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Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142
1001 E 3rd St
Bloomington IN 47405-7005

Dear Dr. Brun,

I am writing to apply for the assistant/associate professor position, as advertised on the NatureJobs website. I am well-acquainted with the excellent reputation of your department, and I would be honored to join the Indiana community as an assistant or associate professor.

For the past 13 years, I have studied genetics, 9 of those years as an assistant professor at Meharry Medical College in Nashville. I have been the primary investigator of a laboratory that has studied the genetics of Alzheimer's disease in African-Americans. Among my duties that would fit with the Assistant/Associate Professor position are:

1) Research in biomolecular networks, including signaling and gene regulation:

- For the past 13 years, my research has focused upon elucidating the genetics of neurodegenerative disease. During this last year, I have used systems genetics in mice to reveal a common regulatory mechanism involved in many of the neurodegenerative diseases in humans. I anticipate my work will soon be in press this year. The research and the projects that would stem from it can be adapted to provide graduate and undergraduate students with research opportunities. In addition, I have been a frequent presenter at genetics and neuroscientific meetings, as well as co-organizer for the Meharry/Vanderbilt Genetics Training Program and the Annual Neuroscience Symposium at Meharry Medical College.

2) Teaching in Biology:

- I have taught classes in Biochemistry Laboratory, Medical Genetics, Topics in Genetics, and Psychiatric Genetics, and have successfully trained postdoctoral researchers, graduate students, and medical students in the laboratory. I have had a successful record of funding and anticipate continued funding with a novel research plan on the use of systems genetics for the study of neurodegenerative disease. I can think of no better environment than the Indiana University Department of Biology and Biocomplexity Institute in which to grow as an educator and scientist.

I am enclosing my CV and statements of research and teaching interests. Copies of publications and four letters of recommendation are being mailed under separate cover. Thank you very much for your consideration.

Sincerely,

Robert Clark, Ph.D.

Robert F. Clark, Ph.D.

Statement of Research Interests

For the last 13 years, I have devoted my research to the study of the genetics of Alzheimer's disease (AD). When I began my studies as an assistant professor at Meharry Medical College, I employed two major approaches to study Alzheimer's disease genetics. In the first approach, I chose to investigate presenilin function using the powerful genetic methods available in *Drosophila*. I characterized the presenilin gene in *Drosophila*, studying its gene structure, its developmental transcription pattern, and its localization in embryos, larvae, pupae, and adult flies. I attempted to produce null mutations of this gene to study their effects in *Drosophila* via P-element insertion mutagenesis. I also am currently determining which genes interact with the presenilin gene. Fly genetics and yeast two-hybrid approaches are being used to find these presenilin-interacting genes.

My second approach in understanding AD genetics was to identify genes that contribute to the risk of late-onset dementia (LOD) in the African-American population. Towards this goal, I ascertained the efficiencies of a variety of different methods in reaching, recruiting, and enrolling African-American Alzheimer's disease and LOD patients and controls. Using this newly recruited cohort of African-American AD and LOD patients and controls, I characterized genes that contribute to the risk of AD and LOD in the African-American population, most significantly in those genes involved in hypertension. I observed many significant genetic associations in African Americans and AD, most significantly being the multi-gene interaction between the ACE, B2AR, A2M, and APOE loci. I hope to increase the significance of these findings as I recruit and analyze more samples in the next few years.

Throughout my AD studies, I have been most interested in the problems of multifactorial genetics. I had used the tools available in my lab to best analyze the relationship on how specific genes can work in concert to produce a disease phenotype. However, I have realized that more powerful methods were needed. The work from Dr. Robert Williams at UT-Memphis has shown me powerful new tools to study and understand complex traits and diseases (like AD) by investigating natural genetic variation in gene expression levels in mice to understand molecular networks. As a Visiting Scientist in the laboratory of Dr. Robert Williams in the Department of Anatomy and Neurobiology at the University of Tennessee - Memphis, I have begun to characterize major common regulatory elements and gene networks involved in neurodegeneration. By exploiting a recently developed microarray technology called transcriptome-QTL mapping (or system genetics), I have recently uncovered a gene network in mice that includes homologues of many of the major genes involved in neurodegenerative diseases in humans. This system genomics approach identifies the sources of variation in gene expression in the mouse brain and enables global mapping of factors regulating such transcriptional responses. Genes in this neurodegenerative disease gene network and the quantitative trait genes that regulate this network will continue to be evaluated, as well as the polymorphisms that control these genes. I would bring such

technologies (i.e. microarray, advanced biostatistics) to my laboratory to illuminate not only the study of AD genetics, but the genetics of other neurodegenerative diseases as well.

