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Dear Search Committee,

I am writing on behalf of Jamie Bacher's application for your position at Indiana University. Jamie was a student of Andy Ellington here at the University of Texas. I interacted with Jamie extensively over a period of maybe three years, at times holding weekly lunch meetings with him and a few other people in Andy's lab, chiefly Ichiro Matsumura. Our discussions centered around evolutionary questions and how some of the then new methods in biotechnology could be used to address those questions. Jamie and I have one paper together out of that time, although my role in that study was minor. Since leaving Texas, Jamie has periodically visited or contacted me for advice about his work; he and I both attended a Gordon Conference this summer, where I was able to view his latest results. I do not know anything of Jamie's teaching experience, so will address only his research.

To place Jamie in perspective, he is one of a handful of junior people working at the interface of classical evolution, biochemistry, and the biotechnology enterprise called directed evolution. There are, of course, many students being trained in biochemistry and directed evoution, but few who take much of an interest in a classical perspective and think about evolution per se. The closest parallel to Jamie I can think of is Niles Lehman, now a professor at Reed College, who worked with Jerry Joyce and later with Mike Lynch. Jamie has worked with Andy (for his Ph.D.), briefly with Pim Stemmer at Maxygen, and now with Valerie Crecy-Lagard at Scripps. So Jamie has not worked directly with a traditional evolutionary type, but he instead has worked with several people who span the gap.

Jamie's projects have included (i) evolution of organisms that use "unnatural" amino acids (at Texas), and (ii) evolutionary significance of recombination (at Scripps). The former topic is one that addresses aspects of the evolution of early life (genetic code) and has been experimentally approached by relatively few people. Jamie did at least two studies on that subject here, one using a bacterium (E. coli) and the other using the RNA phage Q□. Both studies adapted the organism to grow on a fluoridated tryptophan instead of the normal tryptophan. The "unnatural" or novel fluoridated tryptophan is substituted for tryptophan in the media (the bacterium is blocked from synthesizing it), and the novel amino acid has a side group that should interfere with the normal protein folding. Can an organism evolve to accept the novel amino acid in place of the original one? The outcome with E. coli was contrary to the hoped-for evolution, because the bacterium evolved to become highly discriminatory against the fluoridated amino acid and thus very efficient at scavenging normal tryp. I seem to recall that the evolved bacterium

continued to incorporate a large amount of the fluoridated amino acid despite its discrimination. In the Q□ study, the phage acquired several mutations that improved its growth in media with the fluoridated tryptophan, but strangely, none of those changes involved replacing tryptophans with other amino acids. Jamies seems to have continued this line of work at Scripps, with Paul Schimmel.

In his work on recombination, Jamie is tackling one of the most fundamental questions of classical evolution: the significance of recombination. Using a naturally competent bacterium (Acinetobacter), strains that differ only in DNA uptake genes are evolved in parallel to see which type does better. Competence is the natural uptake of DNA by a bacterium with occasional replacement of homologous chromosomal DNA. Thus competent bacteria recombine with other bacteria in the culture (DNA is released into the culture at some low rate). Isogenic strains lacking functional competence genes do not recombine. He has adapted several replicate lines and does not see a significant effect of recombination, matching results in some of the few other studies of this sort.

Jamie is an experimentalist, and I do not think that will change. He is interested in the conceptual foundations of evolution but I do not see him making his own theoretical contributions. However, he is far more knowledgeable about the biochemical foundations of life and vastly more versatile with the molecular techniques needed for this work than is the even the most superbly trained molecular evolutionist. So he offers a great complement to a department that already has traditional evolutionary biologists, and he will pursue a unique and highly relevant research program, addressing questions that appeal to a wide audience. I think Jamie offers a unique combination of questions and perspectives to almost any applicant pool for an evolution position and is worth interviewing for that perspective.

Sincerely yours,

Jim Bull

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