A. CANDIDATE'S BACKGROUND

I am committed to an academic research career as an independent investigator and leader in identifying and understanding the role of glycemic markers and metabolomics in diabetes and the development of microvascular and macrovascular complications. To foster my independence in this research area, I propose to 1) measure nontraditional glycemic markers (glycated albumin, 1,5-anhydroglucitol, and fructosamine) in a prospective cohort study, 2) investigate their role in the development of diabetes and albuminuria, 3) explore potential racial differences in these markers and their association with diabetes and albuminuria, and 4) explore the relation of targeted metabolites with these glycemic markers. This research area is important and addresses key scientific gaps outlined in the interagency Diabetes Research Strategic Plan, including identifying nontraditional biologic risk factors and exploring the contributing factors to racial disparities in diabetes and its complications. My prior training and research experience have helped me to begin my career in health research and the training and mentoring that I will receive during this Mentored Research Scientist Development Award will allow me to marry my experience in epidemiology to training in glycemic markers and metabolomics to develop an independent research program in diabetes and its complications and successfully compete for R01 funding.

My research career began during my freshman year of college when I was selected to participate in an undergraduate research apprenticeship program. My research project was based in a pharmacology lab where I investigated racial and gender differences in vascular responses to medications using vein tissue collected from coronary artery bypass grafting surgery. I worked on this project for two years and had the opportunity to learn about proper laboratory procedures, research protocol development, and present my findings at a national conference. During the latter years of my undergraduate program, I expanded my research experience beyond the laboratory and worked on several public health projects to implement cardiovascular disease prevention programs in underserved communities. This formative research experience introduced me to public health and led me to pursue graduate degrees in epidemiology.

The extensive training in research methods and data analysis that I received while earning my master's and doctoral degrees in epidemiology at the University of North Carolina at Chapel Hill has provided the necessary foundation for me to be able to lead the proposed research project and advance my development as an independent investigator. During my training, I completed secondary data analyses of multi-site research studies, national disease registries, and administrative datasets in which I utilized various statistical methods including categorical data analysis, survival analysis, and multiple imputation. I gained experience in the interpretation of results, writing manuscripts, and responding to reviewer comments and was able to have 5 manuscripts published as a graduate student (1 as first author). After earning my doctoral degree, I completed a one year post-doctoral fellowship which allowed me to further hone my skills in secondary data analysis and prepare manuscripts for publication. Unfortunately, I was unable to complete additional post-doctoral research training because of a family matter that required me to relocate to Alabama. After relocation, I accepted a position with the Alabama Department of Mental Health where I was responsible for training community partners in data entry, leading the statewide epidemiological outcomes workgroup, and preparing reports analyzing data trends. I implemented several community initiatives during my time as the first Epidemiologist in my division; however many of the programs that were regularly funded were not evidence-based and did not have formal evaluation processes in place. This real world experience exposed a fundamental gap between public health practice and evidence-based research that led me to return to academia to become actively involved in scientific research again.

My prior research experience focused on cardiovascular disease. Because cardiovascular disease remains the leading cause of death in the US and its risk is increased among people with diabetes, I intend to focus my research area training to gain expertise in glycemic markers, metabolomics, and their role in the development of diabetes and microvascular complications. This training will complement my prior experience and help foster my research independence. Since I joined the University of Alabama at Birmingham (UAB) as an Assistant Professor in the Department of Epidemiology, I have been actively engaged in several projects that have resulted in 5 published manuscripts (2 as first author) and 3 manuscripts in preparation (2 as first author) related to diabetes and its complications. Also, I was 1 of 6 awardees selected from a field of 43 applications to receive pilot funding in 2011 from the UAB Diabetes Research and Training Center (P60DK079626). This pilot funding is currently supporting my work to develop a longitudinal measure of glycemic control that incorporates multiple measurements of hemoglobin A1c over time and assesses its association with nephropathy and all-cause mortality in an underserved population. While I have learned much about

hemoglobin A1c and diabetes on these projects, I realize there is much more that I need to learn about glycemic markers, microvascular complications, and metabolic profiles in order to attain research independence in this area.

