I am a physician who is currently in the first year of Instructorship in the Division of Nephrology, having completed 3 years as a postdoctoral fellow in the NIH T32 training program in Vascular Biology and Hypertension following a clinical fellowship in Nephrology. My goal in seeking a Mentored Research Career Development Award is to acquire the additional necessary training, practical experience, and knowledge to develop into an independent clinical investigator committed to a career in patient-oriented research. My undergraduate and clinical training, as well as my postdoctoral training, has been steadfastly devoted to the development of a career in academic medicine. I have excelled as a trainee and have taken full advantage of the opportunities afforded to me. My unique fellowship training has led me to pursue a research career devoted to understanding the physiologic role of the vasculature in the progression and development of chronic kidney disease (CKD), with a long-term career goal to identify and/or develop CKD-specific therapies. The work I propose is timely and cutting-edge with the potential to significantly improve clinical outcomes for the large patient population with CKD. Receipt of a K-Award is a crucial next step in my trajectory toward becoming an independent investigator. My outstanding mentoring team, the well-established record of research career development activities at UAB, and the "protected time" afforded by this K23, will allow me to progress toward achieving my long-term career goal of becoming an independent clinical investigator in the area of CKD-specific therapies. My mentors and I have developed an intensive career development plan as outlined in Table I and within this proposal. I will commit 80% effort to this research project and its associated career development program.

Table 1. Outline of Proposal

1. Candidate's Background
- A. Undergraduate & Clinical Training
- B. Postdoctoral Training
- C. Graduate Studies

2. Career Goals and Objectives

3. Career Development Plan
- A. Vascular Function Testing
- B. Physiologic Measures
- C. Didactic Coursework
- D. Professional Development
- E. Mentorship Team
- F. Mentorship Plan
- G. Comp. Activities & Timeline

4. Research Strategy
- A. Significance
- B. Innovation
- C. Approach
- D. Future Directions

1. CANDIDATE'S BACKGROUND

A. Undergraduate and Clinical Training: I graduated *summa cum laude* from Trinity University where I studied engineering science. It was at Trinity University where I discovered my intense scientific curiosity and began developing skills of critical thinking through engineering design and problem solving. Applying these skills in medical school allowed me to excel, particularly in physiology, and I took on leadership positions in education and teaching. While I was attracted to the science of research throughout my internal medicine residency, it was not until the first year of my nephrology fellowship that I actively participated in research. For my first study, I designed and successfully performed a cross-sectional study in close collaboration with two radiologists. Work from this study, "Pneumonia in hemodialysis patients: a challenging diagnosis," was presented at the National Nephrology Young Investigators Forum and published in 2013.

B. Postdoctoral Training: My second year of nephrology fellowship combined work as Chief Fellow with the start of my postdoctoral clinical research fellowship on a T32 training grant (PI: Suzanne Oparil, MD) under the primary mentorship of David A. Calhoun, MD. During my first year as a postdoctoral fellow, I was immersed in clinical trial research in Dr. Calhoun's lab with roles as sub investigator and lead investigator. My work as a lead investigator on one of his pivotal trials investigating aldosterone excess in resistant hypertension [R01 HL075614 (Calhoun)], allowed me to gain first-hand experience working on an R01-level clinical trial and culminated in an oral presentation at the National American Heart Association Scientific Sessions in my second year of postdoctoral training. In this study, I was introduced to performing vascular function testing on study participants. These tests included measuring blood vessel response to endogenous vasodilators, which is an important measure in my proposed research. Ultimately, I plan to expand upon the vascular function testing techniques developed for our resistant hypertension population in order to answer questions of vascular function in kidney disease. In this way, I am building on my experiences as a postdoctoral clinical researcher, which also include patient recruitment techniques, clinical trial troubleshooting, ensuring study participant rights and safety, randomization and masking techniques, data analysis, and manuscript preparation. At the end of my second year of postdoctoral training, I was awarded the Walter B. Frommeyer, Jr., Fellowship in Investigative Medicine, a competitive fellowship awarded to "outstanding physician-scientists." Receipt of this award provided research funding for a feasibility study to define the vascular phenotype of Liddle's Syndrome. In total the work from my postdoctoral training has produced 8 first author publications in peer-review journals, 2 book chapters, a departmental pilot grant, and 2 oral presentations at national conferences.

C. Graduate Studies: In order to build a strong foundation in clinical trial design, I enrolled into the Master's Program at UAB at the start of my 2nd year of postdoctoral training. My coursework has been personalized to include formal training in clinical trial design, biostatistics, and public health, with expected completion in May 2016. Receipt of this K-Award will allow me the protected time to continue my studies.

3. CAREER DEVELOPMENT PLAN: My mentoring team and I have developed a systematic plan that will address needs in training and research experiences utilizing research and educational resources within UAB. The implementation of this plan will address the following needs:

1) Vascular function testing including i) performing noninvasive assessments of endothelial function and arterial stiffness; ii) biochemical measurement of endothelial function, (e.g., oxidative stress).
2) Physiologic measurements including i) reading and interpreting 48 hour ambulatory blood pressure monitoring (ABPM); ii) measuring GFR by iothalamate urine clearance
3) Didactic coursework to gain knowledge of advanced study design and biostatistical methodology.
4) Develop expertise in recruitment and performance of clinical trials.
5) Development of professional skills such as successful grant writing, networking, and communication skills that will contribute to success as an independent investigator.

