Introduction To The Resubmitted Application

I thank the reviewers and the DDK-D subcommittee for their insightful critiques of my original application. I appreciate the recognition of multiple strengths and the suggestions for improvement and focus. I have addressed all major critiques, with each response summarized below and noted by a vertical line in the margin of the revised application. References to specific sections of the revision are in *italics* below.

Responses to Reviewer #1: Overall impact: The original proposal was lauded as clinically relevant with recognition of my outstanding training background in pediatric renal transplantation. Overall concerns included a modest publication record in vascular injury, an unfocused mentoring plan, limited preliminary data in renal chronic rejection, and overly ambitious career development and research plans. I have addressed these concerns by publishing 3 manuscripts in vascular injury (Seifert, *AJN* 2013 and *AJN* 2014; Fang, *JASN* 2014), concentrating the mentoring plan on Drs. , and focusing career development and research plans on studies of chronic kidney disease-mineral bone disorder (CKD-MBD) factors. Candidate: With further progress in the KL2 program (see *Candidate's Background)*, I have continued to demonstrate my potential as an independent investigator to mentors and referees. Updated letters of support reflect their enthusiasm. To address productivity concerns, I have published 3 peer-reviewed manuscripts (2 as first-author), 1 national abstract and 1 textbook chapter, all with Dr. as senior author and focused on vascular injury in kidney disease (see *Candidate's Background*). Research Plan: The original research plan was felt to be overly ambitious, with limited use of Dr. CKD-MBD expertise and limited training in vascular injury. I have now focused the research plan on CKD-MBD factors as biomarkers of transplant glomerulopathy, a common subtype of renal chronic rejection with explicit vascular injury (see *Approach*). Given their perceived similarity, prior specific aims 1-2 have been combined into revised aim 1a/1b: a cross-sectional study to associate blood and urine CKD-MBD factors to the consensus Banff vascular injury score in patients with transplant glomerulopathy and other diagnoses. Prior specific aim 3 is now revised aim 2: a prospective study of CKD-MBD factors as predictors of 3-year outcomes. I have added a new exploratory third aim that leverages our local genomic medicine core to learn emerging genomic medicine principles in kidney transplantation and apply them to my training in vascular injury (see *Approach*). Exciting preliminary data are presented from our novel discovery that kidney injury releases CKD-MBD factors that contribute to vascular injury in CKD and are also biomarkers of renal chronic rejection. Proposed study enrollment has been limited to children 18-21 years and adults > 21 years to reduce potential confounding from young children. Limitations, data analysis, and alternatives are discussed in expanded detail (see *Approach*). Career development: To improve focus, in addition to changes above, I removed the "Biorepositories" content area in favor of additional training in vascular biology: 1) weekly mentoring meetings with Dr. , 2) local vascular research seminar, 3) Banff vascular injury scoring of kidney transplant biopsies with our renal pathologists, Drs. (see *Career Development*). Mentors: Due to concerns for a broad and unfocused mentoring plan, I have streamlined the plan to feature weekly meetings with co-primary mentors Drs. . Formal meetings with other advisors are semi-annual to reduce potential distractions from copious individual meetings (see *Career Development*). Environment: Due to geographic constraints and a shifting research focus, visits to Dr. lab were removed to focus on local vascular expertise. He remains involved as an external advisor and to provide additional expertise in vascular injury of chronic transplant rejection when needed.

Reviewer #2: Overall impact: The acknowledgment of my well-crafted application and outstanding components is appreciated. Overall concerns were limited to reproducibility of certain biomarker measures and lack of preliminary data in urine samples. New preliminary data and the expanded limitations section address these concerns. Candidate: My publication record has been addressed in the response to Reviewer #1. Research Plan: New preliminary data with analysis of CKD-MBD factors in blood and urine of kidney transplants is presented. Limitations, alternatives, and data analysis are discussed in expanded detail (see *Approach*). Career Development/Mentors/Environment: No weaknesses were identified in these areas.

Reviewer #3: Overall impact: I am grateful for the notion that I am likely to achieve my career goals and independent research funding beyond the K23. I value the suggestion to plan for bridge funding (e.g., R03) between the K23 and R01 as needed for dissemination of the proposed work. Career Development/Mentors: I have explained the need for a measured pace of coursework during the KL2 program (see *Candidate's Background*). Dr. 's letter of support better reflects his expanded role in my career development. Research Plan: I agree that instability of urine measures is a potential impediment to their use. Therefore, the proposed work is especially important to determine the utility of urine biomarkers in my research. As suggested, my career development timeline now includes specific plans for abstract presentation and manuscript preparation. Candidate/Environment: No concerns were indicated in these areas, but I welcome the encouragement from the recognition of numerous and varied strengths.

Candidate's Background

My long-term goal is to elucidate the role of vascular injury in chronic allograft nephropathy (CAN), the primary cause of kidney transplant failure in adults and children. During my pediatric nephrology fellowship I became enthralled with the endothelium as the primary barrier between the kidney transplant and the external environment. I cared for too many children whose kidney transplants failed due to CAN despite excellent compliance with medications and transplant care. Therefore, I dedicated myself to become an independent clinical investigator that could improve the health and quality of life of kidney transplant recipients by advancing our understanding of CAN. My research niche is to translate emerging bench findings in the field of transplant vascular injury into clinical practice by improving the diagnosis (through identifying novel biomarkers) and treatment (through identifying novel therapeutic targets) of children and adults with CAN. During the last 6 years, including the past 18 months as a KL2 scholar, I have acquired unique training in pediatric kidney transplantation and vascular biology that has provided a strong foundation to achieve my long-term goal. However, I recognize that my 2-3 years of training under the KL2 award will not provide the complete knowledge and skills that are necessary to become an independent clinical investigator focusing on vascular injury in CAN. Therefore, I have designed an additional **3.5-year program of mentored research training and career development activities** that will continue to leverage the world-class resources of Southern Illinois University (SIU, my professional home) and Washington University (WU, my research training home). This career development plan will complete my training and enable my transition to independence. My academic biography demonstrates dedication and enthusiasm for clinical investigation and a robust track record of success in both transplant vascular injury research and the proposed mentored training environment.

Academic Biography. My passion to become an independent clinical investigator and study vascular injury in CAN is driven by outstanding past and present research experiences that were guided by exceptional mentors, many of whom are engaged in the proposed work.