This Mentored Research Scientist Development Award will allow me to devote 75% of my full-time professional effort to research training and career development activities in addition to being mentored by senior investigators. My mentors will be Cora E. Lewis, MD, MSPH (primary mentor), W. Timothy Garvey, MD (co-mentor), and Paul Muntner, PhD (co-mentor). These internationally-recognized scientists will provide subject matter expertise and assist with my professional development towards research independence. Additionally, Elizabeth Selvin, PhD will be a key collaborator and will provide subject matter expertise. This award will convene an excellent team of mentors and scientists and serve to fill important gaps in my training related to the pathophysiology of diabetes and renal complications, risk prediction methods, metabolomics, and data collection and study management that I will need in order to attain my career goal to become an independent investigator.

B. CAREER GOALS AND OBJECTIVES

My career goal is to become an independent investigator and leader in diabetes research and its microvascular and macrovascular complications, focusing on the role of glycemic markers and metabolomics in the risk prediction of diabetes and its complications. To achieve this goal, there are four important areas where I require additional training, mentoring, and experience: (1) pathophysiology of diabetes and renal complications, (2) advanced statistical methods in risk prediction, (3) metabolomics, and (4) direct experience conducting/overseeing recruitment of research participants, data collection, and study management. As described briefly below, this scientist development award will address these four areas for my development.

This proposal includes 2 research projects to enhance my career development. Research Project 1 will consist of analyzing stored specimens from CARDIA participants to investigate the association of glycated albumin, 1,5-anhydroglucitol, and fructosamine with diabetes and albuminuria and investigate racial differences in these nontraditional glycemic markers. Training in pathophysiology and risk prediction statistical methods will support the completion of this research project. Expertise in the pathophysiology of diabetes and the role of the different glycemic markers in the development of renal disease will build on my prior research training in cardiovascular disease epidemiology and help me to establish my research independence in diabetes research. The advanced statistical training in risk prediction models that I will receive will allow me to gain the skills needed to develop and evaluate the performance of risk prediction models and assess the role of glycemic markers in risk prediction of diabetes and renal disease. Research Project 2 will consist of an independent research project that will include the recruitment of adults with type 2 diabetes from the Birmingham, AL area for a pilot study to assess the relation of targeted metabolites with traditional and nontraditional glycemic markers. Training in metabolomics and research recruitment and study management will be obtained from this research project. Metabolomics training is important for understanding metabolic pathways and the relation of traditional and nontraditional glycemic markers with specific metabolite profiles, which could be informative for risk stratification and identifying underlying mechanisms. The pilot study that I will conduct as part of this scientist development award will allow me to gain experience and training in metabolomics in addition to providing practical experience for me in participant recruitment, data collection, and study management. My prior experience has primarily been secondary data analyses, but to answer some of the research questions that I may address in future research directions, I anticipate that I will need new data that will require skills in primary data collection. Additionally, few epidemiologists have metabolomics expertise and this will provide me with the skills needed to lead larger investigations of metabolomics within epidemiologic studies. All of these training areas are essential for my success as an independent investigator in diabetes research and its complications.

During the requested **three-year** scientist development award, I will have protected time for all of these training activities that will position me to become an independent investigator conducting studies of glycemic markers, metabolomics, and vascular complications. I will be able to gain training in diabetes and renal pathophysiology, risk prediction methods, and metabolomics, while also collecting and analyzing data for my pilot study and increasing my peer-reviewed publications. The findings from this research will be used in subsequent submissions of externally funded grants to investigate the association of nontraditional glycemic markers with retinopathy, chronic kidney disease markers (e.g., eGFR, cystatin c), and macrovascular disease; investigate the use of nontraditional glycemic markers for risk stratification in clinical settings; and evaluate the

relation of glycemic markers, metabolomic profiles, and microvascular outcomes. This scientist development award will be the catalyst for me to successfully obtain external funding and attain research independence.

