

## **B. Career Goals and Objectives:**

My overriding goal is to develop a career as a physician-scientist. Toward that end I have completed my clinical training in internal medicine and nephrology and continue to maintain my skills through limited clinical activities. Through the NKF fellowship I have learned to use a genetic approach for the identification of mutations, which cause kidney disease, specifically nephronophthisis. I am establishing a resource in collaboration with the division of nephrology and the sponsor's lab to recruit patients from the adult nephrology clinics at the University who have medullary cystic kidney disease, a kidney disorder similar to nephronophthisis, which occurs in adults. Analysis of the DNA from these patients will help us to refine the locus for disease and ultimately identify the genetic mutation causing the disease.

I believe that a genetic approach for the identification of proteins operant in the pathogenesis of disease is very powerful. In addition, an important compliment to this approach is the ability to employ the principles and methods of molecular biology to begin to answer questions about the function of these proteins in health and disease. I plan to use the mentored career development award to master these principles and methods using the proteins that I have helped to identify through the use of genetic techniques.

To achieve these goals I have chosen Bill Jones as the sponsor for this project as he is a world leader in the use of the genetic approach for the identification of genes relevant to human disease. He has participated in the identification of all of the genes, which cause nephronophthisis. In addition, I have had the opportunity to establish an excellent working relationship with him over the past two years and have been able to participate in some publications. I have also chosen Tom Lee as a co-sponsor for this project as he is a world class researcher, who has extensive experience in the characterization of proteins using the methods described in this proposal. In addition, both of these men are physician-scientists who will be able to help guide me through the issues related to successfully establishing a career involving both clinical and research components.

In addition, to the opportunity for bench research provided by the award I feel that an additional didactic component focusing on the state of the art of genetics and protein biochemistry will be an important supplement to my experience. I have already taken advantage of some of the opportunities available at the University. For example, during the first year of my NKF fellowship I participated in a training program for the use of fluorescent and confocal microscopes through the imaging core facility at the University.

During the second year of my NKF fellowship and for the remainder of my training I will be engaged in clinical and non-research activities at a level of 25% for the next several years in order to provide sufficient time for the assimilation of the skills required for a career in basic science.

**C. Career Development/Training Activities During Award Period:** During the award period I intend to divide my time between research activities and clinical/non-research activities in a ratio of 75% to 25%.

**C1. Research Activities:** I intend to devote approximately 75% of my effort to the research component during the training period. I intend to further divide that time into bench-top research activities and didactic components.

**a. Bench-top Research Component:** 70% effort/year

This component is to be fulfilled in a supervised setting in the laboratories of the sponsor and the co-sponsor as outlined in section 6. Research Proposal of this grant application.

**b. Didactic Research Component: 5% effort/year**

Year 1

Department of Genetics University

HG 541. Molecular Genetics (Fall, 3 cr.)

A combination of classic and current papers in molecular genetics will be selected to accompany the lecture material (1-2 papers per lecture). The foundations of modern genetics will launch the course, including both the fundamentals and current research methods for analysis of gene structure and gene expression. The gene expression component will include positive and negative regulation of transcription and mRNA splicing and turnover. The basics of DNA recombination, repair, and transposition will be covered in relationship to cancer, evolution, and mutagenesis. Strategies for developmental regulation will be presented. Parallels between prokaryotes and eukaryotes will be drawn, and comparisons will be made between the temporal and spatial control of gene expression in vertebrates and invertebrates. Genetic engineering topics will include gene targeting and transgenesis, with applications to understanding tissue specific control of gene expression. The course will include discussion of the Genome Project, identification of disease genes and an introduction to the medical application of molecular genetics including gene therapy.

Department of Genetics University

HG 544 Basic Concepts in Population and Statistical Genetics

The objective of this module is to introduce the fundamental concepts and methods of population and statistical genetics as they apply to human populations. Topics include the major forces impacting population genetic variation, quantitative genetics, linkage analysis, tests of association, complex or multi-factorial traits and diseases, and the role of the environment. Discussion of many of these topics will be based on particular papers from the literature.

Year 2

Department of Genetics University

HG 803 Fall - 804 Winter - Current Topics in Genetics

This course is intended for second year graduate students and is designed for intensive training in critical analysis of current literature and discussion of new methods in molecular and human genetics. Recent topics have included large-scale analysis of gene expression using SAGE and microarrays, cancer genetics, gene therapy, and developmental genetics. Enrollment is limited to 10 students.

Biological Chemistry 550, Protein Structure and Function

Covers fundamental aspects of protein and nucleic acid structures, macromolecular recognition and interactions in signaling, protein maturation, gene expression and catalysis. This course is composed of lectures, student-led discussions of the primary scientific literature and hands-on computer tutorials designed to integrate and extend the lectures and literature discussions.

