450 reductase and cytochrome *b*5.** While crystalline X-ray structures continue to generate substantial and detailed new information, the inherent limitations, including the slow, one-complex-at-a-time necessity to evaluate ligand binding to such flexible enzymes has driven my lab to seek complementary methods to probe P450 structure. Protein NMR had not been previously used to probe membrane P450 enzymes due to technical difficulties related to their size (55 kDa) and solubility/stability limitations. However we have used our expertise developed in working with these proteins for crystallography in concert with advanced NMR labeling methods and strategies to largely overcome the technical roadblock. We have begun probing CYP17A1 protein dynamics, responses to ligand binding, and the effects of interactions with reductase and b_5 without crystallization. This new perspective has revealed that the various surface P450/protein interactions are modulated by ligands in the buried P450 active site and that reductase and b_5 binding are mutually exclusive. The solution NMR approach is currently being expanded to other human cytochrome P450 enzymes.

a. Estrada, D.F., Skinner, A.L., Laurence, J.S., and Scott, E.E. (2014) Human cytochrome P450 17A1 conformational selection: Modulation by ligand and cytochrome b_5. ***J. Biol. Chem.*** 289:14310-14320. PMC4022897.
b. Johnson, E.F., Connick, J.P., Reed, J.R., Backes, W.L., Desai, M.C., Xu, L., Estrada, D.F., Laurence, J.S. and Scott, E.E. (2014) Correlating Structure and Function of Drug Metabolizing Enzymes: Progress and Ongoing Challenges. ***Drug Metab. Dispos***. 42:9-22. PMC3876788.
c. Estrada, D.F., Laurence, J.S., and Scott, E.E. (2013) Substrate-modulated cytochrome P450 17A1 and cytochrome b_5 interactions revealed by NMR. ***J. Biol. Chem.*** 288:17008-17018. PMC3675632.

A complete list of publications is available:
www.ncbi.nlm.nih.gov/myncbi/browse/collection/41143942/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R37GM076343 (E. E. Scott, PI) 03/01/2015 – 02/28/2020
NIH/NIGMS
Structural Basis of Cytochrome P450 Activity
The objective of this proposal is to extend our structural knowledge across current boundaries by determining the first structures of several human cytochrome P450 enzymes of clinical utility, examining clinically-important new P450/ligand complexes, and probing the structural relationships between cytochrome P450 enzymes and other proteins involved in catalysis.

P41 RR001209 (K. O. Hodgson, PI)
5B12, 2B40, 3B60 (E. E. Scott, Subproject PI) 05/31/2008 – 05/31/2018

NIH/Stanford Synchrotron Radiation Laboratory
Structures of Membrane Cytochrome P450 Enzymes
Each renewal provides 2-years of access to a Department of Energy synchrotron facility for X-ray crystallography data collection.

Completed Research Support (Selected)

R01 GM076343 (E. E. Scott, PI) 01/01/2006 – 02/28/2015
NIH/NIGMS
Structural Basis of Cytochrome P450 Activity
Summary: The objective of this proposal was to expand, test, and apply our understanding of the unique relationships between the structures of human cytochrome P450 2A and 2E enzymes and their ligand selectivity. Renewed as current R37 grant listed above.

R01GM102505 (E. E. Scott and J. Aube, PIs) 07/01/2012 – 03/31/2017
NIH/NIGMS
Structure and Function of Cytochrome P450 17A1
The objective of this proposal is to characterize the structure and function of CYP17A1 with substrates and current inhibitors and to use this information to design new drugs for metastatic castration resistant prostate cancer with improved efficacy and selectivity.

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Limdi, Nita A.

eRA COMMONS USER NAME (credential, e.g., agency login): nlimdi

POSITION TITLE: Professor, Department of Neurology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama at Birmingham	PhD	05/2008	Epidemiology
University of Alabama at Birmingham	MSPH	08/2005	Clinical Research
Samford University, Birmingham, AL	Pharm.D	05/1994	Pharmacy
Samford University, Birmingham, AL	BS	05/1993	Pharmacy
Sardar Patel Univ. Vallabh Vidhya Nagar, India	BS	08/1988	Pharmacy

A. Personal statement.

I am a clinical pharmacist and epidemiologist with significant expertise in pharmacogenomics and pharmacoepidemiology, from research and discovery to its application and implementation in clinical practice. My research portfolio encompasses studies with both observational and a clinical trial designs and is focused on understanding the multiple factors that influence drug efficacy and safety, specifically anticoagulant and antiplatelet response. An established investigator in the field of pharmacogenomics, I have made significant contributions towards understanding of genetic basis of warfarin response. My work has included discovering novel polymorphisms in *CYP2C9,* statistical analytic approaches that has ranged from candidate gene, haplotype based approach to genome-wide association and exome approaches, and a research portfolio that includes both prospective cohort and randomized clinical trials. As a leader in UAB's Hugh Kaul Personalized Medicine Institute, I oversee two strategic initiatives centered on fueling discoveries through research and improving care through implementation of genotype-guided therapy. The implementation initiative aims to identify and overcome barriers, incorporate precision medicine tools and assess clinically relevant outcomes with aims to inform health policy and reimbursement strategies for precision medicine. I bring to my research and training efforts expertise in clinical pharmacy, pharmacology, pharmacogenomics, and clinical research methods, epidemiology and biostatistics. I brought this comprehensive and diverse set of skills to training residents, post-doctoral clinician trainees and junior faculty and high school students through serving as a mentor on various institutional training grants (see below). My specific role in this application will be to serve as an advisor to Dr. Guimbellot as she discovers polymorphisms in the CYP3A family of metabolism enzymes that influence CFTR modulator metabolism, and guide her in the scientific approach, analysis, and presentation of her research. In order to accomplish this, we will meet at least once yearly.

B. Positions and Honors.

Positions and Employment

1994-1997 Clinical Pharmacist, University of Alabama at Birmingham
1997-2003 Clinical Pharmacy Specialist for Neurosciences, University of Alabama at Birmingham
2003-2009 Assistant Professor, Department of Neurology, University of Alabama at Birmingham
2009-2014 Associate Professor, Department of Neurology, University of Alabama at Birmingham
2014 - current Professor, Department of Neurology, University of Alabama at Birmingham
2014 -2017 Interim Director, UAB Personalized Medicine Institute
2016 - current Visiting Professorship, Food and Drug Administration (FDA)

Honors and Awards (in chronological order)

1989 G.P. Nair National Award for Academic Excellence in Pharmacy. Bombay, India
1990, 1991 R.E. Wheeler Scholarship Medal, Samford university, Birmingham, AL
1991, 1992 Rho Chi Award for excellence in Pharmacy, Samford University, Birmingham, AL
1992, 1993 Don Lane Martinez Research Award in Pharmacy, Samford University, Birmingham, AL

1994	President's Cup, Samford University, Birmingham, AL
1997	Abbott Training Grant – Sabbatical University of Madison Wisconsin.
2000	American College of Clinical Pharmacy Award – Sabbatical to understand metabolic enzymatic control at the University of North Carolina at Chapel Hill
2006	NINDS Young Investigator Award; American Neurological Association meeting, Chicago, IL
2008	Young Investigators Award Central Society for Clinical Research meeting, Chicago, IL
2008	Irtaza and Shana Siddique Endowed Award for Academic Excellence in Epidemiology. University of Alabama at Birmingham, AL
2013	Dean's Excellence in Mentorship Award, University of Alabama at Birmingham
2014	Fellow American Heart Association, Functional Genomics – Translational Biology
2015	Executive Leadership in Academic Medicine (ELAM) Program

C. Contribution to Science:

Harnessing the racial diversity of the population, I have built the largest prospective warfarin cohort (n=1809, 44% African American) with detailed collection of clinical, demographic and lifestyle factors over a 2-year prospective follow-up and capture of clinical hemorrhagic events. This has enabled significant contributions to pharmacogenomics predictors of drug response.

1. **Translating pharmacogenomic discoveries to health disparity populations:** A major limitation of existing pharmacogenomic-based therapies is that the bulk of the evidence informing guidelines are derived from populations of European descent. Minority populations such as African Americans have been under-represented. The racial diversity of the population served, and the successful recruitment of a large proportion of African Americans has allowed us to identify novel markers influencing warfarin response in this race group. Moreover, this has allowed us to establish that the effect of known gene variants is different across race groups.
    a. **Limdi NA,** Brown TM, Yan Q, Thigpen JL, Shendre A, Liu N, Hill CE, Arnett DK, Beasley TM. Race influences warfarin dose changes associated with genetic factors. Blood. **2015**: 126:539-45. PMC4513254.
    b. *Perera MA, Cavallari LH, **Limdi NA (3 first authors*)**, et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. Lancet. **2013** 31;382(9894):790-6. PMC3759580
    c. **Limdi NA**, Wadelius M, Cavallari L, Eriksson N, Crawford DC, Lee MM, Chen C, Motsinger-Reif A, Sagreiya H, Liu N, Wu A, Gage B, Jorgensen A, Pirmohamed M, Shin J, Suarez-Kurtz G, Kimmel SE, Johnson JA, Klein TE, Wagner MJ. Warfarin Pharmacogenetics: A single *VKORC1* polymorphism is predictive of dose across three racial groups. Blood**. 2010** 6; 115(18):3827-34. PMC2865873
    d. **NA Limdi ,** G McGwin , JA Goldstein, TM Beasley, DK Arnett, BK Adler, MF Baird, RT Acton. Influence of *CYP2C9* and *VKORC1 1173C/T* Genotype on the Risk of Hemorrhagic Complications in African American and European American patients on warfarin. Clinical Pharmacology & Therapeutics. **2008**; 83(2): 312-321. PMC2683398
2. **Integrating clinical, genetic, socio-demographic and behavioral data:** Most pharmacogenomic studies do not assess non-genetic factors that may influence drug response. Exquisite clinical phenotyping has allowed us to make some seminal contributions on the influence of clinical (e.g. kidney function) and behavioral (physical activity) on drug response.
    a. **Limdi NA**, Nolin TD, Booth SL, et al. Influence of Kidney Function on Risk of Supratherapeutic International Normalized Ratio–Related Hemorrhage in Warfarin Users: A Prospective Cohort Study. *Am J Kidney Dis.* **2015** 65(5):701-709.(NIHMS 645418**).**
    b. **NA Limdi,** Goldstein, TM Beasley, G McGwin, DK Arnett, MF Baird, RT Acton, M Allon. Kidney Function Influences Warfarin Responsiveness and Hemorrhagic Complications. Journal of American Society of Nephrology **2009**;20: 912-921. PMC2663833
    c. **Limdi, NA,** Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, Allon M, Beasley TM. Warfarin dosing in patients with impaired kidney function. AKJD **2010** 56:823-831. PMC2963672

d. Limdi MA, Crowley MC, Beasley TM, **Limdi NA,** Allon M. Influence of kidney function on risk of hemorrhage among patients taking warfarin: A cohort study. AKJD. **2013**;6 (2): 354-357. PMC3654383.

3. **Advancing Pharmacogenomics; working with a consortium of national and international experts** to pool and augment diverse datasets from multiple existing observational studies and clinical trials to enhance predictive power and enable examination of differences between race groups. I have built fruitful collaborations with investigators in the pharmacogenomics arena and the International Warfarin Pharmacogenomics Consortium (>15 countries, and 30 institutions with >120 investigators), providing leadership to bring warfarin pharmacogenetics to the forefront. The data are available through dbGaP and PharmGKB. As an affiliate member of the Pharmacogenomic Research Network, I collaborate on developing guidelines on clinical implementation of genotype-guided therapy through the Clinical Pharmacogenetics Implementation Committee.
    a. The COAG investigators. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, Rosenberg YD, Eby CS, Madigan RS, McBane RB, Abdel-Rahman SZ, Stevens SM, Yale S, Mohler ER, Fang MC, Shah V, Horenstein RB, **N. A. Limdi**, Muldowney JA, Gujral J, Delafontaine P, Desnick RJ, Ortel TL, Billett HH, Pendleton RC, Geller NL, Halperin JL, Goldhaber SZ, Caldwell MD, Califf RM and Ellenberg JM. Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. N Engl J Med **2013**;24:2283-93.PMC3942158
    b. *Horne BD, Lenzini PA, Wadelius M, Jorgensen AL, Kimmel SEm Ridker PM, Eriksson N, Anderson JL, Pirmohamed M, **Limdi NA,** Pendentel RC, McMillin GA, Burmester JK, Kurnik D, Stein MC, Caldwell MD, Eby CS, Rane A, Lindh JD, Shin J, Kim H, Angchaisuksiri P, Glynn, R, Kronquist KE, Carlquist JF, Barrack RL, Li J, Gage BF. Pharmacogenetic Warfarin Dose Refinements Remain Significantly Influenced by Genetic Factors after One Week of Therapy. Thromb Haemost. **2012**; 107(2):232-40. PMC3292349
    c. *P. Lenzini, M. Wadelius, S. Kimmel, J. Anderson, A.L Jorgensen, M. Pirmohamed, M. Caldwell, **N. Limdi**, J. Burmester, M.B. Dowd, P. Angchaisuksiri, A. Bass, J. Chen, N. Eriksson, A. Rane, J.D. Lindh, J.F. Carlquist, B.D. Horne, G. Grice, P. Milligan , C. Eby, R.L. Berg, P. Deloukas, B. Gage. Integration of genetic, clinical, and laboratory data to improve accuracy of warfarin dose-refinement. Clinical Pharmacology & Therapeutics**. 2010;**87(5):572-8. PMC2858245
    d. The International Warfarin Pharmacogenetics Consortium. Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data. New England Journal of Medicine **2009**;360:753-64. PMC2722908
4. **Development of new approaches and methodologies for statistical genetic analysis:** Working with experts in statistical genetics, we have contributed to the development of new methodology in analyzing large genetic datasets, including methods of imputation and controlling population stratification.
    a. *Daneshjou R, Tatonetti NP, Karczewski KJ, Sagreiya H, Bourgeois S, Burmestor J, Mushiroda T, **Limdi NA**, Cavallari LH, Perera M, Johnson JA, Klein TE, Altman RB. Pathway Analysis of Genome-Wide Data Improves Warfarin Dose Prediction. BMC Genomics. 2013;14 Suppl 3:S11. PMC3829086
    b. *Erdal Cosgun, **Nita Limdi** and Christine W. Duarte. High Dimensional Pharmacogenetic Prediction of a Continuous Trait using Machine Learning Techniques with Application to Warfarin Dose Prediction in African Americans. Bioinformatics **2011;** 27:1384-9. PMC3087957
    c. N. Liu, H Zhao, A. Patki, **N. Limdi**, D. Allison. Practical Consideration of Genotype Imputation: Sample Size, Window Size, Reference Choice and Untyped Rate. Statistics and its Interface **2011**; 4: 317-326. PMC3269890
    d. *Boshao Zhang, Degui Zhi, Kui Zhang, Guimin Gao, **Nita Limdi,** Nianjun Liu. Controlling Population Structure in Human Genetic Association Studies with Samples of Unrelated Individuals. Statistics and its Interface **2011**; 4: 339-351. PMC3269888
5. **Contributions related to discovery of novel variants influencing drug response and variants with newly identified influence on response:** Working with bench and clinical scientists we have discovered new markers and identify novel influence of variants on warfarin response, elucidating the role of the folate pathway and identifying the influece of APLO1 variants on lipid profile in African Americans.

a. JA Goldstein, Blaisdell JA, **NA Limdi.** A potentially deleterious new *CYP2C9* polymorphism identified in an African American patient with major hemorrhage on warfarin therapy. Blood Cells Molecules and Disease **2009**;42:155–158. PMC2662477
b. *Daneshjou R, Gamazon ER, Burkley B, Cavallari LH, Johnson JA, Klein TE, **Limdi NA,** Hillenmeyer S, Percha B, Karczewski KJ, Langaee T, Patel SR, Bustamante CD, Altman RB, Perera MA. Genetic Variant in Folate Homeostasis Associated with Lower Warfarin Dose in African Americans. **Blood** 2014 Oct 2;124(14):2298-305. PMC4183989
c. **NA Limdi,** G McGwin, JA Goldstein, TM Beasley, BK Adler, RT Acton DK Arnett. Influence of CYP2C9 and VKORC1 on Warfarin Dose and Anticoagulation Maintenance among European American and African Americans. Pharmacogenomics **2008**; 9 (5):511-526. PMC2757655
d. **NA Limdi,** H Wiener, Goldstein JA, RT Acton TM Beasley. Influence of CYP2C9 and VKORC1 on Warfarin Response during Initiation of therapy. Blood Cells Molecules and Disease **2009**; 43(1): 119-28. PMC2789741.

Complete list of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/nita.limdi.1/bibliography/40594522/public/?sort=date&direction=descending

D. Additional Information: Research Support

Ongoing Research Support

R01HL092173-06A1 Limdi (Role: PI) 02/01/2014–01/31/2019
Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants
The primary objective of this project is to define genetic and environmental predictors of hemorrhagic complications among patients treated with warfarin and novel anticoagulants, specifically dabigatran and define the incremental risk associated with kidney impairment and concurrent antiplatelet therapy to refine clinical prediction rules for hemorrhage.

K24HL1333373 Limdi (Role: PI) 08/01/2016—07/30/2021
Patient Oriented Research in Personalized Antithrombotic Therapy
Clinical, genetic and environmental factors that predict individual variability in antithrombotic response can help identify patients who stand to benefit or be harmed by these drugs. However, the integration of these predictors into clinical decision making requires a paradigm shift based on evidence of their benefit vs. risk (clinical utility) and value (cost-effectiveness). To facilitate this paradigm shift we propose to incorporate genetic information with environmental and clinical predictors to help develop patient-focused and population-based preventive and therapeutic guidelines for “Personalized Antithrombotic Therapy (PAT).”

Completed Research Support

UAB-HSF Limdi (Role: PI) 03/01/2013-02/28/2017
Pharmacogenomic Resource for Improvement of Medication Effectiveness (PRIME)
PRIME aims to incorporate pharmacogenomics along with clinical, demographic and environmental factors to personalize therapy enabling providers to move beyond the “one-size-fits-all” approach.

ROWE, S.M.

ACTIVE

P30 DK072482 (Rowe) 5/1/2012 – 4/30/2015 2.4 CM
NIH/NIDDK $742,037 ($3,710.185 Total Direct)
UAB CF Research and Translation Core Center
This P30 provides 3 Scientific Cores (i.e. Animal Models Core, Single Channel Analysis Facility, and Clinical Core) to CF investigators at UAB and collaborating sites to improve understanding of the most basic underpinnings of cystic fibrosis pathogenesis and the ways this information can be aggressively applied to experimental therapeutics. Two Pilot and Feasibility projects are also supported through the P30.

R35 HL135816 (Rowe) 1/15/2017 – 1/14/2024 6.0 CM
NIH/NHLBI R35 $6,387,112 Total
Translational Program in CFTR-Related Airway Diseases
This program supports investigation into diseases of mucociliary clearance, including their molecular mechanism, clinical phenotype, and precision medicine approaches to intervene.

U54TR001368-01 (Kimberly) 9/1/2015 – 8/31/2020 0.30 CM
NIH/NCATS $6,324,075 (UL1, KL2, TL1)
UAB Center for Clinical and Translational Science (CCTS)
The UAB CCTS will enhance human health by driving scientific discovery and dialogue across the bench, bedside and community continuum. The CCTS support this overall mission in a highly integrative network of relationships. Success in creating such an environment is dependent upon success in achieving five strategic priorities: 1) enhancing research infrastructure; 2) promoting investigator education, training and development; 3) accelerating discovery across the T1 interface; 4) expanding value-added partnerships; and 5) building sustainability.
Note: Dr. Kimberly has submitted the letter for Dr. Rowe to reduce effort to 0.30 CM on this project.

R34HL127166 (Rowe/Dransfield) 9/1/2015 – 5/31/2017 0.06 CM
NIH/NHLBI $225,000
A Pilot Study of the Effect of the CFTR Potentiator Ivacaftor in COPD (P-TOPIC)
This project will conduct a pilot, randomized, double blind placebo controlled trial to evaluate the efficacy, safety, mechanism, and pharmacokinetics of ivacaftor in patients with COPD and chronic bronchitis, under an investigator initiated IND.
Note: We submitted a request that is in process to reduce Dr. Rowe's effort to 0.06 CM.

R43HL134056-01 8/1/2016 – 7/31/2017 0.30 CM
CFD Research Org. (Pandian, Rowe Sub) $100,000
A Predictive In Vitro Model for Screening Personalized Responses to CFTR-Directed Therapeutics

R41HL130207-01 8/6/2016 – 08/31/2017 0.68 CM
Progenera (Mattern, Rowe Sub) $96,265
In vitro human model for individualized response to CFTR modulators

ROWE09CS0 (Rowe) 10/1/2009 - 9/30/2017 0.48 CM
Cystic Fibrosis Foundation Therapeutics $52,640
Special Consultant for Translational Science
The purpose is for Dr. Rowe to serve as a Special Consultant for Translational Science for CFFT.

ROWE15R0 (Rowe) 7/1/2015 - 6/30/2019 0.12 CM
Cystic Fibrosis Foundation $525,000 ($2,100,000 Total Direct)
Research Development Program – Component II
The major goals of this project are to 1) support core capabilities including RT-PCR, immunolocalization, conductance, SPQ based functional analysis, as well as recombinant adenoviral vectors and other biochemical and functional endpoints for CF scientists and their projects on our campus, 2) provide resources for Pilot/Feasibility Studies, postdoctoral fellows and graduate students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.

ROWE17XX0 and ROWE17XX1 (Rowe) 8/1/2016 – 7/31/2018 0.12 CM

Mucociliary Clearance Consortium $350,000
The mechanistic basis and therapeutic approach to abnormal mucus adhesion and mucociliary clearance in cystic fibrosis.
The goal of this project is to develop a novel measure of mucus clearance using reflective tomography.

CFF (Tearney) 8/1/2016 – 7/31/2018 0.12 CM
Mucociliary Clearance Consortium $30,000
The mechanistic basis and therapeutic approach to abnormal mucus adhesion and mucociliary clearance in cystic fibrosis.The goal of this project is to develop a novel measure of mucus clearance using reflective tomography.

Southern Research Institute (SRI) 9/1/2015 – 6/30/2020 0.12 CM
SRI Sub $2,010,893
The Identification of New Treatments for Cystic Fibrosis Caused by Premature Termination Codons.
The purpose of this project is to conduct high throughput screening, secondary validation and pre-clinical development of novel molecules that suppress nonsense mutations in CFTR for the Treatment of Cystic Fibrosis.

GOAL13K1 (Rowe) 9/1/2011 – 8/31/2017 0.06 CM
Cystic Fibrosis Foundation $22,030
G551D Observational Study (GOAL-OB-11)
The purpose of this study is to conduct a multi-center observational study evaluating the effects of Ivacaftor in CF patients with the G551D mutation. Dr. Rowe supervises the multi-center component of four outcome based sub-studies.

ROWE14K1 7/1/2014 – 6/30/2017 0.06 CM
Cystic Fibrosis Foundation Therapeutics $81,625
A Two-Part Multicenter Prospective Longitudinal Study of CFTR-dependent Disease Profiling in Cystic Fibrosis (PROSPECT)
The goal of this project is to identify biomarkers of CFTR function and longitudinal monitoring of disease progression. It will also look at the effect of lumacaftor/ivacaftor combination therapy in people with CF.

ROWE17XX2 2/1/2017 – 1/31/2018 0.06 CM
Cystic Fibrosis Foundation Therapeutics $96,659
Evaluation of Arina - 1 for the treatment of cystic fibrosis lung disease
Renovion is currently in the preclinical stage of developing Arina-1, a combination inhalation product that is intended to improve the redox status of cystic fibrosis (CF) mucus while also addressing its hyperacidic nature. The goal of this collaboration is to test the efficacy Arina-1 in treating CF lung disease. HBE cells isolated from CF donors will be used for this research. CF HBE cells will express two copies of a CFTR null mutation (eg, F508del/F508del). Experiments using 6-month old CFTR-/- rats and their wild type littermates will be performed contingent on in vitro results.

ROWE16XX3 9/1/2016 – 8/31/2017 0.06 CM
Cystic Fibrosis Foundation Therapeutics $66,491
Brevenal Effect on Mucociliary Clearance for Treatment of CF Mucus
The focus of this proposal is to solidify and widen the scope of our evaluation of initial efficacy in CF HBE cells. Evaluation of initial efficacy entailed µOCT imaging and analysis of Brevenal vs. vehicle or positive (VX-70/VX-809) control for N=4 sets of donor cells (from 2 different donors), N=3-4 monolayers per treatment condition, and N=3 time points (baseline, 6 hrs, 24 hrs).

Active Research Contracts

Dr. Rowe's effort on Research contracts will not be more than 1% (0.12 CM) total. These projects pay for Dr. Rowe's staff to do the work for these contracts. Dr. Rowe has minimal day to day activities with these.

Galapagos NV (Rowe) 12/17/2015 – 12/16/2018
Galapagos NV $22,319
Evaluation of Potentiators on HBE-G542X Epithelial Cells in TECC and/or Ussing Chamber
The goal of this project is to determine whether potentiators augment readthrough induced by aminoglycosides.

SHIRE (Rowe) 4/25/2016 – 4/24/2019
SHIRE $91,248
In Vivo and Ex Vivo Evaluation of Nebulized Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mRNA Replacement Therapy in Treating Cystic Fibrosis Lung Disease

AstraZenica AB (Rowe) 2/24/2016 – 2/23/2017
AstraZenica $62,947
In Vivo Evaluation of a Novel ENaC Inhibitor in Treating Cystic Fibrosis Lung Disease

Ionis Pharmaceutical (Rowe) 8/18/2016 – 8/17/2017
IONIS $81,500
In Vivo Evaluation of Antisense Oligonucleotide Technology in Treating Cystic Fibrosis Lung Disease.

PUL-042 (Rowe) 10/5/2016 – 10/4/2017
Pulmotect, Inc. $14,700
In vivo Evaluation of PUL-042 in Ferrets.

PTC124-GD-023 6/26/2014 – 7/31/2017
PTC Therapeutics, Inc. $4,950
An Open-Label Safety and Efficacy Study for Patients with Nonsense Mutation Cystic Fibrosis previously Treated with Ataluren (PTC124)

VX14-661-107 09/15/2015 – 07/14/2017
Vertex Pharmaceuticals $66,410
A Phase 3, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Heterozygous for the F508del.
Role: Principle Investigator

VX14-661-111 09/4/2015 – 07/3/2017
Vertex Pharmaceuticals $81,588
A Phase 2, Randomized, Double-Blind, Placebo Controlled, Parallel-Group, Exploratory Study to Evaluate Effects of VX-61 in Combination with Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older with Cystic Fibrosis.

VX14-661-110 10/5/2015 – 10/4/2017
Vertex Pharmaceuticals $55,756
A Phase 3, Open-Label, Rollover Study to Evaluate the Safety and Efficacy of Long-Term Treatment with VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del.

PTC124-GD-021e-CF 11/13/15 – 7/31/2017
PTC Therapeutics, Inc $419
A Phase 3 Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Cystic Fibrosis.

MDBR-16-120-CF1282X 01/01/2016 – 12/31/2017
University of Pennsylvania $51,500
An Open Label N of 1 Study to Evaluate the Safety and Efficacy of Long-Term Treatment with Ivacaftor in Combination with ATALUREN (PTC124) in Subjects with Nonsense Mutation Cystic Fibrosis.

VX15-809-113 8/15/2016 – 8/14/2017
Vertex Pharmaceutical $1,167,000
A Phase 4, 2 Part Exploratory Study to Assess the Feasibility of Using Micro Optical coherence Tomography (uOCT) and to Evaluate the Effect of Lumacaftor in Combination with Ivacftor on the Nasal Epithelium Using uOCT in Subjects with CF

OVERLAP: None

KIMBERLIN, D.W.

ACTIVE

HHSN272201600017C (Kimberlin) 07/01/16-06/30/21 1.8 CM
NIH-NIAID $9.9 million
Targeted Clinical Research to Address Select Viral Infections: A Phase II, Single-Stage, Single-Arm Investigation of Oral Valganciclovir Therapy in Infants with Asymptomatic Congenital Cytomegalovirus Infection
This contract evaluates the antiviral treatment of infants who are congenitally infected with cytomegalovirus and are asymptomatic at delivery.

HHSN272201600018C (Kimberlin) 07/01/16-06/30/21 1.2 CM
NIH-NIAID $1.5 million
Targeted Clinical Research to Address Select Viral Infections: Burden of Neonatal Herpes Simplex Virus Infections in the United States: Disease Incidence, Adequacy of Diagnostic Assessment, Disease Outcome, and Societal Costs; and Prevalence, Frequency, and Incidence of Neonatal Herpes Simplex Virus Infections in Peru
This contract evaluates the incidence of neonatal herpes simplex virus infections in the Unites States and Peru.

HHSN272201100034C (Kimberlin) 09/28/11-09/27/17 1.7 CM
NIH-NIAID $5.9 million
Targeted Clinical Research to Address Select Viral Infections: Adaptive sequential study evaluating prevention of neonatal HSV: Detection of maternal shedding at delivery followed by preemptive antiviral therapy in exposed neonates
This contract evaluates a novel diagnostic tool for detection of herpes simplex virus in the genital tract of pregnant and nonpregnant women.

HHSN272201100035C (Kimberlin) 09/28/11-09/27/17 0.7 CM
NIH-NIAID $4.9 million
Targeted Clinical Research to Address Select Viral Infections: A Phase II 6 weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss
This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.

HHSN272201100037C (Kimberlin) 09/28/11-09/27/17 0.7 CM
NIH-NIAID $3.9 million
Targeted Clinical Research to Address Select Viral Infections: A pharmacokinetic/pharmacodynamic and resistance evaluation of intravenous ganciclovir in premature infants
This contract evaluates antiviral drug dosing in extremely premature infants with congenital or postnatal cytomegalovirus disease.

HHSN272201100038C (Kimberlin) 09/28/11-09/27/19 2.3 CM
NIH-NIAID $4.4 million
Targeted Clinical Research to Address Select Viral Infections: An Observational Study of Acyclovir Pharmacokinetics, Viral Population Kinetics, and Potential Biomarkers of Disease Severity in Neonatal Herpes Simplex Virus Infections
This contract evaluates viral and drug kinetics in neonates with herpes simplex virus disease, and compares new diagnostic modalities to established tests.

HHSN2722013000231 (Edwards) 09/16/13-09/15/23 0.0 CM
NIH-NIAID
Vaccine and Treatment Evaluation Units (VTEU)
The purpose of this contract is to evaluate vaccines and therapeutic agents through the NIAID VTEU network. UAB serves as a site under Vanderbilt University's prime contract. As studies are identified, developed, and performed within the VTEU network, I serve as the Site PI for those pediatric studies conducted at UAB with assignment of appropriate effort to the subcontract. No task orders have been issued.

ACOSTA, E.P.

ACTIVE

UM1-AI106701-02 (Acosta) 06/01/12 - 11/30/17 2.4 CM
NIH (Brigham & Women's Hospital) $215,000 (direct cost)
AIDS Clinical Trials Group (ACTG) Pharmacology Specialty Laboratory (PSL)
The primary objectives of the PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of adult patients with HIV-infection participating in Adult AIDS Clinical Trials Group (ACTG) studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments.

UM1-AI106716 (Acosta) 06/29/06 -11/30/17 1.8 CM
NIH $101,822 (direct cost)
International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) Pharmacology Specialty Laboratory
The primary objectives of the IMPAACT PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of pediatric patients and pregnant women with HIV-infection participating in IMPAACT studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments in these populations.

ING112578 (Acosta) 01/01/14 -12/31/17 1.2 CM
Merck $256,437 (direct cost)
A Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of GSK 1349572, a novel integrase inhibitor, in combination regimens in HIV-1 Infected Infants, Children, and Adolescents (P1093)
The primary objective is to determine safe and effective doses of dolutegravir for children ranging from 4 weeks to 18 years of age in order to attain pediatric approval. Dr. Acosta's laboratory is performing all bioanalytical and pharmacokinetic assessments in support of this study.

R01AI20790-01A1 (Sterling) 08/01/17 – 07/31/18 1.2 CM
NIH (Vanderbilt University Medical Center) $23,976 (direct cost)
Predictors of Treatment Toxicity, Failure, and Relapse in HIV – related Tuberculosis
The purpose of this project is to analyze the mass spectrometry data from Vanderbilt to develop population-based PK modeling for the analyses in Aims 1 and 2 of the proposal.

PENDING

HHSN272201100035C (Whitley, R., PI) 09/28/17 - 9/27/22 0.72 CM
NIH/NIAID $181,560 (direct cost)
Targeted Clinical Research to Address Select Viral Infections-A Phase II Randomized Six Weeks of Oral Valganciclovir Therapy in CMV Infants withHearing Loss (renewal)
A Phase II 6-weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss. This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.

Project Number N/A (U18) 09/01/17 – 08/31/22 1.2 CM
NIH/CDER $24,347 (direct (year 1))
Global Pediatric Clinical Trials Network
The primary focus of my research program is to apply pharmacometric methods to understand the translational and clinical pharmacology of drugs in pediatric and adult patients. Our focus has traditionally been on antiviral drugs, but we have expanded our capabilities to include drug classes in multiple disease states, including antivirals, antiretrovirals, cystic fibrosis, chemotherapy, antiparasitics, antipsychotics, hormones, and others.

OVERLAP: None

TIWARI, H.

ACTIVE

NIH R01DK074842 (Boyer, Tiwari and Absher; multi-PIs) 09/20/16 – 07/31/20 1.32 CM
NIH/NIDDK $84,975 current direct
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The overall goal of the proposed research is to identify epigenetic factors underlying the relationship between metabolic health and the traditional Yup'ik Alaska Native diet, rich in n-3 polyunsaturated fatty acids (PUFAs) from marine mammals, fish, and other wild country (subsistence) foods.

NIH R01DK112358-01 (Boyer, Tiwari and Absher; multi-PIs) 07/15/17 – 03/31/21 0.24 CM
NIH/NIDDK $208,983 current direct
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The increased prevalence of Type 2 Diabetes is a global health concern that has led to substantial increases in health care costs and increased morbidity and mortality. The proposed research is aimed at identifying diet-induced changes in genomic DNA methylation patterns that are associated with changes in downstream gene expression, as well as phenotypic and metabolic profiles associated with insulin sensitivity and protection from Type 2 Diabetes. Evaluation of the epigenomic impact of a protective dietary exposure may enhance our understanding of the molecular mechanisms underlying metabolic health, and the role that epigenetic factors play in mediating these relationships.

NIH R25 GM093044 (Tiwari) 08/01/10 – 05/31/18 0.6 CM
NIH/NIGMS No Cost Extension
Short Course on Statistical Genetics and Genomics
To offer an annual statistical genetics short course to be focused on applying advanced quantitative approaches to the search for genes that predispose complex human disorders and quantitative traits.

NIH R25HG006110 (Tiwari) 04/01/11 – 01/31/18 0.6 CM
NIH/NHGRI $ 49,968 current direct
Short Course on Next-Generation Sequencing Technology and Statistical Methods
To offer an annual short course focused on technological and statistical approaches pertaining to next-generation sequencing applied to complex human disorders and quantitative traits.

NIH R25GM103798 (Barnes) 09/18/12 – 02/28/18 0.30 CM
NIH/NIGMS $ 99,993 current direct
UAB Metabolomics workshop: From decision to design
To offer an annual 4 day metabolomics workshop to prepare investigators to advance the use of metabolomics in translational research and to direct highly interdisciplinary teams or collaborations in metabolomic studies.

NIH R01 (Brown) 07/01/14 – 06/30/19 0.96 CM
NIH/NIAMS $491,709 current direct
Association of genetic and autoantibody signatures with SLE clinical course
The purpose of this study is to characterize complex interactions between variation in DNA sequence and autoantibody profiles with the rate of progression and severity of lupus-associated nephritis and severe organ damage, which are more common among ethnic minorities. The knowledge gained from this study may help us to lower the risk of lupus-related clinical manifestations and to manage and treat it more effectively.

2R01HL091357-05 (Arnett) 08/01/2015 – 07/31/2019 0.6 CM
NIH/NHLBI $649,961 current direct
Genomewide Association Study of Lipid Response to Fenofibrate and Dietary Fat
This study aims to identify genetic variants that influence fat and cholesterol's response to diet and drugs; this knowledge may someday help doctors tailor prevention efforts and treatments based on individual's genetic endowment.

R01HL129907 (Ambalavanan) 09/15/2015 – 06/30/2018 1.8 CM
NIH/NHLBI $250,000 current direct
STOP BPD

Bronchopulmonary dysplasia (BPD) is a common respiratory disorder in very preterm infants, characterized by impaired lung development, and associated with long-term respiratory complications. In this study, we will evaluate 300 extremely preterm infants to determine alterations in gene expression, protein amounts, or microbial flora in the airway that are associated with resilience (resistance to development of severe BPD, even when considered to be at high risk due to clinical risk factors) or predisposition (higher rate of developing severe BPD even if not initially considered at high risk).

R01HL092173 (Limdi) 08/01/2015 – 07/31/2019 0.6 CM
NIH/NHLBI $499,667 current direct
Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants
Understanding clinical and genetic factors that predict patient specific risk of hemorrhage can help identify patients who stand to benefit or be harmed by oral anticoagulants drugs. The integration of these clinical and genetic predictors into the current treatment approach can help provide personalized treatment, improving outcomes for the individual patient. The increasing burden of atrial fibrillation in the US and the world, highlight the immense potential of such research in facilitating the realization of tangible individual and population health benefits.

1R01 HL123782-01A (Irvin) 09/15/2016-05/31/2021 0.6 CM
NIH/NHLBI $499,791 current direct
Genomic Background of Blood Pressure Response to Thiazide Diuretic in African Americans.
Research shows that better blood pressure control produces cardiovascular benefits in African Americans. This study seeks to discover genetic variants that influence how blood pressure can be controlled in African Americans on a frequently used medication class (thiazide diuretics). In the future, such knowledge could help improve the care of African Americans with high blood pressure.

7R01 HL055679-19 (Arnett) 01/01/2016-04/30/2018 1.2 CM
NIH/NHLBI $5,459,306 current direct
HyperGEN: Genetics of Left Ventricular Hypertrophy
Black people tend to have an enlarged left ventricle (the heart chamber that pumps oxygenated blood throughout the body) more commonly than those in other race groups, putting them at greater risk for having potentially fatal cardiovascular diseases. Enlarged left ventricles are caused, at least in part, by a person's genes. This study seeks to discover which genetic factors may cause an enlarged heart; this may ultimately lead to new diagnoses and treatments to help lower cardiovascular disease risk in blacks.

PENDING

Renewal of HL104135 07/05/2016 (Arnett) 04/01/2017-03/31/2021 1.20 CM
NIH/NHLBI $1,956,169 direct costs Yr 1
Epigenetic Determinants of Lipid Response to Dietary Fat and Fenofibrate
This study aims to discover the epigenetic factors that cause people’s bodies to respond so differently to diet and drugs with the belief that such knowledge could ultimately help lower people’s risk for cardiovascular disease.

1R01DK112358 (Boyer) 12/01/2016 – 11/30/2020 0.24 CM
NIH/NIDDK $18,438 direct costs YR1
*Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids*The overall goal of the proposed research is to identify epigenetic factors underlying the relationship between metabolic health and the traditional Yup’ik Alaska Native diet, rich in n-3 polyunsaturated fatty acids (PUFAs) from marine mammals, fish, and other wild country (subsistence) foods.

OVERLAP

If all of the pending applications were funded, Dr. Tiwari’s percent effort might exceed 100%. In that event, his percent effort on certain projects would be reduced and compensated for by an increase in percent effort by other qualified personnel.

ABAN, I.B.

ACTIVE

1R01 HD084124 (Bamman) 04/01/2015-03/01/2020 0.36 CM
NIH/NICHD $522,810
Overcoming TWEAK signaling to fully restore muscle mass and mobility function after total joint arthroplasty
The goals of the study are: (1) to determine the effects Progressive resistance exercise training (PRT) vs. usual care after elective THA/TKA on muscle mass, muscle performance, and mobility function; (2) to determine whether MuIS status modifies the effects of 16 wk PRT or usual care after THA/TKA

Project Number N/A (Dell'Italia) 1/1/16-12/31/17 1.2 CM
VETERANS ADMINISTRATION $18,306
The Chymase Angiotensin (1-12) Axis in Heart Disease
This study focus on the intracrine synthesis of Ang II produced via a chymase mediated cleavage of Ang-(1-12).

PEDIATRICS RESEARCH OFFICE (Non-federal funding) 4.8 CM
The Pediatric Research Office (PRO) provides assistance to investigators conducting pediatric research at Children's of Alabama at the University of Alabama at Birmingham (UAB). PRO provides pre-award and post-award support for funded investigators as well as those seeking funding or training.

OVERLAP: None

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer		guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner, 214-767-3261

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_justification_Guimbellot.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer		guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner, 214-767-3261

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_justification_Guimbellot.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer		guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner, 214-767-3261

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_justification_Guimbellot.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer		guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner, 214-767-3261

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_justification_Guimbellot.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer		guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**

Total Salary, Wages and Fringe Benefits (A+B)

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

F. Other Direct Costs		Funds Requested ($)*
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
	Total Other Direct Costs	**30,000.00**

G. Direct Costs		Funds Requested ($)*
	Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner, 214-767-3261

I. Total Direct and Indirect Costs		Funds Requested ($)*
	Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Budget Justification*	File Name: Budget_justification_Guimbellot.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Jennifer S Guimbellot, M.D., PHD PD/PI, (9 CM, $). Dr. Guimbellot is an Assistant Professor of Pediatrics in the Division of Pediatric Pulmonary and Sleep Medicine. She has a solid background in clinical pediatric pulmonology with emphasis on cystic fibrosis, as well as genetics, cell and molecular biology. The proposed Mentored Patient-Oriented Research Career Development Award will enable her to increase skills in patient-oriented research, pharmacology, and pharmacogenetics. As the Principal Investigator, she is responsible for the overall direction of the project including experimental design, data analysis, and publication of results. This will enable her to transition to an independent research program. She is requesting funds to cover 75% of her university salary for 5 years. Fringe benefits are figured at 30.8%.

Salary/Fringe total funds requested $

Non-personnel expenses ($).

Materials and Supplies ($19,838 for year one): Supplies for growth and maintenance of primary human airway epithelial cells: plastic ware (sterile pipettes, syringes, culture flasks, tissue culture plates), centrifuge tubes, media, supplements, antibiotics, sera, TC-grade PBS, tubing and microfluidics chips, sterile instruments for sample collection, phlebotomy supplies. Reagents for lysate preparation (protease inhibitors and detergents); RNA and DNA preparation kits; gene expression and sequencing primers; reagents for PCR. These funds will also support microscopy supplies including coverslips, fluorescent dye, functional reagents and slides; labor, equipment use, supplies, and data analysis for mass spectrometry for serum concentrations of ivacaftor and metabolites. Funding from Dr. Rowe's laboratory and Dr. Guimbellot's departmental account will support additional equipment, equipment maintenance, general disposable/consumable lab supplies and materials, gas cylinders, as well as specimen storage.

Sequencing/single nucleotide polymorphism genotyping (year 1 cost $7417; cumulative over 5 years $28,161): Sanger sequencing using standard techniques on the ABI 3730xl Genetic Analyzer will be performed at the Heflin Genomics Core at UAB. Cost is $107.50/sample to sequence both genes. For comprehensive sequencing analysis, sequencing is planned, although if ongoing data analysis indicates that full sequencing is not required in later years, costs will be minimized over the course of this award, if possible, by using SNaPShot® genotyping ($15/10 SNPs/patient) as a more targeted approach based on initial data.

Subject reimbursement costs (year 1 $500; cumulative over 5 years maximum $6500). Specimen reimbursement for collection of nasal epithelial biopsies, $25 per sample (minimum of 40 subjects, maximum of 60 over all 5 years). For more intensive pharmacokinetics studies, specimen reimbursement for collection of serum samples and nasal epithelial biopsies will be reimbursed at the rate of $250 per day as per Cystic Fibrosis Foundation Therapeutics Development Network, with expectation of 20 subjects recruited for one day collection ($5000).

Travel ($1250 per year). In addition to the North American Cystic Fibrosis Conference and American Thoracic Society meetings (which are supported by existing departmental funds), Dr. Guimbellot will attend the American Society for Pharmacology and Experimental Therapeutics at Experimental Biology meeting in order to present data related to this project; network with pharmacologists and pharmacogeneticists to build a collaborative network of investigators with similar interests; learn cutting-edge research regarding drug metabolism, pharmacogenomics, and in vitro model development for drug development and precision medicine.

Formal coursework ($2195 over all 5 years). The Pharmacometrics course at FAES in Bethesda fees are $995 plus travel and accommodations. The NIGMS Short Course on Statistical Genetics and Genomics ($600) and NHGRI Short Course on Next-Generation Sequencing: Technology and Statistical Methods ($600) are located at the home institution. Tuition for formal UAB graduate courses are waived for faculty and thus tuition is not included here.

Other expenses total funds requested $

INDIRECT COSTS UAB will abide by the K23 guidelines for capping IDC at 8% MTDC.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		
1. Materials and Supplies		
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		
Section J, Fee		0.00

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OMB Number: 0925-0001

Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? ○ Yes ● No

*Agency-Defined Phase III Clinical Trial? ○ Yes ○ No

2. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and proved scientific justification

3. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

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4. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

5. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

6. Change of Investigator / Change of Institution Section

❑ Change of Project Director / Principal Investigator

Name of former Project Director / Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Introduction	
1. Introduction to Application (RESUBMISSION)	
Candidate Section	
2. Candidate Information and Goals for Career Development	Training_plan.pdf
Research Plan Section	
3. Specific Aims	Specific_Aims.pdf
4. Research Strategy*	Research_Strategy.pdf
5. Progress Report Publication List (for RENEWAL applications only)	
6. Training in the Responsible Conduct of Research	Training_in_the_Responsible_Conduct_of_Research.pdf
Other Candidate Information Section	
7. Candidate's Plan to Provide Mentoring	
Mentor, Co-Mentor, Consultant, Collaborators Section	
8. Plans and Statements of Mentor and Co-Mentor(s)	Statements_of_advisors.pdf
9. Letters of Support from Collaborators, Contributors, and Consultants	All_consultant_letters.pdf
Environment and Institutional Commitment to Candidate Section	
10. Description of Institutional Environment	Environment.pdf
11. Institutional Commitment to Candidate's Research Career Development	Guimbellot_Institutional_Committment_K23.pdf
Human Subject Section	
12. Protection of Human Subjects	Human_Subjects_Involvement.pdf
13. Data Safety Monitoring Plan	DSMP.pdf
14. Inclusion of Women and Minorities	Inclusion_of_Women_and_Minorities.pdf
15. Inclusion of Children	Inclusion_of_children.pdf
Other Research Plan Section	
16. Vertebrate Animals	
17. Select Agent Research	
19. Consortium/Contractual Arrangements	
19. Resource Sharing	
20. Authentication of Key Biological and/or Chemical Resources	
Appendix	
21. Appendix	

PHS 398 Career Development Award Supplemental Form

Citizenship*:

U.S. Citizen or Non-Citizen National?* ☑ Yes ❑ No

If no, select most appropriate Non-U.S. Citizen option

- ❑ With a Permanent U.S. Resident Visa
- ❑ With a Temporary U.S. Visa
- ❑ Not Residing in the U.S.

If with a temporary U.S. visa who has applied for permanent resident status and expect to hold a permanent resident visa by the earliest possible start date of the award, also check here: ❑

CANDIDATE'S BACKGROUND. My ultimate goal as a physician scientist in pediatric pulmonology is to understand individual variation in disease to improve precision care for children with respiratory diseases. Always fascinated with science, I completed a degree in biochemistry and molecular biology at Mississippi State University, where I was one of their first awardees of the Goldwater Scholarship, the most prestigious undergraduate award in the U.S. for students studying the sciences. Next I enrolled in the Medical Scientist Training Program (MSTP) at University of Alabama at Birmingham (UAB) to bridge clinical medicine and basic science research, where I won several awards for research, successfully obtained NIH funding for training, and presented my work at international conferences. My thesis (laboratory of Eric Sorscher in the UAB Cystic Fibrosis Research Center) addressed the effects of hypoxia on the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR)* gene expression, providing some of the first evidence that acquired CFTR dysfunction influences non-CF disease, resulting in two first author publications. During this time, I also initiated and managed an international genetics research project to identify novel variants in a unique population of Ecuadoreans with hemifacial microsomia. While unrelated to my primary projects, this study enabled me to take a major leadership role in a genetic study and provided me with specific skills applicable to the current application and my overall career, including establishing a collaboration with an international university (Pontificia Universidad Católica del Ecuador), assembling a research team and interpreters, developing the proposal, obtaining regulatory approvals, and securing funding. Overall, the MSTP provided a breadth of training in basic science and clinical medicine, a key stepping stone in my career.

Subsequently, I completed residency in pediatrics at Columbia University Medical Center in New York followed by fellowship at the University of North Carolina at Chapel Hill. My clinical training focused on general pediatric pulmonology. Throughout this time, my desire to improve the lives of my patients with CF through research strengthened, as I twice became a mother myself, while gaining perspective as the primary pulmonologist for the families of children with CF. I witnessed the struggles families experience from the initial diagnosis through periods of illness, and realized that my distinctive skill set in research and medicine could make a significant impact in the delivery of care, understanding of the disease, and finding a cure. In August of 2015, I was recruited to my first faculty position, returning to the CF Center at UAB to solidify my long-term plan to improve precision care in CF by starting to build an independent research program in context of my clinical practice in pulmonology, with Dr. Steven Rowe (Director of the UAB Cystic Fibrosis Research Center) as my primary research mentor. Since joining the faculty at UAB, I continued my training to improve clinical and translational study skills, including attending the Genetics and Genomics Clinical Research Immersion Course; the Clinical and Translational Science Training Program; the Pulmonary Biology Training Program (T32); and the Success in Research workshop. In August of 2016, I was promoted to Assistant Professor of Pediatrics.

These opportunities enabled me to acquire pulmonary biology-focused skills, including assays of CFTR maturation, trafficking, and function; primary cell culture; three-dimensional primary cell models; microscopy; and microfluidics, all at a time when my research direction evolved from CFTR trafficking to primary epithelial model development and pharmacogenetics (to enable better studies of precision medicine) and changed institutions from North Carolina to UAB. In addition, I have advanced skills essential for a successful career in research: laboratory management, human subjects research and proposal writing. In addition to successful grant applications from graduate school and fellowship, I have submitted successful grant proposals as either a principal or co-investigator since my faculty appointment (including NIH R43, CFF pilot award, and the Kaul Pediatric Research Institute; see Biosketch). I have successfully completed a variety of Institutional Review Board protocols, including consent forms, ranging from the inclusion of human subjects, use of human tissue specimens, and retrospective chart studies. I routinely identify, recruit, and consent human subjects for studies and manage a research coordinator for these activities as well. While my publication yield slowed during clinical training and my transition to faculty, in just the last year I have two manuscripts in press, one recently re-submitted after initial peer review, and three additional papers in preparation, all of which are first author publications.

With support from my institution, which provides a wealth of resources for training, mentorship, and collaboration, my experiences have positioned me well to transition to an independent investigator with a variety of skills to launch a research career. Although I have basic research and clinical practice training, I will benefit greatly from additional studies in specific areas: statistics, clinical trials, and pharmacology, as well as further career development mentoring and guidance. The K23 Career Development award is crucial for me to become independent and a leader in precision medicine for CF and other pediatric pulmonary diseases.

CAREER GOALS AND OBJECTIVES. My goal is to develop and implement personalized therapeutic strategies for children with pulmonary disease. My research program focuses on the development of cell-

culture based tools to CFTR modulators on a personalized basis and to study the pharmacometrics of CFTR modulators and other airway drugs, a significant opportunity and unmet medical need. To achieve this goal, I will need further training and mentorship under the K23 Career Development Award to develop my research program and become independent from my mentor over the next five years.

This award will provide me with the protected time and additional training to conduct translational, patient-oriented research in personalized medicine, incorporating pharmacogenetics and pharmacology with biomarker development and clinical research design. With the funds from this grant, I will support my salary, staff, and for supplies to generate publications and preliminary data for an NIH R01 award. This award will provide me with the training to reach my potential to impact bench-to-bedside and bedside-to-bench research, completing the circle of translational and personalized medicine so important to CF and pediatric pulmonology.

My **short-term learning objectives** (see Table on following page) over the next 5 years are selected to enable independent research design and analysis. They include:

- Statistical genetics and statistical methodology. To develop a strong foundation built upon my prior graduate training, additional training in statistical analysis is required. (Aims 1-3)
- Pharmacometrics and metabolism. A solid understanding of pharmacology and its use in developing personalized therapeutic strategies, including biomarkers, is essential to developing a research program in precision medicine. (Aims 2-3)
- Patient-oriented translational research study design and implementation. Further training will prepare me to develop patient-oriented research grants independently. (Aim 3)
- Professional development skills. Grant and manuscript preparation and review, interviewing and negotiating, mentoring and laboratory management. These skills are applicable to the proposal as a whole, particularly as pertains to promoting independence.

My **long-term goals** over the next 5-10 years include:

- Promoting precision treatment strategies for pediatric and pulmonary diseases by producing rigorous evidence to guide clinical care.
- Maintain continuous federal and non-federal funding for patient-oriented basic, translational and clinical research, notably through R01 awards.
- Sustain productivity by publishing 3-4 peer-reviewed basic and translational manuscripts annually.
- Develop a mentoring and training program for graduate and professional students and post-doctoral trainees in my laboratory

CAREER DEVELOPMENT AND TRAINING ACTIVITIES. My career development and training efforts will focus on those areas crucial to my success. Each area and specific activity were selected to integrate with the specific research activities I will complete to reach my short and long-term goals. A member of my mentoring team or scientific advisory committee supports each training area (Table 1).

Table 1. Mentors and Advisors for K23 Proposal.

Mentor/Advisor & Role	Content Areas	Affiliation	Meeting Frequency
Steven M. Rowe, M.D., M.S.P.H. Mentor	Cystic fibrosis, model development, emerging CF therapies, clinical trials, career development (all Aims)	Professor of Medicine and Pediatrics Director, Cystic Fibrosis Research Center	Weekly – lab group meeting Monthly – individually
David W. Kimberlin, M.D. Co-mentor	Clinical trials, grant writing , K-R transition (Aim 3, overall career development)	Professor, Pediatrics Vice Chair, Dept. of Pediatrics, Clinical and Translational Research	Quarterly
Edward Acosta, Pharm.D. Co-mentor	Pharmacometrics, pediatric pharmacology, translational pharmacology (Aims 2, 3)	Professor, Pharmacology Director, Division of Clinical Pharmacology	Quarterly
Hemant Tiwari, Ph.D. Co-mentor	Statistical genetics (Aim 1)	Professor, Biostatistics	Quarterly
Inmaculada Aban, Ph.D. Co-mentor	Clinical trials statistics; statistical methodology (Aims 2, 3)	Professor, Biostatistics	Twice yearly
Emily Scott, Ph.D. Advisor	Cytochrome P450 enzymes, drug metabolism (Aim 2)	Medicinal Chemistry and Pharmacology, U. Michigan	At least once yearly
Nita Limdi, Pharm.D. Advisor	Personalized medicine, pharmacogenomics (Aims 1, 3)	Professor of Neurology and Epidemiology	At least once yearly

MENTORSHIP TEAM: Overall, these mentors and advisors will provide guidance for specific learning objectives and guidance. Group meetings will occur at least once yearly with all mentoring and advisory committee members, including WebEx conferencing to facilitate those advisors not at UAB and the members'

schedules. They will assess my milestones and provide feedback after formal presentation of my research and professional progress during these meetings, after which detailed plans for the next six months will be summarized and communicated to all mentors and advisors.

- Steven Rowe, M.D., M.S.P.H., my primary research mentor, has an outstanding international reputation and extensive expertise in basic, translational, and clinical research in CF and other pulmonary diseases. He is the director of the CF Research Center at UAB, recognized world-wide for leadership in cutting-edge CF research and one of the longest continuously funded such centers nationally. His laboratory has over 20 members currently and he has also successfully mentored many medical students, residents, fellows, and junior faculty, including several who have been promoted to faculty positions, achieved K-level funding, and who are now CF Center Directors elsewhere. Our meetings will focus on the review of data, overall study design, project milestones, presentation of results, and grant preparation.
- David Kimberlin, M.D., will serve as a co-mentor, providing guidance in the conduct of clinical studies, project management, and how to maximize the resources of this award in order to obtain an NIH R01. Dr. Kimberlin has successfully transitioned several investigators to independent research programs and has a long history of career development success at all levels of training.
- Edward Acosta, Pharm.D., co-mentor, has extensive experience in adult and pediatric pharmacokinetic and pharmacodynamics modeling for drug studies, translational pharmacology and the optimization of drug regimens, and development of new assays for drug assessment. Our meetings will focus on one-on-one training in pharmacometric analysis, reviewing data, and assessing pharmacometric study design.
- Hemant Tiwari, PhD, co-mentor, is an expert in statistical genetics, including the analysis of complex genome-wide association studies, next-generation sequencing technology and statistical approaches, and has decades of experience training physicians and scientists in using these tools in their own studies. Our meetings will focus on analysis of genetic variants, review of the data, and study design.
- Inmaculada Aban, PhD, co-mentor, is an expert in clinical studies and statistical methodology (although not statistical genetics). She is the founding statistician in the recently established Pediatric Research Office to further goals of research in the Department of Pediatrics. She will provide guidance in appropriate study design and biostatistics expertise.
- Emily Scott, PhD, is a leader in understanding cytochrome P450 enzymes, drug metabolism, and drug design. She will provide guidance in the study of CYP3A enzymes and drug metabolism.
- Nita Limdi, Pharm.D., Ph.D., M.S.P.H., is an expert in personalized medicine and pharmacogenomics. She will provide guidance in personalized approaches to therapeutic strategies, and career development.

Training activities:

1) **Pharmacogenetics and statistical genetics (Aim 1).** These didactic experiences will improve research design and rigor; enable independent analyses; and improve collaborations with statisticians.
   a) National Institute of General Medical Sciences-funded Short course on statistical genetics and genomics, hosted at UAB with nation-wide faculty (Grant No. R25GM093044 1 week).
   b) National Human Genome Research Institute-funded Short course on Next-Generation sequencing: Technology and Statistical Methods, hosted at UAB with rotating nation-wide faculty (Grant No. R25HG006110, 1 week).
   c) BST 675. Introduction to Statistical Genetics, to solidify statistical genetic analysis methods (UAB Department of Biostatistics, 1 semester).
2) **Pharmacometrics and metabolism (Aim 2).**
   a) Pharmacometric Analysis in Clinical Trials at the Foundation for Advanced Education in the Sciences (FAES), National Institutes of Health. This one-week intensive is for investigators pursuing studies in PK/PD during drug development as well as correlation with clinical outcomes and biomarkers.
   b) Edward Acosta will provide direct, one-on-one guidance in this area. He has over 20 years experience in lecturing and training pharmacologists and health professionals in pharmacology, including pharmacokinetics and pharmacodynamics modeling.
   c) American Society for Pharmacology and Experimental Therapeutics at Experimental Biology meeting, yearly attendance and participation for training and networking with pharmacology and metabolism experts.
3) **Clinical Research Design and Analysis** (**Aim 3**)**.**
   a) The Applied Statistical Independence in Biological Systems (ASIBS) Short Course at Mount Sinai Icahn School of Medicine. This seven-week online course culminates in a week-long in-person hands instruction; combined will serve to train me in biostatistical methodology and computing using SAS (Statistical Analysis System). (Grant No. R25GM111239).

b) Biostatistics, Epidemiology, and Research Design (BERD) at UAB Center for Clinical and Translational Science Webinars and one-on-one consultations with methodologists to enhance study design and training. Quarterly consultations for research design with a methodologist.
c) The Center for Clinical and Translational Science training academy (including the Clinical Investigator Training Program) at UAB to study clinical trial implementation and completion. I will conduct a trial using human subject specimens and data for translational research in preparation for future grant applications. I will learn to apply the data obtained to calculations for subsequent studies. Help from Drs. Rowe, Kimberlin, and Aban will be instrumental to obtaining these skills.

In addition to the previous training foci, I will continue to develop the professional skills critical for independence such as scientific writing, dissemination of research and management skills.

Table 2. Summary of activities and milestones.

	Year 1		Year 2		Year 3		Year 4		Year 5	
	1-6	7-12	1-6	7-12	1-6	7-12	1-6	7-12	1-6	7-12
Didactic training (Person Months)	2.4		2.4		1.8		0.6		0	
RCR										
ASIBS Short Course										
Short course - SGG										
Pharmacometric course at FAES										
Introduction to Statistical Genetics										
Lab management training course										
Next-Gen sequencing Short Course										
CCTS Training Academy										
Conferences (Person Months)	1.0		1.0		1.0		1.0		1.0	
BERD										
Weekly local research conferences										
Clinical Research Seminar series										
ASPET/EB, NACFC, ATS										
K-R Transition group										
Research (Person Months)	5.6		5.6		6.2		7.4		8.0	
Aim 1 SNP profiling										
Aim 1 Clinical data and analysis										
Aim 2 *in vitro experiments*										
Aim 3 Recruitment										
Manuscript submissions										
Write R01										

Seminars and laboratory meetings:

- UAB CF Research Center (CFRC) includes local investigators and invited speakers to discuss the latest developments in CF and related research, weekly
- Grand Rounds speakers for the Department of Pediatrics, weekly
- Child Health Investigative Forum, monthly

Presentation Skills at local and national meetings:

- Present progress in my projects as manuscript drafts and grant proposals for critical review to the Rowe laboratory.
- Annual attendance and presentation at the North American Cystic Fibrosis Conference and the American Thoracic Society meeting will enable me to: (i) participate in educational opportunities in clinical medicine, (ii) stay current with the latest developments in CF and pulmonology research, and (iii) establish and maintain the peer contacts that will form the basis of future research collaborations.
- Present yearly at the CFRC seminar series.
- Present at the CCTS project panels (multidisciplinary experienced faculty review panel) for formal review of study design and progress. Be more specific

Additional didactic training

- Lab Management Course for Postdoctoral Scholars, Office of Postdoctoral Education, incorporating personnel management, budgets, mentoring, data management, and similar topics.

Overall Impact of career development activities: At the end of the five-year award, I will have combined my robust basic science skills with clinical and translational training, improved my knowledge of pharmacology, statistics, and genetics, and developed a precision approach to CF therapy. The skills and expertise I will develop will enable expansion of pediatric pharmacometrics and precision medicine to other pulmonary diseases (e.g., asthma) and other pediatric diseases.

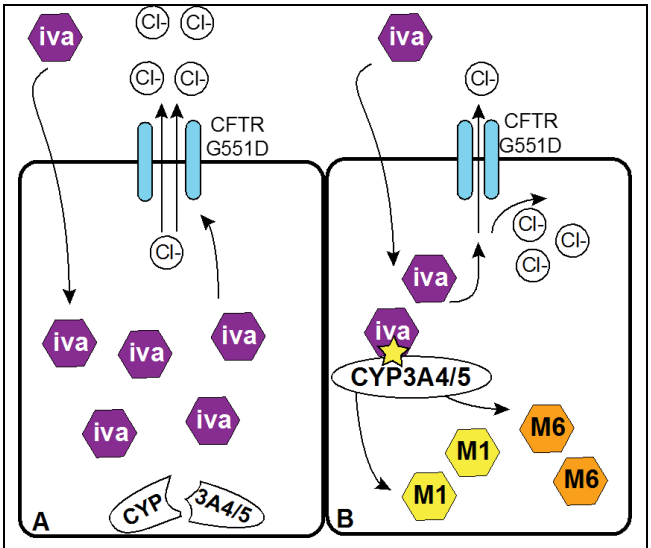
Specific Aims: Cystic fibrosis (CF) is an autosomal recessive disease caused by genetic variants in the CF Transmembrane conductance Regulator (CFTR) gene. This results in dysfunction of epithelial homeostasis in many tissues due to impaired chloride (Cl^-) and bicarbonate transport. In the lung, thick, sticky mucus results in progressive lung decline, ultimately resulting in death. This lifelong, multisystem disease causes a massive burden of disease for patients with CF and their families over decades of life. The recent debut of mutation-specific CFTR modulators that target the molecular defect in the protein to rescue CFTR activity, has begun to revolutionize care. Despite the success of one of these, the potentiator ivacaftor, there is still pronounced variance in drug efficacy, as measured in individuals' phenotypic response to therapy and their *in vitro* cellular response when assessed with cell-based biomarkers. This raises the possibility of untapped efficacy.

Ivacaftor is metabolized by CYP3A4/5, which are expressed in many tissues, including the airway, a key target tissue of CFTR modulators. Single nucleotide polymorphisms (SNPs) can alter the activity of CYP3A enzymes, varying the concentrations and efficacy of many drugs. To maximize efficacy of ivacaftor, it is essential to understand its pharmacokinetics (PK) and the influence of drug metabolism of ivacaftor at the tissue level.

In this proposal, we will test the hypothesis that ivacaftor metabolism influences drug response and can be used as an archetype for precision based CF therapeutics.

Aim 1. Determine whether CYP3A SNPs are associated with the efficacy of ivacaftor. An observational trial to monitor efficacy of ivacaftor is currently in progress (G551D Observational Trial-Extended and Expanded (GOAL-e^2)) and is led by the mentor to this application. This trial includes the collection of airway epithelia and blood for genetic testing, which will be used to:

a) Characterize key metabolism gene variants of CYP3A enzymes in subjects from the observational trial.
b) Determine the association between genetic profile and clinical efficacy, including lung function, sweat chloride, and body mass index.