My work in your institution would be a continuation of the studies I have initiated using system genetics to study neurodegenerative disease in humans. This original research plan is novel and eminently fundable for at least five years. Initially, I will continue my studies described previously of the neurodegenerative disease gene network I have uncovered using the biostatistical suite of programs called WebQTL (http://www.genenetwork.org/) via the internet, as well as studying the expression and polymorphisms of the genes in the network in the laboratory. Next, I will generate a large panel of aged recombinant inbred mice to compare with the younger mouse panel to evaluate genes that are critical for cellular changes in age-related neurodegeneration. Additionally, I will then extend this system genetics approach to human populations. Human homologues of the mouse genes in the gene network will be evaluated. Polymorphisms in these genes will be used to evaluate their association with AD, using molecular genetic methods and biostatistics I have previously employed in my African-American AD panel. Also, microarrays of human brain tissue of a variety of neurodegenerative diseases (from the Brain and Tissue Bank at the University of Maryland) will be evaluated for changes in expression of the genes in the neurodegenerative disease gene transcriptome. The characterization of these genes and their regulation will help not only in revealing the presently unknown functions of many of these genes, but will likely be important in the development of diagnostics and therapeutics for AD and other age-related neurodegenerative diseases. Furthermore, all the experimental procedures necessary to get results from the described aims are easily doable for undergraduate, graduate, and medical students, providing excellent experience in mouse and human molecular genetics and bioinformatics.

Robert F. Clark, Ph.D.

Statement of Teaching Philosophy and Experience

The best part of being a teacher is meeting and interacting with students, and getting to know them and their life goals. Unlike other social endeavors, though, teaching allows the teacher to help students achieve their career goals by training them to think like biologists, and by providing mentorship.

In the field of biology, it is important for students to know basic scientific facts, but also to be able to apply those facts to new situations, and to evaluate the mass of new information that is released to the general public every day. These skills are critically important for those students planning careers in the health-care professions such as medicine and dentistry. However, it is also important for biologists in non-health related fields to learn these skills so that they can make informed decisions about their own health or about their particular work-related problems. In my classes, I strive to teach the basic language and principles of biology, how to apply that basic knowledge to many situations, and the critical thinking processes that biologists use to evaluate new information.

I use several different teaching methods to achieve my learning goals, but the overarching theme in my classroom is active learning. For example, during lecture, students are involved as often as possible by soliciting their input, opinions, and questions, or to determine their level of prior knowledge. Small group activities are used to quickly cover basic information from the textbook and apply it to important concepts, to discover the connections between topics, or to discuss homework assignments. Closure on the small group activities is achieved by bringing the class back together to discuss common problems or to share solutions. Research shows that active learning techniques enhance learning and retention because they allow the students to encounter the material in several forms, such as reading the text, listening to and taking notes on a lecture, and discussing with fellow students. More importantly, these methods provide the opportunity for students to teach each other, the most effective way to learn. Active learning methods also provide the opportunity to interact with students individually, which improves learning.

It is critical that exams be written to reflect the level of difficulty and types of thinking that the students deal with in class or in homework assignments. Students can expect exams to consist of an appropriate mix of recall, application, synthesis, and evaluation questions. For the problem solving and evaluation questions, the students are graded on the process of reaching a well-supported answer, rather than the answer itself.

Student learning is improved when responsibilities are clearly defined. It is important for a teacher to resist their immediate instinct to a student in distress by taking on their responsibilities, which does not aid in their personal or educational development. It is more helpful to work with the student to establish a reasonable plan to enable them to meet their responsibilities.

At the end of my courses, which have all been student-evaluated positively, students will have a solid knowledge of biology, and be able to use that knowledge to solve problems. They will also understand the process by which scientists discover new information so that they can think like scientists and evaluate new information scientifically. These goals are achievable for all students who come to class regularly and participate actively.

I have successfully taught my classes using such methods since my days in graduate school at UC Irvine. I taught and honed my skills in teaching as a teaching assistant in the school's Biochemistry Laboratory course for four years. My success was evident as in my fifth year I was chosen to be the Course Coordinator for all the Biochemistry Laboratory courses that year. Even though I had to devote myself 100% to my research in my years as a postdoctoral research associate and research instructor, I had the opportunity to teach graduate students, medical students, undergraduate students, and technicians in the laboratory, as well as taking classes in Public Speaking. As a faculty member at Meharry Medical College, a small historically-black medical college, I was given the opportunity throughout my years there to teach in courses in Medical Genetics, Psychiatric Genetics, and Topics in Genetics, as well as teach in the laboratory to graduate students, medical students, technicians, and undergraduate students (most notably in the NIH-sponsored program Research Education for Undergraduates). I was always rated very highly by the students in all my courses.

At your institution I am best qualified to teach courses in neuroscience, basic genetics, cell and molecular biology, and bioinformatics. If you had no previous plans on implementing such courses before, I would like to develop these courses at your institution. I would also be interested in developing and teaching courses such as molecular genetics, molecular neurobiology, and biostatistics. All these courses are important in the development of future biologists, as well as for those students planning careers in the health-care professions.