A. Vascular function testing.

(i)Noninvasive assessment of endothelial function and arterial stiffness. My Primary Mentor, David Calhoun, MD, Professor of Medicine and Director of Vascular Biology and Hypertension Clinic, has conducted many studies measuring ultrasound-guided flow-mediated dilation (FMD) of the brachial artery and pulse wave velocity between the carotid and femoral arteries. His laboratory techniques have been externally validated through multi-center clinical trials. This provides me an excellent opportunity to be trained in the skill of measuring brachial artery flow-mediated dilation and pulse wave velocity. While I have been introduced to these measurement techniques in a small number of study participants, dedicated training with Dr. Calhoun will allow me to acquire these measurements unsupervised. Becoming an expert in vascular function testing will equip me with a deep understanding of the testing limitations, which is critical to successful trial design and data analysis. In the first 3 months of year one, I will spend approximately 100 hours in Dr. Calhoun's laboratory becoming proficient in these techniques.

(ii)Biochemical measurement of endothelial function **(e.g., oxidative stress)**. Oxidative stress has emerged as a leading biomarker of endothelial function. Developing a comprehensive understanding of free radical physiology and measurement limitations in humans will complement my training in noninvasive vascular testing and strengthen the results from my clinical trials of vascular function testing. Dr. Rakesh Patel's, PhD (Consultant), research focuses on nitric oxide and redox cell signaling in the vasculature. As part of his guided training in oxidative stress, I will join the Society for Free Radical Biology and Medicine and attend their yearly meetings. I will attend selected Free Radical Biology Seminars at UAB, offered through the Center for Free Radical Biology. Dr. Patel and I will meet monthly in the first year with the goal of gaining a level of expertise in

measuring oxidative stress in clinical trials. Regular meetings with Dr. Patel will foster future collaborations with basic scientists and promote the sharing of research methods across basic and clinical research fields.

B. Physiologic Measures: Ambulatory blood pressure monitoring (ABPM) for 24-48 hours characterizes the circadian rhythm of blood pressure. Beginning in year 2, I will devote 1 hour a week to reading and interpreting ABPM, which will be overseen by Dr. Calhoun. In addition to training in BP physiology, I will learn a gold standard method for measuring GFR in clinical trials. Beginning in year 3, my monthly meetings with Dr. Allon will be expanded to include training in urine clearance of iothalamate. Both iothalamate measured GFR (mGFR) and 48 hr ABPM will be employed in my proposed research project and potential future R01s.

C. Didactic Coursework: Didactic aspects of the plan have been designed to provide the knowledge and research skills that are needed to meet my overall career goal of becoming and independent clinical investigator. I will build on my ongoing Master's Program coursework with the study of advanced study design and biostatistical methodology. Some of the key courses I will take include:

- **Fundamentals of Clinical Research (EPI 607)**: specific tools for designing and conducting ethically sound clinical trials, integrating epidemiological and biostatistical approaches.
- **Survival Analysis (BST 665)**: Training in Kaplan-Meier estimation, parametric survival models, Cox proportional hazards regression models, competing risks models, and multiple events models.

Dr. Gary Cutter, an expert in clinical trials design and analysis, will serve as Content Expert in these areas.
I will also attend didactic conferences as part of the **Nephrology Research and Training Center's Seminar Series** and the **Vascular Biology and Hypertension Seminars**. These weekly conferences attract basic science and clinical researchers from within and outside UAB to present research focused on projects/experimental strategies that integrate basic concepts and clinical insights into translational research.

D. Professional Development

(i) Intramural Activities. The **Center for Clinical and Translational Science (CCTS) at UAB** provides access to numerous resources through the Research Commons, a physical and virtual hub designed to facilitate the use of programs and services by investigators and trainees. Specific resources that I will utilize during the training period are:

1) **Nascent Project Panels** are multidisciplinary, collaborative groups of expert faculty who engage in targeted discussions to positively impact in-process research plans, applications, and manuscripts.
2) **The Professional Skills Training Program** is an ongoing series that includes practical assistance in the areas of scientific writing, scientific presentations, career development and leadership.
3) **Research Methods and Analysis Seminar Series**, a monthly series which provides secondary datasets available for analysis, fosters networking and collaborations campus- and nation-wide.
4) **Training Interdisciplinary Emerging Research Scholars**, a monthly gathering of postdocs, K Scholars and junior faculty with an interest in an academic translational research career. Its design is to encourage networking and promote collaborative learning, and is guided by senior faculty.

(ii) Presentation of Research and Networking Activities. I will present at a minimum of one to two national conferences per year with abstract submissions to the **American Society of Nephrology (ASN) Kidney Week**, **American Heart Association (AHA) Scientific Sessions**, or **National Kidney Foundation (NKF) Spring Clinical Meeting**. Attending these meetings will allow for oral or poster presentations of my research findings and networking opportunities with leaders in nephrology and vascular research.

E. Mentorship Team: I have organized an experienced, interdisciplinary mentoring team with excellent research credentials that will work together to ensure success with the proposed research project and my development as an independent clinical investigator (Table 2). My Primary and Co-mentors will share the mentoring

Table 2. Expertise and meeting schedule for mentors and consultants

	Areas of Expertise	Meeting Frequency
Primary Mentors		
David Calhoun, MD	Aldosterone physiology, vascular function testing in resistant hypertension, clinical trial design and implementation	Weekly
Michael Allon, MD	Vascular access and function in CKD, K23 & K24 mentoring experience	Monthly
Consultants and Research Facilitators		
Rakesh Patel, PhD	Measures of oxidative stress	Monthly in the 1st year then Quarterly
Anupam Agarwal, MD	Leadership, career and professional development	Quarterly
Gary Cutter, PhD	Statistical methods in clinical trials	Quarterly

responsibilities as outlined below.

