University of Michigan Medical School
Department of Ophthalmology
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Ann Arbor, Michigan 48105

November 9, 2004

Biocomplexity Faculty Search Committee
c/o Prof. Rob DeRuyter vanSteveninck,
Department of Physics
Indiana University
Swain Hall West 117
Bloomington, IN 47405-7105

Dear Search Committee:

I take great pleasure in recommending Dr. Rande Worth for a position on your faculty. I have known Dr. Worth for about nine years, as his instructor, graduate mentor, briefly as a post-doctoral advisor, and most recently as a collaborator. I first met Rande as a graduate student when he walked into my office asking to join my research group. He was bright, energetic, and *very* focused for such a young man. As I expected, he did excellent work. When he was finishing his graduate program, he said he wanted to work as a post-doctoral fellow for Dr. Schreiber because he could learn more molecular biology to complement his cell biology and biophysics training in my laboratory, while continuing his work on Fc receptor signaling. I concurred that this was a good choice. He is now in his fifth year of post-doctoral training and is ready to advance to a junior faculty position.

When Rande joined my group, he was given the task of sorting out the possible physical and function interactions of the integral membrane proteins FcγRIIa and CR3. As the neutrophil system had so many receptors and interactions among the receptors, we chose to pursue experiments in transfectants to simplify the task. As CR3 possesses all the machinery to support phagocytosis and a genetically engineered tail-minus form of FcγRIIa could not mediate phagocytosis, we decided to look for a functional interaction by attempting to rescue defective FcγRIIa phagocytosis of the tail-minus form of FcγRIIa by co-transfection with CR3 (so-called reverse genetic complementation). While performing these transfection experiments, Rande noticed that the phagocytosed red cells in the FcγRIIa tail-minus plus CR3 cells weren't being digested properly and had phagosomes that looked different from those of the FcγRIIa wild type. He went on to demonstrate that, indeed, lysosome fusion was heavily dependent upon the presence of the FcγRIIa tail. This genetic complementation system is unique and powerful in sorting out how membrane proteins interact with one another in cell membranes.

While in my group, Rande participated in a landmark study entitled "Imaging Sustained Dissipative Patterns in the Metabolism of Individual Living Cells" in the *Phys. Rev. Lett.* This physics paper showed, for the first time, the existence of dissipative chemical structures in cells, which had been anticipated by theoretical physicists for almost 40 years. This paper utilized a novel high-speed imaging technique developed in my laboratory. This technique uses shutter speeds on a nanosecond time-scale to "freeze" the molecular motion of small molecules, such as calcium ions, within a living cell. By rapidly downloading these images, one can create high-speed stop-action movies of metabolite and signal movements within a cell. Rande played a key role in assembling and trouble-shooting the new imaging/computer system required for this project. He also performed many of the high-speed imaging experiments in this paper. The study will become one of the key papers in the emerging field

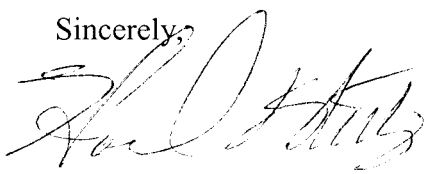
of biocomplexity. These chemical waves are an integral feature of the signal transduction system, as shown by subsequent papers from my group.

Rande continued with the FcγRIIa project in Dr. Schreiber's laboratory. He prepared a variety of FcγRIIa molecules using site-directed mutagenesis. In a collaborative study with my group, Rande found that the LTL sequence of amino acids of the internal domain of FcγRIIa was necessary for phagolysosome formation. Importantly, he combined high speed imaging (my lab) and genetic engineering (Dr. Schreiber's lab) to show that expression of FcγRIIa molecules lacking the cytoplasmic LTL sequence lose a calcium wave which propagates from the plasma membrane to the phagosome, which we published in *PNAS*. Thus, he has begun to define the organelle-to-organelle signaling circuitry that promotes tissue destruction in inflammatory diseases, such as arthritis, and in normal host responses to invading pathogens. Indeed, peptides based on the LTL sequence may become useful as therapeutic agents in certain chronic inflammatory diseases.

I believe that Rande is an excellent candidate. As outlined above, he is well versed in the established fields of molecular and cell biology. In addition, with a proper start-up package, he could set-up cutting-edge high speed imaging methods. He also has established interests in clinical problems. Moreover, he has experience in writing and obtaining funding to support his salary as a post-doctoral fellow. I am confident that you will find him to interact well with other research groups, which should be very useful in establishing team or program project type efforts.

Rande is a very personable young man. He is friendly and outgoing. He is a very popular among his labmates. I am confident that he can only improve the chemistry of any gathering with which he participates. His ability to mentor young students and to get new ideas to work in the laboratory will serve him well in the future. I would rate Rande as one of the best students from my laboratory. I am confident that he will become a leading faculty member with your support.

Sincerely,



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