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September 19, 2005

Yves Brun
Systems Biology/Microbiology
Faculty Search
Department of Biology
Indiana University
Jordan Hall 142, 1001 E 3rd Street
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Dear Mr. Brun:

I am writing to offer my strong recommendation of Dr. Jun Yin for an academic position in your department. I have known Jun for quite a few years, starting as a fellow graduate student at U. C. Berkeley in the laboratories of Professor Peter Schultz from 1997-1999. Jun completed his Ph.D. with Peter several years later before joining Chris Walsh's group at the Harvard Medical School to undertake postdoctoral research. During the last couple years, I have had the opportunity to reacquaint myself with Jun through our discussions and through the presentation of some of his research findings in a group meeting seminar given to my students.

I have found Jun to be remarkable in several respects. His intelligence and creativity combined with his diligence have resulted in a number of high-quality research accomplishments (and publications) during his graduate and postdoctoral studies in the areas of antibody catalysis and evolution, novel phage-display applications, and most recently the development of methods to harness biosynthetic machinery to link small molecules to proteins at specific locations in vivo. Equally important, Jun's infectious, child-like enthusiasm and genuine enjoyment for doing science are outstanding. Together, these abilities and personal qualities have made Jun both extremely likeable, and in my opinion also sufficiently emotionally mature to handle the ups and downs of launching an academic career.

His proposals are a mixture of chemical biology methods development and early applications to study biological systems. Given his excellent track record in exactly this style of research, I believe Jun has an excellent chance of achieving the goals of his proposed program within several years.

As a talented and proven young scientist who is also a pleasure to be around, Jun merits your serious consideration as a junior faculty candidate. I believe Jun will prove to be an asset both to your department and to your larger scientific community.

Sincerely yours,

David Liu
Howard Hughes Medical Institute Investigator
Professor of Chemistry and Chemical Biology

HARVARD MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY
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September 19, 2005
Re: Jun Yin

Dear Search Committee

I am delighted to write as Jun Yin's postdoctoral research supervisor in strongest support of his application for a faculty position in your department. He is a refreshingly innovative and original thinker who also executes his scientific plans with remarkable efficiency. He will bring a wonderful creative element of chemical biology to any department.

Jun was an outstanding undergraduate student in chemistry at Peking University and then conducted his doctoral studies with Prof Peter Schultz, starting at UC Berkeley and moving in mid-cycle to The Scripps Research Institute in LaJolla, California. As a graduate student Jun evolved an antibody with ferrochetalase activity and monitored progress both catalytically and structurally by x-ray cryustalography of the Fab fragments. He then went on to develop a phage display system to evolve an antibody with peroxidase catalytic activity.

In my group as a postdoctoral fellow Jun has turned away from antibody studies and instead taken up aspects of enzymology of natural product biosynthesis. In particular he has focused on nonribosomal peptide assembly and a key enzyme that converts inactive apo forms of carrier protein domains into active holo forms. The activation involves phosphopantetheinylation, from CoASH as donor substrate, of a serine in each carrier protein domain of an assembly line by phosphopantetheinyl transferase action. The installation of the Ppant group with its terminal thiolate is the essential posttranslational modification step that generates the site of chain growth in every carrier domain. For example to make the undecapeptide immunosuppressant cyclosporine all eleven carrier protein domains in the cyclosporine synthetase assembly lines must be so modified as a necessary prerequisite for catalysis.

Jun convinced me that one could apply phage-based methodologies to address and solve unanswered questions in protein-protein recognition of carrier domains and to use the posttranslational modification of carrier domains by the the *Bacillus subtilis* PPTase Sfp. I consider that he has been spectacularly successful, with two JACS communications (JACS 126, 7754 and 13570, 2004), a Chemistry & Biology paper in press, and a PNAS article in press. More publications are sure to ensue. In addition along a completely different line of thought, Jun was a significant contributor to a paper describing the first halogenase activitiy of a nonheme iron enzyme oxygenase (PNAS 102, 10111, 2005).This is remarkable productivity in a new scientific area for him.The impact of Jun's efforts has been to develop methods for site-specific

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labeling of proteins with small molecules and to use Sfp for labeling of specific proteins displayed even transiently at cell surfaces.