Pediatric residency (July 2004-June 2007). My initial clinical research experiences during pediatric residency were driven by my interest in kidney physiology, resulting in three peer-reviewed publications in electrolyte physiology, hypertension, and intensive care nephrology (see Biosketch). This exposure to academic scholarship whetted my appetite for both clinical and research training in pediatric nephrology.

Pediatric nephrology and transplantation fellowships (July 2007-June 2010). During my fellowship at Boston Children's Hospital, I studied biomarkers of angiogenesis and vascular injury under the mentorship of Drs. . I initially studied circulating levels of angiogenesis factors as predictive biomarkers for preeclampsia, a significant cause of cardiovascular morbidity in pregnant mothers. This initial experience served as a training vehicle to learn basic principles of translational research (**T32 DK007726-25**) and resulted in a peer-reviewed publication (Haggerty, Seifert et al, *Pregnancy Hypertension* 2012). As my clinical and research interests became concentrated in kidney transplantation, I committed to a concomitant American Society of Transplantation (AST) Pediatric Renal Transplantation Fellowship. I then applied my knowledge gained from preeclampsia research to study circulating angiogenesis factors as biomarkers of vascular injury in cardiac chronic rejection. This work culminated in multiple oral abstract presentations at the American Transplant Congress (ATC) and a co-first-author publication (Daly, Seifert et al, *JHLT* 2013). During these fellowships I came to understand the considerable unmet scientific and clinical needs in the vascular biology of CAN that I could address as an independent clinical investigator.

Research as junior faculty (August 2010-present). In my current dual faculty position in the Departments of Pediatrics at Southern Illinois University (SIU) and Washington University (WU), I have developed productive mentoring relationships with Drs. at WU, who have committed to be co-primary mentors for the proposed work. Achievements under their guidance include:

1. I successfully competed for a **KL2 Career Development Award** (KL2 TR000450) through the **Institute of Clinical and Translational Sciences** (ICTS - WU CTSA), securing **75% protected time for research** through both SIU and WU, whose support will continue during the K23 award (see Institutional Commitment). The KL2 has facilitated my translational studies of biomarkers of the chronic kidney disease-mineral bone disorder (CKD-MBD) in adults with native stage 3 CKD (Seifert et al, *AJN,* 2013; Seifert et al, *AJN, In Press,* 2014) and in pediatric kidney transplant recipients with CAN (in progress, see Preliminary Data).

2. Using KL2 support, I played a critical role in **the recent seminal discovery that kidney injury directly causes vascular injury through the release of circulating factors involved in renal repair, including pathogenic biomarkers of the CKD-MBD** (Fang et al, *JASN* 2014). This innovation raised the intriguing possibility that therapies addressing the CKD-MBD can abrogate the non-immune vascular injury produced by

kidney transplant injury that leads to CAN, similar to renal injury in native CKD. We plan to explore this novel mechanism and potential therapy of non-immune vascular injury in the proposed work (see Approach).

3. By Fall 2014, I will complete a **Certificate in Clinical Investigation** (CCI), including 18 credit hours of coursework in biostatistics, grantsmanship, epidemiology and ethics. The CCI is administered by the **Clinical Research Training Center** (CRTC – training core of ICTS).

4. I became the WU pediatric nephrology division's liaison to the **Midwest Pediatric Nephrology Consortium**, a network of over 50 centers that is committed to advancing clinical research in pediatric nephrology. **I personally created a multicenter collaboration** with the University of Kentucky, University of Michigan, West Virginia University, and the Cleveland Clinic. In total, this collaboration has enrolled 45 subjects in my KL2 research project on **biomarkers of the CKD-MBD and in pediatric CAN**, due to complete in Fall 2014 after adding 2-3 centers to reach our enrollment target of 60 pediatric kidney transplant recipients. I presented an interim analysis of this study as **a first-author abstract at the 2013 ASN Kidney Week annual meeting** (Seifert et al, *JASN* 2013; see Preliminary Data).

5. I developed a collaboration between Drs. Brennan and Mohanakumar at WU in which we are currently studying circulating antibodies to tissue-restricted self-antigens using biospecimens from the Kidney Translational Research Center (KTRC), a biorepository managed by the Renal Division at WU. These specimens were prospectively collected throughout year-1 post-transplant in recipients with/without BK viremia. **This study served as a model in the design of aim 2 of the proposed work**. **I presented these data as a first-author oral abstract at the 2013 American Transplant Congress** (Seifert et al, *AJT*, 2013).

6. I received a **Clinician-Scientist Award** from the SIU Research Seed Grant program (7/1/2013-6/30/2014) to complete the above antibody assays and associate these immune responses to self-antigens with biomarkers of vascular injury in BK viremia. **These data were submitted as a first-author abstract to the 2014 World Transplant Congress and will be developed into a first-author manuscript in Fall 2014.**

7. I received a **NIH/NIDDK Loan Repayment Program Award** in Pediatric Research (**L40 DK099748-01**) to further support my KL2 studies of non-immune biomarkers of vascular injury in chronic allograft nephropathy.

Current professional activities. A competitive advantage of my joint faculty appointment is that 4 days per workweek are spent on site at WU, a world-class translational research institution and transplant center. Nearly all of my professional effort at WU (75% of total effort) is protected time that is focused on my development as a clinical investigator in vascular injury of CAN. I have committed the remaining 25% of my total effort to the following clinical and educational career development activities: 1) on-site at SIU an average of one day per workweek for an outpatient pediatric nephrology clinic and pediatric resident teaching; 2) inpatient service time of 4 weeks every academic year (exclusive at WU); 3) outpatient attending for 4-6 pediatric kidney transplant clinics at WU each academic year. This unique position supports my development into a well-rounded clinician, educator, and investigator. Specifically, WU provides unmatched clinical and research experiences at a large urban academic center while SIU simultaneously provides clinical and teaching experiences at a rural community-based academic center. This professional model has proven successful during the KL2 and will continue during the K23 award.