Ivacaftor mechanism of action. Ivacaftor acts on CFTR with gating dysfunction (e.g., G551D) to increase chloride transport in the absence of functional CYP3A4/5(A). Active metabolism of the parent compound to **inactive metabolites M1 and M6** would result in less effective CFTR restoration in airway epithelia (B).

Aim 2. Determine the relationship between intracellular drug concentrations and CFTR function. We have already established methods to quantitate ivacaftor and its metabolites in serum and epithelial cell lysates. We have also developed a novel *in vitro* biomarker (nasospheroids) to measure patient-specific CFTR activity.

a) We will prospectively collect human nasal epithelial cells (HNE) in 20 subjects to measure CFTR function treated with ivacaftor. We will correlate CFTR function with intracellular concentrations of the drug.
b) Using ritonavir, a pharmacokinetic enhancer used clinically in other diseases and drug regimens, we will reduce CYP3A activity in the epithelial *in vitro* model and measure CFTR functional activity and changes in ivacaftor concentrations in response to these interventions.

Aim 3. Perform a prospective study of CF patients taking ivacaftor monotherapy to determine the relationship between intracellular and systemic drug exposure with drug response. We will conduct a clinical study on patients already taking ivacaftor to determine if efficacy can be predicted on the basis of SNP profile and achievable drug concentrations in airway epithelia on an individual basis.

a) We will recruit 20 patients on ivacaftor, quantitate the drug in plasma and HNE intracellular lysates, and calculate PK to determine the association between drug exposure and clinical efficacy.
b) For each patient, we will also determine CYP SNP profile and quantitative mRNA and protein expression to detect associations between genotype, gene expression, and drug exposure from 3a.This will allow us to determine predictive capacity of SNPs on PK of ivacaftor.

Significance: Understanding variation in metabolism of ivacaftor and the impact on efficacy as monotherapy is the first key step to understanding pharmacogenetics of CFTR modulators. This will be crucial in CF and a seminal example of precision therapeutics, as ivacaftor will be the basis of complex treatment combinations in the near future. The conceptual framework will also apply to many other pulmonary drugs. Ultimately this will create new treatment paradigms, incorporating drug concentrations and genetic CYP profiles to maximize efficacy of therapy. The training accomplished in this application will lead to an independent career in pulmonary pharmacogenetics for the PI and future R01 proposals on individualized therapy.

Background and Significance: *CFTR* identification - a milestone to treat the underlying cause of cystic fibrosis (CF). The cause of CF was determined in 1989, with the identification of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) [1-3]. Over 2000 genetic variations[4] in *CFTR* make mutation specific therapy very challenging. Disease-causing mutations lead to diminished or absent CFTR function and abnormal secretions in the epithelia of many organs, including the airway, where impaired airway clearance causes infection and inflammation that causes severe morbidity and limits life span [5-9].

CF therapeutics target the underlying protein defects. The development of CFTR modulators – *correctors* that overcome impairments in protein processing and *potentiators* that enhance CFTR gating function – has begun to revolutionize the care of the minority of CF patients (~10%) in whom CFTR modulators are highly active[11-13].Ivacaftor is a single drug therapy targeted to specific mutations[14-19]. It potentiates CFTR channel opening, restoring proper regulation of the mutant ion channel and improving lung function and clinical outcome for some patients. Although it is highly active on a group-wise basis, there remains considerable variability in treatment response, representing unmet therapeutic potential. For example, **approximately 25% of patients with the G551D mutation showed less than 5% percent improvement in predicted Forced Expiratory Volume in 1 second (ppFEV1)[20], and some even demonstrated declines in lung function** (Fig. 1)**.** Sensitivity to small alterations in drug exposure may contribute to this variability (Fig. 2)[21]. Change in sweat chloride, a key clinical measure of CFTR activity, varied from -25 to nearly -80 mEq/L[20]; this difference is substantial, as natural history studies suggest widely different outcomes in those with a lower sweat chloride[22,23]. Approval of ivacaftor was expanded to patients with other rare mutations (e.g., R117H), although in many cases efficacy is not as marked.[24] The etiology of this variability in response represents a significant challenge to optimize therapy. Multi-agent CFTR modulator therapy represents the future of CF care, as combinations of both a corrector (to improve protein processing) and a potentiator are proving more efficacious in many cases.[25-29] While the first combination therapy (lumacaftor+ivacaftor) improved lung function (by a modest ~3%) and an alternative corrector (tezacaftor) with ivacaftor[28] may be somewhat better, the frequency of low responders to either therapy was even greater than that seen with ivacaftor in patients with gating mutations. Hence we expect this to be a significant challenge in CF for years to come.

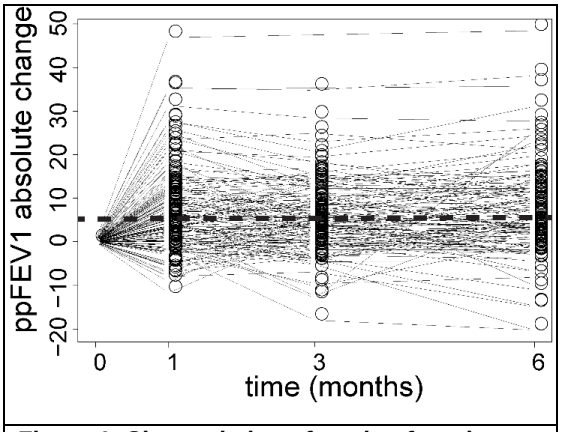


Figure 1. Change in lung function from baseline (time 0) over six months is variable. ppFEV1 of patients with the G551D mutation on ivacaftor were followed over 6 months.[10] Each line represents a single individual tracked over time. Horizontal dotted line at +5% improvement. The magnitude and persistence of response was variable. Several patients had active decline during the period of observation greater than expected normal rate of decline (usually ~2%/year). We hypothesize that individual variation in drug metabolism is a major contributor.

Pharmacokinetics vary among individuals with CF. A critical part of the basic characterization of all CFTR modulators in development[30-34] includes pharmacokinetic (calculations of drug exposure) and pharmacodynamics (relationship of drug exposure to efficacy) modeling (PK/PD). The intensive monitoring of blood levels for pharmacokinetics is typically done in a small selected group of patients who enroll in clinical trials. Variation in drug exposures among CF patients, who often have altered metabolism, is well recognized and is known to have pronounced impact on drug efficacy[35-39]. For example, ciprofloxacin has such a wide variation in plasma concentrations that some CF patients cannot reach therapeutic levels with standard dosing[36]. Another example, tacrolimus, an immunosuppressant used in solid organ transplant, requires a substantially higher dose in CF recipients than non-CF to achieve therapeutic concentrations (see also below) [40-42]. Up to 67% of variation in plasma concentrations of tacrolimus has been attributed in part to differences in metabolism enzymes, particularly the CYP3A superfamily including CYP3A4 and CYP3A5[43]. This has been further demonstrated *in vitro* in the kidney, where genetic variation in CYP3A5 influenced CYP protein expression and metabolic activity[44]. This suggests CYP3A4 and CYP3A5 may also be important to CFTR modulators.

Cytochrome P450 enzymes play an important role in systemic and tissue-specific metabolism of CFTR modulators and other drugs. Like ciprofloxacin and tacrolimus, ivacaftor is metabolized by the CYP3A family members, including CYP3A4 and CYP3A5[45]. These enzymes metabolize up to 60% of available drugs[46]. They have been implicated in alterations in PK and drug response in a number of medications. Although the relationship between genetic variation and clinical efficacy is not always consistent[47-49], there is substantial evidence these enzymes contribute to inter-individual variation in dose requirements and drug response[50-53]. Single nucleotide polymorphisms (SNPs) in ***CYP3A4*** have been implicated in variation in drug responses (e.g., calcineurin inhibitors[51-54], amlodipine[55], statins[56-58], cyclosporin A[53], and fluticasone[59]). CYP3A4 has substantial

variation (40-100 fold) in activity among individuals.[60] While CYP3A4 is primarily a hepatic enzyme, it is also expressed in airway epithelia in ~20% of individuals, influencing tissue-specific drug concentrations[59,61,62]. ***CYP3A5*** is a key extra-hepatic CYP3A isoform and has been implicated in variation in drug exposure and response in several drugs (e.g. tacrolimus[43,44,48,63,64], statins[65,66], amlodipine[67,68], cabazitaxel[69], and beclomethasone[70]). It is found in most subjects at both the mRNA and protein level in the lung[61,71-75] and other tissues[76-80]. CYP3A5 expression and/or activity is variable (identified in 6-70% of Caucasians) [76,81-83].

Notably, the relationship of SNPs in *CYP3A5* to dose requirements is well characterized; tacrolimus is a prominent example and is clinically important in CF. Patients with the SNP *CYP3A5*1* have high metabolic activity of the enzyme, significantly reducing systemic drug exposures and requiring higher doses to achieve therapeutic concentrations[43,44,48,63,64]. Therapeutic drug monitoring (TDM) ensures tacrolimus levels remain within a narrow therapeutic window; the identification of this SNP explained the suboptimal plasma concentrations which were overcome by simply increasing the dose to avoid treatment failure[64]. In the case of ivacaftor, no TDM is used because the therapeutic window is broader, and simplicity in dosing was desired by the manufacturer. However, highly variable plasma concentrations of ivacaftor have been reported[85], which is a significant concern considering the dose-dependent response to ivacaftor[21] (Fig. 2). The fact that metabolism enzymes important in ivacaftor clearance are variably expressed in the airway epithelia underscores the need to understand not only systemic, but also tissue-specific metabolism. The fact that both CYP3A4 and CYP3A5 are expressed in airways, the primary tissue target for ivacaftor, raise the importance of understanding the effect of CYP metabolism in CF, which could also explain differences in dose-response observed among tissues that partially confounded its clinical development.

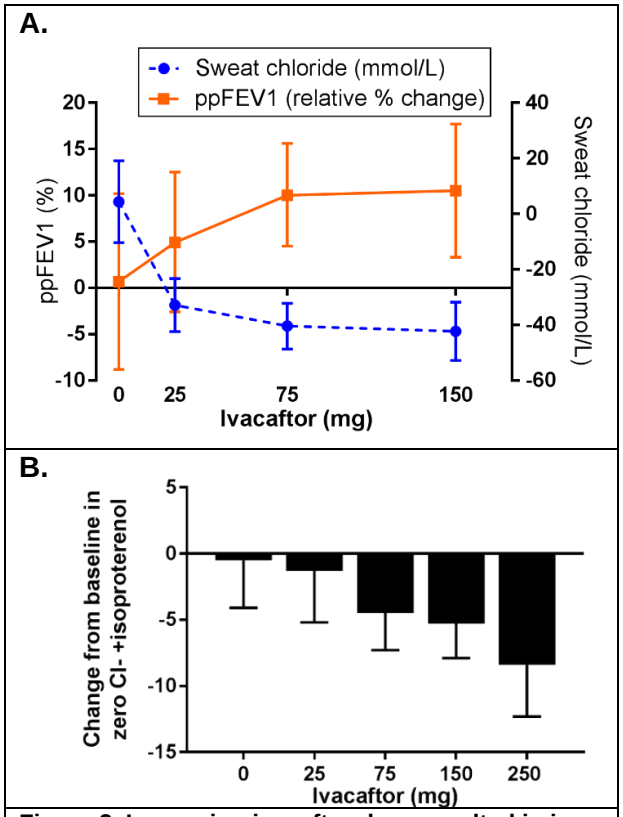


Figure 2. Increasing ivacaftor dose resulted in increasing drug response. A. In the original Phase II trials, multiple drug concentrations showed a clear dose-response. A. Summary of changes in ppFEV1, NPD, and sweat chloride adapted from Accurso FJ et al. *N Engl J Med* 2010;363:1991-2003. **B.** The greatest restoration of CFTR –activity by NPD was observed at the highest tested dose of ivacaftor (250 mg), even though 150 mg is the approved dose[84]. NPD (nasal potential difference). Adapted from: Rowe SM et al. PLoS One. 2013 Jul 26;8(7):e66955.

CYP3A enzymes can be manipulated to enhance efficacy. Increased metabolism of ivacaftor would risk treatment failure. Conversely, attenuation of ivacaftor metabolism could enhance efficacy. **This represents a highly significant treatment opportunity: strategies to target increased ivacaftor concentrations in airway epithelia could maximize efficacy at an individual level.** Proof-of-principle for this approach is exemplified by studies in Dr. E. Acosta's laboratory (advisor to this application). Ritonavir and cobicistat are used as pharmacokinetic enhancers (PE) in human immunodeficiency virus (HIV) regimens[86]. When used at low doses as a PE, it suppresses CYP3A4 metabolism to create a tolerable treatment regimen for HIV patients. Similarly, inhibition of CYP3A enzymes significantly reduced ivacaftor dosing requirements, while maintaining or improving drug response[87]. In a pair of siblings with G551D, one took ivacaftor twice weekly while concomitantly taking itraconazole, a CYP3A inhibitor; the other took standard dosing. The sibling taking itraconzole, which acted as a PE to increase plasma exposure, had twice the increase in ppFEV1[87]. This strategy was further demonstrated in a proof of concept study in healthy volunteers who were administered a low dose of ritonavir concomitantly with ivacaftor, which significantly increased circulating plasma concentrations of ivacaftor by ~20-fold with a low side effect profile[88]. This recent literature provides substantial evidence for the approach. Further, not only can the manipulation of ivacaftor metabolism achieve maximal drug concentrations and efficacy, it could reduce dosing significantly, improve adherence (by converting to single daily dosing, for example), and reduce cost. At a current yearly cost to insurance companies of >$300,000, combination therapy of ivacaftor plus a pharmacokinetic enhancer such as ritonavir could conceivably reduce the yearly list cost to ~ $45,000 (current list price ~$411/ pill, given twice/week based on current evidence[87,88], plus cost of ritonavir, estimated at ~$150/month assuming 50mg/day). While drug cost is a moving target, CFTR modulator pricing structures have certainly restricted access to patients around the world -- cost reduction with novel therapeutic strategies could help address this.

Summary:

- CYP3A-mediated metabolism is an important source of variance between individual responses to therapeutics.
- Ivacaftor efficacy is variable in patients and dose-dependent, underscoring the need to optimize dosing strategies and account for differences in CYP3A metabolism, including the airways.
- Active management of ivacaftor metabolism could provide optimal dosing, maximize efficacy, and reduce cost.

Approach. Preliminary Results, Experimental Design and Methods:

Scientific Premise: My objective is to understand drug metabolism of ivacaftor and incorporate pharmacogenetics of CYP metabolism enzymes in the use of CFTR modulators. The rigorous experimental design assures the collection of robust and unbiased results. Recent literature and significant preliminary data detailed below support the premise and feasibility. In addition, my prior clinical and research training, as well as the diverse and experienced mentoring team provide a strong foundation to achieve the overarching goals of this proposal.

Overall Rationale: In this proposal, we will **1)** determine whether there is an association between SNPs in *CYP3A* enzyme alleles and ivacaftor efficacy in a large, national cohort of patients on ivacaftor monotherapy; **2)** perform mechanistic studies that include PEs to measure the impact of CYP3A enzyme activity on the concentrations of ivacaftor within airway cells and its consequences on CFTR functional activation *in vitro*; and **3)** conduct a prospective pilot study incorporating pharmacometric analysis of patients to determine if SNP profile can predict intracellular and extracellular drug concentrations, CFTR activation, and clinical response.

Aim 1. Are *CYP3A* SNPs associated with response (measured by lung function with ppFEV1) to ivacaftor? We *hypothesize* that the function of CYP3A metabolism enzymes contribute to altered concentrations of ivacaftor in blood and the airway cells, leading to observed differences in treatment effects. SNPs in *CYP3A* genes have profound effects on drug metabolism. Despites its clear importance, the effect of SNPs on CYP3A enzymes among the CF population has not been characterized outside of a single study[35]. Widespread use of ivacaftor alone and in combination highlights the need to revisit this knowledge gap, particularly considering its dose-dependence (Fig. 2).

Preliminary data: To determine the effects of genetic variation in *CYP3A genes* on ivacaftor, we will use existing clinical data and DNA from national observational trials sponsored by the Cystic Fibrosis Foundation (CFF) and co-led by my mentor (GOAL and GOAL-e^2). These trials include 207 participants, a large cohort considering the rarity of the mutations approved for ivacaftor monotherapy. In a small subset of these patients, our collaborators **identified SNPs in CYP3A5 in a genome-wide association study as potential modifiers of the efficacy of ivacaftor** (please see attached letters from Dr. Garry Cutting and Dr. Michael Knowles). Table 2 lists a selection of known and common SNPs, minor allele frequencies, and predicted effect on activity. We have already performed targeted genotyping on a subset of our CF population. Of particular interest, the non-expresser allele *CYP3A5*3* was found as expected in ~70% of our predominantly Caucasian patients; however, the remainder were either wild type or heterozygote expressers. As the predominant extra-hepatic CYP3A5 isoform, expression of active CYP3A5 in airway epithelia would be expected to result in increased metabolism of ivacaftor. While the SNPs with known functional effect are of particular interest, many others (53 in *CYP3A4*, 26 in *CYP3A5*, 6 in *CYP3A7*[90]) may also affect CYP function and will be included in our analysis.

Table 2. Examples of common SNPs

SNP	Effect on activity	Reference SNP	Minor Allele Freq. (MAF)
CYP3A4			
CYP3A4*22[51]	Reduced	**rs35599367**	T=0.015
CYP3A4 int 7	Increased	**rs4646437**	A=0.3632
CYP3A5			
CYP3A5*1	Normal	**rs15524**	G=0.3480
CYP3A5*3	Reduced	**rs28371759**	T=0.3786
CYP3A7			
CYP3A7*2[89]	Increased	rs2257401	C=0.3305

SNPs in CYP3A isoforms as described at http://www.cypalleles.ki.se, the Human Cytochrome P450 database. Reference SNPs are listed where known; MAF from dbSNP (NCBI, https://www.ncbi.nlm.nih.gov/SNP/index.html; 1000 Genomes or if not available there, EXaC) or reference.

Aim 1a Methodology: What are the allele frequencies of SNPs in *CYP3A4* and *CYP3A5* in the CF population? In this Aim, we will use the Heflin Genomics Core facility for *CYP3A4/5* genotyping of all subjects in the GOAL and GOAL-e^2 studies. Regulatory approvals are in place to perform these studies; as detailed in the collaborator letters we will also have access to the DNA from the GOAL cohorts. We will use Sanger sequencing using primers for each exon (and adjacent intronic sequences). Standard techniques will be used with the ABI 3730xl Genetic Analyzer to identify known and novel genetic variants in our CF population in *CYP3A4* and *CYP3A5*. Targeted genotyping alone may not identify novel variants in the CF population; sequencing will achieve more comprehensive analysis. We will also perform targeted genotyping in the Core facility for any known functional

SNPs in the CYP genes that lie outside of the sequenced regions. *This analysis will determine CYP SNPs in a well characterized CF population and maximize the identification of novel variants*.

Aim 1b Methodology: Are specific SNPs associated with measures of clinical response? All clinical data necessary to perform this aim has already been collected. We will assess the association of SNPs identified in Aim 1a with change in sweat chloride, a measure of CFTR activity which is very sensitive to drug effects; we will also examine their influence on $ppFEV_1$ response. We will control for baseline ppFEV1 and age, and include analyses that incorporate a ceiling effect (i.e. FEV_1 > 90-100%); we will stratify our analysis by age (since metabolism is known to change with age[91]). FEV_1 was chosen as a key analysis since it is the most important marker of clinical efficacy, and specifically reflects drug metabolism in airway cells. *Results will determine if CYP SNP expression is associated with CFTR function and clinical outcome*.

Analysis (Aims 1a, 1b): Analysis will be completed with help from Dr. Tiwari, biostatistics expert and advisor to this proposal. Standard quality control procedures will be applied to the data using all SNPs. SNPs with MAF less than 0.05 and Hardy-Weinberg Equilibrium (HWE) p-value less than 0.05 will be excluded from the association analysis. All statistical genetic analyses (including calculating allele frequencies) will be performed using PLINK1[92]. We will use linear regression model for association analysis between clinical efficacy and SNP. We will use additive mode of inheritance for SNPs and age and baseline $ppFEV_1$ will be used as covariates. We will use Bonferroni correction for multiple testing. Primary analysis is change in outcome measure/month, but we will also examine change over five years using repeated measures analysis to increase statistical power. Power: We have calculated power for the sample size of 207 based on the effect size measured by R^2 (variance explained by the clinical efficacy) at the overall significance level fixed at Bonferroni corrected threshold 0.005 accounting for multiple testing of 100 SNPs. With the given sample size, we will have at least 78% and 86% power to detect at least 6% and 7% variance of clinical efficacy measures, respectively.

Anticipated results and significance. We expect several SNPs will be prevalent among the CF population. Some may be associated with CYP expression or activity. We expect to find association between one or more SNPs and the change in $ppFEV_1$ and/or sweat chloride, both key indicators of drug response. We may also find novel SNPs, given that this population has not been well characterized. An association between the presence of specific SNPs and $ppFEV_1$ will show that variation in drug metabolism contributes to variation in drug efficacy, and *suggests the potential to optimize drug response by overcoming altered drug metabolism (by increasing dose[21,84] or inhibiting metabolism[86,88]).*

Potential difficulties and alternative approaches. We have sufficient patients available given our *a priori* sample estimates. If prevalence of SNPs is lower than expected, we will recruit additional patients at UAB (of which greater than 90% of *G551D* patients are already on ivacaftor) and by accessing the Therapeutic Development Network of the Cystic Fibrosis Foundation (of which we are an active participating center), a consortium of 89 CF centers with nearly two decades of clinical research experience. The mentor to this application has already worked with Vertex Pharmaceuticals, Inc., on investigator-initiated projects[93], which is another source of banked specimens for almost all participants in relevant trials. On the off chance that actual results do not satisfy our assumptions, there are additional genes involved in metabolism of ivacaftor that we will consider; notably, variation in the drug transporter P-glycoprotein has previously been shown to influence drug responses, as well as *CYP3A7* and *CYP3A43*, which are also known to be expressed in adults in various tissues[71,75,76,80,94-99].

Aim 2: Does the intracellular concentration of ivacaftor predict CFTR activity in airway epithelia? Systemic drug exposure (measured by blood concentrations) may or may not correlate with ivacaftor response since airway-specific metabolism may dominate response. We hypothesize that the variation in airway epithelial intracellular drug concentrations of ivacaftor may be a substantial contributor to variation in the pulmonary drug response (Fig. 1). For example, the evaluation of ivacaftor in *G551D* patients demonstrated maximal activity and clinical efficacy at the maximal dose tested (250 mg bid) [21,84], whereas 150 mg bid was brought forward as a cautionary approach and driven by sweat chloride results, leaving the possibility that untapped efficacy remains. This could be particularly important for less responsive mutations, and warrants further study.

Preliminary data: To accomplish the goals of this aim, I developed a novel, three-dimensional assay derived from patients' own cells to measure CFTR-dependent fluid transport (Fig.3); confirmed expression of CYP3A enzymes in this tissue (Fig. 4); and developed methods to measure concentrations of modulators in the intracellular compartment (Fig. 5).

Novel, three-dimensional *in vitro* assay (nasospheroids) are derived from human nasal epithelial cells to measure CFTR activity on an individual basis. We have already established culture methods to isolate and expand human nasal epithelial cells from adults and children using a minimally invasive nasal brushing. While ion

transport measurements are a common method to measure CFTR activity, cells must be manipulated in culture ~ one month to be used for such assays; further, we have previously shown this technique may be less predictive of efficacy than using downstream measures of epithelial function dependent on CFTR activity[100]. To overcome these limitations, the model I developed is derived from a patient's own terminally differentiated nasal epithelial cells (Fig. 3), requiring less time and no manipulation in culture since they are a tissue explant ready for testing days after collection, and provides a simple outcome measure (cross sectional area change over time) dependent on fluid transport (a CFTR-dependent downstream measure). Multiple measures from a single individual are possible, allowing for within-subject analysis comparable to that of the sweat secretion bioassay[101,102] that enhances n-of-1 trial design, but in a model that recapitulates airway physiology.

CYP3A enzyme mRNA expression in our subjects is similar to published reports. The relevance of human nasal epithelial (HNE) cells as a surrogate for lower airway epithelial drug response and metabolism has been demonstrated previously. They have similar physiology, ion channel profile, and overall gene expression[103-105] to the airway. Other data has shown ivacaftor effects can be observed in excised cells when measured *in vitro* days after explant[106]. In addition, drug metabolism protein expression profile is similar in nasal and lower airway epithelia[107]. We have confirmed in CF subject nasal epithelia that expression of the relevant CYP3A enzymes is present using quantitative RT-PCR (Fig. 4).

Mass spectrometric detection of CFTR modulators is established. Drug concentrations have so far been limited to the detection of the drug in plasma [30,31,108,109], rather than accessing intracellular levels in the epithelium. Recent *in vitro* studies have suggested that ivacaftor may accumulate at concentrations much higher inside the cells [110], suggesting that plasma level monitoring alone may not be sufficient to optimize efficacy of these drugs. Our own data support this finding; with our advisor, Dr. Acosta, we developed methods to quantitate ivacaftor and its metabolites (M1, M6) in as few as 40,000 cells, at concentrations as low as 0.5 ng/mL[111] (Fig. 5); we have also used these methods for plasma concentrations[111]. We exposed monolayers of a human bronchial epithelial cell line (CFBE41o-, commonly used in studies of CFTR modulators) to either 1 or 5 µM ivacaftor for 24 hours, then exchanged for drug-free media. We collected whole cell lysate immediately after exposure (day 1) or days 3 and day 7 (Fig. 5B). Quantification of the intracellular concentration showed increasing initial concentrations. At the higher dose tested, ivacaftor was significantly reduced by day 7. Ivacaftor is known to induce its own metabolism, which may occur at higher concentrations as the compound accumulates. These changes at the site of action of the drug would not be detected by plasma drug concentrations, indicating the importance of this work. *We will be the first to quantify the intracellular concentrations of CFTR modulators and their metabolites, which could be critical to understanding how the target tissues handle these novel class of drugs and ultimately impact CFTR.*

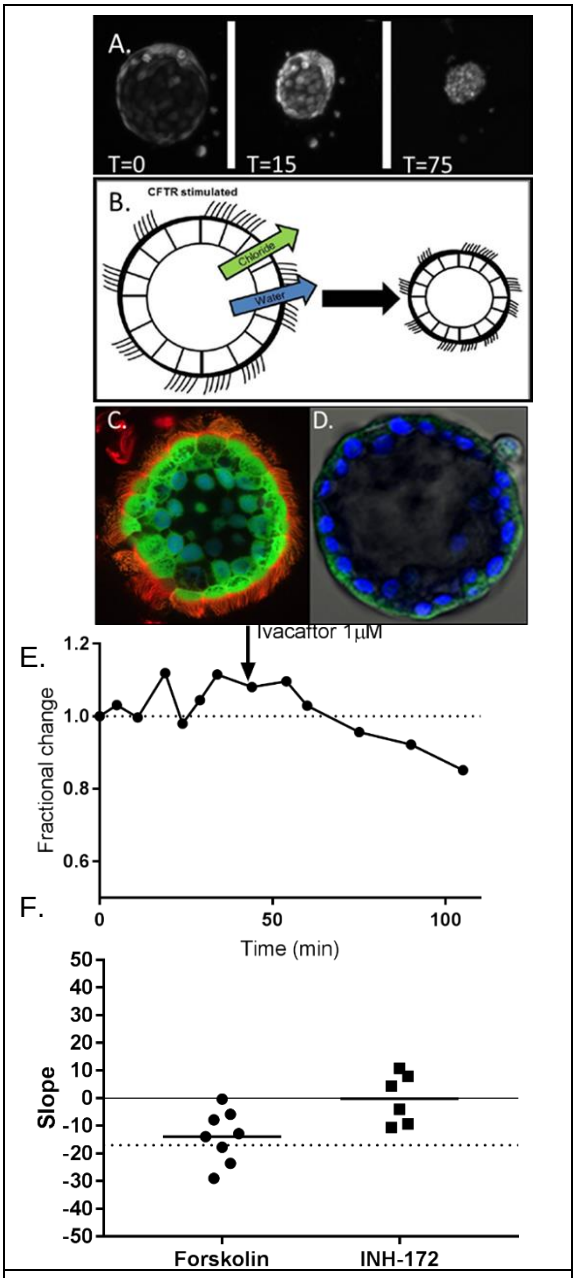


Figure 3. Nasospheroids. A. Progression of non-CF nasospheroids/time (stimulation by the CFTR agonist forskolin). B. As CFTR is activated, chloride (and fluid) moves out of the lumen, through the cell, and to the outside. C. Nasospheroid dyed with plasma membrane orange, calcein green (a marker of cell viability), and DRAQ5 in blue (nuclear stain), 40x. D. Methanol-fixed organoid with CFTR in green, on the apical surface, and nuclei stained with DAPI (blue), 40x. E. Fractional reduction of nasospheroids in a single G551D subject not treated *a priori* with ivacaftor. Nasospheroids are then stimulated with forskolin; at the same time, the epithelial sodium channel, an additional contributor to fluid transport, is inhibited with amiloride. No reduction in size is seen until ivacaftor is added. F. Nasospheroids from a patient on ivacaftor show reduced size over time (slope) reflective of CFTR-mediated fluid transport in the presence of forskolin, but not the CFTR inhibitor $CFTR_{inh}$-172. Note no ivacaftor was added to assay, as reduced size was entirely dependent on the presence of ivacaftor prior to HNE harvest.

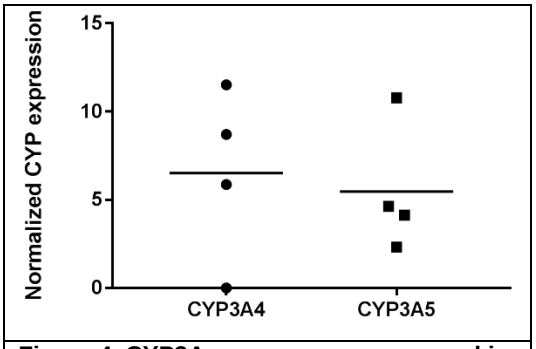


Figure 4. CYP3A enzymes are expressed in nasal epithelia. We isolated RNA from human nasal epithelial cells of four CF subjects. Quantitative RT-PCR was performed using the QuantStudio 3 Real-Time PCR System. Data were normalized to GAPDH internal control. Each dot represents averages from an individual (n=3 replicates each). CYP3A5 was detected in all four subjects; CYP3A4 was detected in 3/4 subjects.

Aim 2a Methodology: Do intracellular concentrations of ivacaftor predict CFTR activity? We hypothesize that variation in intracellular drug concentrations alter CFTR activity in a dose-dependent manner. To assess this, we will collect and analyze new nasal epithelial brushings from 20 subjects. In our laboratory, we typically obtain between 0.5-1 x 10^6 cells per brushing. All cells will be processed and maintained under the same maintenance conditions for 3-5 days to allow for nasospheroid formation. We will isolate a portion of these cultures (approximately 1 x 10^5 total cells in nasospheroids) to assay the intracellular concentration of ivacaftor at standardized time-points (3-5 days). For the nasospheroid assay, cross-sectional area of 10-20 organoids per subject will be directly measured before and after treatment with the cAMP agonist forskolin (to activate CFTR) with live cell microscopy. We will also inhibit ENaC with amiloride to isolate the effects to CFTR, but can repeat the experiments in the absence of amiloride if ENaC activity also proves informative. $CFTR_{Inh}$-172 co-administration at standard concentrations (10 µM) can be used to assess CFTR specificity. The primary readout will be the rate of change in organoid size over time (every 15 minutes for 90 minutes), as in Fig 3. Both fractional reduction and rate of decline (i.e. slope, using linear regression) will be calculated to characterize changes in organoids. On the day of this assay, the portion of nasospheroids set aside for ivacaftor detection will be lysed using 1% NP-40 lysis buffer; mass spectrometry will then be performed to detect ivacaftor and principle active metabolites M1 and M6. We will also sequence *CYP3A4* and *CYP3A5* as in Aim 1 to assess potential for clinically-relevant SNPs that could alter the intracellular concentration of ivacaftor.

Analysis: We will use linear regression to determine association between CFTR-dependent nasospheroid size change and intracellular drug concentration. Secondary analyses will be performed to characterize the mechanism of intracellular drug concentrations, control for contributing factors such as expression and activity, and to assess this *in vitro* data in context of Aim 1 data. To control for CYP3A isoform expression, we will quantitatively measure mRNA and protein expression of CYP3A4/5 in each subject. We will calculate parent:metabolite ratios as a measure of enzymatic activity. Linear regression will be used to correlate the SNP profile and metabolic activity with the intracellular concentrations. Overall results will help determine which enzyme (or enzyme ratios) principally drive ivacaftor metabolism in this model, and the relationship between SNPs and ivacaftor degradation efficiency.

Anticipated results and significance. We anticipate that the intracellular concentration of ivacaftor will directly correlate with CFTR-dependent nasospheroid swelling. We will be the first to directly measure intracellular concentrations in patients and correlate them with functional activity of CFTR and relationship to airway CYP function, progressing toward individualization of CF therapies. *These studies will clarify the mechanisms by which ivacaftor can accumulate inside the cells in vitro, determine the effect on CFTR activity measurements, and help to develop better pre-clinical models for this novel class of therapeutic compounds.*

Aim 2b Methodology: Can pharmacokinetic (PK) inhibitors influence CYP3A metabolism of ivacaftor? PK inhibitors are used to enhance systemic drug exposure and could be used to improve clinical status of CF patients[87]. To establish that PK variance can alter metabolism and efficacy *in vitro*, we will use ritonavir, a CYP3A inhibitor used clinically as a pharmacokinetic enhancer (PE) in HIV drug regimens[60,86]. Ritonavir has also been used in a proof-of-concept study, increasing the plasma exposure of ivacaftor by 20-fold when used at low dose of 50 mg daily in non-CF volunteers.[88] We will use ritonavir at pharmacologically appropriate *in vitro* doses of 0.5-3 µg/mL, as previously described[112] to reduce CYP3A activity in nasal epithelial cells in the nasospheroid model and measure shrinking responses and intracellular concentrations of ivacaftor as described in Aim 2a; nasopheroids from the same subjects will be used in this aim. Using a clinically available inhibitor provides an approach that is readily translatable to *in vivo* studies intended to overcome CYP3A4 activity that reduces ivacaftor efficacy, a concept I would propose as part of a future R01 submission.

Analysis: Analysis of variance will be used to compare the use of inhibitors and effects on ivacaftor concentrations and CFTR function.

Anticipated results and significance: We will be the first to study the effect of a PE on intracellular ivacaftor concentrations and CFTR activity in cells derived from CF patients. This study will serve as proof-of-concept of an

approach to modulate ivacaftor concentrations in the airway by enhancing intracellular levels and improve CFTR restoration.

Potential difficulties and alternative approaches. Nasospheroid measurements and analysis are already established - I personally developed the protocols for the model and three-dimensional culture of nasal epithelial cells. If the expected results do not match actual findings, we will perform similar studies evaluating CFTR-dependent short-circuit current, using the same patient-derived specimens (which will be expanded and banked for this purpose; a single specimen provides sufficient cells for all described studies). In this case ivacaftor will be applied at concentrations typically used for *in vitro* studies (1 µM) for 48 hours, and the ion transport measurements performed as previously described[100]; intracellular concentrations will be determined to examine CYP-dependent effects (as in Aim 2a). To ensure recruitment, we will rely on our NIH funded CF P30 Human Subjects Core and the CFF-funded Center for CFTR Detection at UAB to assist in regulatory approvals and patient recruitment, as I have already done to prepare for this application.

<u>Aim 3.</u> Does the steady-state intracellular exposure of ivacaftor influence clinical drug response? In Aim 1, we will test the association of genetic variation in *CYP3A* enzymes with clinical efficacy of ivacaftor. In Aim 2, we test the hypothesis that the intracellular concentration of ivacaftor influences drug-dependent CFTR activity. In Aim 3, we will bring these concepts together in humans by conducting a pilot study to test the *hypothesis* that the exposure to ivacaftor at steady-state determines the degree of CFTR activity and therefore, drug response *in vivo*. The approved dose of ivacaftor for adults (150 mg twice daily) was advanced based on a conservative but arbitrary decision based on the sweat chloride biomarker (which we now know is not necessarily linked to clinical response), even though the maximal dose tested (250 mg twice daily) [21,84] showed maximal clinical efficacy (Fig. 2). We now also have the benefit of additional safety data that has shown no dose-dependent adverse events. This suggests that a higher dose, and thus, **a greater exposure to ivacaftor in the target airway cell, will yield untapped potential for improvement without significant safety liabilities.**

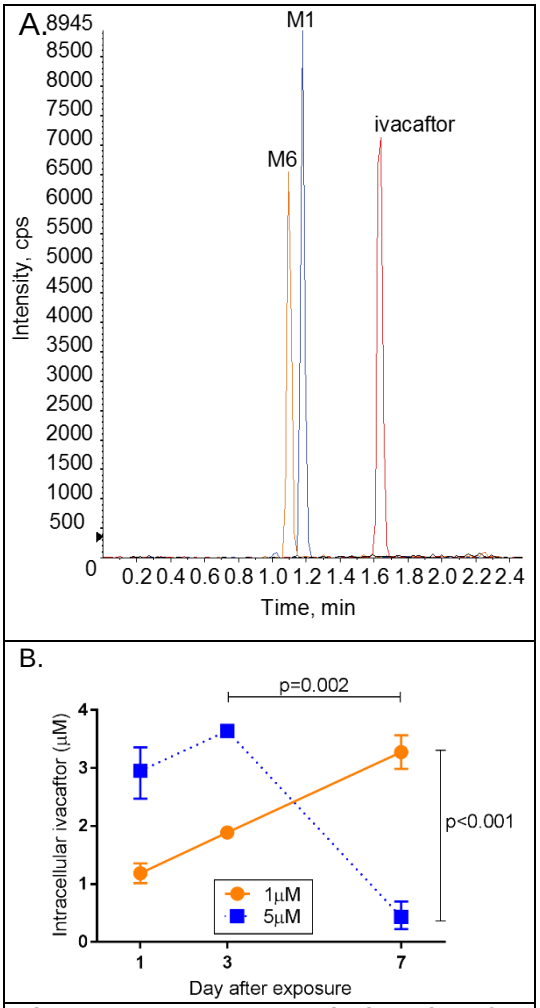


Figure 5. Mass spectrometric detection of ivacaftor and its metabolites. A, mass spectrophotometric chromatogram showing identification of distinct peaks for the parent compound ivacaftor (VX-770) and its two metabolites (M1 and M6), This technique is well established by my collaborator, Dr. Acosta's laboratory and enables quantitative detection of all compounds in as little as 10 microliters of plasma or whole cell lysate. Counts per second (cps). Panel B, intracellular detection of ivacaftor parent drug in whole cell lysate (NP-40 lysis buffer) after a 24 hour exposure in CFBE41o- cell line. Day 1 is the concentration immediately after exposure. Days 3 and 7 are concentrations from whole cell lysate 72 hours and 7 days after the drug is removed.

Rationale: Understanding the relationship between ivacaftor exposure and drug response *in vivo* in ivacaftor monotherapy will improve precision approaches in CF. We have conducted PK studies[111,113,114], measured CFTR function *in vivo*[84,115,116], led investigator-initiated drug studies[111], measured ivacaftor and its metabolites (Fig. 5) and sampled airway cells (Fig. 3-5). Since ivacaftor is a key component in almost all combination therapies presently being advanced[28,29], we will initially target the ivacaftor monotherapy population, with the intent to expand to more complex drug PK analysis of double and triple combination CFTR modulator regimens in future R01 applications.

Aim 3a methodology: For this pilot study, we will recruit 20 stable CF subjects with the *G551D* or other gating mutations on ivacaftor (150 mg) to measure intracellular concentrations of the drug and metabolites (Fig. 6). We will only include patients on ivacaftor for at least 5 days to ensure steady-state blood levels and instruct patients to time dosing q12h in the run up to our study. Because systemic exposure is expected to influence intracellular concentrations, we will also examine plasma levels in patients by conducting traditional PK studies. At Visit 1, we will collect plasma at time 0, 1, 2, 4, 5, 6, 8, 10 and 12 hours (a frequency of timepoints essential for PK calculations). We will also perform spirometry (ppFEV1), calculate a KNorma score (age-normalized lung function) [117] and extract retrospective data from the patient's records augmented by Cystic Fibrosis Patient Registry information to include ppFEV1, BMI, and sweat chloride prior to initiation of ivacaftor.

Analysis: Using non-compartmental methods, we will calculate the 12 hours area under the curve (AUC12); time to reach maximum concentration in plasma and IC (Tmax); maximum concentration in plasma and IC (Cmax); elimination rate constant and half-life; and the metabolite formation rate constants (using modeling approaches) as an assessment of p450 enzyme activity. For intracellular detection, we will collect HNE at 8h post-dose. This time point is selected to be after the peak plasma concentrations for most individuals, to allow time for peak intracellular accumulation. After calculating these parameters, we will coordinate visits 2 and 3 for repeat HNE collections to coincide with individualized peak plasma concentrations to better model intracellular PK (Fig. 6). Linear and maximum effect regression will be used to correlate the calculated ivacaftor exposure (AUC) in plasma and intracellular space with change in ppFEV1 (from baseline prior to ivacaftor). Secondary analysis will evaluate association of Δ sweat chloride and BMI with AUC for plasma and intracellular PK.

Anticipated results and significance: We will be the first to directly model intracellular and plasma PK with ivacaftor. We expect that higher AUC will directly correlate with larger change in ppFEV1. This will show that a higher intracellular concentration will result in higher drug response. A relationship of AUC (either plasma or intracellular) with sweat chloride and BMI may also be observed, if tissue-specific levels in the airway are similar to that in GI and skin. We will determine if there is a threshold for observing efficacy using intracellular PK data, since attempts to detect this by plasma studies alone have not been forthcoming.

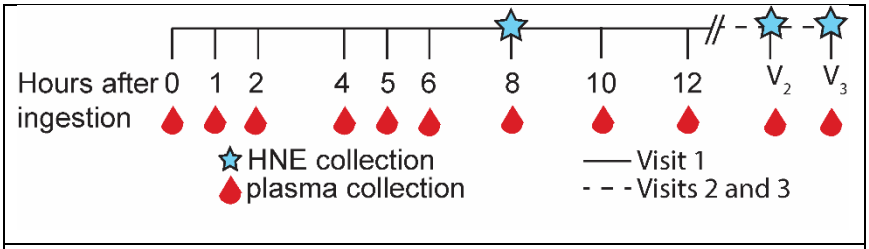


Figure 6. Collection of plasma and HNE for drug levels and culture. Intensive PK monitoring of steady state levels to determine ivacaftor exposure will be performed on Visit 1. HNE will initially be collected at 8h after ingestion of standard dose of ivacaftor 150mg. Visits 2 and 3 will be coordinated with the subject for additional HNE collection for intracellular PK. The timing will be based on calculated exposure per subject; as a control an additional plasma collection will be performed with Visits 2 and 3.

Potential difficulties and alternative approaches. Quantitation of ivacaftor and metabolites are well established (Fig. 5). The study design requires a relatively intensive commitment (at least 12 hours and three visits) with frequent blood sampling, which may limit recruitment, but we have a large number of G551D CF subjects at UAB (N=39) from which to recruit who are experienced and have been highly committed to similar studies (including 12 hr visits). If we experience difficulty, we will add additional sites by using the CFF TDN (see Letters), or incorporate home nurse visits to ease subject burden. If the complex nature of this study limits recruitment, we will revise frequency of sampling based on initial results.

Aim 3b Methodology: Is there an association between SNPs in *CYP3A* enzymes and exposure to ivacaftor? We hypothesize that variation in efficacy is a result of variation in CYP3A enzymes, particularly in the airway epithelium which may not be reflected by levels in the plasma. In this aim, we will perform targeted genotyping of *CYP3A4/5* in each subject. Secondary analysis will include characterization of CYP3A expression: mRNA assessment via absolute quantitative real-time PCR (i.e. digital PCR; QuantStudio 3, ThermoFisher) and validated TaqMan® primer sets (see Figure 3) enabling cross study comparisons; immunoblotting with commercial antibodies against CYP3A4 and CYP3A5 to detect protein level expression.

Analysis: These results will be analyzed using statistical methodology as described in Aim 1. We will use the data from Aims 3a and 3b for power calculations for the next clinical study, which will be designed to manipulate ivacaftor levels using increased dose (250 mg BID) and/or pharmacokinetic enhancers (low dose ritonavir) to achieve maximum improvement in lung function. If insufficient numbers were selected for this pilot study, we will expand recruitment to achieve sufficient numbers for these power calculations.

Anticipated results, significance, alternative approaches: Low ivacaftor AUC12 will be associated with SNPs causing low enzyme activity or expression. There may be no change in expression, but altered metabolic activity (parent:metabolite ratio). We expect to find expression of CYP3A5 in all subject's samples at low levels, but that CYP3A4 expression in airway epithelial cells may be more sporadic (i.e. ~20% of patients[59]). We will focus on CYP3A4/5, but if their expression profiles are not associated with altered ivacaftor metabolism, we will expand SNP evaluation to other metabolism proteins, including the drug transporter P-glycoprotein. Understanding the influence of SNP profile on gene expression of CYP3A enzymes and correlation with AUC12 of ivacaftor will be the first report of genetic variation influencing PK and drug response in CFTR modulator therapy.

Summary. This study will provide new pharmacokinetic understanding of a novel class of drugs (CFTR modulators) and help develop a new *in vitro* biomarker (nasospheroids), enabling novel concepts for precision medicine. The training required to conduct these studies will provide a platform to grow an independent research program focused on precision therapeutics.

Training in the Responsible Conduct of Research

1. Format: The Principles of Scientific Ethics course (GRD 717) is a 3 credit hour class that includes a blended approach of on-line training and in-person discussion on topics related to the responsible conduct of research (RCR). Specifically, the on-line training component includes completion of all RCR-related CITI Program modules; participants are required to successfully complete each of these modules, achieving a score of 80% or better. Once completed, participants then attend an in-person discussion session that consists of an all-day (8 hours) Saturday workshop facilitated by training program directors, preceptors, and administrators. Three Saturday sessions are offered so that participants and facilitators have the opportunity to select a date that best fits their schedules. These sessions debate case-studies in a team-based learning format as well as allow for additional RCR-related activities, such as panel discussions with faculty and administrators regarding 'real-world' RCR examples and role-playing RCR scenarios. **Notably, Dr. Guimbellot will discuss her participation in class with Dr. Rowe, her primary research mentor and Dr. Kimberlin (Director of PRO); she will also discuss similar themes with students she mentors, as well as her laboratory staff.**

2. Subject Matter: Topics covered in GRD 717 include the nature, extent, and causes of fraud in science; UAB policies on fraud; ideals of good science; the responsibilities of authorship and peer review; potential problems raised by the commercialization of research; scientists as public policy advisors; and ethical issues involved in animal experimentation and in clinical trials. Among the areas previously discussed are:
    - Ethical Decision Making
    - UAB Policies on Research Misconduct
    - Protection of Human Subjects in Research
    - Welfare of Laboratory Animals
    - Best Practices for Data Management
    - Identifying and Managing Conflicts of Interest
    - Ethical Authorship and Avoiding Plagiarism
    - Best Practices in Collaborative Research
    - Mentor and Trainee Responsibilities
    - Expectations of the Peer Review Process

3. Faculty Participation: GRD 717 is led by Lisa Schwiebert, Ph.D, Associate Dean, UAB Graduate School, using a "Team Based Learning" approach. She is assisted by faculty facilitators who maintain active research labs and have graduate faculty status.

4. Duration of Instruction: For the 12 on-line learning modules, each module may take from 10 to 30 minutes to complete; average completion time for all modules is four hours. The modules do not have to be completed all in one login session. The in-person workshop provides 8 contact hours of instruction.

5. Frequency of Instruction: This course is offered in the Fall, Spring, and Summer semester of each year meeting weekly over the course of the semester. On-line modules are available at all times. In-person workshops are offered on Saturdays in order to accommodate schedules.

Steven Rowe, M.D., M.S.P.H. (Primary research mentor)

This is my strongest statement of support for Dr. Jennifer Guimbellot's K23 career development proposal to the National Institutes of Health, entitled "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." As her primary mentor, I am strongly committed to provide dedicated guidance to her scientific career and professional development. I have known Jennifer at least ten years, since her time as a graduate student in the Gregory Fleming James Cystic Fibrosis Research Center (CFRC) when she worked alongside me in Eric Sorscher's laboratory. She has been exquisitely trained for a career as a physician scientist, and I am absolutely confident in her ability to successfully conduct the project proposed in this application with the highest level of scientific accomplishment and integrity. Her dedication, curiosity, and commitment to science clearly demonstrate her maturity as an outstanding investigator. This award will allow her to have intensive training in basic and translational science in personalized medicine, pharmacometrics, and pharmacogenomics related to cystic fibrosis and will provide the needed tools for her development into an independent physician scientist.

Candidate's background and eligibility for the award

Dr. Guimbellot completed her PhD in 2007 and her MD in 2008 as part of the Medical Scientist Training Program at the University of Alabama at Birmingham. The results of her graduate work, under the tutelage of Dr. Eric Sorscher, were funded by a Ruth L. Kirschstein NRSA F30 award and were presented in two first author, peer-reviewed publications and several abstracts, including podium presentations, on regulation of cystic fibrosis transmembrane conductance regulator (CFTR) expression and function at various local, national and international conferences including the North American Cystic Fibrosis Conference (NACFC), American Society of Human Genetics, and the European Respiratory Society Lung Science Conference. She was also the recipient of the Outstanding Graduate Student award for two consecutive years in the Department of Genetics as well as was the recipient of a best abstract award in the Medical Scientist Training Program and the School of Medicine finalist at Medical Student Research Day.

Following her graduate work, Jennifer completed residency at Columbia University Medical Center in New York, and pediatric pulmonology fellowship at the University of North Carolina at Chapel Hill. She was noted as an outstanding clinical and research fellow in the laboratory of Martina Gentzsch, PhD, an international leader in CFTR protein trafficking and correction. During her time at UNC, Jennifer presented multiple research abstracts including a podium presentation at the NACFC in October 2014. She won the Best Overall Research Award in 2013 in the Department of Pediatrics at UNC as well as an American Thoracic Society Abstract Award in 2014. She is first or senior author on three accepted abstracts to the North American Cystic Fibrosis conference in November 2017 and has been an invited roundtable moderator in 2016 and 2017. Notably, she was recruited to research faculty positions around the country, including at UNC, but we were fortunate to recruit her back to UAB in August of 2015.

Potential for excellence as an independent investigator

Dr. Guimbellot will be successful as an independent investigator, given her personal qualities and individual skill set. She is very curious, insightful, well-organized, with remarkable technical skills and a tenacity to seek the answers to questions that interest her. She has made outstanding progress on the research projects she has led throughout her career thus far, and I expect that her publication record will soon reflect her progress as she has multiple manuscripts either accepted, in revision, or under review at this time. She has already initiated collaborations with members of the CFRC and other entities related to precision medicine, including bioinformatics, statistics, pharmacology, pharmacogenetics, and cell and developmental biology. She has taken the lead in directing a collaborative project, recruiting a local advisory team of experts in pharmacogenomics, pharmacology, and statistical genetics, among others. She maintains collaborative relationships with her former mentors at UNC (Dr. Gentzsch) and continues to develop new relationships at other institutions (Dr. Emily Scott in pharmacology at the University of Michigan; Garry Cutting at Johns Hopkins; and Michael Knowles at UNC). In addition to her personal attributes, she has demonstrated a clear track record toward progressive independence. Despite being fully funded in her MST program, she pursued an individual NRSA F30 award which was awarded and supported the final years of her education. She also received pilot grants during graduate school, and again in fellowship, to develop new ideas, including using human nasal airway epithelial cells for organoid culture. She was awarded grants for all three years of her fellowship training from the CFF, and since joining the faculty at UAB, she has obtained an internal pilot award

from the Kaul Pediatric Research Institute (for enhancing the reproducibility of the sphere model), an NIH R43 as a co-investigator (leading the project at UAB), and a pilot award from CFF.

Since joining the faculty at UAB, she has focused her scientific program, with specific attention to manuscript productivity, which had the typical delay associated with transition between institutions. As she has become established at UAB in the last year, she has clearly rectified this expected gap -- she has recently had two first author manuscripts accepted for publication, one of which is to the prestigious *JCI Insight* and is directly relevant to this proposal, an additional first-author manuscript in revision, and two additional first-author manuscripts expected to be submitted shortly. These papers are in addition to two first author and four total peer-reviewed publications during graduate school. Overall they reflect substantial research productivity in the last year now that her transition between institutions and to the faculty is complete, and a she has achieved this despite becoming a mother to two children during fellowship, and moving from UNC-Chapel Hill to UAB to establish her own research program. She has been the recipient of multiple awards for research, as detailed above. She is an exceptional scientist and faculty member, and in recognition of her progress, she was promoted from Instructor to Assistant Professor in August of 2016.

Career development

Dr. Guimbellot's plan for her career development includes formal and informal settings for training. She is a member of the UAB Center for Clinical and Translational Science (CCTS) and has already attended multiple development courses. During the period of this award, she will focus on grant and manuscript preparation and review, scientific ethics, interviewing and negotiating skills, mentoring and laboratory management. All of these topics are covered in seminars and formal coursework at UAB, specifically developed by the Pediatric Research Office, the CCTS, and the Office for Post-doctoral Education. She will also undertake self-directed training in the Responsible Conduct of Research using resources in the UAB Center for Ethics and Values in the Sciences.

I have particular expertise in pediatric research and the development of junior faculty to independent investigators. She will meet monthly with me, her primary research mentor. I am uniquely suited for this role with my background in cystic fibrosis clinical, basic, and translational research with particular expertise in clinical trials, modeling and novel imaging modalities. She will meet at least quarterly with Dr. David Kimberlin, the Vice Chair for Clinical and Translational Research in the Department of Pediatrics, an expert in pediatric infectious disease clinical and translational research with expertise in transitioning junior faculty to independence. He will serve as a key career development mentor. She will meet at least quarterly with her other co-mentors, Dr. Edward Acosta, an established investigator over 20 years' experience in pharmacology, mass spectrometry, and pediatric PK/PD modeling; and Dr. Hemant Tiwari, a recognized leader in statistical genetics responsible training countless individuals in genetic analysis. She will meet at least twice yearly with Dr. Inmaculada Aban, an expert in biostatistical modeling with whom Jennifer has an established collaborative relationship. Additional advisors include Dr. Nita Limdi, an expert in pharmacogenomics and personalized medicine and Dr. Emily Scott, a well-known investigator in cytochrome P450 metabolism. She will discuss the project 1-2 times yearly as needed for critical feedback and direction.

Dr. Guimbellot will attend a variety of formal coursework and seminars regarding issues in career development outlined in her training plan. I expect that Dr. Guimbellot will develop two manuscripts per year and present at two scientific meetings for each year of her application. I am also confident she will prepare an R01 application within the timeframe of this award. Working with Dr. Hector Gutierrez (Division Chief and Cystic Fibrosis Center Director) and Dr. Mitchell Cohen (Department Chair), I have ensured that Jennifer will have at least 75% protected time to conduct research. Such protected time will continue for the duration of the award to provide adequate support to build her research program and to allow her to obtain additional funding.

Transition toward independence

Dr. Guimbellot started a laboratory investigating novel three-dimensional cell cultures and pharmacogenomics for personalized medicine, an area that is distinct from my own but utilizes techniques and expertise from my laboratory and others on campus. She has already trained personnel who can perform the needed techniques and is well on the pathway to a fully independent laboratory. She has mentored several trainees on research projects, including undergraduate, medical, and masters students, as well as a post-doctoral fellow. The Division of Pulmonary and Sleep Medicine and the Department of Pediatrics recognize Dr. Guimbellot's

potential to succeed in independence and have dedicated funding for the start-up for her research program, space, and protected time, especially as her research focus is squarely in one of the pillars of UAB's mission for personalized medicine. In both the Departments of Pediatrics and Medicine (where I have joint appointments), we have several junior faculty members who have been recipients of Career Development awards and will serve as role models for career advancement.

Benchmarks for the candidate

To realize her goals, she will do the following:

- Complete the aims of this proposal through publication in peer-reviewed scientific journals, anticipated at least 2 per year.
- Present this research at least annually at international conferences, including the North American Cystic Fibrosis Conference and the American Thoracic Society meeting.
- Submit an R01 application in the final year of this award

Dr. Guimbellot has access to all the equipment, facilities, funding, training, and technical expertise to train her and accomplish all aims outlined in this proposal. She will also acquire advanced skills in statistics, clinical research design and conduct, responsible conduct of research, grant writing, manuscript preparation, and other skills required for independence. While her writing skills are excellent, she will emphasize manuscript preparation and presentation at meetings. The studies outlined in this proposal will provide opportunities to hone these skills as well as provide results for future funding applications.

Mentors track record

I have extensive mentoring experience, supervising over 20 researchers currently. I have supervised others at various levels of training from undergraduates to post-doctoral fellows (8 undergraduate and medical students; 5 graduate students; 5 post-doctoral fellows, and 8 clinical residents/fellows), including four post-doctoral trainees successfully transitioned to faculty appointments at UAB (all of whom have received K or other mentored awards) and one who has become CF Center Director elsewhere. A list of trainees is included in my biosketch.

In summary, I believe that Dr. Guimbellot is an outstanding young investigator with the potential to make a lasting and unique contribution to her field. She has the personal drive, qualities, and skills to be successfully as an independent physician-scientist. She has my highest recommendation for this award.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Steven M. Rowe
Professor, Departments of Medicine and Pediatrics
Director, Gregory Fleming James Cystic Fibrosis Research Center
University of Alabama at Birmingham

David Kimberlin, M.D.

Dr. Guimbellot has my highest support for her K23 career development proposal to the National Institutes of Health, entitled "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." I first met her when I precepted her as a medical student rotating through inpatient pediatrics ten years ago and was delighted to welcome her back to our department in 2015 as a faculty member. Our mentoring relationship will provide her with career development guidance and training in human subjects research and aspects of clinical trial design that are relevant to developing precision approaches in medicine. These elements are essential for her transition to independence.

She will meet at least quarterly with me. As a clinical trial expert, with extensive experience in designing and conducting clinical and translational research, I will mentor Jennifer in broad aspects of career development. Specifically, I will assist with research program development, project management, human subject trials design, manuscript preparation, and grantsmanship. As Vice Chair for Research in the Department of Pediatrics, I will coordinate with the Mitchell Cohen (Chair of the Department of Pediatrics), Dr. Steven Rowe, Director of the Cystic Fibrosis Research Center and Jennifer's primary research mentor, and the Division of Pulmonary and Sleep Medicine, to provide Jennifer's departmental funding to assist with equipment

purchasing, support staff salary support, research consumables, and other costs to supplement funds provided by the K23, as described in her detailed budget.

Dr. Guimbellot's plan for her career development includes formal and informal settings for training. During the period of this award, in addition to specific research training outlined in Dr. Rowe's letter and her training plan, she will focus on grant and manuscript preparation and review, scientific ethics, interviewing and negotiating skills, mentoring and laboratory management. All of these topics are covered in seminars and formal coursework here at UAB. Jennifer will meet quarterly with each of the other members of her scientific advisory committee, and convene the entire committee for presentation of progress and group feedback twice yearly for formal presentation and constructive criticism. She has clearly demonstrated a capacity for excellent productivity, as she has just two manuscripts accepted and in press, and one additional first-author publication has been re-submitted after initial peer review. She also has two additional manuscripts in preparation, soon to be submitted for peer review. Her achievements are particularly impressive given the fact that she accomplished them despite a significant change in research direction while participating in a clinical fellowship; changing institutions to establish her own research program; and taking time out for maternity leave on two separate occasions during fellowship.

I have every confidence that Jennifer will achieve the goals of this application. I am looking forward to helping her develop into a mature and independent scientist, as I am sure she will be a leader in her field.

Sincerely,

David Kimberlin
Professor, Pediatrics
Co-Division Director, Pediatric Infectious Diseases
Vice Chair for Clinical and Translational Research
University of Alabama at Birmingham

Edward Acosta, Pharm.D.

Please allow me to express my enthusiastic support for Jennifer's research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This proposal is innovative and exciting and, if successful, will help to better understand the metabolism of CFTR modulators; provide insight into the variation in optimal efficacy among individuals taking ivacaftor monotherapy; and lead to improved strategies to gain maximal benefit from ivacaftor and combination therapies of which it is a part.

I am fully committed to serve as a co-mentor on this research project by providing expertise in pharmacokinetics and mass spectrophotometric detection of CFTR modulators. As the director of the Pediatric Pharmacology Laboratory and the UAB Comprehensive Cancer Center Pharmacometrics Core Laboratory, I have over two decades of experience in pharmacology, mass spectrometry, and a wide variety of pharmacokinetic modeling, particularly in children. I have extensive expertise in the use of mass spectrometry to detect low concentrations of small molecules in biological specimens. I am also a member of the UAB CF Center and have successfully collaborated with Dr. Rowe, including a co-authored publication of the first findings regarding ivacaftor metabolism in patients with chronic obstructive lung disease.

We have already established a collaborative relationship over the past year, having met three separate times over the past year to discuss experimental approaches to this and related projects. In order to solidify this advisory relationship during the course of this award, we will meet regularly at least quarterly to review data, discuss results, and plan experiments that are relevant to the rapidly evolving field of CFTR modulators. Dr. Guimbellot's extensive training as an MD/PhD in pediatric pulmonology, genetics, cell biology, and molecular biology will enable her to complete all aspects of this project and develop new strategies for the treatment of cystic fibrosis, and to understand basic mechanisms of ivacaftor metabolism and CFTR rescue. This forms the basis of her independent translational research program. In fact, we are preparing a manuscript detailing the methodology for quantifying CFTR modulators in biological specimens with Jennifer at this time.

My role is focused on pharmacometrics studies relevant to this and future projects, to help guide Dr. Guimbellot's training in these areas. I am confident that this proposal will be a success and I look forward to collaborating with Jennifer on this project.

Sincerely,

Edward Acosta
Professor and Director
Division of Clinical Pharmacology
University of Alabama at Birmingham

Emily Scott, Ph.D.

I would like to express my enthusiastic support for Dr. Guimbellot's K23 research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This builds on her previous studies translating them into relevant clinical applications. Her proposal will help fill significant gaps in the understanding of the metabolism and pharmacogenomics of CFTR modulators, a new class of drugs for which there is still little known. I would be pleased to serve as an advisor during this proposal and meet with her at least once yearly to discuss the project and review progress.

I have nearly two decades of experience in drug metabolism and pharmacology. My expertise in the structure and function of cytochrome P450 enzymes, has recently focused on pediatric drug metabolism by CYP3A7 vs. adult drug metabolism by CYP3A4/5. I believe this in-depth knowledge will complement the studies in this proposal to understand the role of CYP3A4/5 single nucleotide polymorphisms in the systemic and tissue-specific airway metabolism of ivacaftor and related compounds. Specifically relevant to Aim 2, we have been characterizing itraconazole and related azole inhibitors in adult CYP3A4 vs. infant CYP3A7. In doing such, we recombinantly express and purify these human (membrane) P450 enzymes, characterizing them with a variety of in vitro assays and structurally using X-ray crystallography. All of these are specific assets that would be available to Dr. Guimbellot if helpful at some point in her studies with ivacaftor, for future applications.

This project is novel, feasible, and consistent with the goals of the NIH. I believe that this project provides ample opportunities for future investigator-initiated proposals and contribution to the field of cystic fibrosis research. I am confident that this proposal will be a success and I look forward to advising Dr. Guimbellot further on this project.

Sincerely,

Emily Scott
Professor, Department of Medicinal Chemistry
University of Michigan

Hemant Tiwari, Ph.D.

I am enthusiastic to serve as a co-mentor for Dr. Guimbellot's career development proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." She is well suited to perform the research outlined in this proposal. The training plan she has devised will add significant skills to the use of pharmacogenomics in pediatric pulmonology and related fields. She has devised a research plan and career development approach that builds on her prior training and work, and will increase her skills for your transition to independence.

It has been a pleasure to advise her during the development of this proposal. I am pleased to guide her by providing expertise in statistical genetics. I have trained many students, post-doctoral scholars, and physician-scientists like Dr. Guimbellot as an advisor, as well as by directing local and national courses in statistical genetics. To facilitate this advisory relationship, I will meet with her quarterly each year during the project period to review data and help with statistical analysis of the genetic studies proposed in all three aims.

The pharmacogenomics studies of ivacaftor have applications beyond those described in this proposal and I expect it will yield preliminary data for additional proposals (R01 and similar) on CFTR modulators. I am confident that this proposal will be a success and look forward to a fruitful advisory relationship with Dr. Guimbellot.

Sincerely,

Hemant Tiwari

Professor, Department of Biostatistics
Director, Biostatistics Pre-Doctoral NHLBI Training Program
Director, Post-Doctoral NHLBI Training Program in Statistical Genetics

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Inmaculada Aban, Ph.D.

Please allow me to express my strong support for Dr. Guimbellot's research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This proposal is innovative and if successful, will help understand the mechanism uptake and processing of CFTR modulators, fill gaps in current understanding of CFTR dysfunction, and bring precision medicine to cystic fibrosis. I have already worked with Dr. Guimbellot on the development of statistical approaches to nasospheroid models, for which we have a manuscript recently resubmitted after initial peer review. We will continue our work together as she continues to develop this and other models as relevant to this application.

