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Biocomplexity Faculty Search
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To Whom it May Concern:

I am pleased to write a letter of recommendation for Dr. Chenglong Li, who is applying for the position of Assistant Professor in the Department of Physics at Indiana University. It is clear to me that Dr. Li is ready to embark on a successful independent career of research and teaching. If you are fortunate enough to recruit him to your institution, you will find that he has the motivation and qualities that make him a first-rate scientist and academic colleague.

Dr. Li came to my laboratory a little over two years ago as a Senior Research Associate in order to expand his expertise in computational molecular biology with a focus on docking methodologies. He arrived with a wealth of experience in experimental and computational methods for biomolecular structure analysis, as well as a firm grounding in organic and physical chemistry. His objectives in joining my laboratory were not only to learn and help develop new approaches to predicting biomolecular interactions, but also to develop and pursue independent research on important biological problems. In my opinion, he has succeeded in achieving these goals, and has demonstrated a keen ability to seek out interesting and important problems, and the ingenuity and perseverance to move them significantly forward.

Funded under a National Cancer Institute core grant, Dr. Li was given the opportunity to establish a collaboration with other NCI funded projects at TSRI to help advance their cancer research goals. He quickly identified a project that fit both the objectives of the grant, and his own professional objectives. The laboratory of Prof. Ian Wilson had been working on the structures of several enzymes in the purine biosynthetic pathway, with the goal of developing new anti-cancer therapies based upon the inhibition of this pathway. Much prior work had been done on folate-based inhibitors of the GAR transformylase enzyme. Recent crystallographic

work in the Wilson lab had lead to a number of structures from several species of the bifunctional enzyme ATIC (AICAR transformylase and IMP cyclohydrolase), which catalyzes the final two steps in the pathway. The project was at the stage where expertise in molecular modeling was needed to establish the best structural templates with which to pursue novel non-folate based inhibitors of the AICAR tranformylase activity. Dr. Li undertook analysis of both the GAR and ATIC structures with this goal in mind, while at the same time quickly coming up to speed in applying our flexible ligand docking code, AutoDock. He also utilized a number of other computational approaches, including semi-empirical quantum methods to establish models for the transition states of these enzymes, including the role of active waters. Having identified suitable template structures for further exploration, Dr. Li then developed protocols for computational screening of libraries of ligands against these targets. Since AutoDock was originally developed for generating accurate structural models of ligand-protein complexes, adapting it for screening purposes represented a novel and challenging task. Dr. Li was able to accomplish this quickly and effectively, and was then set to develop his screening strategy. By utilizing a diversity subset of the National Cancer Institute Compound Database, comprised of about 2,000 compounds selected to cover a wide range of chemical space, Dr. Li was able to run the dockings on a large computer cluster, and identify 40 promising molecules. These were ordered from the NCI and tested in the Wilson Laboratory. Of these, 16 compounds were soluble enough to be assayed. Of those 8 were found to have significant inhibition against the AICAR transformylase activity. This 50% hit rate was a remarkable achievement in itself, but was only a first step for Dr. Li. He then devised a hierarchical docking strategy, to improve on these initial lead compounds. By conducting a similarity search from these identified lead compounds, against the entire NCI compound database of over 100,000 compounds he was able to identify 11 additional inhibitors that were confirmed by in vitro inhibition assay. This work has not only dramatically enlarged the range of chemical scaffolds and candidate inhibitors of this important target, it has demonstrated the efficacy of the hierarchical docking approach developed by Dr. Li. He is now using this strategy to discover new inhibitors for the 2nd enzymatic function of the ATIC, the IMP cyclohydrolase activity. Since this work was initiated and conducted in an independent manner by Dr. Li, I would anticipate that, after taking a new academic position, he would continue with this collaboration (and be a co-investigator) in follow-on projects that are currently being pursued by the Wilson Lab.

Dr. Li has established a number of other collaborations where his expertise on structure and modeling has contributed. He has worked with the Peter Schultz lab on developing homology models for a series of G-protein coupled receptors, and has done protein-protein docking studies on proteins involved in cell signaling and protein degradation with the Ely, Liddington and Reed groups at the Burnham Institute.

In pursuing these applications, Dr. Li has also been involved directly in improving the computational methodology. He has initiated studies on developing more accurate methods to estimate changes in the Gibbs Free Energy upon binding of two interacting molecules. Needless to say, this is of fundamental importance in improving the predictive ability of docking methods.

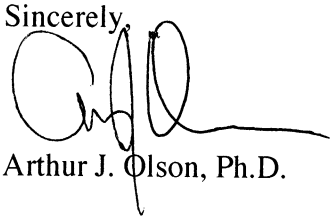
In this work Dr. Li has shown a scholarly and thorough approach to the underlying theory, as well as a practical approach to the computational methodologies required. I anticipate that this will be a growing part of his future research agenda.

Dr. Li's accomplishments during his 2 years in my lab have demonstrated that he is a self-motivated scientist with a wide range of experimental and computational skills, and a strong desire to make significant contributions to our understanding of fundamental molecular biology and its application to the area of human health. In addition to his strengths as an independent research scientist, Dr. Li has shown excellent communication skills. His writing and his oral presentations are well organized and clear, While he has had no teaching obligations here at TSRI, I feel that he will make an excellent teacher at the undergraduate and graduate school level.

Thus, I feel that Dr. Li is on a trajectory that points to a productive and successful career as an academic scientist. His keen insight, warm and friendly manner, and eagerness to help others will make him a valuable colleague and a strong asset to your department. I recommend him without reservation.

If you have any further questions, Please feel free to contact me.

Sincerely,



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