Career Goals and Objectives

My prior experiences have been critical to develop my long-term career goal of performing high-quality, high-impact clinical investigation to elucidate the role of vascular injury in chronic allograft nephropathy (CAN). My achievement of this long-term goal will improve the health and quality of life of countless adults and children that rely on kidney transplantation as a treatment for end-stage kidney disease. As a pediatric nephrologist, **I understand the problems of our aging clinical workforce and the diminishing cadre of well-trained clinical investigators.** I will use support from the K23 mentored career development program to firmly establish myself as an independent clinical investigator, advance our understanding of kidney transplant diseases and become a mentor to other junior pediatric nephrologists. This cycle will ensure that the field of pediatric nephrology attracts and retains a talented pool of clinical investigators for years to come. My initial clinical research training in the KL2 program has taken me from a novice to a proficient clinical investigator. However, to make the transition to an **expert independent clinical investigator**, I require additional knowledge and skills that can only be obtained during an additional period of mentored research training that builds on my KL2 experience. To work toward my long-term career goal, I have set the following **career goals and objectives for the next 5 years**:

1. To become an expert in kidney transplantation and mechanisms of transplant failure (including CAN) by providing clinical service to the WU pediatric transplant program, conducting clinical research in kidney transplant recipients and completing coursework in immunology and survival analysis.
2. To improve my knowledge of vascular biology/pathology in kidney transplantation by performing translational studies of kidney recipients, receiving mentorship in vascular biology, and learning new research skills to identify novel mechanisms of transplant vascular injury.
3. To become a productive independent clinical investigator who advances our understanding of vascular injury in CAN to improve kidney transplant outcomes.

Continuity of prior research and career development activities with the current proposal. Each goal listed above was developed from progress during my pediatric nephrology fellowship and more recently in the KL2 program. I need additional time and training provided by the K23 award to achieve these goals. Therefore, my K23 application builds upon and extends these prior research efforts and career development activities to establish a strong foundation for long-term success. This foundation will provide numerous opportunities to conduct independent research and obtain funding via institutional, foundation (e.g., AST and ASN) and NIH (e.g., R21 and R01) mechanisms. **During the recent period of KL2 support, we made the seminal discovery that kidney injury causes non-immune vascular injury through circulating factors involved in renal injury/repair in animal models of native stage 2 CKD.** This is similar to the kidney transplant paradigm in which acute injury of a healthy donor kidney is followed by ongoing vascular injury and loss of function that leads to CAN (**Figure at right**). Therefore, these novel findings need to be explored in human kidney transplantation as proposed in my research plan. The positive outcome of these studies raises the intriguing possibility of developing novel therapies to abrogate the non-immune vascular injury that leads to CAN in kidney transplantation, which will complement existing therapies that reduce immune-mediated vascular injury. Importantly, these studies will serve as a research training opportunity for me to achieve my career goals and objectives.

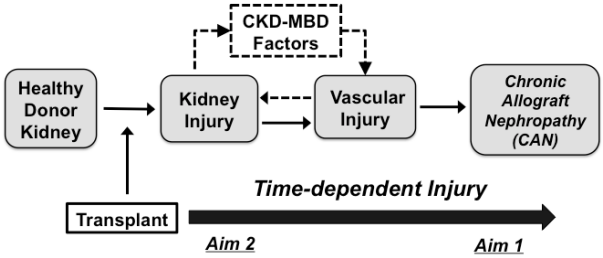


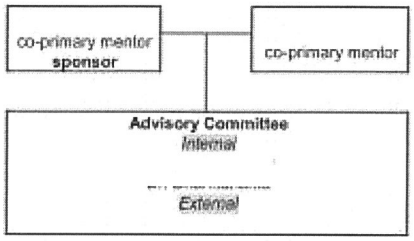
Figure. Proposed model and research design. Time-dependent kidney/vascular injury begins at transplant and leads to CAN through production of factors involved in renal repair, including pathogenic CKD-MBD factors.

Further mentored research and career development needed to develop independence. The KL2 award has allowed me to develop a strong foundation in the fundamentals of clinical research and transition from a novice to a proficient clinical investigator. This transition is evidenced by my success in developing multidisciplinary and multicenter collaborations, institutional-level and NIH-level grant support, and data dissemination. However, I require additional knowledge and skills in the areas of transplant nephrology, vascular biology and academic development that will be addressed by the proposed research and career development plans. Successful completion of the career development plan outlined below will facilitate my transition to independence and my progression to become an expert clinical investigator. This plan will effectively leverage my outstanding institutional environment at SIU and WU, especially the unique expertise of my mentoring team and the Institute for Clinical and Translational Sciences (WU CTSA), which supports the many educational and research cores that are utilized in my career development and research plans.

Career Development and Training Activities

To achieve my career goals and objectives, I designed a career development plan around 3 key content areas: **transplant nephrology, vascular biology and academic development**. My mentoring team and I have worked diligently to design a career development timeline that will facilitate my transition to an independent clinical investigator (**Table 5, below**). This 3.5-year career development plan features a five-member mentoring/advisory committee, completion of a Master of Science in Clinical Investigation (MSCI) degree and a research plan, which are all integrated to support my career goals (**Table 6, below, and Research Strategy**). I have designed additional customized learning experiences in vascular biology that will further integrate with my research training plan (**Table 2**).

Mentoring/advisory committee (Figure at right). I have created a multidisciplinary mentoring team with complementary expertise in my 3 key content areas. The entire committee will meet with me every 6 months during the K23 award to discuss my career development and research progress. The mentoring plan focuses on weekly interactions with my co-primary mentors Drs. , who will provide critical mentoring and expertise in vascular biology, transplant nephrology, and chronic allograft nephropathy.



, MD – Co-primary mentor and sponsor. Dr. is Professor of Pediatrics and Director Emeritus of Pediatric Nephrology at WU. He is a past-president of the American Society for Bone and Mineral Research and is an internationally renowned expert in vascular injury associated with the CKD-MBD. He has 2 active R01 grants (**R01 DK070790-07** and **R01 DK089137-01A1**) to study mechanisms of vascular injury and calcification in native CKD. Dr. Hruska has published over 300 peer-reviewed manuscripts including recent seminal work in vascular injury caused by reactivation of repair programs after kidney injury. These novel concepts in vascular injury associated with native CKD have been integrated into my revised research plan (see **Approach**). While his primary clinical and research interests are in the immense cardiovascular risk associated with native CKD and contributed to by CKD-MBD, he has maintained interests in kidney transplantation both through clinical service and a **25-year career as Medical Director of Mid-America Transplant Services, our local organ procurement organization**. I collaborate with his studies of translational mouse models of stage 2 CKD and clinical CKD. Therefore, by participating in Dr. 's lab meetings each week, I will increase my knowledge of vascular injury caused by kidney injury and apply these novel concepts to vascular injury in CAN. As my research supervisor, Dr. will ensure the successful completion of the study aims and guide my academic development through discussion of hypotheses, data analysis, and budget management. We will meet weekly to discuss my progress and review selected readings from William Aird's *Endothelial Biomedicine* textbook and emerging literature every other week (**Table 2**); these sessions will further my understanding of basic endothelial/vascular biology.