I would be pleased to serve as a co-mentor on the research project by providing expertise in biostatistical analysis of human subjects datasets. I have extensive expertise in the development of risk score models, which will significantly aid the development of better pre-clinical predictive tools. I am confident that this proposal will be a success and I look forward to a long and productive advisory relationship. To cement this relationship, I will meet with her at least twice yearly throughout the project period to review data, discuss statistical approaches and methodology, and perform ongoing calculations to ensure adequate recruitment for the goals of this study, and to estimate needs for future applications, including R01 applications.

Sincerely,

Inmaculada Aban
Professor, Biostatistics

Nita Limdi, Pharm.D., Ph.D., M.S.P.H.

Jennifer Guimbellot has my highest support for her career development proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." The work outlined in this is well suited to increase her research and career development skill set and portfolio to aid in her transition to independence. I am looking forward to serving as research and career development advisor during this proposal. Her project is directly relevant to my career goals and substantial expertise in pharmacogenetics.

My expertise in pharmacogenomics and personalized medicine will be helpful to expanding Dr. Guimbellot's basic and clinical skills to precision approaches to cystic fibrosis treatment. Her project will fill crucial gaps in knowledge regarding the novel class of drugs (CFTR modulators), increase understanding of the pharmacokinetics and pharmacogenomics of these drugs, and lead to improved efficacy among the cystic fibrosis patient population. This project will also provide her with crucial skills to develop rigorously validated biomarkers that have a high predictive capacity. In combination with her basic science background developing in vitro models and genetics, these skills will help her build an independent research program.

The proposal outlined in Dr. Guimbellot's application is well suited to future studies for K23 applications and ultimately, R01 applications. I am delighted to advise her on the next steps in her research program and career development. Specifically, I will meet with her at least once yearly to ensure appropriate research design and progress. I am excited to watch her develop her research program in pharmacogenomics and in vitro biomarkers, which has relevance and applications far beyond the studies described here and provides opportunities for professional growth, skill acquisition, and funding opportunities in the future. I am sure it will be a success.

Sincerely,

Nita A. Limdi
Professor, Department of Neurology

JOHNS HOPKINS
UNIVERSITY

Garry R. Cutting, MD
Professor, Pediatrics and Medicine
Aetna/U.S. Healthcare Professor of Medical Genetics
Director, DNA Diagnostic Laboratory
EMAIL: gcutting@jhmi.edu

Institute of Genetic Medicine
733 N. Broadway
BRB Suite 551/Room 559
Baltimore, MD 21205
PHONE: 410-955-1773/FAX: 410-614-0213

To: National Institutes of Health
Jennifer S. Guimbellot, P.I., Application to K23
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

October 1, 2017

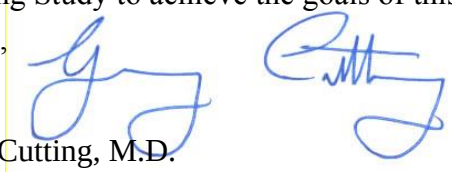
Dear Committee,

Please allow me to express my strong support for Dr. Guimbellot's proposal, *"Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients."* This proposal is innovative and exciting and, if successful, will help understand the mechanism of the metabolism of CFTR modulators, fill gaps in current understanding of CFTR modulators, and help bring new aspects of precision medicine to cystic fibrosis.

My career is focused on the causes of phenotypic variation in cystic fibrosis (CF). I direct the CF Twin and Sibling Study that has characterized the genetic contribution to varation to key CF traits and has resulted in sucessful identification of genetic loci associated with variation in these traits (NHLBI and CF Foundation funded). I also direct CFTR2, a worldwide-project to characterize the clinical and functional consequences of variants in the Cystic Fibrosis Transmembrane Conductance Regulator gene (*CFTR)*(NIDDK and CF Foundation funded). In recent years, Dr. Michael Knowles (at the University of North Carolina at Chapel Hill) and I have striven to understand genetic variation that influences the response of individuals to CFTR modulators, outside of mutations in *CFTR.* In this role, we have recently conducted a preliminary Genome-Wide Association Studies in a subset of patients with the G551D mutation (a gating mutation first identified as responsive to the CFTR modulator ivacaftor); we plan a more complete analysis with Dr. Guimbellot's mentor Dr. Rowe. These studies are highly compatible with the work that Dr. Guimbellot proposes in this application, as we found an association between three single nucleotide polymorphisms (SNPs) in *CYP3A5* (a cytochrome P450 enzyme involved in Ivacaftor metabolism) and Ivacaftor efficacy in our initial analysis. These three SNPs are inherited together and RNA expression data from the public resource GTeX indicates that all three SNPs influence expression of CYP3A5 in liver. This preliminary result needs to be replicated but it indicates biologic plausibility based on the predicted effect of variation in CYP function. Dr. Guimbellot proposes to pursue this concept in greater depth in her proposal. Thus the focus of her work addresses an important question in the treatment of individuals with CF that we hope will be further informed by GWAS and whole genome sequencing studies currently underway in CF subjects enrolled in modifier studies.

I am confident that this proposal is structured to determine the degree to which the metabolism of Ivacaftor affects response of CF subjects. The pharmacologic studies proposed by Dr. Guimbellot could provide a compelling biologic rationale to pursue the genetic and non-genetic causes of variation in Ivacaftor metabolism. I am delighted to be able to collaborate with Drs. Guimbellot and Rowe to genotype polymorphisms in CYP3A5 and related genes in the DNA obtained from GOAL participants. I can also meet with Dr. Guimbellot by teleconference or in person during my visits to UAB as an external advisor as required to help her interpret the data. In addition, I can assist with sequencing of CYP and other candidate genes, as well as genome-wide searches for causative loci. Finally, I am ready to provide genetics expertise and the resources of the CF Twin and Sibling Study to achieve the goals of this project.

Sincerely,



Garry R. Cutting, M.D.
Professor of Pediatrics and Medicine

Michael R. Knowles, M.D.
School of Medicine, UNC, Chapel Hill Marsico Lung Institute CF Research Center 125 Mason Farm Road; Room 7214, CB#7248 Chapel Hill, NC 27599-7248

Tel. (919) 966-6780 FAX: 919-966-5178; HIPAA FAX: (919) 966-7524
http://www.med.unc.edu/wrkunits/3ctrpgm/cystfib/Staff/knowles.htm

September 29, 2017

To: National Institutes of Health
RE: K23 Award, Jennifer Guimbellot
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

To the Review Committee

I am writing to express my most enthusiastic support for Dr. Guimbellot's research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients". I have ongoing research that interfaces with this project, and this proposal has the potential to improve our understanding of drug response to novel therapies for cystic fibrosis, which would be an enormous breakthrough.

I am very excited to serve as a collaborator on this proposal. I have over three decades of experience as a Professor of Pulmonary medicine at UNC-Chapel Hill. My laboratory studies the genetic modifiers of disease severity in cystic fibrosis, and I lead a Consortium across North America to study rare genetic disorders of mucociliary clearance. Recently, with Dr. Garry Cutting at Johns Hopkins University, we performed Genome-Wide Association studies in a subset patients with cystic fibrosis (CF) to understand genetic influences on the response of individuals to one of the new small molecule CF therapeutics (ivacaftor). During this study, we found an association of single nucleotide polymorphisms (SNPs) with ivacaftor efficacy. A key metabolism enzyme in Dr. Guimbellot's proposal, CYP3A5, was one of these, supporting her hypothesis that genetic variation in CYP3A5 may contribute to drug response. Her Aims are designed to not only support this association, but also to identify the mechanisms by which CYP3A5 and other metabolism enzymes may modulate the pharmacokinetics of the drugs in the blood and at the site of action in the cells. In addition, she proposes preliminary studies that may allow manipulation of the ivacaftor metabolism pathways to enhance efficacy, an approach used in other diseases including transplantation and retroviral therapy.

I knew Dr. Guimbellot as a Pediatric Pulmonary Fellow while at UNC, and I am delighted to support her continued development and excellent career trajectory as a researcher in CF precision therapeutics. I am committed to a collaborative relationship with Dr. Guimbellot and her primary mentor, Dr. Steven Rowe, who I know well and have supported from afar for many years. As part of this relationship, I will work together with them to genotype and/or sequence the genes of interest in the cohort of patients with CF that I study. Collectively, we will ensure the success of this project, and the continued development of this promising young scientist. Overall, I am hopeful this work could make a pronounced impact in our understanding of emerging and exciting CF therapies, and I believe it is an excellent project to support career development.

This project is novel, feasible, and consistent with the goals of the NHLBI. Further, this project provides ample opportunities for future investigator-initiated proposals and contribution to the field of cystic fibrosis research. I am confident that this proposal is feasible and will generate important new insights. I look forward to collaborating further with Dr. Guimbellot, and I urge you to give this proposal the most careful consideration.

Sincerely,

Michael Knowles, MD
Professor of Medicine, Division of Pulmonary/Critical Care Medicine
The University of North Carolina at Chapel Hill

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

The Heflin Center Genomics Core

To: National Institutes of Health
RE: Jennifer S. Guimbellot, P.I., Application to K23
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

October 1, 2017

Dear Jennifer,

As Director of the UAB Heflin Genomics Core, I am pleased to offer the Core's services for your K23 submission entitled "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." Your proposal is an interesting approach to bridging pharmacology with biomarker development, and increasing the scope of pharmacogenomics in cystic fibrosis modulator therapy beyond mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR)* gene.

Our facility offers an expansive array of services to the UAB community, several of which you have already utilized for preliminary data for your proposal. We offer single nucleotide polymorphism (SNP) detection, standard Sanger sequencing and Next-Generation sequencing (including whole exome profiling, whole transcriptome profiling, microRNA sequncing, methylation sequencing, custom capture and sequencing, and microbiome/metagenomic sequencing). For your proposal, we have provided consultant services in the design of targeted SNP analysis using SNaPShot® technology as well as the use of Sanger sequencing for more comprehensive variant detection in your population. The core has already had the pleasure of helping you design SNP genotyping assays to interrogate the genotypes of your cohort in a subset of CYP450 genes, CYP3A4 and CYP3A5. We have performed the SNaPshot assay from Life Technologies to identify targeted SNP variations in your cohort. The SNaPshot assay will allow us to interrogate 10 SNPs in one pool and has worked well on your preliminary samples and will complement Sanger sequencing for more comprehensive genetic evaluation. We look forward to a continued relationship as this project moves forward to help improve precision optimization in cystic fibrosis, especially as modulators are expanded to additional populations and ethnicities in which pharmacogenomics may play an even greater role.

We wish you the best with your application.

Sincerely,

Michael Crowley, Ph.D.
Associate Professor
Director, The Heflin Center Genomics Core

UAB CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

Knowledge that will change your world

October 1, 2017

Jennifer Guimbellot, MD
Assistant Professor
Department of Pediatrics
ACC 620

Dear Jennifer,

As Director of the UAB Center of Clinical and Translational Science (CCTS), I am pleased to offer the Center's full support (i.e., services, resources, and expertise) for your K23 submission entitled "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." The CCTS is strongly committed to training the next generation of clinician scientists, who are at the important intersection of clinical/basic questions and implementation. Your proposal, which aims to optimize treatment for cystic fibrosis by combining pharmacometrics, pharmacogenomics, and biomarker development, is an exciting proposal of translational science targeting precision medicine in an orphan disease.

As you are aware, the CCTS is supported through an NIH Clinical and Translational Science Award (CTSA, grant number UL1TR001417). As a member of the CCTS, you can continue to utilize the CCTS to further your research and career development during this award. Among the many opportunities we offer, the following may be specifically helpful to this proposal:

1. Access to our Panels Done Quickly, grant workshops and mock study sections for proposal development and formal NIH-style reviews.
2. Peer learning opportunities offered by TIERS (Training Interdisciplinary and Emerging Research Scholars) where we promote problem solving, exchange of ideas, and collaborations for recipients of K-type career development awards at UAB. The TIERS Seminars will provide training in team management, conflict resolution and negotiation, grant management, budgeting, and life balance.
3. Four seminars – a) Faculty Biostatistics Forum; b) Research Methods and Secondary Data Analysis Seminar Series; c) Work-In-Progress Seminars; and d) Health Disparities Seminar Series – will offer ongoing training and networking opportunities.
4. Research design support through our Biostatistics, Epidemiology and Research Design (BERD) Group where we provide support during the design and initial implementation phases through the transition into funding and execution. We also offer Biostatistics Drop-in Clinics to assist you with methodological questions, manuscripts, responses to peer reviews, published articles, etc.

The goal of the CCTS is to help build effective translational research programs. We look forward to working with you and your mentors on this important undertaking. Best wishes for your application.

Sincerely,

Robert P. Kimberly, MD
Howard L. Holley Professor of Medicine
Director, UAB Center for Clinical and Translational Science
Senior Associate Dean for Clinical and Translational Research, UAB School of Medicine
Associate Vice President for Medicine and Biomedical Research

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CCTS
Center for Clinical and Translational Science

Mailing Address:
PCAMS 111
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Web: www.uab.edu/ccts

To: National Institutes of Health
RE: Jennifer S. Guimbellot, P.I., Application to K23
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

October 09, 2017

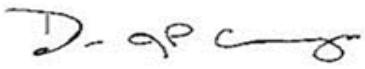
Dear Dr. Guimbellot,

We are glad to support your proposal “Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients” as potential collaborators for your pilot clinical study evaluating ivacaftor PK/PD relationships in patients with the G551D mutation. While we understand that your proposal may not need additional sites to assist with enrollment, we also acknowledge that clinical research includes some uncertainties that could make it necessary to increase the number of subjects available. To that end, we at the Cystic Fibrosis Therapeutics Development Network (TDN) are glad to support you by helping to identify and coordinate potential additional sites if needed. Supporting junior investigators is an important part of the work we do at the TDN and your study may yield important results for CF patients. We understand that the study involves 3 visits for CF patients with the G551D mutation who are taking ivacaftor, are clinically stable, and will require one intensive PK visit and two additional visits for nasal cell procurement. Our center is facile with these methods, and can readily contribute patients if helpful.

We wish you the best of luck with your proposal, and we look forward to the opportunity to collaborate with you and Dr. Rowe as your mentor on this or future studies.

Sincerely yours,

Scott D. Sagel, MD, PhD
Professor of Pediatrics
Director, University of Colorado Cystic Fibrosis Center
Director, University of Colorado Pediatric Clinical Translational Research Center Core Laboratory
Children’s Hospital Colorado
University of Colorado School of Medicine



JP Clancy, MD
Professor, Gunnar Esiason/Cincinnati Bell Endowed Chair, and
Director of Pulmonary Medicine Research
Cincinnati Children’s Hospital Medical Center
University of Cincinnati
Cincinnati, OH
Phone: 513-636-0325
Email: john.clancy@cchmc.org

UAB SCHOOL OF MEDICINE
Hugh Kaul Personalized Medicine Institute

To: Jennifer Guimbellot
RE: K23 Award, National Institutes of Health
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

October 1, 2017

Dear Dr. Guimbellot,

You have my enthusiastic support for your career development proposal, “Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients.” Using pharmacogenomics of drug metabolism to pinpoint variation in ivacaftor efficacy will help optimize drug response on an individual basis and has the potential to further increase patients’ lifespans. The personalized nasospheroid model described in your proposal is an exciting advancement in *ex vivo* cell culture models, as it has the potential to measure CFTR-dependent fluid transport on an individual basis. Combining this novel model with pharmacometrics will elevate the development of precision biomarkers in cystic fibrosis.

As the newly appointed director of the Hugh Kaul Personalized Medicine Institute (PMI) at the University of Alabama at Birmingham, I am thrilled you have chosen to focus your career on the intersection of genetics and precision therapeutics. The PMI is very active in supporting the CF Center under your mentor Dr. Rowe’s leadership, thus we will be glad to assist you in any way possible, including tapping into our faculty who lead pharmacogenetics projects in other diseases. The fact that your work is applicable to diseases beyond cystic fibrosis, and your enthusiasm for bridging research disparities to children and adults with rare diseases, makes it a welcome addition to our program. The PMI has dedicated funds to build an administrative infrastructure to improve grant acquisition and administration; support training initiatives in personalized medicine; and to acquire a biobank of DNA samples for use as a tool by PMI investigators. I am eager to collaborate with you and others in the CF Center as you build your research program.

I am excited to watch you develop your research program on *ex vivo* precision medicine and pharmacogenomics, which has relevance and applications beyond the studies described here and provides opportunities for professional growth, skill acquisition, and funding opportunities in the future. This project is novel, feasible, and consistent with the goals of the K23. I am sure your proposal will be a success.

Sincerely,

Matthew Might

858 Faculty Office Tower
510 20th Street South
205.996.1489
Fax 205.934.0333

The University of
Alabama at Birmingham
Mailing Address:
FOT 858
1720 2nd Ave S
Birmingham, AL 35294-3412

The University of Alabama at Birmingham (UAB). Dr. Guimbellot's institution offers 133 degree programs including doctoral and professional degrees, with an emphasis on medicine and research. UAB has maintained status with the Carnegie Foundation as a doctoral university with "**highest research activity**." It ranks **15th in federal research funding** among public universities with grants and contracts exceeding **$452 million** (FY2016). Particularly important for Dr. Guimbellot's career development and research, UAB has recently formed three new research entities in **genomic medicine, precision medicine and informatics**. It also offers 23 University-Wide Interdisciplinary Research Centers (UWIRCs) and over 80 core facilities, supporting a collaborative environment recognized by *The Scientist* as one of the Top 5 Best Places to Work in Academia.

Gregory Fleming James Cystic Fibrosis Research Center (CFRC). Established in 1981, the UAB CFRC was the first in the U.S. to receive a Research Development Program grant from the Cystic Fibrosis Foundation (CFF). Since its inception, the CFRC has maintained continuous CFF and NIH funding, and is **one of a handful of centers in the country funded through the CFF RDP (**ROWE15R0), as well as an NIH P30 (DK072482). Today, the CFRC is a UWIRC with total direct annual funding of **$21 million** and has a **major emphasis on the development of physician-scientist junior faculty.** It houses over 110 faculty, including Dr. Steven Rowe, primary mentor to this application. The CFRC is known world-wide as a leader in cutting-edge cystic fibrosis (CF) research, as key players in the development of novel therapeutics and technologies (i.e., CFTR modulators and μ-optical coherence tomography). The CFRC is collaborative with the Cystic Fibrosis Care Center at Children's of Alabama and UAB, caring for approximately 500 patients. Notably, the CFRC is **one of only six National Resource Centers** within the CFF Therapeutics Development Network (clinical research centers across the U.S. that focus on CF clinical trials). The CFRC maintains **five core facilities** to support studies in primary cell culture, cell biology, ion transport and translational research in CF. As an Associate Scientist in the CFRC, Dr. Guimbellot has access to all of these resources.

Department of Pediatrics and Children's of Alabama (COA). As the only Children's Hospital in the State of Alabama, COA and the Department provide access to a large pediatric population. The Department's focus on research is evident in its steadily increasing research accomplishments and funding, totaling $17.5 million from NIH (12th among all Departments of Pediatrics, FY 2016) and overall research funding of nearly $30 million. The Department supports the Pediatric Research Office (providing biostatistics – including Dr. Aban, advisor to this proposal, bioinformatics, proposal preparation, regulatory assistance and research coordination) and the Child Health Research Unit (2,547 sf housing exam rooms, equipment, and office space for clinical studies), as well as a satellite unit with a primary focus on CF research. Dr. Guimbellot's career development mentor, Dr. David Kimberlin, is Vice Chair for Clinical and Translational Research for the Department.

UAB Comprehensive Cancer Center Pharmacometrics Core Laboratory and Pediatric Pharmacology Laboratory. Led by Dr. Edward Acosta, advisor to Dr. Guimbellot's proposal, this Core supports pharmacokinetic/pharmacodynamic analysis of pre-clinical and clinical studies. Dr. Acosta's laboratory has over 20 years' experience conducting pharmacometric studies, with particular expertise in pediatrics, antivirals, antiretrovirals, cancer-related drugs and CFTR modulators. In collaboration with the CFRC, this Core has expanded mass spectrometry assays to quantitate ivacaftor and its metabolites; lumacaftor; and tezacaftor – with the capacity to add additional drugs to the assays as they become available. These methods can detect drugs in multiple human tissues (plasma, urine, CSF, tissue, intracellular). For regulatory purposes, the Core can perform these services under Good Laboratory Practices and operates under CLIA and HIPAA standards.

Heflin Center for Genomics Sciences. This UWIRC was established in 2002 to provide training and resources to enhance the use of genomics and genetics across UAB's campus. The Center provides ongoing training and seminars for education. It houses the Genomics Core Laboratory, which is key to Dr. Guimbellot's proposal, and includes cutting-edge equipment to provide Next Generation Sequence analysis, whole genome and targeted gene expression analysis, high- and low-throughput whole genome and custom genotyping, among other resources. The Center maintains partnerships with the Section on Statistical Genetics (of which Dr. Tiwari, advisor to this application, is a key member); the Center for Clinical and Translational Sciences (UAB's CTSA); the HudsonAlpha Institute for Biotechnology (HAIB); the UAB-HAIB Center for Genomic Medicine; the Kaul Personalized Medicine Institute and others to expand resources to investigators.

Center for Clinical and Translational Sciences (CCTS). UAB's CCTS is funded by a Clinical and Translational Science Award (CTSA) from the NIH (UL1TR001417). Dr. Guimbellot has been a member of the CCTS since 2015. A key mission of the Center is to develop junior investigators, including establishment of a K-club to improve publications, research funding and career planning. The CCTS provides robust resources in monthly seminars and workshops (mentoring, ethics, scientific writing) and access to expertise in all aspects of research (biostatistics, bioinformatics, research methodology, data analysis, regulatory approvals).

UAB MEDICINE
PEDIATRICS

Children's of Alabama

Institutional Commitment to Dr. Guimbellot' s Career Development:

It is my pleasure to provide strong institutional commitment to Jennifer G. Guimbellot's application for a K23 Mentored Patient-Oriented Research Career Development Award. Dr. Guimbellot is bright and innovative. Her particular interest in bringing precision medicine advances to cystic fibrosis patients is aligned with our institutional initiative. As a successful K23 recipient, Dr. Guimbellot will combine her formal training in pulmonology and genetics into a project that will expand precision medicine in pulmonary disease and simultaneous provide her with key training and research data that will facilitate her transition to independence.

The Department of Pediatrics was fortunate to recruit her as a full-time Assistant Professor into the Division of Pulmonary and Sleep Medicine. The Department of Pediatrics wholly supports her research without reservation and has confidence that she will succeed in the goals of the K23 application. To this end, we provided Dr. Guimbellot with salary support and additional start-up funding of over $440,000. . Given her progress, we intend to sustain this financial commitment to cover the costs of her proposal beyond that supported by her primary research mentor and external funding, including the K23 award. Her continued appointment and support is not contingent on receipt of this award. Dr. Guimbellot will devote at least 75% of total effort to her research project and career development activities. As part of her generous faculty start-up package, she has dedicated research space, support for her laboratory technician, substantial assistance from the CF Research Center at UAB (including support from Core Facilities), and access to additional departmental and institutional resources to assist with her career development, grants management and professional progress. She has established her laboratory in her designated research space of ~530sq ft, supplemented by access to 10,000 sq ft within the CF Center, where she will continue to base her research throughout the course of this award. She has access to all facilities, equipment, and other resources required to complete the research and training outlined in the proposal. In addition, Dr. Guimbellot has a research office, appropriately outfitted with computers, printers, phones, which is down the hallway from her primary mentor and adjacent to her laboratory space, as well as office space and equipment for her research staff.

The Division of Pulmonary and Sleep has provided an additional office, with allocated computer and office equipment, for Dr. Guimbellot located within the division's clinical space. There she has additional staff support, including administrative, nursing, ancillary care, and research coordination. Her proximity to the other members of the Division facilitates communication and coordination of the research proposed. She has full-time access to the real-time electronic medical records of Children's of Alabama and the University of Alabama at Birmingham. This will enhance identification of potential subjects and recruitment. She also has access to our recently renovated Child Health Research Unit and the full support of the Pediatric Research Office, including an informaticist, biostatistician, and grants administrators supported jointly by the Department and the University's successful CTSA award.

Dr. Guimbellot is already devoting ~75% protected time to her research. This is comprised of ½ day per week in clinic at Children's of Alabama and five weeks on the inpatient pulmonary service. Upon funding of this award, no more than 25% of her time will be devoted to patient care, administration, and teaching.

I enthusiastically support the application of Jennifer Guimbellot, M.D., Ph.D. for this K23 award. She will be an exceptional leader in her field. As we expected, her productivity has recently significantly increased as her laboratory has become established at UAB. I have every expectation that she will achieve academic success and am committed to fully supporting her during and beyond this award to achieve her goal of becoming a highly productive and independent physician-scientist.

Mitchell B. Cohen, MD
UAB Department of Pediatrics, Office of the Chair, Lowder Suite 600
1600 7th Avenue South, Birmingham, Al 35233 tel 205-638-9650 fax 205-934-1150 www.uab.edu/medicine/ peds

Human Subjects Involvement, Characteristics, and Design

This proposal involves the recruitment of 40 subjects with cystic fibrosis (CF); 20 subjects in Aim 2 and 20 subjects in Aim 3. However, as described in the methods we may need to readjust this recruitment goal as estimates are revised based on statistical analysis, and I anticipate potential recruitment of an additional 20 subjects, for a maximum of 60 expected subjects. Involvement will be limited to the collection of nasal epithelial biopsy for culture, phlebotomy, and limited collection of PHI. Study visits will be coordinated with visits for clinical indications where feasible, but also independently in the Child Health Research Unit of Children's Hospital of Alabama.

All procedures for the collection of human samples and use of these samples for cell culture and drug quantitation have been approved by the University of Alabama at Birmingham Institutional Review Board. We are already in the process of submitting a new protocol specific to the procedures outlined in this proposal, primarily to reflect the pharmacokinetic studies (requiring repeated phlebotomy).

Inclusion criteria for CF subjects include: 1) documentation of CF diagnosis per CFF diagnostic criteria and known CFTR genotype; 2) age 6 months to 75 years; 3) ability to provide written informed consent and/or assent (by subject and/or legal guardian)

Exclusion criteria include subjects with CF who have a history of a bleeding disorder or a history of nasal surgery within the past 6 months.

Rationale for Involvement of Vulnerable Populations
Children under the age of 21 years with and without CF will be recruited for this program. Children with CF represent a large part of the CF population and are already recipients of CFTR modulator therapy. Those with gating mutations over the age of 2 years have already started on an expected lifetime of therapy with ivacaftor, and F508del homozygotes 12 years of age and older are already on this therapy. In addition, drug metabolism may also be significantly different in children, which will be essential to understand to maximize therapies in this age group. Therefore, recruitment of children to this study will provide benefit to both the success of the study, as well as allow some degree of assessment of differences in assay that may be related to the age of the patient, which would be further explored in future applications. The study will be explained in detail to parents and subjects and informed consent will be obtained. Assent for children ages 7-17 will also be obtained.

Collaborating Sites
There are no collaborating sites at this time, but are prepared to modify this if required to meet our enrollment objectives.

SOURCES OF MATERIALS
Human subject specimens in this proposal are limited to nasal epithelial cell biopsy via curettage or brushing and whole blood samples collected in EDTA tubes for plasma and buffy coat separation. These samples will be collected as described in the approach section under IRB approved protocols. The specimens will be cultured and portions of either primary tissue or passaged cells will be frozen for future study as per IRB approved protocols. Protected health information to be collected includes CFTR genotype (if subject has a diagnosis of CF), age, gender, BMI, FEV1, sweat chloride.

Potential Risks
The procedure confers risk of minor, temporary bleeding from the nose or phlebotomy site, which is managed by pressure for 5-10 minutes. Nasal brushing may cause discomfort, which will be minimized by using small brushes most appropriate to the patient size (brushes 2-5mm in diameter), oxymetazoline for vasoconstriction and ease passage of the brushes, and topical lidocaine for numbing.

Adult and pediatric subjects will be approached for collection. The nasal brushing and phlebotomy procedures are commonly used for diagnostic purposes in this age group (i.e., primary ciliary dyskinesia). For all ages, the procedures may take place while the patient is sedated for clinically-indicated procedures. In these cases, participation in this study will not substantially alter the methodology, duration, or risks of the sedation. While there are well defined risks to sedation, participants will be exposed to these risks regardless of their

participation in this study. Subjects who agree to participate without sedation will be exposed to the risk of transient discomfort that passes after procedure is complete after approximately 2-5 minutes.

As part of the IRB protocol, we will be collecting protected health information on subjects, and there is the potential risk of inadvertent dissemination of this information.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent

Potential CF subjects for this study will be identified during regular review of the bronchoscopy, lung function testing, admission, and clinic schedules for Pediatric Pulmonary, and the clinic schedules and admissions for the adult CF clinic. Potential subjects and/or their families will be approached by telephone, in the clinic, or in the hospital setting for informed consent.

Informed consent will be obtained from subjects and their families using IRB approved protocols. For children 7 years or old and older, parental/legal guardian written consent and written assent from the child will be obtained. For adults and children who have reached the age of majority or are legally emancipated, an adult consent form will be used and no parental permission will be obtained. Children who refuse to assent to the study will not been enrolled. All consents will be obtained by appropriately trained, IRB approved individuals connected with the study. Study information and consent forms will be reviewed with the study subject and his/her parent or guardian, as appropriate, and a copy of the IRB-approved consent and assent forms will be provided. After having the chance to consider the trial and all questions/concerns are addressed by the research coordinator, Investigator, and/or another member of the study team, the parent and/or child may be verbally "quizzed" about the study in order to confirm their understanding of it. The consent forms will then be signed and dated and a copy will be given to the parent and/or subject. A Consent Process Checklist Form will be filled out by the member of the study team obtaining consent and filed with the consent forms.

Subjects will be recruited for an anticipated one-time consent. For those enrolled in Aim 3, pharmacokinetics study, will undertake nine blood samplings and one brush biopsy at Visit 1; Visits 2 and 3 will require a single blood sampling and collection of the nasal epithelial biopsy each. There is a chance that some subjects may be approached for recruitment a second time, but only if initial collection fails for the proposed studies and we are unable to identify a similar subject for recruitment given the rarity of certain mutations. The same procedures for re-recruitment will apply, including a new consent, and only a single additional study visit would be required.

Protection Against Risk

Risks for participation in this study are minimal. There is a small risk of slight bleeding from the nasal epithelial brushing , which does not occur in most patients. Subjects with a history of a bleeding disorder or a history of nasal surgery within the past 6 months will be excluded to protect against this risk. If bleeding occurs, it will be treated by squeezing the tip of the nose for 5-10 minutes. There is also transient discomfort associated with this procedure in a conscious patient, which is described during the consent process. To protect against this risk, only highly trained personnel conduct the biopsy and subjects may withdraw at any time. Subjects who are sedated will not experience this discomfort because they will be receiving clinically indicated sedation for a clinically indicated procedure that is being concomitantly performed. This is a small risk of discomfort and bleeding from the phlebotomy site, which will also be treated with pressure for 5-10 minutes.

Subjects who are undergoing a clinically indicated procedure requiring sedation will be enrolled. There are risks to both the clinically indicated procedure and related sedation. These risks are specific to the relevant clinically indicated procedure and are controlled using standard clinical protocols. Such risks will be assumed by the subjects regardless of participation in the study.

The most significant risk to participation is the risk of inadvertent release of protected health information (PHI). To minimize this risk, all subject research records containing PHI will be stored in locked offices and/or secure computer files. All study samples will be identified with a study number or code and initials. The master list that links the subject’s name to their study number or code and initials will be stored in a secure UAB CF research office and/or on a secure computer. Only the principal investigator and members of the study team approved by the IRB will have access to this information.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The individual participants we plan to enroll in this proposal will not directly benefit from their participation in this study. The increased risks to these individuals are very small and are greatly outweighed by the potential long term benefits to the population under study.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Understanding pharmacogenetic variation and personalized CFTR modulator response is crucial to the optimization of the use of these novel compounds; expansion to all patients who might benefit from them; and development of predictive biomarkers. In addition, the ability to determine *a priori* those individuals who will or will not respond to existing therapies will avoid needless risk of side effects and the high cost of a potentially ineffective treatment regimen. Understanding the way these drugs work in the body and the best way to study them and the downstream effects is critical to expanding the use of these drugs to all patients with CF. We feel the minimal risks involved in participating in this study are reasonable given the importance of the potential knowledge to be gained by conducting the study.

Data Safety Monitoring Plan

All data safety and monitoring will be performed by the Principal Investigator (PI). If any unanticipated adverse event or serious adverse event occurs that is related or possibly related to study procedures, trial procedures will be immediately halted, and notice sent to the IRB. If any events are thought to pose a risk to previously enrolled individuals, all efforts will be made to notify all affected study subjects.

Inclusion of Women and Minorities

While we plan to enroll an equal number of male and female subjects, the small number of participants required and the inclusion of a subgroup with a rare mutation may affect our ability to have entirely equal populations on the basis of gender. We will make every effort to balance our population on the basis of gender and will not exclude any potential subject on the basis of gender. We also plan to include individuals of all racial and ethnic groups and will not exclude any potential subject on the basis of race or ethnicity. However, given that cystic fibrosis (CF) affects predominantly those of Caucasian descent (91% Caucasian, 5% African American, and 4% Hispanic at our institution), it is likely that minorities will be underrepresented in our enrolled subject groups relative to the U.S. population.

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number:0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title:** Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients

***Delayed Onset Study?** ❑ Yes ☑ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☑ Planned ❑ Cumulative (Actual)

Using an Existing Dataset or Resource ☑ Yes ❑ No

Enrollment Location ☑ Domestic ❑ Foreign

Clinical Trial ❑ Yes ☑ No

NIH-Defined Phase III Clinical Trial ❑ Yes ☑ No

Comments: Note that an existing dataset with biological specimens will be used for part of this study, including 207 distinct individuals information and specimens. The following table reflects only those subjects planned to be enrolled prospectively for Aims 2 and 3 of this study.

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					0
Asian	0	0		0	0					0
Native Hawaiian or Other Pacific Islander	0	0		0	0					0
Black or African American	3	2		3	2					10
White	18	17		4	3					42
More than One Race	3	3		1	1					8
Unknown or Not Reported										
Total	24	22		8	6					60

Inclusion of Children

Both children over age 6 months and adults will be included in this study. Children comprise a substantial portion of patients with CF and studies on tissue samples from them are essential to assay development and understanding modulator efficacy among the entire CF population. While nasal epithelial brushing and phlebotomy cause some minor discomfort, they are used routinely in clinical practice on children of all ages. In our clinic, we have found that children tolerate both procedures, as shown by the clinical use of nasal epithelial brushing for diagnostic purposes (i.e., for primary ciliary dyskinesia diagnosis). Phlebotomy is routine for many indications in children. Because of this, children will be offered the opportunity to participate but will have the ability to refuse without impact to any aspect of care. All children enrolled in this study will be evaluated and specimens collected in the clinical setting, including the operating room and procedural suites, with appropriate personnel including anesthesiologists and nurse anesthetists, registered nurses, and pulmonary physicians. The specimens from subjects who are children are collected only by trained pediatric pulmonologists, respiratory therapists, and phlebotomists who have extensive experience working with children as young as birth in a clinical setting. Because of the preliminary nature of assay development proposed in this application, specimens collected from children will not be analyzed as a separate group. Therefore we have not designated a specific number of children to include. However, based on past experience, we expect to enroll approximately half of our total subjects among the pediatric population.

SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **03/30/2018**
Revised Date:

Application Number: **1 K23 HL143167-01**

Principal Investigator

GUIMBELLOT, JENNIFER S

Applicant Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Review Group: **MPOR (MA)**
NHLBI Mentored Patient-Oriented Research Review Committee

Meeting Date: **02/22/2018**
Council: **MAY 2018**
Requested Start: **09/01/2018**

RFA/PA: **PA16-198**
PCC: **LLAI N**

Project Title: **Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients**
SRG Action: **Impact Score:46**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **1A-Both Children and Adults, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	160,200	173,016
2	160,200	173,016
3	160,200	173,016
4	160,200	173,016
5	160,200	173,016
TOTAL	801,000	865,080

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1 K23 HL143167-01 GUIMBELLOT, JENNIFER

RESUME AND SUMMARY OF DISCUSSION: This is a new K23 application from Dr. Jennifer Guimbellot in which she has proposed a mentored research career development plan investigating the role of genetic variation of cytochrome P4503A in ivacaftor metabolism and variability in therapeutic response in patients with cystic fibrosis. The Candidate is well trained but her record of academic output is lower than would be expected. The Career Development Plan is well developed and tailored to her career goals and the research proposed except for training in basic pharmacological principles and pharmacogenetics. The Research Plan is well thought out, but there are weaknesses in design, thought to be the result of a poorer foundational knowledge of pharmacology and pharmacogenetics, and the study is not statistically robust. The mentors and environment are ideal. While the research plan has numerous weaknesses, the reviewers were confident that with guidance from the excellent mentors and supportive environment, the Candidate will be successful.

DESCRIPTION (provided by applicant): Cystic fibrosis (CF) is an autosomal recessive disorder caused by dysfunction of the CF Transmembrane Conductance Regulator (CFTR) channel. The care of patients with CF has rapidly evolved with the development of CFTR modulators, novel pharmaceuticals that address the basic CF defect and restore CFTR function. Despite the success of one of these, the potentiator ivacaftor, there is still pronounced variance in drug efficacy, as measured in individuals' phenotypic response to therapy and there in vitro cellular response when assessed with cell-based biomarkers. Ivacaftor is metabolized by cytochrome P450 (CYP3A enzymes), which are responsible for both hepatic and tissue-specific metabolism, including in airway epithelia. Genetic variation in these enzymes cause altered activity, resulting in variation in efficacy in many drugs. The preliminary data demonstrate CYP3A SNPs may be associated with drug efficacy, and the ability to detect ivacaftor metabolism in vitro in an individualized, cell-based format the applicant personally developed. To maximize efficacy of ivacaftor, and thus, any therapy including it, it is essential to understand pharmacogenetics and effect of variability of CYP3A enzyme activity on the metabolism of ivacaftor. The Specific Aims are: 1) to determine frequencies of genetic variants (single nucleotide polymorphisms) of these enzymes in the CF population and measure association with clinical efficacy; 2) measure intracellular concentrations of ivacaftor using mass spectrometry and quantitate the effect of altering concentrations of the drug on CFTR activity in a novel in vitro biomarker, using fluid transport as a surrogate endpoint; and 3) conduct a pilot study in people to determine population pharmacokinetics of ivacaftor in plasma and the intracellular space, and measure the effect on CFTR activity and in vivo drug response. Ivacaftor is a significant component of many combination therapies, so understanding its variation in metabolism and impact on efficacy as monotherapy is the first key step to understanding pharmacogenetics in complex combinations, and will set the stage for an independent career focused on precision-directed therapeutics in CF. The applicant has dedicated her professional life to becoming a physician-scientist, studying pediatric pulmonology in general and cystic fibrosis in particular. To achieve this, she accepted a faculty position at the University of Alabama at Birmingham, where a supportive research environment in the Department of Pediatrics and School of Medicine, as well as the Gregory Fleming James Cystic Fibrosis Research Center, has made career advancement and approach to independence possible. To accomplish the goals of this research, the candidate has assembled a mentoring team with decades of experience in clinical trials, pharmacology, genetics, statistics, pharmacogenetics, and drug metabolism to advise and guide her during her career development. She also proposes to undertake formal training in pharmacology, advanced statistics, clinical trial conduct, and genetics to complement her prior medical and graduate studies and acquire the relevant skills to transition to independence.

PUBLIC HEALTH RELEVANCE:
CFTR modulators are a novel class of therapeutic compounds, and this research will contribute significantly to the understanding of the metabolism of these compounds in patients with cystic fibrosis to optimize therapy and usher in an era of precision therapeutics. The findings will enhance efficacy of

CFTR modulator therapy for all patients with cystic fibrosis and help expand these novel therapies to all patients who might benefit from them. The knowledge gained in metabolism enzyme pharmacogenomics also has important implications for other diseases, including chronic obstructive pulmonary disease and asthma.

CRITIQUE 1:

Candidate: 3
Career Development Plan/Career Goals /Plan to Provide Mentoring: 1
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment Commitment to the Candidate: 1

Overall Impact:
The applicant has received previous training at the institution that led to a PhD. The training environment is excellent and the mentorship will be outstanding. Her research productivity has been somewhat limited during her pediatric training, but she recently has regained momentum after returning to UAB. The research program is well developed, but there are some concerns regarding the proposed experiments outlined in more detail below. Given the high quality of the environment and the excellent mentorship I expect that she will be successful even when there may be need to modify some of her proposed experiments along the way.

1. Candidate:
Strengths
- Excellent training in both Pediatric Pulmonology and Experimental Medicine.
- Successfully completed a PhD.
- Previous publication record in the field with 2 publications in the last year.

Weaknesses
- Research activity has been somewhat limited after completion of her PhD in 2008.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:
Strengths
- Top notch environment.
- Well-developed career development framework.

Weaknesses
- No significant weaknesses.

3. Research Plan:
Strengths
- Relevant topic related to CFTR modulator therapy.
- Well-structured experimental plan.
- Results could be directly translated into clinical care.

Weaknesses
- Preliminary data regarding the modifier gene approach in AIM 1 are mentioned, but not adequately presented. It is stated in the application that a preliminary GWAS for the GOAL study was performed. It is stated that these data support the concept that SNPs in CYP3A affect treatment response to ivacaftor in G551D study, but are not presented. Neither the LOD score for this finding nor the outcome measure of response that was chosen in this analysis are included, so it is not feasible to appreciate the strength of this association. Other genetic modifiers of ivacaftor response such as SLC 26A9 have been described (Strug L et al., 2016) and it is unclear how this would be accounted for in the study.

- Using inhibitors of CYP3A as an experimental approach seems to be unnecessary as there is no significant does limiting toxicity of ivacaftor and the medication could just be administered at a higher dose.
- The clinical study will be challenging regarding patient recruitment as the protocol is burdensome for patients and there might not be a perceived benefit.
- While this is certainly an important factor potentially affecting treatment response, the applicant fails to describe how they will deal with another important factor which is adherence to therapy.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths

- Excellent career mentors.
- Well-structured mentoring team for all aspects of the research program.

Weaknesses

- None

5. Environment and Institutional Commitment to the Candidate:
Strengths

- Excellent environment; this is certainly a strength of this application.

Weaknesses

- None

CRITIQUE 2:

Candidate: 4
Career Development Plan/Career Goals /Plan to Provide Mentoring: 3
Research Plan: 5
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment Commitment to the Candidate: 1

Overall Impact:
The dedication of the PI to addressing the needs of patients with CF and overall credentials of the PI are a strength of the application. Further, the research environment and faculty mentors involved in this project are also a significant strength and provide confidence that PI will benefit from these strengths.
The studies related to genetic variation in CYP3A are not well justified by the description and level of detail provided and lowers enthusiasm for this aspect of the proposed project.

1. Candidate:
Strengths

- The candidate Dr. Jennifer Guimbellot is currently an Assistant Professor in the Department of Pediatrics at the University of Alabama at Birmingham. Dr. Guimbellot has established research collaborations within the Cystic Fibrosis Research Center at UAB.
- The candidate has a great deal of experience and expertise in the study and treatment of cystic fibrosis.
- The candidate has an established record of successfully competing for research funding.
- The candidate has developed a novel in vitro model to measure CFTR activity in primary cultures and obtain information on individual patient responses to CFTR modulators.

Weaknesses

- The candidate’s record of publication has suffered somewhat as a consequence of her career transition, but this appears to be temporary based on the number of publications currently under review.

- There is a subtle indication in the application to suggest that the applicant does not have a complete grasp of the pharmacogenetics of the CYP3A4/5 system.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:
Strengths

- The candidate has identified a very talented team of mentors and advisors with expertise in the disease state of interest, Cystic Fibrosis, clinical trial design and oversight, statistics, pharmacometrics, and pharmacogenetics.
- The candidate will participate in formal courses in the areas of statistical genetics, massively parallel sequencing, pk/pd and correlation with biomarkers and biostatistical methodology.
- The candidate routinely attends relevant national scientific conferences including ASPET.
- UAB offers formal training support in the areas of biostatistics, epidemiology, research design and clinical trials. The candidate plans to participate in these programs.

Weaknesses

- It is not clear from the career development plan that sufficient training in basic pharmacological principles and pharmacogenetics has been planned.

3. Research Plan:
Strengths

- The primary culture of patients' nasal epithelial cells as nasospheroids and the ability to measure CFTR activity as a function of fluid transport is a significant strength of the application.
- The ability to measure ivacaftor concentrations in cells cultured in the presence of the medication is a strength. However, there does not appear to be any evidence that the drug or metabolites can be measured in the nasosphere cultures.
- Aim 3a of the proposal to measure intracellular concentrations of ivacaftor and its metabolites in nasal epithelial cells as well as in plasma at multiple time points is a well-designed approach with consideration given to all elements of patient preparation, timing and dosage.

Weaknesses

- There does not appear to be any consideration given to the frequency of CYP3A variants relative to the study design.
- The power analysis is very difficult to interpret, and the anticipated results are extremely vague given what is currently known regarding the frequencies of CYP3A4 and CYP3A5 alleles in the general population.
- Insufficient information is provided to suggest that the frequencies of CYP3A SNP's are different in patients with CF vs the general population.
- An example of concern regarding the PI's grasp of pharmacogenetics is the statement "Of particular interest, the non-expresser allele CYP3A5*3 was found as expected in ~70% of our predominantly Caucasian patients; however, the remainder were either wild type or heterozygote expressers" This statement is confusing at best. Are 70% CYP3A5*3 carriers, or are 70% *3 homozygous and therefore poor metabolizers?
- How will the investigators deal with mixed CYP3A4/CYP3A5 genotypes?
- Insufficient detail is provided to convince the reviewers that the study has sufficient power to achieve the Aim 1b goal of demonstrating association between specific SNP's and clinical response.
- The explanation for the hypothesis presented in Aim 2 does not corroborate the hypothesis. The PI provides an example that there appears to be a relationship between dose and response, however the context of the hypothesis appears to be that for standard dosing, variation in metabolic activity in the epithelial cells leads to variability in pulmonary drug response. These are very different circumstances.
- It is not clear that a sample of 20 patients will allow for meaningful insights into the influence of genetic variation of CYP3A on the drug or metabolite concentrations

- The experimental design of Aim 2 does not mention patient preparation, dosing or time of nasal epithelial cell collection relative to the most recent dose and verification that the patient is indeed at steady-state.
- Aim 2 does not mention measurement of patient plasma concentration of ivacaftor or its metabolites.
- Aim 3b. The PI does not provide sufficient information to convince the reviewers that they will be able to adequately address the question of CYP3A4/5 variability and genetic polymorphism on ivacaftor. There also seems to be a dislike in terms of the influence of this variation on plasma vs intracellular concentrations, as thought there would be no effect on plasma but effects would be measurable in the intracellular concentrations.
- The anticipated results are concerning. It is not clear why the PI would anticipate a low AUC12 to be associated with SNPs that cause low activity.
- The investigators do not address how they will deal with contributions to variation from the two CYP3A isoforms.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths

- The candidate's primary mentor is Dr. Stephen Rowe, Professor and physician scientist with an exceptional track record of mentoring physician scientists towards productive careers.
- The candidate has enlisted the support of a strong team of clinical and basic science investigators with the necessary skills needed to support the proposed career development plan.

Weaknesses

- Annual meeting with advisors may not provide the level of support needed relative to drug metabolism and pharmacogenetics.

5. Environment and Institutional Commitment to the Candidate:
Strengths

- The research environment and facilities at the University of Alabama Birmingham are excellent and provide the resources needed for all aspects of the proposed studies as well as the career development plans.
- Dr. Mitchell B. Cohen, Chair UAB Department of Pediatrics has provided a strong letter of support and commitment and has provided assurance of no less than 75% protected time for research.

Weaknesses

- No concerns.

Resource Sharing Plans: Unacceptable

- No resource sharing plans are presented

CRITIQUE 3:

Candidate: 2
Career Development Plan/Career Goals /Plan to Provide Mentoring: 1
Research Plan: 5
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment Commitment to the Candidate: 1

Overall Impact:
Overall, this application comes from a very strong candidate with an excellent set of mentors. The institutional environment and commitment are outstanding. The proposed training will help ensure that

she will become a highly successful clinician-researcher. There are some substantive concerns with the research approach, mostly dealing with statistical issues (i.e. sample size justifications and proposed analytical strategies).

1. Candidate:
Strengths
- Well educated (MD/PhD with pediatric pulmonary fellowship).
- 6 publications (3 recent)
- Recipient of 2 current foundation-funded studies as PI plus several other grants that are completed.
- The candidate is clearly passionate about CF, treating CF patients, and working on better therapeutics.

Weaknesses
- None

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:
Strengths
- The proposed coursework will suit the applicant well in terms of complementing her prior education, fitting in nicely with the proposed research.

Weaknesses
- None

3. Research Plan:
Strengths
- The aims fit nicely together and overall would provide the applicant with a strong research foundation on which to build in the future.

Weaknesses
- Aim 1: There is a notable error in the power calculation. To correct for 100 hypothesis tests, the Bonferroni-adjusted p-value threshold should be 0.0005 (=.05/100), not 0.005. This means that the study will have much less power to detect the stated effect sizes than what is currently stated.
- Aim 2. ANOVA will not be appropriate for comparing the use of inhibitors and effects on ivacaftor concentrations and CFTR function, since presumably the inhibitors would be applied to samples on the same subjects. A statistical technique such as linear mixed models will be necessary in order to account for the fact that observations made using the same subjects' samples will likely be correlated with one another.
- Aim 3. It isn't clear what is meant by "maximum effect regression".
- There is no justification for the proposed sample size within Aims 2 or Aim 3. The sample sizes may be a reasonable choice, but there should be better statistical justification provided, perhaps with some discussion that deals with widths of confidence intervals and/or statistical power.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths
- Overall a very strong team of mentors.
- Dr. Steven Rowe's letter is especially positive.

Weaknesses
- None

5. Environment and Institutional Commitment to the Candidate:
Strengths
- UAB has a strong research environment for this type of work. They currently have a number of large relevant grants (e.g. CF Research and Translation Core Center funded by NIDDK, and the

UAB Center of Clinical and Translational Science (CCTS), their Clinical and Translational Science Award)
- The institutional commitment is very strong. They have provided her with start-up funds and have protected 75% of her time for research.

Weaknesses
- None

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (RESUME): ACCEPTABLE

INCLUSION OF WOMEN PLAN (RESUME): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (RESUME): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (RESUME): ACCEPTABLE

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH: ACCEPTABLE

RESOURCE SHARING PLANS: NOT APPLICABLE (NO RELEVANT RESOURCES)

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES: NOT APPLICABLE (NO RELEVANT RESOURCES)

COMMITTEE BUDGET RECOMMENDATIONS: RECOMMENDED AS REQUESTED

Footnotes for 1 K23 HL143167-01; PI Name: Guimbellot, Jennifer S

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

NHLBI Mentored Patient-Oriented Research Review Committee
Heart, Lung, and Blood Initial Review Group
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
MPOR (MA)
02/22/2018 - 02/23/2018

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

PI: **Guimbellot, Jennifer S**	Title: Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients	
Received: 03/11/2019	FOA: PA19-119 Clinical Trial:Not Allowed	Council: 10/2019
Competition ID: FORMS-E	FOA Title: Mentored Patient-Oriented Research Career Development Award (Parent K23 Independent Clinical Trial Not Allowed)	
1 K23 HL143167-01A1	Dual:	Accession Number: 4283644
IPF: 1288803	Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM	
Former Number:	Department: School of Medicine	
IRG/SRG: MPOR (OA)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 159,400 Year 2: 159,400 Year 3: 159,400 Year 4: 159,400 Year 5: 159,400	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N HFT: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Hemant Tiwari	The University of Alabama at Birmingham	Other (Specify)-Co- Mentor
Inmaculada Aban	The University of Alabama at Birmingham	Other (Specify)-Co- Mentor
Emily Scott	University of Michigan	Other (Specify)-Advisor
NITA LIMDI	The University of Alabama at Birmingham	Other (Specify)-Advisor
Edward Acosta	The University of Alabama at Birmingham	Other (Specify)-Co- Mentor
Jennifer Guimbellot	UNIVERSITY OF ALABAMA AT BIRMINGHAM	PD/PI
Steven Rowe	The University of Alabama at Birmingham	Other (Specify)-Mentor
DAVID KIMBERLIN	The University of Alabama at Birmingham	Other (Specify)-Co- Mentor

Reference Letters

Victor Thannickal	University of Alabama at Birmingham	03/11/2019
Mitchell Cohen	UAB	03/11/2019
Eric Sorscher	Emory University School of Medicine	03/11/2019
Martina Gentzsch	University of North Carolina at Chapel Hill	03/11/2019

Terry Noah	University of North Carolina at Chapel Hill	03/11/2019

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
HL143167

b. Agency Routing Number

2. DATE SUBMITTED	**Application Identifier**	**c. Previous Grants.gov Tracking Number**
		GRANT12500590

5. APPLICANT INFORMATION **Organizational DUNS*:** 0636907050000

Legal Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: Office of Sponsored Programs
Division:
Street1*: 1720 2nd Ave South, AB 1170
Street2:
City*: BIRMINGHAM
County: AL
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 351240111

Person to be contacted on matters involving this application
Prefix: First Name*: Alice Middle Name: Last Name*: Harding Suffix:
Position/Title: Grants and Contracts Officer
Street1*: 1720 2nd Ave. South, AB 1170
Street2:
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352490111
Phone Number*: 205-996-9345 Fax Number: 205-975-5977 Email: aharding@uab.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1636005396A6

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*	**10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER**
National Institutes of Health	TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients

12. PROPOSED PROJECT		**13. CONGRESSIONAL DISTRICTS OF APPLICANT**
Start Date*	Ending Date*	AL-007
09/01/2019	08/31/2024	

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Jennifer Middle Name: S Last Name*: Guimbellot Suffix:
Position/Title: Assistant Professor
Organization Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: School of Medicine
Division: Pediatrics- Pulmonary
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Country*: USA: UNITED STATES
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15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$860,760.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$860,760.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Melinda Middle Name: T Last Name*: Cotten Suffix:
Position/Title*: AVP of Research Business Operations
Organization Name*: The University of Alabama at Birmingham
Department: Office of Sponsored Programs
Division:
Street1*: 1720 2nd Ave. South, AB 1170
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State*: AL: Alabama
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Country*: USA: UNITED STATES
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Phone Number*: 205-934-5266 Fax Number: 205-975-5977 Email*: OSP-NGA@mail.ad.uab.edu

Signature of Authorized Representative*
Alice Harding

Date Signed*
03/11/2019

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_letter.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	UNIVERSITY OF ALABAMA AT BIRMINGHAM
Duns Number:	0636907050000
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County:	
State*:	AL: Alabama
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	352940001
Project/Performance Site Congressional District*:	AL-007

Additional Location(s) File Name:

Funding Opportunity Number: PA-19-119. Received Date: 2019-03-11T14:45:25.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ❍ **Yes** ● **No**

IRB Approval Date: 01-08-2019

Human Subject Assurance Number 00005960

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Abstract.pdf
8. Project Narrative*	Project_narrative.pdf
9. Bibliography & References Cited	bibliography.pdf
10.Facilities & Other Resources	facilities_and_other_resources.pdf
11.Equipment	

Funding Opportunity Number: PA-19-119. Received Date: 2019-03-11T14:45:25.000-04:00

Cystic fibrosis (CF) is an autosomal recessive disorder caused by dysfunction of the CF Transmembrane Conductance Regulator (CFTR) channel. The care of patients with CF has rapidly evolved with the development of CFTR modulators, novel pharmaceuticals that address the basic CF defect and restore CFTR function. Despite the success of one of these, the potentiator ivacaftor, there is still pronounced variance in drug efficacy, as measured in individuals' phenotypic response to therapy and their *in vitro* cellular response when assessed with cell-based biomarkers. Ivacaftor is metabolized by cytochrome P450 (CYP3A enzymes), which are responsible for both hepatic and tissue-specific metabolism, including in airway epithelia. Genetic variation in these enzymes cause altered activity, resulting in variation in efficacy in many drugs. The preliminary data demonstrate CYP3A variants may be associated with drug efficacy, and the ability to detect ivacaftor metabolism *in vitro* in individual patients' epithelia that the applicant personally co-developed. To maximize efficacy of ivacaftor, and thus, any therapy including it, it is essential to understand pharmacogenetics and effect of variability of CYP3A enzyme activity on the metabolism of ivacaftor. The Specific Aims are: 1) conduct a pilot study in people to determine population pharmacokinetics of ivacaftor in plasma and epithelia, and correlate drug exposure with drug response 2) to determine frequencies of genetic variants of these enzymes in the CF population and measure association with clinical efficacy; 3) compare the contribution of CYP3A isoforms to ivacaftor metabolism and understand impact in primary epithelial cells on CFTR activity. Ivacaftor is a significant component of many combination therapies, so understanding its variation in metabolism and impact on efficacy is the first key step to understanding pharmacogenetics in complex combinations, and will set the stage for an independent career focused on precision-directed therapeutics in CF.

The applicant has dedicated her professional life to becoming a physician-scientist, studying pediatric pulmonology in general and cystic fibrosis in particular. To achieve this, she accepted a faculty position at the University of Alabama at Birmingham, where a supportive research environment in the Department of Pediatrics and School of Medicine, as well as the Gregory Fleming James Cystic Fibrosis Research Center, has made career advancement and approach to independence possible. To accomplish the goals of this research, the candidate has assembled a mentoring team with decades of experience in clinical trials, pharmacology, genetics, statistics, pharmacogenetics, and drug metabolism to advise and guide her during her career development. She also proposes to undertake formal training in pharmacology, advanced statistics, clinical trial conduct, and genetics to complement her prior medical and graduate studies and acquire the relevant skills to transition to independence.

CFTR modulators are a novel class of therapeutic compounds, and this research will contribute significantly to the understanding of the metabolism of these compounds in patients with cystic fibrosis to optimize therapy and usher in an era of precision therapeutics. The findings will enhance efficacy of CFTR modulator therapy for all patients with cystic fibrosis and help expand these novel therapies to all patients who might benefit from them. The knowledge gained in metabolism enzyme pharmacogenomics also has important implications for other diseases, including chronic obstructive pulmonary disease, pulmonary infections, and asthma.

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13. Derichs N. Targeting a genetic defect: cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. Eur Respir Rev 2013;22(127):58-65.
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16. Kapoor H, Koolwal A, Singh A. Ivacaftor: a novel mutation modulating drug. J Clin Diagn Res 2014;8(11):SE01-5.
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FACILITIES AND OTHER RESOURCES

All facilities and resources necessary to conduct the experiments described in this research proposal are already available in the clinical research units of UAB and COA, and the laboratories of Dr. Guimbellot, Dr. Rowe, and the UAB CF Research Center on MCLM 7th floor.

Children's Hospital of Alabama

Dr. Guimbellot has access to clinical research facilities at UAB and in the Child Health Research Unit (CHRU), a facility affiliated with the UAB Center for Clinical and Translational Science (S.M. Rowe and D. Feig, Co-Directors). Together they direct clinical research facilities at UAB and for the CHRU. The CHRU Satellite, which is dedicated solely to CF research and is nationally recognized for its research excellence in respiratory diseases, employs 4 research coordinators and a research technician. This facility includes an ancillary physician's office in proximity to the clinic, 4 patient examination rooms, and a nasal potential difference laboratory (2 setups, each capable of electronic and conventional data capture). This facility also houses a specimen processing lab (refrigerated centrifuge, microscope, hemocytometer, -80^{o}C freezers, pipettes, etc.). Further, the team operates a third potential difference apparatus dedicated and optimized for the measurement of Potential Difference at other anatomic locations such as the lower airway (LAPD). Each Potential Difference Apparatus includes 4/30 PowerLab Analog-Digital Converter (AD Instruments), Human grade bioamplifier (CWE), Isolation headstage (CWE), Laptop Personal Computer with Windows XP or better (Dell), KCl calomel electrodes, 60 mL Perfusion pumps (3 for LAPD rig, 5 for each NPD setup), and requisite tubing and disposables. Each of the 4 patient examination rooms are dedicated for research subjects and are fully-equipped for patient care (stethoscopes, illuminating rhinoscopes and otoscopes, patient tables, computers, open office space, etc.). Specialized equipment for CFTR clinical science are housed in the CHRU, including two sweat iontophoresis devices (each compatible with the Macroduct collection system), two sweat evaporimeters (Cyberderm RG), a carbon monoxide monitor, an Lung Clearance Index measurement device (EcoMedics) for use by the nitrogen washout technique, nasal and exhaled nitric oxide measurement (EcoMedics), two spirometers with calibration equipment (NSpire), an EKG machine, a Code cart, and general laboratory supplies. Medications and solutions used during the nasal and lower airway PD's are stored and provided through the Children's Hospital research pharmacy, which is experienced with ivacaftor administration to adults and children. The facility has a large body of experience conducting PK and PK/PD studies in CF patients, as proposed in Dr. Guimbellot's application.

UAB Pediatric Pharmacology Laboratory and Comprehensive Cancer Center Pharmacometrics Core

The UAB Clinical Pharmacology Laboratory and Division of Clinical Pharmacology is located on the second floor in room 258 of Volker Hall. The enclosed space consists of approximately 1700 sq. ft.; room 270 has 620 sq. ft., room 275 has 593 sq. ft. and room 280 has 287 sq. ft. The laboratory also has 200 sq. ft. of adjacent shared equipment space. The UAB Comprehensive Cancer Center PK/PD Core Laboratory is located on the first floor of Volker Hall and directly below the Clinical Pharmacology Laboratory and Division of Clinical Pharmacology. The Laboratory operates under GLP conditions, has been CLIA certified since May 2002, and undergoes regular inspections by the state agency. Laboratory personnel also participate in bi-annual proficiency testing rounds which are organized through the Office of HIV/AIDS Network Coordination. All of its assays used for ACTG studies are reviewed and approved by the Network. All laboratory personnel have undergone HIPAA training in addition to specialized training to handle infectious substances. The Laboratory currently has an LC/MS/MS assay that simultaneously quantitates 6 commonly used antiretrovirals; another that measures tenofovir, emtricitabine and their intracellular anabolites simultaneously; a method for nevirapine and maraviroc; and FDA-approved methods for raltegravir and dolutegravir. Other non-standard assays include measuring these drugs in various matrices, such as urine, CSF, genital secretions, breast milk, and tissue biopsies. Laboratory personnel have also developed methods to quantitate protein-free drug concentrations using equilibrium dialysis and LC/MS/MS. Other assays include acyclovir, ganciclovir, CMX001 and cidofovir, pleconaril, azithromycin, enfuvirtide, elvitegravir, cobicistat and oseltamivir. Drug assays in the PK/PD core include ABT-888, an orally bioavailable poly(ADP-ribose) polymerase (PARP) inhibitor, simultaneous measurement of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), VX770, metformin and a simultaneous method to quantitate estradiol, estrone, estriol and estetrol. Methods in development include MLN8237, dabigatran, prednisolone 21-acetate, and latanoprost. Individual pharmacokinetic data analyses and modeling is conducted on a Dell Latitude E6410 laptop computer with a docking station. This system runs Office Professional 2007 using the Windows 7 64 bit operating system. In

addition, the Laboratory has the necessary data analysis resources including: a Dell Optiplex 980, two Optiplex 780 systems, and a Precision T3500 - all Pentium III, IV, or dual processing; four additional laptop computers; an HP Color LaserJet 4600dn printer; and LaserJet 4100tn, 4050tn, and 2200dt printers. All lab personnel have internet access, and all necessary software, including the ADAPT 5 Package of Pharmacokinetic and Pharmacodynamic Modeling Programs, NONMEM (nonlinear mixed effect modeling) integrated with PDx-POP and S-Plus, the Pharsight package of Phoenix 6.4, and R software. Additional available computer software resources include: Microsoft Office 2010 (Word, Excel, PowerPoint, Access); Intel Visual Fortran Compiler Professional Edition 11.1.070 Update 8 for Windows; Intel Math Kernel Library 10.2 Update 7 for Windows; GraphPad Prism 5.0; and Adobe Acrobat 10.0.

Clinical Research Support Program (CRSP)

Dr. Guimbellot has access to CRSP personnel for regulatory and research coordinator support for her clinical studies. The CRSP has a pool of trained and certified research nurses and coordinators to assist with all aspects of conducting clinical studies, including data management, subject recruitment, regulatory adherence, and other issues. Dr. Guimbellot has an established relationship with the program and the research coordinators are already familiar with her protocols and studies.

Pediatric Research Office (PRO)

Dr. Guimbellot is supported by the PRO through her appointment in the Department of Pediatrics. The PRO provides assistance to investigators conducting pediatric research at Children's of Alabama. It provides pre-award and post-award support for funded investigators as well as those seeking funding or training. The Office's activities are well-integrated with other research and training efforts across the university. Office personnel provide special expertise in the pre-award stage with the completion of forms for the Office of Sponsored Programs and navigation of their systems. They also provide help identifying funding and training opportunities and with the planning and editing of applications, including editorial assistance. They ensure that guidelines are followed appropriately and provide assistance with informatics and with statistical planning and analysis.

