COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS

INTEGRATED PROGRAM IN CELLULAR,
MOLECULAR AND BIOPHYSICAL STUDIES

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Jeremy Bennett
Faculty Search Coordinator
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Indiana University
1001 East 3rd Street
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RE: David X. Liu, Ph.D.

Dear Dr. Bennett:

It is my great pleasure to write this letter in support of Dr. David Liu's application for an assistant professorship in your Department. I have known David for a number of years as his work has paralleled some of ours and therefore we have had many strategy sessions, technical discussions, and paper studies. I can state unambiguously that David is one of those few in any department that is always enjoyable to talk to. He is thoroughly positive and stimulating in exchange of ideas big and small, makes connections of all forms. David's intellectual prowess and creativity is truly exceptional. His research accomplishments in neuronal apoptosis and his approach to study neural differentiation from his vantage of cell cycle regulation give him the making of a franchise player in any department. I will support these contentions below.

I first met David in 1999 after he introduced himself as a postdoctoral fellow in Lloyd Greene's laboratory in our Department and stopped by to discuss p53 and other cell cycle regulators that play a role in neuronal apoptosis. He had just completed an 18-months Postdoctoral training in Michele Pagano's cell cycle laboratory at New York University Medical Center, from there he published works in mechanisms of tumor-promotion by PKC (MCB 18:839) and in cyclin B regulation by ubiquination pathway (JBC 273:1387). I was impressed by his broadly trained-background and his clear plan to tackle the question of neuronal apoptosis. This was exciting because activation of certain cell cycle elements was not long ago proposed as a cause of neuronal death, and despite the wealth of information about cell cycle regulation, many of the major questions remained unsolved regarding what roles cell cycle regulators play in postmitotic neurons and how they regulate death. He went on to show that E2F acts as a repressor in neurons and de-repression of E2F is required for neuronal apoptosis (Neuron 32:425). He then investigated the roles of the Rb family members in neuronal survival/death and demonstrated that p130 is the sole repressor that controls E2F activity and promotes neuron survival. These findings shattered a long-held assumption of Rb playing that role. He further discovered that p130 recruits the histone deacetylase HDAC1 and the histone H3 methyltransferase Suv39H1 and thus promotes the repression of E2F target genes. Apoptotic stimuli such as DNA damage or NGF deprivation lead to phosphorylation and inactivation of p130 and de-repression of E2F target genes (Genes&Dev. 19:719).

Uncovering the link between the activated apoptotic cell cycle pathway and the core apoptotic pathway in neurons, he found that B- and C-mybs, two of E2F-de-repression targets and cell cycle-related

transcription factors, are essential downstream mediators in E2F de-repression-mediated neuron death (J. Neurosci. 24:8420). B- and C-myb promote neuronal apoptosis through their binding to the Bim promoter and up-regulation of Bim, an apoptotic BH-3 only protein of the Bcl-2 family (J. Neurosci., 2005). His work delineated an activation cascade of E2F>Myb>Bim>neuron death, which links cell cycle activation with apoptotic apparatus in neurons. What particular impresses me is David's ability to identify important questions in the field and then to employ diverse technologies to crack the problems. This was shown clearly for instance in his recent work published in Genes&Dev. (19:719, 2005) and also in his approach to study ATF5 function. He had laid the ground work to use the "protein-tagging" techniques that we have used (as in our recent paper Cell 121:1071) and is on his way to identify components of ATF5 complexes. He has also used successfully "in utero gene delivery" techniques he learned from experts in Arnold Kriegstein's lab and demonstrated that ATF5 blocks and ATF5-Azip promotes neurogeneisis. These attest his flexibility and skills in rallying forces for problem solving.

One unique arrangement in Lloyd Greene's lab is that David, first as a Postdoctoral Fellow and then an Associate Research Scientist, is given tremendous latitude to develop and execute his research plan. This is reflected in the projects he has worked on during the years and also by the corresponding authorship David has in most of his papers published with Lloyd – a show of confidence from his boss, indeed. I think this experience bodes extremely well for his future career as an independent investigator.

David's recent work on ATF5 and stem cell represents another advancement in his career and probably constitutes a similar phase of excitement he enjoined as he first joined Lloyd Greene's laboratory. In a relative short time period, he becomes a driving force and a project leader in ATF5 research. He quickly made some important, as yet unpublished, discoveries that include 1) expression pattern analysis between ATF5 and cell cycle molecules such as Rb family membersand CDKs in differentiating PC12 cells and telencephalic neural progenitor cells, 2) identification of ATF5 DNA-binding sequences and down-stream target genes, 3) ATF5 function in neurogeneisis and in glioblastoma survival regulation. I believe he is on his way to address many of the fundamental questions in neuronal differentiation and in stem cell biology. My sense is that David view ATF5 as a major, and yet underexploited, regulator of neural progenitor/stem cells and want to take the lead in this area. And I believe he will succeed brilliantly and make major contributions in discovering the intriguing connections between cell cycle regulation and neuron development.

In summary I know David had done great work, has a strong record of success, and has a proven track record of productivity. And he has earned a reputation for intellectual rigor and integrity. His present focus on the two transcription factors E2F and ATF5 holds great promise with regards to contributions to the unknown. I recommend him to you in the highest terms. Please contact me if I can provide additional information.

Sincerely,

Wei Gu, Ph. D.
Associate Professor
Institute for Cancer genetics and Department of Pathology