(i) Mentors: **Primary Mentor: David Calhoun, MD,** serves as the Medical Director of the Vascular Biology and Hypertension Program and as my primary mentor during my postdoctoral training. He is a worldwide expert in aldosterone excess in resistant hypertension, and his research has been well funded with current NIH R01 funding through 2019. His ongoing studies are investigating the pathophysiology of hypertension refractory to medical therapy, obstructive sleep apnea, and aldosterone excess. These clinical trials have regularly included vascular function testing with published data on over 200 participants. Overall, Dr. Calhoun has a greater than 20 year experience as an independent clinical investigator and provides an ideal role model for a young, developing clinical investigator. He and I will continue to meet weekly to discuss my research projects. He will oversee training in both FMD and ABPM reading and interpretation. Importantly, he will provide ongoing guidance in the management of clinical trials.

Table 3. Benchmarks for candidate evaluation by mentors

Time	Career	Research
6 months	Training in responsible conduct of research	Completion of vascular function training (oxidative stress & FMD)
12 months	Completion of Master's Degree in Biostatistics	Recruitment of 12 participants for Aims 1 & 2
18 months	Participation in TIERS Attend Southern Salt and Water Kidney Club and Society for Free Radical Biology and Medicine*	External evaluation of source documentation and adverse event reporting.
24 months	Submission of 2 research manuscripts in peer reviewed journals Attend Southern Society of Clinical Investigators*	Recruitment of 36 participants for Aims 1 & 2 and 12 for Aim 3
36 months	Oral presentation at ASN Kidney Week and/or AHA Scientific Sessions	Completion of training in ABPM interpretation. Recruitment of 50 participants for Aims 1 & 2 and 20 for Aim 3
48 months	Manuscript submission for Aims 1 & 2 Preparation of R01	Completion of training in iothalamate measured GFR. Recruitment complete for Aims 1 & 2, 30 for Aim 3
60 months	Manuscript submission for Aim 3 Submission/resubmission of R01	Recruitment complete for Aim 3

*In addition to yearly ASN and AHA conferences
ABPM = ambulatory blood pressure monitoring

Co-Mentor: Michael Allon, MD, is a Professor of Medicine in the Division of Nephrology at UAB. He is an expert in clinical trials involving vascular access in the late stages of CKD, with active NIDDK funding investigating fistula non-maturation. He has experience as a patient-oriented research mentor, having held an NIDDK K24 mentoring grant and serving as a K23 Primary Mentor (Ivan Maya). With his mentoring experience, Dr. Allon will ensure that I meet my benchmarks for evaluation (Table 3) and provide the needed support to get back on schedule should unanticipated problems arise. In addition, he will oversee training in clinical nephrology-related research methods including measurement of GFR using iothalamate clearance.

(ii) Consultants and Content Experts: In order to enhance the mentorship of Drs. Calhoun and Allon, I have assembled an advisory team of consultants, content experts, and research facilitators to advise in the research plan implementation, monitor my progress through the career development program, and identify opportunities for the next steps in my research. My advisory team includes:

Anupam Agarwal, MD, UAB Nephrology Division Director. Dr. Agarwal serves as the PI for the NIDDK funded O'Brien Center and will assist with the resources available in the Center including the Biostatistical Core and the Bioanalytical Core for measures of oxidative stress. In addition, he is a leader in nephrology and will provide insights into my career development.

Rakesh Patel, PhD, Professor of Pathology and Chair for the Gordon Research Conferences of Oxygen Radicals, 2016. Dr. Patel researches redox cell signaling pathways involved in the regression of inflammation and their role in chronic inflammatory diseases. He is an expert in measuring nitric oxide metabolites and assessing their role in biological processes, and their therapeutic potential. He will provide expert training in reactive oxygen species and ensure appropriate measurement of oxidative stress in the proposed research project. In addition, he will be instrumental in formulating hypotheses for future RO1 grant proposals.

Gary Cutter, PhD, Professor of Biostatistics and Head of the Section on Research Methods and Clinical Trials. Dr. Cutter is the Biostatistical Resource Director for the O'Brien Center. He is an expert in the design, analysis, conduct, and interpretation of clinical trials and will guide the statistical methods of this research proposal as well as assist in the design of future clinical trials to be proposed as part of an R01 submission.

F. Mentorship Plan: Each of my mentors is committed to my development into an independent clinical investigator. In addition to the individual meetings outlined in Table 2, my entire team will convene every 6 months in the first 2 years and then yearly to evaluate my progress. These group meetings will ensure that I am meeting my career and research benchmarks (Table 3). If I fall behind, meeting frequency will increase, as needed. The goal of these add-on meetings will be to identify the problem(s) impeding my progress and define a plan to get back on schedule.

G. Complementary Activities & Timeline: To complement my research activities, I will devote 20% effort to clinical duties and teaching in the Nephrology Division. This time will be dedicated to a one half day a week outpatient clinic, 4 weeks/year of attending on the renal consult service at UAB, and attending the Nephrology Division journal clubs, and Renal and Medical Grand Rounds.