Laboratory Facilities

Dr. Guimbellot has recently been upgraded to 655 sq. ft. of laboratory space in the Kaul Genetics Building and has continued access to the laboratory of her mentor (Dr. Rowe), which is next door to Kaul and directly connected via shared hallways. In addition, she has access to the UAB Cystic Fibrosis Research Center, also directed by Dr. Rowe, with over 13,000 sq.ft. of research space on the 7th floor of the McCallum Basic Health Sciences Building. Major capabilities relevant to this proposal include cell culture facilities including dedicated labs for primary human airway cell culture and multiple core facilities provided by the NIH P30 and the Cystic Fibrosis Foundation (CFF) Research Development Program, including the Clinical and Translational Core (Core C) co-directed by Dr. Rowe. Major resources within the Center support assays of CFTR and protein biology, including iodide efflux studies and Ussing chamber studies of cell monolayers and intact airway tissues. The lab is also fully equipped for protein biochemistry studies including Western blotting, protein isolation, and ELISA and other colorimetric assays. Dr. Rowe's laboratory also has all equipment necessary to conduct RNA isolation, real time and digital RT-PCR for precise and absolute mRNA quantitation, protein purification and isolation, and Western blotting.

Wet Laboratory of the Primary Mentor

Dr. Rowe has approximately 1370 sq. ft. of contiguous laboratory space in the McCallum Basic Health Science Building (MCLM 714, 725, 725A, 735, 736) and is also assigned multiple rooms within the CF Research Center (i.e., MCLM 791 for Ussing chamber studies, MCLM 789 for optical coherence tomography studies and other live tissue imaging, and MCLM 776 for high throughput screening using equivalent current/transepithelial conductance measurements). Major resources within his laboratory support assays of CFTR activity, including nasal potential differnece, iodide efflux studies, and Ussing chamber studies of cell monolayers and intact airway tissues. This includes an 18-chamber Ussing chamber apparatus with electronic data analysis (Physiologic Instruments) capable of monitoring cells or excised tissues. We also have a 24-channel conductance/equivalent current assay custom designed by R. Bridges (Rosalind-Franklin University) that is joined with an automated robot controlled assay head (Precise Automation) for high throughput evaluation of ion transport activity in cell monolayers. Laboratories are fully equipped for protein biochemistry, Western blotting, and ELISA and mRNA analysis by qPCR. Dr. Rowe directs the Clinical and Translational Core within the NIH P30. Capabilities of this core include primary human airway cell culture (including lung and sinus

origin) and conduct of clinical studies using CFTR related endpoints. Complementing this resource, Dr. Rowe is also Co-PI of the CFF Translational Therapeutics Development Network site, which specializes in CF related clinical trials, and he is the PI of the Center for CFTR Detection, which provides evaluation and analysis of a variety of potential difference measurements (e.g., nasal, lung) in humans throughout the world, quality assurance regarding these outcome measures, and training for operators throughout the TDN network.

Cystic Fibrosis Research Center

The CF Research Center at UAB is an accredited center for both adult and pediatric patients and is a designated University-Wide Interdisciplinary Research Center. It includes close to 500 patients, 95% of which are enrolled in the CF Registry. The CF Registry has been approved as a recruiting tool under UAB IRB approval X000509005 entitled “Cystic Fibrosis Center for Care, Teaching and Research.” The Center is a leading enroller in CF clinical trials through its performance in the CF Therapeutics Development Network (ranked No. 2 of 54 sites for enrollment, controlled for study complexity).

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Jennifer Middle Name S Last Name*: Guimbellot Suffix:

Position/Title*: Assistant Professor
Organization Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: School of Medicine
Division: Pediatrics- Pulmonary
Street1*: 1600 7th Ave. South, ACC 620
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Phone Number*: (205) 934-6066 Fax Number: 205-934-7593

E-Mail*: GUIM@UAB.EDU

Credential, e.g., agency login: GUIM01

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD, PhD Degree Year: 2008

Attach Biographical Sketch*: File Name: GUIMBELLOT_BIOSKETCH.pdf

Attach Current & Pending Support: File Name:

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: Steven Middle Name Mark Last Name*: Rowe Suffix:

Position/Title*: Professor
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Department: School of Medicine
Division: Pulmonary Allergy Critical Car
Street1*: 1918 University Blvd, MCLM 706
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State*: AL: Alabama
Province:
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Zip / Postal Code*: 352330006

Phone Number*: 205-934-9640 Fax Number: 205-934-1721

E-Mail*: srowe@peds.uab.edu

Credential, e.g., agency login: rowe02

Project Role*: Other (Specify) Other Project Role Category: Mentor

Degree Type: MD,BA,MSPH Degree Year: 1998,1994,2005

Attach Biographical Sketch*: File Name: Rowe_NIH_Blo_SKETCH.pdf

Attach Current & Pending Support: File Name: ROWE_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: DAVID Middle Name W Last Name*: KIMBERLIN Suffix:

Position/Title*: Professor
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Department: School of Medicine
Division: Pediatrics- Infectious Disease
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Street2:
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County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
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Phone Number*: (205) 934-5316 Fax Number: (205) 934-8559

E-Mail*: PEDPLLL@UABDPO.DPO.UAB.EDU

Credential, e.g., agency login: DKIMBERLIN

Project Role*: Other (Specify) Other Project Role Category: Co- Mentor

Degree Type: MD,BS Degree Year: 1989

Attach Biographical Sketch*: File Name: KIMBERLIN_BIOSKETCH.pdf

Attach Current & Pending Support: File Name: KIMBERLIN_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Edward Middle Name P Last Name*: Acosta Suffix:

Position/Title*: Professor
Organization Name*: The University of Alabama at Birmingham
Department: School of Medicine
Division: Clinical Pharmacology
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Phone Number*: (205) 934-2655 Fax Number: (205) 934-6201

E-Mail*: eacosta@uab.edu

Credential, e.g., agency login: eacosta

Project Role*: Other (Specify) Other Project Role Category: Co- Mentor

Degree Type: PHMD Degree Year: 1992

Attach Biographical Sketch*: File Name: ACOSTA_BIOSKETCH.pdf

Attach Current & Pending Support: File Name: ACOSTA_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Hemant Middle Name K. Last Name*: Tiwari Suffix:

Position/Title*: Professor
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Department: School of Public Health
Division: Biostatistics
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E-Mail*: htiwari@uab.edu

Credential, e.g., agency login: htiwari

Project Role*: Other (Specify) Other Project Role Category: Co- Mentor

Degree Type: PHD Degree Year: 1986

Attach Biographical Sketch*: File Name: Tiwari_Biosketch.pdf

Attach Current & Pending Support: File Name: TIWARI_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Inmaculada Middle Name B Last Name*: Aban Suffix:

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Division: Biostatistics
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State*: AL: Alabama
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Zip / Postal Code*: 352940000

Phone Number*: 205-967-2516 Fax Number:

E-Mail*: caban@uab.edu

Credential, e.g., agency login: chichiaban

Project Role*: Other (Specify) Other Project Role Category: Co- Mentor

Degree Type: PHD,MS,BS Degree Year: 1995,1988,1985

Attach Biographical Sketch*: File Name: AbanBIOSKETCH.pdf

Attach Current & Pending Support: File Name: ABAN_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: Emily Middle Name E Last Name*: Scott Suffix:

Position/Title*: Professor
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Division:
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City*: Ann Arbor
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State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 481090000

Phone Number*: 7347643530 Fax Number:

E-Mail*: scottee@umich.edu

Credential, e.g., agency login: eescott

Project Role*: Other (Specify) Other Project Role Category: Advisor

Degree Type: PHD,BS Degree Year: 1998,1992

Attach Biographical Sketch*: File Name: SCOTT_BIOSKETCH.pdf

Attach Current & Pending Support: File Name: SCOTT_OS.pdf

PROFILE - Senior/Key Person

Prefix: First Name*: NITA Middle Name A Last Name*: LIMDI Suffix:

Position/Title*: Professor
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Department: School of Medicine
Division: Department of Neurology
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State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 352940021

Phone Number*: (205) 934-4385 Fax Number: (205) 996-9912

E-Mail*: nlimdi@uabmc.edu

Credential, e.g., agency login: nlimdi

Project Role*: Other (Specify) Other Project Role Category: Advisor

Degree Type: PHMD,PHD,MS,BS Degree Year: 1994,2007,2005,1993

Attach Biographical Sketch*: File Name: LIMDI_BIOSKETCH.pdf

Attach Current & Pending Support: File Name: LIMDI_OS.pdf

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: Guimbellot, Jennifer S.

eRA COMMONS USER NAME (credential, e.g., agency login): GUIM01

POSITION TITLE: Assistant Professor of Pediatrics

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Mississippi State Univ., Starkville, MS (*summa cum laude)*	B.S.	05/2000	Biochemistry, Molecular Biology
University of Alabama at Birmingham	M.D./Ph.D.	12/2008	Genetics
New York-Presbyterian Morgan Stanley Children's Hospital, New York, NY	N/A	06/2012	General pediatrics internship/residency
University of North Carolina at Chapel Hill	N/A	06/2015	Pediatric pulmonary fellowship

A. Personal Statement

My research career goal is to develop personalized therapeutic strategies for children with cystic fibrosis (CF), incorporating pharmacometrics and cell-culture based predictive tools. I optimize cell-culture based tools to understand the use of CF Transmembrane conductance Regulator (CFTR) modulators on a personalized basis and to study pathophysiology in CF. As a fellow, I initiated projects in the effect of airway colonization by bacteria on CFTR trafficking as well as epidemiologic evaluation on the effects of chronic bacterial colonization of patients with tracheostomy. During this time, I significantly changed my research direction due to a serendipitous finding in nasal epithelial culture, resulting in the development of a novel cell-culture based three-dimensional model for assessing CFTR function. Because of this change, my productivity slowed while I developed the new model; however, I have now published an original research article on this topic (first author). I have also published a second publication on work completed during fellowship regarding bacterial colonization and clinical outcomes in patients with tracheostomies. I have also published four additional manuscripts since then, all as first or senior author. My work has continued to progress in the development of primary cell culture models and pharmacometric analysis for application to precision medicine in cystic fibrosis. I currently have one additional manuscript under review and two additional first-author manuscripts in preparation, directly relevant to this application. I have developed expertise in three-dimensional modeling, airway epithelial biology, modulator therapy, biochemical and electrophysiological techniques, and clinical studies of cystic fibrosis, making me uniquely suited to complete the proposed project. As a graduate student and fellow, I received extensive training in both basic science and clinical skills including cell-culture model development; primary human epithelial culture; correction of mutant CFTR proteins by small molecule compounds; CFTR biochemistry, trafficking, and electrophysiology; microscopy; human subjects (including the recruitment of children and their families); and animal studies. My expertise in genetics, cell biology, and biochemistry is broad and encompasses many relevant skills to bring this project to fruition. My career development and training plan includes studies in pharmacology and pharmacogenetics; advanced clinical study design such as personalized medicine trials; and additional professional development skills, all selected to maximize the success of this project and enable my transition to an independent investigator.

B. Positions and Honors

Positions and Employment

2009 Adjunct Faculty, Department of Biology, Millsaps College, Jackson, MS
2015-2016 Instructor, Department of Pediatrics, Div. of Pulmonary and Sleep Medicine, Dept. of Pediatrics, University of Alabama at Birmingham

2015	Associate Scientist Gregory Fleming James Cystic Fibrosis Research Center University of Alabama School of Medicine
2016	Assistant Professor, Div. of Pulmonary and Sleep Medicine, Dept. of Pediatrics, University of Alabama at Birmingham
2018	Assistant Program Director for Research, Div. of Pulmonary and Sleep Medicine, Dept. of Pediatrics, University of Alabama at Birmingham

Board Certification

2013	American Board of Pediatrics, General Pediatrics
2016	American Board of Pediatrics, Pulmonology

Other Experience and Professional Memberships

2009-	American Academy of Pediatrics
2013-	American Thoracic Society
2018-	Medical Association of the State of Alabama
2018-	Jefferson County Medical Society

Honors

1999	Barry M. Goldwater Scholar
2005	Genetics Award, National Student Research Forum, UTMB, Galveston, Texas
2005	Best Poster Award, MSTP, University of Alabama, Birmingham
2006	American Society of Human Genetics Annual Meeting Travel Award
2006	European Respiratory Society 4th Lung Science Conference Travel Award
2007 & 2006	Outstanding Graduate Student (Doctoral), Department of Genetics, University of Alabama at Birmingham
2013	Johnny Carson Award for Best Overall Research, Department of Pediatrics Evening of Scholarship, University of North Carolina at Chapel Hill
2014	American Thoracic Society, Assembly on Pediatrics Abstract Scholarship
2018	Travel Award to North American Cystic Fibrosis Conference, StemCell Technologies

C. Contributions to Science

1. My laboratory has a focus on three-dimensional model development to be used as *in vitro* biomarkers in children and adults. I developed novel three-dimensional cell culture models from the nasal epithelial airway using a non-invasive biopsy and designed new assays to isolate and evaluate CFTR channel activity and fluid transport. The first of these models results in rapid development of spherical airway models with a simple measurement outcome that correlates with small changes in CFTR activity, and may represent an *in vitro* biomarker for determining cystic fibrosis patient responses to modulator drugs.
    a. **Guimbellot JS,** Sharma J, Rowe SM. “Toward Inclusive Therapy with CFTR Modulators: Progress and Challenges.” Pediatr Pulmonol. 2017 Nov;52(S48):S4-S14. PMID:28881097
    b. **Guimbellot JS,** Leach JM, Chaudhry, IG, Quinney NL, Boyles, SE, Chua, M, Aban, I, Jaspers, I, Gentzsch, M. “Nasospheroids permit novel measurements of CFTR-dependent fluid transport.” JCI Insight. 2017 Nov 16;2(22). PMID:29202459

2. My research program encompasses clinical impact of CFTR modulator use, including clinical studies, pharmacogenomics, and pharmacometrics evaluating the pediatric and adult variation in drug efficacy and metabolism of CFTR modulators. In collaboration with the Pediatric Pharmacology Core Laboratory, we have developed specific assays for the plasma quantitation of ivacaftor and its metabolites; lumacaftor; and tezacaftor. We have also developed methodologies for the intracellular concentration of these drugs for evaluation of tissue-specific metabolism.
    a. **Guimbellot JS,** Acosta E, Rowe SM. Sensitivity of ivacaftor to drug-drug interactions with rifampin, a cytochrome P450 3A4 inducer. *Pediatr Pulmonol.* 2018 Feb 28. [Epub ahead of print]
    b. **Guimbellot JS*,** Solomon GM*, Baines A, Heltshe SL, VanDalfsen J, Joseloff E, Sagel S, Rowe SM. Effectiveness of ivacaftor in non-G551D gating mutations. J Cystic Fibrosis. 2018. In press. *co-first authors.

3. During my graduate career, I discovered that CFTR is negatively impacted by hypoxemia, a phenomenon

with relevance to acquired CFTR dysfunction, the first finding to suggest that individuals with normal CFTR genes may develop illnesses similar to cystic fibrosis, such as chronic obstructive pulmonary disease. During my thesis work I also presented the first evidence that microRNAs are differentially regulated in epithelial cells by hypoxemia.

a. **Guimbellot JS**, Fortenberry JA, Siegal GP, Moore B, Wen H, Venglarik C, Chen YF, Oparil S, Sorscher EJ, Hong JS. Role of Oxygen in Cystic Fibrosis Transmembrane Conductance Regulator Expression and Function. Am J Respir Cell Mol Biol. 2008 May 12. PMCID: PMC2574524
b. **Guimbellot JS**, Erickson SW, Mehta T, Wen H, Page GP, Sorscher EJ, Hong JS. Correlation of microRNA levels during hypoxia with predicted target mRNAs through genome-wide microarray analysis. BMC Med Genomics. 2009 Mar 25;2:15. PMCID: PMC2667434

4. During my graduate career, I was a contributing author to a seminal publication proving that normal endogenous CFTR protein is efficiently processed. Prior to this publication, it was thought that a large portion of normal, endogenous protein was degraded due to studies in cell models.
   a. Varga K, Jurkuvenaite A, Wakefield J, Hong JS, **Guimbellot JS**, Venglarik CJ, Niraj A, Mazur M, Sorscher EJ, Collawn JF, Bebok Z. Efficient intracellular processing of the endogenous cystic fibrosis transmembrane conductance regulator in epithelial cell lines. J Biol Chem. 2004 May 21;279(21):22578-84. PMID 15066992

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1hqx7zl0EXf/bibliography/40344656/public/?sort=date&direction=ascending

D. Additional Information: Research Support

Ongoing Research Support

Cystic Fibrosis Foundation — Guimbellot (PI) — 04/01/18 – 03/31/21
Clinical Investigator Award
This award is designed for the development of pharmacogenomics analysis for CFTR modulator therapy in patients and in *in vitro* studies, as well as the use of three-dimensional cell culture models for predicting drug effectiveness.
Role: PI

Cystic Fibrosis Foundation — Guimbellot (PI) — 04/01/17 – 03/31/19
Pilot and Feasibility Award
This pilot award will evaluate a two-phase cell-culture based biomarkers for prediction of modulator efficacy and distinction of subtle levels of CFTR activation using three-dimensional cell culture models.
Role: PI

Completed Research Support

Kaul Pediatrics Research Institute — Guimbellot (PI) — 02/01/16 – 01//31/18
Development of Personalized Approaches to CFTR Modulator
This award provides funding for human nasal epithelial-derived three-dimensional sphere cultures for personalized medicine in cystic fibrosis using size change imaged by confocal microscopy as a surrogate for fluid transport.
Role: PI

NIH/NHLBI 1 R43 HL134056-01 — Prabhakar pandian (PI) — 08/15/16 – 07/31/17
Title: A Predictive In Vitro Model for Screening Personalized Responses to CFTR-directed Therapeutics
The purpose of this project was to develop a novel microfluidics-based platform of epithelial and endothelial co-culture for testing of CFTR modulator efficacy.
Role: Co- Investigator

Cystic Fibrosis Foundation GUIMBE14DO — Guimbellot (PI) — 07/01/14 – 06/30/15
Third year Cystic Fibrosis Foundation Clinical Fellowship Grant
The goal of this grant was to provide advanced clinical and research training for pediatric pulmonology fellowship.

Role: PI

NC Trans. & Clinical Sciences Inst. 2KR541401 Guimbellot (PI) 04/01/14 – 04/01/15
Variation in response to correctors in F508del homozygotes.
The goal of this grant was to develop the use of nasal epithelial culture for use in studies of CFTR trafficking and correction.
Role: PI

Cystic Fibrosis Foundation GUIMBE12B0 Guimbellot (PI) 07/01/12 – 06/30/14
First and second year Cystic Fibrosis Foundation Clinical Fellowship Grant
The goal of this grant was to provide clinical training and research support for pediatric pulmonology fellowship.
Role: PI

Children's Promise, XMRSA, UNC-Chapel Hill Guimbellot (PI) 07/01/13 – 06/30/14
Epidemiology of tracheostomy infections
The goal of this project was to evaluate retrospective and prospective cultures from tracheostomies from pediatric patients to understand the evolution of infection and colonization and to inform ways to reduce new infections by quality improvement.
Role: PI

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Steven Mark Rowe

eRA COMMONS USER NAME (credential, e.g., agency login): ROWE02

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Virginia	B.A.	05/94	Interdisplinary
Vanderbilt University	M.D.	05/98	Medicine
University of Alabama at Birmingham	MSPH	05/05	Biostatistics

A. Personal Statement – Dr. Rowe is an academic physician scientist – a pioneer in the field of personalized therapeutics for CF, cutting-edge discovery in airway disease biology and ciliary dynamics, and translational research in CF, COPD, and other airway diseases. As detailed below and in his letter of support, his scientific and career development experience him well suited to serve as Dr. Guimbellot's primary research mentor. He maintains a robust translational research laboratory program that includes both human-oriented clinical studies and fundamental research of substantive breadth and impact, ranging from cell based drug discovery to animal modeling to Phase 3 clinical trials. He has significant experience and training in the design and conduct of clinical trials testing new therapeutic agents intended to address the basic CF defect and resulting abnormalities in mucus clearance, has led academic-industry partnerships in this regard, spoke on the topic with Dr. Francis Collins at the Keynote Plenary Session during the North American CF Meetings, and discussed new developments in CF clinical approaches in the Plenary Session of the North American CF Meetings 3 years later. Dr. Rowe is an expert regarding the mechanistic features underlying cystic fibrosis and the role of the cystic fibrosis transmembrane conductance regulator (CFTR) towards regulating mucociliary clearance. He has advanced, developed, and invented biomarkers in human subject to monitor these aspects. He is an expert in the measures of epithelial function, the growth and procurement of primary human airway cells required for the experiments, and co-invented µOCT imaging technology used to evaluate mucociliary transport and airway epithelial functional microanatomy in real time at the cellular level *in vitro* and *in vivo*. Dr. Rowe's previous record of training of medical students (including several in the competitive T35 research program), medical residents (several who have been placed in highly competitive pulmonary fellowships and accomplished first author publications in the Rowe laboratory), pulmonary fellows and junior faculty (*including those who have presented at local and national meetings, published their findings in the literature, received funding by NIH K08 and CFF-equivalent mechanisms, and have been promoted to CF Center Director elsewhere*), provide evidence of his mentoring capacity. He also has supported the development of minorities, hosting 1 graduate student and 1 post-doctoral fellow with federally funded minority-directed awards in the last 2 years. Seminal publications representing overall expertise include (4):

1. **Rowe SM**, Miller S, Sorscher EJ. "Mechanisms of Disease: Cystic Fibrosis." *New England Journal of Medicine,* 2005; 352: 1992-2001.
2. **Rowe SM,** Hoover W, Solomon GM, Sorscher EJ. "Cystic Fibrosis." IN: *Murray & Nadel's Textbook of Respiratory Medicine,* (6th) edition. Editor: Steve Lazarus. [Book Chapter, 2016].
3. Montoro DT, Haber AL, Biton M, Vinarsky V, Chen S, Villoria J, Rogel N, Tata PR, **Rowe SM**, Engelhardt JF, Rgev A, Rajagopal J. "Novel cell types and lineages of the airway epithelium." *Nature*. 2018 Aug;560(7718):319-324.

4. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, Griese M, McKone E, Wainwright C, Konstan M, Moss R, Ratjen F, Sermet-Gaudelus I, **Rowe SM**, Dong Q, Rodriguez S, Yen K, Ordoñez C, Elborn JS on behalf of the VX08-770-102 Study Group. "A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *N Engl J Med* 2011 Nov 3;365(18):1663-72. (PMCID:PMC3230303)

B. Positions and Honors

1998-01 Intern and Resident, Combined Internal Medicine and Pediatrics, UAB
2001-02 Chief Resident, Combined Internal Medicine and Pediatrics, UAB
2002-05 Fellow, Combined Pulmonary and Critical Care Medicine and Pediatric Pulmonology, UAB.
2006- Assistant Professor, Pulmonary, Allergy, and Critical Care Medicine, Pediatric Pulmonology, UAB
2006-14 Director, Cystic Fibrosis Transition Clinic, Children's Hospital, UAB
2006-08 Associate Director, National CF-Therapeutics Development Network Center for CFTR Detection
2007-16 Co-Chair, International Mucociliary Clearance Research Consortium, Cystic Fibrosis Foundation
2008-16 Director, Center for CFTR Detection, CFF Therapeutics Development Network
2009- Special Consultant for Translational Science, Cystic Fibrosis Foundation
2011-14 Associate Professor with Tenure, UAB
2014- Professor with Tenure, Department of Medicine, Pediatrics, and Cell Developmental and Integrative Biology, UAB
2015- Director, Gregory Fleming James Cystic Fibrosis Research Center; Nancy & Eugene Gwaltney Chair for Medical Research

Awards and Honors

2009 Plenary Session Keynote Address, North American Cystic Fibrosis Conference. **Rowe SM and Collins F**. "Two Decades of CFTR Research: From Gene Discovery to Therapeutic Target", Minneapolis, MN
2006- Ad hoc reviewer for Journals including *Nature*, *New England Journal of Medicine, JAMA, JCI, Science Translational Medicine,* and *American Journal of Respiratory and Critical Care Medicine;* Editorial board for *JCI Insight, AJP Lung* and *Journal of CF*
2012 Plenary Session, Keynote Speaker, North American CF Conference. "Correcting the Basic Defect: A Vision for the Future", Rowe SM and Skach W.
2012 Inducted to the *Southern Society of Clinical Investigation*
2014 Dean's Award for Excellence in Mentorship
2014 Inducted to the *American Society of Clinical Investigation*
2015 Max Cooper Award for Excellence in Research
2017 Inducted, Faculty *AOA*, University of Alabama at Birmingham
2017 Visiting Pulmonary Scholar. University of North Carolina at Chapel Hill, Duke, University, EPA, and National Institutes of Environmental Health Sciences
2017 Visiting Professor, NHLBI, NIH, Bethesda, Maryland
2017 Thomas Hazinski Memorial Lecture, Vanderbilt University, Nashville, TN
2018 Talamo Lecture, Ether Dome, Massachusetts General Hospital, Harvard University.

C. Contributions to Science

1. Dr. Rowe is a respected international authority with regard to the design and conduct of clinical trials targeting the basic CF defect, and his contributions have provided a roadmap to the cure of CF. For example, Dr. Rowe played a key role in the clinical development of ivacaftor, a novel CFTR potentiator, and established in vivo endpoints of CFTR function. The results firmly established CFTR as a therapeutic target in CF, and Dr. Rowe has directed large academic-led multicenter studies of mechanism of action to further characterize the approach.

a. Accurso FJ, **Rowe SM**, Clancy JP, Boyle MP, Dunitz J, Durie PR, Sagel SD, Hornick DB, Konstan MW, Donaldson SH, Moss RB, Pilewski JM, Rubenstein R, Uluer AZ, Aitken ML, Freedman SD, Rose LM, Mayer-Hamblett N, Dong Q, Zha J, Stone AJ, Olson ER, Ordonez CL, Campbell PW, Ashlock MA, Ramsey BW. "Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation". *N Engl J Med* Nov 18:363(21):1991-2003, 2010. Epub 2011 (PMCID PMC3148255)
b. **Rowe SM**, Heltshe SL, Gonska T, Donaldson S, Borowitz D, Gelfond D, Sagel S, Khan U, Mayer-Hamblett N, Van Dalfsen J, Joseloff E, Ramsey B, on behalf of the GOAL investigators. "Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic

Fibrosis. *Am J Respir Crit Care Med*. 2014;190(2):175-184. Please see accompanying editorial. (PMCID:PMC4226057)

c. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, Flume PA, Konstan MW, McColley SA, McCoy K, McKone EF, Munck A, Ratjen F, **Rowe SM**, Waltz D, Boyle MP; TRAFFIC and TRANSPORT Study Groups.Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med*. 2015 Jul 16;373(3):220-31. Epub 2015 May 17 (PMCID: PMC4764353).

d. **Rowe SM**, Daines C, Ringshausen F, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. "Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and Phe508del and Residual Function Mutations." *New England Journal of Medicine* 2017 Nov 23;377(21):2024-2035. PMCID in process.

2. Dr. Rowe co-invented an imaging technique (one-micron resolution optical coherence tomography) that captures 3D imaging in real-time at the cellular level. The technique is highly sensitive to the epithelial function of airway tissues and can provide simultaneous and non-invasive measurements of airway surface liquid depth, ciliary beat frequency, mucociliary transport, mucus viscosity and cilia coordination, providing a first-in-kind measures of functional epithelial anatomy. The technology is unprecedented, and is significantly advancing our understanding of airway disease pathogenesis.

a. Birket SE*, Chu KK*, Liu L, Houser GH, Diephuis BJ, Wilsterman EJ, Dierksen G, Mazur M, Shastry S, Li Y, Watson JD, Smith AT, Schuster BS, Hanes J, Grizzle WE, Sorscher EJ, Tearney GJ*, **Rowe SM***. "A Functional Anatomic Defect of the CF Airway." *Am J Respir Crit Care Med*. 2014;190(4):421-32. *Note: Authors contributed equally to this manuscript. Please also see accompanying editorial.(PMCID: PMC4214131)

b. Birket SE, Chu KK, Houser GH, Liu L, Fernandez CM, Solomon GM, Lin V, Shastry S, Mazur M, Sloane P, Hanes J, Grizzle WE, Sorscher EJ, Tearney GJ, **Rowe SM**. "Combination therapy with cystic fibrosis transmembrane conductance regulator modulators augment the airway functional microanatomy." *Am J Physiol Lung Cell Mol Physiol* 2016 Mar 11. (PMCID:PMC4896103).

c. Solomon GM, Francis R, Chu K, Birket SE, Gabriel G, Trombley JE, Lemke KL, Klena N, Turner B, Tearney GJ, Lo CW, **Rowe SM**. Assessment of ciliary phenotype in primary ciliary dyskinesia by micro-optical coherence tomograph. *JCI Insight* 2017 Mar 9;2(5):e91702. (PMCID:PMC5333960)

d. Birket S, Davis J, Fernandez C, Tuggle K, Oden A, Chu K, Tearney GJ, Sorscher EJ, **Rowe SM**. "Development of an Airway Mucus Defect in the CF Rat." *JCI Insight* 2018 Jan 11;3(1). PMCID in process.

3. Dr. Rowe has discovered that COPD patients exhibit 'acquired CFTR dysfunction' through a pathway that causes delayed mucociliary clearance and confers chronic bronchitis. He also made the surprising discovery that acquired CFTR dysfunction is a systemic phenomenon, which could explain why smokers have an increased incidence of pancreatitis, infertility, and diabetes mellitus (systemic manifestations of COPD in which CFTR plays has a causative role). After establishing the preclinical basis of this novel mechanism, Dr. Rowe now leads an investigator-initiated IND study to evaluate ivacaftor in patients with chronic bronchitis. These results could alter the paradigm for COPD treatment.

a. Raju SV, Jackson PL, Courville CA, McNicholas CM, Sloane PA, Sabbatini G, Tidwell S, Tang LP, Liu B, Fortenberry JA, Jones CW, Boydston JA, Clancy JP, Bowen L, Accurso FJ, Blalock JE, Dransfield MT, **Rowe SM**. "Cigarette Smoke Induces Systemic Defects in Cystic Fibrosis Transmembrane Conductance (CFTR) Regulator Ion Transport." *Am J Respir Crit Care Med,* 2013;188(11):1321-30. (PMCID:PMC3919073). Please also see accompanying editorial

b. Raju SV, Lin VY, Liu L, McNicholas CM, Karki S, Sloane PA, Tang LP, Jackson PL, Wang W, Wilson L, Macon KJ, Mazur M, Kappes J, DeLucas LJ, Barnes S, Kirk K, Tearney GT, **Rowe SM**. "The CFTR potentiator ivacaftor augments mucociliary clearance abrogating acute and chronic CFTR inhibition by cigarette smoke." *Am J Respir Cell Mol Biol.* 2017 Jan;56(1):99-108. (PMCID:PMC5248967)

c. Snelgrove RJ, Jackson PL, Hardison MT, Noerager BD, Gaggar A, Shastry S, **Rowe SM**, Shim YM, Hussell T, Blalock JE. "A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation". *Science* Oct1;330(6000);90-4, 2010. (PMCID PMC3072752)

d. Solomon GM, Dransfield MT, **Rowe SM**. "Pilot Evaluation of the CFTR Potentiator Ivacaftor for the Treatment of Chronic Bronchitis." *Lancet Respir Med*. 2016 [EPub ahead of print]. (PMCID:MC49169140).

e. Raju SV, Kim H, Byzek S, Tang LP, Trombley J, Jackson PL, Rasmussen L, Wells JM, Falk Libby E, Dohm E, Winter L, Samuel S, Zinn K, Blalock JE, Schoeb T, Dransfield MT, **Rowe SM**. "A ferret model of COPD-related chronic bronchitis." *JCI Insight* 2016 Sep 22;1(15)e87536. (PMCID: PMC5033751)

4. Dr. Rowe has advanced both the molecular and clinical understanding of suppression of premature termination codons, representing an exciting strategy for treatment of cystic fibrosis and other genetic diseases caused by nonsense mutations.

a. Xue X, Mutyam V, Tang LP, Biswas S, Du M, Jackson LA, Dai Y, Belakhov V, Shalev M, Chen F, Schacht J, Bridges RT, Baasov T, Hong J, *Bedwell DM, ***Rowe SM**. "Synthetic Aminoglycosides Efficiently Suppress CFTR Nonsense Mutations and Are Enhanced by Ivacaftor." *Amer J Resp Cell Mol Biol* 2014 Apr;50(4):805-16. Epub 2013 Nov 19. (PMCID: PMC4068923)
b. Kerem E*, Konstan M*, De Boeck K, Accurso F, Sermet-Gaudelus I, Wilschanski M, Elborn JS, Melotti P, Bronsveld I, Fajac I, Malfroot A, Rosenbluth D, Walker P, McColley S, Knoop C, Quattrucci S, Rietchel E, Zeitlin P, Barth J, Elfring G, Welch E, Spiegel R, Peltz SW, Ajayi T, **Rowe SM**, for the Cystic Fibrosis Ataluren Study Group. "Ataluren for the treatment of nonsense mutation cystic fibrosis: a randomized, double-blind, placebo-controlled phase 3 trial." *Lancet Respir Med*. 2014 Jul;2(7):539-47. Epub 2014 May 15. *Note: Authors contributed equally to this manuscript. (PMCID: PMC4154311)
c. Mutyam V, Du M, Xue X, White EL, Bostwick JR, Rasmussen L, Liu B, Mazur M, Hong JS, Falk Libby E, Liang F, Shang H, Mense M, Suto MJ, Bedwell DM, **Rowe SM**. "Discovery of Clinically Approved Agents that Promote Nonsense Mutations". *Am J Respir Crit Care Med* 2016 Nov 1;194(9):1092-1103. (PMCID: PMC5114449) Featured as editor's choice in *Science Translational Medicine* 11 May 2016:Vol. 8, Issue 338, pp. 338ec74. Featured as editor's choice in *Science Translational Medicine* 11 May 2016:Vol. 8, Issue 338, pp. 338ec74. See accompanying editorial by I. Sermet-Gaudelus and O. Namy, "New Pharmacological Approaches to Treat Patients with Cystic Fibrosis with Nonsense Mutations." *Am J Respir Crit Care Med*. 2016 Nov 1;194(9):1042-1044.
d. Roy B, Friesen WJ, Tomizawa Y, Leszyk JD, Zhuo J, Johnson B, Dakka J, Trotta CR, Xue X, Mutyam V, Keeling KM, Mobley JA, **Rowe SM**, Bedwell DM, Welch EM, Jacobson A. Ataluren stimulates ribosomal selection of near-cognate tRNAs to promote nonsense suppression. *Proc Natl Acad Sci* 2016 Nov 1;113(44):12508-12513. (PMCID:PMC5098639)

Complete List of Published Work in MyBibliography (over 130 peer reviewed publications):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1-YI6Ybqp2-kA/bibliography/47290266/public/?sort=date&direction=ascending

D. Research Support
Ongoing Research Support

P30 DK072482 05/01/2012 – 04/30/2023
NIH/NIDDK
Title: *UAB CF Research and Translation Core Center*
This P30 provides 3 Scientific Cores (i.e. Animal Models Core, Single Channel Analysis Facility, and Clinical Core) to CF investigators at UAB and collaborating sites to improve understanding of the most basic underpinnings of cystic fibrosis pathogenesis and the ways this information can be aggressively applied to experimental therapeutics. Two Pilot and Feasibility projects are also supported through the P30.
Role: Overall Program Director; Co-Director of Core C: Clinical and Translational Core

NIH R35 HL135816 (Rowe) 12/01/16 – 11/30/23
Title: *Translational Program in CFTR-Related Airway Diseases*
This program supports investigation into diseases of mucociliary clearance, including their molecular mechanism, clinical phenotype, and precision medicine approaches to intervene.
Role: Principal Investigator

R464-CR11 (Rowe) 07/01/15 - 06/30/19
Cystic Fibrosis Foundation
Research Development Program (ROWE15R0)
The major goals of this project are to 1) support basic research core capabilities including construction of cell lines, immunolocalization, conductance, SPQ based functional analysis, as well as recombinant adenoviral vectors and other biochemical and functional endpoints for CF scientists and their projects on our campus, 2) provide resources for Pilot/Feasibility Studies, postdoctoral fellows and graduate students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.
Role: Program Director

U54TR001368-01 (Kimberly) 09/01/2015 – 08/31/20
NIH/NCATS
UAB Center for Clinical and Translational Science (CCTS)
The UAB CCTS will enhance human health by driving scientific discovery and dialogue across the bench, bedside and community continuum. The CCTS support this overall mission in a highly integrative network of relationships. Success in creating such an environment is dependent upon success in achieving five strategic priorities: 1) enhancing research infrastructure; 2) promoting investigator education, training and development; 3) accelerating discovery across the T1 interface; 4) expanding value-added partnerships; and 5) building sustainability.
Role: Co-Director of Pediatric CCTS

R34HL127166 (Rowe/Dransfield) 09/01/2015 – 08/31/17 [NCE]
NIH/NHLBI
A Pilot Study of the Effect of the CFTR Potentiator Ivacaftor in COPD (P-TOPIC)
This project will conduct a pilot, randomized, double blind placebo controlled trial to evaluate the efficacy, safety, mechanism, and pharmacokinetics of ivacaftor in patients with COPD and chronic bronchitis, under an investigator initiated IND.
Role: Multiple Principal Investigator

ROWE15R0 (Rowe) 07/01/2015 - 6/30/2019
Cystic Fibrosis Foundation
Research Development Program – Component II
The major goals of this project are to 1) support core capabilities including RT-PCR, immunolocalization, conductance, SPQ based functional analysis, as well as recombinant adenoviral vectors and other biochemical and functional endpoints for CF scientists and their projects on our campus, 2) provide resources for Pilot/Feasibility Studies, postdoctoral fellows and graduate students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.
Role: Program Director; Co-Director, Core A. Note: Currently under competitive renewal review.

GOAL11K1 (Rowe) 09/01/2011 – 12/31/2020
Cystic Fibrosis Foundation
Title: *G551D Observational Study (GOAL-OB-11)*
The purpose of this study is to conduct a multi-center observational study evaluating the effects of Ivacaftor in CF patients with the G551D mutation. Dr. Rowe supervises the multi-center component of four outcome based sub-studies.
Role: Principal Investigator of national multicenter trial

R43HL134056-01 08/01/2016 – 07/31/20
CFD Research Organization (Pandian)
A Predictive In Vitro Model for Screening Personalized Responses to CFTR-Directed Therapeutics
Role: Principle Investigator of Subcontract

ROWE14Y0 (Rowe) 01/01/14 – 12/31/19 (renewed annually)
Cystic Fibrosis Foundation Therapeutics; Title: *UAB Cystic Fibrosis Translational Development Center*
The main goals of this project are to provide funding and infrastructure for support of Phase I and Phase II clinical trials in Cystic Fibrosis patients through the Therapeutic Development Network.
Role: Principal Investigator

NIH R43 DK107004 (Baker) 08/01/2015 –0 2/28/2017 [NCE]
NIH/NHLBI
Prevention and Treatment of GI Obstruction Syndromes in Cystic Fibrosis
This project will assess efficacy of a novel mucolytic on prevention and treatment of intestinal obstruction in a cystic fibrosis rat model.
Role: Principal Investigator of Subcontract

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Kimberlin, David Winston**

eRA COMMONS USER NAME (credential, e.g., agency login): **DKIMBERLIN**

POSITION TITLE: **Professor of Pediatrics**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Vanderbilt University (*summa cum laude*)	B.S.	1981-1985	Molecular Biology
University of Texas Southwestern Medical School	M.D.	1985-1989	Medicine
University of Texas Southwestern Medical School	Intern/Res	1989-1992	Pediatrics
University of Texas Southwestern Medical School	Fellowship	1992-1994	Infectious Diseases
University of Alabama at Birmingham (UAB)	Fellowship	1994-1996	Virology

A. Personal Statement

I am very well suited to assist in the success of Dr. Guimbellot as she establishes her independent academic career. I have 25 years of experience in Phase I, II, and III clinical trials conducted by the established, highly successful, NIH-funded network known as the Collaborative Antiviral Study Group (CASG) that has overseen the design and conduct of multicenter national and international studies. I have extensive experience in implementation of impactful pediatric clinical trials resulting in labeling changes, including the full breadth of clinical research, from concept development to protocol and study materials preparation to Investigative New Drug preparation to oversight of study performance to data management and analysis to Final Study Report generation and NLM upload. The scientific accomplishments of the CASG are documented in Section C, below, and include the generation of data that have resulted in 12 labeling changes for rare pediatric diseases, as well as the sole data that supported the Emergency Use Authorization for use of oseltamivir in infants under 12 months of age during the 2009 H1N1 influenza pandemic. In addition, I led a study supported by GlaxoSmithKline that resulted in a label change for valacyclovir in children. I will bring all this expertise to bear in my career mentorship of Dr. Guimbellot, as she embarks in a career to optimize therapeutic strategies for children and adults with cystic fibrosis. In addition to my expertise in clinical trials, I also have extensive experience in the education and training of pediatric trainees and faculty. From 2001 to 2014, I served as Director of Subspecialty (Fellowship) Education for the University of Alabama at Birmingham Department of Pediatrics. During this time, I directed the education of over 200 fellows who completed subspecialty pediatric training at UAB. I currently am Vice Chair for Clinical and Translational Research for the UAB Department of Pediatrics, providing leadership guidance for new and established investigators. I also am Editor of the American Academy of Pediatrics (AAP) Red Book: Report of the committee on Infectious Diseases, and am Past-President of the Pediatric Infectious Diseases Society, which is the world's largest organization of professionals dedicated to the treatment, control and eradication of infectious diseases affecting children. All of these prior and current roles prepare me very well to mentor Dr. Guimbellot's career development. **I commit to being available to mentor Dr. Guimbellot as she establishes her independent academic career in the field of cystic fibrosis research. The full scope of my mentorship is outlined in my statement.**

B. Positions and Honors

Positions and Employment

1989-1990 Pediatric Intern, Children's Medical Center of Dallas, University of Texas Southwestern Medical School, Dallas, Texas

1990-1992 Pediatric Resident, Children's Medical Center of Dallas, University of Texas Southwestern Medical School, Dallas, Texas
1992-1994 Fellow, Division of Infectious Disease, Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, Texas
1994-1996 Fellow, Division of Clinical Virology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
1996-2002 Assistant Professor, Division of Clinical Virology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
2002-2007 Associate Professor with tenure, Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
2007-present Professor with tenure, Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama

Other Experience

1999-present Scientist, Center for Outcomes and Effectiveness Research and Education, University of Alabama at Birmingham, Birmingham, Alabama
1999-present Associate Scientist, Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, Alabama
2001-2014 Director of Subspecialty Medical Education, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama
2014-present Vice Chair for Clinical and Translational Research, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama

Professional Memberships

American Academy of Pediatrics
American Pediatric Society / Society for Pediatric Research
Pediatric Infectious Diseases Society
Infectious Diseases Society of America
International Society for Antiviral Research

C. Contribution to Science

My contributions to science include developing and overseeing the conduct of multicenter therapeutic studies of treatment of rare infectious diseases affecting neonates.

1. With respect to label changes, multicenter studies of rare diseases that I have developed, implemented, overseen, and analyzed have led to successful supplemental New Drug Applications that have resulted in approval of: 1) a pediatric indication from the U.S. Food and Drug Administration (FDA) for valganciclovir down to 1 month of age (April 2015); 2) a new pediatric indication from the European Medicinal Agency for valganciclovir (Fall 2014); 3) a new valganciclovir formulation (tutti-frutti flavored Valcyte for Oral Solution) from the U.S. FDA (August 2009); 4) patent extension for valganciclovir in the European Union (Fall 2014); 5) pediatric dosing and instructions for extemporaneous preparation of oral suspension of valacyclovir from the U.S. FDA (September 2008); 6) a pediatric indication from the U.S. FDA for use of oseltamivir down to 2 weeks of age for the treatment of influenza infection (December 2012); and 7) Emergency Use Authorization for oseltamivir under 12 months of age during the 2009 H1N1 influenza pandemic (April 2009). With regard to the oseltamivir study, the U.S. FDA Division of Antiviral Products stated in a memorandum to NIAID on May 19, 2010, that “we think the conduct of this study is a model for future efforts to obtain needed PK and safety data in difficult to study populations and translate that data into treatment recommendations.”

a. **Kimberlin DW**, Acosta EP, Sánchez PJ, Sood S, Agrawal V, Homans J, Jacobs RF, Lang D, Romero JR, Griffin J, Cloud GA, Lakeman FD, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: A pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital CMV disease. J. Infect. Dis. 2008; 197:836-845. PubMed PMID:18279073

b. **Kimberlin DW**, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels M, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR, Sood SK, Whitworth MS, Abzug MJ, Caserta MT, Fowler S, Lujan-Zilbermann J, Storch GA, DeBiasi RL, Han J-Y, Palmer A, Weiner LB, Bocchini JA, Dennehy PH, Finn A, Griffiths P, Gutierrez K, Halasa N, Homans J, Shane A, Sharland M, Simonsen K, Vanchiere JA, Woods CR, Sabo DL, Aban I, Kuo H, James SH, Prichard MN, Griffin J, Giles G, Acosta EP, Whitley RJ, for the

NIAID Collaborative Antiviral Study Group (CASG). Valganciclovir for symptomatic congenital cytomegalovirus disease. N. Engl. J. Med. 2015;372(10):933-943. PubMed PMID: 25738669. PMCID: PMC4401811

c. **Kimberlin DW**, Jacobs RF, Weller S, van der Walt J-S, Heitman CK, Man CY, Bradley JS: Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month to 12 years of age. Clin. Infect. Dis. 2010; 50:221-228. PubMed PMID:20014952

d. **Kimberlin DW**, Acosta EP, Prichard MN, Sánchez PJ, Ampofo K, Lang D, Ashouri N, Vanchiere JA, Abzug MJ, Abughali N, Caserta MT, Englund JA, Sood SK, Spigarelli MG, Bradley JS, Lew J, Michaels MG, Wan W, Cloud G, Jester P, Lakeman FD, Whitley RJ, for the NIAID Collaborative Antiviral Study Group: Oseltamivir pharmacokinetics, dosing, and resistance among children aged < 2 years with influenza. J. Infect. Dis. 2013; 207:709-720. PubMed PMID: 23230059. PMCID: PMC3563309

2. **With respect to CMV**, we initially determined in a randomized controlled trial that six weeks of antiviral therapy using intravenous ganciclovir improved audiologic outcomes in neonates with symptomatic congenital CMV involving the central nervous system, but there was suggestion that this benefit could wane over the first 2 years of life. We then conducted a pharmacokinetic/pharmacodynamic study of oral valganciclovir (ganciclovir's prodrug) to determine what dose of oral valganciclovir provides the same systemic exposure to ganciclovir as does valganciclovir. This was followed by a Phase III randomized, placebo controlled trial of six weeks versus six months of oral valganciclovir in neonates with symptomatic congenital CMV disease. Results of this study demonstrated that longer treatment of babies with symptomatic congenital CMV disease improved hearing and developmental outcomes to 2 years of age beyond that provided by six weeks of treatment. The benefit of treatment was seen equally whether therapy was started earlier or later during the first month of life. As a result of these CASG trials, the U.S. Food and Drug Administration modified the valganciclovir Package Insert to cite the dose used in CASG studies, and the American Academy of Pediatrics now recommends six months of oral valganciclovir as therapy for infants throughout the United States born with symptomatic congenital CMV disease.

a. **Kimberlin DW**, Lin C-Y, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Kiell JM, Soong SJ, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: Effect of ganciclovir on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: A randomized, controlled trial. J. Pediatr. 2003; 143:16-25. PubMed PMID: 12915819

b. Acosta EP, Brundage RC, King JR, Griffin J, Cloud GA, Whitley RJ, **Kimberlin DW**, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid formulation of valganciclovir. Clin. Pharmacol. Therapeut. 2007; 81:867-872. PubMed PMID: 17392728

c. **Kimberlin DW**, Acosta EP, Sánchez PJ, Sood S, Agrawal V, Homans J, Jacobs RF, Lang D, Romero JR, Griffin J, Cloud GA, Lakeman FD, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: A pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital CMV disease. J. Infect. Dis. 2008; 197:836-845. PubMed PMID:18279073

d. **Kimberlin DW**, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels M, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR, Sood SK, Whitworth MS, Abzug MJ, Caserta MT, Fowler S, Lujan-Zilbermann J, Storch GA, DeBiasi RL, Han J-Y, Palmer A, Weiner LB, Bocchini JA, Dennehy PH, Finn A, Griffiths P, Gutierrez K, Halasa N, Homans J, Shane A, Sharland M, Simonsen K, Vanchiere JA, Woods CR, Sabo DL, Aban I, Kuo H, James SH, Prichard MN, Griffin J, Giles G, Acosta EP, Whitley RJ, for the NIAID Collaborative Antiviral Study Group (CASG). Valganciclovir for symptomatic congenital cytomegalovirus disease. N. Engl. J. Med. 2015;372(10):933-943. PubMed PMID: 25738669

3. **With respect to neonatal HSV disease**, the multicenter studies that I have developed, overseen, and analyzed have defined the standard of care nationally for the management of this life-threatening disease. This includes determining that polymerase chain reaction (PCR) to the cerebrospinal fluid of babies with neonatal HSV central nervous system (CNS) disease could supplant the need for a brain biopsy in these patients. We then determined that mortality and morbidity outcomes are improved with the use of higher dose intravenous acyclovir. Most recently we proved that oral acyclovir suppressive therapy administered for six months following neonatal HSV disease improves both neurologic (for CNS disease classification) and

cutaneous (in all neonatal HSV disease classifications) morbidity. This has critically important implications in our understanding of the pathogenesis of this disease, since the only way that suppressive therapy could improve neurodevelopmental outcomes is if there is subclinical reactivation of virus occurring "silently" in the brain following treatment of the initial acute disease. As with congenital CMV, the dose and duration of parenteral acyclovir established by our CASG studies and the use of oral acyclovir suppressive therapy are now recommended by the American Academy of Pediatrics as the standard of care for babies with neonatal HSV disease throughout the United States. We also have proven that suppressive antiviral treatment of pregnant women does not prevent the transmission of HSV to the baby at delivery, with the subsequent development of neonatal herpes. I also analyzed and published the pharmacokinetic analyses of valacyclovir in children, which led to a label change for that drug as well.

a. **Kimberlin DW**, Lakeman FD, Arvin AM, Prober CG, Corey L, Powell DA, Burchett SK, Jacobs RF, Starr SE, Whitley RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group: Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. J. Infect. Dis. 1996; 174:1162-1167. PubMed PMID: 8940204
b. **Kimberlin DW**, Lin C-Y, Jacobs RF, Powell DA, Corey L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, Murguía de Sierra T, Weller S, Soong S-J, Kiell J, Lakeman FD, Whitley RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 2001; 108:230-238. PubMed: 11483782
c. **Kimberlin DW**, Lin C-Y, Jacobs RF, Powell DA, Frenkel L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, Murguía de Sierra T, Soong S-J, Kiell J, Lakeman FD, Whitley RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. The natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001; 108:223-229. PubMed: 11483781
d. **Kimberlin DW**, Whitley RJ, Wan W, Powell DA; Storch G, Ahmed A, Palmer A, Sánchez PJ, Jacobs RJ, Bradley JS, Robinson JL, Shelton M, Dennehy PH, Leach C, Rathore M, Abughali N, Wright P, Frenkel LM, Brady RC, Van Dyke R, Weiner LB, Guzman-Cottrill J, McCarthy CA, Griffin J, Jester P, Parker M, Lakeman FD, Kuo H, Lee CH, Cloud GA, for the NIAID Collaborative Antiviral Study Group: Oral acyclovir suppression and neurodevelopment after neonatal herpes. N. Engl. J. Med. 2011;365(14):1284-1292. PMCID: PMC3250992. PMCID: PMC3250992

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/16oVh0raPCNka/bibliography/43799096/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

HHSN272201600017C (Kimberlin, PI) 07/01/16 – 06/30/21
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: A Phase II, Single-Stage, Single-Arm Investigation of Oral Valganciclovir Therapy in Infants with Asymptomatic Congenital Cytomegalovirus Infection
This contract evaluates the antiviral treatment of infants who are congenitally infected with cytomegalovirus and are asymptomatic at delivery

HHSN272201600018C (Kimberlin, PI) 07/01/16 – 06/30/21
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: Burden of Neonatal Herpes Simplex Virus Infections in the United States: Disease Incidence, Adequacy of Diagnostic Assessment, Disease Outcome, and Societal Costs; and Prevalence, Frequency, and Incidence of Neonatal Herpes Simplex Virus Infections in Peru
This contract evaluates the incidence of neonatal herpes simplex virus infections in the Unites States and Peru

HHSN272201100034C (Kimberlin, MPI) 09/28/11 – 09/27/20
NIH-NIAID

Targeted Clinical Research to Address Select Viral Infections: Adaptive sequential study evaluating prevention of neonatal HSV: Detection of maternal shedding at delivery followed by preemptive antiviral therapy in exposed neonates
This contract evaluates a novel diagnostic tool for detection of herpes simplex virus in the genital tract of pregnant and non-pregnant women.

HHSN272201100035C (Kimberlin, MPI) 09/28/11 – 09/27/20
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: A Phase II 6 weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss
This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.

HHSN272201100037C (Kimberlin, MPI) 09/28/11 – 09/27/20
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: A pharmacokinetic/pharmacodynamic and resistance evaluation of intravenous ganciclovir in premature infants
This contract evaluates antiviral drug dosing in extremely premature infants with congenital or postnatal cytomegalovirus disease.

HHSN272201100038C (Kimberlin, MPI) 09/28/11 – 09/27/20
NIH-NIAID
Targeted Clinical Research to Address Select Viral Infections: An Observational Study of Acyclovir Pharmacokinetics, Viral Population Kinetics, and Potential Biomarkers of Disease Severity in Neonatal Herpes Simplex Virus Infections
This contract evaluates viral and drug kinetics in neonates with herpes simplex virus disease, and compares new diagnostic modalities to established tests.

75D301-18-R-67879 (Kimberlin, PI) 10/01/18 – 09/30/19
CDC
Approaches to prevention and control of parasitic infections in the U.S.
This contract will support the conduct of a cross-sectional cohort study to determine the prevalence of Soil Transmitted Helminth (STH) infections in school age children in a rural poor community in southern Alabama

HHSN2722013000231 (Edwards, PI) 09/16/13 – 09/15/23
NIH-NIAID
Role: Site PI
Vaccine and Treatment Evaluation Units (VTEU)
The purpose of this contract is to evaluate vaccines and therapeutic agents through the NIAID VTEU network. UAB serves as a site under Vanderbilt University's prime contract. As studies are identified, developed, and performed within the VTEU network, I serve as the Site PI for those pediatric studies conducted at UAB with assignment of appropriate effort to the subcontract. No task orders have been issued to date.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Acosta, Edward P.

eRA COMMONS USER NAME (credential, e.g., agency login): eacosta

POSITION TITLE: Professor and Director, Division of Clinical Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Minnesota-Duluth, Duluth, MN	BS	05/1988	Biology
University of Minnesota, Minneapolis, MN	BS	12/1991	Pharmacy
University of Minnesota, Minneapolis, MN	PHMD	06/1992	Clinical Pharmacy
University of Minnesota, Minneapolis, MN	Postdoctoral Fellow	06/1994	Pharmacometrics

A. Personal Statement

The primary focus of my research program is to apply pharmacometric methods to understand the translational and clinical pharmacology of drugs in pediatric and adult patients. Our focus has traditionally been on antiviral drugs, but we have expanded our capabilities to include drug classes in multiple disease states, including antivirals, antiretrovirals, cystic fibrosis, chemotherapy, antiparasitics, antipsychotics, hormones, and others. The UAB Pediatric Pharmacometrics Laboratory (PPL) currently has the capability to quantitate over 100 different compounds and metabolites from multiple matrices. My program uses mass spectrometry to develop novel assay methods under GLP regulations to support innovative study designs, several of which have subsequently led to new or supplemental pediatric indications. In addition to quantitative pharmacology, my program has the expertise to conduct noncompartmental pharmacokinetic analyses and to apply complex state-of-the-art individual and population pharmacokinetic, pharmacodynamic, and drug-disease models to concentration-time and -response data. My role in this proposal will be as a co-mentor and a key part of the advisory committee to ensure the training and research plan is completed as described; specifically, I will advise Dr. Guimbellot on pharmacometric training and analyses that are described in the proposal by meeting with her at least quarterly.

B. Positions and Honors

Positions and Employment

1986 - 1988 Research Assistant, University of Minnesota-Duluth Medical School, Duluth, MN
1992 - 1994 Post-Doctoral Fellowship in Antiviral Pharmacometrics, University of Minnesota
1994 - 1997 Research Associate, University of Minnesota
1997 - 1999 Assistant Professor (Research), University of Minnesota
1999 - 2002 Assistant Professor (Research), University of Alabama at Birmingham
2002 - 2004 Assistant Professor , University of Alabama at Birmingham
2004 - 2008 Associate Professor, University of Alabama at Birmingham
2008 - Professor (with tenure), University of Alabama at Birmingham
2011 - Director, Division of Clinical Pharmacology, University of Alabama at Birmingham School of Medicine
2012 - Director, Comprehensive Cancer Center Pharmacometrics Core, University of Alabama at Birmingham School of Medicine

Other Experience and Professional Memberships

1995 - Member, American Society of Clinical Pharmacology and Therapeutics

1995 -	Member, American Society for Microbiology
2004 - 2006	Chair, Pediatric Pharmacology Committee , Pediatric AIDS Clinical Trials Group
2007 – 2011	Member, AIDS Drug Development and Therapeutics Study Section, NIH
2009 - 2011	Chair, AIDS Drug Development and Therapeutics Study Section, NIH
2010	Chair, ZRG1 AARR-J (02) M, HIV Pathogenesis, Therapy and NeuroAIDS Study Section, NIH
2012	Chair, Next Generation PrEP II Special Emphasis Panel (RFA-AI-11-023), NIH
2012	Reviewer, AIDS-Associated Opportunistic Infections and Cancer (AOIC) Study Section, NIH
2013	Reviewer, ZRG1 AARR-K (04) Special Emphasis Panel, NIH

Honors

1993	Miles Pharmaceuticals Research Fellowship Award in Infectious Disease
1994	American Society for Microbiology Fellow Travel Grant Award
1995	American Society for Microbiology Fellow Travel Grant Award
2007	Journal of Chromatography Most Cited Author Award, Journal of Chromatography

C. Contributions to Science

1. **Pediatric Registrational Studies.** Historically, pediatric clinical pharmacology has not received the attention it needs, and pediatric drug indications are still lacking. The advent of the Best Pharmaceuticals for Children Act (BPCA) helped bring pediatric clinical pharmacology to the forefront but much work is still needed. The PPL has been involved with pediatric labeling trials since 2007 and our efforts have assisted in attaining 2 new indications and one supplemental indication for antiretroviral therapy thus far. We have also been integrally involved with multiple Collaborative Antiviral Study Group (CASG) trials which have also led to pediatric indications. Based on the need for advanced pediatric clinical pharmacology indication trials, the PPL has evolved into a fully-functional Good Laboratory Practices (GLP) facility capable of supporting new labels and label changes under of FDA guidance. We also have extensive experience in trial development, contracts and budgetary matters, study completion reports, and filing documents. Our long-term goal is to maintain our GLP status and expand our capacities in terms of different drugs and disease states where pediatric indications are needed.
   a. Nachman S, Zheng N, Acosta EP, Teppler H, Homony B, et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-infected children aged 2 through 18 years. *Clin Infect Dis* 2014;58:413-22. PubMed PMID: 24145879; PubMed Central PMCID: PMC3890333.
   b. Viani RO, Alvero C, Fenton T, Acosta EP, Hazra R, O'Gara E, Steimers D, Min S, Wiznia A, on behalf of the P1093 study team. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatric Infectious Disease Journal* 2015;34:1207-1213. PubMed PMID: 26244832; PubMed Central PMCID: PMC4604048.
   c. Nachman S, Alvero C, Acosta EP, Teppler H, Homony B, Graham B, Fenton T, Xu X, Rizk ML, Spector SA, Lisa M. Frenkel LM, Worrell C, Handelsman E, Wiznia A. Pharmacokinetics and 48-week safety and efficacy of raltegravir for oral suspension in human immunodeficiency virus type-1-infected children 4 weeks to 2 years of age. *Journal of the Pediatric Infectious Diseases Society* 2015; 1-8. PMID: 26582887; PubMed Central PMCID PMC4681385.
   d. Kimberlin DW, Acosta EP, Prichard MN, Sánchez PJ, Ampofo K, Lang D, Ashouri N, Vanchiere JA, Abzug MJ, Abughali N, Caserta MT, Englund JA, Sood SK, Spigarelli M, Bradley JS, Lew J, Michaels MG, Wan W, Cloud G, Jester P, Lakeman FD, Whitley RJ, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Oseltamivir pharmacokinetics, dosing, and resistance in children from birth to two years of age with influenza (Editor's Choice). *Journal of Infectious Diseases*, 2013;207:709-20. PMID: 23230059; PubMed Central PMCID: PMID: PMC3563309.

2. **Pharmacometrics and Drug-Disease Pharmacology.** Pharmacometrics encompasses many aspects traditionally considered in clinical pharmacology, including drug assay development and validation and pharmacokinetic/pharmacodynamic analyses. More recently, linking these analyses to disease biomarkers or outcomes allows more precise definitions of drug dosing and target drug exposure to maximize efficacy and minimize toxicity. My laboratory continues to use state-of-the-art

pharmacometric methodologies to delineate drug pharmacokinetics, link these parameters to biomarker outcome measures, and perform predictive simulations to identify target exposures and increase the probability of successful treatment responses.

a. Wang K, D'Argenio DZ, Acosta EP, Sheth AN, Delille C, et al. Integrated population pharmacokinetic/viral dynamic modelling of lopinavir/ritonavir in HIV-1 treatment-naïve patients. *Clin Pharmacokinet*. 2014 Apr;53(4):361-71. PubMed PMID: 24311282; PubMed Central PMCID: PMC3962720.
b. Kamal MA, Acosta EP, Kimberlin DW, Gibiansky L, Jester P, et al. The posology of oseltamivir in infants with influenza infection using a population pharmacokinetic approach. *Clin Pharmacol Ther*. 2014 Sep;96(3):380-9. PubMed PMID: 24865390.
c. Rizk ML, Du L, Bennetto-Hood C, Wenning L, Teppler H, Homony B, Graham B, Fry C, Nachman S, Wiznia A, Worrell C, Smith B, Acosta EP. Population pharmacokinetic analysis of raltegravir pediatric formulations in HIV-infected children 4 weeks to 18 years of age. *Journal of Clinical Pharmacology* 2015;55:748-56. PubMed PMID: 25753401; PubMed Central PMCID: PMID: PMC4572519.
d. Sutton AL, Acosta EP, Larson KB, Kerstner-Wood CD, Tita AT, Biggio JR. Perinatal pharmacokinetics of azithromycin for cesarean prophylaxis. *American Journal of Obstetrics & Gynecology* 2015;212:812.e1-6. PubMed PMID: 25595580; PubMed Central PMCID: PMC4612366.

3. **Bioanalytical Pharmacology.** Mass spectrometry has become the standard in drug quantitation technologies. It provides highly accurate and precise measurements of drug quantity in multiple clinically relevant matrices. My laboratory utilizes mass spectrometry to develop new bioanalytical procedures that are meticulously quality controlled, CLIA compliant, and have been proven to pass even the most stringent reviews by FDA inspectors by following FDA Good Laboratory Practice (GLP) Regulations and Laboratory Standard Operating Procedures (SOPs). We have supported many different types of studies, including animal studies, and apply the same stringent measures to each method developed.

a. Bennetto-Hood C, Tabolt G, Savina P, Acosta EP. A sensitive HPLC-MS/MS method for the determination of dolutegravir in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2014 Jan 15;945-946:225-32. PubMed PMID: 24361860; PubMed Central PMCID: PMC4229012.
b. Long MC, Bennetto-Hood C, Acosta EP. A Sensitive HPLC-MS-MS method for the determination of raltegravir in human plasma, *J Chromatogr B Analyt Technol Biomed Life Sci.* 2008;867:165-71. PubMed PMID: 18430616.
c. Bennetto-Hood C, King JR, Long MC, Acosta EP. Development of a sensitive and specific liquid chromatography/mass spectrometry method for the determination of tenofovir in human plasma. *Rapid Communications in Mass Spectrometry* 2007;21:2087-94. PubMed PMID: 17546653.
d. Bennetto-Hood C, Bryson YJ, Stek A, King JR, Mirochnick M, Acosta EP. Zidovudine, lamivudine and nelfinavir concentrations in amniotic fluid and maternal serum. *HIV Clinical Trials* 2009;10:41-7. PubMed PMID: 19362995.

4. **Translational Pharmacology and Clinical Therapeutics.** Translational pharmacology bridges the gap between basic science and clinical therapeutics. My laboratory has helped develop and conduct a multitude of studies *in vitro*, *in silico*, animal, and in pediatric and adult patients that serve to bridge this gap. One of our foci has been to better define therapeutic drug concentration targets, in lieu of adequate Phase II dosing evidence, needed in patients to optimize long-term clinical outcomes. My laboratory has also played a key role in various Phase I-III trials in pediatrics and adults which have led to new or supplemental pediatric indications as well as changes in treatment guidelines. Our long-term goals are to understand the heterogeneity in drug pharmacokinetics, better define therapeutic targets and account for these targets in patients, and by applying these multi-faceted approaches, ultimately improve clinical outcomes for patients.

a. Haas DW, Ribaudo H, Kim RB, Tierney C, Wilkinson GR, Clifford D, Gulick R, Hulgan T, Acosta EP. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004;18:2391-2400. PubMed PMID: 16392089.

b. Shen L, Peterson S, Sedaghat AR, McMahon MA, Callender M, Zhang H, Zhou Y, Pitt E, Anderson KS, Acosta EP, Siliciano RF. Dose-response curve slope sets class-specific limits on inhibitory potential of anti-HIV drugs. *Nature Medicine* 2008;14:762-66. PubMed PMID: 18552857; PMCID: PMC2743464.
c. Gulick RM, Ribaudo HJ, Shikuma CM, Lustgarten S, Squires KE, Meyer III WA, Acosta EP, Schackman BR, Pilcher CD, Murphy RL, Maher WE, Witt MD, Reichman RC, Snyder S, Klingman KL, Kuritzkes DR, for the ACTG A5095 Protocol Team. Triple nucleoside analogue vs. efavirenz-containing regimens for the initial treatment of HIV-1 infection: AIDS Clinical Trials Group (ACTG) Study A5095. *New England Journal of Medicine* 2004; 350:1850-61. PubMed PMID: 15115831.
d. Acosta EP, Grigsby PL, Buckoreelall K, James AM, Long MC, Duffy LB, Waites KB, Novy MJ. Transplacental transfer of azithromycin and its application for eradicating intraamniotic ureaplasma infection in a primate model. *Journal of Infectious Diseases* 2014;209:898-904. PubMed PMID: 24179112; PMCID: PMC3935474.