Jun has been the prime intellect and experimentalist in this program since it represents a completely new direction from any prior efforts in my group. This has given me an excellent calibration of his ability to organize and conduct an independent research program. I predict he will be spectacularly successful as a junior faculty member. He is indefatigable but wonderfully even-tempered and open, qualities that will be much appreciated by students who should flock to his group. He shows genius in collaborations, picking the right people and sparking mutual interest. His communication skill are in the top 10% and he should be a particularly effective teacher across a broad range of chemistry and chemical biology.

In sum, I think Jun Yin is a can't miss prospect as a research intensive faculty member. I am very positively impressed with his proposals for independent faculty research. They are innovative and I think they have ahigh probability of turning up new and useful information. He has proven himself both in the Schultz group and at HMS and will raise the quality and innovation index of any faculty he joins.

Sincerely,

Christopher T. Walsh

Christopher Walsh

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September 22, 2005

Professor Yves Brun
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Dear Professor Brun,

I am delighted to write a letter on behalf of Jun Yin for a position in your department. Jun was involved in the catalytic antibody effort in my lab. His work focused largely on characterizing the mechanism, structure and immunological evolution of the ferrochelatase antibody 7G12. This included resonance Raman experiments (with Tom Spiro), extensive mutagenesis experiments and, most recently, solution of the x-ray crystal structure of the Michaelis complex. Jun's work provided a textbook example of the classic Haldane strain mechanism in biological catalysis (in particular the x-ray crystal structure of a strained substrate). In addition, Jun cloned and characterized the germline antibody and carried out a detailed analysis of the role of somatic mutations in the evolution of both binding and catalysis. Using a combination of structural, spectroscopic and kinetic experiments, he was able to show that the germline antibody is polyspecific and can bind multiple ligands by reconfiguring the structure of the active site. He then showed that the somatic mutations which occurred during affinity maturation locked a "distorted porphyrin" specific configuration of the active site. The effects of the individual somatic mutations on binding and catalysis were also dissected. Jun's studies have provided critical insights into the role of structural plasticity in determining the tremendous binding potential of the germline antibody repertoire. Moreover, this work represents perhaps the most comprehensive analysis of antibody catalysis to date.

Jun also developed a clever selection to evolve the peroxidase activity of 7G12 using a phage displayed antibody library and a mechanism-based inhibitor. There were quite a few technical issues that needed to be solved to make this selection work. Jun identified all and came up with clever solutions, including the synthesis of a variety of suicide substrates and the development of a scavenging system. He also showed that he could evolve antibodies with increased catalytic efficiency using this selection. This system, for the first time, allowed us to rationally evolve improved efficiencies in catalytic antibodies generated against transition state analogues. Jun was also involved in a number of other projects including a large scale mutagenesis study of an oxidative antibody.

Jun was remarkably productive in the lab. He is a superlative experimentalist and is adept at organic synthesis, molecular biology, protein biochemistry and structural biology. He functions completely independently and has tremendous energy and drive. Jun has done very well in the Walsh lab on projects that appear to be largely self- initiated. His proposals for his independent career reflect a combination of Walsh/Schultz approaches in which he will harness novel enzymes to engineer systems for evolving proteins with new catalytic functions or that can be used as novel probes of cell signaling networks. Jun is remarkably adept at reducing such ideas to practice and will likely be successful in both the development and application of these new *in vitro* protein evolution strategies.

In conclusion, Jun is extremely productive, very bright and highly creative in his approach to science. He is in the very top group of students I have had in my career (Ellman, UCB; Hsieh-Wilson, Caltech; Shokat/Scanlan, UCSF; Liu, Harvard; Ting/Licht, MIT; Romesberg/Ding, Scripps; Harbury, Stanford; Gray/Yang, HMS; Thorson, Wisconsin; etc.). In addition, he is a very pleasant and helpful coworker, has excellent communication skills and will likely make an excellent teacher.

I have no doubt Jun will be highly successful- he has the intellect, experimental ability and drive to be a leader of his generation of biological chemists and succeed at any major research institution. He is an outstanding candidate for you.

Sincerely,

Peter G. Schultz
Professor, Department of Chemistry
The Scripps Research Institute
and
Director, Genomics Institute of the
Novartis Research Foundation

PGS/er