

November 9, 2005

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Dear Search Committee,

It is a pleasure to recommend Jamie Bacher for a faculty position at Indiana University. Jamie originally joined my lab with the intent to study the origin and evolution of the genetic code, a fundamental characteristic of all of life. His accomplishments were both unique and brilliant. He made an unnatural organism. He slowly but decisively managed to evolve an organism from the use of tryptophan to the use of 4-fluorotryptophan, an unnatural amino acid analogue. This took over 3,500 hours of continuous evolution, which in practice meant that Jamie spent many, many nights transferring strains at 11 PM, or 2 AM, or 5 AM, or whenever the strain happened to be ready for a fresh batch of media. He worked tirelessly and with a dedication that I have seldom encountered, especially given that the outcome was always at best an educated hunch about the evolutionary capabilities of organisms. This work excited such interest that it was the subject of several articles, including one in the Austin American Statesman and one in New Scientist magazine, not to mention our publication in the scientific literature.

In the end, Jamie generated an 'unColi' that could grow (albeit slowly) solely in the presence of 4-fluorotryptophan. He characterized a number of genes and gene products from this organism, and it appeared as though while the proteome is filled with fluorotryptophan, the organism still managed to scavenge a very small amount of natural, contaminating amino acid from solution to maintain growth. These results contrasted with those previously obtained by Wong, who managed to evolve an 'unSubtilis' that not only grew on but preferred 4-fluorotryptophan for growth. Jamie obtained the 'unSubtilis' from Wong's lab and compared its growth strategies with the 'unColi.' Interestingly, while the mutations in the 'unColi' allowed it to better incorporate and grow on a number of tryptophan analogues, the 'unSubtilis' was extraordinarily specific for 4-fluorotryptophan. These results were consistent with the 'unColi' having adopted a scavenger strategy, while the 'unSubtilis' likely changed several critical proteins to specifically accommodate 4-fluorotryptophan.

In order to further understand how unnatural amino acids affect proteins and proteomes, Jamie evolved novel variants of cyan fluorescent protein that contained tryptophan analogues, and Q beta phage that can utilize tryptophan analogues. From the Q beta work we noted that a relatively small number of mutations were required to adapt an organism to unnatural amino acids. Most importantly, this work allowed us to comment on a model for the early evolution of the genetic code, as this was one of the first

experimental demonstrations of the feasibility of ambiguous codon definition, as opposed to complete codon capture.

What is truly astounding is the creativity that Jamie showed with regards to these projects. The hallmark of Jamie's scientific persona is that he would take a known technique or result and convert it to a totally unique experiment. Moreover, he largely initiated the projects he worked on. For example, he acquired phage and technical advice from Jim Bull in Integrative Biology for the work on Q $\beta$ . In order to evolve the cyan fluorescent protein, he established the requisite collaboration with George Georgiou in Chemical Engineering for using FACS for the directed evolution of proteins.

It should be obvious from these accomplishments that Jamie was a brilliant and productive student. It was no surprise that he won the Harrington Dissertation Fellowship, an award of very high prestige. In addition, he has a great deal of biotechnological as well as scientific savvy; after graduating from my lab, he accepted a job with Maxygen, a firm which is the leader in applying molecular evolution to practical problems. His experience in industry made him even more aware of the need to solve basic biological problems as a prelude to technology applications, and so he segued to a position at the Scripps Research Institute. From the very first in Paul Schimmel's lab he set himself apart as someone who had the ability to think theoretically (he has written a paper about exploring sequence spaces) but could also apply these thoughts practically.

I guess I will best remember Jamie as being a fount of new ideas. Other students who were stuck on particular aspects of their projects frequently ended up going to Jamie to try to figure out a way around, over, or through their problems; he was widely recognized as one of the lab's 'wizards.' From my frequent conversations with him (as he pushes me to finish up the several papers that continue to flow from his efforts), his 'arc' has not diminished since going to industry and then the Schimmel lab, and he remains an outstanding scientist with a very bright future. Indeed, many members of the lab, some of whom have never actually met Jamie in person, continue to discuss science with him from afar, because of his great knowledge of directed and bacterial evolution.

Obviously, much of the foregoing was adapted from Jamie's various recommendations for graduate and post-doctoral fellowships. I kept the words because they are true to the time and the person I knew best. But I have in fact kept in relatively close touch with Jamie over the years, and I wanted to put in a final paragraph about his prospects for a faculty position. Of the many students I have mentored over the years, Jamie is one of the very few that either (a) wants a faculty position (most students are daunted by the amount of work they perceive goes into this job, and eventually ply their talents elsewhere) or (b) would be a good faculty member. Jamie can handle the workload, can put up with the vagaries of funding, can herd the cats (read: students, projects, administria, whatever), can handle the pressures of academia, and can in general take the many blows to the ego that inevitably result from a pursuit of, well, truth. He can do all of this because he loves the science so very much. I am not sure I have ever had a student who just plain loved the science so much. He reads about it, thinks it, breathes it.

It is what he was meant to do. And just imparting that love and joy to his own students will make him a good if not great faculty member.

I recommend Jamie most highly. If you need any additional accolades, please do not hesitate to contact me.

Sincerely,

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