Full bibliography can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/edward.acosta.1/bibliography/41144491/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

UM1AI068636-13, NIAID/UCLA 06/01/2012 – 11/30/2019
AIDS Clinical Trials Group (ACTG) Pharmacology Specialty Laboratory (PSL)
The primary objectives of the PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of adult patients with HIV-infection participating in Adult AIDS Clinical Trials Group (ACTG) studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments.
Role: Subaward PI

UM1AI068636-13, NIAID/UCLA 12/01/2017 – 11/30/2019
AIDS Clinical Trials Group (ACTG): Pharmacology Specialty Laboratory (PSL – Protocol A5324)
As the pharmacology lab, we will be quantitating both maraviroc and dolutegravir in plasma and CSF from patients enrolled in this study. We are providing this service to the protocol team in order to support the objectives of the study.
Role: Subaward PI

UM1AI068636-13, NIAID/UCLA 05/01/2018 – 11/30/2019
AIDS Clinical Trials Group (ACTG): Pharmacology Specialty Laboratory (PSL – Protocol A5315)
A5315 is examining the clinical use of romidepsin to deplete sanctuary sites of HIV. Participants are also receiving either raltegravir, dolutegravir, or efavirenz. The UAB PSL will be quantitating these latter drugs and performing pharmacokinetic analyses on the data. We are providing this service to the protocol team in order to support the objectives of the study.
Role: Subaward PI

UM1AI068636-13, NIAID/UCLA 05/01/2018 – 11/30/2019
AIDS Clinical Trials Group (ACTG): Pharmacology Specialty Laboratory (PSL – Protocol A5347)
A5347s will quantify concentrations of ARVs in tissue from HIV-infected participants on suppressive ART to characterize exposure-response relationships between tissue drug concentrations and HIV-1 DNA and RNA levels in plasma and PBMCs.
Role: Subaward PI

UM1AI068632-13, NIH/UCLA 06/29/2006 – 11/30/2019
Nachman, Sharon (Network Chair)
International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) Pharmacology Specialty Laboratory (Prime Study)
The primary objectives of the IMPAACT PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of pediatric patients and pregnant women with HIV-infection participating in IMPAACT studies and 2) to

design, implement, and perform pharmacokinetic and pharmacodynamic assessments in these populations.
Role: Subaward PI

ING112578, Merck/JHU 01/01/2014 – 12/31/2019
Nachman, Sharon (Network Chair)
A Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of GSK 1349572, a novel integrase inhibitor, in combination regimens in HIV-1 Infected Infants, Children, and Adolescents (P1093)
The primary objective is to determine safe and effective dose of dolutegravir for children ranging from 4 weeks to 18 years of age in order to obtain additional pediatric approvals.
Role: Subaward PI

MK-0518-080, Merck/JHU 01/01/2014 – 12/31/2019
Nachman, Sharon (Network Chair)
A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1 Exposed Neonates at High Risk of Acquiring HIV-1 Infection (P1110)
The primary objective is to determine safe and effective neonatal raltegravir dose from birth through 6 weeks of age in order to obtain a supplemental indication.
Role: Subaward PI

HHSN272201100035C, NIH/NIAID 09/28/2011 – 09/27/2020
Whitley, Richard (PI)
Targeted Clinical Research to Address Select Viral Infections
A Phase II 6 weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss. This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.
Role: Co-Investigator

HHSN272201100037C, NIH/NIAID 09/28/2011 – 09/27/2020
Whitley, Richard (PI)
Targeted Clinical Research to Address Select Viral Infections
A pharmacokinetic/pharmacodynamic and resistance evaluation of intravenous ganciclovir in premature infants. This contract evaluates antiviral drug dosing in extremely premature infants with congenital or postnatal cytomegalovirus disease.
Role: Co-Investigator

HHSN272201100038C, NIH/NIAID 09/28/2011 – 09/27/2020
Whitley, Richard (PI)
Targeted Clinical Research to Address Select Viral Infections
A multiple ascending dose-finding pharmacokinetic and pharmacodynamic study of CMX-001 in infants with neonatal herpes simplex virus (HSV). This contract evaluates a novel antiviral drug for the treatment of neonatal herpes simplex virus disease involving the central nervous system.
Role: Co-Investigator

CCR17483682, Komen (Susan G.) Breast Cancer Foundation 08/01/2018 – 07/31/2021
Stringer-Reasor, Erica (PI)
A New Paradigm: Using PARP Inhibitors to Treat HER2+ Breast Cancer
The main goal is to develop novel therapies to improve the survival of breast cancer patients who are at risk of relapse.
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Tiwari, Hemant K.

eRA COMMONS USER NAME (credential, e.g., agency login): htiwari

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Kanpur, Kanpur, UP, India	B.Sc.	08/76	Math, Physics, Statistics
Indian Institute of Technology, Kanpur, UP, India	M.Sc.	08/78	Mathematics
University of Notre Dame, Indiana	M.S.	12/83	Mathematics
University of Notre Dame, Indiana	Ph.D.	08/86	Mathematics
LSU Medical Center, New Orleans, Louisiana	Post-Doc	05/93-06/95	Statistical Genetics
Case Western Reserve University, Cleveland, Ohio	Post-Doc	06/96	Statistical Genetics

A. Personal Statement

Dr. Tiwari has extensive experience in both developing statistical methods and their application to biomedical research. He is MPI of the recently funded project on "*Epigenome modification by a dietary pattern rich in polyunsaturated fatty acid*s" to investigate epigenomic biomarkers and biological mechanisms underlying the protective role of the Yup'ik (Alaska Native) traditional diet, rich in n-3 polyunsaturated fatty acids. Also, he is sub-contract PI on the "*Stroke Investigative Research & Educational Network (SIREN)"* to investigate genomic and environmental factors predisposing to stroke. Dr. Tiwari possesses deep expertise in statistical genetics software programs, bioinformatics, and developing new methods for genomics data. In addition, he is interested in developing methods for next gen sequencing technology including Structural variations, Exome sequencing, genome-wide methylation, microbiome, metabolome, and transcriptome data types and integration of different data domains. In addition, he was a PI of funded educational programs, R25s, to deliver national short courses in statistical genetics/genomics (R25 GM093044 (Tiwari)) and short courses on Next-Generation Sequencing Technology and Statistical Methods (R25HG006110 (Tiwari)) and co-PI on "UAB Metabolomics Workshop: From Design To Decision" (PI: Barnes; R25GM103798). He was a PI of NHLBI funded pre-doctoral T32 training program in biostatistics (T32HL79888) and is also director of the post-doctoral T32 training program in the statistical genetics (T32HL072757).

He has unique expertise in computational, mathematical and applied research having PhD in mathematics, teaching and doing research in theoretical statistics, and collaborations with biomedical community. He has extensive experience in statistical genetics, bioinformatics, and training pre-doctoral, post-doctoral and junior faculty members**.** Currently, he is mentoring Dr. Aslibekyan (K01 Awardee) and co-mentoring Dr. Hidalgo (K01 Awardee) in Epidemiology Department. With his extensive experience in statistical genetics, bioinformatics, and training pre-doctoral, post-doctoral and junior faculty members, he is well qualified and highly enthusiastic to advise Dr. Guimbellot in her proposed research project "*Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients*"**.** Specifically, he will meet with her at least quarterly to review this project and determine associations of variants with clinical study results.

B. Positions and Honors

Positions and Employment

1986 - 1988	Visiting Assistant Professor of Mathematics, University of Notre Dame, Indiana
1988 - 1990	Visiting Assistant Professor of mathematics, Loyola University of Chicago, Chicago, Illinois
1990 - 1993	Asst. Prof. of Mathematics and Computer Science, University of Maine, Fort Kent, Maine
1993 - 1995	Post-Doc, LSU Medical Center, New Orleans, LA
1995 - 1996	Post-doc, Case Western Reserve University, Cleveland, OH
1996 - 1999	Senior Instructor, Department of Epi and Biostatistics, CWRU, Cleveland, Ohio
1999 - 2001	Asst. Prof., Department of Epi and Biostatistics, CWRU, Cleveland, Ohio
2002 - 2006	Assistant Professor, Section on Statistical Genetics, Department Biostatistics, & Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama
2006 - 2011	Associate Professor, Section on Statistical Genetics, Department Biostatistics, University of Alabama at Birmingham, Birmingham, Alabama
2010 -	William “Student: Sealy Gosset Professor in Biostatistics in the School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama
2011- 2015	Professor, UAB

Other Experience

2002 – 2006	Charter Member of NAME Study Section (formally known as ECDA), CSR,NIH
2010 – 2013	Member of CIDR Study Section NIH/NHGRI

Honors

1993-1995	NIH Postdoctoral Fellowship, Louisiana State University Medical School
1995	NIH Postdoctoral fellowship, Case Western Reserve University
2010	Graduate Dean’s Excellence in Mentoring Award, School of Public Health, UAB

C. Contribution to Science

I have published more than 100 peer-reviewed papers including methodological work, collaborative work, and review work. A complete listing can be found in my bibliography at: http://www.ncbi.nlm.nih.gov/sites/myncbi/1bq3yXt-b-tAd/bibliography/47568868/public/?sort=date&direction=ascending.

Statistical Genetics Methods Development. Due to my training in mathematics, I have always been interested in developing optimal statistical methods for the analyses of the data produced by current genomic technologies. We have always taken lead in developing methods comparing existing methods to determine optimal method or develop a new optimal method with respect to validity and power. Examples of the some of the publications are given below.

- Wineinger NE, **Tiwari HK**. The impact of errors in copy number variation detection algorithms on association results. PLoS One. 2012;7(4):e32396. doi:10.1371/journal.pone.0032396. Epub 2012 Apr 16. PubMed PMID: 22523537; PubMed Central PMCID: PMC3327691.
- Wineinger NE, Pajewski NM, **Tiwari HK**. A Method to Assess Linkage Disequilibrium between CNVs and SNPs Inside Copy Number Variable Regions. Front Genet. 2011 Apr 25;2:17. doi: 10.3389/fgene.2011.00017. eCollection 2011. PubMed PMID: 21660233; PubMed Central PMCID: PMC3109359.
- Waite LL, Weaver B, Day K, Li X, Roberts K, Gibson AW, Edberg JC, Kimberly RP, Absher DM, **Tiwari HK**. Estimation of Cell-Type Composition Including T and B Cell Subtypes for Whole Blood Methylation Microarray Data. *Front Genet*. 2016 Feb 18;7:23. doi: 10.3389/fgene.2016.00023. eCollection 2016. PMID: 26925097; PMCID: 4757643
- Mallick H, **Tiwari HK**. EM Adaptive LASSO-A Multilocus Modeling Strategy for Detecting SNPs Associated with Zero-inflated Count Phenotypes. Front Genet. 2016 Mar 30;7:32. eCollection 2016. PMID: 27066062. PMCID: PMC4811966

Population Genetics. I published very first paper on population genetics to start my career in statistical genetics. I have taught courses in population genetics, bioinformatics, and molecular evolution. He had developed a course in population genetics pertaining to gene discovery in diseases or traits while at Case Western Reserve University. Here are few examples of publications using population genetics methodology.

- Knight A, Batzer MA, Stoneking M, **Tiwari HK**, Scheer WD, Herrera RJ, Deininger PL (1996): DNA Sequences of Alu Elements Indicate a Recent, Single Origin for Modern Humans. *Proc Nat Acad Sci* USA 93:4360-4364. PMCID: PMC39542
- Makowsky R, Yan Q, Wiener HW, Sandel M, Aissani B, **Tiwari HK**, Shrestha S. The utility of mitochondrial and Y chromosome phylogenetic data to improve correction for population stratification. Front Genet. 2012;3:301. doi: 10.3389/fgene.2012.00301. Epub 2012 Dec 21. PMCID: PMC3527715
- Vaughan LK, Divers J, Padilla M, Redden DT, **Tiwari HK**, Pomp D, Allison DB. The use of plasmodes as a supplement to simulations: A simple example evaluating individual admixture estimation methodologies. Computational Statistics and Data Analysis. 2009. 53(5):1755-1766. PMCID: PMC2678733
- Hill AE, Plyler ZE, **Tiwari H**, Patki A, Tully JP, McAtee CW, Moseley LA, Sorscher EJ. Longevity and plasticity of CFTR provide an argument for noncanonical SNP organization in hominid DNA. PLoS One. 2014 Oct 28;9(10):e109186. doi: 10.1371/journal.pone.0109186. eCollection 2014. PMCID: PMC4211684

Collaborative Research. I have had extensive record of productive collaborations in searching for genes for obesity, cardiovascular diseases, Rheumatoid Arthritis, SLE, Stroke, and Multiple Sclerosis, to name few. I have served as a lead statistical geneticist in several collaborative projects. My role has been as collaborative scientist to design the study and if funded use most optimal method of analysis. I always test a method through simulations for validity and power before using it for the analysis. Some of the long collaborations have been very productive and have resulted in several papers. Below are few examples of my recent collaborative publications in genomic research.

- Aslibekyan S, Irvin MR, Hidalgo BA, Perry RT, Jeyarajah EJ, Garcia E, Shalaurova I, Hopkins PN, Province MA, **Tiwari HK**, Ordovas JM, Absher DM, Arnett DK. Genome- and CD4+ T-cell methylome-wide association study of circulating trimethylamine-N-oxide in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN). J Nutr Intermed Metab. 2017 Jun;8:1-7. doi: 10.1016/j.jnim.2017.03.002. Epub 2017 Mar 8. PMID: 28439531. PMCID: PMC5400362 [Available on 2018-06-01]
- Akinyemiju T, Do AN, Patki A, Aslibekyan S, Zhi D, Hidalgo B, **Tiwari HK**, Absher D, Geng X, Arnett DK, Irvin MR. Epigenome-wide association study of metabolic syndrome in African-American adults. Clin Epigenetics. 2018 Apr 10;10:49. doi: 10.1186/s13148-018-0483-2. eCollection 2018. PMID: 29643945. PMCID: PMC5891946
- Irvin MR, Aslibekyan S, Do A, Zhi D, Hidalgo B, Claas SA, Srinivasasainagendra V, Horvath S, **Tiwari HK**, Absher DM, Arnett DK. Metabolic and inflammatory biomarkers are associated with epigenetic aging acceleration estimates in the GOLDN study. Clin Epigenetics. 2018 Apr 18;10:56. doi: 10.1186/s13148-018-0481-4. eCollection 2018. PMID: 29713391. PMCID: PMC5907301
- Sayols-Baixeras S, **Tiwari HK**, Aslibekyan SW. Disentangling associations between DNA methylation and blood lipids: a Mendelian randomization approach. BMC Proc. 2018 Sep 17;12(Suppl 9):23. doi: 10.1186/s12919-018-0119-8. eCollection 2018. PMID: 30275879. PMCID: PMC6157243

Reviews of current topics. Reviews are most time consuming manuscripts to write, but they provide all the information in one place and are great service to scientific community. Of course, they require vast knowledge of the topic in question and an author's ability to summarize the large body of work by others in succinct form. Thus, reviews are also very important as methodological work. Here we provide few examples of recent reviews.

- Akinyemi RO, Owolabi MO, Oyeniyi T, Ovbiagele B, Arnett DK, **Tiwari HK**, Walker R, Ogunniyi A, Kalaria RN; SIREN group of H3Africa Consortium. Neurogenomics in Africa: Perspectives, progress, possibilities and priorities. J Neurol Sci. 2016 Jul 15;366:213-23. doi: 10.1016/j.jns.2016.05.006. Epub 2016 May 6. Review. PMID: 27288810. PubMed Central PMCID: PMC4920548
- Barnes S, Benton HP, Casazza K, Cooper SJ, Cui X, Du X, Engler J, Kabarowski JH, Li S, Pathmasiri W, Prasain JK, Renfrow MB, Tiwari HK. Training in metabolomics research. I. Designing the experiment, collecting and extracting samples and generating metabolomics data. J Mass Spectrom. 2016 Jul;51(7):461-75. doi: 10.1002/jms.3782. PMID: 27434804 PMCID: PMC4964969

- Barnes S, Benton HP, Casazza K, Cooper SJ, Cui X, Du X, Engler J, Kabarowski JH, Li S, Pathmasiri W, Prasain JK, Renfrow MB, Tiwari HK. Training in metabolomics research. II. Processing and statistical analysis of metabolomics data, metabolite identification, pathway analysis, applications of metabolomics and its future. J Mass Spectrom. 2016 Aug;51(8):535-548. doi: 10.1002/jms.3780. PMID: 28239968 PMCID: PMC5584587
- Owolabi M, Peprah E, Xu H, Akinyemi R, **Tiwari HK**, Irvin MR, Wahab KW, Arnett DK, Ovbiagele B. Advancing stroke genomic research in the age of Trans-Omics big data science: Emerging priorities and opportunities. J Neurol Sci. 2017 Nov 15;382:18-28. doi: 10.1016/j.jns.2017.09.021. Epub 2017 Sep 18. Review. PMID: 29111012. PMCID: PMC5685670

D. Research Support

Ongoing Research Support

NIH R01DK104347 (Boyer, Tiwari and Absher (multi-PIs)) 09/20/16 – 07/31/20
NIH/NIDDK
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The overall goal of the proposed research is to identify epigenetic factors underlying the relationship between metabolic health and the traditional Yup'ik Alaska Native diet, rich in n-3 polyunsaturated fatty acids (PUFAs) from marine mammals, fish, and other wild country (subsistence) foods.
Role: MPI

NIH R01DK112358-01 (Boyer, Tiwari and Absher (multi-PIs)) 07/15/17 – 03/31/21
NIH/NIDDK
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The proposed research is aimed at identifying diet-induced changes in genomic DNA methylation patterns that are associated with changes in downstream gene expression, as well as phenotypic and metabolic profiles associated with insulin sensitivity and protection from Type 2 Diabetes.
Role: MPI

R01CA178441 (Tollefsbol) 04/01/2014 – 02/28/2019
NIH/NCI
Combinatorial Epigenetic-Based Prevention of Breast Cancer
The overall goal of this application is to develop a combinatorial dietary approach consisting of green tea polyphenols and sulforaphane-rich broccoli sprouts for efficacious and safe use in preventing the epigenetic aberrations of breast cancer.
Role: Co-investigator

1R01CA204346 (Tollefsbol) 01/01/2017-12/31/2021
NIH/NCI
Early Life Prevention of Breast Cancer with Combined Epigenetic Botanicals
The goal of this application is to develop efficacious dietary regimens of epigenetic aberration-neutralizing dietary botanicals consumed at various stages of life for preventing estrogen receptor-negative breast cancer.
Role: Co-investigator

2R01HL091357-05 (Arnett) 08/01/2015 – 07/31/2019
NIH/NHLBI
Genomewide Association Study of Lipid Response to Fenofibrate and Dietary Fat
This study aims to identify genetic variants that influence fat and cholesterol's response to diet and drugs; this knowledge may someday help doctors tailor prevention efforts and treatments based on individual's genetic endowment.
Role: Co-investigator

1R01HL123782-01A (Irvin) 09/15/2016-05/31/2021
NIH/NHLBI
Genomic Background of Blood Pressure Response to Thiazide Diuretic in African Americans.
Research shows that better blood pressure control produces cardiovascular benefits in African Americans. This study seeks to discover genetic variants that influence how blood pressure can be controlled in African Americans on a frequently used medication class (thiazide diuretics). In the future, such knowledge could help improve the care of African Americans with high blood pressure.

Role: Co-investigator

NIH R01AR073850 (Brown) 07/01/18 – 06/30/23
NIH/NIAMS
Characterization of the Lupus Nephritis microRNAome
The purpose of this study is to characterize role of genome-wide microRNA in lupus nephritis.
Role: Co-Investigator

NIH R01HL140493 (Broeckel) 07/01/18 – 06/30/23
NIH/NHLBI
Characterization and Genetics of KI toxicity in iPSC-derived cardiomyocytes
The purpose of the study is to identify genetic markers and understanding the underlying mechanisms using human induced pluripotent stem cell derived cardiomyocytes.
Role: Sub-contract PI

NIH P30DK079337 (Agarwal) 08/01/18 – 07/31/23
NIH/NIDDK
UAB-UCSD O'Brien Center For Acute Kidney Injury Research
The UAB-UCSD O'Brien Center has brought together a team of investigators to serve unmet needs of our investigator base and to fill the gaps in knowledge in the field of Acute kidney injury (AKI) and AKI-related research.
Role: Co-Investigator

NIH R01HL129907 (Ambalavanan) 09/15/15 – 06/30/19
NIH/NHLBI
Stop BPD
Purpose of the study is to evaluate extremely preterm infants to determine alterations in gene expression, protein amounts, or microbial flora in the airway that are associated with resilience (resistance to development of severe Bronchopulmonary dysplasia (BPD)) or predisposition (higher rate of developing severe BPD even if not initially considered at high risk).
Role: Co-Investigator

NIH R01HL055673 (Arnett) 07/15/16 – 04/30/19
NIH/NHLBI
HyperGEN: Genetics of Left Ventricular Hypertrophy
This study seeks to discover which genetic factors may cause an enlarged heart; this may ultimately lead to new diagnoses and treatments to help lower cardiovascular disease risk in blacks.
Role: Co-Investigator

No Number (Aslibekyan) 07/01/18 – 06/30/20
American Heart Association
A High-Resolution Integrative-Omic Analysis of Cardiorenal Traits in African Americans
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Aban, Inmaculada

eRA COMMONS USER NAME (credential, e.g., agency login): chichiaban

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of the Philippines at Diliman, Philippines, Quezon City	BS	10/1985	Statistics
Bowling Green State University, Bowling Green, OH	MS	05/1988	Applied Statistics
Bowling Green State University, Bowling Green, OH	PHD	08/1995	Mathematics

A. Personal Statement

I am currently Professor in the Department of Biostatistics at UAB and a member of the Pediatric Research Office providing biostatistical expertise and analysis at all stages of project development. I have worked with Dr. Guimbellot for three years in CF research. For this application I will be working with Dr. Guimbellot to apply human subjects biostatistics approaches to translational studies in personalized medicine for cystic fibrosis. For this application my role will be to serve in an advisory capacity to aid in Dr. Guimbellot's understanding of the application of biostatistics and help her in the design of human subjects studies as well as data analysis and modeling. I have considerable experience in clinical trial studies and statistical methodology research in the past 20 years. I am a co-investigator in the TWEAK trial funded by NICHD investigating the effects of progressive resistance exercise training on muscle mass and mobility function after total joint arthroplasty. I am the Director of the Data Coordinating Center and Protocol Biostatistician of several studies: 1 FDA clinical pediatric trials (Phase II), 1 device diagnostic study, 2 natural history studies (pediatric and adult), and 1 observational pediatric study all funded by NIH/DMID in the area of infectious diseases. I was the PI of the Biostatistics Core of a NHLBI-sponsored SCCOR program on Heart Failure which involved 2 randomized phase 2 clinical trials. I was involved in collaborative research in the area of aging, HIV and obesity. My areas of interest in statistical methods research are in the clinical trials, dose-finding designs, analyses of count data, survival analysis, analysis and modeling of spatio-temporal data from structural magnetic resonance imaging, developing methods of inference for heavy tailed distribution, and developing methods for goodness of fit and model diagnostics. I have been a member of Data Safety Monitoring Board for several clinical studies and currently a member of the NIAMS AMSC Clinical Trial Review Committee. Previously I was a member of the Institute of Medicine Committee on the Review of the Safety of Vaccines and also an ad-hoc member of several study sections and special emphasis panel NHLBI, NIDDK, and NINDS.

B. Positions and Honors

1985 - 1986 Instructor, University of the Philippines, Quezon City
1986 - 1988 Teaching Assistant, Department of Applied Statistics and Operations Research, Bowling Green State University, Bowling Green, OH
1988 - 1990 Statistician, Intel-Philippines, Makati
1991 - 1995 Teaching/Research Assistant, Department of Mathematics, Bowling Green State University, Bowling Green, OH
1995 - 2001 Assistant Professor, Department of Mathematics, University of Nevada, Reno, Reno, NV
2001 - 2004 Associate Professor(with tenure), Department of Mathematics and Statistics, University of

	Nevada Reno,, Reno, NV
2004 - 2008	Assistant Professor, Department of Biostatistics, University of Alabama at Birmingham,, Birmingham, AL
2008 - 2014	Associate Professor(with tenure), Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL
2014 -	Professor, Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL

Other Experience and Professional Memberships

- Member, American Statistical Association
- Member, ENAR
- Member, Society for Clinical Trials

Honors

1985	Cum Laude, University of the Philippines at Diliman
2007	Best Paper Award (Statistics Research), Science Unbound Foundation
2010	UAB President's Award for Excellence in Teaching, University of Alabama at Birmingham

C. Contributions to Science

1. Clinical Trials: Since 2004, I have been involved in the design, conduct, management and analysis of clinical trials in the areas of neurology (myasthenia gravis, multiple sclerosis), cardiology (cardiac dysfunction and disease), infectious disease, and pediatrics.

    a. Ahmed MI, Aban I, Lloyd SG, Gupta H, Howard G, Inusah S, Peri K, Robinson J, Smith P, McGiffin DC, Schiros CG, Denney T Jr, Dell'Italia LJ. A randomized controlled phase IIb trial of beta(1)-receptor blockade for chronic degenerative mitral regurgitation. J Am Coll Cardiol. 2012 Aug 28;60(9):833-8. PubMed PMID: 22818065; PubMed Central PMCID: PMC3914413.

    b. Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR, Sood SK, Whitworth MS, Abzug MJ, Caserta MT, Fowler S, Lujan-Zilbermann J, Storch GA, DeBiasi RL, Han JY, Palmer A, Weiner LB, Bocchini JA, Dennehy PH, Finn A, Griffiths PD, Luck S, Gutierrez K, Halasa N, Homans J, Shane AL, Sharland M, Simonsen K, Vanchiere JA, Woods CR, Sabo DL, Aban I, Kuo H, James SH, Prichard MN, Griffin J, Giles D, Acosta EP, Whitley RJ. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669; PubMed Central PMCID: PMC4401811.

    c. Travers CP, Carlo WA, Nakhmani A, Bhatia S, Gentle SJ, Amperayani VA, Indic P, Aban I, Ambalavanan N. Environmental or Nasal Cannula Supplemental Oxygen for Preterm Infants: A Randomized Cross-Over Trial.J Pediatr. 2018 Apr 25. pii: S0022-3476(18)30342-1. doi: 10.1016/j.jpeds.2018.03.010. [Epub ahead of print] PMID: 29705116

2. Statistical Methodology: Over the last 20 years, I have conducted statistical methodological research in the areas of survival analysis, heavy-tailed distribution, pool screening, spatiotemporal modeling of imaging data, and more recently Continuous Reassessment Method (CRM) for phase 1 clinical trial studies.

    a. Aban I, Meerschaert M, Panorska A. Parameter Estimation for the Truncated Pareto Distribution. Journal of the American Statistical Association. 2006; 101:270-277.

    b. George B, Aban I. Selecting a separable parametric spatiotemporal covariance structure for longitudinal imaging data. Stat Med. 2015 Jan 15;34(1):145-61. PubMed PMID: 25293361; PubMed Central PMCID: PMC4262538.

    c. Salter A, O'Quigley J, Cutter GR, Aban IB. Two-group time-to-event continual reassessment method using likelihood estimation. Contemp Clin Trials. 2015 Nov;45(Pt B):340-5. doi: 10.1016/j.cct.2015.09.016. Epub 2015 Sep 25. PMID: 26409251

    d. Lirette S, Smith AD, Aban I. A tool to visualize and analyze perfusion data: Development and application of the R package "CTP". Computer Methods and Programs in Biomedicine. Epub 2017 Oct 05, Volume 153, January 2018, Pages 11-17.

3. Pediatric Research: Since 2008, I have supported pediatric infectious disease research. In 2015, I became Biostatistician in the Pediatrics Research Office of UAB.

    a. Aban I., Baddam S, Hilliard LM, Howard TH, Feig D, Lebensburger JD. Severe anemia early in life as a risk factor for sickle cell kidney disease. Blood. 2016 Dec 5. pii: blood-2016-09-738104. [Epub ahead of print] No abstract available. PMID: 27919909
    b. Alten JA, Rahman AF, Zaccagni HJ, Shin A, Cooper DS, Blinder JJ, Retzloff L, Aban IB, Graham EM, Zampi J, Domnina Y, Gaies MG. The Epidemiology of Health-Care Associated Infections in Pediatric Cardiac Intensive Care Units. Pediatr Infect Dis J. 2017 Dec 26. doi: 10.1097/INF.0000000000001884. [Epub ahead of print] PMID: 29280785
    c. Guimbellot JS, Leach JM, Chaudhry IG, Quinney NL, Boyles SE, Chua M, Aban I, Jaspers I, Gentzsch. M.Nasospheroids permit measurements of CFTR-dependent fluid transport. JCI Insight. 2017 Nov 16;2(22). pii: 95734. doi: 10.1172/jci.insight.95734. [Epub ahead of print] PMID: 29202459

4. Cardiology Research: Since 2005, I have been actively collaborating with researchers in the area of cardiology -- basic science, clinical trials, epidemiological studies, and cardiac imaging.

    a. Zheng J, Wei CC, Hase N, Shi K, Killingsworth CR, Litovsky SH, Powell PC, Kobayashi T, Ferrario CM, Rab A, Aban I, Collawn JF, Dell'Italia LJ. Chymase mediates injury and mitochondrial damage in cardiomyocytes during acute ischemia/reperfusion in the dog. PLoS One. 2014;9(4):e94732. PubMed PMID: 24733352; PubMed Central PMCID: PMC3986229.
    b. Ahmed MI, Guichard JL, Rajasekaran NS, Ahmad S, Mariappan N, Litovsky S, Gupta H, Lloyd SG, Denney TS, Powell PC, Aban I, Collawn JF, Davies JE, McGiffin DC, Dell'Italia LJ. Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function. J Thorac Cardiovasc Surg. 2016 Jun 25. pii: S0022-5223(16)30647-X. doi: 10.1016/j.jtcvs.2016.06.017. [Epub ahead of print]
    c. Lam PH, Dooley DJ, Fonarow GC, Butler J, Bhatt DL, Filippatos GS, Deedwania P, Forman DE, White M, Fletcher RD, Arundel C, Blackman MR, Adamopoulos C, Kanonidis IE, {\bf Aban IB}, Patel K, Aronow WS, Allman RM, Anker SD, Pitt B, Ahmed A. Similar clinical benefits from below-target and target dose enalapril in patients with heart failure in the SOLVD Treatment trial. Eur J Heart Fail. 2018 Feb;20(2):359-369. doi: 10.1002/ejhf.937. Epub 2017 Oct 5. PMID: 28980368

5. Other collaborative research: In the past 20 years, I have also been involved in research in the areas of psychology, nutrition, diabetes and geriatrics. In 2015, I became involved in a clinical trial regarding an exercise intervention for osteoarthritis patients undergoing joint anthroplasty.

    a. Baltazar JC, Ancheta CA, Aban IB, Fernando RE, Baquilod MM. Prevalence and correlates of diabetes mellitus and impaired glucose tolerance among adults in Luzon, Philippines. Diabetes Res Clin Pract. 2004 May;64(2):107-15. PubMed PMID: 15063603.
    b. St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks. Am J Clin Nutr. 2007 Jun;85(6):1503-10. PubMed PMID: 17556685; PubMed Central PMCID: PMC3666855.
    c. Kvale E, Ekundayo OJ, Zhang Y, Akhter S, Aban I, Love TE, Ritchie C, Ahmed A. History of cancer and mortality in community-dwelling older adults. Cancer Epidemiol. 2011 Feb;35(1):30-6. PubMed PMID: 20708995; PubMed Central PMCID: PMC3062071.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

04/09/2018 – 08/31/2018
1UG3TR002450-01 NIH/National Center for Advancing Translational Sciences
Dransfield (PI)
AZD9688: A FIRST IN CLASS DISEASE MODIFYING THERAPY TO TREAT ALPHA-1 ANTITRYPSIN DEFICIENCY A GENETICALLY LINKED ORPHAN DISEASE

Alpha-1 antitrypsin deficiency (AATD) is the most common genetic cause of chronic obstructive pulmonary disease (COPD) and early-onset emphysema, and AATD is characterized by low AAT levels, leading to excessive neutrophil elastase (NE) mediated lung destruction. Current treatment requires the periodic infusion of pooled AAT derived from human plasma, but this therapeutic approach does not definitively slow the rate of emphysema progression and is very expensive with annual direct costs over $100,000 per patient. We propose to study the safety, tolerability, and efficacy of AZD9668, an orally available NE-inhibitor, in patients with AATD.

04/01/2015-03/01/2020
NIH/NICHD 1R01 HD084124
Bamman (PI)
Overcoming TWEAK signaling to fully restore muscle mass and mobility function after total joint arthroplasty
The goals of the study are: (1) to determine the effects Progressive resistance exercise training (PRT) vs. usual care after elective THA/TKA on muscle mass, muscle performance, and mobility function; (2) to determine whether MuIS status modifies the effects of 16 wk PRT or usual care after THA/TKA; and (3) to determine whether MuIS status modifies the effects of 16 wk PRT or usual care after THA/TKA.
Role: Co-Investigator, Protocol Biostatistician

09/01/2016 – 08/31/2019
Wright State University 670266-1
Bamman (PI)
Precision High Intensity Training through Epigenetics (PHITE)
Role: Protocol Biostatistician

05/01/2017 – 04/30/2020 .
NIH/NCI 1R01CA217179
Markert (PI)
A PHASE 1 STUDY OF M032, A GENETICALLY ENGINEERED HSV-1 EXPRESSING IL-12, IN PATIENTS WITH RECURRENT/PROGRESSIVE GLIOBLASTOMA MULTIFORME, ANAPLASTIC ASTROCYTOMA, OR GLIOSARCOMA.
We conduct a first-in-human Phase I clinical trial to assess the safety and tolerability of M032, to define any unexpected toxicities, to obtain correlative biologic information, and to determine a Phase 2 Dose.
Role: Protocol Biostatistician

2011/10/01-2018/09/30
BAA-NIAID-DMID-NIHAI2010101, NIH/NIAID
Kimberlin, David (PI)
A Phase II 6 Weeks Oral Valganciclovir versus Placebo in Infants with Congenital CMV Infection and Hearing Loss
The major goals of this project are to determine if a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss, to define the systemic exposure to ganciclovir, describe the safety and tolerability of valganciclovir syrup in children of this age and to define the pharmacokinetics of ganciclovir when valganciclovir is administered to children of these ages.
Role: Director of the Data Coordinating Center / Protocol Biostatistician

2011/10/01-2018/09/30
BAA-NIAID-DMID-, NIH/NIAID
Kimberlin, David (PI)
Evaluation of the Pharmacokinetics and Pharmacodynamics of Ganciclovir in Premature Infants Receiving Treatment for Cytomegalovirus Infection
The major goals of this project are to define the pharmacokinetics of ganciclovir in premature infants, to assess changes in quantitative viral DNA in whole blood as a function of drug pharmacokinetics, to assess clearance of CMV in urine (by culture) as a function of drug pharmacokinetics, to assess development of neutropenia as a function of drug pharmacokinetics and to determine the potential for the development of resistance to ganciclovir as a function of pharmacokinetics, dose, age, and duration of therapy.
Role: Director of the Data Coordinating Center / Protocol Biostatistician

2011/10/01-2018/09/30
BAA-NIAID-DMID-NIHAI2010101, NIH/NIAID
Kimberlin, David (PI)
An Observational Study Of Acyclovir Pharmacokinetics, Viral Population Kinetics, And Potential Biomarkers Of Disease Severity In Neonatal Herpes Simplex Virus Infections.
The major goal of this project to describe the population pharmacokinetics of high-dose parenteral acyclovir (60 mg/kg/day) in neonates with virologically confirmed neonatal HSV disease.
Role: Director/ Protocol Biostatistician, Data Coordinating Center

2011/10/01-2018/09/30
BAA-NIAID-DMID-NIHAI2010101, NIH.NIAID
Kimberlin, David (PI)
Identification of Herpes Simplex Virus (HSV) Shedding in the Female Genital Tract of Pregnant and Nonpregnant Women by the XPERT HSV 1/2 Assay, Routine PCR, and Culture
The major goals of this project are to evaluate the sensitivity and specificity of the GeneXpert real-time PCR test for detecting herpes simplex virus (HSV) DNA in the genital tract of women in active labor or in sexually transmitted infections (STI) clinics. Additionally this study will determine rates of neonatal HSV disease, attempt to quantify HSV viral load in the genital tract of women shedding the virus who are in active labor and assess the type of maternal infection (first-episode primary, first-episode non-primary, recurrent) among women shedding HSV during active labor.
Role: Director of the Data Coordinating Center / Protocol Biostatistician

2011/10/01-2018/09/30
BAA-NIAID-DMID-NIHAI2010101 , NIH/NIAID
Gnann, John (PI)
Natural History of Infection Caused by BK Virus (and other Opportunistic Viral Pathogens) in Renal and Renal-Pancreas Transplant Recipients
Targeted Clinical Research to Address Select Viral Infections-Safety, Tolerability and Pharmacokinetic Properties of CMX001 in Renal Transplant Recipients with BK Viremia T
he primary objective is to define the natural history of BK viremia. In order to understand the natural history of infection, we will measure the time (days post-transplant) to the development of BK viremia and its correlation with progression to end-organ disease (BKVN or BK hemorrhagic cystitis). Data from this prospective monitoring will allow for the identification of the types of high-risk patients who might benefit from future studies of therapeutic interventions for BKV infection (when effective therapy becomes available). This will be accomplished by serial quantitative BK DNA measurements in blood (plasma), assayed by polymerase chain reaction (PCR).
Role: Director of the Data Coordinating Center / Protocol Biostatistician

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Scott, Emily

eRA COMMONS USER NAME (credential, e.g., agency login): EESCOTT

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Texas at Galveston, Galveston, TX	B.S.	12/1992	Marine Biology
Rice University, Houston, TX	Ph.D.	05/1998	Biochemistry, Cell Biology
Rice University, Houston, TX	Postdoctoral	06/1999	Biochemistry, Cell Biology
University of Texas Medical Branch, Galveston, TX	Postdoctoral	04/2004	Pharmacology, Toxicology

A. Personal Statement

The focus of my research career is to characterize cytochrome P450 (CYP) structure/function relationships in order to understand and manipulate the metabolism of drugs and key endogenous molecules toward the prevention and treatment of multiple disease states. My own Ph.D. training focused on heme protein structure/function, followed by NRSA-funded postdoctoral studies determining some of the earliest X-ray structures of membrane cytochrome P450 enzymes (CYP2B4). Since then our laboratory has significantly contributed to defining the structure and function of >25 human cytochrome P450 enzymes with key roles in drug metabolism, procarcinogen activation, and steroidogenesis. My laboratory is perhaps best known for structures of human P450 enzymes CYP1A1, CYP2A6, CYP2A13, CYP2E1, and CYP17A1, most of which were the first structures available of each of these membrane proteins. In recent years our expertise has expanded to define critical P450/protein interactions using orthogonal structural techniques including protein solution NMR, in order to identify new inhibitor strategies not directed at the active site. All structural studies have been integrated with a wide variety of functional analysis to generate a detailed understanding of the respective capabilities of each enzyme. This work supports both an understanding of human drug metabolism that can guide the usage of drugs already developed and support the design of new pharmaceutical agents. This work has been continuously funded by a series of NIH grants since 2004.

I have extensive mentoring experience. Over the 14 years of my independent career I have maintained a relatively small group of 10-12 trainees in order to closely work with and develop each of them in terms of scientific thinking, experimental practice, and the professional and networking skills essential for a successful, productive, and fulfilling scientific career. Being in the Medicinal Chemistry Department at the University of Kansas (2004-2016) and in the Departments of Medicinal Chemistry and Pharmacology at the University of Michigan (since 2016) I have been fortunate to have the opportunity to mentor students with a diverse range of capabilities and career interests. I have mentored graduate students from the Departments of Medicinal Chemistry, Chemistry, Molecular Biosciences, Pharmacology, and programs in Chemical Biology and Biophysics. Former graduate students and postdocs are now assistant and associate professors in research and primarily undergraduate institutions, pharmacy residents, in regulatory affairs, governmental positions involving analytical testing, teaching, research core laboratories, and major agricultural and pharmaceutical companies. At my institutions I have supported a broader range of student training by previous service on the Chemical Biology Training Grant Steering Committee at the University of Kansas, as a mentor to the Postdoctoral Association, by teaching in an ethics course for many years, and as a part of the Preparing Future Faculty Series,

a Doctoral Education Work Group and Postdoctoral Task Force. In addition to my own previous trainees, I currently mentor three junior faculty at other institutions and have had major responsibilities for mentoring a range of other junior faculty as part of my role on the Leadership Committee of an NIH Center of Biomedical Research Excellence Program focused on Protein Structure and Function, particularly in the area of grant writing. At the national level, I am very active in leadership and mentoring activities with the American Society of Pharmacology and Experimental Therapeutics.

Overall, as evidenced by the productive research track records of my trainees and their successful careers in academic, professional, and pharmaceutical arenas, I am well suited to serve as both advisor and collaborator for this proposal.

B. Positions and Honors

Positions and Employment

2004 – 2010 Assistant Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS
2007 – present Affiliate Faculty, Department of Molecular Biosciences, University of Kansas, Lawrence, KS
2008 – present Courtesy Faculty, Department of Chemistry, University of Kansas, Lawrence, KS
2010 – 2015 Associate Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS
2013 Visiting Scholar, Laboratory of Dr. Tom Pochapsky, Dept. of Chemistry, Brandeis University, Waltham, MA
2015 – 2016 Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS
2016 – present Professor, Department of Medicinal Chemistry, University of Michigan, Ann Arbor, MI
2016 – present Professor, Department of Pharmacology, University of Michigan, Ann Arbor, MI
2016 – present Professor, Biophysics Program, University of Michigan, Ann Arbor, MI

(Selected) Other Positions

2006 – 2009 Councilor, Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics
2009 – 2012 Secretary/Treasurer (Elect, Current, Past), Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics
2011 National Institutes of Health, Ad hoc reviewer for study sections: Molecular Structure and Function A (MSFA) and Xenobiotic and Nutrient Disposition and Action (XNDA)
2012 – 2016 National Institutes of Health, Regular member, Molecular Structure and Function Study A (MSFA) Section
2014 – 2017 Chair (Elect, Current, Past), Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics

(Selected) Honors and Awards

1996 – 1998 NIH Predoctoral Fellowship, Houston Area Molecular Biophysics Training Grant
2000 – 2003 NIH National Research Service Award (NRSA) Individual Postdoctoral Fellowship
2003 Best Postdoctoral Scientist Presentation, Drug Metabolism Division, American Society for Pharmacology and Experimental Therapeutics Annual Meeting
2009 James R. Gillette Drug Metabolism Best Paper, *Drug Metabolism and Disposition*
2011 Early Career Achievement Award, Drug Metabolism Division, The American Society of Pharmacology and Experimental Therapeutics
2012 James R. Gillette North American New Investigator Award, The International Society for the Study of Xenobiotics
2015 MERIT Award, National Institute of General Medical Science, National Institutes of Health

C. Contributions to Science

1. Determination of some of the earliest membrane cytochrome P450 structures and establishing the unexpected flexibility of the membrane P450 conformational changes related to ligand access.

All mammalian cytochrome P450 enzymes are membrane proteins. Difficulties in expression, detergent extraction, purification, and stabilization precluded crystallization and structure determination until 2000. Shortly thereafter as a postdoctoral fellow I initiated efforts to determine the first structure of a CYP2B enzyme, by engineering protein constructs; by developing and adapting expression and purification methods that maintained

protein structure, function, and solubility; and by simultaneously learning and establishing crystallography as a new technique in my PI's laboratory. This work resulted in CYP2B4 structures showing CYP2B4 in both a closed conformation (typical of structures up to that time) and an unprecedented open conformation that enabled substrate access from the protein surface to the buried active site. The availability of this open conformation dramatically changed the way the field thought about P450 enzyme conformations and numerous subsequent publications and structures are interpreted with discussion of the substrate access channel. All subsequent CYP2B structures in the PDB (15 structures of CYP2B4 and 7 structures of CYP2B6) have their origins in the initial constructs and protocols my work established at that time. The main papers establishing this work have been cited more than 750 times:

a. Scott E.E., Spatzenegger M., and Halpert J.R. (2001) A truncation of 2B subfamily cytochromes P450 yields increased expression levels, increased solubility, and decreased aggregation while retaining function. ***Arch. Biochem. Biophys.*** 395:57-68.
b. Scott E.E., He Y.A., Wester M.R., White M.A., Chin C.C., Halpert J.R., Johnson E.F., and Stout C.D. (2003) An open conformation of mammalian cytochrome P450 2B4 at 1.6 Å resolution, ***Proc. Nat. Acad. Sci. U.S.A.*** 100:13196-13201.
c. Scott E.E., White M.A., He Y.A., Johnson E.F., Stout C.D., and Halpert J.R. (2004) Structure of mammalian cytochrome P450 2B4 complexed with 4-(4-chlorophenyl)imidazole at 1.9 Å resolution: Insight into the range of P450 conformations and coordination of redox partner binding. ***J. Biol. Chem.*** 279:27294-27301.
d. A movie made using these structures has been frequently requested and used to illustrate and teach about P450 conformational changes: **http://tinyurl.com/2B4-movie**

2. Structure/function studies of 2A enzymes

Early work in my own lab yielded the first structure of human CYP2A13, a lung enzyme responsible for the critical step in the conversion of nicotine into a human carcinogen. Subsequent series of structures of both active human CYP2A enzymes, CYP2A13 and hepatic CYP2A6, bound to common and selective ligands, in concert with site-directed mutagenesis and enzymatic analysis, identified key features of responsible for differential metabolism of nicotine and other substrates. This was accompanied by inhibitor analysis and high-throughput screening and medicinal chemistry developing selective CYP2A13 inhibitors intended to serve as chemopreventative compounds in human smokers.

a. Smith, B.D., Sanders, J.L., Porubsky, P.R., Lushington, G.H., Stout, C.D., and Scott, E.E. (2007) Structure of the human lung cytochrome P450 2A13. ***J. Biol. Chem.*** 282:17306-17313.
b. DeVore, N.M., Smith, B.D., Wang, J.L., Lushington, G.H., and Scott, E.E. (2009) Key residues controlling binding of diverse ligands to human cytochrome P450 2A Enzymes. ***Drug Metab. Dispos.*** 37:1319-1327. PMCID: PMC2683692. ***Selected paper of the year in Drug Metabolism and Disposition***
c. DeVore, N.M. and Scott, E.E. (2012) Nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) binding and access channel in human cytochrome P450 2A6 and 2A13 enzymes. ***J. Biol. Chem.*** 287:26576-26585. PMCID: PMC3410998.
d. Blake, L.C., Roy, A., Neul, D., Schoenen, F.J., Aubé, J. and Scott, E.E. (2013) Benzylmorpholine analogs as selective inhibitors of lung cytochrome P450 2A13 for the chemoprevention of lung cancer in tobacco users. ***Pharm. Res.*** 30: 2290-2302. PMCID: PMC3781598. ***Patent approved***

3. Structure/function studies of 2E1 enzymes

No structures were available for human CYP2E1, which is responsible for the metabolism of many low molecular weight molecules such as ethanol and carcinogens. CYP2E1 hydroxylates fatty acids at the ω-1 position. How this enzyme accommodates both types of ligand scaffolds was unknown. Our first structure of CYP2E1 with low molecular weight ligands revealed a small enclosed active site, but subsequent structures with fatty acid analogs revealed a very different active site. Finally, a structure with the drug pilocarpine revealed yet a third significantly different active site topography. Such structures are important because they underscore the difficulty of *in silico* docking studies successfully predicting binding and drug metabolism, even when structures are known.

a. Porubsky, P.R., Meneely, K.M., and Scott, E.E. (2008) Structures of human cytochrome P450 2E1: Insights into the binding of inhibitors and both small molecular weight and fatty acid substrates. ***J. Biol. Chem.*** 283:33698-33707. PMCID: PMC2586265.

b. Porubsky, P.R., Battaile, K.P., and Scott, E.E. (2010) Human cytochrome P450 2E1 structures with fatty acid analogs reveal unexpected binding mode ***J. Biol. Chem.*** 285:22282-22290. PMCID: PMC2903405.
c. DeVore, N.M., Meneely, K.M., Bart, A.G., Stephens, E.S., Battaile, K.P., and Scott, E.E. (2012) Structural comparison of cytochromes P450 2A6, 2A13, and 2E1 with pilocarpine. ***FEBS J.*** 279:1621-1631. PMCID: PMC3572744.

4. Structure/function studies of steroidogenic cytochrome P450 enzymes

Cytochrome P450 enzymes largely dominate human steroidogenesis. Our work has focused on CYP17A1, CYP21A2, and CYP11B enzymes. CYP17A1, a key enzyme in the production of androgenic sex steroids, has become a new target for prostate cancer treatment. Our initial contribution to this field was to determine the first structure of CYP17A1, revealing how that inhibitors then in human clinical trials bind very differently than the proposed orientation parallel to the heme. These structures have suggested several ways by which for these clinical inhibitors could be improved to reduce side effects that limit the clinical regimen. In collaboration with a synthetic chemist, we iteratively perform structure-based drug design, inhibition analysis, and structure determination with the goal of developing advanced compounds that selectively inhibit the lyase activity of CYP17A1 without negatively impacting other aspects of steroidogenesis that cause substantial side effects. Most recently we determined the first structure of human CYP11B1 (preliminary data in this proposal). This complex revealed an intriguing stereospecificity of CYP11B1 for *S*-fadrozole in a very different orientation compared to CYP11B2 selective binding of *R*-fadrozole. This may provide the basis for improved design of drugs that should be selective for CYP11B1 (Cushing's Disease) and CYP11B2 (hypertension).

a. DeVore, N.M. and Scott, E.E. (2012) Structures of cytochrome P450 17A1 with prostate cancer drugs abiraterone and TOK-001. ***Nature*** 482:116-119. PMCID: PMC3271139.
b. Petrunak, E.M., DeVore, N.M., Porubsky, P.R., and Scott, E.E. (2014) Structures of human steroidogenic cytochrome P450 17A1 with substrates. ***J. Biol. Chem.*** 289: 32952-32964. PMCID: PMC4239641.
c. Brixius-Anderko, S. and Scott, E.E. (2019) Structure of human cortisol-producing cytochrome P450 11B1 bound to the breast cancer drug fadrozole provides insights for drug design. ***J. Biol. Chem.*** 294:453-460. PMCID: PMC6333875.

5. Establishing solution NMR as a viable technique for probing membrane P450 enzymes and interactions with NADPH-cytochrome P450 reductase and cytochrome b_5

While crystalline X-ray structures continue to generate substantial and detailed new information, the inherent limitations, including the slow, one-complex-at-a-time necessity to evaluate ligand binding to such flexible enzymes has driven my lab to seek complementary methods to probe P450 structure. Protein NMR had not been previously used to probe membrane P450 enzymes due to technical difficulties related to their size (55 kDa) and solubility/stability limitations. However we have used our expertise developed in working with these proteins for crystallography in concert with advanced NMR labeling methods and strategies to largely overcome the technical roadblock. We have begun probing CYP17A1 protein dynamics, responses to ligand binding, and the effects of interactions with reductase and b_5 without crystallization. This new perspective has revealed that the various surface P450/protein interactions are modulated by ligands in the buried P450 active site and that reductase and b_5 binding are mutually exclusive. The solution NMR approach is currently being expanded to other human cytochrome P450 enzymes.

a. Estrada, D.F., Skinner, A.L., Laurence, J.S., and Scott, E.E. (2014) Human cytochrome P450 17A1 conformational selection: Modulation by ligand and cytochrome b_5. ***J. Biol. Chem.*** 289:14310-14320. PMCID: PMC4022897.
b. Johnson, E.F., Connick, J.P., Reed, J.R., Backes, W.L., Desai, M.C., Xu, L., Estrada, D.F., Laurence, J.S. and Scott, E.E. (2014) Correlating Structure and Function of Drug Metabolizing Enzymes: Progress and Ongoing Challenges. ***Drug Metab. Dispos***. 42:9-22. PMCID: PMC3876788.
c. Estrada, D.F., Laurence, J.S., and Scott, E.E. (2013) Substrate-modulated cytochrome P450 17A1 and cytochrome b_5 interactions revealed by NMR. ***J. Biol. Chem.*** 288:17008-17018. PMCID: PMC3675632.

A complete list of publications is available:
www.ncbi.nlm.nih.gov/myncbi/browse/collection/41143942/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R37 GM076343 (E. E. Scott, PI) 03/01/2015 – 02/28/2025
National Institutes of Health/NIGMS
Structural Basis of Cytochrome P450 Activity
The objective of this proposal is to extend our structural knowledge across current boundaries by determining the first structures of several human cytochrome P450 enzymes of clinical utility, examining clinically-important new P450/ligand complexes, and probing the structural relationships between cytochrome P450 enzymes and other proteins involved in catalysis.

R01 GM130997-01 (Scott and Pochapsky, MPI) 01/01/19 – 11/30/22
National Institutes of Health/NIGMS
Structure and dynamics of clinically-relevant cytochrome P450 enzymes
The objective is to generate the NMR assignments needed to understand cytochrome P450 interactions with their ligands and catalytic partner proteins in solution, without the necessity of crystallizing each.

R01 GM128508-01 (Lampe, PI; Scott, Co-Investigator) 08/01/18 – 05/31/23
National Institutes of Health/NIGMS
The Role of CYP3A7 in the Disposition and Toxicity in HIV Inhibitors in the Developing Infant
The objective of this grant is to determine the functional consequences and mechanistic basis of the differences in HIV drug metabolism and inhibition between CYP3A7 and CYP3A4.

R01 GM086596-08 (Auchus, PI; Scott, Consultant) 07/01/18 – 04/30/2022
National Institutes of Health/NIGMS
Activation of Androgen Biosynthesis and Drug Metabolism by Cytochrome b_5
The main goal of this grant is to elucidate the biochemical and physical properties of the b_5-P450 17A1 complex that enhance the 17,20-lyase reaction.

R01 GM123253-02 (Backes, PI; Scott, co-investigator) 04/01/18 – 03/31/20
LSU/National Institutes of Health/NIGMS
Interactions Among P450 System Proteins and Their Distribution into Endoplasmic Reticulum Microdomains
The objective of this grant is to better understand how the proteins of the P450 monooxygenase system are organized in the ER and the role of P450-P450 interactions on the function of these enzymes.

P41 RR001209 (K. O. Hodgson, PI)
5B12, 2B40, 3B60 (E. E. Scott, Subproject PI) 05/31/2008 – 05/31/2020
National Institutes of Health/Stanford Synchrotron Radiation Laboratory
Structures of Membrane Cytochrome P450 Enzymes
Each renewal provides 2-years of access to a Department of Energy synchrotron facility for X-ray crystallography data collection.
Overlap: This is the synchrotron beamtime for all of our crystallographic work under various proposals.

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Nita A. Limdi, Pharm.D, PhD, MSPH**

eRA COMMONS USER NAME (credential, e.g., agency login): **nlimdi**

POSITION TITLE: **Professor, Department of Neurology**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama at Birmingham	**PhD**	**05/2008**	**Epidemiology**
University of Alabama at Birmingham	**MSPH**	**08/2005**	**Clinical Research**
Samford University, Birmingham, AL	**Pharm.D**	**05/1994**	**Pharmacy**
Samford University, Birmingham, AL	**BS**	**05/1993**	**Pharmacy**
Sardar Patel Univ. Vallabh Vidhya Nagar, India	**BS**	**08/1988**	**Pharmacy**

A. Personal statement.

Dr. Limdi is a clinical pharmacist and epidemiologist with significant expertise in pharmacogenomics and pharmacoepidemiology, from research and discovery to its application and implementation in clinical practice. Her research portfolio encompasses studies with both observational and a clinical trial designs and is focused on understanding the multiple factors that influence drug efficacy and safety, specifically anticoagulant and antiplatelet response. An established investigator in the field of pharmacogenomics, she has made significant contributions towards understanding of genetic basis of anticoagulant response. Her work has included discovering novel polymorphisms in *CYP2C9,* statistical analytic approaches that has ranged from candidate gene, haplotype based approach to genome-wide association and exome approaches, and a research portfolio that includes both prospective cohort and randomized clinical trials.

Through her work, Dr. Limdi has collaborated extensively with pharmacogenomics researchers including with the International Warfarin Pharmacogenomics Consortium (IWPC), the Clinical Pharmacogenetics Implementation Committee (CPIC), and the Implementation of Genomics In pracTicE (IGNITE). As the Associate Director of Pharmacogenomics and Implementation Science lead in the Hugh Kaul Personalized Medicine Institute, Dr. Limdi oversees discovery and clinical implementation of pharmacogenomics across the health UAB system. Through this initiative, her team has identified and overcome barriers, incorporated genotype-guided therapy and assessed clinically relevant outcomes to conduct economic analysis and inform health policy and reimbursement strategies for pharmacogenomics. She brings research and training expertise in clinical pharmacy, pharmacology, pharmacogenomics, and clinical research methods, epidemiology and biostatistics to her role as advisor on this application. She has extensive experience training residents, post-doctoral clinician trainees and junior faculty through serving as a mentor on various institutional training grants.

Her specific role will be to serve as an advisor to Dr. Guimbellot as she discovers polymorphisms in the CYP3A family of metabolism enzymes that influence CFTR modulator metabolism, and guide her in the scientific approach, analysis, and presentation of her research. In order to accomplish this, we will meet at least once yearly with the entire advisory committee and quarterly to guide the project and ensure timely completion of all training and objectives.

B. Positions and Honors.

Positions and Employment

1994-1997 Clinical Pharmacist, University of Alabama at Birmingham
1997-2003 Clinical Pharmacy Specialist for Neurosciences, University of Alabama at Birmingham
2003-2009 Assistant Professor, Department of Neurology, University of Alabama at Birmingham

2009-2014	Associate Professor, Department of Neurology, University of Alabama at Birmingham
2014 -	**Professor, Department of Neurology, University of Alabama at Birmingham**
	Adjunct appointments
	Division of Nephrology Department of Medicine, School of Medicine
	Department of Clinical Pharmacology and Toxicology, School of Medicine
	Department of Epidemiology, School of Public Health
2014 - 2017	Interim Director, UAB Hugh Kaul Personalized Medicine Institute
2016-2017	Oak Ridge Institute of Science and Education (ORISE) fellow Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER)
2017 -	Senior Affiliate Scientist, Centerstone Research Institute
2017 -	Associate Director for Pharmacogenomics and Implementation Science, UAB Hugh Kaul Personalized Medicine Institute

Honors and Awards (in chronological order)

1989	G.P. Nair National Award for Academic Excellence in Pharmacy. Bombay, India
1990, 1991	R.E. Wheeler Scholarship Medal, Samford university, Birmingham, AL
1991, 1992	Rho Chi Award for excellence in Pharmacy, Samford University, Birmingham, AL
1992, 1993	Don Lane Martinez Research Award in Pharmacy, Samford University, Birmingham, AL
1994	President's Cup, Samford University, Birmingham, AL
1997	Abbott Training Grant – Sabbatical University of Madison Wisconsin.
2000	American College of Clinical Pharmacy Award – Sabbatical to understand metabolic enzymatic control at the University of North Carolina at Chapel Hill
2006	NINDS Young Investigator Award; American Neurological Association meeting, Chicago, IL
2008	Young Investigators Award Central Society for Clinical Research meeting, Chicago, IL
2008	Irtaza and Shana Siddique Endowed Award for Academic Excellence in Epidemiology. University of Alabama at Birmingham, AL
2013	Dean's Excellence in Mentorship Award, University of Alabama at Birmingham
2014	Fellow American Heart Association, Functional Genomics – Translational Biology
2016	Executive Leadership in Academic Medicine (ELAM) Program

C. Contribution to Science (*publications by mentees): Harnessing the racial diversity of the population, I have built the largest prospective warfarin cohort (n=1809, 44% African American) with detailed collection of clinical, demographic and lifestyle factors over a 2-year prospective follow-up and capture of hemorrhagic events. This has enabled significant contributions to pharmacogenomics predictors of drug response.

1. **Translating pharmacogenomic discoveries to health disparity populations:** A major limitation of existing pharmacogenomic-based therapies is that the bulk of the evidence informing guidelines are derived from populations of European descent. The successful recruitment of a large racially diverse population has allowed us to identify novel markers influencing warfarin response in African Americans. Moreover, we have elucidated the differential impact of known gene variants across race groups.
   a. Liu N, Irvin MR, Zhi D, Patki A, Beasley TM, Nickerson DA, Hill CE, Chen J, Kimmel SE, Limdi NA. Influence of common and rare genetic variation on warfarin dose among African Americans and European Americans using the exome-array. Pharmacogenomics. 2017 Jul;18(11):1059-1073 PMC5619051
   b. Shendre A, Brown TM, Liu N, Hill CE, Beasley TM, Nickerson DA and Limdi NA. Race-Specific Influence of CYP4F2 on Dose and Risk of Hemorrhage Among Warfarin Users. *Pharmacotherapy*. 2016;36:263-72. PMC4803610.
   c. Do AH, Srinivasasainagendra V, Aslibekyan S, Tiwari H, Limdi NA, Shah S, Zhi D, Broeckel U, Gu C, Rao DC, Schwander K, Zhao W, Smith J, KardiaS, Arnett DK, Irvin MR. Whole exome analyses to examine the impact of rare variants on left ventricular traits in African American participants from the HyperGEN and GENOA studies The effects of rare variants in left ventricular traits in African Americans: analysis of exome chip data from HyperGEN and GENOA studies. J Hypertens Manag. 2017;3(1). PMC5831560

d. Perera MA, Cavallari LH, Limdi NA (**3 first authors***), et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. Lancet. 2013 31;382(9894):790-6. PMC3759580

2. **Integrating clinical, genetic, socio-demographic and behavioral data:** Most pharmacogenomic studies do not assess non-genetic factors that may influence drug response.
   a. Limdi MA, Crowley MC, Beasley TM, Limdi NA, Allon M. Influence of kidney function on risk of hemorrhage among patients taking warfarin: A cohort study. ***Am J Kidney Dis.***. 2013;6 (2): 354-357. PMC3654383
   b. Limdi, NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, Allon M, Beasley TM. Warfarin dosing in patients with impaired kidney function. ***Am J Kidney Dis.*** 2010 56:823-831. PMC2963672
   c. Yanik MV, Irvin MR, Beasley TM, Jacobson PA, Julian BA, Limdi NA. Influence of kidney transplant status on warfarin dose, anticoagulation control, and risk of hemorrhage. ***Pharmacotherapy*.** 2017;37:1366-1373. PMC5681429.
   d. Shendre A, Parmar GM, Dillon D, Beasley TM, Limdi NA. Influence of age on warfarin dose, anticoagulation control, and risk of hemorrhage. ***Pharmacotherapy***. 2018;38(6):588-596. PMC6014885

3. **Advancing Pharmacogenomics; working with a consortium of national and international experts** to pool and augment diverse datasets from multiple existing observational studies and clinical trials to enhance predictive power and enable examination of differences between race groups. I have built fruitful collaborations with investigators in the pharmacogenomics arena and the International Warfarin Pharmacogenomics Consortium (>15 countries, and 30 institutions with >120 investigators), providing leadership to bring warfarin pharmacogenetics to the forefront. The data are available through dbGaP.
   a. Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D, Kimmel SE, McDonough CW, Gong Y, Dave CV, Pratt VM, Alestock TD, Anderson RD, Alsip J, Ardati AK, Brott BC, Brown L, Chumnumwat S, Clare-Salzler MJ, Coons JC, Denny JC, Dillon C, Elsey AR, Hamadeh IS, Harada S, Hillegass WB, Hines L, Horenstein RB, Howell LA, Jeng LJB, Kelemen MD, Lee YM, Magvanjav O, Montasser M, Nelson DR, Nutescu EA, Nwaba DC, Pakyz RE, Palmer K, Peterson JF, Pollin TI, Quinn AH, Robinson SW, Schub J, Skaar TC, Smith DM, Sriramoju VB, Starostik P, Stys TP, Stevenson JM, Varunok N, Vesely MR, Wake DT, Weck KE, Weitzel KW, Wilke RA, Willig J, Zhao RY, Kreutz RP, Stouffer GA, Empey PE, Limdi NA**,** Shuldiner AR, Winterstein AG and Johnson JA. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. **2017**.
   b. The COAG investigators. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, Rosenberg YD, Eby CS, Madigan RS, McBane RB, Abdel-Rahman SZ, Stevens SM, Yale S, Mohler ER, Fang MC, Shah V, Horenstein RB, N. A. Limdi, Muldowney JA, Gujral J, Delafontaine P, Desnick RJ, Ortel TL, Billett HH, Pendleton RC, Geller NL, Halperin JL, Goldhaber SZ, Caldwell MD, Califf RM and Ellenberg JM. Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. N Engl J Med **2013**;24:2283-93.PMC3942158
   c. Horne BD, Lenzini PA, Wadelius M, Jorgensen AL, Kimmel SEm Ridker PM, Eriksson N, Anderson JL, Pirmohamed M, Limdi NA**,** Pendentel RC, McMillin GA, Burmester JK, Kurnik D, Stein MC, Caldwell MD, Eby CS, Rane A, Lindh JD, Shin J, Kim H, Angchaisuksiri P, Glynn, R, Kronquist KE, Carlquist JF, Barrack RL, Li J, Gage BF. Pharmacogenetic Warfarin Dose Refinements Remain Significantly Influenced by Genetic Factors after One Week of Therapy. Thromb Haemost. 2012; 107(2):232-40. PMC3292349
   d. The International Warfarin Pharmacogenetics Consortium. Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data. New England Journal of Medicine 2009;360:753-64. PMC2722908

4. **Development of new approaches and methodologies for statistical genetic analysis:** Working with experts in statistical genetics, we have contributed to the development of new methodology in analyzing large genetic datasets, including methods of imputation and controlling population stratification.
   a. Daneshjou R, Tatonetti NP, Karczewski KJ, Sagreiya H, Bourgeois S, Burmestor J, Mushiroda T, Limdi NA, Cavallari LH, Perera M, Johnson JA, Klein TE, Altman RB. Pathway Analysis of Genome-Wide Data Improves Warfarin Dose Prediction. BMC Genomics. 2013;14 Suppl 3:S11. PMC3829086

b. Erdal Cosgun, Nita Limdi and Christine W. Duarte. High Dimensional Pharmacogenetic Prediction of a Continuous Trait using Machine Learning Techniques with Application to Warfarin Dose Prediction in African Americans. Bioinformatics 2011; 27:1384-9. PMC3087957
c. N. Liu, H Zhao, A. Patki, N. Limdi, D. Allison. Practical Consideration of Genotype Imputation: Sample Size, Window Size, Reference Choice and Untyped Rate. Statistics and its Interface 2011; 4: 317-326. PMC3269890
d. Boshao Zhang, Degui Zhi, Kui Zhang, Guimin Gao, Nita Limdi, Nianjun Liu. Controlling Population Structure in Human Genetic Association Studies with Samples of Unrelated Individuals. Statistics and its Interface 2011; 4: 339-351. PMC3269888

5. **Contributions related to discovery of novel variants influencing drug response and variants with newly identified influence on response:** We have discovered new markers and identify novel influence of variants on warfarin response, elucidating the role of the folate pathway and identifying the influece of APLO1 variants on lipid profile in African Americans.
   a. JA Goldstein, Blaisdell JA, NA Limdi. A potentially deleterious new CYP2C9 polymorphism identified in an African American patient with major hemorrhage on warfarin therapy. Blood Cells Molecules and Disease 2009;42:155–158. PMC2662477
   b. Daneshjou R, Gamazon ER, Burkley B, Cavallari LH, Johnson JA, Klein TE, Limdi NA, Hillenmeyer S, Percha B, Karczewski KJ, Langaee T, Patel SR, Bustamante CD, Altman RB, Perera MA. Genetic Variant in Folate Homeostasis Associated with Lower Warfarin Dose in African Americans. Blood 2014 Oct 2;124(14):2298-305. PMC4183989
   c. NA Limdi, G McGwin, JA Goldstein, TM Beasley, BK Adler, RT Acton DK Arnett. Influence of CYP2C9 and VKORC1 on Warfarin Dose and Anticoagulation Maintenance among European American and African Americans. Pharmacogenomics 2008; 9 (5):511-526. PMC2757655
   d. NA Limdi, H Wiener, Goldstein JA, RT Acton TM Beasley. Influence of CYP2C9 and VKORC1 on Warfarin Response during Initiation of therapy. Blood Cells Molecules and Disease 2009; 43(1): 119-28. PMC2789741.