Table 4. Integrated timeline for career development plan and research activities

Year	Career development activities	Research activities
1st	- Coursework in epidemiology, fundamentals of clinical research, advanced statistical analysis, and responsible conduct of research - Attend weekly didactic research conferences: Nephrology Research and Training Center Seminars, Free Radical Biology Seminars, and Vascular Biology and Hypertension Seminars - Weekly meeting with Dr. Calhoun, monthly meetings with Drs. Allon and Patel, quarterly meetings with Drs. Agarwal and Cutter	- Participant recruitment and data collection, including performing vascular function testing, for Aims 1 and 2. - Frommeyer Fellowship Manuscript submission
2nd	- Attend weekly didactic research conferences: Nephrology Research and Training Center Seminars, Free Radical Biology Seminars, and Vascular Biology and Hypertension Seminars - Continue weekly meeting with primary mentor, monthly meetings with co-mentor, and quarterly meetings with collaborators.	- Participant recruitment and data collection, including performing vascular function testing for all 3 Aims.
3rd	- Attend weekly didactic research conferences: Nephrology Research and Training Center Seminars, Free Radical Biology Seminars, and Vascular Biology and Hypertension Seminars - Continue weekly meeting with primary mentor, monthly meetings with co-mentor, and quarterly meetings with collaborators - Presentation at UAB's Vascular Biology and Hypertension Seminars	- Continued participant recruitment for all 3 Aims. - Preliminary data analysis - Abstracts submitted to national conferences
4th	- Continue weekly meeting with primary mentor, monthly meetings with co-mentor, and quarterly meetings with collaborators - Attendance and presentation at ASN Kidney Week - Attendance and presentation at AHA Scientific Sessions - Attend weekly didactic research conferences: Nephrology Research and Training Center Seminars, Free Radical Biology Seminars, and Vascular Biology and Hypertension Seminars	- Study completion of Aims 1 & 2. - Manuscript(s) for Aims 1 & 2 prepared - grant submission to the ASN – Carl Gottschalk award - Preparation and submission of an R01 Award
5th	- Attendance and presentation at ASN Kidney Week - Attendance and presentation at AHA Scientific Sessions - Continue weekly meeting with primary mentor, monthly meetings with co-mentor, and quarterly meetings with collaborators	- Study completion of Aim 3. - Manuscript for Aim 3 prepared -Revision and resubmission of R01 Award

2. CAREER GOALS AND OBJECTIVES: My long-term goal is to become an independent clinical investigator and a leader in the field of vascular function as it relates to CKD and hypertension. My experiences as a postdoctoral clinical researcher have provided me a foundational level of competence in performing clinical trials that are designed to answer specific physiologic questions. My ongoing coursework in biostatistics and clinical trial design has advanced my skills of data analysis and understanding of bias and power as it relates to trial design. In order to continue progress toward achieving my career goals, I need to develop expertise in four additional content areas: (1) vascular function testing, (2) advanced study design and biostatistical methodology, (3) recruitment and performance of clinical trials and (4) focused mentorship and career development through the UAB Center for Clinical and Translational Science's Training Interdisciplinary Emerging Research Scholars (TIERS). My mentors and I have developed a detailed career development plan to fill these gaps with additional training and mentored research experiences that will allow me to successfully transition into an independent clinical investigator. A K23 award is a vital component to my continued, upward career trajectory and offers the ideal mechanism to transition towards independence. Under the mentorship of Drs. Calhoun (Primary Mentor) and Allon (Co-Mentor), experts in vascular function testing and conducting clinical trials, I will perform original research in the vascular physiology of CKD. Results from my research proposal will offer insights into therapeutic targets for patients with CKD and, importantly, create the background for an R01 proposal.

RESUBMISSION MODIFICATIONS

Introduction: We thank the reviewers for their careful review and excellent suggestions. We are encouraged by the impact score of and their comments … "The research proposal is clinically relevant … The research plan has good training potential … Research is logical, relevant, and achievable … Outstanding mentor, co-mentor, and consultants." **Based on recommendations by the reviewers we have revised the application with changes to the Career Development Plan and Research Strategy denoted by vertical line along the left margin and referenced in our responses below.**

1) Mentorship Team *"The mentorship plan should be strengthened and more clearly outlined…Except for weekly meetings with primary mentor, the frequency of individual meetings … is not defined. Also, annual mentorship team meetings are insufficient…No description of evaluation plan…Dr. Allon's complementary role in providing expertise … is unclear…Overlap with his primary mentor R01."*

Response: A separate mentorship plan section has been added, which includes (i) a timetable of benchmarks for candidate evaluation during each of the team meetings (ii) a contingency strategy of add-on meetings to address unmet benchmarks, and (iii) better defined mentor roles with meeting times **(Section 3.F. & Tables 2 & 3).** Individual meeting times have been outlined in Table 2. Mentorship team meetings have been increased to every 6 months in the first 2 years with benchmarks for candidate evaluation at these time points outlined in Table 3. Meeting frequency will increase if the candidate is falling behind **(Section 3.F & Tables 2 & 3).** Benchmarks for mentors to evaluate the candidate's progress have been detailed in a table of career and research timelines **(Section 3.F, Table 3).** Dr. Allon will oversee training in clinical nephrology-related research methods including GFR measurements. His mentoring experience will be especially valuable during add-on meetings when a trajectory change in the candidate's career or research is needed **(Section 3.F).** Dr. Calhoun's current R01 focuses on refractory hypertension and has no overlap with this proposal **(Calhoun Biosketch).**

