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Dear David,

I write to express grateful appreciation to the organizers of SAMPL community experiments and voice enthusiastic support for the continuation of the SAMPL program. Participation in SAMPL challenges has been a significant and important component of my research activities for the past six years. These experiences have motivated the development of novel methods and theories of binding and have helped shape our computational protocols. SAMPL has also promoted relevant chemical systems and applications that we would have not otherwise considered.

Our first participation to the host-guest binding free energy challenge (SAMPL3 in 2011/2012) has been instrumental in the refinement and validation of our Binding Energy Distribution Analysis Method and has given insights on general theoretical aspects of binding, such as the definition of the bound conformational ensemble. The SAMPL4 edition has been a particularly productive experience for us. We formulated the participation to the host-guest challenge as part of a graduate course laboratory whereby students obtained binding free energy estimates using an automated workflow and co-authored the article. Our contribution to the SAMPL4 protein-ligand challenge, which earned top marks among computational submissions, has been the first application of our integrated docking and free energy scoring protocol and showed for the first time that physical free energy models could outperform docking and energy-based scoring in ligand screening and ranking. Finally, in SAMPL5 we successfully explored the modeling of water expulsion and ionic charge screening effects, which are currently being exploited in biological contexts.

Participations to SAMPL experiments have taught us important lessons that are now benefitting ongoing interdisciplinary medicinal chemistry projects aimed at the exploration of small molecule inhibitors of viral targets and of inhibitory peptides for proteins involved in autism and cancer. Thanks to SAMPL, we learned for example the critical importance of the detailed modeling of the chemical system (protonation state, ring conformations, ionic strength, etc.). SAMPL experiments have also highlighted to us the need to explore multiple binding modes and to thoroughly sample the corresponding conformational states in order to properly estimate the balance between energetic and entropic effects and to reliably rank inhibitors. We have integrated new methods and algorithms in our computational protocols to address these challenges.

We track the origin of our recent progress directly to our participations to SAMPL experiments and to their unique structure centered around curated datasets specifically designed to probe the applicability of computational models. Thanks to confidence we acquired by validating our

models in an unbiased manner, we can now more reliably interpret the outcomes of computational predictions in medicinal chemistry and other applied contexts.

It is for these reasons that I enthusiastically support the activities described in your proposal. I particularly look forward to SAMPL experiments based on high-quality binding data on protein targets as you have outlined, and to the progress on the modeling of acid/base and tautomerization equilibria which are so critical to achieving reliable predictions.

Sincerely,

Emilio Gallicchio, Ph.D.