C. CAREER DEVELOPMENT/TRAINING ACTIVITIES DURING AWARD PERIOD

The protected time provided by this scientist development award will foster my development as an independent investigator by focusing on four areas of training: 1) pathophysiology of diabetes and renal complications; 2) risk prediction statistical methods; 3) metabolomics; and 4) direct experience in research recruitment, data collection, and study management. The training activities for this scientist development award are expanded upon in Table 1 and the ensuing text.

Table 1 — Planned Didactic Coursework for Dr. Carson's Scientist Development Award

Training	Course Description
Goal 1: Pathophysiology of Diabetes and Renal Complications	
Kidney, Heart, and Lung Systems (GBS 751)	Course (2 credits) will provide a comprehensive introduction to integrative physiology and pathobiology of renal disease (sub-modules include cardiovascular and respiratory systems). Course will explore fundamental principles and mechanisms modulating normal and abnormal function of the kidney and examine numerous disease states including albuminuria and chronic kidney disease. **(To be taken Spring Semester of Year 1)**
Endocrine, Gastrointestinal, and Immune Systems (GBS 752)	Course (2 credits) will examine the physiology and pathobiology of the endocrine system (sub-modules include gastrointestinal tract and immunology). Course will explore how the endocrine system integrates homeostasis of multiple organ systems through a comprehensive approach and the mechanisms and consequences of endocrine dysregulation. **(To be taken Spring Semester of Year 1)**
Introduction to Diabetes and Obesity Epidemiology (JHU 340.644.11)	Course (2 credits) will examine diabetes, obesity, and associated complications. Course will explore methodological issues associated with evaluating these in epidemiologic studies, environmental and genetic risk factors, as well as interventions to improve diabetes outcomes and weight management. (Course given by Johns Hopkins Graduate Summer Institute: **To be taken Summer of Year 1**)
Goal 2: Advanced Statistical Methods in Risk Prediction Models	
Risk Assessment and Evaluation of Predictions (BST 795)	This graduate course (1 credit) will cover the development and evaluation of prediction models, risk reclassification methods, and individualized disease risk prediction. (**To be taken Fall Semester of Year 1**)
Design and Analysis of Biomarker Studies for Risk Prediction (Short course)	Short course will introduce recent statistical developments for constructing and evaluating risk prediction models. Topics will include an overview of emerging technologies and the incorporation of biologic specimen data into risk prediction models. (Workshop given by Joint Statistical Meeting: **To be taken Summer of Year 1**)
Goal 3: Metabolomics	
Biochemistry/Metabolism (GBS 707)	Course (2 credits) provides an in-depth investigation of the principles of biological chemistry, particularly as they relate to research protocols and performance. Topics include glycolysis, lipid metabolism, amino acid metabolism, integration of metabolism, and use of mass spectrometry. (**To be taken Fall Semester of Year 1**)
Metabolomics (Short course)	This NIH-funded (R25) course is hosted by the UAB Targeted Metabolomics and Proteomics Lab and will provide an in-depth review of metabolomic profiling, including use of NMR and LC-MS, clinical applications of metabolomics, bioinformatics, quality control, and data analysis. (**To be taken Summer of Year 2**)
Statistical Bioinformatics (BST 676)	Course (3 credits) will cover the analysis of data generated by high throughput genomic technologies, as well as issues in the experimental design and implementation of these technologies. High throughput technologies that will be covered include metabolomics. (**To be taken Summer of Year 2**)
Goal 4: Research Recruitment, Data Collection, and Study Management	
Overview of Research Study Operations and Management (CRM 671)	Course (3 credits) will provide an in-depth review of a broad range of issues related to the planning, implementation and evaluation of research studies**.** Topics include responsibilities, expertise and tasks of research team members, organizational and logistical issues, data management tools, implementation of quality assurance measures, and specimen repository tracking. (**To be taken Summer of Year 1**)

1. *Advanced understanding of the pathophysiology of diabetes and renal disease.* I have formal training in cardiovascular disease, but I have very limited training in diabetes and renal disease. The proposed training will prepare me to identify and understand underlying mechanisms related to glycemic markers and diabetes and their relation to renal disease. As part of my training activities for this area, I plan to take graduate-level courses (Table 1). Also, I will participate in the UAB Diabetes Research and Training Center monthly seminars and the UAB Nephrology Research and Training Center monthly seminars.