2) Training Plan *"…research activities timeline is without details regarding completion of specific aims within the timeline…It is unclear how much time will be dedicated to learn how to measure the FMD with ultrasound…The laboratory training plan in biomarkers is not well described."*

Response: Thank you. Recruitment goals for each aim have been added in Table 3 and completion further clarified in Table 4 **(Sections 3.E & 3.F).** The 1st 3 months of year 1 are dedicated to training in the measurement of FMD with Doppler flow **(Section 3.Ai).** The biomarker section has been narrowed to focus on markers of oxidative stress and the training plan outlined in **Section 3.A.ii.** as well as in **Dr. Rakesh Patel's letter**. Training in ambulatory blood pressure monitoring and GFR has been added **(Section 3.B).**

3) Research Strategy: *"The project has some critical design flaws…Patients with diabetes per se usually have endothelial dysfunction ...The inclusion of well-controlled diabetic patients, despite the paired analysis, may lead to variability…The cut-off values for each of the biomarkers selected were not reported…Lack preliminary ROC analysis, in at least a few of the selected biomarkers… Methods and assays for measuring biomarkers are not mentioned and can be critically-important. A table with the various methods/techniques should be included…Small changes in FMD (2%) will be considered biological significant, and it is unclear how the presence/absence of diabetes, other anti-HT medications, caffeine, tobacco, etc., will affect these measurements…Aim 3, many confounding variables can affect the outcome of proteinuria independently of the spironolactone treatment…Inclusion of time control studies for FMD are not mentioned or planned… The research plan is too limited to be turned into an R01 and the small sample size may not take the entire funded period to complete."*

Response: Thank you for these concerns. Diabetic patients have been excluded (Table 5). Biomarker measurements have been focused to markers of oxidative stress, and plasma and urine F_2-isoprostanes will be measured by liquid chromatography tandem-mass spectrometry with accuracy and precision included in **Section 4.C.1.2.2.** Participants will be contacted 1-2 days prior to FMD measurement to limit potential confounders on the morning of FMD measurement **(Section 4.C.2.1.5).** In CKD, FMD measurements range from 0 to 8%; therefore a change in FMD by 2% is considered significant **(Section 4.C.2.1.3.1).** Aim 3, the statistical analysis has been changed to include treatment group as a covariate in the general linear model and the number of potential adjusted covariates increased to 6 in the sample size calculation **(Sections C.4.1.3 & C.4.1.4).** The crossover study design will minimize unmeasured confounders. Time control studies have been previously performed, and 5 minute occlusion has been adopted as the standard time [18]. ABPM and GFR have been added to Aims 3 and sample sizes expanded to 58 and 42 participants **(Section 4.D).**

Additional revisions include clarification of the choice of amiloride as the active control **(Section 4.B.2.1)** and a diagram describing the proposed methods for assessing endothelial function **(Figure 1).**

SUMMARY STATEMENT

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(Privileged Communication) ***Release Date:*** **04/14/2015**

Application Number: **1 K23 DK102660-01A1**

Principal Investigator

JUDD, ERIC K MD

Applicant Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Review Group: **DDK-D**
Kidney, Urologic and Hematologic Diseases D Subcommittee

Meeting Date: **03/03/2015**
Council: **MAY 2015**
Requested Start: **07/01/2015**

RFA/PA: **PA14-049**
PCC: **KTR KTR**

Project Title: **Vascular effects of mineralocorticoid receptor antagonism in kidney disease.**

SRG Action: **Impact Score:**
Next Steps: **Visit http://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**
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1		
2		
3		
4		
5		
TOTAL		

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.

ADMINISTRATIVE NOTE

SCIENTIFIC REVIEW OFFICER'S NOTES

RESUME AND SUMMARY OF DISCUSSION: This resubmission application was submitted in response to program announcement PA14-049 entitled “Mentored Patient-Oriented Research Career Development Award (Parent K23)”. The overall goal of these clinically relevant studies is to examine: (1) the effects of the mineralocorticoid receptor antagonist, spironolactone, on endothelial cell function, and (2) the contribution of endothelial dysfunction to albuminuria in patients with chronic kidney disease. Previously noted strengths such as the well-trained candidate; an outstanding team of mentors with complementary expertise; and the outstanding environment remain. The candidate has addressed previous concerns and has significantly improved the career development plan. The modified research plan is better focused and logical. However, preliminary data are still lacking and overall recruitment goals and outcome of the study are somewhat uncertain. Modest institutional commitment to the candidate and lack of recent research publications are also concerning. The strengths outweigh the weaknesses and, overall, this application is the excellent to outstanding range.