Complete list of published work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/nita.limdi.1/bibliography/40594522/public/?sort=date&direction=descending

D. EXTRAMURAL Research Support (Ongoing)

R01HL092173-06A1 Limdi (Role: PI) 02/01/2014–01/31/2020 (NCE)
NHLBI: Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants
The primary objective of this project is to define genetic and environmental predictors of hemorrhage among patients on warfarin or novel anticoagulants, specifically dabigatran and define the incremental risk associated with kidney impairment and concurrent antiplatelet therapy to refine clinical prediction rules for hemorrhage.

K24HL1333373 Limdi (Role: PI) 08/01/2016—07/30/2021
NHLBI: Patient Oriented Research in Personalized Antithrombotic Therapy
Clinical, genetic and environmental factors that predict individual variability in antithrombotic response can help identify patients who stand to benefit or be harmed by these drugs. However, the integration of these predictors into clinical decision making requires a paradigm shift based on evidence of their benefit vs. risk (clinical utility) and value (cost-effectiveness). To facilitate this paradigm shift we propose to incorporate genetic information with environmental and clinical predictors to help develop patient-focused and population-based preventive and therapeutic guidelines for “Personalized Antithrombotic Therapy (PAT).”

Intramural Research Support (Ongoing; no faculty effort)

Center for Genomic Medicine Grant Limdi (Role: PI) 10/01/2018 to 9/30/2019
Leveraging commercial genome-wide arrays to enable pharmacogenetically guided medication therapy.
The project aims to leverage genotype data from precision medicine cohort(s) to determine the prevalence of pharmacogenomic (PGx) variants with high level of actionability by race and actionability of PGx variants based on medication history, develop race specific metabolizer phenotypes, and develop a framework for returning results to engage patients and enable practitioners to tailor medication therapy and educate patients.

Center for Genomic Medicine Grant Limdi (Role: Co-I) 10/01/2018 to 9/30/2019

A high-resolution ancestry prediction pipeline for Alabama Genomic Health Initiative and HudsonAlpha GSL datasets.

The project aims to develop a high-resolution ancestry pipeline and web interface for visualizing ancestry results for a given individual. This project will provide a platform for ancestry analysis that will be compatible with both GSA and WGS datasets, and will enable novel interpretations of the AGHI data with respect to population-based allele frequencies and disease associations.

OTHER SUPPORT

ROWE, STEVEN M.

ACTIVE:

2P30DK072482-12 (Rowe) **4/01/18 – 3/31/23** **2.4 CM**
NIH/NIDDK **$5,622,378**
UAB CF Research and Translation Core Center
This P30 provides 3 Scientific Cores (i.e. Cell Model and Assay Core; Animal Models Core; Clinical and Translational Core) to CF investigators at UAB and collaborating sites to improve understanding of the most basic underpinnings of cystic fibrosis pathogenesis and the ways this information can be aggressively applied to experimental therapeutics. Two Pilot and Feasibility projects are also supported through the P30.
Role: Program Director; Co-Director of Core C: Clinical and Translational Core
Overlap: None

R35 HL135816 (Rowe) **1/15/17 – 1/14/24** **6.0 CM**
NIH/NHLBI R35 **$6,387,112 Total**
Translational Program in CFTR-Related Airway Diseases
This program supports investigation into diseases of mucociliary clearance, including their molecular mechanism, clinical phenotype, and precision medicine approaches to intervene.
Role: Principal Investigator
Overlap: None

U54TR001368-01 (Kimberly) **4/01/15 – 6/30/20** **0.6 CM**
NIH/NCATS **$8,535,155 (UL1, KL2, TL1)**
UAB Center for Clinical and Translational Science (CCTS)
The UAB CCTS will enhance human health by driving scientific discovery and dialogue across the bench, bedside and community continuum. The CCTS support this overall mission in a highly integrative network of relationships. Success in creating such an environment is dependent upon success in achieving five strategic priorities: 1) enhancing research infrastructure; 2) promoting investigator education, training and development; 3) accelerating discovery across the T1 interface; 4) expanding value-added partnerships; and 5) building sustainability.
Role: Co-Director of Pediatric CCTS
Overlap: None.

R34HL127166 (Rowe/Dransfield) **9/01/15 – 5/31/18** **0.6 CM**
NIH/NHLBI **$225,000**
A Pilot Study of the Effect of the CFTR Potentiator Ivacaftor in COPD (P-TOPIC)
This project will conduct a pilot, randomized, double blind placebo controlled trial to evaluate the efficacy, safety, mechanism, and pharmacokinetics of ivacaftor in patients with COPD and chronic bronchitis, under an investigator initiated IND.
Role: Multiple Principal Investigator
Overlap: None
Note: This is in NCE status covering clinical aspects run by Dr. Dransfield.

DoD (Schwartz) **07/01/17 – 06/30/21** **0.60 CM**
W81XWH-16-PRMRP-FPA **$46,497**
Title: Idiopathic Pulmonary Fibrosis, a Disease Initiated by Mucociliary Dysfunction
Role: Sub – PI
Overlap: None

CFF FUNDING

The CF Foundation has authorized effort on each project with 0.48 CM to be represented under the Special Consultant for Translational Science award. The total CFF funding under this understanding will not exceed 1.2 CM.

ROWE17A0 (Rowe) **10/01/09 - 9/30/19** **0.48 CM**
Cystic Fibrosis Foundation Therapeutics **$52,640**
Special Consultant for Translational Science
The purpose is for Dr. Rowe to serve as a Special Consultant for Translational Science for CFFT.
Role: Translational Science Consultant
Overlap: None

ROWE15R0 (Rowe) **7/01/15 - 6/30/19** **0.12 CM**
Cystic Fibrosis Foundation **$525,000 ($2,100,000 Total Direct)**
Research Development Program – Component II
The major goals of this project are to 1) support core capabilities including RT-PCR, immunolocalization, conductance, SPQ based functional analysis, as well as recombinant adenoviral vectors and other biochemical and functional endpoints for CF scientists and their projects on our campus, 2) provide resources for Pilot/Feasibility Studies, postdoctoral fellows and graduate students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.
Role: Program Director
Overlap: None

Southern Research Institute (SRI) **9/01/15 – 6/30/20** **0.12 CM**
SRI Sub **$2,010,893**
The Identification of New Treatments for Cystic Fibrosis Caused by Premature Termination Codons.
The purpose of this project is to conduct high throughput screening, secondary validation and pre-clinical development of novel molecules that suppress nonsense mutations in CFTR for the Treatment of Cystic Fibrosis.
Role: Co-Investigator for the Subaward
Overlap: None

GOAL13K1 (Rowe) **9/01/11 – 12/31/20** **0.06 CM**
Cystic Fibrosis Foundation **$90,363**
Title: *G551D Observational Study (GOAL-OB-11)*
The purpose of this study is to conduct a multi-center observational study evaluating the effects of Ivacaftor in CF patients with the G551D mutation. Dr. Rowe supervises the multi-center component of four outcome based sub-studies.
Role: Principal Investigator of national multicenter trial
Overlap: None

ROWE14K1 **7/1/14 – 12/31/18** **0.06 CM**
Cystic Fibrosis Foundation **$30,573**
Title: A Two-Part Multicenter Prospective Longitudinal Study of CFTR-Dependent Disease Profiling in Cystic Fibrosis (PROSPECT)
The goal of this project is to determine the clinical efficacy of ivacaftor/lumacaftor therapy in CF patients homozygous for F508del CFTR.
Role: Principal Investigator
Overlap: None

11162SUB (Seattle) **7/1/14 – 9/30/20** **0.06 CM**
A Two-Part Multicenter Prospective Longitudinal Study of CFTR-Dependent Disease Profiling in Cystic Fibrosis (PROSPECT) (Clinical Study) **$95,491.53**
The goal of this project is to determine the clinical efficacy of ivacaftor/lumacaftor therapy in CF patients homozygous for F508del CFTR.

Role: Co-I on Subaward
Overlap: None

ROWE14Y0 **01/01/19 – 12/31/19** **.006 CM**
UAB CF TRANSLATIONAL DEVELOPMENT CENTER $201,350
The main goals of this project are to provide funding and infrastructure for support of Phase I and Phase II clinical trials in Cystic Fibrosis patients through the Therapeutic Development Network.
Role: Co-Principal Investigator

ROWE14Y4 (Rowe) **12/1/14 – 11/30/19** **0.0 CM**
CF Foundation
Additional Research Coordinator (ARC) Award
Funds towards an Additional Research Coordinator for ROWE14Y0

ROWE17XX1 **8/1/16 – 7/31/2020** **0.05 CM**
CFF **$211,600**
Core center for measurements of mucus and mucociliary clearance

Active Research Contracts
Dr. Rowe's effort on Research contracts will not be more than 1% (0.12 CM) total. These projects pay for Dr. Rowe's staff to do the work for these contracts. Dr. Rowe has minimal day to day activities with these awards.

SHIRE (Rowe) **4/25/16 – 4/24/19**
Translate Bio $91,248
Title: *In Vivo and Ex Vivo Evaluation of Nebulized Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mRNA Replacement Therapy in Treating Cystic Fibrosis Lung Disease*
Role: Principal Investigator
Overlap: None

Arrowhead (Rowe) **6/20/17 – 6/19/19**
Arrowhead
Title: Evaluation of Nebulized Alpha ENaC RNAi Therapy in Treating Cystic Fibrosis Lung Disease
Role: Principal Investigator
Overlap: None

Active Clinical Trials
Dr. Rowe's effort on Clinical Trials will not be more than 2% (0.24 CM) total

GOAL13K1 **9/1/18 – 8/31/19**
G551D OBSERVATIONAL STUDY (GOALOB11)
CF Foundation

CFFC-08-11 (Ramsey) **7/6/2012 – 8/1/2022**
CYSTIC FIBROSIS FIBROSING COLONOPATHY OBERVATIONAL (CFFC-OB-11)
Passthrough from Seattle Children's
Role: Co – I

CHEC-OB-17 **7/1/2017 – 9/30/2020**
Characterizing CFTR Modulated Changes in Sweat Chloride & Clinical Outcomes
Passthrough from Seattle Children's **$12,232**
Role: Co-I

PROMISE-OB-18 **6/1/2018 – 5/31/2019**
Cystic Fibrosis Foundation **$260,736**

A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function (the PROMISE Study) (PROMISE-OB-18)

CFFC-OB-11 **7/6/2012 – 3/31/2022**
CFFT $24,235
CYSTIC FIBROSIS FIBROSING COLONOPATHY OBERVATIONAL (CFFC-OB-11)

VX16-661-114 **8/31/17 – 11/30/19**
Vertex Pharmaceutical
Phase 3b, Randomized, Double-blind, Placebo controlled, Parallel Group Study

PENDING
ROWE15R0 (Rowe) **7/01/19 - 6/30/23** **1.2 CM**
Cystic Fibrosis Foundation **$600,000**
Research Development Program – Component II
The major goals of this project are to 1) support core capabilities including RT-PCR, immunolocalization, conductance, SPQ based functional analysis, as well as recombinant adenoviral vectors and other biochemical and functional endpoints for CF scientists and their projects on our campus, 2) provide resources for Pilot/Feasibility Studies, postdoctoral fellows and graduate students, 3) support managerial and program enhancement aspects of the UAB Cystic Fibrosis Research Center.
Role: Program Director
Overlap: None

OTHER SUPPORT

KIMBERLIN, D.W.

ACTIVE

HHSN272201600017C (**Kimberlin, PI**) 07/01/16-06/30/21 1.8 CM
NIH-NIAID $7,762,677
Targeted Clinical Research to Address Select Viral Infections: A Phase II, Single-Stage, Single-Arm Investigation of Oral Valganciclovir Therapy in Infants with Asymptomatic Congenital Cytomegalovirus Infection
This contract evaluates the antiviral treatment of infants who are congenitally infected with cytomegalovirus and are asymptomatic at delivery

HHSN272201600018C (**Kimberlin, PI**) 07/01/16-06/30/21 1.2 CM
NIH-NIAID $1,670,730
Targeted Clinical Research to Address Select Viral Infections: Burden of Neonatal Herpes Simplex Virus Infections in the United States: Disease Incidence, Adequacy of Diagnostic Assessment, Disease Outcome, and Societal Costs; and Prevalence, Frequency, and Incidence of Neonatal Herpes Simplex Virus Infections in Peru
This contract evaluates the incidence of neonatal herpes simplex virus infections in the Unites States and Peru

HHSN272201100034C (**Kimberlin, MPI**) 09/28/11-08/15/20 1.7 CM
NIH-NIAID $4,683,023
Targeted Clinical Research to Address Select Viral Infections: Adaptive sequential study evaluating prevention of neonatal HSV: Detection of maternal shedding at delivery followed by preemptive antiviral therapy in exposed neonates
This contract evaluates a novel diagnostic tool for detection of herpes simplex virus in the genital tract of pregnant and nonpregnant women.

HHSN272201100035C (**Kimberlin, MPI**) 09/28/11-08/15/20 0.7 CM
NIH-NIAID $4,932,916
Targeted Clinical Research to Address Select Viral Infections: A Phase II 6 weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss
This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.

HHSN272201100037C (**Kimberlin, MPI**) 09/28/11-08/15/20 0.7 CM
NIH-NIAID $2,996,880
Targeted Clinical Research to Address Select Viral Infections: A pharmacokinetic/pharmacodynamic and resistance evaluation of intravenous ganciclovir in premature infants
This contract evaluates antiviral drug dosing in extremely premature infants with congenital or postnatal cytomegalovirus disease.

HHSN272201100038C (**Kimberlin, MPI**) 09/28/11-08/15/20 2.3 CM
NIH-NIAID $3,101,385
Targeted Clinical Research to Address Select Viral Infections: An Observational Study of Acyclovir Pharmacokinetics, Viral Population Kinetics, and Potential Biomarkers of Disease Severity in Neonatal Herpes Simplex Virus Infections
This contract evaluates viral and drug kinetics in neonates with herpes simplex virus disease, and compares new diagnostic modalities to established tests.

75D301-18-R-67879 (**Kimberlin, PI**) 10/01/18 – 09/30/19 1.2 CM

CDC $781,523
Approaches to prevention and control of parasitic infections in the U.S.
This contract will support the conduct of a cross-sectional cohort study to determine the prevalence of Soil Transmitted Helminth (STH) infections in school age children in a rural poor community in southern Alabama

HHSN2722013000231 (Edwards and Creech, PI) 09/16/13-09/15/23 0.7 CM
NIH-NIAID (Vanderbilt passthrough) $250,938
Role: Site PI
Vaccine and Treatment Evaluation Units (VTEU)
Task C-5 - A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpaitnet Therapy of Community Acquired Pneumonia in Children (SCOUT CAP)
This a task order under a contract is to evaluate vaccines and therapeutic agents through the NIAID VTEU network.

Novavax, Inc (Tita, PI) 8/28/17 – 8/27/2022 0.6 CM
Role: Sub-investigator $643,745
A Phase 3, Randomized, Observer-Blind, Placebo-Controlled, Group-Sequential Study to Determine the Immunogenicity and Safety of a Respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine with Aluminum in Healthy Third-trimester Pregnant Women; and Safety and Efficacy of Maternally Transferred Antibodies in Preventing RSV Disease in their Infants (Tita, PI)

PENDING

GRANT12725415 (**Kimberlin, PI**) 07/01/19 – 06/30/24 3.7 CM
NIH-NCATS/NIAID
Congenital and Perinatal Infections Rare Diseases Clinical Research Consortium
The overall goal of the Congenital and Perinatal Infections Consortium is to establish infrastructure and institutional cooperation – focusing on rare congenital and perinatal viral infections – to advance understanding of these diseases, improve clinical trial readiness, test therapies, advance patient care, and ultimately reduce disease burden. These infections include congenital cytomegalovirus (CMV) disease, neonatal herpes simplex virus (HSV) infection, and neonatal viral sepsis caused by enteroviruses (EVs) and the related human parechoviruses (HPeVs).

OVERLAP

None

CONFLICT OF INTEREST

None

OTHER SUPPORT

ACOSTA, Edward P.

ACTIVE:

HHSN272201100035C (Whitley, R., PI) 09/28/11 - 9/27/20 0.72 CM
NIH/NIAID $187,120 direct cost
Targeted Clinical Research to Address Select Viral Infections
A Phase II 6-weeks oral valganciclovir versus placebo in infants with congenital CMV infection and hearing loss. This contract evaluates antiviral treatment of infants with hearing loss related to congenital cytomegalovirus infection.
Role: Co-I
Overlap: None

HHSN272201100037C (Whitley, R., PI) 09/28/11 - 09/27/20 0.72 CM
NIH/NIAID $175,355 direct cost
Targeted Clinical Research to Address Select Viral Infections
A pharmacokinetic/pharmacodynamic and resistance evaluation of intravenous ganciclovir in premature infants. This contract evaluates antiviral drug dosing in extremely premature infants with congenital or postnatal cytomegalovirus disease.
Role: Co-I
Overlap: None

HHSN272201100038C (R. Whitley, PI) 09/28/11 - 09/27/20 0.72 CM
NIH/NIAID $195,235 direct cost
Targeted Clinical Research to Address Select Viral Infections
A multiple ascending dose-finding pharmacokinetic and pharmacodynamic study of CMX-001 in infants with neonatal herpes simplex virus (HSV). This contract evaluates a novel antiviral drug for the treatment of neonatal herpes simplex virus disease involving the central nervous system.
Role: Co-I
Overlap: None

UM1AI068636-12 (Aldrovandi, G., PI) 06/01/12 - 11/30/19 1.2 CM
NIH/NIAID (Subaward - Brigham & Women's Hospital) $215,000 direct cost
AIDS Clinical Trials Group (ACTG) Pharmacology Specialty Laboratory (PSL)
The primary objectives of the PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of adult patients with HIV-infection participating in Adult AIDS Clinical Trials Group (ACTG) studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments.
Role: Subaward PI
Overlap: None

UM1AI068636-12, NIAID/BWH 12/01/2017 – 11/30/2019 2.4 CM
NIH/NIAID (Subaward - Brigham & Women's Hospital) $189,720 direct cost
AIDS Clinical Trials Group (ACTG): Pharmacology Specialty Laboratory (PSL – Protocol A5324)
As the pharmacology lab, we will be quantitating both maraviroc and dolutegravir in plasma and CSF from patients enrolled in this study. We are providing this service to the protocol team in order to support the objectives of the study.
Role: Subaward PI
Overlap: None

UM1AI068636-12 (Aldrovandi, G., PI) 05/01/2018 – 11/30/2019 0.35 CM
NIAID (Subaward - Brigham & Women's Hospital) $42,000 direct cost
AIDS Clinical Trials Group (ACTG): Pharmacology Specialty Laboratory (PSL – Protocol A5315)
A5315 is examining the clinical use of romidepsin to deplete sanctuary sites of HIV. Participants are also receiving either raltegravir, dolutegravir, or efavirenz. The UAB PSL will be quantitating these latter drugs and

performing pharmacokinetic analyses on the data. We are providing this service to the protocol team in order to support the objectives of the study.
Role: Subaward PI
Overlap: None

UM1AI068636-12, NIAID/BWH 05/01/2018 – 11/30/2019 0.07 CM
NIAID (Subaward - Brigham & Women's Hospital) $14,994 direct cost
AIDS Clinical Trials Group (ACTG): Pharmacology Specialty Laboratory (PSL – Protocol A5347)
A5347s will quantify concentrations of ARVs in tissue from HIV-infected participants on suppressive ART to characterize exposure-response relationships between tissue drug concentrations and HIV-1 DNA and RNA levels in plasma and PBMCs.
Role: Subaward PI
Overlap: None

UM1AI068632-12 (Aldrovandi, G., PI) 06/29/06 -11/30/19 1.8 CM
NIH (Subaward - UCLA Children's Discovery and Innovation Institute) $101,822 direct cost
International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) Pharmacology Specialty Laboratory
The primary objectives of the IMPAACT PSL are to 1) quantitate drug/metabolite concentrations in biological fluids of pediatric patients and pregnant women with HIV-infection participating in IMPAACT studies and 2) to design, implement, and perform pharmacokinetic and pharmacodynamic assessments in these populations.
Role: Subaward PI
Overlap: None

ING112578 (E. Acosta, UAB Project Director) 01/01/14 -12/31/19 1.2 CM
Merck (Subaward – John Hopkins Univ.) $252,791 direct cost
A Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of GSK 1349572, a novel integrase inhibitor, in combination regimens in HIV-1 Infected Infants, Children, and Adolescents (P1093)
The primary objective is to determine safe and effective doses of dolutegravir for children ranging from 4 weeks to 18 years of age in order to attain pediatric approval. Dr. Acosta's laboratory is performing all bioanalytical and pharmacokinetic assessments in support of this study.
Role: Subaward PI
Overlap: None

UM1AI068632 (Nachman, S., PI) 01/01/14 – 11/30/19 1.2 CM
NIH (Project Specific Task Orders thru John Hopkins University) $663,148 direct cost
International Maternal Pediatric Adolescent AIDS Clinical Trials Group
The UAB PSL is committed to the analysis of samples obtained from protocols P1066, P1093, P1058A, P1097, P1097A, and P1101.
Role: Subaward PI
Overlap: None

UM1AI068632 (Nachman, S., PI) 12/01/16 – 11/30/19 0.01 CM
NIH (Project Specific Task Orders thru John Hopkins University) $190,545 direct cost
IMPAACT 2007 – Phase I Safety and Pharmacokinetics of Maraviroc in HIV-1 Exposed Infants at Risk of Acquiring HIV-1 Infection
To assay the maraviroc smaples for the study.
Role: Subaward PI
Overlap:None

CCR17483682 (Stringer-Reasor, E., PI) 08/01/17 – 07/31/20 0.01 CM
Susan G. Komen Breast Cancer Foundation $120,000 direct cost
A New Paradigm: Using PARP Inhibitors to Treat HER2+ Breast Cancer

The goal of the study is to develop novel therapies to improve the survival of breast cancer patients who are at risk of relapse.
Role: Committee Member
Overlap: None

K08CA234225-01 (Williams, G., PI) 09/01/18 – 08/31/23 0.01 CM
NIH/NCI $191,237 annual direct cost
Myopenia and Mechanisms of Chemotherapy Toxicity in Older Adults with Colorectal Cancer: The M&M Study
The central goal of our prospective longitudinal study is to better understand myopenia and its association with chemotherapy toxicity and overall survival in older adults with metastatic CRC.
Role: Mentor
Overlap: None

R01AI135122-01A1 (McKenna, C., PI) 01/01/19 – 12/31/23 0.6 CM
NIH (Subaward with the Univ. of Southern California) $126,633 direct cost
Small Molecule Inhibitors Targeting Adenovirus
The goal of this project is to investigate a new nucleoside oral prodrug approach to treatment of adenovirus (Ad) infections.
Role: Co-Inv
Overlap: None

PENDING
U54TR002827 (Kimberlin, D., PI) 07/01/19 – 06/30/24 1.2 CM
NIH/NCI $43,650 annual direct
Congenital and Perinatal Infections Rare Diseases Clinical Research Consortium
The RDCRCs are intended to advance the diagnosis, management, and treatment of rare diseases with a focus on clinical trial readiness. Our role is to prepare, plan, and analyze all pharmacokinetic data and to develop quantitative assays for the compounds under study.
Role: Co-Inv
Overlap: None

R21CA23222 (Suswam, E., PI) 07/01/19 – 06/30/21 0.24 CM
NIH/NCI $150,000 direct cost
Targeting Peptldyl Arginine Deiminase (PAD) Enzymes for Glioma Therapy
The goal is to define the contribution of posttranslational mechanism of deamination to glioma progression, and evaluate PAD inhibitors as potential therapeutic modalities for malignant glioma.
Role: Co-Inv
Overlap: None

No Number (Collier, A. and Ho, R., Pls) 07/01/19 – 06/30/22 2.00 CM
NIH (Subaward with the Univ. of Washington) $71,251 direct cost
NextGen Long-acting Platform: Targeted Combination Antiretrovirals
The Antiviral Pharmacology Lab will will develop and validate plasma assays for lopinavir, ritonavir, and tenofovir under Good Clinical Laboratory Practices (GCLP) guidance for regulatory purposes.
Role: Co-Inv
Overlap: None

*****If any of the pending project is awarded, effort will be reduced (within guidelines) in order not to exceed 100%.***

OTHER SUPPORT

HEMANT K. TIWARI, PhD

ACTIVE

NIH R01DK104347 (Boyer, Tiwari and Absher (multi-PIs)) 09/20/16 – 07/31/20 1.32 months/year
NIH/NIDDK $84,975 current direct
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The overall goal of the proposed research is to identify epigenetic factors underlying the relationship between metabolic health and the traditional Yup'ik Alaska Native diet, rich in n-3 polyunsaturated fatty acids (PUFAs) from marine mammals, fish, and other wild country (subsistence) foods.
Role: MPI

NIH R01DK112358-01 (Boyer, Tiwari and Absher (multi-PIs)) 07/15/17 – 03/31/21 0.24 months/year
NIH/NIDDK $20,893 current direct
Epigenome modification by a dietary pattern rich in polyunsaturated fatty acids
The increased prevalence of Type 2 Diabetes is a global health concern that has led to substantial increases in health care costs and increased morbidity and mortality. The proposed research is aimed at identifying diet-induced changes in genomic DNA methylation patterns that are associated with changes in downstream gene expression, as well as phenotypic and metabolic profiles associated with insulin sensitivity and protection from Type 2 Diabetes. Evaluation of the epigenomic impact of a protective dietary exposure may enhance our understanding of the molecular mechanisms underlying metabolic health, and the role that epigenetic factors play in mediating these relationships.
Role: MPI

R01CA178441 (Tollefsbol) 04/01/2014 – 02/28/2019 0.32 months/year
NIH/NCI $202,807 current direct
Combinatorial Epigenetic-Based Prevention of Breast Cancer
Breast cancer is a significant health problem worldwide and is a leading cause of cancer morbidity and mortality. The overall goal of this application is to develop a combinatorial dietary approach consisting of green tea polyphenols and sulforaphane-rich broccoli sprouts for efficacious and safe use in preventing the epigenetic aberrations of breast cancer.
Role: Co-investigator

1R01CA204346 (Tollefsbol) 01/01/2017-12/31/2021 0.32 months/year
NIH/NCI $202,632 current direct
Early Life Prevention of Breast Cancer with Combined Epigenetic Botanicals
Estrogen receptor-negative breast cancer is a leading cause of cancer morbidity and mortality because few treatment options exist for this often fatal disease. The goal of this application is to develop efficacious dietary regimens of epigenetic aberration-neutralizing dietary botanicals consumed at various stages of life for preventing estrogen receptor-negative breast cancer.
Role: Co-investigator

2R01HL091357-05 (Arnett) 08/01/2015 – 07/31/2019 0.6 months/year
NIH/NHLBI $89,147 current direct
Genomewide Association Study of Lipid Response to Fenofibrate and Dietary Fat
This study aims to identify genetic variants that influence fat and cholesterol's response to diet and drugs; this knowledge may someday help doctors tailor prevention efforts and treatments based on individual's genetic endowment.
Role: Co-investigator

1R01HL123782-01A (Irvin) 09/15/2016-05/31/2021 1.8 months/year
NIH/NHLBI $499,040 current direct
Genomic Background of Blood Pressure Response to Thiazide Diuretic in African Americans.
Research shows that better blood pressure control produces cardiovascular benefits in African Americans. This study seeks to discover genetic variants that influence how blood pressure can be controlled in African Americans on a frequently used medication class (thiazide diuretics). In the future, such knowledge could help improve the care of African Americans with high blood pressure.

Role: Co-investigator

NIH R01AR073850 (Brown) 07/01/18 – 06/30/23 0.12 months/year
NIH/NIAMS $486,800 current direct
Characterization of the Lupus Nephritis microRNAome
The purpose of this study is to characterize role of genome-wide microRNA in lupus nephritis.
Role: Co-Investigator

NIH R01HL140493 (Broeckel) 07/01/18 – 06/30/23 1.8 months/year
NIH/NHLBI $99,005 current direct
Characterization and Genetics of KI toxicity in iPSC-derived cardiomyocytes
The purpose of the study is to identify genetic markers using human induced pluripotent stem cell derived cardiomyocytes. This will enable us in understanding the underlying mechanisms that can improve cardiotoxicity testing, identification of individuals at increased risk and guide the development of novel drugs with a reduced risk profile.
Role: Sub-contract PI

NIH P30DK079337 (Agarwal) 08/01/18 – 07/31/23 0.3 months/year
NIH/NIDDK $958,742 current direct
UAB-UCSD O'Brien Center For Acute Kidney Injury Research
Acute kidney injury (AKI) is a major cause for morbidity and mortality in hospitalized patients and is being increasingly recognized as a cause for chronic kidney disease. AKI doubles the length of stay in the hospital, increasing health care resources. The UAB-UCSD O'Brien Center has brought together a team of investigators to serve unmet needs of our investigator base and to fill the gaps in knowledge in the field of AKI and AKI-related research.
Role: Co-Investigator

NIH R01HL129907 (Ambalavanan) 09/15/15 – 06/30/19 1.8 months/year
NIH/NHLBI $250,000 current direct
Stop BPD
Bronchopulmonary dysplasia (BPD) is a common respiratory disorder in very preterm infants, characterized by impaired lung development, and associated with long-term respiratory complications. In this study, we will evaluate 300 extremely preterm infants to determine alterations in gene expression, protein amounts, or microbial flora in the airway that are associated with resilience (resistance to development of severe BPD, even when considered to be at high risk due to clinical risk factors) or predisposition (higher rate of developing severe BPD even if not initially considered at high risk).
Role: Co-Investigator

NIH R01HL055673 (Arnett) 07/15/16 – 04/30/19 1.2 months/year
NIH/NHLBI $5,459,306 current direct
HyperGEN: Genetics of Left Ventricular Hypertrophy
Black people tend to have an enlarged left ventricle (the heart chamber that pumps oxygenated blood throughout the body) more commonly than those in other race groups, putting them at greater risk for having potentially fatal cardiovascular diseases. Enlarged left ventricles are caused, at least in part, by a person's genes. This study seeks to discover which genetic factors may cause an enlarged heart; this may ultimately lead to new diagnoses and treatments to help lower cardiovascular disease risk in blacks.
Role: Co-Investigator

No Number (Aslibekyan) 07/01/18 – 06/30/20 0.24 months/year
American Heart Association $181,768 current direct
A High-Resolution Integrative-Omic Analysis of Cardiorenal Traits in African Americans
Role: Co-Investigator

PENDING

NIH R01 no number (Mayowa) 09/01/18 – 08/31/23 .52 months/year
NIH $10,701 current direct
Systematic Investigation of Blacks with Stroke (SIBS) Genomics

The purpose of this study is to perform GWAS analysis aimed at discovering common novel genetic variants associated with ischemic stroke among 8,000 continental Africans (4,200 subjects recruited on the genomics study combined with 3,800 already existing subjects from the SIREN project).
Role: Sub-contract PI

NIH R01 no number (Tollefsbol)	07/01/18 – 06/30/23	0.6 months/year
NIH/NCI	$2,259,427 total current direct	

Effects of Soy Against Breast Cancer: The Epigenome, Microbiome and Metabolome
To integrate microbiome, metabolome, and epigenome to study the role of consumption of soy in breast cancer.
Role: Co-Investigator

OVERLAP

If all of the pending applications were funded, Dr. Tiwari's percent effort might exceed 100%. In that event, his percent effort on certain projects would be reduced and compensated for by an increase in percent effort by other qualified personnel.

OTHER SUPPORT

ABAN, INMACULADA B.

ACTIVE:

1UH3TR002450-02 (Dransfield) 04/09/2018 – 08/31/2021 2.4 CM
NIH/National Center for Advancing Translational Sciences $1,451,098 current year directs
AZD9688: A First in Class Disease Modifying Therapy to Treat Alpha-1 Antitrypsin Deficiency a Genetically Linked Orphan Disease
Alpha-1 antitrypsin deficiency (AATD) is the most common genetic cause of chronic obstructive pulmonary disease (COPD) and early-onset emphysema, and AATD is characterized by low AAT levels, leading to excessive neutrophil elastase (NE) mediated lung destruction. Current treatment requires the periodic infusion of pooled AAT derived from human plasma, but this therapeutic approach does not definitively slow the rate of emphysema progression and is very expensive with annual direct costs over $100,000 per patient. We propose to study the safety, tolerability, and efficacy of AZD9668, an orally available NE-inhibitor, in patients with AATD.
Role: Co-investigator
Overlap: None

1R01 HD084124 (Bamman) 04/01/2015-03/01/2020 0.36 CM
NIH/NICHD $522,810
Overcoming TWEAK signaling to fully restore muscle mass and mobility function after total joint arthroplasty

The goals of the study are: (1) to determine the effects Progressive resistance exercise training (PRT) vs. usual care after elective THA/TKA on muscle mass, muscle performance, and mobility function; (2) to determine whether MuIS status modifies the effects of 16 wk PRT or usual care after THA/TKA
Role: Co-Investigator/Biostatistician
Overlap: None

670266-1 (Bamman) 09/01/2016 – 08/31/2019 1.2CM
Wright State University $387,186
Precision High Intensity Training through Epigenetics (PHITE)
Role: Biostatistician
Overlap: None

BAA-NIHAI2010101 (Gnann) 10/01/2011 – 09/30/2019 0.42 CM
NIH/NIAID-DMID $1,690,432
Targeted Clinical Research to Address Select Viral Infections-Safety, Tolerability and Pharmacokinetic Properties of CMX001 in Renal Transplant Recipients with BK Viremia T
The primary objective is to define the natural history of BK viremia. In order to understand the natural history of infection, we will measure the time (days post-transplant) to the development of BK viremia and its correlation with progression to end-organ disease (BKVN or BK hemorrhagic cystitis). Data from this prospective monitoring will allow for the identification of the types of high-risk patients who might benefit from future studies of therapeutic interventions for BKV infection (when effective therapy becomes available). This will be accomplished by serial quantitative BK DNA measurements in blood (plasma), assayed by polymerase chain reaction (PCR).
Role: Director/ Protocol Biostatistician, Data Coordinating Center
Overlap: None

BAA-NIHAI2010101 (Kimberlin) 10/01/2011 – 09/30/2019 0.12 CM
NIH/NIAID-DMID $1,256,322
A Pharmacokinetic/Pharmacodynamic and Resistance Evaluation of Intravenous Ganciclovir in Premature Infants
The major goals of this project are to define the pharmacokinetics of ganciclovir in premature infants, to assess changes in quantitative viral DNA in whole blood as a function of drug pharmacokinetics, to assess clearance of CMV in urine (by culture) as a function of drug pharmacokinetics, to assess development of neutropenia as a function of drug pharmacokinetics and to determine the potential for the development of resistance to ganciclovir as a function of pharmacokinetics, dose, age, and duration of therapy.

Role: Director/ Protocol Biostatistician, Data Coordinating Center
Overlap: None

BAA-NIHAI2010101 (Kimberlin) 10/01/2011 – 09/30/2019 0.42 CM
NIH/NIAID-DMID $1,406,968
An Observational Study Of Acyclovir Pharmacokinetics, Viral Population Kinetics, And Potential Biomarkers Of Disease Severity In Neonatal Herpes Simplex Virus Infections.
The major goal of this project to describe the population pharmacokinetics of high-dose parenteral acyclovir (60 mg/kg/day) in neonates with virologically confirmed neonatal HSV disease.
Role: Director/ Protocol Biostatistician, Data Coordinating Center
Overlap: None

BAA-NIHAI2010101 (Kimberlin) 10/01/2011 – 09/30/2019 0.12 CM
NIH/NIAID-DMID $2,640,923
Adaptive Sequential Study Evaluating Prevention of Neonatal HSV: Detection of Maternal Shedding at Delivery Followed by Preemptive Antiviral Therapy in Exposed Neonates
The major goals of this project are to evaluate the sensitivity and specificity of the GeneXpert real-time PCR test for detecting herpes simplex virus (HSV) DNA in the genital tract of women in active labor or in sexually transmitted infections (STI) clinics. Additionally this study will determine rates of neonatal HSV disease, attempt to quantify HSV viral load in the genital tract of women shedding the virus who are in active labor and assess the type of maternal infection (first-episode primary, first-episode non-primary, recurrent) among women shedding HSV during active labor.
Role: Protocol Biostatistician
Overlap: None

BAA-NIHAI2010101 (Kimberlin) 10/01/2011 – 09/30/2019 0.12 CM
NIH/NIAID-DMID $1,587,582
A Phase II 6 Weeks Oral Valganciclovir versus Placebo in Infants with Congenital CMV Infection and Hearing Loss
The major goals of this project are to determine if a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss, to define the systemic exposure to ganciclovir, describe the safety and tolerability of valganciclovir syrup in children of this age and to define the pharmacokinetics of ganciclovir when valganciclovir is administered to children of these ages.
Role: Protocol Biostatistician
Overlap: None

1R01CA217179 (Markert) 05/01/2017 – 04/30/2020 1.80 CM
NIH/NCI $408,148
A PHASE 1 STUDY OF M032, A GENETICALLY ENGINEERED HSV-1 EXPRESSING IL-12, IN PATIENTS WITH RECURRENT/PROGRESSIVE GLIOBLASTOMA MULTIFORME, ANAPLASTIC ASTROCYTOMA, OR GLIOSARCOMA.
High-grade malignant gliomas are the most prevalent intracranial malignant brain tumor in adults with a dismal prognosis evidenced by a 12-15 month median survival and a 5-year survival <5%, evincing the need for more effective therapies. We created a novel, oncolytic Herpes Simplex Virus (oHSV) termed M032 (NSC 733972) that expresses human Interleukin-12 and the NExT (NCI) program manufactured clinical grade M032 (>560 doses) for which we have been issued an investigational new drug approval (#14,946) by the FDA. We propose to conduct a first-in-human Phase I clinical trial (NCT02062827) to assess the safety and tolerability of M032, to define any unexpected toxicities, to obtain correlative biologic information, and to determine a Recommended Phase 2 Dose.
Role: Protocol Biostatistician
Overlap: None

PEDIATRICS RESEARCH OFFICE (Non-federal funding) 4.8 CM
The Pediatric Research Office (PRO) provides assistance to investigators conducting pediatric research at Children's of Alabama at the University of Alabama at Birmingham (UAB). PRO provides pre-award and post-award support for funded investigators as well as those seeking funding or training.

Role: Biostatistician
Overlap: None

OTHER SUPPORT
EMILY E. SCOTT

ACTIVE

R37 GM076343-14 (Scott, PI) 01/01/06 – 02/29/25 1.5 CM
NIH/NIGMS $230,000
Structural Basis of Cytochrome P450 Activity
The objective of this proposal is to extend our structural knowledge across current boundaries by determining the first structure of several human cytochrome P450 enzymes of clinical utility, examining clinically-important new P450/ligand complexes, and proving the structural relationships between cytochrome P450 enzymes and other proteins involved in catalysis.
Overlap: None

P41 GM103393-36 (Hodgson, PI) 03/01/97 - 02/29/20
NIH/NIGMS
5B12 (Scott, Subproject PI) 05/31/18 - 05/31/20 0 CM
Stanford Synchrotron Radiation Laboratory $0
Structures of Membrane Cytochrome P450 Enzymes
The objective of this proposal is to provide access to the SSRL synchrotron facility for X-ray crystallography data collection.
Role: Subproject/Beamline Proposal PI
Overlap: This award provides instrument time necessary to determine cytochrome P450 structures.

R01 GM123253 (Backes, PI; Scott, co-investigator) 03/01/18 – 02/28/21 0.12 CM
LSU/NIH $8,226
Interactions Among P450 System Proteins and Their Distribution into Endoplasmic Reticulum Microdomains
The objective of this grant is to better understand how the proteins of the P450 monooxygenase system are organized in the ER and the role of P450-P450 interactions on the function of these enzymes.
Overlap: None

1 R01 GM128508 (Lampe, PI; Scott, Co-Investigator) 04/01/18 – 03/31/23 0.96 CM
NIH/NIGMS $57,021
The Role of CYP3A7 in the Disposition and Toxicity in HIV Inhibitors in the Developing Infant
The objective of this grant is to determine the functional consequences and mechanistic basis of the differences in HIV drug metabolism and inhibition between CYP3A7 and CYP3A4.
Overlap: None

1 R01 GM086596 (Auchus, PI; Scott, Consultant) 07/01/18 – 06/30/23 0.0 CM
NIH/NIGMS $2,970
Activation of Androgen Biosynthesis and Drug Metabolism by Cytochrome b_5
The main goal of this grant is to elucidate the biochemical and physical properties of the b_5-P450 17A1 complex that enhance the 17,20-lyase reaction.
Overlap: None

1 R01 GM130997 (Scott and Pochapsky, MPI) 01/01/19 – 11/30/22 1.2 CYM
NIH/NIGMS $377,250
Structure and Dynamics of Clinically-Relevant Cytochrome P450 Enzymes
The objective of this proposal is to develop and apply NMR as a new and orthogonal approach to obtaining the detailed structural information needed to understand cytochrome P450 interactions with their ligands and catalytic partner proteins, without the necessity of crystallizing each protein and complex.
Overlap: None

PENDING

1 R01 GM132228 (Scott, PI; Ohi, co-I)	09/01/19 – 08/31/24	1.5 CYM
NIH/NIGMS	$318,557	

Studies of Human Cortisol- and Aldosterone-Producing Cytochrome P450 11B Enzymes

The objective of this proposal is to the key interactions of CYP11B1 and CYP11B2 enzymes with small molecules and other proteins that regulate and distinguish their activity.

Overlap: None

OTHER SUPPORT

Limdi, Nita A

Ongoing; extramural

5RO1 HL092173-08 Limdi (Role: PI) 2/01/2014-1/31/2020 5.4 CM

Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants

The primary objective of this project is to define genetic and environmental predictors of hemorrhagic complications among patients treated with warfarin and novel anticoagulants, specifically dabigatran and define the incremental risk associated with kidney impairment and concurrent antiplatelet therapy to refine clinical prediction rules for hemorrhage.

K24HL133373 Limdi (Role: PI) 8/01/2016 to 7/31/2021 3.0 CM

Patient-Oriented Research in Personalized antithrombotic therapy.

Clinical, genetic and environmental factors that predict individual variability in antithrombotic response can help identify patients who stand to benefit or be harmed by these drugs. However, the integration of these predictors into clinical decision making requires a paradigm shift based on evidence of their benefit vs. risk (clinical utility) and value (cost-effectiveness). To facilitate this paradigm shift we propose to incorporate genetic information with environmental and clinical predictors to help develop patient-focused and population-based preventive and therapeutic guidelines for “Personalized Antithrombotic Therapy (PAT).”

Overlap

None

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer	S	Guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 1**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	30,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**30,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification*	File Name: Budget_justification_Guimbellot_v2.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer	S	Guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 2**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	30,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**30,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification*	File Name: Budget_justification_Guimbellot_v2.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer	S	Guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 3**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	30,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**30,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification*	File Name: Budget_justification_Guimbellot_v2.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer	S	Guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 4**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	30,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**30,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification*	File Name: Budget_justification_Guimbellot_v2.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2023 **End Date*:** 08-31-2024 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jennifer	S	Guimbellot		PD/PI		9.0					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2023 **End Date*:** 08-31-2024 **Budget Period: 5**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2023 **End Date*:** 08-31-2024 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	30,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**30,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8.0		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification*	File Name: Budget_justification_Guimbellot_v2.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

Jennifer S Guimbellot, M.D., PHD PD/PI, (9 CM). Dr. Guimbellot is an Assistant Professor of Pediatrics in the Division of Pediatric Pulmonary and Sleep Medicine. She has a solid background in clinical pediatric pulmonology with emphasis on cystic fibrosis, as well as genetics, cell and molecular biology. The proposed Mentored Patient-Oriented Research Career Development Award will enable her to increase skills in patient-oriented research, pharmacology, and pharmacogenetics. As the Principal Investigator, she is responsible for the overall direction of the project including experimental design, data analysis, and publication of results. This will enable her to transition to an independent research program. She is requesting funds to cover 75% of her university salary for 5 years. Fringe benefits are figured at 29.4%.

Salary/Fringe total funds requested $

Non-personnel expenses ($).

Materials and Supplies ($17,219 for year one): Supplies for growth and maintenance of primary human airway epithelial cells: plastic ware (sterile pipettes, syringes, culture flasks, tissue culture plates), centrifuge tubes, media, supplements, antibiotics, sera, TC-grade PBS, tubing and microfluidics chips, sterile instruments for sample collection, phlebotomy supplies. Reagents for lysate preparation (protease inhibitors and detergents); RNA and DNA preparation kits; gene expression and sequencing primers; reagents for PCR. These funds will also support functional reagents and slides; labor, equipment use, supplies, and data analysis for mass spectrometry for serum concentrations of ivacaftor and metabolites. Funding from Dr. Rowe's laboratory and Dr. Guimbellot's departmental account will support additional equipment, equipment maintenance, general disposable/consumable lab supplies and materials, gas cylinders, as well as specimen storage.

Genotyping (year 1 cost $4631): Genotyping will be performed at the Heflin Genomics Core at UAB. Cost is $49/sample, plus processing and analysis fees.

Subject reimbursement costs (year 1 $4900). For pharmacokinetics studies, specimen reimbursement for collection of serum samples and nasal epithelial biopsies will be reimbursed at the rate of $250 per day for Visit 1 as per Cystic Fibrosis Foundation Therapeutics Development Network, with expectation of 10 subjects recruited; Visits 2 and 3 are paid at the rate determined by the Network of $30/hour, estimated maximum 4 hours participation.

Travel ($1250/year). Dr. Guimbellot will attend American Thoracic Society meetings and the American Society for Pharmacology and Experimental Therapeutics at Experimental Biology meetings over the five year period in order to present data related to this project; network with pharmacologists and pharmacogeneticists to build a collaborative network of investigators with similar interests; learn cutting-edge research regarding drug metabolism, pharmacogenomics, and in vitro model development for drug development and precision medicine.

Formal coursework ($2000/year). ASIBS statistical course is $375 plus travel and accommodation. The Pharmacometrics course at FAES in Bethesda fees are $995 plus travel and accommodations. Certara workshops for modeling instruction are $1495, plus travel and accommodation. Tuition for formal UAB graduate courses are waived for faculty and thus tuition is not included here. Additional coursework described in the Training Plan will extend beyond year 1, and anticipated cost of training courses are a minimum of $2000/year. Additional costs beyond this request will be covered by departmental funds as delineated in the Institutional Commitment letter as a necessary resource for the completion of this award.

Other expenses total funds requested $30,000

INDIRECT COSTS UAB will abide by the K23 guidelines for capping IDC at 8% MTDC.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		
1. Materials and Supplies	150,000.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		
Section J, Fee		0.00
Section K, Total Costs and Fee (I + J)		

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

Tracking Number: GRANT12813369

Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

Tracking Number: GRANT12813369 Funding Opportunity Number: PA-19-119 . Received Date: 2019-03-11T14:45:25.000-04:00

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	response_to_reviewers_Guimbellot_v5.pdf
Candidate Section	
2. Candidate Information and Goals for Career Development	Training_plan_final.pdf
Research Plan Section	
3. Specific Aims	Specific_Aims_Guimbellot_v4.pdf
4. Research Strategy*	Research_Strategy_Guimbellot_v_final.pdf
5. Progress Report Publication List (for Renewal applications)	
6. Training in the Responsible Conduct of Research	Training_in_the_Responsible_Conduct_of_Research.pdf
Other Candidate Information Section	
7. Candidate's Plan to Provide Mentoring	
Mentor, Co-Mentor, Consultant, Collaborators Section	
8. Plans and Statements of Mentor and Co-Mentor(s)	Statements_of_advisors_final.pdf
9. Letters of Support from Collaborators, Contributors, and Consultants	support_letters-3-11.pdf
Environment and Institutional Commitment to Candidate Section	
10. Description of Institutional Environment	Environment.pdf
11. Institutional Commitment to Candidate's Research Career Development	Guimbellot_Insitutional_Commitment.pdf
Other Research Plan Section	
12. Vertebrate Animals	
13. Select Agent Research	
14. Consortium/Contractual Arrangements	
15. Resource Sharing	
16. Authentication of Key Biological and/or Chemical Resources	
Appendix	
17. Appendix	

Funding Opportunity Number: PA-19-119. Received Date: 2019-03-11T14:45:25.000-04:00

PHS 398 Career Development Award Supplemental Form

Citizenship*:

18. U.S. Citizen or Non-Citizen National?* ● Yes ○ No

If no, select most appropriate Non-U.S. Citizen option

- ❑ With a Permanent U.S. Resident Visa
- ❑ With a Temporary U.S. Visa
- ❑ Not Residing in the U.S.

If you are a non-U.S. citizen with a temporary visa applying for an award that requires permanent residency status, and expect to be granted a permanent resident visa by the start date of the award, check here: ❑

INTRODUCTION TO THE APPLICATION: We are grateful to the favorable review, which emphasized the strengths of the candidate, mentoring plan, research environment, and the importance of the overall research concept. To address critiques, I have substantially focused the scope and content of my application as follows:
Research Design: Clinical study feasibility*:* Reviewer (R) 1 questioned feasibility of the clinical study. To address this, we initiated the protocol as proposed to assess feasibility and patient recruitment. From Sep 2018 to Feb 2019, we successfully recruited 10 subjects who completed intensive PK analysis. Data presented in the application support our hypothesis and helped refine the analysis plan. Further, these data also support the possibility of reduced sampling strategies to model total drug exposure (i.e., peak and trough) to confirm this finding, and will further improve feasibility. We bolstered assessments of adherence and focused the grant to remove the clinical study of a pharmacologic enhancer, which was questioned. In response to R1's critiques regarding the premature nature of the GWAS study, given the association was suggestive but not statistically significant, this was de-emphasized. We have refined the genotype/drug response study to confirm the association and allow greater focus on pharmacologic mechanisms and intracellular studies. Similarly, R1 suggested accounting for contribution of SLC26A9; its association with ivacaftor response has been shown to have conflicting effects in two separate studies; nevertheless, we propose to examine if SLC26A9 is actually a modifier of response and adjust for it if needed.
Improved analysis of contribution of CYP3A isoforms: To address the need to assess the contribution from mixed CYP3A isoform genotypes, I have conducted additional preliminary studies in both primary epithelial cells and airway epithelial cell lines which demonstrated phenotypic distinctions in isoform expression between individuals. I have removed the prior Aim 2 to allow for more mechanistic studies to evaluate the contribution of each isoform in the CYP3A family using recombinant CYP3A enzymes to test binding affinities and metabolite production, as well as variation between cell cultures derived from individuals with distinct isoform expression and activity. Our new preliminary data suggest CYP3A5 is the key extra-hepatic isoform relevant to intracellular concentrations of ivacaftor in epithelia, and thus it is now the major focus of this application. The new approach in Aim 3 will determine the relative contribution of each isoform in epithelia and distinguish the impact of airway cell expression of each isoform on ivacaftor metabolism and response.
Statistical analysis insufficiently detailed: Multiple critiques recommended revision of the statistical analysis plan, which was not described thoroughly. I have addressed all concerns by revising the statistical plan in its entirety. Specifically, power calculations in Aim 1 have been revised using estimates of variability of all outcome measures (ppFEV1, weight, and sweat chloride) from the Phase 3 clinical trials of ivacaftor. Estimates of plasma drug concentration variance were included in these estimates based on new preliminary data in the target population. These estimates reveal our sample size is sufficient to detect correlation of ≥ 0.5 with at least 85% power, which would be clinically relevant and confirm our hypothesis. Aim 2 power analysis was revised using allele frequencies derived after conducting a new preliminary study (provided in the revised application) that verified mutation frequencies in our CF population. The approach has also been revised to limit the number of variants tested in *CYP3A5* and employ diplotypes to assign metabolism phenotypes, as suggested. Together, this approach improves the experimental design and statistical analysis. Aim 3 statistical analysis has been revised to reflect the new mechanistic studies employing primary cells. Cluster randomization power analysis of two independent means has been employed to reflect repeated measures from samples from the same individuals within two groups. Estimates of variability for the outcome measure (change in short circuit current) were determined from preliminary data and published literature. Given these estimates we will have at least 85% power to detect a meaningful difference between groups. This process also helped me refine my plan for training in biostatistics, which we have further enhanced (see below).
Candidate, Mentorship and Training: Productivity delay: Having completed my transition to UAB, I have *published six peer-reviewed manuscripts since the original submission; one additional manuscript in review, and two additional manuscripts in preparation*. My work was presented in four abstracts at North American Cystic Fibrosis Conference in 2018, three directly relevant to this proposal.
Mentorship: We have revised the mentoring plan to meet quarterly with all mentors and advisors independently and at least once yearly with all committee members. To address statistical concerns, I will meet with Drs. Tiwari, Aban, and Limdi quarterly and more often as needed for analysis, as I have done in preparation of the revised grant. I already have monthly meetings with Dr. Acosta for pharmacology training, review of data, and research planning, in addition to frequent meetings with my primary mentor, Dr. Rowe.
Training: To improve background in statistics, pharmacology, and pharmacogenetics, I have added additional training including certification in Principles of Clinical Pharmacology, Certara workshops in PK/PD modeling, continued my training with Dr. Acosta which includes one-on-one instruction, and intensive coursework in biostatistics and pharmacogenetics.

CANDIDATE'S BACKGROUND. My ultimate goal as a physician scientist in pediatric pulmonology is to understand individual variation in disease to improve precision care for children with respiratory diseases. *Since my original submission, I gained momentum with improved productivity and research skills.*

Always fascinated with science, I completed a degree in biochemistry and molecular biology at Mississippi State University, where I was one of their first awardees of the Goldwater Scholarship, the most prestigious undergraduate award in the U.S. for students studying the sciences. Next I enrolled in the Medical Scientist Training (MST) Program at University of Alabama at Birmingham (UAB) to bridge clinical medicine and basic science research, where I won several awards for research, successfully obtained NIH funding for training, and presented my work at international conferences. My thesis (laboratory of Eric Sorscher in the UAB Cystic Fibrosis Research Center) addressed the effects of hypoxia on the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR)* gene expression, providing some of the first evidence that acquired CFTR dysfunction influences non-CF disease, resulting in two first author publications. During this time, I also initiated and managed an international genetics research project to identify novel variants in a unique population of Ecuadoreans with hemifacial microsomia. While unrelated to my primary projects, this study enabled me to take a major leadership role in a genetic study and provided me with specific skills applicable to the current application and my overall career, including establishing a collaboration with an international university (Pontificia Universidad Católica del Ecuador), assembling a research team and interpreters, developing the proposal, obtaining regulatory approvals, and securing funding. Overall, the MST program provided a breadth of training in basic science and clinical medicine, a key stepping stone in my career.

Subsequently, I completed residency in pediatrics at Columbia University Medical Center in New York followed by fellowship at the University of North Carolina at Chapel Hill. My clinical training focused on general pediatric pulmonology. Throughout this time, my desire to improve the lives of my patients with CF through research strengthened, as I twice became a mother myself, while gaining perspective as the primary pulmonologist for the families of children with CF. I witnessed the struggles families experience from the initial diagnosis through periods of illness, and realized that my distinctive skill set in research and medicine could make a significant impact in the delivery of care, understanding of the disease, and finding a cure. In August of 2015, I was recruited to my first faculty position, returning to the CF Center at UAB to solidify my long-term plan to improve precision care in CF by starting to build an independent research program in context of my clinical practice in pulmonology, with Steven Rowe (Director of the UAB Cystic Fibrosis Research Center) as my primary research mentor. Since joining the faculty at UAB, I continued my training to improve clinical and translational study skills, including attending the Genetics and Genomics Clinical Research Immersion Course; the Clinical and Translational Science Training Program; the Pulmonary Biology Training Program (T32); and the Success in Research workshop. In August of 2016, I was promoted to Assistant Professor of Pediatrics.

In pursuit of my goals, I have acquired pulmonary biology-focused skills, including assays of CFTR maturation, trafficking, and function; primary cell culture; three-dimensional primary cell models; and microscopy, all at a time when my research direction evolved from CFTR trafficking to primary epithelial model development and pharmacogenetics (to enable better studies of precision medicine) and changed institutions from North Carolina to UAB. In addition, I have advanced skills essential for a successful career in research: laboratory management, human subjects research and proposal writing. I have also been invited as a lecturer in precision medicine and pharmacogenomics (Depts. Medicine and Pharmacology, UAB). In addition to successful grant applications from graduate school and fellowship, I have submitted successful grant proposals as either a principal or co-investigator since my faculty appointment (including an NIH R43, a CFF pilot award, the CFF's prestigious Harry Shwachman Clinical Investigator Award, and the Kaul Pediatric Research Institute). I have successfully completed a variety of Institutional Review Board protocols, ranging from the inclusion of human subjects, use of human tissue specimens, consent form authoring, and retrospective chart studies. I routinely identify, recruit, and consent human subjects for studies and manage a research coordinator and technician for these activities as well. While my publication yield transiently slowed during clinical training and my transition to UAB*, I have authored six first or senior author publications since the original submission of this application; one manuscript under review; and two additional first author original research manuscripts in preparation.*

With support from my institution, which provides a wealth of resources for training, mentorship, and collaboration, my experiences have positioned me well to transition to an independent investigator with a variety of skills to launch a research career. Although I have basic research and clinical practice training, I will benefit greatly from additional studies in specific areas: statistics, clinical trials, and pharmacology, as well as further career development mentoring and guidance. *The K23 Career Development award is crucial for me to become fully independent and a leader in precision medicine for CF and other pediatric pulmonary diseases.*

CAREER GOALS AND OBJECTIVES. My goal is to develop and implement personalized therapeutic strategies for children with pulmonary disease. My research program focuses on the development of cell-culture based tools to study CFTR modulators on a personalized basis and to study the pharmacometrics of CFTR modulators and other airway drugs, a significant opportunity and unmet medical need. To achieve this goal, I will need further training and mentorship under the K23 Career Development Award to develop my research program and become independent from my mentor over the next five years.

This award will provide me with the protected time and additional training to conduct translational, patient-oriented research in personalized medicine, incorporating pharmacogenetics and pharmacology with biomarker development and clinical research design. With the funds from this grant, I will support my salary, staff, and for supplies to generate publications and preliminary data for an NIH R01 award in a cutting-edge area with excellent opportunities related to my specific approach. This award will provide me with the training to reach my potential to impact bench-to-bedside and bedside-to-bench research, completing the circle of translational and personalized medicine so important to CF and pediatric pulmonology.

My **short-term learning objectives** (see Table on following page) over the next 5 years are selected to enable independent research design and analysis. They include:

- Statistical genetics and statistical methodology. To develop a strong foundation built upon my prior graduate training, additional training in statistical analysis is required. (Aims 1-3)
- Pharmacometrics and metabolism. A solid understanding of pharmacology and its use in developing personalized therapeutic strategies, including biomarkers, is essential to developing a research program in precision medicine. (Aims 1-3)
- Patient-oriented translational research study design and implementation. Further training will prepare me to develop patient-oriented research grants independently. (Aim 1)
- Professional development skills. Grant and manuscript preparation and review, interviewing and negotiating, mentoring and laboratory management. These skills are applicable to the proposal as a whole, particularly as pertains to promoting independence.

My **long-term goals** over the next 5-10 years include:

- Promoting precision treatment strategies for pediatric and pulmonary diseases by producing rigorous evidence to guide clinical care.
- Maintain continuous federal and non-federal funding for patient-oriented basic, translational and clinical research, notably through R01 awards.
- Sustain productivity by publishing 3-4 peer-reviewed basic and translational manuscripts annually.
- Develop a mentoring and training program for graduate and professional students and post-doctoral trainees in my laboratory

CAREER DEVELOPMENT AND TRAINING ACTIVITIES. My career development and training efforts will focus on those areas crucial to my success. Each area and specific activity were selected to integrate with the specific research activities I will complete to reach my short and long-term goals. A member of my mentoring team or scientific advisory committee supports each training area (Table 1).

Table 1. Mentors and Advisors for K23 Proposal.

Mentor/Advisor & Role	Content Areas	Affiliation	Meeting Frequency
Steven M. Rowe, M.D., M.S.P.H. Mentor	Cystic fibrosis, model development, emerging CF therapies, clinical trials, career development (all Aims)	Professor of Medicine and Pediatrics Director, Cystic Fibrosis Research Center	***Monthly***
David W. Kimberlin, M.D. Co-mentor	Clinical trials, grant writing , K-R transition (Aim 1,2, overall career development)	Professor, Pediatrics Vice Chair, Dept. of Pediatrics, Clinical and Translational Research	***Quarterly***
Edward Acosta, Pharm.D. Co-mentor	Pharmacometrics, pediatric pharmacology, translational pharmacology (all Aims)	Professor, Pharmacology Director, Division of Clinical Pharmacology	***Monthly***
Hemant Tiwari, Ph.D. Co-mentor	Statistical genetics (Aim 1, 2)	Professor, Biostatistics	***Quarterly***
Inmaculada Aban, Ph.D. Co-mentor	Clinical trials statistics; statistical methodology (all Aims)	Professor, Biostatistics	***Quarterly***
Emily Scott, Ph.D. Advisor	Cytochrome P450 enzymes, drug metabolism (Aim 3)	Medicinal Chemistry and Pharmacology, U. Michigan	***Quarterly***
Nita Limdi, Pharm.D. Advisor	Personalized medicine, pharmacogenomics (Aims 1, 2)	Professor of Neurology and Epidemiology	***Quarterly***

MENTORSHIP TEAM: Overall, these mentors and advisors will provide guidance for specific learning objectives and guidance. Individual meeting will occur at least quarterly, increasing to monthly as needed for training and research planning. Group meetings will occur at twice yearly with all mentoring and advisory committee members, including WebEx conferencing to facilitate those advisors not at UAB and the members' schedules. *We have already met once this year as a group.* They assess my milestones and provide feedback after formal presentation of my research and professional progress during these meetings, after which detailed plans for the next six months will be summarized and communicated to all mentors and advisors.

