

FACULTY OF MEDICINE

University of Toronto

Department of Medical Genetics and Microbiology
Graduate Department of Molecular and Medical Genetics

November 1, 2005

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

To Yves Brun:

I am writing in support of Geoff Clarke's application for a faculty position in the Department of Biology at Indiana University. I was on Geoff's graduate supervisory committee for five years. I saw real growth in Geoff's scientific ability over that time. He started with little more than a desire to study developmental biology and to make a knock-out mouse. He has done both admirably, but also much more. He has done a superb job in analysing the phenotype of the ROM1 null mouse he made. He learned anatomy and physiology in doing this analysis and now has by far the best analysed retinal mutant known. I was particularly impressed with his ability to take a hard nosed quantitative approach to the work. I think his acquisition of new conceptual and technical skills in analysing his mutant speaks well for this future independent research career.

In addition to being a good researcher, Geoff is a very pleasant fellow to interact with as well. He has a good and subtle sense of humour. In a graduate course on developmental biology that I taught, Geoff was an active participant and an able discussant. He is a very nice guy. Although Geoff can sometimes seem a bit quiet on first meeting, he is a thoughtful person who considers his points before blurting them out. He does not overwhelm you with his brilliance, but impresses over the longer term with his considered and hard working approach and careful analyses. I'm happy to strongly recommend Geoff for this position.

Sincerely,

Derek van der Kooy
Professor

Medical Sciences Building, Room 4388
1 King's College Circle, Toronto, ON, M5S 1A8

<http://www.utoronto.ca/medicalgenetics/>

GREAT MINDS FOR
A GREAT FUTURE

November 8, 2005

Re: Letter of Support For Dr. Geoff Clarke

Dear Sir/madam,

Dr. Geoff Clarke joined my lab in May 2004, and expressed an interest in the cell-based proteomics strategies we were using to study protein function and topology of complex cellular networks involved in insulin-dependent biological and biochemical processes. Dr. Clarke completed his PhD at the University of Toronto in the lab of Rod McInnes (Hospital for Sick Children) where he analyzed the *in vivo* function of the rod photoreceptor-specific protein rom1 (**Clarke, G.**, et al (2000) Rom-1 is required for rod photoreceptor viability and the regulation of disk morphogenesis. *Nature Genet.* **25**: 67-73.) This research led to his developing an interest in using computational techniques to address problems in cell biology. Specifically, he had observed a common pattern in the kinetics of cell loss in several examples of inherited blindness, and subsequently developed a mathematical model able to describe the kinetics of cell loss that occur in a variety of inherited and acquired neurodegenerative diseases. This model, referred to as the *Mutant Steady State* (MSS) model, contradicted the established dogma that neurodegenerative cell loss was the result of a gradual accumulation of intracellular damage that slowly increased the risk of any cell undergoing apoptosis. Instead, his analysis demonstrated that the risk of cell death remained constant over the lifetime of a cell, suggesting that apoptotic commitment results from stochastic fluctuations in cellular events (**Clarke, G.**, et al (2000) A one-hit model of cell death in inherited neuronal degenerations. *Nature* 406: 195-199.)

One of Dr. Clarke's goals as a postdoctoral fellow in my lab is to develop quantitative models of the biochemical networks regulating the spatial deployment of GLUT4 in muscle cells and has begun this work by building small 'toy' models of biochemical switches in the hope that the analysis of these simple networks will yield important information regarding the behaviour of the larger, more realistic networks functioning within insulin-sensitive target tissues. My lab has recently used a mass spectrometry-based protein complex identification (MS-PCI) strategy to identify networks that may link changes in the actin cytoskeleton to the spatial interaction and dynamic deployment of insulin signaling intermediates that promote GLUT4 transport to the plasma membrane. Our efforts have led to the identification of a vast array of previously uncharacterized proteins, representing different functional classes, including raft-associated proteins, exocyst proteins, molecular motors, GTPase activating proteins, transcription factors and cytoskeletal regulators. In a preliminary validation of the MS-PCI data sets, Dr. Clarke observed that one of the proteins we refer to as COP1 (complexed with PHIP) codes for a novel actin-binding protein which displays striking

polarized morphologies and co-localization with IRS-1 and activated AKT in response to insulin treatment of skeletal muscle cells. Within the one year tenure in my lab, Dr. Clarke has mastered the use of an automated spinning disc confocal digital imaging platform and which allowed him to capture images of the intracellular itinerary of COP1 under insulin stimulated conditions. He was not able to complete any of the biochemical analysis of COP1 and how it may contribute to the nucleation of the IRS-1/PI3K/AKT signalosome and in the transmission of signals that promote GLUT4 distribution.

Although I have only known Dr. Clarke for only 12 months, there is no question that he is one of the brightest post-doctoral fellows I have met. He easily conversant in cell biology systems as with complex technologies of the physical sciences, computation and mathematics. He is also a methodical scientist who will undoubtedly bring to fruition his computational objectives which is the area he is most passionate about and has the potential to become a leader in the field of interdisciplinary bioscience.

Sincerely,

Dr. Maria Rozakis Adcock, PhD.
Canadian Institutes of Health Research Scholar
Associate Professor
Faculty of Medicine
University of Toronto