DESCRIPTION (provided by applicant): This is an application for a K23 award for Dr. Eric Judd, a nephrologist at the University of Alabama at Birmingham. Dr. Judd proposes a novel treatment pathway for chronic kidney disease (CKD), and his long-term career goal is to become an independent clinical investigator devoted to identifying and/or developing CKD-specific therapies. This award will allow Dr. Judd the resources and protected time to achieve the following career development goals: (1) to become an expert in endothelial and vascular function in CKD; (2) to implement advanced biostatistical methods in clinical trials (3) to become an independent, translational clinical investigator in the fields of vasculature and CKD. To achieve these goals, Dr. Judd has assembled a mentoring team comprised of a primary mentor, Dr. David Calhoun (an expert in vascular function testing including ultrasound assessment of flow-mediated dilation (FMD) and aldosterone physiology), a co-mentor, Dr. Michael Allon (an expert in clinical trials and vascular access in the late stages of CKD), and 3 content experts: Dr. Anupam Agarwal, PI for the NIDDK funded O’Brien Center at our institution; Dr. Rakesh Patel, an authority in measuring oxidative stress as a marker of endothelial function; and Dr. Gary Cutter, an expert in the statistical methods in clinical trials. Vascular endothelial dysfunction increases cardiovascular (CV) risk and contributes to the progression of CKD. Mineralocorticoid receptor (MR) antagonists have been shown to improve endothelial function, as well as decrease CV mortality and proteinuria. The specific biochemical pathways that produce these pharmacological effects for MR antagonists, however, are poorly understood. Dr. Judd will investigate the effect of MR antagonism on endothelial function in patients with moderate (stage III) CKD by performing a randomized, controlled trial. Three specific aims are proposed: Aim 1: To determine if spironolactone improves endothelial function as compared to amiloride in patients with stage III CKD; Aim 2: To determine if oxidative stress is associated with changes in endothelial function by spironolactone compared to amiloride in patients with stage III CKD; and Aim 3: To determine if endothelial dysfunction contributes to albuminuria in patients with stage III CKD. Relevance: A better understanding of the mechanisms of kidney function decline in CKD could lead to important interventions and prevention strategies, translating into alleviating patient suffering, caregiver burden, and health care costs.

PUBLIC HEALTH RELEVANCE: A better understanding of the mechanisms of kidney function decline in chronic kidney disease could lead to important interventions and prevention strategies, translating into alleviating patient suffering, caregiver burden, and health care costs.

CRITIQUES

(Note: The critiques below were prepared by the reviewers assigned to this application. These commentaries and criterion scores do not necessarily reflect the position of the authors at the close of the group discussion, nor the final majority opinion of the group, although reviewers are asked to amend their critiques if their position changed during the discussion. The resume and other initial sections of the summary statement are the authoritative representation of the final outcome of group discussion. If there is any discrepancy between the peer reviewers' commentaries and the priority/impact score on the face page of this summary statement, the priority/impact score should be considered the most accurate representation of the final outcome of the group discussion.)

CRITIQUE 1:

Candidate:

Career Development Plan/Career Goals:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Environment Commitment to the Candidate:

Overall Impact: This is an interesting revised application submitted by a strong candidate who wishes to explore the role of aldosterone antagonist as a novel treatment for endothelial function in patients with stage III CKD. The central hypothesis is that MR antagonism will have a direct, beneficial effect on endothelial function in patients with stage III CKD. The candidate has been responsive to previous criticisms. A separate mentorship plan section has been added to the proposal providing a timetable of benchmarks for candidate evaluation and more frequent meetings with the mentorship team. More training time has been dedicated to learn how to measure FMD, ambulatory BP, and GFR measurements. The research plan has improved, diabetic patients were excluded, the biomarker section has been narrowed to focus on markers of oxidative stress, the methodology is described in more depth, patients will be contacted 1- 2 days prior to the FMD measurements, the sample size was expanded, and the statistical analysis was improved. The mentors, resources, and environment are all outstanding to pursue this project. The research plan continues to have some limitations, is missing preliminary data to support feasibility, and the institutional commitment to the candidate appears to be modest. Overall, the application has improved and is supported with more enthusiasm.

1. Candidate:

Strengths

- The candidate has high potential for developing into a productive independent scientist.
- Outstanding medical training, MD from LSU, residency (Internal Medicine), Fellowship (Nephrology) all from the UAB.
- Seven publications as a first author, including, 2 book chapters, case reports, and clinical reviews related to hypertension.
- Funded by a T32 to study a similar topic in patients with obstruct sleep apnea and resistant hypertension.
- He is completing a Master's Program and taking formal coursework in epidemiology and biostatistics

Weaknesses

- No original publications related to the current proposal, and none since the last submission.

2. Career Development Plan/Career Goals & Objectives:

Strengths

- The research proposal aims to describe the potential connection between the vasculature and CKD, namely through the demonstration of the beneficial effects of aldosterone antagonism on endothelial function in patients with stage III CKD
- The candidate will receive good training in endothelial and vascular functioning and GFR measurements, acquire experience in clinical trials, develop a more comprehensive understanding of free radical physiology, and undertake didactic coursework to gain knowledge in advanced study design and biostatistical methodology.

- Plan to develop additional professional skills such as grant writing, networking, and improved his communication skills and further career development through the UAB Center for Clinical and Translational Science's Training Interdisciplinary Emerging Research Scholars (TIERS).
- In the revised proposal the training plan is described in clearer manner.
- Additional meeting have been planned to assure that all mentors are committed to facilitate the transition to become an independent clinical investigator.

Weaknesses

- None noted

3. Research Plan:

Strengths

- The research proposal aims to address a clinically relevant topic of research.
- The central hypothesis is that MR antagonism will have a direct, beneficial effect on endothelial function in patients with stage III CKD.
- The research plan will attempt to answer important questions 1) whether spironolactone improves endothelial function as compared to amiloride in patients with stage II CKD; 2) determine if oxidative stress is associated with changes in endothelial function by spironolactone compared to amiloride in these patients; 3) define whether endothelial dysfunction contributes to albuminuria in patients with stage III CKD.
- In Aim 1, fifty-eight participants (enrolled over 4 years) will undergo endothelial function assessment using brachial artery dilation by ultrasound assessment of flow-mediated dilation (FMD) before and after spironolactone or amiloride use.
- Aim 2 will test the hypothesis that urine levels of F2-isoprostanes decrease following treatment with spironolactone when compared to amiloride, and in correlation with changes in endothelial function.
- Aim 3 will determine if endothelial dysfunction contributes to albuminuria in patients with stage III CKD. Here improvements in FMD following study medication will be associated with decreases in albuminuria, after adjusting for treatment group, changes in GFR, and changes blood pressure.
- The crossover study design is a strength of the proposal.

