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"Developing New Methods for Computing Binding Free Energy and Dissecting Thermodynamic Forces in Drug-Receptor Interaction"

The molecular recognition involving protein, DNA and small molecules plays vital roles in many critical biochemical processes and is responsible for the underlying mechanism of actions of most drugs. Accurately computing binding affinity and obtaining robust insights into binding thermodynamics are of fundamental importance to biophysical chemistry. In this proposal, I propose to use the Budge fund to help develop powerful new methods for computing binding affinity and analyzing the thermodynamic forces in molecular recognition.

The proposal contains the following specific goals:
1. Develop a new pathway method that combines alchemical transformation with physical pathway to accurately compute the binding free energies of anticancer drug candidates targeting DNA G-quadruplex and antivirals targeting HIV-1 integrase and capsid.

2. Develop a new end-point method on parallel computing platforms to dissect the thermodynamic forces in molecular recognition.

3. Apply the new methods to investigate the small molecule recognition by G-quadruplex, HIV-1 integrase, and HIV-1 capsid. These interdisciplinary research projects will be carried out in close collaboration with Prof. Danzhou Yang's lab at Purdue University, Prof. Dmitry Lyumkis at Salk Institute and Prof. Stefan Sarafianos' lab at Emory University, who will test our computational predictions in their labs.