Table 2. Customized additional learning experiences in vascular biology.

Additional Learning Experience	Description and Integration with Research Plan
Review of *Endothelial Biomedicine* textbook (William C. Aird, editor)	Discuss selected readings with Dr. [redacted] at our mentoring meetings during year 1 to **improve my understanding of endothelial/vascular biology and apply the knowledge gained to my data analysis.**
Banff vascular injury scoring of kidney transplant biopsies (Drs. [redacted] Renal Pathology, WU)	Perform Banff vascular injury (g+ptc) scoring of kidney transplant biopsies in aims 1-2 with renal patholgists Drs. [redacted] **to better understand phenotypic variations of vascular injury in CAN and compare to vascular injury in our animal models of native CKD.**

, MD – Co-primary mentor. Dr. is the Alan A. and Edith L. Wolff Professor of Renal Diseases and Director of Transplant Nephrology at WU. He has published over 200 peer-reviewed publications in clinical transplant nephrology and is a renowned expert on the impact of immunosuppression regimens and BK viral immunity on long-term renal transplant outcomes. He has directed prospective clinical research projects and clinical trials in kidney transplant recipients. Dr. just completed 11 consecutive years of K24 funding for mentoring in transplant nephrology (**5K24 DK002886-10, revised with 1-year extension**) and has expertise in investigator-initiated industry studies. He is my primary mentor for the current period of KL2 support and has committed to serve as the co-primary mentor for the K23 award period as well. We will meet weekly to discuss my career development and research-in-progress. He will review my manuscripts, grants,

study designs, and facilitate my interactions with transplant leaders at the local and national level. He will contribute content expertise in transplant nephrology and academic development. He will facilitate access to biospecimens and clinical data in the KTRC that are required to complete aim 1a/1b.

, PhD – Internal advisor. Dr. is Professor of Surgery and Immunology and Director of the Histocompatibility Laboratory at WU. He is an international expert in transplant immunology and has a unique research niche in transplant autoimmunity, which is an important contributor to chronic transplant rejection. He will provide content expertise in basic mechanisms leading to CAN and chronic rejection of other solid organs. We will meet formally every 6 months as part of the entire mentoring/advisory committee meeting schedule. He remains available for individual meetings as needed.

, MD, MPH – Internal advisor. Dr. is Associate Professor of Pediatrics and Director of Pediatric Nephrology at WU. He will monitor my clinical activities and my relationship with SIU and WU to ensure my protected time for research is maintained. He will facilitate interactions with leaders in the field of pediatric kidney transplantation. He provides content expertise in pediatric transplant nephrology, CAN, biostatistics and academic development. We will meet formally every 6 months as part of the entire mentoring/advisory committee meeting, and he remains available for individual meetings as needed.

, MD, ASCI – External advisor. Dr. is Associate Professor of Medicine at Boston Children's Hospital and Harvard Medical School. He is an expert in transplant vascular biology with unique expertise in the role of angiogenesis and vascular injury in chronic transplant rejection. He has committed to participate in semi-annual mentoring/advisory committee meetings via videoconference and is available to meet individually as needed, whether the setting is at a national meeting or by videoconference.

Didactic training. I will have completed a Certificate of Clinical Investigation (CCI) by Fall 2014 that provides basic clinical research education. During the KL2 program, I purposefully limited myself to one course per semester so that didactics are complementary to my career development rather than a distraction. With additional support from the K23, I will build on this fund of knowledge by completing a MSCI degree (administered by the WU CTSA). My planned coursework (**Table 3, above**) includes 2 years of training in immunology, bioinformatics, genomic medicine, study design, and survival analysis. In my timeline (**Table 5**), I have allotted 3 years to complete these courses to provide flexibility in my schedule. I will complement these courses with a cadre of seminars, conferences, and meetings (**Table 4**) that will improve my presentations, networking, data analysis and career development.

Table 3. Courses to Complete MSCI Degree (33 credits) at WU

Course Title	Credits	Course Synopsis and Integration with Research/Career Plan
Survival Analysis (M21-618, Spring '15)	3	This course will cover modeling of **time-to-event data, an indispensible skill for prospective clinical studies in transplantation such as those in aim 2.**
Genomics in Medicine (M17-532, Fall '15)	2	Intro to genomic principles and practical molecular biology as they apply to clinical research, including my **interpretation of gene expression profiles data from the exploratory aim.**
Biomedical Informatics (M17-530, Fall '15)	3	Overview of bioinformatics and its use in **analyzing complex clinical and biomarker datasets in aim 1, aim 2 and the exploratory aim.**
Study Design (M21-617, Spring '16)	3	Instruction in statistical and epidemiological concepts of study design. Topics include **study management and power analysis that are applicable to aims 1-2 and future studies.**
Foundations in Immunology (L41-5071, Fall '16)	4	An in-depth immunology course updating topics **germane to mechanisms of transplant injury.**
Total Credits Earned by Spring 2016	**15**	**Total Credits Earned During KL2 and K23 = 33**

Table 4. Planned meetings, seminars, and conferences during the K23 award period.

Local	Frequency and Description
[redacted] Lab Meeting (WU)	Weekly conference discussing preliminary data emerging concepts from our animal models of vascular injury caused by kidney injury. I will attend each week as my schedule permits.
Cardiovascular Research Seminar (WU)	Weekly conference attended by basic scientists in vascular biology. I will attend one seminar per month.
Pediatric Nephrology Research Conference (WU)	Conference at WU with pediatric nephrology colleagues. I will present an annual research-in-progress talk.
Renal Division Research Conference (WU)	Conference at WU with adult nephrology colleagues. I will present an annual research-in-progress talk.
Regional	**Frequency and Description**
Midwest Pediatric Nephrology Consortium Meeting	Semi-annual pediatric nephrology conference to establish/maintain clinical research collaborations. I will attend 1-2 times per year.
National	**Frequency and Description**
American Transplant Congress (ATC)	Annual meeting for transplant physicians and surgeons. I will present an abstract each year. I will attend additional vascular biology symposia when they are offered.
American Society of Nephrology (ASN) Kidney Week	Annual meeting for adult and pediatric nephrologists. I will present an abstract each year. I will attend vascular biology symposia when they are offered.

