



The Hospital for
Sick Children

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

Dear Sir:

Re: Dr. Geoff Clarke/Faculty Position/Department of Biology/Biocomplexity Institute

It gives me great pleasure to write a letter in strong support of Dr. Geoff Clarke's application for a faculty position in Systems Biology/Microbiology in the Department of Biology/Biocomplexity Institute, at Indiana University.

Geoff was an outstanding graduate student in my laboratory from 1992-2000. He obtained one of the finest degrees of any student I have ever had (in a group of more than 30 graduate students). Moreover, I would place him in the top 3% of all students with whom I have been familiar (more than 200) in the Dept. of Molecular and Medical Genetics over the past 25 years.

As inspection of his transcripts demonstrates, his first two years of undergraduate education were not outstanding, but subsequently he has been an 'A' student in marks and performance.

Geoff's research in my lab was complex, elegant, and time-consuming, but the results were pretty remarkable. His project was to begin to determine the biological function of a photoreceptor-specific membrane protein that we had discovered, ROM1. Geoff did a knockout of the *Rom1* gene in mouse. This work has led to two first-class papers. The first of these, entitled 'Rom-1 is required for photoreceptor viability and the regulation of disk morphogenesis', was published in *Nature Genetics* in 2000. In my view, this work by Geoff is one of the better characterizations of a photoreceptor protein mutant that has ever been done. The paper makes a major contribution to knowledge of how photoreceptors are made and maintained. The research was almost entirely Geoff's, although he enlisted the help of a number of key collaborators from the US and Canada.

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Geoff's second major paper was published in Nature in 2000. It was entitled "A one-hit model of cell death in inherited neuronal degenerations. This work was an unexpected product of the *Rom1* knockout research, and began when we started to think about the biological meaning of the fact that cell death in the mutant photoreceptors observed exponential kinetics. The outcome, which was the result of an exciting game of intellectual ping-pong between Geoff and I, turned out to be of general significance and appears to be generalizable to most retinal degenerations and perhaps other neurodegenerative diseases as well.

In addition to these two major projects, easily enough work for a first-class Ph.D. by themselves, Geoff collaborated with a group in Dallas to provide direct evidence that the *ROM1* gene interacts with another gene called *RDS* to cause a form of human retinal degeneration called digenic retinitis pigmentosa.

Finally, he wrote most of an excellent review article on inherited retinal degenerations for Clinical Genetics (Clin. Gen. Special issue 2000).

All of this work was done with admirable independence and skill. Geoff undertook an important and ambitious project and succeeded. He was also one of four finalists in the Student Award competition (predoctoral basic science category), at the American Society of Human Genetics Annual Meeting, San Francisco, Oct. 1996, for his research on the genetics of the *ROM1* gene. The competition for this prestigious award is intense and the honour of being a finalist is very substantial. His selection as a finalist reflects the strong positive view of the human genetics community of his work.

Geoff was probably the most unusual student I have ever had, in terms of the originality and independence of this thinking. He fascinated me, for example when he would read physics texts at the bench while he was running protein gels. Without his mathematical interest and intuition, the work on cell death would never have progressed and reached the exciting maturity it has achieved. I have every reason to believe that Geoff will become a first-class independent scientist.

Geoff is unusually intelligent and industrious, very reflective and analytical, very good at the bench, interactive and able to learn from others. It goes without saying that he is superb at interpreting his data. I would be more than happy to have him as junior faculty member, if I was leading a department at present, and knowing him as I do.

Geoff has no substantial weaknesses although I note that, until his success in my lab generated a lot of interest and tremendously positive comments, he was somewhat lacking in self-confidence initially. However, this tendency resolved when he got such outstanding results. His work led me to being asked to write a review article for the Annual Reviews of Neuroscience in 2003 (Pacione et al. Ann. Rev. Neuroscience 26, 657 -700), an invitation that reflected the impact of his article in Nature.

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Finally, I should add that Geoff was my lab manager for three years, and also did an excellent job in this position. This position requires both interpersonal and organizational skills, and he has an abundance of both.

In summary, I have every confidence that Indiana University would be a superb place for Geoff, one where he will be able to continue to productively and originally fuse his interests in biology and computation. I am certain that Geoff will make important contributions.

Yours sincerely,

A handwritten signature in cursive script that reads "Roderick R. McInnes".

Roderick R. McInnes, M.D., Ph.D.
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University Professor,
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RRM/dc