2. *Advanced statistical methods in risk prediction model development and application.* Epidemiology is transitioning from identifying risk factors and outcome associations to investigating how risk factors contribute to disease prediction. There have been several recent developments in the statistical approaches used for risk prediction and additional statistical training in risk prediction models is needed for

my career development. Risk prediction skills will be useful for comparing the performance of the different glycemic markers in my research. Recent examples of how risk prediction models may be used to shape clinical guidelines and evidence based medicine include the use of the Framingham Risk Score for establishing lipid treatment guidelines[1] and recommendations for the combined use of cystatin-c and creatinine equations to improve chronic kidney disease prediction.[2] As part of my training activities, I will take a graduate-level course and a short course (Table 1).

3. *Metabolomics.* As an epidemiologist, I have no training in metabolomics. This area is relevant to my development as an independent researcher so that I may gain an understanding of metabolic pathways and how hyperglycemia, assessed through traditional and nontraditional glycemic markers, may exhibit varying metabolic profiles that elicit diabetes complications.   As part of my training activities for this area, I plan to take graduate-level coursework (Table 1). Additionally, I will participate in a weeklong training course and lab-based experiences at UAB Targeted Metabolomics and Proteomics Lab.

4. *Experience in conducting research and study management.* I have formal training in epidemiology and extensive experience with secondary data analyses of large datasets. However, I am lacking experience with study management, primary data collection, and recruitment. As part of my training activities for this area, I will take graduate-level coursework (Table 1) and gain practical experience, with mentor guidance, in participant recruitment, data collection, and study management through my pilot study.

Professional skills development will be ongoing and will include participation in the UAB Center for Clinical and Translational Science (CTSA) professional skills training program that hosts monthly workshops on topics such as grant development, scientific presentation, career development, and leadership. I will also take a graduate-level course (GRD 717: Principles of Scientific Integrity) that examines ethical issues of scientific research.

The measurable milestones for completing the training activities as part of this scientist development award in addition to activities related to professional productivity are listed in table 2.

Table 2 — Developmental Milestones for Dr. Carson's Scientist Development Award

Developmental Milestones for Training and Research Activities	Year 1		Year 2		Year 3	
	Months 1-6	Months 7-12	Months 1-6	Months 7-12	Months 1-6	Months 7-12
Didactic and Applied Training	40%		25%		5%	
Goal 1: Pathophysiology of Diabetes and Renal Complications						
Complete coursework	X	X				
Goal 2: Advanced Statistical Methods in Risk Prediction Models						
Coursework		X				
Directed readings	X	X				
Goal 3: Metabolomics						
Coursework		X	X			
Directed readings		X	X			
Lab-based sessions		X	X	X		
Goal 4: Research Recruitment, Data Collection, and Study Management						
Complete coursework		X				
Applied experience in recruitment, data collection, study management		X	X	X	X	
Research Activities	20%		40%		60%	
Research planning/Subcontract execution	X					
Manuscript analyses/completion Specific Aim 1		X	X			
Manuscript analyses/completion Specific Aim 2			X	X		
Manuscript analyses/completion Specific Aim 3			X	X	X	
Complete Specific Aim 4 (pilot study recruitment, data collection, and close-out)			X	X	X	
Submit first-authored abstracts to national meetings (at least 2/year)	**Ongoing**					