Table 5. Career Development Timeline

Career Development Activity	Year 1 (starts 12/2014)				Year 2 - 2016				Year 3 - 2017				Year 4 - 1/2018-6/2018			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1		Q2	
Aim 1a/1b- CKD-MBD factors as biomarkers of transplant vascular injury																
- Generate biomarker data and vascular injury scores in training set (1a)																
- Generate biomarker data and vascular injury scores in validation set (1b)																
- Analyze data and submit abstract to ASN annual meeting																
- First-author publication in *Amer J Transplant or CJASN*																
Aim 2 - CKD-MBD factors as predictors of kidney transplant outcomes																
- Enroll incident kidney transplant recipients (n=40)																
- Collect and store biospecimens (6 mos/subject)																
- Collect clinical data (3 yrs/subject)																
- Generate biomarker data and vascular injury scores in stored samples																
- Analyze biomarker and 1-year outcomes data, submit abstract to ATC																
- First-author publication (1-year outcomes) in *CJASN or Transplantation*																
- Analyze biomarker and 3-year outcomes data, submit abstract to ASN																
- First-author publication (3-year outcomes) in *Amer J Transplant or JASN*																
Exploratory aim - novel mechanistic pathways in transplant vascular injury																
- Genome Technology Access Core: generate RNA, perform microarrays																
- Analyze data and submit abstract to ASN annual meeting																
- First-author publication in *Amer J Transplant or Kidney International*																
First-author publication to complete KL2 project: CKD-MBD in Pediatric CAN																
Endothelial Biomedicine - review of selected readings (Hruska)																
Complete coursework for MSCI degree																
Weekly mentoring and semi-annual advisory committee meetings																
Attend and present at seminars, conferences, and meetings																
[redacted] Lab meetings - learn from animal model of vascular injury from CKD																
Clinical and educational activities at SIU (20% total effort)																
Clinical activities in pediatric kidney transplant program at WU																
Submit R03 and/or foundation grants to fund research in July 2018-June 2020																
Collect 5-year outcomes data from aim 2 cohort through June 2020																
Submit R01 proposal by Feb 2020 to take advantage of ESI status																

Table 6. Synopsis of K23 Training Program

Content Area	Contributing Mentors	Educational Program	Benchmark for Progress
1) Transplant Nephrology	Dr. [redacted] Dr. [redacted] Dr. [redacted]	1) Weekly mentoring meetings ([redacted]) 2) Semi-annual advisory committee meeting (all) 3) Seminars and conferences 4) Research plan 5) L41-5071 - Immunology 6) M21-618 – Survival Analysis 7) Clinical service to WU pediatric kidney transplant program	1) Presentation of 1-2 abstracts at ATC annually 2) Publication of 1-2 peer-reviewed manuscripts annually 3) Completion of aims 4) Completion of MSCI degree
2) Vascular Biology	Dr. [redacted] Dr. [redacted]	1) Weekly mentoring and laboratory meetings ([redacted]) 2) *Endothelial Biomedicine* review ([redacted]) 3) Semi-annual advisory committee meeting (all) 4) Seminars and conferences 5) Research plan 6) Banff vascular injury scoring with Drs. [redacted] 7) M17-530 – Bioinformatics (supports exploratory aim) 8) M17-532 – Genomics in Medicine (supports exploratory aim)	1) Completion of aims 2) Completion of *E.B.* textbook review with Dr. [redacted] 3) Publication of abstracts and manuscripts as above 4) Completion of MSCI degree 5) Attendance at vascular biology symposia at national meetings
3) Academic Development	Dr. [redacted] Dr. [redacted] Advisory committee	1) Mentoring/advisory committee meetings 2) Seminars and conferences 3) Research plan 4) M21-617 – Study Design 5) Clinical and educational activities at SIU and WU 6) Training in RCR	1) Completion of aims 2) Publication of abstracts and manuscripts 3) Recognition of expertise (invited speaker at national meetings) 4) Completion of MSCI degree 5) Completion of training in RCR 6) Submission of R03, R01, and/or foundation grants (AST, ASN)

SUMMARY STATEMENT

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(Privileged Communication) ***Release Date:*** **07/21/2014**

Application Number: **1 K23 DK101690-01A1**

Principal Investigator

SEIFERT, MICHAEL E MD

Applicant Organization: SOUTHERN ILLINOIS UNIVERSITY SCH OF MED

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

Meeting Date: **06/18/2014**
Council: **OCT 2014**
Requested Start: **12/01/2014**

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

Project Title: **Novel Biomarkers of Angiogenesis and Vascular Injury in Chronic Rejection**

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		
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 revised application was submitted in response to program announcement PA14-049 entitled “Mentored Patient-Oriented Research Career Development Award (Parent K23)”. The overall goal is to test the hypothesis that kidney transplant injury contributes to ongoing vascular injury leading to chronic allograft nephropathy through non-immune pathogenic factors involved in the chronic kidney disease-mineral bone disorder. The candidate has adequately addressed the main concerns raised in the previous review and the resubmitted application is improved. Previously noted strengths such as clinical relevance of the proposed studies; a very well trained candidate; the mentoring team consisting of experienced mentors; and the excellent research environment and institutional support remain. The improved publication record is an additional strength. The revised career development plan is better focused and aligned with the candidate’s career goals; however, training in vascular biology is still limited. The mentoring plan would be strengthened by the addition of a mentor with expertise in vascular biology. The revised research plan continues to weaken the application: Specific Aim 1 appears premature as relevant preliminary data are lacking; potential limitations and confounding factors are insufficiently discussed; retention plans appear overly optimistic; and statistical analyses are limited. Given the balance of the strengths and weaknesses, overall, this application is rated in the very good to excellent range.