Years 3-5

Anticipate 5% effort per year and will select additional didactics from the curriculum available through the University graduate programs or technical seminars based upon the needs of my professional development and the recommendations of sponsors.

#### Basic Science Seminar in Nephrology

This is a seminar supported by the Division of Nephrology at the University which focuses on topics in basic science research relevant to nephrology. The seminar is roughly divided equally between journal article review and the presentation of original research from faculty at the University as well as invited faculty from outside institutions. The applicant presents 2 times per year in this setting.

**C2. Clinical/Non-research Activities:** I intend to devote 25% effort to clinically related non-research activities during the training period. This will be divided into activities directly relating to patient care and clinical conferences or seminars.

**a. Direct Patient Care Activities:** 20% effort/year

The applicant will function as the attending physician on one of the three renal consult services at the University for a maximum of 4-6 weeks in two-week blocks of time. In addition, the applicant will maintain a continuity clinic in the general nephrology section for one-half day/week.

**b. Clinical Conferences:** 5% effort/year

Nephrology clinical conference is one hour per week and reviews clinical cases seen on one of the three renal consult services at the University or the VA medical center affiliated with the University.

Nephrology journal club and research conference is one hour per week and addresses the clinical literature pertinent to the practice of nephrology or the original research of one of the faculty or fellows in the division or an invited outside speaker distinguished in the field of clinical or basic science renal research. The applicant presents 1-2 times per year in this forum.

Medical grand rounds is one hour per week and covers the spectrum of topics in internal medicine.

**C3. Committee for career development and consultants with technical expertise:** I have assembled a committee of senior faculty members from the research community. The candidate will meet at least biannually with committee members to review interval progress with regard to the research proposal as well as to evaluate progress toward the ultimate goal of establishing a career as an independent investigator. Committee members will also be available for questions of experimental design or methodologies relevant to their particular area of expertise throughout the duration of the training period. Consultants were chosen to supplement the skills of the sponsor and co-sponsor in particular areas of expertise relevant to this project. Consultants will be available for technical advice throughout the duration of the training period.

Committee Members:

- a. **Bill Jones, MD.** Professor in the Departments of Human Genetics and Pediatrics & Communicable Diseases. Has taken a leading role in the identification of all of the genes, which are presently known to cause nephronophthisis and has participated in the early characterization of all of these protein products of these genes.
- b. **Tom Lee, MD.** Associate Investigator, Medical Institute, Professor in the Departments of Biological Chemistry and Internal Medicine. His laboratory is interested in the role of protein-protein interaction domains in cell biologic processes. They are presently studying the role of these interaction domains in cell signaling and polarity.
- c. **Adam Lane, MB, BChir.** Professor of Internal Medicine Division of Nephrology. Fifteen years of experience as the division chief for nephrology has given him an unparalleled experience with career guidance and development in the context of a career in academic medicine. His research focuses on the biology of glomerulosclerosis. This includes a particular focus on the biology of the podocyte and the role of decreased podocyte number in glomerulosclerosis. He is also examining the role of the aging process on glomerular biology and learning how this is linked to the remarkable increase in ESRD in later life.

Technical Consultants

- a. **Ann Miller, MD, PhD.** Associate Professor of Pathology at the University. Director of the electron microscopy laboratories at the University of Michigan. Dr. Miller's research interests include investigations of basement membranes, the specialized extracellular matrices, which provide a substratum for cell attachment and thereby influence the differentiated phenotype of cells.

**D. Responsible Conduct of Research:** The applicant has undergone training through a web-based training program offered at the University found at <http://www.university.edu/training/RCRtrainingmodules.html>. The following is a summary of the program and excerpts from the website. All of the modules listed have been successfully completed by the applicant and will be maintained throughout the training experience. Program for Education and Evaluation in Responsible Research and Scholarship, PEERRS, is a web-based instruction and certification program for members of the University community engaged in or associated with research. All University faculty, staff and students are required to use the modules and certification tests to improve their knowledge and awareness of responsible research practices.

Modules:

1. **Foundations of Responsible Research Conduct:** publication/authorship, intellectual property, conflict of interest, signatures, plagiarism, misconduct reporting
2. **Research Administration:** UM procedures/forms, PI responsibilities, pre- and post-award activities, federal regulations, important contacts
3. **Conflict of Interest:** definitions and recognizing potential conflicts, responsibilities toward students/colleagues, consulting and conflict of commitment, sponsored project and technology transfer issues
4. **Human Research:** It covers definition of human subjects research, why human subjects research is regulated, regulatory and ethical responsibilities of the PI, IRB, and University.
5. **Animal research:** principles and regulations for animal care and use, regulatory and ethical obligations of researchers, reporting requirements, obtaining approval