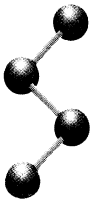

THE SCRIPPS RESEARCH INSTITUTE

Ian A. Wilson, D. Phil., D.Sc., FRS
Professor, Department of Molecular Biology and
Skaggs Institute for Chemical Biology, BCC206
The Scripps Research Institute

10550 North Torrey Pines Road
La Jolla, California 92037
(858) 784-9706
FAX 784-2980
e-mail wilson@scripps.edu

02 December 2004

Biocomplexity Faculty Search
c/o C. Howard
Department of Physics
Indiana University
Swain West 117
727 East 3rd Street
Bloomington, IN 47405-7105

RE: Recommendation of Chenglong Li for Assistant Professorship

Dear Chair of the Faculty Search Committee,

I have known Chenglong since May 2002 when we began collaborating on structure-based/computer-aided inhibitor design against the two folate-dependent enzymes in the *de novo* purine biosynthetic pathway, which are the GAR and AICAR transformylases.

During this time, Chenglong has produced some spectacular results. On GAR transformylase, he carried out a comparative docking study of the native folate-cofactor against all of our avian and human enzyme structures (a sort of "reverse" docking to assess the protein binding site features with a small molecule probe), to determine which structure best emulates the bound transition state conformation that would then provide the best template for GAR inhibitor design. The study also facilitated our understanding of the GAR transformylase reaction mechanism. Shortly afterwards, Chenglong developed a novel hierarchical virtual screening method. In the first stage, inhibitor leads were discovered from the NCI diversity library; in the second stage, compounds similar to these initial leads were screened in larger databases to identify potential new inhibitors. The method was applied to the inhibitor search against AICAR transformylase with an extremely high success rate.

Recently, Chenglong attempted to design transition-state analogue inhibitors of IMP cyclohydrolase (the final enzyme in the *de novo* purine pathway). In a binding free energy simulation based on the combined molecular dynamics/Poisson-Boltzmann electrostatics/normal mode analysis methods, he discovered that when a sulfonyl-containing transition-state analog binds to avian IMP cyclohydrolase, internal vibrations in the enzyme contribute to the free energy of binding. The enzyme surprisingly becomes more flexible upon complexation, a result consistent with the observation that the crystallographic B-values in the complex are much higher than those in the *apo* enzyme. The study may offer general insights into our understanding of its transition state stabilization during the enzymatic catalysis (more of an entropic contribution than conventional thinking).

Throughout these studies, Chenglong has demonstrated enormous scientific creativity, many original insights, high initiative, scientific independence, and diverse knowledge of physics, chemistry, and biology. He has also demonstrated a remarkable ability to perceive and interpret the broader meaning of his data in the context of the relevant literature, as well as to connect and synthesize ideas from disparate sources. His writing skills are evident in the eloquent presentation of these ideas in his papers. In a mere two years, we have written three papers together, and he also assisted in the writing for one of our grants. Our collaboration has been highly successful, and we will continue to extend this collaboration to obtain deeper, and broader insights into the design of potent, anti-cancer leads. I am confident that his ability, creativity, and dedication will enable him to establish a strong, independent, and unique research program that will be highly competitive for NIH funding.

Chenglong has been a pleasure to have as a colleague. He has a positive influence on his working environment, and is easy to work with and generously helps others from all backgrounds. Indeed, he has provided valuable assistance to several people in my lab and in other labs at Scripps in topics ranging from organic chemistry to molecular immunology. For all these reasons, I enthusiastically recommend Chenglong Li for an Assistant Professorship in your Institution.

Yours sincerely,

Ian A. Wilson, D.Phil., D.Sc., FRS
Professor, Department of Molecular Biology &
Skaggs Institute for Chemical Biology

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