Weaknesses

- Spironolactone-mediated natriuresis and BP effects may be the predominant factor improving endothelial function, and the proposed approach might not be able to isolate the vascular effects of spironolactone per se.
- It might be difficult to interpret the data related to F2-isoprostanes as a marker of endothelial dysfunction without comparing the results with other well established markers of endothelial dysfunction.
- Preliminary data showing the sensitivity or specificity of F2-isoprostanes to detect endothelial dysfunction, relative to the gold standards are missing.

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

Strengths

- The primary mentor, Dr. David Calhoun, is a Professor of Medicine in the Vascular Biology and Hypertension, University of Alabama at Birmingham and Medical Director of the UAB Hypertension Program.
- He is a worldwide expert in aldosterone excess in resistant hypertension, and the PI of one R01 grant that has been renewed last year. He is also a co-investigator in other NIH grants (P50, P60, etc.).
- Co-mentor, Dr. Allon, a Professor of Medicine in the Division of Nephrology at UAB, is an expert in vascular access in the late stages of CKD, with active NIDDK funding that has to be renewed this year.
- He has experience as a patient-oriented research mentor, having held an NIDDK K24 mentoring grant and serving as a K23 Primary Mentor (Ivan Maya).
- Dr. Agarwal, Senior Vice President for Medicine, Dean of the School of Medicine, and PI for the NIDDK funded O'Brien Center at UAB, will assist with the resources available in the Center, including the Biostatistical Core and the Bioanalytical Core for markers of endothelial function.
- Rakesh Patel, PhD, a Professor of Pathology, will provide expert advice to measure inflammatory markers and NO.
- Gary Cutter, PhD, will provide training in statistics.

Weaknesses

- Dr. Patel's CV, who will play a critical role in the training and assessment of biomarkers is not included in the application, and his funding status is unknown.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Outstanding environment to pursue clinical research in hypertension.

Weaknesses

- A letter from the Director of the Division of Nephrology and the Chair of the Department of Medicine written for the 1st submission stated that the candidate was going to be offered a full time tenure track position as an Assistant Professor of Medicine on July 1st, 2014, independent of his recipient of the current Career Development Award. Nonetheless, the candidate continues to be an instructor.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- All topics well discussed

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C3A - No Children Included, Acceptable

- All topics are well covered

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Resubmission:

- Responsive to previous criticisms.

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Appropriate

Comments on Subject Matter (Required):

- Appropriate

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- Appropriate

Comments on Duration (Required):

- Appropriate

Comments on Frequency (Required):

- Appropriate

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

- The budget does not include the measurements F2-isoprostanes and it is unclear how these studies will be funded, since they are not discussed in Dr. Patel's letter of support either.

CRITIQUE 2:

Candidate:

Career Development Plan/Career Goals:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Environment Commitment to the Candidate:

Overall Impact: Excellent candidate with outstanding investigative resources and a relevant rigorously-planned clinical trial to investigate vascular biology in CKD. In this revised application, the candidate sufficiently addresses concerns of previous reviewers by providing a strong career development plan, clarification of mentor roles and much more cohesive research plan.

1. Candidate:

Strengths

- Confirming his scientific potential, the applicant has been awarded a competitive institutional *Investigative Medicine* fellowship to study vascular biology in Liddle's Syndrome with primary mentor since last review
- He has added one first author publication since last submission

Weaknesses

- None noted

2. Career Development Plan/Career Goals & Objectives

Strengths

- Timeline and benchmarks are well outlined in this revision
- Mentorship plan, skill set development and coursework are clearly-outlined.

Weaknesses

- None noted

3. Research Plan:

Strengths

- The applicant provided adequate clarifications on study design to isolate effects of MR antagonism on endothelial function. Overall, the study design is quite rigorous.
- The applicant will now exclude patients with diabetes
- The use of ABPM and mGFR are well-justified.
- The more-focused approach to measure F2-isoprostanes as a marker of oxidative stress is an improvement in the study design

Weaknesses

- Concerned that final recruitment is still on-going in year 5, not allowing significant time for manuscript preparation and submission prior to the end of the funding period
- Although the applicant justifies the 2% change in FMD based on the range in CKD, this argument would have been strengthened by the inclusion of reproducibility data from the applicant's supervised measurements in preliminary data or, at least, from the mentor's lab.
- How ADMA levels will be interpreted in studies is unclear.