- Steven Rowe, M.D., M.S.P.H., my primary research mentor, has an outstanding international reputation and extensive expertise in basic, translational, and clinical research in CF and other pulmonary diseases. He is the director of the CF Research Center at UAB, recognized world-wide for leadership in cutting-edge CF research and one of the longest continuously funded such centers nationally. His laboratory has over 20 members currently and he has also successfully mentored many medical students, residents, fellows, and junior faculty, including several who have been promoted to tenure-earning faculty positions, achieved K-level funding, and who are now CF Center Directors elsewhere. Our meetings will focus on the review of data, overall study design, project milestones, presentation of results, and grant preparation.
- David Kimberlin, M.D., will serve as a co-mentor, providing guidance in the conduct of clinical studies, project management, and how to maximize the resources of this award in order to obtain an NIH R01. Dr. Kimberlin has successfully transitioned several investigators to independent research programs and has a long history of career development success at all levels of training.
- Edward Acosta, PharmD, co-mentor, has extensive experience in adult and pediatric pharmacokinetic and pharmacodynamics modeling for drug studies, translational pharmacology and the optimization of drug regimens, and development of new assays for drug assessment. Our meetings will focus on one-on-one training in pharmacometric analysis, reviewing data, and assessing pharmacometric study design.
- Hemant Tiwari, PhD, co-mentor, is an expert in statistical genetics, including the analysis of complex genome-wide association studies, next-generation sequencing technology and statistical approaches, and has decades of experience training physicians and scientists in using these tools in their own studies. Our meetings will focus on analysis of genetic variants, review of the data, and study design.
- Inmaculada Aban, PhD, co-mentor, is an expert in clinical studies and statistical methodology (although not statistical genetics). She is the founding statistician in the recently established Pediatric Research Office to further goals of research in the Department of Pediatrics. She will provide guidance in appropriate study design and biostatistics expertise.
- Emily Scott, PhD, is a leader in understanding cytochrome P450 enzymes, drug metabolism, and drug design. She will provide guidance in the study of CYP3A enzymes and drug metabolism.
- Nita Limdi, Pharm.D., Ph.D., M.S.P.H., is an expert in personalized medicine and pharmacogenomics. She will provide guidance in personalized approaches to therapeutic strategies, and career development.

Training activities:

1) **Pharmacogenetics and statistical genetics (Aim 1, 2).** These didactic experiences will improve research design and rigor; enable independent analyses; and improve collaborations with statisticians.
   a) BST 675. Introduction to Statistical Genetics, to solidify statistical genetic analysis methods (UAB Department of Biostatistics, 1 semester).
   b) Pharmacogenomics Certificate Program, University of Colorado. Course includes fundamentals o pharmacogenomics, interpretation and implementation into clinical care.
2) **Pharmacometrics and metabolism (Aim 1,3).**
   a) Principles of Clinical Pharmacology, NIH. Online, self-directed course for basics of clinical pharmacology certification.
   b) Pharmacometric Analysis in Clinical Trials at the Foundation for Advanced Education in the Sciences (FAES), National Institutes of Health. This one-week intensive is for investigators pursuing studies in PK/PD during drug development as well as correlation with clinical outcomes and biomarkers.
   c) Certara University courses (Pharmacokinetic/Pharmacodynamic modeling) including 1) Non-compartmental analysis, 2) Population Modeling, 3) Physiologic-Based Pharmacokinetic Modeling.
   d) Edward Acosta provides one-on-one training with over 20 years' experience in lecturing and training pharmacologists and health professionals in pharmacology.
3) **Clinical Research, Design and Analysis** (**Aim 3**).
   a) *The Applied Statistical Independence in Biological Systems (ASIBS) Short Course at Mount Sinai Icahn School of Medicine.* This seven-week online course culminates in a week-long in-person

hands instruction; combined will serve to train me in biostatistical methodology and computing using SAS (Statistical Analysis System). (Grant No. R25GM111239).

b) Biostatistics, Epidemiology, and Research Design (BERD) at UAB Center for Clinical and Translational Science Webinars and one-on-one consultations with methodologists to enhance study design and training. Quarterly consultations for research design with a methodologist.

c) The Center for Clinical and Translational Science training academy (including the Clinical Investigator Training Program) at UAB to study clinical trial implementation and completion. I will conduct a trial using human subject specimens and data for translational research in preparation for future grant applications. I will learn to apply the data obtained to calculations for subsequent studies. Drs. Rowe, Kimberlin, and Aban will be instrumental to these skills.

In addition to the previous training foci, I will continue to develop the professional skills critical for independence such as scientific writing, dissemination of research and management skills.

Table 2. Summary of activities and milestones.	**Year 1**		**Year 2**		**Year 3**		**Year 4**		**Year 5**	
	1-6	7-12	1-6	7-12	1-6	7-12	1-6	7-12	1-6	7-12
Didactic training (Person Months)	2.4		2.4		1.8		0.6		0	
Responsible Conduct of Research										
ASIBS Short Course										
Clinical Pharmacology Certificate										
Pharmacometric course at FAES										
Introduction to Statistical Genetics										
Certara courses										
Pharmacogenomics Certificate										
CCTS Training Academy										
Conferences (Person Months)	1.0		1.0		1.0		1.0		1.0	
BERD										
Weekly local research conferences										
Clinical Research Seminar series										
ASPET/EB, NACFC, ATS										
K-R Transition group										
Research (Person Months)	5.6		5.6		6.2		7.4		8.0	
Aim 1 PK study										
Aim 1 Clinical data and analysis										
Aim 2 Variant correlation with outcomes										
Aim 3 *in vitro* mechanistic studies										
Manuscript submissions										
Write R01										

Seminars and laboratory meetings:

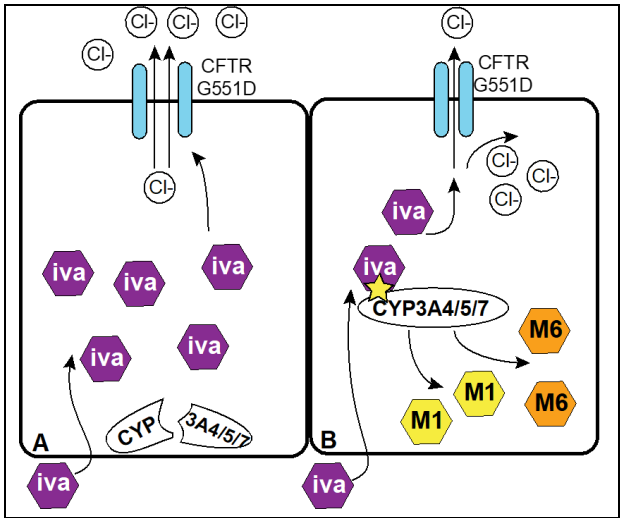
- UAB CF Research Center (CFRC): invited speakers to discuss the latest developments in CF, weekly
- Grand Rounds speakers for the Department of Pediatrics, weekly

Presentation Skills at local and national meetings:

- Present progress as manuscript drafts and grant proposals for critical review to committee.
- *Teach in undergraduate and graduate level courses: Precision Medicine (Genetics, ongoing role beginning March 2019) and Pharmacogenomics (Pharmacology, initiating 2020)*
- Regular attendance and presentation at the North American Cystic Fibrosis Conference, American Thoracic Society, and American Society for Pharmacology and Experimental Therapeutics at Experimental Biology meetings will enable me to: (i) keep current with updates in research and clinical medicine pediatrics, pulmonology, CF, and pharmacology and establish and maintain the peer contacts that will form the basis of future research collaborations.
- Present yearly at the CFRC seminar series.
- Present at the CCTS project panels (multidisciplinary experienced faculty review panel) for formal review of study design and progress for R01 and other grant applications.

Overall Impact of career development activities: At the end of the five-year award, I will have combined my robust basic science skills with clinical and translational training, improved my knowledge of pharmacology, statistics, and genetics, and developed a precision approach to CF therapy. I will have unique training and experience to combine pulmonary physiology, epithelial biology, pharmacology, and pharmacogenomics to apply to the understanding of drugs targeted to the lung and measurements of clinical response. The skills and expertise I will develop will enable expansion of pediatric pharmacometrics and precision medicine to other pulmonary diseases (asthma, pulmonary infection, COPD).

Specific Aims: Cystic fibrosis (CF) is an autosomal recessive disease caused by genetic variants in the CF Transmembrane conductance Regulator (CFTR) gene. This results in dysfunction of epithelial homeostasis in many tissues due to impaired chloride (Cl^-) and bicarbonate transport. In the lung, thick, viscous mucus results in progressive lung decline, ultimately resulting in death. This lifelong, multisystem disease causes a massive burden of disease for patients with CF and their families over decades of life. The recent debut of mutation-specific CFTR modulators that target the molecular defect in the protein to rescue CFTR activity has begun to revolutionize care. Despite the success of one of these, the potentiator ivacaftor, there is still pronounced variance in drug efficacy, as measured in individuals' phenotypic response to therapy and their *in vitro* cellular response when assessed with cell-based biomarkers. This raises the possibility of untapped efficacy. Ivacaftor is metabolized by members of the CYP3A family, found in airways and other tissues. Single nucleotide polymorphisms (SNPs) alter their activity, varying the concentrations and efficacy of many drugs. To maximize efficacy of ivacaftor, given its strong dose-dependence, it is essential to understand its pharmacokinetics (PK) and the influence of drug metabolism of ivacaftor. Our preliminary data shows considerable variation in drug concentrations and CYP3A isoform expression, and confirms variant alleles in the CF population that may affect metabolism, particularly in the target tissue, epithelial cells. *In this proposal, we will test the hypothesis that epithelial ivacaftor metabolism influences drug response and can be used for precision CF therapeutics.*



Ivacaftor mechanism of action. Ivacaftor acts on CFTR with gating dysfunction (e.g., G551D) to increase chloride transport in the absence of functional CYP3A4/5/7(A). Active metabolism of the parent compound to **metabolites M1 and M6** would result in less effective CFTR restoration in airway epithelia (B).

Aim 1. Perform a prospective study of CF patients taking ivacaftor monotherapy to determine the relationship between drug exposure with drug response. We will conduct a clinical study on patients already taking ivacaftor to determine correlations between drug response, drug exposure (including the epithelial intracellular compartment), and metabolism genotype.

a) We will recruit 30 patients on ivacaftor, quantitate the drug in plasma and HNE intracellular lysates, and calculate PK parameters to determine the association between drug exposure and clinical effectiveness.
b) For each patient, we will also determine CYP3A SNP profile to detect associations between genotype and drug exposure. This will allow us to determine predictive capacity of genotype on the pharmacokinetics and expected levels of ivacaftor.

Aim 2. Determine whether CYP3A variant alleles are associated with the efficacy of ivacaftor. DNA and clinical data will be collected from a recent large observational trial, which will be used to:

a) Characterize key metabolism gene variants of CYP3A enzymes in CF subjects.
b) Determine the association between metabolism genotype and clinical efficacy, including lung function (i.e. spirometry), sweat chloride, and nutritional status (i.e. body mass index).

Aim 3. Determine the impact of drug concentrations on epithelial CFTR function and the contribution of different CYP3A isoforms to ivacaftor metabolism. We have already established methods to quantitate ivacaftor and its metabolites (including intracellular levels) and evaluate CFTR function *in vitro*.

a) We will perform short-circuit current measurements in *in vitro* human airway monolayers from CYP3A expressors and non-expressors in response to ivacaftor exposure after treatment with ivacaftor. We will correlate CFTR function with intracellular concentrations of the drug and metabolites.
b) Using recombinant CYP3A enzymes, we will determine the binding affinities and metabolite production of each in response to ivacaftor exposure to quantitatively determine the relative contribution of each isoform to ivacaftor metabolism.

Significance: We hypothesize the concentrations of ivacaftor and its relationship to drug metabolism are key to understanding variation in efficacy among the CF population. This is the first step to understanding pharmacogenetics in complex CFTR modulator combinations (double and triple) that will soon be expanded to ~90% of CF patients with greater genotypic diversity. Ultimately this will create new treatment paradigms, incorporating drug concentrations and metabolism genotype to maximize efficacy of modulators. The training accomplished in this application will lead to an independent career for the PI and future R01s in pulmonary pharmacogenetics.

Background and Significance: Since identification of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*)[2-4], development of mutation-specific therapy has been challenging. Disease-causing mutations lead to diminished CFTR function; in the airway, impaired airway clearance, infection and inflammation causes morbidity and limited life span. [5-9]

CF therapeutics target the underlying protein defects. The development of CFTR modulators – *correctors* that overcome impairments in protein processing and *potentiators* that enhance CFTR gating function – has begun to revolutionize the care of certain CF patients (presently ~10%) in whom CFTR modulators are highly active.[11-13] Ivacaftor is a potentiator targeted to specific mutations, used as monotherapy[14-19] and in combination with correctors.[20-23] It potentiates CFTR channel opening, restoring proper regulation of the mutant ion channel. Early studies of patients with the severe *G551D* mutation showed that while the majority of patients had a robust response to the drug, **approximately 25% had less than 5% improvement in predicted Forced Expiratory Volume in 1 second (ppFEV1)[24], and some demonstrated declines (Fig. 1).** A recent 5-year observation of this population revealed similar numbers of patients had considerable decline despite adherence to therapy.[25] Change in sweat chloride, a key clinical measure of CFTR activity, varied from -25 to nearly -80 mEq/L[24]; notable since disparate outcomes are seen in those with higher sweat chloride.[26,27] These differences may be due to sensitivity of response to small alterations in drug exposure. Similar relationships are seen between oral dose and CFTR activation *in vitro;*[28] between oral dose and clinical measures of CFTR activation (Fig. 2)[29] and between oral dose and plasma concentration.[30] Therefore, a close relationship between the dose, plasma concentration, and CFTR potentiation is likely to exist but has not yet been reported. Because ivacaftor is an essential component of currently approved agents and is part of next generation therapy that will treat ~90% of CF patients,[21,31] understanding the role of ivacaftor's concentration to CFTR activation on an individual basis is critical.

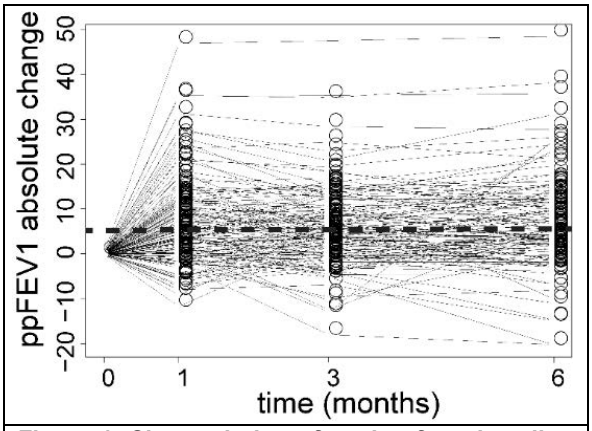


Figure 1. Change in lung function from baseline is variable over 5 years. ppFEV1 of patients with the *G551D* mutation on ivacaftor over 6 months.[1] Each line represents a single individual tracked over time. Horizontal dotted line at +5% improvement. We hypothesize that individual variation in exposure in the target tissue may be a factor.

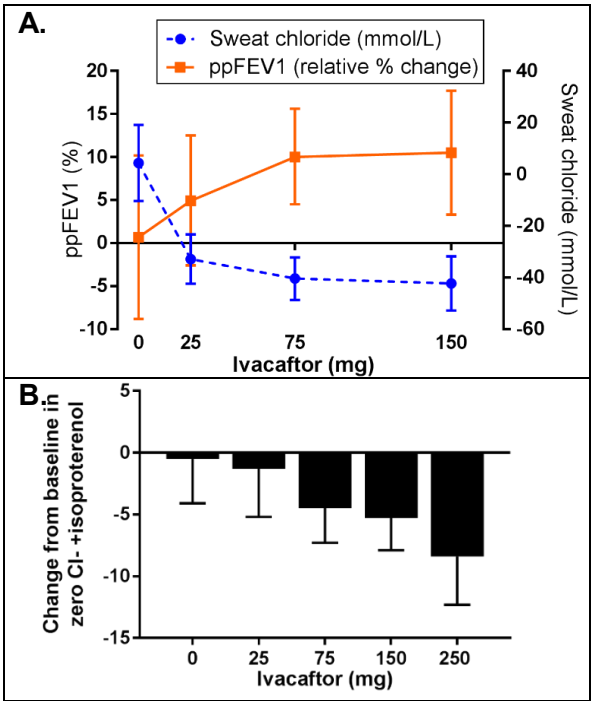


Figure 2. Increasing ivacaftor dose resulted in increasing drug response. A. In the original Phase II trials, multiple drug concentrations showed a clear dose-response. A. Summary of changes in ppFEV1, NPD, and sweat chloride adapted from Accurso FJ et al. *N Engl J Med* 2010;363:1991-2003. **B.** The greatest restoration of CFTR activity by NPD was observed at the highest tested dose of ivacaftor (250 mg), even though 150 mg is the approved dose[10]. NPD (nasal potential difference). Since dose is linearly related to plasma concentration, this suggests a similar relationship between concentration and response. Adapted from: Rowe SM et al. PLoS One. 2013 Jul 26;8(7):e66955.

Pharmacokinetics vary among individuals with CF. Characterization of CFTR modulators during development[32-36] includes pharmacokinetic (measures of drug exposure) and pharmacodynamic (relationship between drug exposure and response) modeling (PK/PD) in a small selected group of patients. Variation in drug exposure among CF patients, due to altered absorption, metabolism and transport of drugs, is well recognized and known to have pronounced impact on drug efficacy.[37-41] For example, ciprofloxacin, metabolized by CYP3A4 and CYP1A2, has such a wide variation in plasma concentrations that some CF patients cannot reach therapeutic exposure with standard dosing.[38] Another example, tacrolimus, an immunosuppressant used in solid organ transplant, requires altered dosing in CF recipients vs. non-CF to achieve therapeutic concentrations.[42-44] Up to 67% of variation in plasma concentrations of tacrolimus has been attributed to differences in metabolic enzymes, particularly the CYP3A superfamily including CYP3A4, CYP3A5, and CYP3A7.[45]

Cytochrome P450 enzymes play an important role in systemic and tissue-specific metabolism of CFTR modulators and other drugs. Like ciprofloxacin and tacrolimus, ivacaftor is metabolized by CYP3A isoforms, including CYP3A4 and CYP3A5[46]; the family members are known to overlap in substrate specificity.[47] These

enzymes metabolize up to 60% of available drugs[48]. Although the relationship between genetic variation and clinical efficacy is not always consistent,[49-51] there is substantial evidence these enzymes contribute to inter-individual variation in dose requirements and drug response.[52-55] Single nucleotide polymorphisms (SNPs) in ***CYP3A4*** have been implicated in variation in drug responses (e.g., calcineurin inhibitors,[53-56] amlodipine[57], statins,[58-60] cyclosporin A,[55] and fluticasone[61]). CYP3A4 has substantial variation (40-100 fold) in activity among individuals.[62] While CYP3A4 is primarily a hepatic enzyme, it may also expressed in airway epithelia in some individuals, influencing tissue-specific drug concentrations.[61,63,64] ***CYP3A5*** is a key extra-hepatic CYP3A isoform implicated in variation in drug exposure and response in several drugs (e.g. tacrolimus,[45,50,65-67] statins,[68,69] amlodipine,[70,71] cabazitaxel,[72] and beclomethasone[73]). It is found in most subjects in the lung[63,74-78] and has variable activity[79-82]. A third member of the family, ***CYP3A7*****,** is expressed in the liver and extra-hepatic tissues of children and adults. These isoforms may have overlapping or distinct substrate specificity,[83] but as yet, their relative contribution to ivacaftor metabolism has not been established. The relationship of SNPs in *CYP3A5* to dose requirements is well characterized; tacrolimus is a clear example. Patients with the variant *CYP3A5*1* have extensive metabolic activity of the enzyme, which reduces tacrolimus drug exposures unless higher doses are given to achieve therapeutic concentrations.[45,50,65-67] For ivacaftor, no therapeutic drug monitoring (TDM) is used because the therapeutic window is broader, and simplicity in dosing was desired by the manufacturer. However, highly variable plasma concentrations of ivacaftor are seen[84] (Fig. 3), which is a significant concern considering the dose-dependent response to ivacaftor[29] (Fig. 2). All PK/PD relationships were initially determined using plasma concentrations, **but the intracellular concentration in the tissues may be key** given the relationship between increasing concentrations of ivacaftor and CFTR potentiation in epithelia[28] . Differences in dose-response observed among different tissues confounded ivacaftor's clinical development, which may be explained by the highly variable expression of the CYP3A family in airway and other tissues. **Targeted drug concentrations can be employed to enhance efficacy.** To reduce variability in the plasma and tissue concentration of ivacaftor, TDM could be employed to target thresholds of efficacy. The cost and availability of incremental ivacaftor formulations may make this simple approach impossible. Inexpensive treatment strategies exist to enable dose-targeting available despite this barrier by using pharmacokinetic enhancers (PE) to suppress CYP3A metabolism.[85] Inhibition of CYP3A enzymes using PE such as an antifungal[86] or RTV[87] significantly reduced ivacaftor dosing requirements, while maintaining or improving drug response[86] or exposure.[87] **This represents a highly significant treatment opportunity: strategies to identify and target thresholds of ivacaftor concentrations in airway epithelia could maximize efficacy for individuals.**

Not only can TDM help achieve maximal drug concentrations and efficacy, it could reduce cost. At a current yearly cost of >$300,000, combination therapy of ivacaftor plus a PE such as ritonavir could theoretically reduce the yearly cost to ~$45,000 (current list price ~$411/tablet, given twice a week based on current evidence[86,87], plus the cost of RTV, estimated at $150/month assuming 50mg/day). While drug cost is a moving target, CFTR modulator pricing structures have restricted access to patients around the world -- cost reduction with novel therapeutic strategies could help address this. Our study is designed to identify the thresholds of ivacaftor efficacy, which will lead to future studies employing dose titration or the use of PE to achieve optimal drug exposure.

Summary:

- CYP3A-mediated metabolism is an important source of variance between individual drug responses.
- Ivacaftor efficacy is variable in patients and dose-dependent, underscoring the need to optimize dosing strategies and account for differences in drug concentration and metabolism, including the airways.
- Active management of ivacaftor metabolism could optimize dosing, maximize efficacy, and reduce cost.

Approach. Preliminary Results, Experimental Design and Methods:

Scientific Premise: My objective is to understand variation in ivacaftor concentrations in plasma and the target tissue, identify concentration thresholds of drug efficacy, and incorporate knowledge of ivacaftor metabolism in precision therapeutic strategies. The rigorous experimental design assures the collection of robust and unbiased results. Recent literature and *additional preliminary data from studies conducted since the original submission of this application are detailed below support the premise and feasibility*. In addition, my prior clinical and research training, as well as the diverse and experienced mentoring team provide a strong foundation to achieve the overarching goals of this proposal.

Overall Rationale: We will **1)** conduct PK studies in CF patients to determine ivacaftor concentration variability in plasma and target tissue, and correlate quantitative measurements with clinical outcomes and genetic variants; **2)** examine whether there is an association between SNPs in *CYP3A* alleles and ivacaftor efficacy in a

large, national cohort of patients on ivacaftor monotherapy; and **3)** perform mechanistic studies to clarify the role of CYP3A isoforms in metabolism of ivacaftor.

<u>Aim 1.</u> Does the steady-state plasma or intracellular concentration of ivacaftor influence clinical drug response? In this aim, we will test the *hypothesis* that ivacaftor exposure determines the degree of CFTR activity and drug response *in vivo*. Variability in plasma concentrations is evident in our preliminary data (Fig. 3) and in other studies,[30,87,88] but no clear threshold for optimal clinical response has been defined, an important caveat given the clear relationships between dose, exposure, and CFTR activation in epithelia. The simulated exposure-response model published by the manufacturer was developed based on data after 14-28 days of treatment.[30] Five years of ivacaftor use have revealed that maximal responses are likely to occur 3-6 months after initiation of the drug, suggesting that the original exposure-response model is not sufficient to determine exposures to elicit maximal responses. Furthermore, no studies have ever been performed on the target tissue (epithelial cells) to determine an exposure-response for CFTR activation, an important omission since there is a direct relationship between increasing ivacaftor dose and CFTR activity *in vitro*[28] and in clinical trials (Fig. 2). Observational trials have clearly shown that 25% or more of patients have suboptimal responses despite adherence to therapy. Determining exposure-response relationships with more data will advance the possibility of using TDM and precise dose titration. The maximal dose tested (250 mg twice daily)[10,29] showed maximal clinical efficacy (Fig. 2) without any evidence of dose-dependent adverse events. This suggests that **dose titration and targeted exposure to ivacaftor in the airway cell will yield untapped potential for improvement without significant safety liabilities.**

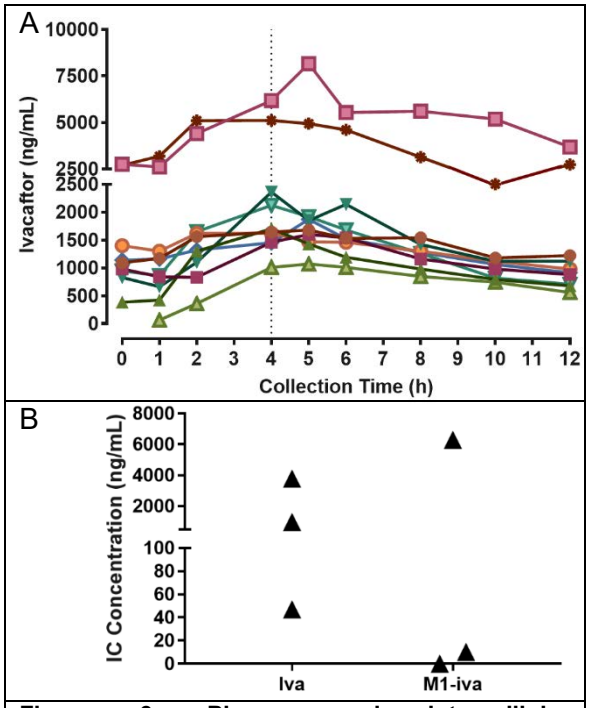


Figure 3. Plasma and intracelllular concentrations are detected in a multiplex mass spectrometric assay. A. Ivacaftor (Iva) concentrations in plasma over time at steady-state in 10 CF patients on therapy. All patients were confirmed to be adherent for at least 5 days prior to study and were directly observed to take iva on the day of the study. Time 0 is just prior to dose, hours 1-12 are relative to dose ingestion. Vertical dotted line represents anticipated peak based on FDA review. Variation in concentration/time curve show that some patients reach higher than anticipated concentrations, whereas others reach lower than anticipated concentrations, based on available trial data. M1 and M6 metabolites were simultaneously detected in a multiplex assay (data not shown). Epithelial cells for all subjects were donated at time 0 and 4h (expected peak) and are undergoing analysis. **B.** Iva and M1-iva concentrations in intracellular (IC) lysate from three subjects in a separate study who consented for epithelial donation. Both plasma and intracellular quantitation show wide (~5x - 100x) variation in ivacaftor monotherapy despite collection at expected peak. M1-iva is detected in epithelia, but not M6-iva.

Rationale: Determining a clinical exposure-response relationship will allow precision approaches in CF. Our center has conducted many clinical studies (including PK),[89-91] as well as measured CFTR function *in vivo,*[10,92,93] including my recent contributions.[94-96] Since this application was initially submitted, we assessed feasibility by collecting peak intracellular drug levels of patients on monotherapy and 12 hour PK sampling on 10 subjects. This was well tolerated and initial data is presented in Fig. 3. Clinical data collection, CYP genotyping, and peak and trough epithelial drug concentrations are not yet complete; however, two subjects had markedly higher plasma exposures than the others and also had sweat chloride (SC) markedly reduced (by 82 and 86 mmol/L) after initiation of ivacaftor, a reduction 40% greater than the mean reduction in clinical trials). Notably, both the C_{max} ("peak", 8170 and 5110 ng/mL) and AUC_{12} (total drug exposure over 12 hours, 61.68 and 45.61 h*mg/L) are also well above the max reported in the clinical trials, and could explain their superior response and also suggest untapped efficacy if similar concentrations could be achieved in others.[30]

Aim 1a methodology: For this pilot study, we will recruit 30 stable CF subjects with the *G551D* or other gating mutations on ivacaftor (150 mg) to measure plasma and intracellular concentrations of the drug and metabolites. This number was selected due to feasibility of recruitment of patients with rare mutations and budgetary constraints. Only patients with a high medication possession ratio (MPR, a measure of adherence) will be included. Patients will be instructed to take drugs as per manufacturer's recommendations (q12) for at least five days as per original PK studies to ensure steady-state blood levels in the run up to our study. Because absorption is influenced by diet, patients will be given a standard high fat diet as per the manufacturer's instructions at Visit 1, plasma collected at time 0, 1, 2, 4, 5, 6, 8, 10 and 12 hours (a frequency of time-points essential for PK parameter determinations) and HNE at 0 and 4 hours. Data regarding spirometry (ppFEV1) and SC between

baseline and change at 6 months will serve as an estimate of response; long-term observational trials have shown greatest improvement to occur by 6 months as well as high adherence rate to therapy in that time frame. We will extract retrospective data from the patient's records to include ppFEV1, weight, and baseline SC.

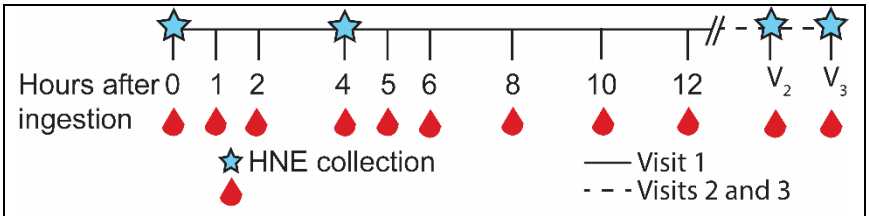


Figure 4. Collection of plasma and HNE for drug levels and culture. Intensive PK monitoring of steady state levels to determine ivacaftor exposure will be performed on Visit 1. HNE will be collected at 4h after ingestion of standard dose of ivacaftor 150mg. Visits 2 and 3 will be coordinated with the subject for additional HNE biopsy and plasma peak and trough collection.

Analysis: Using non-compartmental methods, we will calculate the AUC_{12}; time to reach maximum concentration in plasma (T_{max}); maximum concentration in plasma (C_{max}); elimination rate constant and half-life; and the metabolite formation rate constants (using modeling approaches) as an assessment of p450 enzyme activity. We will collect HNE at 4h post-dose for intracellular concentrations. At visits 2 and 3, repeat HNE collection will coincide with peak plasma concentrations to better model intracellular PK (Fig. 4). Maximum effect (E_{max}) models (linear, simple, and sigmoidal E_{max}) will be used to determine relationships between ivacaftor exposure and response. Exposure variables to be assessed include ivacaftor PK parameters (AUC_{12}, C_{max}, C_{trough}, etc.) and PD markers of response including change from baseline in ppFEV1, sweat chloride, and weight. PK modeling (plasma and HNE) with covariates will be accomplished using a population approach with nonlinear mixed effect models (NLME) in Phoenix 8.1 (Certara, Princeton, NJ). Power analyses was calculated based on n=30 and a two-sided 5% level test for the slope between and plasma (PC) and intracellular (IC) concentration and response for each outcome measure in a regression model (null hypothesis, slope=0), assuming a linear association. Table 1 shows the minimum value of the slopes for each outcome measure (all corresponding to a correlation of ~0.5, accounting for the SD of each variable) to be detected with the associated power. The assumed SDs of the outcomes and concentrations used in this power analyses are given at the bottom of this table. The primary analysis will use regression models assuming linear association; however, we will also consider if there is evidence of a non-linear relationship by fitting polynomial models (e.g. quadratic or cubic). Since this study is exploratory, we did not correct for multiple testing to avoid missing a potential association that could be evaluated further.

Table 1. Power analysis-PC		
Outcome measure	Slope	Power (%)
Absolute change in ppFEV1 (%)	0.28	87
Absolute change in SC (mmol/L)	0.47	86
Absolute change in weight (kg)	0.12	83
Power analysis-IC		
Absolute change in ppFEV1 (%)	0.65	86
Absolute change in SC (mmol/L)	1.11	86
Absolute change in weight (kg)	0.30	88
Sample size= 30, correlation = 0.5, SD PC 11.7μg/mL, SD IC 4.94 μg/mL. SD ppFEV1 6.5%, SD SC 11 mmol/L, SD weight 2.91 kg, two sided significance = 0.05.		

Anticipated results and significance: We will be the first to directly model intracellular and plasma PK of ivacaftor. Higher IC will correlate with larger changes in ppFEV1. A relationship between IC and SC and weight may be seen. We will determine if a threshold for maximal response exists using both plasma and intracellular PK data, although limited studies in plasma alone have not yet revealed a relationship[97].

Potential difficulties and alternative approaches. Quantitation of ivacaftor and metabolites are well established (Fig. 3). Although the study design requires an intensive commitment with frequent blood sampling, we have already had significant recruitment in our feasibility study, and also have support from other CF Centers (see letters) to enable recruitment from other sites. We have a large number of G551D CF subjects at UAB (N=39). In addition, ongoing analysis of patient data will be performed and will include feasibility of using peak and trough concentrations to model total exposure, which may reduce need for intensive sampling in later subjects.

Table 2

PGx allele nomenclature	Metabolizer status	Local CF patients (n)
*3/*3, *6/*6, *7/*7 or in combination	Poor	83% (19)
*1/*1	Extensive	0%
*1/*3, *1/*6, *1/*7	Intermediate	17.4% (4)

	Reference sequence number
*3	rs776746 (6986T>C)
*6	rs10264272 (14690C>T)
*7	rs41303343 (27131_27132insA)

Aim 1b Methodology: Is there an association between SNPs in *CYP3A5* and exposure to ivacaftor? We hypothesize that variation in drug concentration is a result of variation in CYP3A enzymes. The systemic concentration, measured in plasma and determined primarily by absorption and metabolism in the gut and liver, may be an important determinant of efficacy, but no study has yet reported such a relationship. On the other hand, the tissue concentration is driven by both the

systemic concentration and tissue-specific metabolism and transport, *and the latter has never been investigated*. Ivacaftor is rapidly metabolized by CYP3A isoforms,[30] which would affect its concentration in tissues of patients that express CYP3A. Our preliminary data show variation in expression of *CYP3A5* isoforms between individuals, which appears to correspond with specific variant alleles (Fig. 6). Our collaborators found a non-significant but suggestive signal for a *CYP3A5* SNP in a GWAS of patients on ivacaftor (unpublished). This SNP, rs776746, is important for plasma concentrations of tacrolimus.[65] We hypothesize that it is also a major contributor to ivacaftor epithelial concentrations. We will perform targeted genotyping of *CYP3A5* SNPs in each subject for rs776746, rs10264272, and rs41303343 using the SNaPshot® Multiplex System for SNP genotyping (ThermoFisher); together, these SNPs are those most likely associated with poor, intermediate, or extensive metabolism activity of CYP3A5.[65] The dbSNP number (rs), corresponding sequence variation, and pharmacogenomics (PGx) allele designation (*3) is described in Table 3; *1 is the normal allele. Table 3 also describes the allele diplotypes and the metabolizer status they confer for categorization of each patient in this study. Each subject will be categorized by phenotype based on CYP3A5 phenotype and the relationship to PK data will be determined.

Analysis: We will perform SNPs quality control using PLINK.[98] We will follow well-established quality control protocol as described.[99] Association analysis will be performed using linear regression with the outcome variable defined as concentration (plasma or intracellular) and predictor as metabolizer status as defined by diplotype (Table 2). Linear regression power analysis was completed; for a sample size of 30, we will have a power of 80% to detect a minimum correlation of 0.47.

Anticipated results, significance, alternative approaches: High ivacaftor concentration in the epithelia will be associated with poor metabolizer status; intermediate status may result in variable (high to low depending on contribution of the different alleles) concentrations and normal metabolizer status low ivacaftor concentrations. Altered metabolic activity (parent:metabolite ratio) may also be seen with lower metabolite production in poor metabolizers. Plasma concentrations may not be correlated with CYP3A5 metabolizer status due to the role of CYP3A4 in liver metabolism. CYP3A7 may also complicate correlation with both the systemic and epithelial data; formerly thought to be expressed only in fetal livers and infants, CYP3A7 is expressed in some older children and adults and may have overlapping substrate specificity.[47] Investigating genetic variants in CYP3A7 and CYP3A4 is not within the scope of this Aim, but we will store samples for future research, should Aim 3 suggest a role for these other isoforms.

Aim 2. Are *CYP3A5* SNPs associated with response (measured by lung function with ppFEV1) to ivacaftor? As described in Aim 1, we *hypothesize* that the function of CYP3A5 contributes to altered concentrations of ivacaftor in blood and epithelia, leading to observed differences in treatment effects. Variant alleles in *CYP3A5* have profound effects on drug metabolism and response and are described in the pharmacogenomics (PGx) literature (cpicpgx.org, Table 2). Impact of these variants on ivacaftor response is unknown. Widespread use of ivacaftor alone and in combination in CF patients highlights the critical need to understand this relationship, particularly in light of the anticipated indication of ivacaftor-containing triple combination therapy to ~90% of CF patients with at least one F508del allele. This expansion will lead to a much more genetically diverse population taking ivacaftor and higher numbers of normal and intermediate metabolizers.

Preliminary data: To determine the effects of genetic variation in *CYP3A genes* on ivacaftor response, we will use existing clinical data and DNA from national observational trials sponsored by the Cystic Fibrosis Foundation (CFF GOAL study), co-led by my mentor, and recruit additional subjects locally and through the network of partner CF sites. As described above, our collaborators found a signal for rs776746 related to ivacaftor efficacy that did not reach statistical significance but suggested biological plausibility (see letter from Dr. Cutting). The number of patients on ivacaftor in this study was very small (24) and therefore was likely underpowered; a larger confirmatory study is currently underway in collaboration. We have already performed targeted genotyping on a subset of our local CF population, and determined that allele frequencies of PGx variants, including those listed in the table, are very similar as compared to a general population of similar background (Fig. 5). As expected based on their ethnic background, the majority of patients included would be classified as CYP3A5 poor metabolizers (Table 2), but over 17% were intermediate in this small sample size (23). The use of ivacaftor in more ethnically diverse individuals would be expected to increase the number of intermediate and normal metabolizers, those individuals at risk for lower ivacaftor concentrations and treatment failure.

Aim 2a Methodology: <u>What are the allele frequencies of the relevant SNPs in *CYP3A5* in the CF population?</u> Preliminary results in our cohort suggest PGx allele frequencies are not different in the CF population as compared to non-CF populations of similar ethnicity (Fig. 5). Therefore, allele frequencies of the 1000 Genomes CEU population (European-Americans in Utah) were used for power calculations. In this Aim, we will use the

Heflin Genomics Core facility for *CYP3A5* genotyping of 200 subjects from the GOAL study to determine metabolizer status. Regulatory approvals are in place to perform these studies; as detailed in the collaborator letters we will also have access to the DNA from the GOAL cohorts. *This analysis will confirm the allele frequencies of key CYP3A5 variants in a larger population of CF patients.*

Aim 2b Methodology: Are specific SNPs associated with measures of clinical response? Clinical data necessary to perform this aim has already been collected for all subjects in the GOAL study; for those subjects newly recruited we will obtain pre-ivacaftor baseline outcome measures and at 6 months post-therapy; only those with a high MPR (for newly recruited subjects) and reported adherence to therapy (all subjects) during the first 6 months will be included. We will assess the association of metabolizer status via diplotype as in Aim 1b with change in ppFEV1 at 6 months after therapy as primary analysis. Secondary analysis will include correlation of metabolizer status with SC, a measure of CFTR activity which is very sensitive to drug effects; and response in weight at 6 months. We will control for baseline ppFEV1 and age, and include analyses that incorporate a ceiling effect (i.e. FEV_1 > 90-100%), as I recently reported can occur.[100] FEV_1 was chosen as a key analysis since it is the most important marker of clinical efficacy, and specifically reflects drug metabolism in airway cells. Results will determine if CYP3A5 variant expression is associated with clinical outcomes dependent on CFTR restoration.

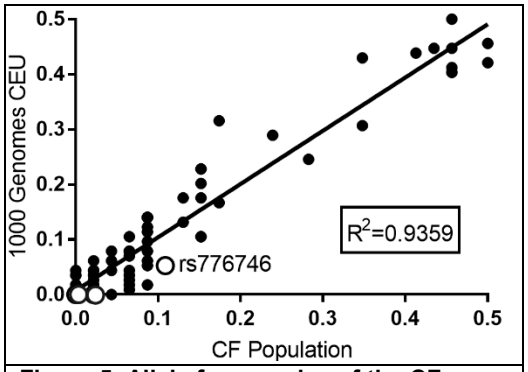


Figure 5. Allele frequencies of the CF population compared to 1000Genomes CEU. A European-American population was used as a comparison to check if the allele frequencies of known variants in *CYP3A5, CYP3A4, CYP3A7*, and *ABCB1*, all known or hypothesized to be involved with ivacaftor metabolism and transport. White circles are the three SNPs that comprise diplotypes in Table 2; rs776746 (*3) is labeled.

Analysis (Aims 2a, 2b): Standard quality control will use PLINK,[98,99] including batch effect, MAF estimation, and HWE. For association analysis, we will use regression with the outcome being response to ivacaftor measured by lung function (ppFEV1), with covariates sex, age, baseline FEV1 and metabolizer status (defined by diplotype). Secondary analysis with SC and weight as outcomes will be completed in the same manner. Power Analysis: Power calculations were performed similar to Aim 1. Outcome measures are described in Table 1, with predictor of metabolizer status as defined by diplotype (Table 2). With a sample size of 200, we have 83% power to detect a minimum correlation of 0.25 or better for all outcome measures; calculations made with Bonferroni correction for multiple tests (alpha level of 0.008).

Anticipated results and significance. Those subjects with *CYP3A5* variants conferring poor metabolism will have a change in ppFEV1/SC/weight of greater magnitude from baseline within the first 6 months of therapy in comparison with CYP3A5 intermediate and normal metabolizers. An association between metabolizer status and $ppFEV_1$ will show that variation in drug metabolism contributes to variation in drug efficacy; when combined with data in Aim 1 to identify variation in drug concentration both in plasma and the epithelia, these data will lay the groundwork to predict dosing strategies (by increasing dose[10,29] or inhibiting metabolism[85,87]) before initiating treatment using targeted genotyping.

Potential difficulties and alternative approaches. We have sufficient patients available given our *a priori* sample estimates. GOAL subjects are expected to be predominantly of Caucasian descent and majority poor metabolizers, which may yield insufficient subjects with intermediate and normal metabolizer status. To address we will recruit additional patients at UAB as well as by referral from our partner CF centers (see letters of support). One notable difficulty is the contribution of other CYP3A isoforms, especially CYP3A4 and CYP3A7, and other potential modifiers of response like ABCB1 (drug transporter) and SLC26A9, for which conflicting reports suggest a role. Targeted genotyping of variant alleles in each of these may be included if needed. CYP3A7 is of particular interest since it is expressed beyond infancy in the liver and also in other tissues,[74,78,81,101-107] and may complicate our analysis. To combat this, we have identified variants predicting adult expression of this isoform, which may be used in a multi-variant model for predicting drug response, and include CYP3A7 in Aim 3.

Aim 3: Do CYP3A isoforms impact the concentration of ivacaftor and its effect in epithelia? *CYP3A5* has been implicated as a key extra-hepatic CYP3A isoform. Evidence for its involvement in ivacaftor metabolism is extensive. As pointed out in the critique for the original submission, contributions from CYP3A isoforms other than *CYP3A5* complicate analysis of the relationship between plasma concentrations, epithelial concentrations, *CYP3A5* variants, and drug response. Since there is a gap in knowledge about the metabolism and transport of ivacaftor in its target tissue, we will characterize the P450 enzyme expression in epithelia and conduct mechanistic studies to better understand how contributions from the different isoforms interact with ivacaftor concentrations. These studies will be entirely conducted *in vitro* on samples derived from patients. These

results will inform future studies of ivacaftor and other modulators (including tezacaftor and other next-generation correctors) to apply precision strategies for cystic fibrosis.

Preliminary data: To accomplish this aim, I will use well-established monolayer culture of HNE for studies in differentiated epithelia, confirm expression of CYP3A enzymes (Fig. 6); and examine relative contributions of the CYP3A isoforms by using recombinant microsomes. We have already established culture methods to isolate and expand human nasal epithelial cells from adults and children using a minimally invasive nasal brushing on over 50 patients with cystic fibrosis. These are part of our laboratory's established biorepository of HNEs which will eliminate need for patient recruitment.

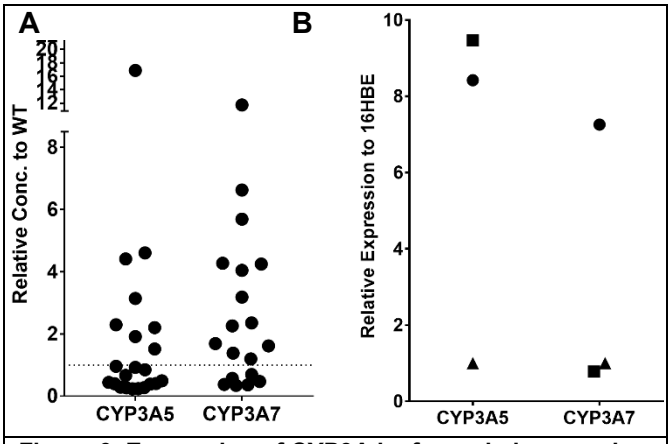


Figure 6. Expression of CYP3A isoforms in human airway epithelia. A. CYP3A5 and CYP3A7 mRNA was detected at variable levels in the primary airway epithelial cells of most CF patients tested. Notably, the defect conferred by *3/*3 genotype results in defective splicing and a nonfunctional truncated protein. While some defective mRNA may be produced, the overall function is severely decreased. Dotted line is level of control non-CF sample to which CF expression is compared. **B.** In three cell lines derived from human airway epithelia (Calu3■, CFBE●, and 16HBE▲) CYP3A5 and 7 are detected and highly variable. CYP3A4 was not detected in any epithelial sample.

<u>CYP3A enzyme mRNA expression in our subjects is similar to published reports.</u> The use of human nasal epithelial (HNE) cells as a surrogate for lower airway epithelial drug response and metabolism has been demonstrated previously. They have similar physiology, ion channel profile, and overall gene expression[108-110]. Drug metabolism protein expression profile is similar in nasal and lower airway epithelia.[111] We have confirmed in CF subjects that expression of the relevant CYP3A enzymes is present and highly variable between individuals using quantitative RT-PCR (Fig. 6A), normalized across individuals using the $\Delta\Delta$Ct method with a standard curve and compared to non-CF subject sample. Cell lines (Fig. 6B) were also tested to assess utility as a tool for mechanistic studies.

<u>Mass spectrometric detection of CFTR modulators is established.</u> As described above, drug concentrations have been limited to the detection of the drug in plasma.[32,33,112,113] We developed methods to quantitate ivacaftor and its metabolites (M1, M6) in as few as 40,000 cells, at concentrations as low as 0.5 ng/mL[89] (Fig. 3). As shown in Fig. 3, we are the first to quantitate epithelial concentrations *in vitro* and *ex vivo* and will help delineate tissue-specific metabolism of this class of drugs and impact on CFTR.

Aim 3a Methodology: <u>Does metabolism of ivacaftor impact CFTR activity in vitro?</u> As described above, ivacaftor exhibits a dose-dependent effect on CFTR activation.[28] We hypothesize that variation in metabolism of ivacaftor will produce a similar effect. Expressors (extensive metabolizers, Table 2) of CYP3A isoforms would be expected to rapidly metabolize ivacaftor to less lipophilic metabolites for excretion. At the low concentrations expected to reach the cell *in vivo,*[114] metabolism could significantly reduce the available parent ivacaftor for CFTR activation. To assess this, we will analyze epithelial cells after expansion in culture and differentiation at air liquid interface. These cells will be derived from 10 *a priori*-determined 'expressors' and 10 'non-expressors'. Non-expressors (poor metabolizers, Table 2) are defined as those having no detectable CYP3A isoform mRNA and/or characterized genotype conferring severe decrease in enzymatic activity. Protein immunoblot will be performed to further confirm expressor status. Non-expressors can also be induced by reducing the enzymes via siRNA (Fig.7) to further validate this hypothesis in the same individual's cells, to control for intra-individual factors influencing metabolite production and CFTR activity that may not be immediately apparent. Varying concentration of ivacaftor consistent with tissue levels based on Aim 1 and published reports[114] (1nM -1μM) will be applied for 24-48 hours. CFTR activity will be measured by short-circuit current (Ussing chamber) after inhibition of ENaC with amiloride, and stimulation of CFTR with forksolin. Cells will be lysed using 1% NP-40 lysis buffer and mass spectrometry performed to detect ivacaftor, M1 and M6. Enzyme activity will be defined as production of metabolite:parent ratio.

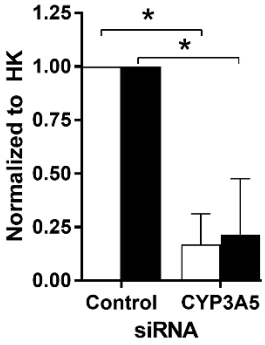


Figure 7. siRNA down-regulates enzyme protein expression to mimic non-expressor status. siRNA 3850 (ThermoFisher) was identified to significantly down-regulate both mRNA (white) and protein (black) of CYP3A5 in airway epithelial cells (Calu3). HK is housekeeping gene (GAPDH or tubulin); Control is negative siRNA control; CYP3A5 is siRNA 3850. *p<0.05.

<u>Power analysis</u> is based on comparing the mean difference in CFTR activation between expressors and non-expressors for a given concentration of ivacaftor. With 10 expressors and 10

non-expressors each contributing 3 monolayers, the total sample size is 60 monolayers (30 each group). Data from the same individual will be considered as a cluster and will be accounted for in the power and data analyses. We calculated power based on a two-sided t-test for clustered design using 5% level of significance for two independent means with the null hypothesized mean difference value of 0, and assuming a conservative intra-cluster correlation coefficient of 0.01. With this, we will achieve 85% power to detect a difference between the group means of at least 1.59, assuming a standard deviation of 2. This SD value was based on the largest SD reported *in vitro* for ivacaftor response.[115] Note that as the intracluster correlation increases, the minimum effect size to be detected increases. For example, for intracluster correlation coefficient of 0.30, the minimum effect size (difference in mean) to be detected is 1.99 compared to 1.59 for intracluster correlation coefficient of 0.01. PASS version 14 was used for this analysis.

Statistical analysis: To determine association of CFTR-dependent short-circuit current change and intracellular drug and metabolite concentration, we will use mixed models with random intercept to account for the correlation of the observations from the same subject. The 4 different dose levels, group (expressors and non-expressors), and their interaction will be in the model. This will allow the group effects to differ by dose level and vice versa. We are working under the assumption that the differences between the two groups may depend on the dose levels; based on this, instead of stratifying the analyses by dose level, using all the data from the different doses and fitting a model with interaction between dose and group will result in more efficient analyses.

Anticipated results and significance. We anticipate that the intracellular concentration of ivacaftor will directly correlate with CFTR activity. We will be the first to directly measure intracellular concentrations *in vitro* and correlate them with functional activity of CFTR. These studies will clarify the mechanisms by which ivacaftor can accumulate inside the cells *in vitro* and determine the effect on CFTR activity measurements.

Aim 3b Methodology: Do CYP3A isoforms exhibit preferential metabolism of ivacaftor? As seen in Fig. 6, CYP3A7 and CYP3A5 are expressed in the epithelia. Our preliminary data also show production of M1-ivacaftor in cells isolated directly from patients taking ivacaftor and from cultured cells that have been treated with ivacaftor. No M6-ivacaftor has been detected in any epithelial sample despite high concentrations in plasma, suggesting that M6-ivacaftor cannot be transported into epithelia and is not produced there. M1-ivacaftor would also not be expected to transport into epithelial cells based on its pharmacologic properties, and thus most likely is produced in the epithelial cell. Because some CYP3A5 “non-expressors” also have M1-ivacaftor, there is some concern that another isoform is active. Despite reports that CYP3A4 is expressed in lung, there has been no detectable CYP3A4 in any epithelial sample in our laboratory as yet (Fig.6). CYP3A7, which is 87% identical to CYP3A4,[47] is expressed in airway epithelia and may be involved in ivacaftor metabolism. This novel finding is not described in the literature nor in the assays completed by the manufacturer. Our advisor, Dr. Scott (see letter of support) has generously offered to provide recombinant CYP3A enzymes for these studies. We will use methods described previously[47] to determine the binding affinity of ivacaftor to each of these isoforms, as well as ivacaftor’s inhibition of CYP3A. Mass spectrometry will be used to determine enzymatic activity by production of metabolites after incubation with the recombinant isoforms. Analysis of variance will be used to compare the difference in metabolite:parent ratio between the three recombinant enzymes, and also to compare the Michaelis-Menten-derived binding affinities for each isoform.

Anticipated results and significance: CYP3A4, 5, and 7 are very similar and have overlapping substrate specificity, but have been previously shown to have different affinities for various drugs.[47,116] These studies will clarify the roles of each isoform with potential impact on ivacaftor metabolism, including differential affinities for the substrate. This will allow more sophisticated interpretation of the variation in ivacaftor concentration and P450 genotypes by taking relevant isoforms into account in a comprehensive approach, including their impact on the epithelial compartment, under-recognized in its importance as compared to plasma.

Potential difficulties and alternative approaches. All assays described in this Aim are established in our laboratory and that of our advisor. Sufficient samples are already collected for these *in vitro* studies. It is possible that additional metabolites are produced that are not included in these studies; however, based on the manufacturer’s comprehensive analysis, M1 and M6 are the predominant metabolites in humans. For Aim 3a, expressor status may also be examined by utilizing subjects with varying isoform profiles to distinguish enzyme activity in epithelia. Isolated liver microsomes with characterized enzyme expression may also be used in lieu of recombinant enzymes, but this will not determine epithelial activity, which may be of significant importance.

Summary. This study will provide new pharmacokinetic, pharmacodynamic, and pharmacogenomic understanding of a novel class of drugs (CFTR modulators), enabling novel concepts for precision medicine in CF and optimization of therapy in up to 90% of individuals with CF. The training required to conduct these studies will provide a platform to grow an independent research program focused on precision therapeutics.

Training in the Responsible Conduct of Research

1. Format: The Principles of Scientific Ethics course (GRD 717) is a 3 credit hour class that includes a blended approach of on-line training and in-person discussion on topics related to the responsible conduct of research (RCR). Specifically, the on-line training component includes completion of all RCR-related CITI Program modules; participants are required to successfully complete each of these modules, achieving a score of 80% or better. Once completed, participants then attend an in-person discussion session that consists of an all-day (8 hours) Saturday workshop facilitated by training program directors, preceptors, and administrators. Three Saturday sessions are offered so that participants and facilitators have the opportunity to select a date that best fits their schedules. These sessions debate case-studies in a team-based learning format as well as allow for additional RCR-related activities, such as panel discussions with faculty and administrators regarding 'real-world' RCR examples and role-playing RCR scenarios. **Notably, Dr. Guimbellot will discuss her participation in class with Dr. Rowe, her primary research mentor and Dr. Kimberlin (career development mentor); she will also discuss similar themes with students she mentors, as well as her laboratory staff.**

2. Subject Matter: Topics covered in GRD 717 include the nature, extent, and causes of fraud in science; UAB policies on fraud; ideals of good science; the responsibilities of authorship and peer review; potential problems raised by the commercialization of research; scientists as public policy advisors; and ethical issues involved in animal experimentation and in clinical trials. Among the areas previously discussed are:
    - Ethical Decision Making
    - UAB Policies on Research Misconduct
    - Protection of Human Subjects in Research
    - Welfare of Laboratory Animals
    - Best Practices for Data Management
    - Identifying and Managing Conflicts of Interest
    - Ethical Authorship and Avoiding Plagiarism
    - Best Practices in Collaborative Research
    - Mentor and Trainee Responsibilities
    - Expectations of the Peer Review Process

3. Faculty Participation: GRD 717 is led by Lisa Schwiebert, Ph.D, Associate Dean, UAB Graduate School, using a "Team Based Learning" approach. She is assisted by faculty facilitators who maintain active research labs and have graduate faculty status.

4. Duration of Instruction: For the 12 on-line learning modules, each module may take from 10 to 30 minutes to complete; average completion time for all modules is four hours. The modules do not have to be completed all in one login session. The in-person workshop provides 8 contact hours of instruction.

5. Frequency of Instruction: This course is offered in the Fall, Spring, and Summer semester of each year meeting weekly over the course of the semester. On-line modules are available at all times. In-person workshops are offered on Saturdays in order to accommodate schedules.

Steven Rowe, M.D., M.S.P.H. (Primary research mentor)

I strongly support Dr. Jennifer Guimbellot's K23 career development proposal to the National Institutes of Health, entitled "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." As her primary mentor, I am soundly committed to provide dedicated guidance to her scientific career and professional development. I have known Jennifer at least eleven years, since her time as a graduate student in the Gregory Fleming James Cystic Fibrosis Research Center (CFRC) when she worked alongside me in Eric Sorscher's laboratory. She has been exquisitely trained for a career as a physician scientist, and I am absolutely confident in her ability to successfully conduct the project proposed in this application with the highest level of scientific accomplishment and integrity. This award will allow her to have intensive training in basic and translational science in personalized medicine, pharmacometrics, and pharmacogenomics related to cystic fibrosis and will provide the needed tools for her development into an independent physician scientist. In response to critiques from the original submission of this application, she has improved her productivity and scientific direction (with a remarkable six papers published in the interim), a track she was already on after completing her transition to UAB. She has further developed her expertise in pharmacology and biostatistics with additional training, and has refined her research questions with additional preliminary data, including human studies. You will find her resubmission to be highly responsive to the reviewers' critiques.

Candidate's background and eligibility for the award

Dr. Guimbellot completed her PhD in 2007 and her MD in 2008 as part of the Medical Scientist Training Program at the University of Alabama at Birmingham (UAB). The results of her graduate work, under the tutelage of Dr. Eric Sorscher, were funded by a Ruth L. Kirschstein NRSA F30 award and were presented in two first author, peer-reviewed publications and several abstracts, including podium presentations, on regulation of cystic fibrosis transmembrane conductance regulator (CFTR) expression and function at various local, national and international conferences including the North American Cystic Fibrosis Conference (NACFC), American Society of Human Genetics, and the European Respiratory Society Lung Science Conference. She was also the recipient of the Outstanding Graduate Student award for two consecutive years in the Department of Genetics as well as was the recipient of a best abstract award in the Medical Scientist Training Program and the School of Medicine finalist at Medical Student Research Day.

Following her graduate work, Jennifer completed residency at Columbia University Medical Center in New York, and pediatric pulmonology fellowship at the University of North Carolina (UNC) at Chapel Hill. She was noted as an outstanding clinical and research fellow in the laboratory of Martina Gentzsch, PhD, an international leader in CFTR protein trafficking and correction. During her time at UNC, Jennifer presented multiple research abstracts including a podium presentation at the NACFC in October 2014. She won the Best Overall Research Award in 2013 in the Department of Pediatrics at UNC as well as an American Thoracic Society Abstract Award in 2014. She was first or senior author on four accepted abstracts to the North American Cystic Fibrosis conference in October 2018 and was an invited symposium chair in 2018, in which capacity she will act again in 2019. Notably, she was recruited to research faculty positions around the country, including at UNC, but we were fortunate to recruit her back to UAB in August of 2015.

Potential for excellence as an independent investigator

Dr. Guimbellot will be successful as an independent investigator, given her personal qualities and individual skill set. She is very curious, insightful, and well-organized, with remarkable technical skills and a tenacity to seek the answers to questions that interest her. She has made outstanding progress on the research projects she has led throughout her career thus far, with her publication record reflecting her progress. She is maturing as a principal investigator, with one manuscript under review and two additional first author, original research manuscripts that will soon be submitted. I also anticipate that she will have two more publications as a senior author by the end of 2019. She has established collaborations with members of the CFRC and other entities related to precision medicine, including bioinformatics, statistics, pharmacology, pharmacogenetics, and cell and developmental biology. She has taken the lead in directing a collaborative project, recruiting a local advisory team of experts in pharmacogenomics, pharmacology, and statistical genetics. She maintains collaborative relationships with her former mentor at UNC (Dr. Gentzsch) and continues to develop new relationships at other institutions (Dr. Emily Scott in pharmacology at the University of Michigan; Garry Cutting at Johns Hopkins; and Michael Knowles at UNC) and locally (Dr. Carmel McNicholas-Bevensee and Dr. Rui

Zhao). In addition to her personal attributes, she has demonstrated a clear track record toward progressive independence. Despite being fully funded in her MST program, she pursued an individual NRSA F30 award that was awarded to support the final years of her education. She also received pilot grants during graduate school, and again in fellowship, to develop new ideas, including using human nasal airway epithelial cells for organoid culture. She was awarded grants for all three years of her fellowship training from the CFF, and since joining the faculty at UAB, she has obtained an internal pilot award from the Kaul Pediatric Research Institute (for enhancing the reproducibility of the sphere model), an NIH R43 as a co-investigator (leading the project at UAB), a pilot award from CFF, a clinical investigator award from CFF, and two research vouchers from the Center for Clinical and Translational Science at UAB.

Since joining the faculty at UAB, she has focused her scientific program with specific attention to manuscript productivity, which had the typical delay associated with transition between institutions. As she has become established at UAB, she has clearly rectified this gap – since submission of the original application, she has published six peer-reviewed manuscripts, one of which is to the prestigious *JCI Insight* and is directly relevant to this proposal, has an additional manuscript under review, and has two additional first-author manuscripts expected to be submitted shortly. These papers are in addition to two first author and four total peer-reviewed publications during graduate school. Overall they reflect substantial research productivity in the last year now that her transition between institutions and to the faculty is complete, and a she has achieved this despite becoming a mother to two children during fellowship, changing her research direction, and moving from UNC-Chapel Hill to UAB to establish her own research program. She is an exceptional scientist and faculty member, and in recognition of her progress, she was promoted from Instructor to Assistant Professor in August of 2016.

Career development

Dr. Guimbellot's plan for her career development includes formal and informal settings for training. She is a member of the Center for Clinical and Translational Science (CCTS), UAB's CTSA award, and has already attended multiple development courses. During the period of this award, she will focus on grant and manuscript preparation and review, scientific ethics, negotiating skills, and mentoring. All of these topics are covered in seminars and formal coursework at UAB, specifically developed by the Pediatric Research Office, the CCTS, and the Office for Post-doctoral Education. She will also undertake self-directed training in the Responsible Conduct of Research using resources in the UAB Center for Ethics and Values in the Sciences.

I have particular expertise in pediatric research and the development of junior faculty to independent investigators. She will meet monthly with me, as her primary research mentor. I am uniquely suited for this role because of my background in cystic fibrosis clinical, basic, and translational research with particular expertise in clinical trials, modeling and novel imaging modalities. She will meet at least quarterly with Dr. David Kimberlin, the Vice Chair for Clinical and Translational Research in the Department of Pediatrics, an expert in pediatric infectious disease clinical and translational research with expertise in transitioning junior faculty to independence. He will serve as a key career development mentor. She will meet at least quarterly with her other co-mentors, including Dr. Edward Acosta, an established investigator with over 20 years of experience in pharmacology, mass spectrometry, and pediatric PK/PD modeling; and Dr. Hemant Tiwari, a recognized leader in statistical genetics, responsible for training countless individuals in genetic analysis. She will also meet quarterly with Dr. Inmaculada Aban, an expert in biostatistical modeling with whom Jennifer has an established relationship. Additional advisors include Dr. Nita Limdi, an expert in pharmacogenomics and personalized medicine and Dr. Emily Scott, a well-known investigator in cytochrome P450 metabolism. She will discuss the project 1-2 times per year as needed for critical feedback and direction from the entire advisory committee.

Dr. Guimbellot will attend a variety of formal coursework and seminars regarding issues in career development outlined in her training plan. I expect that she will develop at least two manuscripts per year and present at two scientific meetings during each year of support. I am also confident she will prepare an R01 application within the timeframe of this award. Working with Dr. Hector Gutierrez (Division Chief and Cystic Fibrosis Center Director) and Dr. Mitchell Cohen (Department Chair), I have ensured that Jennifer will have at least 75% protected time to conduct research. To that end, we recently brought inpatient service time to a hiatus to accelerate her research program. Such protected time will continue for the duration of the award to provide adequate support to build her research program and to allow her to obtain additional funding.

Transition toward independence

Dr. Guimbellot started a laboratory investigating novel three-dimensional cell cultures and pharmacogenomics for personalized medicine, an area that is distinct from my own but utilizes techniques and expertise from my laboratory and others on campus. She has already trained personnel who can perform the needed techniques and is well on the pathway to a fully independent laboratory. She has mentored several trainees on research projects, including undergraduate, medical, and masters students, as well as a post-doctoral fellow. The Division of Pulmonary and Sleep Medicine and the Department of Pediatrics recognize Dr. Guimbellot's potential to succeed in independence and have dedicated funding for the start-up for her research program, space, and protected time, especially as her research focus is squarely aligned with one of the pillars of UAB's mission for personalized medicine. In both the Departments of Pediatrics and Medicine (where I have joint appointments), we have several junior faculty members who have been recipients of Career Development awards and will serve as role models for career advancement.