DESCRIPTION (provided by applicant): The PI is a pediatric transplant nephrologist whose long-term career goal is to elucidate the role of vascular injury in chronic allograft nephropathy, the primary cause of kidney transplant failure in adults and children. Chronic allograft nephropathy has no effective treatment and is prevalent in nearly all functioning kidney transplants within 10 years. Novel pathogenic biomarkers that can detect early (and perhaps reversible) forms of disease will provide new therapeutic targets that are needed to improve kidney transplant survival. Chronic allograft nephropathy is a vascular disease resulting from time-dependent immune and non-immune vascular injury that begins early post-transplant. Since therapies that reduce immune injury have not reduced the incidence of chronic allograft nephropathy, the contributions of non-immune vascular injury need further investigation. The proposed research training plan will investigate the central hypothesis that kidney transplant injury contributes to ongoing vascular injury that leads to chronic allograft nephropathy through non-immune pathogenic factors involved in the chronic kidney disease-mineral bone disorder (CKD-MBD). This hypothesis was formed by recent seminal discoveries (with critical contributions from the PI) in translational models of CKD. The research plan is a component of the proposed career development plan that has the following three goals: 1) to become an expert in kidney transplantation and mechanisms of transplant failure, including chronic allograft nephropathy; 2) to improve the PI's knowledge of vascular biology/pathology in kidney transplantation; 3) to become a productive independent clinical investigator who advances our understanding of vascular injury in chronic allograft nephropathy to improve kidney transplant outcomes. To achieve these goals the PI will receive advanced clinical research training by completing a Master of Science in Clinical Investigation degree. The PI will receive exceptional mentoring from a team of experts in transplant nephrology and vascular biology. The proposed research and career development plans will be carried out in a superior training environment supported by Southern Illinois University (PI's professional home) and Washington University (WU, his research training and CTSA home). Aim 1a/1b will establish and validate CKD-MBD factors as biomarkers of transplant vascular injury in a cross-sectional study of kidney transplant recipients (n=120) enrolled in our biorepository. Aim 2 will evaluate CKD-MBD factors as biomarkers of kidney transplant outcomes in a prospective 3-year longitudinal study of incident kidney transplant recipients (n=40). A third exploratory aim will identify novel mechanistic pathways involved in transplant vascular injury using RNA-seq studies of subjects from aims 1 and 2 with transplant vascular injury. This will help the PI learn and apply emerging genomic technologies, available through the WU-CTSA core, to his studies of transplant vascular injury. The PI expects that completion of the proposed

research and career development plans will advance our understanding of vascular injury in chronic allograft nephropathy and enable his transition to an independent clinical investigator.

PUBLIC HEALTH RELEVANCE: All kidney transplants eventually fail due to chronic rejection, also known as chronic allograft nephropathy. Unfortunately there is no meaningful diagnostic, preventive, or treatment strategy for the disease. This project will develop a non-invasive predictive and diagnostic test for chronic allograft nephropathy that will also provide important insights into the mechanism of disease. We expect this will improve the health of adults and children with kidney transplants by allowing for earlier detection of the disease process and identifying novel targets for treatment of the disease.

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 a well-crafted application by a well-trained physician-investigator to pursue innovative, potentially high impact studies of non-immune biomarkers in kidney chronic transplant rejection. The proposed study is hypothesis-driven, rationally designed, exploits a high volume transplant program and active biorepository, and is feasible. The career development plan, mentorship team, institutional environment, and joint institutional commitment are also strong. Weaknesses include potential “noise” in the reproducible measurement of certain biomarkers, and the lack of validation and prioritization protocols for the exploratory aim.

1. Candidate:

Strengths

- The candidate is a well-trained pediatric nephrologist and transplant nephrologist with a particular interest in transplant vascular injury in the pathogenesis of chronic rejection.
- He obtained his M.D from the University of Connecticut. He completed pediatric nephrology and transplant fellowships at Boston Children’s Hospital. M.D. Since July 2010, he has been faculty dually appointed in the Department of Pediatrics Southern Illinois University and the transplant nephrology section of Washington University School of Medicine Institute for Clinical and Translational Sciences with the support of a KL2 Mentored Career Development Award. He has nearly completed his certificate level training in clinical investigation.
- He has published 3 peer-reviewed manuscripts (2 as first-author), 1 national abstract and 1 textbook chapter, all with Dr. as senior author, focused on vascular injury in kidney disease.

- Letters of reference are supportive.

Weaknesses

- Limited productivity and impact of publication of original research articles, although it has recently improved.

2. Career Development Plan/Career Goals & Objectives:

Strengths

- His stated long-term goal is to elucidate the role of vascular injury in chronic allograft nephropathy, an understudied area. He has designed a career development plan around 3 key content areas: transplant nephrology, vascular biology, and academic development
- He has concentrated his mentoring plan on Drs. , and refocused career development and research plans on studies of chronic kidney disease-mineral bone disorder (CKD-MBD) factors. He removed the "Biorepositories" content area in favor of additional training in vascular biology, which will include weekly mentoring meetings and readings in endothelial biology with Dr. , a local vascular research seminar, and Banff vascular injury scoring of kidney transplant biopsies with renal pathologists.
- His investigative training will be supplemented by formal coursework to obtain an MS in clinical investigation, which should further his development as a rigorous clinical investigator. These experiences will be supplemented by a rich array of local seminars, lab meetings, and conferences.
- Appropriate interactions with the mentorship team and a detailed timeline for career milestones are proposed.

Weaknesses

- In-depth, hands-on vascular biology training is improved, but still somewhat limited. The concern is that he will develop familiarity with vascular biology knowledge and methods, but not be developing as a thought leader in the area as it applies to CAN.

3. Research Plan:

Strengths

- The proposal is innovative and potentially high impact in that it addresses non-immune mechanisms of vascular injury in CAN the potential for rational development of novel therapies to abrogate this non-immune component to complement existing immune therapies. The central hypothesis that kidney transplant injury contributes to ongoing vascular injury that leads to CAN through non-immune pathogenic factors involved in the CKD-MBD is bolstered by recent published and unpublished data from the applicant's KL2 work.
- Preliminary data showing the ability to acquire Banff criteria histologic and genomic data for Aims 1, 2, and the exploratory aim using local CTSA cores are provided.
- Aim 1 is a cross-sectional study of kidney transplant recipients (n=120) selected from the KTRC biorepository with TG, acute rejection, or no rejection. It will attempt to establish and validate the CKD-MBD factors plasma/urine FGF23, DKK1, sclerostin and klotho levels as biomarkers of transplant vascular injury. He predicts that subjects with the TG subtype of CAN will have high Banff vascular injury (g+ptc) scores, and that levels of CKD-MBD factors will discriminate $[g+ptc]^{hi}$ from $[g+ptc]^{low}$. The rationale for the specific biomarkers and the overall study design is appropriate.
- Aim 2 is a longitudinal study of incident kidney transplant recipients, including children 18-21 years and adults > 21 years of age (total n=40) that seeks to determine whether these CKD-

MBD biomarkers measured during the first 3 months post-transplant are predictive of kidney transplant outcomes at 3 years.