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

Strengths

- The applicant has clarified the role of Dr. Allon in providing general guidance in nephrology-specific clinical research development, which will complement Dr. Calhoun's expertise in vascular biology

Weaknesses

- None noted

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Excellent environment with significant access to O'Brien Center, CTSA, hypertension center and nephrology division research resources

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 21: Including ages < 21 justified scientifically

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Training in the Responsible Conduct of Research:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Candidate:

Career Development Plan/Career Goals:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Environment Commitment to the Candidate:

Overall Impact: The applicant for this K23 award is Eric Judd, MD, an Instructor in the Division of Nephrology at the University of Alabama (UAB). The overall objectives of the proposal are to investigate the effect of mineralocorticoid receptor (MR) antagonism on endothelial function in patients with stage 3 CKD. This application is a resubmission of a grant which was reviewed in March 2014 and given a score of . Concerns of the initial review were focused on the career development plan (lack of re timeline and evaluation of candidate's progress) and research plan (regarding study design and analytic approaches). Concerns of the initial review are for the most part well addressed Strengths of the resubmitted application include the excellent candidate, the strong team of mentors, and a research plan focused on an area of significance which leverages the extensive resources at UAB. Limitations include a relatively low number of primary research publications despite several years of research fellowship/training and lack of primary research publications with his primary mentor with whom he has worked since 2011. In the research plan, the aim focused on measures of oxidative stress (Aim 2) is not clearly articulated and is dependent on finding positive findings in Aim 1. In addition, no information is provided regarding previous mentoring experience of the primary mentor.

1. Candidate:

Strengths

- Eric Judd, MD, is an Instructor in the Division of Nephrology at UAB. He is well trained (MD Louisiana State University, residency and fellowship UAB). He was on a T32 training grant in vascular biology and hypertension from 2011-2014 and has received support from an

institutional fellowship in investigative medicine since 07/2013. Letter from the Division Chief states that in July 2015, he will be appointed as an Assistant Professor. He is pursuing a MS in biostatistics. He has ten publications and is first author on all of these.

- The letters of support for Dr. Judd are all exceptionally strong. He is well regarded by the UA faculty.

Weaknesses

- Dr. Judd has had very few if any primary research publications despite being on T32 for three years and support from an institutional fellowship in investigative medicine since 07/2013. The publications listed are reviews, case reports and two book chapters. He does have retrospective study derived from chart review regarding pneumonia in dialysis patients. Of further concern is that there have been no primary research publications with the primary mentor despite working together since 2011.
- Enrolled in Master's since start of second year of postdoctoral training but provides conflicting information re: expected completion; in Biosketch states May 2015 but on page 50 states May 2016.

2. Career Development Plan/Career Goals & Objectives

Strengths

- The career development plan is well developed. Learning objectives, timeline, and benchmarks are well delineated. The planned didactic coursework are linked to the research activities and will advance the applicant's knowledge and skillset.

Weaknesses

- None noted

3. Research Plan:

The research has three specific aims: 1) To determine if spironolactone improves endothelial function as compared to amiloride in patients with stage III CKD; 2) To determine if oxidative stress is associated with changes in endothelial function by spironolactone compared to amiloride in patients with stage III CKD; and 3) To determine if endothelial dysfunction contributes to albuminuria in patients with stage III CKD.

Strengths

- The proposal is focused on an area of significance.
- The proposal leverages resources available at UAB.

Weaknesses

- Aim 2 focusing on the potential role is oxidative stress is not clearly written. From the manner in which the aim is stated and the statistical plan it is not clear which of the covariates are predictors and which are outcomes. In addition, Aim 2 is dependent on finding a positive outcome in Aim 1 (i.e., that treatment with MR antagonist will be associated with an improvement of endothelial function).
- No justification for measurement of GFR in Aim 3 is provided. There is accumulating literature suggesting that estimated GFR would be sufficient. Need to provide stronger rationale for measuring GFR since this adds to participant burden and cost.
- Investigator may have underestimated the percentage of drop-out since the 12 week protocol is somewhat burdensome.
- References cited are incorrectly numbered in the introduction to Specific Aims on page 66.

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

Strengths

- The applicant has assembled a strong multidisciplinary team of mentors and consultants, including Drs. David Calhoun (primary mentor, expertise in vascular biology and resistant hypertension), Michael Allon (co-mentor, vascular access in advanced CKD), Anupam Agarwal (vascular biology), Radesh Patel (redox signaling pathways), and Gary Cutter (biostatistics).
- Dr. Calhoun is well-funded investigator. Dr. Allon had a K24 in the past and has worked with two K23 recipients.

Weaknesses

- Mentor letters do not detail their previous experience with mentoring in their letter of support. No information regarding primary mentors track-record as a mentor
- As mentioned, it is concerning that the candidate does not have a substantial number of primary research publications with Dr. Calhoun despite working with him since June 2011.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The environment at UAB is exceptional
- Statement from department chair demonstrates a strong institutional commitment to the candidate.

Weaknesses

- In previous submission, it was stated that appointment to Assistant Professor would occur in July 2014 but in this version it states will occur in July 2015.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- Risks and protections are adequately discussed and addresses.
- Recommend describing incentives planned for participants.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- Adequately detailed.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Issues related to inclusion of women, minorities, and children were adequate.

Vertebrate Animals:

Not applicable.

Resubmission:

- See overall impact paragraph. In general, concerns in the initial review were adequately addressed.

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Well described.

Comments on Subject Matter (Required):

- Subject matter delineated.

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- Described.

Comments on Duration (Required):

- Adequately described.

Comments on Frequency (Required):

- Described

Resource Sharing Plans:

Not Acceptable

- Not included.

Budget and Period of Support:

Recommend as requested.

- The budget justification is detailed and well written.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWER'S 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

SCIENTIFIC REVIEW OFFICER'S NOTES:

The plans outlined in the application to obtain training in the responsible conduct of research are adequate to satisfy this requirement.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Recommended direct cost levels are estimated and are subject to further adjustment based on the Institute's standard budget calculation practices.

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

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NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
DDK-D 1
March 03, 2015 - March 05, 2015

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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.