Benchmarks for the candidate

To realize her goals, Dr. Guimbellot will do the following:

- Complete the aims of this proposal and disseminate results through publication in peer-reviewed scientific journals (at least 2 per year anticipated).
- Present this research at least annually at international conferences, including the North American Cystic Fibrosis Conference and the American Thoracic Society meeting.
- Submit an R01 application at the end of the fourth year of this award.

Dr. Guimbellot has access to all the equipment, facilities, funding, training, and technical expertise to train her and accomplish all aims outlined in this proposal. She will also acquire advanced skills in statistics, clinical research design and conduct, pharmacology and pharmacogenomics, responsible conduct of research, grant writing, manuscript preparation, and other skills required for independence. While her writing skills are excellent, she will emphasize manuscript preparation and presentation at meetings. The studies outlined in this proposal will provide opportunities to hone these skills as well as provide results for future funding applications.

Mentor's track record

I have extensive mentoring experience, supervising over 20 researchers currently. I have supervised others at various levels of training (8 undergraduate and medical students; 5 graduate students; 5 post-doctoral fellows, and 8 clinical residents/fellows), including four post-doctoral trainees successfully transitioned to faculty appointments at UAB (all of whom have received K or other mentored awards) and one who has become CF Center Director elsewhere. A list of trainees is included in my biosketch.

In summary, I believe that Dr. Guimbellot is an outstanding young investigator with the potential to make a lasting and unique contribution to her field. She has the personal drive, qualities, and skills to be successful as an independent physician-scientist. She has my highest recommendation for this award.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Steven M. Rowe
Professor, Departments of Medicine and Pediatrics
Director, Gregory Fleming James Cystic Fibrosis Research Center
University of Alabama at Birmingham

David Kimberlin, M.D.

Dr. Guimbellot has my highest support for the resubmission of her proposal to the National Institutes of Health, entitled "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." I first met her when I precepted her as a medical student rotating through inpatient pediatrics eleven years ago and was delighted to welcome her back to our department in 2015 as a faculty member. Our mentoring relationship will provide her with career development guidance and training in human subjects research and aspects of clinical trial design that are relevant to developing precision approaches in medicine. These elements are essential for her transition to independence.

She will meet at least quarterly with me. As a clinical trial expert, with extensive experience in designing and conducting clinical and translational research resulting in labeling changes for 12 drugs, I will mentor Jennifer in broad aspects of career development. Specifically, I will assist with research program development, project management, human subject trials design, manuscript preparation, and grantsmanship. As Vice Chair for Research in the Department of Pediatrics, I will coordinate with Dr. Mitchell Cohen (Chair of the Department of Pediatrics), Dr. Steven Rowe (Director of the Cystic Fibrosis Research Center and Jennifer's primary research mentor), and the Division of Pulmonary and Sleep Medicine, to provide Jennifer's departmental funding to assist with equipment purchasing, support staff salary support, research consumables, and other costs to supplement funds provided by the K23, as described in her detailed budget.

Dr. Guimbellot's plan for her career development includes formal and informal settings for training. During the period of this award, in addition to specific research training outlined in Dr. Rowe's letter and her training plan, she will focus on gaining expertise in pharmacology and pharmacogenomics, grant and manuscript preparation and review, scientific ethics, interviewing and negotiating skills, and mentoring. All of these topics are covered in seminars and formal coursework here at UAB. Jennifer will meet quarterly with each of the other members of her scientific advisory committee, and convene the entire committee for presentation of progress and group feedback at least yearly for formal presentation and constructive criticism. She has clearly demonstrated a capacity for excellent productivity, as she has six peer-reviewed manuscripts published since the original submission of this proposal, one manuscript under review, and two more original research manuscripts in preparation. Her achievements are particularly impressive given the fact that she accomplished them despite a significant change in research direction while participating in a clinical fellowship; changing institutions to establish her own research program; and taking time out for maternity leave on two separate occasions during fellowship. She responded well to the reviewers' critiques for productivity, and has gained momentum.

I have every confidence that Jennifer will achieve the goals of this application. I am looking forward to helping her develop into a mature and independent scientist, as I am sure she will be a leader in her field.

Sincerely,

David W. Kimberlin
Professor, Pediatrics
Co-Division Director, Pediatric Infectious Diseases
Vice Chair for Clinical and Translational Research
University of Alabama at Birmingham

Edward Acosta, Pharm.D.

Please allow me to express my enthusiastic support for Jennifer's research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This proposal is innovative and exciting and, if successful, will help to better understand the metabolism of CFTR modulators; provide insight into the variability in efficacy among individuals taking ivacaftor monotherapy; and lead to improved strategies to gain maximal benefit from ivacaftor and combination therapies of which it is a part.

I am fully committed to serve as a co-mentor on this research project by providing expertise in pharmacology and mass spectrometry detection of CFTR modulators. As the director of the Pediatric Pharmacology Laboratory, I have over two decades of experience in clinical pharmacology, mass spectrometry, and a wide variety of pharmacokinetic analysis techniques, particularly in children. I have extensive expertise in the use of mass spectrometry to detect low concentrations of small molecules in biological specimens from very small sample sizes. I am also a member of the UAB CF Center and have successfully collaborated with Dr. Rowe, including a co-authored publication of the first findings regarding ivacaftor metabolism in patients with chronic obstructive lung disease.

We have already established a collaborative relationship over the past two years, having met monthly to discuss experimental approaches to this and related projects, including an upcoming submission of an original research article for which Jennifer is first author. In order to solidify this advisory relationship during the course of this award, we will meet regularly and at least quarterly to train her in pharmacokinetic data analysis methods, review data, discuss results, and plan experiments that are relevant to the rapidly evolving field of CFTR modulators. Dr. Guimbellot's extensive training as an MD/PhD in pediatric pulmonology, genetics, cell biology, and molecular biology will enable her to complete all aspects of this project and develop new

strategies for the treatment of cystic fibrosis, and to understand basic mechanisms of ivacaftor metabolism and CFTR rescue. This forms the basis of her independent translational research program. We anticipate at least two publications to arise from the work we are doing together currently.

My role is focused on pharmacometrics studies relevant to this and future projects, to help guide Dr. Guimbellot's training in these areas. I am confident that this proposal will be a success and I look forward to collaborating with Jennifer on this project.

Sincerely,

Edward Acosta
Professor and Director
Division of Clinical Pharmacology
University of Alabama at Birmingham

Emily Scott, Ph.D.

I would like to express my enthusiastic support for Dr. Guimbellot's K23 research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This builds on her previous studies translating them into relevant clinical applications. Her proposal will help fill significant gaps in the understanding of the metabolism and pharmacogenomics of CFTR modulators, a new class of drugs for which there is still little known. I would be pleased to serve as an advisor during this proposal and meet with her at least once a year to discuss the project and review progress, and more often as needed.

I have nearly two decades of experience in drug metabolism and pharmacology. My expertise in the structure and function of cytochrome P450 enzymes has recently focused on pediatric drug metabolism by CYP3A7 vs. adult drug metabolism by CYP3A4/5. I believe this in-depth knowledge will complement the studies in this proposal to understand the role of CYP3A4, 5, and 7 in the systemic and tissue-specific airway metabolism of ivacaftor and related compounds. Specifically relevant to Aim 3, we have been characterizing itraconazole and related azole inhibitors in adult CYP3A4 vs. infant CYP3A7. In doing such, we recombinantly express and purify these human (membrane) P450 enzymes, including CYP3A5, and characterize them with a variety of in vitro assays and structurally using X-ray crystallography. We are pleased to join in a collaboration with Dr. Guimbellot to assess the contribution of the different isoforms to ivacaftor metabolism.

This project is novel, feasible, and consistent with the goals of the NIH. This project provides ample opportunities for future investigator-initiated proposals and contribution to the field of cystic fibrosis research. I am confident that this proposal will be a success and I look forward to guiding Dr. Guimbellot in this project.

Sincerely,

Emily Scott
Professor, Department of Medicinal Chemistry
University of Michigan

Hemant Tiwari, Ph.D.

I am enthusiastic to serve as a co-mentor for Dr. Guimbellot's career development proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." She is well suited to perform the research outlined in this application. The training plan she has devised will provide significant skills in the use of pharmacogenomics in pediatric pulmonology and related fields. She has devised a research plan and career development approach that builds on her prior training and work, and will increase her skills for sufficiently to transition to independence.

It has been a pleasure to advise her during the development of this proposal and to provide expertise in statistical genetics. I have trained many students, post-doctoral scholars, and physician-scientists like Dr. Guimbellot, as well as by directing local and national courses in statistical genetics. To facilitate this advisory relationship, I will meet with her quarterly each year during the project period to review data and help with statistical analysis of the genetic studies proposed in all three aims.

The pharmacogenomics studies of ivacaftor have applications beyond those described in this proposal and I expect it will yield preliminary data for additional proposals (R01 and similar) on CFTR modulators. I am

confident that this proposal will be a success and look forward to a fruitful advisory relationship with Dr. Guimbellot.

Sincerely,

Hemant Tiwari
Professor, Department of Biostatistics
Director, Biostatistics Pre-Doctoral NHLBI Training Program
Director, Post-Doctoral NHLBI Training Program in Statistical Genetics

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Inmaculada Aban, Ph.D.

Please allow me to express my strong support for Dr. Guimbellot's research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This proposal is innovative and, if successful, will help describe the mechanism uptake and processing of CFTR modulators, fill gaps in current understanding of CFTR dysfunction, and bring precision medicine to cystic fibrosis. I have already worked with Dr. Guimbellot on the development of statistical approaches to nasospheroid models, for which we published a manuscript together since the original submission of this application. We will continue our work together as she continues to develop this and other models relevant to this application.

I am pleased to serve as a co-mentor on the research project by providing expertise in biostatistical analysis of human subjects datasets. I have extensive expertise in the development of risk score models, which will significantly aid the development of better pre-clinical predictive tools. I am confident that this proposal will be a success and I look forward to a long and productive advisory relationship. I commit to meeting with Dr. Guimbellot at least quarterly throughout the project period to review data, discuss statistical approaches and methodology, perform ongoing calculations to ensure adequate recruitment for the goals of this study, and to estimate needs for future applications, including R01 applications.

Sincerely,

Inmaculada Aban Professor, Biostatistics

Nita Limdi, Pharm.D., Ph.D., M.S.P.H.

Jennifer Guimbellot has my highest support for her career development proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." The work outlined in this application is well suited to increase her research and career development skill set and portfolio to aid in her transition to independence. I am looking forward to serving as a research and career development advisor during this proposal. Her project is directly relevant to my area of research and will benefit from my substantial expertise in pharmacogenetics.

My expertise in pharmacogenomics and personalized medicine will help expand Dr. Guimbellot's basic and clinical skills related to precision approaches to cystic fibrosis treatment. Her project will fill crucial gaps in knowledge regarding the novel class of drugs (CFTR modulators), increase understanding of the pharmacokinetics and pharmacogenomics of these drugs, and lead to improved efficacy among the cystic fibrosis patient population. This project will also provide her with necessary skills to develop rigorously validated biomarkers that have a high predictive capacity. In combination with her basic science background developing in vitro models and genetics, these skills will help her build an independent research program.

The proposal outlined in Dr. Guimbellot's application is well suited to lay the foundation for future studies such as R01 applications. I am delighted to advise her on the next steps in her research program and career development. I will meet with her at least quarterly to ensure appropriate research design and progress. I am excited to watch her develop her research program in pharmacogenomics and in vitro biomarkers, which has relevance and applications far beyond the studies described here and provides opportunities for professional growth, skill acquisition, and funding opportunities in the future. I am sure she will be a success.

Sincerely,

Nita A. Limdi
Professor
Department of Neurology

Associate Director for Pharmacogenomics and Implementation Science
UAB Hugh Kaul Personalized Medicine Institute

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Garry R. Cutting, MD
Professor, Pediatrics and Medicine

To: National Institutes of Health
RE: K23 Award, Jennifer Guimbello
Jennifer S. Guimbellot, P.I., Application to K23 P.I. ERA Users Commons Name: GUIM01 Funding Opportunity Announcement: PA-16-198
February 26, 2019

Dear Committee,

Please allow me to express my strong support for Dr. Guimbellot's proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients." This proposal is innovative and exciting and, if successful, will help understand the mechanism of the metabolism of CFTR modulators, fill gaps in current understanding of CFTR modulators, and help bring new aspects of precision medicine to cystic fibrosis.

My career is focused on the causes of phenotypic variation in cystic fibrosis (CF). I direct the CF Twin and Sibling Study that has characterized the genetic contribution to variation to key CF traits and has resulted in successful identification of genetic loci associated with variation in these traits (NHLBI and CF Foundation funded). I also direct CFTR2, a worldwide-project to characterize the clinical and functional consequences of variants in the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR)(NIDDK and CF Foundation funded). In recent years, Dr. Michael Knowles (at the University of North Carolina at Chapel Hill) and I have sought to understand genetic variation that influences the response of individuals to CFTR modulators, outside of mutations in CFTR.

Recently, my laboratory conducted a GWAS restricted to a small cohort of G551D individuals and found weak association of change in lung function with three variants in LD with each other, including rs776746. This association did not reach statistical significance, but suggested biologic plausibility for a role for CYP3A5 in response to ivacaftor. An effort to replicate this finding with greater power is currently underway. These studies are highly compatible with the work that Dr. Guimbellot proposes in this application. These three SNPs are inherited together and RNA expression data from thepublic resource GTeX indicates that all three SNPs influence expression of CYP3A5 in liver. Dr. Guimbellot proposes to pursue this concept in greater depth in her proposal, including to recruit additional subjects on Ivacaftor monotherapy as well as to conduct mechanistic studies on additional isoforms that may be contributing to drug response. Thus the focus of her work addresses an important question in the treatment of individuals with CF that we hope will be further informed by studies currently underway in CF subjects.

I am confident that this proposal is structured to determine the degree to which the metabolism of Ivacaftor affects response of CF subjects. The pharmacologic studies proposed by Dr. Guimbellot could provide a compelling biologic rationale to pursue the genetic and non-genetic causes of variation in Ivacaftor metabolism. I am delighted to be a current collaborator with Drs. Guimbellot and Rowe to genotype specific polymorphisms in CYP3A5, and am also looking forward to considering genotyping of related genes in the DNA obtained from GOAL participants and Dr. Guimbellot's prospectively recruited subjects. I will meet with Dr. Guimbellot by teleconference and in person during my visits to UAB as an external advisor to help her interpret the data. In addition, I will assist with sequencing of CYP and other candidate genes, as well as genome-wide searches for causative loci. Finally, I am ready to provide genetics expertise and the resources of the CF Twin and Sibling Study to achieve the goals of this project.

Sincerely,

Garry R. Cutting, M.D.
Professor of Pediatrics and Medicine
Aetna/U.S. Healthcare Professor of Medical Genetics
Director, Clinical Genetics Laboratory Training Program
Director, DNA Diagnostic Laboratory

Michael R. Knowles, M.D.
Marsico Lung Institute
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February 26, 2019

To: National Institutes of Health
RE: K23 Award, Jennifer Guimbellot
Jennifer S. Guimbellot, P.I., Application to K23
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

To the Review Committee

I am writing to express my enthusiastic support for Dr. Guimbellot's research proposal, "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients". I have ongoing research that interfaces with this project, and this proposal has the potential to improve our understanding of drug response to novel therapies for cystic fibrosis, which would be an enormous breakthrough.

I am very excited to serve as a collaborator on this proposal. I have over three decades of experience as a Professor of Pulmonary medicine at UNC-Chapel Hill. My laboratory studies the genetic modifiers of disease severity in cystic fibrosis, and I lead a Consortium across North America to study rare genetic disorders of mucociliary clearance. I knew Dr. Guimbellot as a Pediatric Pulmonary Fellow while at UNC, and I am delighted to support her continued development and excellent career trajectory as a researcher in CF precision therapeutics. She has accelerated her productivity since her original submission and is actively engaged in ongoing collaborations. I am committed to a collaborative relationship with Dr. Guimbellot and her primary mentor, Dr. Steven Rowe, who I know well and have supported from afar for many years.

Dr. Guimbellot's proposal regarding CYP3A metabolism enzymes is designed to explore associations between CYP3A5, the key extra-hepatic member of this family and ivacaftor exposure and effectiveness. In addition, she has also proposed studies to identify the mechanisms by which CYP3A isoforms may modulate the pharmacokinetics of the drugs in the blood and at the site of action in the cells. These studies will inform future genetic studies as well as targeted interventions to optimize care on an individual basis.

As part of this relationship, I will work together with them to rigorously characterize the clinical outcome measures Dr. Guimbellot will need to appropriately correlate drug exposures and genotypes. Collectively, we will ensure the success of this project, and the continued development of this promising young scientist. Overall, I am hopeful this work could make a pronounced impact in our understanding of emerging and exciting CF therapies, and I believe it is an excellent project to support career development. This project is novel, feasible, and consistent with the goals of the NHLBI. Further, this project provides ample opportunities for future investigator-initiated proposals and contribution to the field of cystic fibrosis research. I am confident that this proposal is feasible and will generate important new insights. I look forward to collaborating further with Dr. Guimbellot, and I urge you to give this proposal the most careful consideration.

Sincerely,

Michael R. Knowles, MD
Professor of Medicine

Peter J. Mogayzel, Jr., M.D., Ph.D., M.B.A.
Professor of Pediatrics
Director, Eudowood Division of Pediatric Respiratory Sciences
Director, Cystic Fibrosis Center
Medical Director, Pediatric Specialty Clinic

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JOHNS HOPKINS MEDICINE
CYSTIC FIBROSIS CENTER

February 26, 2019

Jennifer Guimbellot, MD, PhD
Assistant Professor of Pediatrics
Associate Scientist, Gregory Fleming James Cystic Fibrosis Research Center
University of Alabama
Birmingham, Alabama

Dear Dr. Guimbellot,

I am delighted to be in a position to support the resubmission of your proposal entitled "*Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis (CF) patients*" as a potential collaborator for this pilot clinical study evaluating ivacaftor PK/PD relationships and pharmacogenomics in patients taking ivacaftor monotherapy. While I understand that your proposal may not need additional sites to assist with enrollment, I also acknowledge that clinical research includes some uncertainties that could make it necessary to recruit from other CF Centers. To that end, we at the Johns Hopkins Cystic Fibrosis Center are glad to support you by helping to identify and coordinate potential subjects if needed. Your study may yield important results for people with CF. I understand that the pharmacokinetics study involves 1-3 visits for patient with CF who are taking ivacaftor, adherent to therapy, and are clinically stable, and that this study will require one intensive PK visit and two additional visits for nasal cell procurement. I also understand that the genotyping study to correlate clinical measures of ivacaftor effectiveness with variants in CYP3A isoforms will require only one visit for blood and clinical data collection. Our center is facile with these methods, and can readily contribute patients if helpful. Our patients are very engaged in clinical research and would be interested in participating in this valuable study.

I wish you the best of luck with your proposal, and we look forward to the opportunity to collaborate with you and Dr. Rowe as your mentor on this or future studies.

Sincerely,

Peter J. Mogayzel Jr.

Peter J. Mogayzel, Jr., M.D., Ph.D., M.B.A.
Professor of Pediatrics
Director, Eudowood Division of Pediatric Respiratory Sciences
Director, Cystic Fibrosis Center
Medical Director, Pediatric Specialty Clinic

STANFORD
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March 09, 2019

To: National Institutes of Health

RE: Jennifer S. Guimbellot, P.I., Application to K23

P.I. ERA Users Commons Name: GUIM01

Funding Opportunity Announcement: PA-19-119

Dear Dr. Guimbellot,

I write this letter in strong support of your resubmission proposal “Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients”, as well as to confirm my commitment to potentially collaborate with your clinical study. I find of great interest to our research group your proposal to evaluate ivacaftor PK/PD relationships and pharmacogenomics in cystic fibrosis (CF) patients taking ivacaftor monotherapy. The proposed study has great potential to yield important results for the management of CF patients.

While we understand that your proposal may not need additional sites to assist with enrollment, we also acknowledge that clinical research includes some uncertainties that could make it necessary to recruit from other CF Centers. To that end, we at the Stanford Cystic Fibrosis Center are glad to support you by helping to identify and coordinate potential subjects if needed. We understand that the Pharmacokinetics study involves 1-3 visits for CF patients who are taking ivacaftor, adherent to therapy, and are clinically stable, and that this study will require one intensive PK visit and two additional visits for nasal cell procurement. We also understand that the genotyping study to correlate clinical measures of ivacaftor effectiveness with variants in CYP3A isoforms will require only one visit for blood and clinical data collection. Our center is facile with these methods, and can readily contribute patients if helpful. Not only we follow a large patient population (close to 700), but in addition our patients are highly enthusiastic about participation in the types of studies you propose.

We wish you the best of luck with your proposal, and we look forward to the opportunity to collaborate with you and Dr. Rowe as your mentor on this or future studies.

Sincerely,

Carlos E. Milla, MD
Professor and Director,
The Stanford Cystic Fibrosis Center
Center for Excellence in Pulmonary Biology
Stanford University

University of Colorado Denver

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Office Fax: 720-777-7284

To: National Institutes of Health
RE: Jennifer S. Guimbellot, P.I., Application to K23
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-19-119

February 26, 2019

Dear Dr. Guimbellot,

We are glad to support the resubmission proposal "Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients" as potential collaborators for your pilot clinical study evaluating ivacaftor PK/PD relationships and pharmacogenomics in patients taking ivacaftor monotherapy. While we understand that your proposal may not need additional sites to assist with enrollment, we also acknowledge that clinical research includes some uncertainties that could make it necessary to increase the number of subjects available. If you are having difficulty meeting your enrollment goals, our site will be more than happy to assist in recruitment efforts. We understand that the study involves 1-3 visits for CF patients who are taking ivacaftor, adherent to therapy, and are clinically stable. While the PK study will require one intensive PK visit and two additional visits for nasal cell procurement, the genotyping study to correlate clinical measures of ivacaftor effectiveness with variants in CYP3A isoforms will require only one for blood and nasal cell procurement. Our center is facile with these methods, and can readily contribute patients if helpful.

We wish you the best of luck with your proposal, and we look forward to the opportunity to collaborate with you and Dr. Rowe on this and future studies.

Sincerely yours,

Scott D. Sagel, MD, PhD
Professor of Pediatrics
Asher-Accurso Endowed Chair in Cystic Fibrosis
Director, University of Colorado Cystic Fibrosis Center
Children's Hospital Colorado
University of Colorado School of Medicine

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

February 26, 2019

To: National Institutes of Health
RE: Jennifer S. Guimbellot, P.I., Application to K23
P.I. ERA Users Commons Name: GUIM01
Funding Opportunity Announcement: PA-16-198

Dear Jennifer,

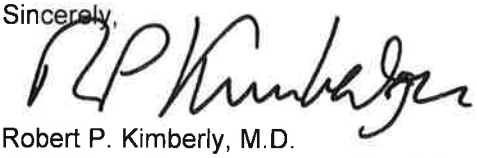
As Director of the Center for Clinical and Translational Science (CCTS), I am pleased to offer the Center's enthusiastic endorsement of your K23 resubmission entitled "*Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients*." The CCTS is strongly committed to training the next generation of clinician scientists, who are at the important intersection of clinical/basic questions and implementation. Your proposal, which aims to optimize treatment for cystic fibrosis by combining pharmacometrics, pharmacogenomics, and biomarker development, is an exciting proposal of translational science targeting precision medicine in an orphan disease.

As a member of the CCTS, you can continue to engage the CCTS to further your research and career development during your mentored career development. Among the many opportunities we offer, the following may be specifically helpful to this proposal:

1. Access to our Panels Done Quickly, grant workshops and mock study sections for proposal development and formal NIH-style reviews.
2. Peer learning opportunities offered by TIERS (Training Interdisciplinary and Emerging Research Scholars) where we promote problem solving, exchange of ideas, and collaborations for recipients of K-type career development awards at UAB. The TIERS Seminars will provide training in team management, conflict resolution and negotiation, grant management, budgeting, and life balance.
3. Four seminars – a) Faculty Biostatistics Forum; b) Research Methods and Secondary Data Analysis Seminar Series; c) Work-In-Progress Seminars; and d) Health Disparities Seminar Series – will offer ongoing training and networking opportunities.
4. Research design support through our Biostatistics, Epidemiology and Research Design (BERD) Group where we can connect investigators to expert methodologists during the design and initial implementation phases of a project through the transition into funding and execution. We also offer Biostatistics Drop-in Clinics to assist you with methodological questions, manuscripts, responses to peer reviews, published articles, etc.

The goal of the CCTS is to help build effective translational research programs to improve health. We look forward to working with you and your mentors on this important undertaking. Best wishes for your application.

Sincerely,



Robert P. Kimberly, M.D.
Howard L. Holley Professor of Medicine
Director, Center for Clinical and Translational Science
Senior Associate Dean for Clinical and Translational Research, UAB School of Medicine
Associate Vice President for Medicine and Biomedical Research

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The University of Alabama at Birmingham (UAB). UAB offers 162 degree programs with an emphasis on medicine and research. UAB has maintained status with the Carnegie Foundation as a doctoral university with "**highest research activity**." Its research funding reached $527 million in FY2018, with over half coming from federal sources such as the National Institutes of Health. Crucial for Dr. Guimbellot's career development and research, UAB has recently formed three new research entities in **genomic medicine, precision medicine and informatics**. UAB is known for its collaborative research environment, best highlighted through its support of 23 University-Wide Interdisciplinary Research Centers (UWIRCs) and over 80 core facilities.

Gregory Fleming James Cystic Fibrosis Research Center (CFRC). The UAB CFRC was the first in the U.S. to receive a Research Development Program grant from the Cystic Fibrosis Foundation (CFF) in 1981. Since its inception, the CFRC has maintained continuous CFF and NIH funding, and is **one of a handful of centers in the country funded through the CFF Research Development Program** (ROWE15R0), as well as an NIH P30 (DK072482). Today, the CFRC is a designated UWIRC with total direct annual funding of **$21 million** and a **major emphasis on the development of junior faculty physician-scientists.** It houses over 110 faculty, including Dr. Steven Rowe, primary mentor to this application. The CFRC is known world-wide as a leader in cutting-edge cystic fibrosis (CF) research, as key players in the development of novel therapeutics and technologies (i.e., CFTR modulators and μ-optical coherence tomography). The CFRC is collaborative with the Cystic Fibrosis Care Center at Children's of Alabama and UAB, caring for approximately 500 patients. Notably, the CFRC is **one of only six National Resource Centers** within the CFF Therapeutics Development Network (clinical research centers across the U.S. that focus on CF clinical trials). The CFRC maintains **five core facilities** to support studies in primary cell culture, cell biology, ion transport and translational research in CF. As an Associate Scientist in the CFRC, Dr. Guimbellot has access to all of these resources.

Department of Pediatrics and Children's of Alabama (COA). As the only Children's Hospital in the State of Alabama, COA and the Department provide access to a large pediatric population. The Department's focus on research is evident in its steadily increasing research accomplishments and funding, totaling $15.8 million from NIH (17th among all Departments of Pediatrics, FY 2018) and overall research funding of nearly $30 million. The Department supports the Pediatric Research Office (providing biostatistics – including Dr. Aban, advisor to this proposal, bioinformatics, proposal preparation, regulatory assistance and research coordination) and the Child Health Research Unit (2,547 sf housing exam rooms, equipment, and office space for clinical studies), as well as a satellite unit with a primary focus on CF research. Dr. Guimbellot's career development mentor, Dr. David Kimberlin, is Vice Chair for Clinical and Translational Research for the Department.

UAB Comprehensive Cancer Center Pharmacometrics Core Laboratory and Pediatric Pharmacology Laboratory. Led by Dr. Edward Acosta, advisor to Dr. Guimbellot's proposal, this Core supports pharmacokinetic/pharmacodynamic analysis of pre-clinical and clinical studies. Dr. Acosta's laboratory has over 20 years' experience conducting pharmacometric studies, with particular expertise in pediatrics, antivirals, antiretrovirals, cancer-related drugs and CFTR modulators. In collaboration with the CFRC, this Core has expanded mass spectrometry assays to quantitate ivacaftor and its metabolites, lumacaftor, and tezacaftor – with the capacity to add additional drugs to the assays as they become available. These methods can detect drugs in multiple human tissues (plasma, urine, CSF, tissue, intracellular). For regulatory purposes, the Core can perform these services under Good Laboratory Practices and operates under CLIA and HIPAA standards.

Heflin Center for Genomics Sciences. This UWIRC was established in 2002 to provide training and resources to enhance the use of genomics and genetics across UAB's campus. The Center provides ongoing training and seminars for education. It houses the Genomics Core Laboratory, which is key to Dr. Guimbellot's proposal, and includes cutting-edge equipment to provide Next Generation Sequence analysis, whole genome and targeted gene expression analysis, high- and low-throughput whole genome and custom genotyping, among other resources. The Center maintains partnerships with the Section on Statistical Genetics (of which Dr. Tiwari, advisor to this application, is a key member); the Center for Clinical and Translational Science (UAB's CTSA); the HudsonAlpha Institute for Biotechnology (HAIB); the UAB-HAIB Center for Genomic Medicine; the Kaul Personalized Medicine Institute and others to expand resources to investigators.

Center for Clinical and Translational Science (CCTS). UAB's CCTS is funded by a Clinical and Translational Science Award (CTSA) from the NIH's National Center for Advancing Translational Science (UL1TR001417; Kimberly, PI). Dr. Guimbellot has been a member of the CCTS since 2015. A key mission of the Center is to develop junior investigators, including establishment of a K-club to improve publications, research funding and career planning. The CCTS provides robust resources in monthly seminars and workshops (mentoring, ethics, scientific writing) and access to expertise in all aspects of research (biostatistics, bioinformatics, research methodology, data analysis, regulatory approvals).

UAB MEDICINE
PEDIATRICS

Children's of Alabama

February 26, 2019

Institutional Commitment to Dr. Guimbellot's Career Development:

It is my pleasure to provide strong institutional commitment to Jennifer Guimbellot's application for a K23 Mentored Patient-Oriented Research Career Development Award. Dr. Guimbellot is bright and innovative. Her particular interest in bringing precision medicine advances to cystic fibrosis patients is well-aligned with our institutional priorities. As a successful K23 recipient, Dr. Guimbellot will combine her formal training in pulmonology and genetics into a project that will expand precision medicine in pulmonary disease and simultaneously provide her with key training and research data that will facilitate her transition to independence.

The Department of Pediatrics was fortunate to recruit her as a full-time Assistant Professor into the Division of Pulmonary and Sleep Medicine. The Department of Pediatrics wholly supports her research without reservation and has confidence that she will succeed in the goals of the K23 application. To this end, we provided Dr. Guimbellot with salary support and start-up funding of over $400,000. Given her progress, we intend to sustain this financial commitment to cover the costs of her proposal beyond that supported by her primary research mentor and external funding, including the K23 award. Her continued appointment and support is not contingent on receipt of this award. Dr. Guimbellot will devote at least 75% of total effort to her research project and career development activities. As part of her generous faculty start-up package, she has dedicated research space, support for her laboratory technician, substantial assistance from the CF Research Center at UAB (including support from Core Facilities), and access to additional departmental and institutional resources to assist with her career development, grants management and professional progress. She has recently moved to a larger research space of 655 sq ft, supplemented by access to 10,000 sq ft within the CF Center, where she will continue to conduct her research throughout the course of this award. She has access to all facilities, equipment, and other resources required to complete the research and training outlined in this proposal. In addition, Dr. Guimbellot has a research office, appropriately outfitted with computers, printers and phones, which is adjacent to her laboratory space, as well as office space and equipment for her research staff.

The Division of Pulmonary and Sleep Medicine has provided an additional office, with allocated computer and office equipment, for Dr. Guimbellot located within the division's clinical space. There she has additional staff support, including administrative, nursing, ancillary care, and research coordination. Her proximity to the other members of the Division facilitates communication and coordination of the research proposed. She has full-time access to the real-time electronic medical records of Children's of Alabama and the University of Alabama at Birmingham. This will enhance identification of potential subjects and recruitment. She also has access to our recently renovated Child Health Research Unit and the full support of the Pediatric Research Office, including an informaticist, biostatistician, and grants administrators supported jointly by the Department and the University's successful CTSA award.

Dr. Guimbellot is already devoting ~75% protected time to her research. This is comprised of 1 day per week in clinic at Children's of Alabama and no inpatient responsibilities. Upon funding of this award, no more than 25% of her time will be devoted to patient care, administration, and teaching.

I enthusiastically support the application of Jennifer Guimbellot, M.D., Ph.D. for this K23 award. She will be an exceptional leader in her field. As we expected, her recent productivity has significantly increased as her laboratory has become established at UAB. I have every expectation that she will achieve academic success and am committed to fully supporting her during and beyond this award to achieve her goal of becoming a highly productive and independent physician-scientist.

Sincerely,

Mitchell B. Cohen, MD
Katherine Reynolds Ireland Chair of Pediatrics
University of Alabama at Birmingham
Physician-in-Chief, Children's of Alabama

UAB Department of Pediatrics, Office of the Chair, Lowder Suite 600
1600 7th Avenue South, Birmingham, Al 35233 tel 205-638-9650 fax 205-934-1150 www.uab.edu/medicine/ peds

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	❍ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Cystic fibrosis

2.2. Eligibility Criteria

Documentation of CF diagnosis per CFF diagnostic criteria and known CFTR genotype;
Documentation of CFTR modulator therapy (ivacaftor)
Age 12 months to 70 years;
Ability to provide written informed consent and/or assent (by subject and/or legal guardian).

2.3. Age Limits	Min Age: 12 Months	Max Age: 75 Years
2.4. Inclusion of Women, Minorities, and Children	Inclusion_of_Women_and_Minorities_and_Children.pdf	
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Plan.pdf	
2.6. Recruitment Status	Active, not recruiting	
2.7. Study Timeline	Human_Subjects_Study_Timeline.pdf	
2.8. Enrollment of First Subject	09/03/2018	Actual

Inclusion of Women and Minorities

While we plan to enroll an equal number of male and female subjects, the small number of participants required and the inclusion of a subgroup with a rare mutation may affect our ability to have entirely equal populations on the basis of gender. We will make every effort to balance our population on the basis of gender and will not exclude any potential subject on the basis of gender. We also plan to include individuals of all racial and ethnic groups and will not exclude any potential subject on the basis of race or ethnicity. However, given that cystic fibrosis (CF) affects predominantly those of Caucasian descent (91% Caucasian, 5% African American, and 4% Hispanic at our institution), it is likely that minorities will be underrepresented in our enrolled subject groups relative to the U.S. population.

Inclusion of Children

Both children over age 12 months and adults will be included in this study. Children comprise a substantial portion of patients with CF and studies on tissue samples from them are essential to assay development and understanding modulator efficacy among the entire CF population. While nasal epithelial brushing and phlebotomy cause some minor discomfort, they are used routinely in clinical practice on children of all ages. In our clinic, we have found that children tolerate both procedures, as shown by the clinical use of nasal epithelial brushing for diagnostic purposes (i.e., for primary ciliary dyskinesia diagnosis). Phlebotomy is routine for many indications in children. Because of this, children will be offered the opportunity to participate but will have the ability to refuse without impact to any aspect of care. All children enrolled in this study will be evaluated and specimens collected in the clinical setting, with appropriate personnel including anesthesiologists and nurse anesthetists, registered nurses, and pulmonary physicians. The specimens from subjects who are children are collected only by trained pediatric pulmonologists, respiratory therapists, and phlebotomists who have extensive experience working with children as young as birth in a clinical setting. In addition, modified, limited sampling for children under the age of 12 years has been proposed to limit risk and discomfort to children. Because of the preliminary nature of assay development proposed in this application, specimens collected from children will not be analyzed as a separate group. Therefore we have not designated a specific number of children to include. However, based on past experience, we expect to enroll approximately half of our total subjects among the pediatric population ages 12 years and up.

Subjects with a documentation of CF diagnosis per Cystic Fibrosis Foundation diagnostic criteria and known CFTR genotype; documentation of CFTR modulator therapy (ivacaftor); age 12 months to 70 years, and ability to provide written informed consent and/or assent (by subject and/or legal guardian) are eligible for enrollment in this pharmacokinetic/pharmacodynamics study (Aim 1) and genotype correlation with drug effectiveness (Aim 2) to assess drug concentrations of ivacaftor in plasma, epithelial cells of the airway, and genotype of pharmacogenes and each measure's correlation with drug effectiveness as measured by change in lung function (ppFEV1), weight (BMI), and sweat chloride. Patients will be recruited under IRB-approved protocols to review clinic, admission, and procedure schedules at Children's of Alabama and the University of Alabama at Birmingham. In addition, we have recruited the participation of Cystic Fibrosis Center directors around the country to help identify and recruit additional participants who meet eligibility requirements should we need to expand recruitment beyond our local population. Study subjects will be at least 12 months of age at the time of enrollment; for those under 12 years study procedures have been revised to reflect a reduced sampling protocol for intensive PK limited to 2 timed collections of blood and epithelial cells. Study will last no more than 6 months to complete all study procedures.

All studies are already approved by UAB's IRB. Study personnel will contact eligible participants after review of clinical schedules and the patient's record; waiver of consent for these procedures for identification of patients has already been approved by the IRB. Potential participants and/or families will be contacted by telephone or approached during clinic visits by study research coordinators to assess their interest in participating in it. The investigational nature and research objectives of this study and its attendant risks and discomforts will be carefully explained to the study participant/study participant's legal guardian. A signed informed consent document will be obtained from each study participant/study participant's legal guardian prior to entry into this study. At any time during participation in the protocol, if new information becomes available relating to risks or adverse events (AEs), this information will be provided orally or in writing to all enrolled or prospective study participant/study participants' legal guardian. Documentation will be provided to the IRB and, if necessary, the informed consent will be amended to reflect any relevant information. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. Subjects/subject's legal guardian will sign the informed consent document prior to any study-related procedures being done specifically for the study. Subjects/subject's legal guardian will have the opportunity to discuss the study with their family, friends or personal physician, or think about it prior to agreeing to participate. Subjects/subject's legal guardian may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects /subject's legal guardian for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The process of obtaining informed consent must be documented in the medical records, clinic chart, and/or research chart. The consent form must be signed and dated by the study participant/study participant's legal guardian before participation in the study. A copy of the signed consent form must be provided to the study participant/study participant's legal guardian. Signed consent forms must remain in each study participants study file and must be available for verification at any time.

While we expect sufficient recruitment at UAB, we have anticipated the possibility that additional recruitment at other sites will be necessary; each site has a similar number of patients to UAB and we expect that 30-40 patients at each site will be on ivacaftor. All sites have robust clinical

study infrastructure and a long history of CF research. It must be noted that several of these sites are not able to look into the records to see the current residential location of these former subjects without IRB approval, which cannot occur until after study funding is acquired and the protocol is written for the additional sites. However, based on past enrollments, each of these site could be anticipated to contribute between 5-10 subjects each for the above studies, well above what we would anticipate needing to expand beyond our local population.

The PK/PD study requires three visits. The first visit is intensive but visits 2 and 3 are brief and can be coordinated with regular clinic visits. Our initial 11 patients have all completed visit 1 and all have completed or scheduled visit 2. Because we have the capability to see patients independently at their convenience or in coordination with clinic visits, we do not anticipate retention to be a problem. For the Aim 2 study, only one visit is required and we do not anticipate retention to be a challenge. Contact information will be obtained by the patient, parent(s) or legal guardian(s) of subjects enrolled into this longitudinal study to ensure follow up for Aim 1 studies.

Dr. Guimbellot will hold meetings with staff from the the Child Health Research Unit (Aim 1 V2, V3, and Aim 2) and Clinical Research Unit (Aim 1 V1) staff weekly during active recruitment to discuss progress and assess data collection, and troubleshoot any problems. Should recruitment expand to other sites, Dr. Guimbellot will contact the sites monthly to evaluate potential recruitment. UAB research coordinators will schedule travel for those subjects traveling to UAB for the study and they will coordinate directly with the subject identified by the other site. She will also coordinate with the local investigator and research coordinator for collections of blood and clinical information monthly for any subject recruited for Aim 2 studies. Data will be transferred using a coded and de-identified encrypted system UAB has set up for clinical study exchange. She will contact site coordinators as needed to ensure that the data generated are of sufficient quality to allow for assessment of the study endpoints. Best practices will be shared among sites. Clarification or additional detail will be requested of the site as needed.

Human Subjects Study Timeline

Year 1-Year 3. 5 Initiate Pharmacokinetic recruitment and collection for Aim 1, Visit 1, 2, and 3.

Within one year of the award, clinical analysis and correlation analysis of PK data with clinical measures will be initiated.

Concurrently with Recruitment in Aim 1, DNA from GOAL participants for genotyping will be collected. Active recruitment to increases total participants as described in the Research Strategy will begin.

By Year 2 all DNA will be available and genotyping will take place over the next 3 years; this may be completed by the end of Year three if budget allows.

Clinical measures will be collected and analyzed beginning Year 2 and continued throughout the remaining award, completed within Year 5.

Correlation of genotype with clinical measures from subjects in Aim 2 will begin in Year 3.

	Year 1	Year 2	Year 3	Year 4	Year 5
Initiation/set-up of Aim 1 PK study					
Recruitment Aim 1 PK study					
V1-V3 Aim 1					
Analysis of clinical data Aim 1					
Correlation analysis of PK data with clinical measures					
Aim 2 Collection of subjects beyond GOAL					
Aim 2 clinical analysis					
Genotyping of all variants Aim 1 and Aim 2					
Correlation analysis of genotype with clinical measures					

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	University of Alabama at Birmingham, Children's of Alabama, Birmingham Alabama
Study 1, IER 2	Domestic	GOAL-e2 observational trial from the Cystic Fibrosis Foundation

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): University of Alabama at Birmingham, Children's of Alabama, Birmingham Alabama

Comments: Note that the Planned Inclusion Enrollment Report includes planned actual recruitment for those in

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	4	2	3	2	11
White	23	22	5	4	54
More than One Race	4	3	2	2	11
Total	31	27	10	8	76

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	1	0	0	0	0	0	1
White	5	5	0	0	0	0	0	0	0	10
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	5	5	0	1	0	0	0	0	0	11

Inclusion Enrollment Report 2

Using an Existing Dataset or Resource* : ● Yes ❍ No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): GOAL-e2 observational trial from the Cystic Fibrosis Foundation

Comments: 207 subjects have been enrolled in the GOAL-e2 dataset with biospecimens (buffy coat). However the complete details of the distribution of these patients is not available until data is received. Estimates based on the Cystic Fibrosis Foundation's general information on these specimens was used to populate the cumulative report below.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	3	2	0	1	1	0	0	0	0	7
White	90	110	0	0	0	0	0	0	0	200
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	93	112	0	1	1	0	0	0	0	207

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	Human_Subjects_Involvement.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	❍ Yes ❍ No ● N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	DSMP.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	

1. Risks to Human Subjects.

a. Human Subjects Involvement, Characteristics, and Design

This proposal involves the recruitment of 30 subjects with cystic fibrosis (CF) in Aim 1, and as described in the Research Strategy, up to 100 additional patients in Aim 2. Involvement will be limited to the collection of nasal epithelial biopsy for culture, phlebotomy, sweat chloride measurements and limited collection of PHI. Study visits will be coordinated with visits for clinical indications where feasible, but also independently in the Child Health Research Unit of Children's Hospital of Alabama.

All procedures for the collection of human samples and use of these samples for cell culture and drug quantitation have been approved by the University of Alabama at Birmingham Institutional Review Board as described in the application.

Inclusion criteria for CF subjects include: 1) documentation of CF diagnosis per CFF diagnostic criteria and known CFTR genotype; 2) age 12 months to 75 years; 3) ability to provide written informed consent and/or assent (by subject and/or legal guardian)

Exclusion criteria include subjects with CF who have a history of a bleeding disorder or a history of nasal surgery within the past 6 months.

b. Study Procedures, Materials, and Potential Risks

Human subject procedures to obtain specimens in this proposal are limited to nasal epithelial cell biopsy via curettage or brushing and whole blood samples collected in EDTA tubes for plasma and buffy coat separation. Additional procedures include the performance and analysis of sweat chloride from subjects who have not previously had sweat chloride performed. Sweat chloride collection will be performed and chloride content measured under standardized protocols. These samples will be collected as described in the approach section under IRB approved protocols. The cell specimens will be cultured and portions of either primary tissue or passaged cells will be frozen for future study as per IRB approved protocols. Blood samples will be processed as above and frozen or immediately used under currently approved IRB protocols. Protected health information to be collected includes CFTR genotype (if subject has a diagnosis of CF), age, gender, BMI, FEV1, sweat chloride.

Potential Risks

The procedure confers risk of minor, temporary bleeding from the nose or phlebotomy site, which is managed by pressure for 5-10 minutes. Nasal brushing may cause discomfort, which will be minimized by using small brushes most appropriate to the patient size (brushes 2-5mm in diameter), oxymetazoline for vasoconstriction and ease passage of the brushes, and topical lidocaine for numbing.

Adult and pediatric subjects will be approached for collection. The nasal brushing and phlebotomy procedures are commonly used for diagnostic purposes in this age group (i.e., primary ciliary dyskinesia).

As part of the IRB protocol, we will be collecting protected health information on subjects, and there is the potential risk of inadvertent dissemination of this information.

2. Adequacy of Protection Against Risks

a. Informed Consent and Assent

Potential CF subjects for this study will be identified during regular review of the lung function testing, admission, and clinic schedules for Pediatric Pulmonary, and the clinic schedules and admissions for the adult CF clinic. Potential subjects and/or their families will be approached by telephone, in the clinic, or in the hospital setting for informed consent.

Informed consent will be obtained from subjects and their families using IRB approved protocols. For children 7 years or old and older, parental/legal guardian written consent and written assent from the child will be obtained. For adults and children who have reached the age of majority or are legally emancipated, an adult consent form will be used and no parental permission will be obtained. Children who refuse to assent to the study will not been enrolled. All consents will be obtained by appropriately trained, IRB approved individuals

connected with the study. Study information and consent forms will be reviewed with the study subject and his/her parent or guardian, as appropriate, and a copy of the IRB-approved consent and assent forms will be provided. After having the chance to consider the trial and all questions/concerns are addressed by the research coordinator, Investigator, and/or another member of the study team, the parent and/or child may be verbally "quizzed" about the study in order to confirm their understanding of it. The consent forms will then be signed and dated and a copy will be given to the parent and/or subject. A Consent Process Checklist Form will be filled out by the member of the study team obtaining consent and filed with the consent forms.

Subjects will be recruited for an anticipated one-time consent. For those enrolled in Aim 1, pharmacokinetics study, will undertake nine blood samplings and one brush biopsy at Visit 1; Visits 2 and 3 will require two blood sampling and collections of the nasal epithelial biopsy each.

b. Protection Against Risk
Risks for participation in this study are minimal. There is a small risk of slight bleeding from the nasal epithelial brushing, which does not occur in most patients. Subjects with a history of a bleeding disorder or a history of nasal surgery within the past 6 months will be excluded to protect against this risk. If bleeding occurs, it will be treated by squeezing the tip of the nose for 5-10 minutes. There is also transient discomfort associated with this procedure in a conscious patient, which is described during the consent process. To protect against this risk, only highly trained personnel conduct the biopsy and subjects may withdraw at any time. There is a small risk of discomfort and bleeding from the phlebotomy site, which will also be treated with pressure for 5-10 minutes.

The most significant risk to participation is the risk of inadvertent release of protected health information (PHI). To minimize this risk, all subject research records containing PHI will be stored in locked offices and/or secure computer files. All study samples will be identified with a study number or code and initials. The master list that links the subject's name to their study number or code and initials will be stored in a secure UAB CF research office and/or on a secure computer. Only the principal investigator and members of the study team approved by the IRB will have access to this information.

c. Rationale for Involvement of Vulnerable Populations
Children under the age of 21 years with and without CF will be recruited for this program. Children with CF represent a large part of the CF population and are already recipients of CFTR modulator therapy. Those with gating mutations over the age of 1 year have already started on an expected lifetime of therapy with ivacaftor, and F508del homozygotes 12 years of age and older are already on this therapy. In addition, drug metabolism may also be significantly different in children, which will be essential to understand to maximize therapies in this age group. Therefore, recruitment of children to this study will provide benefit to both the success of the study, as well as allow some degree of assessment of differences in assay that may be related to the age of the patient, which would be further explored in future applications. The study will be explained in detail to parents and subjects and informed consent will be obtained. Assent for children ages 7-17 will also be obtained.

3. Potential Benefits of the Proposed Research to Research Participants and Others
The individual participants we plan to enroll in this proposal will not directly benefit from their participation in this study. The increased risks to these individuals are very small and are greatly outweighed by the potential long term benefits to the population under study. These long-term benefits will yield greater insight into the clinical use of CFTR modulator ivacaftor, including optimization of therapy, avoidance of treatment failure, and precision therapeutic strategies for individual patients.

4. Importance of the Knowledge to be Gained
Understanding pharmacogenetic variation and personalized CFTR modulator response is crucial to the optimization of the use of these novel compounds; expansion to all patients who might benefit from them; and development of predictive biomarkers. In addition, the ability to determine *a priori* those individuals who will or will not respond to existing therapies will avoid needless risk of side effects and the high cost of a potentially ineffective treatment regimen. Understanding the way these drugs work in the body and the best way to study them and the downstream effects is critical to expanding the use of these drugs to all patients with CF. We feel

the minimal risks involved in participating in this study are reasonable given the importance of the potential knowledge to be gained by conducting the study.

Collaborating Sites
There are no collaborating sites at this time, but are prepared to modify this if required to meet our enrollment objectives.

Data Safety Monitoring Plan

All data safety and monitoring will be performed by the Principal Investigator (PI). If any unanticipated adverse event or serious adverse event occurs that is related or possibly related to study procedures, trial procedures will be immediately halted, and notice sent to the IRB. If any events are thought to pose a risk to previously enrolled individuals, all efforts will be made to notify all affected study subjects.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **08/14/2019**
Revised Date:

Application Number: **1 K23 HL143167-01A1**

Principal Investigator

GUIMBELLOT, JENNIFER S

Applicant Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Review Group: **MPOR (OA)**
NHLBI Mentored Patient-Oriented Research Review Committee

Meeting Date: **06/27/2019**
Council: **OCT 2019**
Requested Start: **09/01/2019**

RFA/PA: **PA19-119**
PCC: **LLAI N**

Project Title: **Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients**
SRG Action: **Impact Score:30**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Age: **1A-Children, Adults, Older Adults, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	159,400	172,152
2	159,400	172,152
3	159,400	172,152
4	159,400	172,152
5	159,400	172,152
TOTAL	797,000	860,760

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1 K23 HL 143167 - 01A1 GUIMBELLOT, JENNIFER

RESUME AND SUMMARY OF DISCUSSION: This is a resubmission of a K23 application from Dr. Jennifer Guimbellot in which she proposes a research career development plan focused on identifying genetic variation in CYP3a metabolism of ivacaftor, a Cystic Fibrosis therapeutic. The reviewers agreed that this application in its current form is considerably improved from the prior submission. The Candidate's productivity has increased since the original submission. The mentoring team remains strong. The Career Development Plan now includes training in pharmacogenetics and statistical genetics and she will pursue certification in clinical pharmacology. The Research Plan is now strengthened with new preliminary data, supporting feasibility, but some study design issues remain. Institutional Commitment and the Environment are also strong. Overall, reviewers were in agreement that the Candidate has significantly improved the application; this with the Candidate's improved academic output lend high confidence that the career development plan as proposed will lead to her independence.

DESCRIPTION (provided by applicant): Cystic fibrosis (CF) is an autosomal recessive disorder caused by dysfunction of the CF Transmembrane Conductance Regulator (CFTR) channel. The care of patients with CF has rapidly evolved with the development of CFTR modulators, novel pharmaceuticals that address the basic CF defect and restore CFTR function. Despite the success of one of these, the potentiator ivacaftor, there is still pronounced variance in drug efficacy, as measured in individuals' phenotypic response to therapy and their in vitro cellular response when assessed with cell-based biomarkers. Ivacaftor is metabolized by cytochrome P450 (CYP3A enzymes), which are responsible for both hepatic and tissue-specific metabolism, including in airway epithelia. Genetic variation in these enzymes cause altered activity, resulting in variation in efficacy in many drugs. The preliminary data demonstrate CYP3A variants may be associated with drug efficacy, and the ability to detect ivacaftor metabolism in vitro in individual patients' epithelia that the applicant personally co-developed. To maximize efficacy of ivacaftor, and thus, any therapy including it, it is essential to understand pharmacogenetics and effect of variability of CYP3A enzyme activity on the metabolism of ivacaftor. The Specific Aims are: 1) conduct a pilot study in people to determine population pharmacokinetics of ivacaftor in plasma and epithelia, and correlate drug exposure with drug response 2) to determine frequencies of genetic variants of these enzymes in the CF population and measure association with clinical efficacy; 3) compare the contribution of CYP3A isoforms to ivacaftor metabolism and understand impact in primary epithelial cells on CFTR activity. Ivacaftor is a significant component of many combination therapies, so understanding its variation in metabolism and impact on efficacy is the first key step to understanding pharmacogenetics in complex combinations, and will set the stage for an independent career focused on precision-directed therapeutics in CF. The applicant has dedicated her professional life to becoming a physician-scientist, studying pediatric pulmonology in general and cystic fibrosis in particular. To achieve this, she accepted a faculty position at the University of Alabama at Birmingham, where a supportive research environment in the Department of Pediatrics and School of Medicine, as well as the Gregory Fleming James Cystic Fibrosis Research Center, has made career advancement and approach to independence possible. To accomplish the goals of this research, the candidate has assembled a mentoring team with decades of experience in clinical trials, pharmacology, genetics, statistics, pharmacogenetics, and drug metabolism to advise and guide her during her career development. She also proposes to undertake formal training in pharmacology, advanced statistics, clinical trial conduct, and genetics to complement her prior medical and graduate studies and acquire the relevant skills to transition to independence.

PUBLIC HEALTH RELEVANCE:
CFTR modulators are a novel class of therapeutic compounds, and this research will contribute significantly to the understanding of the metabolism of these compounds in patients with cystic fibrosis to optimize therapy and usher in an era of precision therapeutics. The findings will enhance efficacy of CFTR modulator therapy for all patients with cystic fibrosis and help expand these novel therapies to all

patients who might benefit from them. The knowledge gained in metabolism enzyme pharmacogenomics also has important implications for other diseases, including chronic obstructive pulmonary disease, pulmonary infections, and asthma.

CRITIQUE 1:

Candidate: 2
Career Development Plan/Career Goals /Plan to Provide Mentoring: 2
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment Commitment to the Candidate: 1

Overall Impact:
Pharmacometric approaches to precision optimization of ivacaftor response in cystic fibrosis patients. This application received a score of 46 on the first review in February of 2018. In the initial review, the candidate was recognized for her training, however academic productivity was lower than would be expected. The career development plan was viewed as well-developed and was encouraged to add additional training in basic pharmacological principles and pharmacogenetics. The research plan was found to be well thought out, but weaknesses in design related to expertise in pharmacology and pharmacogenetics and perceived statistical power of the study lessened enthusiasm. In this revised application, the applicant demonstrates significant productivity and has been responsive to criticisms of the initial application. New preliminary data strengthen the proposal and demonstrate feasibility. Overall this is a much improved proposal.

1. Candidate:
Strengths
- Dr Jennifer Guimbellot is an Assistant Professor in the Department of Pediatrics at the University of Alabama at Birmingham.
- Four first author publications since 2017 listed on bibliography.
- Cites multiple awards from Cystic Fibrosis Foundation related to current studies.

Weaknesses
- Minor

2. Career Development Plan/Career Goals & Objectives:
Strengths
- Has added training in pharmacogenetics and statistical genetics.
- Will take an online self-directed course for basics of clinical pharmacology certification.
- Has identified several training opportunities in pharmacology, as well as biostatistics and translational research.

Weaknesses
- Timing, frequency of mentor interactions as well as methods of candidate evaluation throughout the career development plan are not described.

3. Research Plan:
Strengths
- Preliminary data demonstrating feasibility of 12 hr PK sampling and measurement of intracellular (nasal cell) ivacaftor and the M1 metabolite.
- Interesting and encouraging concentration/response data on two subjects.
- Preliminary evidence of CYP3A7 expression in airway epithelial cells.
- Significant improvements in experimental design and data analysis.

Weaknesses

- Aim 1b, Figure 6 does not present findings with respect to specific variant alleles of CYP3A5.
- It would be helpful for the investigators to provide an estimate of the diplotype distribution anticipated among the 30 subjects to be monitored. It is not clear that any of these would be likely to be a normal metabolizer, and further it is not clear what representation would be observed for the *6 and *7 alleles. Figure 5 demonstrates that these are very rare.
- It would have been helpful to know the diplotypes of the 3 cases where IC ivacaftor concentrations were measured.
- The experimental design of the relationship between avacaftor and CYP3A5 diplotypes is very unclear. Again, what distribution of diplotype are expected? What is the significance of a slope of the relationship being 0.47? How would this be interpreted, applied?
- What is FEV range/distribution in the GOAL cohort? If most subjects are CYP3A5 PM (>80%), and PM's are expected to demonstrate greater efficacy, how does this reconcile with the observed outcomes?
- Unclear that a correlation slope between CYP3A5 diplotype and outcomes of 0.25 will be clinically significant.
- Unclear what significance there is of a correlation of 0.47 between diplotype and plasma or intracellular concentrations?
- Overall inadequate description of power analysis to convince this reviewer that meaningful associations can be made between CYP3A5 diplotypes and outcomes or concentrations giving the rare frequency of the alleles, the number of patients included, and the inherent degree of variability demonstrated in the preliminary data.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths
- No changes in mentoring team which was viewed as a significant strength of the initial application.

Weaknesses
- None

5. Environment and Institutional Commitment to the Candidate:
Strengths
- Excellent environment and commitment to the candidate. Again, viewed as a strength for the initial application.

Weaknesses
- None

Study Timeline:
Strengths
- Appropriate

Weaknesses
- None

CRITIQUE 2:

Candidate: 1
Career Development Plan/Career Goals /Plan to Provide Mentoring: 1
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment Commitment to the Candidate: 1

Overall Impact:

Overall this application scores well in terms of the candidate, career development plan, the research goals, the mentors, and the research environment. The statistical approaches and power analyses were deemed to be problematic though.

1. Candidate:
Strengths
- She has an MD and PhD in genetics, with a pediatric pulmonary fellowship.
- 10 publications, 6 as first author, several that are quite relevant to the proposed research.
- She is the PI of a pilot award and a clinical investigator award from the CF Foundation. She has also been PI of a number of other foundation-funded studies over her career.

Weaknesses
- None

2. Career Development Plan/Career Goals & Objectives:
Strengths
- Nice discussion of short and long-term career goals.
- Knowledge gap analysis is thoroughly addressed in the planned coursework.

Weaknesses
- None

3. Research Plan:
Strengths
- The aims are well designed to address the lack of understanding in the way ivacaftor affects CF patients.
- Addresses a significant medical problem and may lead to improvements in the treatment of CF patients with ivacaftor.
- Preliminary data on n=10 patients on therapy is presented.
- Analysis plans for Aim 1a (correlating drug concentrations and outcomes) have been well-described, and the power analysis seems reasonable.

Weaknesses
- In Aim 1, it isn't clear when visits # 2 and 3 will take place. At visits #2 and 3, it isn't clear if the PK experiments from visit #1 will be repeated over 12 hours, or if there will be only 1 blood draw per visit.
- The analysis plans for Aim 1b and Aim 2a/b seem to treat metabolizer status (defined by diplotype) as a continuous variable, when in reality it is probably dichotomous (Table 2). Thus, the power analysis for Aim 1b doesn't seem at all appropriate, as it mentions detecting correlations between diplotype status and outcomes. Aim 1b will actually have very little power to detect differences between diplotype groups. The power within Aims 2a/b will be higher, but they should be focusing on detecting group differences (e.g. poor vs intermediate metabolizers) rather than correlations.
- For Aim 3a, they claim that an intra-cluster correlation of 0.01 is "conservative". Since 3 monolayers will be derived for each subject, the ICC is probably going to be much higher, maybe even above 0.5. If that is the case, then the detectable effect size will be extremely large, meaning that they will be underpowered to detect subtler differences between expressors and non-expressors.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths
- The team of mentors and collaborators has a wealth of experience in a number of relevant fields (CF and other pulmonary diseases, research career development, pharmacology, statistical genetics, other biostatistics topics, cytochrome P450, and personalized medicine.
- The meeting frequencies seem appropriate as does the overall timeline of activities.

Weaknesses
- None

5. Environment and Institutional Commitment to the Candidate:
Strengths
- Having the resource of a CTSA will be beneficial.
- The institutional commitment is fairly strong. Her department chair's letter of support says that "Dr. Guimbellot is already devoting ~75% protected time to her research. This is comprised of 1 day per week in clinic at Children's of Alabama and no inpatient responsibilities. Upon funding of this award, no more than 25% of her time will be devoted to patient care, administration, and teaching."

Weaknesses
- None

Study Timeline:
Strengths
- Not applicable

Weaknesses
- None

Resubmission:
- The applicant seems to have been very responsive to the prior concerns, which had to do with lack of productivity, statistical approaches, training plan, and feasibility.

CRITIQUE 3:

Candidate: 3
Career Development Plan/Career Goals /Plan to Provide Mentoring: 3
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 4
Environment Commitment to the Candidate: 1

Overall Impact:
This resubmitted application shows responsiveness to prior critiques. The applicant is strong and has a significantly improved publication record compared to 2018. The major strengths of the application are the candidate's focus and background, the novel nature of the research and the robust institutional environment and commitment. There are minor weaknesses in the career development plan and with research feasibility issues. Thought the mentors are very strong the plan to provide mentoring has weaknesses that dampen enthusiasm.

1. Candidate:
The candidate is Assistant Professor, Division of Pediatric and Sleep Medicine at UAB, appointed in 2016. She earned her MD/PhD from UAB (12/08) and did her pediatric residency at Columbia University and her pulmonary fellowship at University of North Carolina. She has 4 first authored, one senior authored and one other manuscript published 2017-2019. The applicant has current funding from the CF Foundation and received a travel award to the North American CF meeting in 2018.
Strengths
- Well trained candidate with very strong focus on drug mechanisms in the treatment of CF.
- Improved publication record compared to the prior submission (2/22/18 review).
- Publications are in her area of research.

- Candidate clearly has enthusiastic support from her current and prior mentors.

Weaknesses

- Though improved, the publication track record is still relatively modest given 4 years on faculty at her current institution.

2. Career Development Plan/Career Goals & Objectives:

The career development plan proposes additional training in statistical genetics/statistical methodology, pharmacometrics, patient oriented research, professional development skills.

Strengths

- A time line is provided that integrates the research with the didactic and hands-on training.
- Justification is provided for the training.

Weaknesses

- Some of the proposed training comes late in the grant cycle (years 3 and 4).
- A gap analysis is not provided; the candidate already has a PhD, but the content of the PhD is not described.
- The career development plan includes only monthly or quarterly meetings with the mentors/co-mentors.

3. Research Plan:

The overarching hypothesis is that epithelial ivacaftor metabolism influences drug response and can be used for precision CF therapeutics. Aim 1 is to perform a prospective study of CF patients taking ivacaftor monotherapy to determine the relationship between drug exposure and drug response. Aim 2 is to determine whether CYP3A variant alleles are associated with ivacaftor efficacy. Aim 3 is to determine the impact of drug concentrations on epithelial CFTR function and the contribution of different CYP3A isoforms to ivacaftor metabolism.

Strengths

- The proposal is novel and has important clinical relevance.
- The candidate and her mentoring team are ideally qualified to perform this type of research.
- The candidate has some preliminary data to support feasibility.

Weaknesses

- Subject recruitment may be challenging given the small number of CF subjects with the G551D or other gating mutations. Although other sites have agreed to provide subjects if needed this may complicate the completion of the study within the frame work on the K23.
- There is no discussion of the impact of co-morbidities, other medications and exacerbations on the data being collected in the trial.
- It is unclear that FEV1 is the best endpoint; the enrolled subjects will be on ivacaftor and hence already seen benefit from the drug. More preliminary data would help to show that FEV1 is the proper endpoint.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

The primary mentor is Steven Rowe MD; the other mentor is Edward Acosta. Four co-mentors are also listed as well as two advisors.

Strengths

- The mentoring team members have complementary skills.
- The candidate is already well integrated into the mentoring scheme.

Weaknesses

- Meetings with the primary mentor and the other mentor (Acosta) are relatively infrequent (monthly) and only quarterly or less with other members of the team.
- Metrics/milestones are relatively vague.
- How the primary mentor will organize and coordinate the large mentoring team is not described.
- A detailed record of prior mentees and their academic outcomes is not provided by any of the mentors.

5. Environment and Institutional Commitment to the Candidate:
Strengths

- The environment at UAB is outstanding for this research with the various relevant disciplines already coordinating.
- The institutional letter of support from the chair of pediatrics is enthusiastic about the candidate.
- Ongoing 75% protected time for research is promised.

Weaknesses

- None

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (RESUME): ACCEPTABLE

INCLUSION OF WOMEN PLAN (RESUME): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (RESUME): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (RESUME): ACCEPTABLE; children involved, scientifically justified.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH: ACCEPTABLE

RESOURCE SHARING PLANS: NOT APPLICABLE (NO RELEVANT RESOURCES)

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES: UNACCEPTABLE; none provided.

COMMITTEE BUDGET RECOMMENDATIONS: RECOMMENDED AS REQUESTED

Footnotes for 1 K23 HL143167-01A1; PI Name: Guimbellot, Jennifer S

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

NHLBI Mentored Patient-Oriented Research Review Committee
Heart, Lung, and Blood Initial Review Group
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
MPOR (OA)
06/27/2019 - 06/28/2019

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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