- An exploratory aim using RNA-seq and/or gene expression microarrays in a subset of [g+ptc] vs. $[g+ptc]^{low}$ biopsies from Aims 1-2 is proposed.
- The research plan is based on sound scientific and clinical rationale, and leverages the KTRC biorepository and the very active renal transplant program at WU as major resources.
- Limitations of the study, sample size, and statistical considerations appear adequate.
- Future directions are proposed, which highlight the significance of the proposed pilot study.

Weaknesses

- For the exploratory aim, there are no validation or prioritization protocols proposed.

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

Strengths

- One co-primary mentor is Dr. , Professor of Medicine and Director of Transplant Nephrology at WU. He is co-director of the KTRC biorepository at WU. He is an internationally regarded expert in transplant nephrology on the impact of immunosuppression regimens and BK viral immunity on long-term renal transplant outcomes. He has directed prospective clinical research projects and clinical trials in kidney transplant recipients, and recently completed 10 consecutive years of K24 funding for mentoring in transplant nephrology. He has been the applicant's primary mentor during the current KL2 application. He has considerable mentorship experience.
- The second co-primary mentor is Dr. , Professor of Pediatrics and Director Emeritus of Pediatric Nephrology at WU. He is a past-president of the American Society for Bone and Mineral Research and is an internationally renowned expert in the CKD-MBD and Wnt biology. He has 2 active R01 grants to study vascular pathobiology in CKD. He, too, has considerable mentorship experience, and has worked productively with the applicant to publish original research in the area.
- An expert advisory panel with will content expertise in chronic rejection, biomarkers, and biorepositories, and genomics is proposed.
- The applicant will also benefit from the input of an advisory group of three established investigators with complementary expertise in three other relevant content areas. The entire committee will meet with me on a semi-annual basis.

Weaknesses

- None noted

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The environment is exceptional.
- The joint institutional commitment provides 75% protected time, seed funds already provided, and additional access to lab space, key core services, and administrative support.

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Appropriate informed consent, security of data storage, and limitation of potential risks are included.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

Revision:

- The proposal was reviewed 10/23/2013 and received an impact score of . The career development plan was criticized for being too broad and lacking sufficient in-depth training in the field of vascular injury. The research plan was viewed as overly ambitious and unfocused, with inadequate rationale for selection of markers, a lack of compelling preliminary data, and inadequate consideration of potential limitations and pitfalls. In general, the applicant has addressed the major criticisms through extensive revisions and new data

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Face-to-face workshops, which include didactic lectures and small group discussions, as well as web-based learning modules.

Comments on Subject Matter (Required):

- Content is appropriate to the applicant's prior RCR training and career development.

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

- Faculty-led workshops, seminars, and small group discussions.

Comments on Duration (Required):

- Estimated at 15 hours of training during the award period.

Comments on Frequency (Required):

- Annual training is proposed.

Select Agents:

Not Applicable (No Select Agents)

Budget and Period of Support:

Recommend as Requested

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: The applicant is well-qualified and demonstrates high-potential for career independence. The proposal is aligned with research goals and will provide him critical expertise in an area that is important to the field of kidney transplantation. The mentors and advisory group are outstanding and institutional environment is very strong. The applicant appears to have addressed most of the comments mentioned in the last review. My enthusiasm is dampened by some of the limitations in the research proposal.

1. Candidate:

Strengths

- The applicant received excellent training with BA from Washington U, MD and Pediatric Residency from U Conn and fellowship at Boston Children's Hospital. He received T32 and HHMI funding, Loan Repayment, SIU institutional funding and was supported by the KL2 of CTSA program.
- In 2013-14, the applicant has published 5 publications. Three are first-author original manuscripts. All 5 publications are with members of his mentorship team. He has a total of 12 publications (reviews, case reports make up the remaining ones). In addition, he has a recent abstract highlighted in the research which demonstrates continued research productivity.
- The applicant is jointly appointed by SIU and WU with letters confirming this arrangement.
- The letters of support in this revised application are enthusiastic and supportive.

Weaknesses

- None noted

2. Career Development Plan/Career Goals & Objectives:

Strengths

- The applicant's goal is to establish a niche in clinical investigation focused on transplant vascular biology.
- The applicant developed initial exposure to vascular biology guided by notable investigators in the field, Drs.
- To accomplish these goals, he has a well-outlined development plan including an advisory committee with collective expertise in immunology, pediatric nephrology and transplant vascular biology. This group will be a strong complement to the co-mentors
- The applicant will meet with co-mentors weekly. The timeline for accomplishments is well-described.
- The applicant, addressing previous comment about finalizing coursework, states that he is intentionally limiting himself to 1 course/semester. Coursework is well-aligned with research project and career goals

Weaknesses

- None noted

3. Research Plan:

Strengths

- The applicant plans to build on very interesting series of preliminary information implicating CKD-MBD factors in vascular injury in this proposal. He proposed that early kidney injury after transplantation leads to endothelial injury via CKD-MBD mediators. The applicant will 1) establish and validate the specificity of these biomarkers for CAN in small transplant populations, 2) determine whether these biomarkers are predictive of 3-year renal function outcomes and 3) aim to identify other pathways in histopathologically-characterized biopsies by gene expression signatures
- The project addresses a clinically-relevant issue which needs further exploration and will allow him to develop the intended niche
- The aims are logical extensions from the preliminary data and appropriately-focused.
- Although the applicant has 3.5 years, the proposal seems feasible due to transplant activity and banked samples
- Limitations are, overall, well-described.

Weaknesses

- There is concern that biomarker analysis is not controlled for eGFR. For example, in preliminary data (Figures 4a and regression model for CAN), the inverse correlation of FGF-23 and GFR are not taken into account. There may be confounding.
- Limited data on plasma and urinary biomarker reproducibility. It would have been helpful to review assay performance information on all the biomarker data highlighted.
- There is concern that in Aim 2 biomarker samples will not be measured with tissue samples to confirm specificity of these markers for CAN
- Planning for up to a 30% attrition rate is not an acceptable study design.
- Some information regarding biomarker assay performance should be included.

