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Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142, 1001 E 3rd St
Bloomington IN 47405-7005

Dear Dr. Brun,

It is a pleasure to write a letter of recommendation for Zefeng Wang for the position of Assistant Professor. Zefeng is a fellow in Chris Burge's lab at MIT and since our labs share an interest in understanding the specificity of RNA splicing, particularly in mammalian cells, I have followed his research closely. Zefeng's research has been outstanding. He is the first fellow to do wet cell biology in Chris's lab and thus in this part of his research program he had to work independently. Chris is an expert in computation and bioinformatics and Zefeng has mastered this area during his fellowship. The results of Zefeng's work were published in an important *Cell* paper which I read many times because of its brilliance. This paper contains enough material for three conventional papers, it is 20 pages long. I have not seen a comparable paper in many years in terms of density of content. Before joining Chris's lab, Zefeng did his graduate work at John Hopkins where he published several excellent papers and won the Paul Ehrlich Research Award. He also was awarded a Damon Runyon Fellowship for his research at MIT. All of this bespeaks an excellent preparation from Tsinghua University in Bejing, considered the "MIT" of China because of its "technology" emphasis in education. He graduated with highest honors from Tsinghua. This is a very accomplished young scientist.

Zefeng, in the paper mentioned above, has defined a class of elements, the exonic splicing silencers, which confer specificity in the recognition of exons. About 1% of the sequences in the human genome are recognized as exons and the RNA splicing code for this recognition is poorly understood. In my opinion, this is the most important unsolved problem in RNA splicing, at least from the perspective of vertebrate biology. First identification of these sequence elements is a critical step in identifying the protein factors controlling the specificity of splicing. Further, changes in the specificity of RNA splicing are the bases of regulation of alternative splicing, which is a critical but poorly understood aspect of biology. Also, many mutations which inactivate a gene alter splicing recognition resulting in reduced expression. Since in many cases these mutations do not change the amino acid sequence of the protein encoded by the gene, they are almost impossible to interpret without a better understanding of the specificity of splicing. Zefeng's *Cell* paper contains both wet experiments and computation. He first used an expression system to select from a library of short sequence inserts which caused the skipping of an exon, i.e. silenced it. He then computationally grouped them on the basis of related sequences and tested individual members. This was followed by statistical testing as to whether these sequences occurred more frequently in regions where one would expect silencers, next to cryptic splice sites for example. Finally, they used the set in computational models to test if they would increase the accuracy of prediction of exons. These exon silencing elements are the most critical information for exon recognition as compared to exonic enhancers of splicing or known intronic elements. He is currently extending this research with recent results indicating that exon silencing elements are important in controlling alternative splicing. He is also screening for intronic elements which suppress splicing.

Zefeng is a very strong and well trained young scientist. He is an expert in both cell biology and computation. To have been able to accomplish so much in such a short time in Chris's lab, starting from ground zero in terms of wet cell biology indicates he capable of excellent independent science. I note that Zefeng has taught an undergraduate seminar at MIT and been a tutor at John Hopkins. At a personal level, I can attest that he communicates clearly and easily in small settings. I strongly recommend him for the position of Assistant Professor.

Sincerely yours,

Phillip A. Sharp