30 May 2017

To:

**Dr. David L. Mobley**

**Associate Professor, Department of Pharmaceutical Sciences**

**University of California, Irvine**

Dear David,

I am writing to express my enthusiastic support for our proposal to utilize blind challenges to drive advancements in quantitative predictive modeling.

We have both also been involved in organizing or participating in the SAMPL blind community challenges since their inception in 2007. In the work we describe in this proposal, we will go far beyond these previous iterations of SAMPL by designing experiments from the very start that focus on current challenges to quantitative physical modeling, rather than simply repurposing datasets that have been collected for alternative purposes. In this way, we will be able to rapidly drive the community toward solutions in modeling physical effects and significant improvements in accuracy in a manner that has otherwise not been possible..

Our laboratories will share responsibilities for the formation, management, supervision, and execution of industry-academic collaborations to collect physical property datasets in **Aim 1** for use in blind challenges. This model worked very well for the recent SAMPL5 challenge, where a graduate student from my laboratory spent 10 weeks during the summer at Genentech to collect a new experimental dataset of small molecule cyclohexane-water partition coefficients that were used in a blind challenge in which numerous research groups participated, revealing both successes and deficiencies in current approaches to modelign small molecule protonation states, tautomers, and interactions with aqueous and nonpolar environments. Given the high amount of industry support expressed for this project, I expect this Aim to be highly successful with both of our laboratories participating in colloborative partnerships for physical property data collection. Our laboratories will also share the responsibility for the analysis and curation of this data, drawing on our considerable combined expertise in physical property measurement and calculation.

My laboratory will be primarily responsible for the execution of **Aim 3**, in which we will identify and develop new protein:ligand model systems that focus on specific challenges in curent predictive physical modeling of small molecule interactions with biomolecular targets. In order to be able to rapidly field timely challenges that address current accuracy-limiting issues, we will develop a novel structural, chemical, and bioinformatics platform for the rapid identification of useful model protein:ligand systems. We fully intend to again draw on our combined expertise regarding the selection of appropriate systems. We will make use of our newly-built automated wetlab facilities to screen these model systems for useful expression, and will automate the collection of high-quality experimental affinity data using the multitude of automated biophysical methods at our disposal (fluorescence, absorbance, ITC, and SPR).

Our laboratories will jointly coordinate, run, and analyze results from blind challenges described in **Aim 4** as future iterations of SAMPL. In addition, our laboratories will share responsibility for performing the reference calculations to accompany these simulations, which makes use of our again considerable combined expertise in both physical property and protein:ligand binding affinity calculation. We will build on our strong collaborative relationship that spans more than a decade, in which we’ve coauthored twelve publications together

This project has the potential to greatly accelerate rate at which quantitative physical modeling makes advances in accuracy, reliability, and expansion of its domain of applicability, all of which will greatly increase the utility and adoption of these techniques throughout academia and industry and aid numerous researchers in their pursuit of rational small molecule ligand design. I very much look forward to continuing our productive collaboration in this regard.

Sincerely,



John D. Chodera

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