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

Strengths

- Dr. is a highly-established, well-published senior scientist with 3 R01s who has and will continue to provide outstanding pre-clinical expertise in CKD-MBD. He is complemented by the well-established co-mentor, Dr. , who will provide equally strong expertise in CAN, transplant research. Dr. has 200 publications, directs the transplant research core, and is currently participating in a U01. Both mentors have had K24 grants and demonstrate success in mentoring.
- Dr. will provide renal histopathology expertise, including vascular scoring.
- These investigators are joined by the advisory group which, combined, form an outstanding group of senior scientist for the applicant.

Weaknesses

- None noted

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The institutional environment is excellent. The formal arrangement between SIU and WU is confirmed in the letters and the guarantee of 75% protected time is mentioned from representatives of both institutions. The applicant should transition seamlessly from the KL2 to this award. The applicant has access to patient population and biorepository for planned studies.

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:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The applicant appears to have addressed comments related to a more focused application. The development plan is well-outlined, and mentoring plan is logical.
- Likewise, the research plan is focused on MBD markers and vascular injury.
- Letters are excellent.
- See above comments

Training in the Responsible Conduct of Research:

Acceptable

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

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 initial application from this candidate was reviewed in October 2013 and given a priority score of . This application is for 3.5 years of mentored training, with the reduced time due to his time on a KL2. He has had 5 publications since January 2013 with 3 related to this work. His current KL2 project appears to be on target with several abstracts presented, but no publications to date. More of a mentoring relationship with one of the pathologists would have suggested more of a learning opportunity in the area of vascular biology that was a weakness also in the prior application. It's not clear if the work proposed entirely describes the work needed to complete the master's in Clinical Investigation. The research plan has been streamlined and is both feasible and a good learning experience, but potential issues with recruitment are not completely addressed. He is in a highly supportive environment.

1. Candidate:

Strengths

- The candidate is a pediatric nephrologist who also did training as a transplant nephrologist. He will receive a certificate in clinical investigation in the fall of 2014.
- He was previously noted to have minimal publications with none related to the role of vascular injury in kidney transplant rejection. He has 5 publications since Jan 2013, with 3 on vascular injury in CKD (2 as first author). He also still has a biomarker patent pending in conjunction with prior mentor and current external advisor, Dr. : "Non-invasive methods for diagnosing chronic organ transplant rejection." He is also co-author with a mentor on a book chapter on vascular injury in kidney disease.
- He is working on 3 current projects that are highly relevant and have been presented as abstracts, but are not yet complete for publication. They all seem on target (45 of 60 recruited for his KL2 project) and are used for preliminary data for this proposal.

Weaknesses

- None noted

2. Career Development Plan/Career Goals & Objectives:

Strengths

- He has outlined 5 relevant formal courses. He will take no more than one per semester over 3 years.
- He states that he will expand his certificate in Clinical Investigation to complete an MS degree in this field.
- Participation in local, regional and national meetings is described and relevant to his training.

Weaknesses

- It's not clear that the courses described meet the requirements to complete the MS degree and how other degree requirements, such as a master's thesis, fit in with into his research plan, career development plan and timeline.
- In the prior review it was noted he had allowed limited time to learn vascular biology/pathology. Although he has added co-investigators and pathologists, Drs. , they are not mentors or advisors and so their role beyond conducting the Banff scoring is not expected to include teaching. Their letter of support acknowledges that they will include him in the Banff scoring process, but the mentoring aspect is not noted and, in fact, is not included as part of the Career Development Plan.

3. Research Plan:

Strengths

- Aim 1 will be a cross-sectional evaluation of blood and urine CKD-MBD factors and their association with to the Banff vascular injury score in patients with transplant glomerulopathy and other diagnoses. Aim 2 will look at up to 40 patients longitudinally to associate the markers with vascular injury and kidney function over 3 years. Aim 3 is described as exploratory and will evaluate genomic microarrays to seek novel pathways.
- Drs. will work with the candidate on this aim to evaluate the Banff score and variation in vascular injury in chronic allograft nephropathy.
- Design set up and longitudinal measures and assays are well described.

Weaknesses

- Statistical modeling for Aim 2 describes proportional hazards modeling, but the outcome is the 3-year eGFR. This is a continuous measure and not described as a time-to-event measure. Although drop-out is described and accounted for in recruitment for Aim 2, definitions for censoring patients are not laid out.
- Aim 2 will require recruitment and consenting that is not a part of Aim 1. Capacity to recruit and potential difficulties with recruitment and retention are not described except by saying that only 25 patients are really needed.

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

Strengths

- He now has 2 co-mentors (Drs.), 2 internal advisors and 1 external advisor (Dr.).
- Dr. held a K24 for 11 years, which just ended, and has provided mentorship for the candidate's KL2 mentored research.
- Advisors have expertise in areas that will support the candidate's research and career development.

Weaknesses

- It is not clear why at least one of the pathologist or a vascular biology expert is not in more of a mentorship role.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- KL2 placement and an internal seed grant attest to his overall support in his joint appointment.
- The joint appointment between S. Ill Univ and Wash. U has worked now for almost 4 years and has contributed to his ability to do research and publish with 75% protected time. Ongoing protected time is guaranteed for this award.

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- There are minimal risks and adequate protections are in place.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Children from 18 up to 21 will be included, but it's not clearly stated why those less than 18 will be excluded.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- He will complete a Program for the Ethical and Responsible Conduct of Science and Scholarship, participate in the CRTC Career Development Seminars that include some topics on ethics, and attend a Research Ethics lecture series.

Comments on Subject Matter (Required):

- A variety of relevant topics as well as case studies are described.

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

- Mentors will be included and senior research ethics faculty will be a part of the Program for the Ethical and Responsible Conduct of Science and Scholarship workshops and case study discussions.

Comments on Duration (Required):

- The Program for the Ethical and Responsible Conduct of Science and Scholarship is for contact hours, the CRTC seminars are 90 minutes and the ethics lectures are 1 hour.

Comments on Frequency (Required):

- The Program for the Ethical and Responsible Conduct of Science and Scholarship will be taken once, the CRTC seminars and ethics lectures will be attended for about 3 hours per year while on the award.

Select Agents:

Not Applicable (No Select Agents)

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

- No travel to national meetings is budgeted.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE, G1A

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE, M1A

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE, C1A

Only children 18-21 years old are included.

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.

In the event of an award, NIDDK staff must verify that the training requirement will be met.

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
June 18, 2014 - June 19, 2014

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