Submit first-authored manuscripts for publication (at least 2/year)	**Ongoing**					
Prepare and submit NIH R01 grant application				**X**	**X**	**X**
Professional Development	**15%**		**10%**		**10%**	
Meetings with mentors/collaborators	**Ongoing**					
Attend local seminars and journal clubs	**Ongoing**					
Participate in local CTSA professional skills training program	**Ongoing**					
Participate in national professional conferences	**Ongoing**					
Scientist Development Award Total Percent Effort	**75%**		**75%**		**75%**	
Other Responsibilities (Teach 1 course per year; Committee Service)	**25%**		**25%**		**25%**	

Mentoring Overview

The mentoring team for this scientist development award has expertise in diabetes research and its complications and a track record for developing junior investigators. My primary mentor for this scientist development award will be Cora E. Lewis, MD, MSPH, a Professor in the Division of Preventive Medicine. She is the principal investigator of the Birmingham clinical center for Action for Health in Diabetes (Look AHEAD) Study (3U01DK057008), the Birmingham field center for the Coronary Artery Risk Development in Young Adults (CARDIA) Study (N01HC48047), and the International Clinical Research Training Program at the Madras Diabetes Research Foundation in Chennai, India (5D43TW005816-08). She has an extensive publication and research funding portfolio, has participated in several NIH study sections, and has a history of mentoring early career investigators. Dr. Lewis has expertise in diabetes pathophysiology and its relation to macrovascular complications and has led several clinical and observational research studies of diabetes and its complications. Dr. Lewis will provide overall mentorship for my day to day research activities, research direction, and professional development. Dr. Lewis has assisted me with developing previous manuscript proposals in CARDIA and has always been available to answer research and career related questions. I will have standing bi-weekly meetings with Dr. Lewis to review my progress and research direction, with more frequent in-person meetings occurring when needed and communication via email and telephone.

My co-mentors for this scientist development award will be W. Timothy Garvey, MD and Paul Muntner, PhD. Dr. Garvey is an internationally recognized endocrinologist and principal investigator of the Diabetes Research and Training Center (5P60DK079626). He will provide expertise in the clinical utility of glycemic markers, genetic admixture analysis based on his prior work with Gullah-speaking African Americans in South Carolina, and metabolomics based on current work from one of his studies. I will have standing monthly meetings with Dr. Garvey to review my progress and research findings, with more frequent in-person meetings occurring when needed and communication via email and telephone. Dr. Muntner is a Professor in the Department of Epidemiology with extensive experience in renal epidemiology and risk prediction methods. He was a co-investigator for the Chronic Renal Insufficiency Cohort (5U01DK061022) Study and currently is a co-investigator for the Renal Reasons for Geographic and Racial Differences in Stroke Study (5U01NS041588) and the CARDIA Study (N01HC48047). Dr. Muntner is on the editorial board of *the American Journal of Kidney Diseases* and has served on several NIH study sections. He will provide expertise in renal disease and clinical risk prediction methods. I will have standing monthly meetings with Dr. Muntner to review my progress and research findings, with more frequent in-person meetings occurring when needed and communication via email and telephone.

Drs. Lewis, Garvey, and Muntner will foster my research capabilities and professional development by providing feedback on my progress and guided mentorship to develop me as an independent investigator. The entire mentoring team will meet in-person twice a year to review my progress. These meetings will be led by Dr. Lewis during which we will review my research findings, publications, grant submission opportunities, training activities, and overall professional development. Additionally, a key collaborator for this scientist development award will be Dr. Elizabeth Selvin, an internationally recognized expert in the epidemiology of glycemic markers. Dr. Selvin is the principal investigator of an ancillary study to the Atherosclerosis Risk in Communities Study (1R01DK089174) and will provide her expertise in the area of glycemic markers in addition to informal mentoring for my overall career development. As part of my overall mentoring and career development, I will have the opportunity to receive additional research feedback from other senior investigators in the CARDIA study during meetings and conference calls to discuss findings and future research directions.

The career development activities and strong mentoring team that I have for this scientist development award will help me to develop the necessary skill set to become an independent investigator and successfully obtain external funding by the conclusion of this scientist development award.