

July 3, 2013

Peter E. Wright, PhD

Editor-in-Chief

Journal of Molecular Biology

Dear Dr. Wright:

I am pleased to submit the accompanying manuscript entitled “Mechanism of Inhibition of the Human Sirtuin Deacetylase SIRT3: Computational and Experimental Studies” for publication as an Original Article in *Journal of Molecular Biology*. In this study, our group has investigated the kinetics and mechanism of inhibition of human SIRT3, as well as that of Sir2 and human SIRT1 *in vitro* and computationally. Using induced fit protein-ligand docking along with subsequent binding affinity estimation using molecular mechanics/generalized born surface area (MM/GBSA) calculations and experimental approach, we have been able to

* Indicate the inhibition mode of nicotinamide for human recombinant SIRT3 versus NAD+ under its physiological concentration *in vitro*;
* Describe the critical roles of nicotinamide and its analogue (isonicotinamide) as inhibitor/activator of SIRT3;
* Provide important insights for the computationally driven development of SIRT3-specific modulators.

The results of the current work suggest that congeneric series of small molecules targeted to the SIRT3 C pocket can be used to train a Linear response methods, which can then be applied to computationally prescreen for inhibitors and activators.

Thank you for your attention, and I look forward to your reply.

 Sincerely,

 Raj Chakrabarti, Ph.D.

 Associate Professor of Chemical Engineering &

 Center for Advanced Process Decision-Making

