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Professor Yves Brun,
Systems Biology/Microbiology Faculty Search,
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CONFIDENTIAL

Re: Dr. Geoff Clarke's Application for the Department's Assistant Professorship in Computational Systems Biology

Dr. Clarke has asked that I send you a letter in support of his application to your Center's faculty competition. I am very pleased to do recommend this exceptional candidate to you.

I can recommend Dr. Clarke in the strongest terms. He is a future leader and innovator. After completing a first class doctoral thesis in experimental cell biology (the results of which were published in *Nature* and other maximum impact scientific journals), Dr. Clarke attracted CIHR (Canadian Institutes of Health Research; the Canadian equivalent of the NIH) Postdoctoral Fellowship support to work with me and so expand his research skills to include mathematical and computer-based methods in cell science research and the biochemical control of programmed cell death. In his doctoral studies, Dr. Clarke had discovered that the degeneration of neural tissues by programmed cell death follows the same kinetic mechanism in all cases thus far reported. This process of cell attrition has been termed "one-hit cell death." A preliminary mathematical analysis of the one-hit kinetic death mechanism was reported at that time by Dr. Clarke, myself, and our colleagues.

During his CIHR postdoctoral period with me, Dr. Clarke expanded his skills into biomathematical and computational methods and then applied this knowledge to substantively advance the understanding of (a.), the dynamics of one-hit cell death and (b.), the role of this attrition process in complex heterogeneous tissues. This work has recently appeared in the *Brain Research Bulletin* and the *Journal of Theoretical Biology*. Its principal finding is that all neuronal death kinetic patterns reported to date exhibit what is known as scaling universality. (The universality culprit identified by our analysis is the so-called stretched exponential family of distributions.) This means, in essence, that the one-hit death trigger

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model of the single neuron's demise can quantitatively explain all neurodegeneration trends thus far reported for both homogeneous and heterogeneous neuropils. Moreover, our methods for the first time allow the death-induction heterogeneity of these richly complex environments to be quantified.

Dr. Clarke has now returned to the experimental setting to prepare for an academic career in which he will direct studies that combine empirical, mathematical, and computational methods in cell science. Having worked with Dr. Clarke on a daily basis for several years in my laboratory, I can affirm his commitment to maximum excellence in all phases of the planning, execution, and reporting of scientific investigation. A confident and completely dedicated scholar, Dr. Clarke is also exceptionally pleasant, congenial, and modest.

Dr. Clarke's track record of significant accomplishments is already impressive. I take the liberty of suggesting that, from the Institute's perspective, Geoff brings multiple distinct strengths: He is a young scientist for whom "boundaries" or "walls" alienating experimental from mathematical discovery do not exist in biology, or indeed in any discipline. Although trained originally in strong experimental settings for molecular cell biology, he has dedicated himself to acquiring modeling and theory skills and using these creatively to advance his work. Geoff's own gift for clear, precise communication, both oral and written, will also help make him a productivity center and a role model for colleagues and trainees.

Since Geoff came to me with a classic molecular cell biology background I concentrated his biomathematical training in stages that built naturally from this foundation. His computational work advanced his capability with both deterministic and stochastic modeling of kinetic models using MATLAB and Mathematica. I cannot speak to any development of his programming skills in, for example, C++ or LISP or S, or in bioinformatics database engineering, that may have taken place since his departure from my group.

True to his strong foundation in empirical cell biology, Geoff had limited tolerance for the "toy models" that theorists like myself find so useful in searching for and expressing the essential design themes of living matter. For that reason I focused his work in the cell death scaling problem, where he could stay in immediate contact with the data while assessing the models. Geoff's vision, as I experienced it, is biological research carried out in new settings where experiment and computer-based modeling and simulation are essential partners.

Please do not hesitate to contact me if there is additional information I can provide.

With best wishes,

Yours truly,

Charles J. Lumsden, Ph.D.(Theoretical Physics, University of Toronto, 1977)
Professor of Medicine