UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

Department of Cell & Developmental Biology

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Yves Brun,
Systems Biology/Microbiology Faculty Search,
Department of Biology,
Indiana University,
Bloomington IN 47405-7005

Dear Dr. Brun,

I am writing to recommend Dr. Ke Hu, who has applied for a position in your department. I have known Dr. Hu since her graduate student days in Dr. David Roos' lab in Biology here at UPenn, when I was a member of her thesis committee. She carried out some of the experiments for her thesis in my lab, and after she finished her Ph.D., stayed on at UPenn as a post-doc in my lab for a year.

Dr. Hu was very productive, on a diverse set of projects. She was first author on three of the four papers from her thesis work. She was also a major contributor on two other papers published by collaborators during that time. From her post-doctoral work, one first-author manuscript is currently under review, one is in final preparation, and she will be first author on two more manuscripts for which experiments are presently being completed.

The first thesis paper was a quantitative comparison of confocal and deconvolution microscopy, setting out the general principles for when to use these partially complementary methods. This paper was motivated by her dissatisfaction with the confocal images she was able to obtain of the microtubules in *Toxoplasma*. The explanation turned out to be a surprising, pervasive, but not widely appreciated defect in all the commercially available laser scanning confocals (*PNAS* 2002).

The second thesis paper was based on a totally unexpected observation made in the course of unrelated studies. She found that, contrary to the dogma among parasitologists, *Toxoplasma* has the unusual capability of forming a variable number of daughters when it divides. Normally it forms two, but at low frequency it forms 3, or 4, or more, all with a complete set of internal organelles, and all fully viable. The work has profound implications for cell cycle regulation in *Toxoplasma,* which is poorly understood but critically important, since the pathogenicity of this human parasite is completely dependent on proliferation.

The third paper reported an entirely new form of tubulin polymer that makes up an intriguing motile structure (the "conoid") used for invasion of host cells by *Toxoplasma.* This paper sprang from the quantitative analyses of tubulin content that Dr. Hu carried out in her earlier comparison of confocal and deconvolution microscopy. There had been an argument for many years about whether the conoid was made from microtubules. The experimental observations were heavily, but not conclusively, against this. Indeed, David Roos and I had a long-standing bet, he against, me for, the idea. Unthinkingly, both of us equated tubulin with microtubules in this wager. Dr. Hu had the insight to realize that a third possibility existed, and went on to prove that the conoid is made from polymerized tubulin,

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but not microtubules, a startling outcome! The tubulin is instead organized into a novel polymeric form, never before seen (*J. Cell Biol.* 2002).

The conoid is one of nature's most beautiful macromolecular machines, and it really captured Dr. Hu's imagination. After finishing her thesis, she decided to stay on for a post-doc year in order to have a go at isolating the conoid, with the goal of identifying some of the non-tubulin proteins that contribute to its structure. She quickly worked out a simple method for conoid purification, and then set up a collaboration with John Yates' lab at Scripps for a comprehensive mass spec analysis (MudPIT) of both the conoid and of other cytoskeletal fractions. A long slog followed, of sorting wheat from chaff in the MudPIT data, but ultimately the results have turned out to be a gold mine of information. In total, Dr. Hu identified ~200 novel proteins, one-third of which are Apicomplexan specific, and thus prime targets for the new drugs that are desperately needed against this group of devastating diseases. She cloned and characterized seven, which led directly to the discovery of two astonishing new cytoskeletal structures in *Toxoplasma* whose existence had not even been suspected (under review at *PLOS Pathogens)*.

Dr. Hu brought to UPenn a world-class intellect, a solid foundation in modern biology, and strong quantitative skills. While here, she developed into a superb experimentalist in cell and molecular biology, and acquired a deep understanding of and technical expertise in microscopy, both LM and EM. By the time she left, it is no exaggeration to say that her discoveries had set the research agenda in my lab, and probably in several collaborators' labs as well, for the next decade.

Having Dr. Hu in my lab was a joy. She's incredibly smart, appropriately ambitious, works hard, and thinks even harder. Perhaps her most valuable talent is that she thinks differently -- she came up with the ideas that occurred to no one else; many were right, some were wrong, but they always provoked experiments that wouldn't have occurred to me. Dr. Hu is also observant. She noticed phenomena that had been overlooked by many labs, then almost single-handedly converted those chance observations into two amazing stories in the cell biology of *Toxoplasma* (*Mol. Biol. Cell* 2002 and *J. Cell Science* 2004).

These intellectual traits, and an instinctive generosity in helping others, combine to make Dr. Hu an effective teacher. For that reason, several years ago I recruited her to lecture in a course that I direct annually at Cold Spring Harbor. I have been particularly impressed with the wonderfully creative teaching materials she developed for explaining advanced light microscopy techniques to intelligent but naive students in that course.

To summarize, Dr. Hu is an extraordinarily talented young scientist.. To put those adjectives in perspective, she was far and away the best post-doc I have encountered, in my own lab or others, in the last 20 years at UPenn. It is a safe bet that she will be a star, no matter where she goes or what problems she ultimately studies. I am delighted to have the opportunity to give her my highest recommendation for the position in your department. If I can supply any other information, please don't hesitate to call me at 215-898-3045.

Best regards,

John M. Murray

John M. Murray MD, Ph.D.