Area of Science Designation: 10 Quantitative and Computational Biology

NOVEL PARADIGMS FOR DRUG DISCOVERY: COMPUTATIONAL MULTITARGET SCREENING

ABSTRACT

We will create a comprehensive computational drug discovery platform by enhancing a novel technique for a dynamic, fragment based, screening of small molecule compounds against the three dimensional structures of multiple protein targets from infectious disease causing pathogens, followed by prospective *in vitro* and *in vivo* experimental verification. We will further modify the most promising lead candidates computationally and screen them against all known human proteins and variants simultaneously to assess for side effects against essential proteins, and to ensure that they possess safe and effective absorption, distribution, metabolism, and excretion profiles against major proteins in known drug delivery pathways. The top ranking leads will again be experimentally verified, and the computational protocol will be iteratively refined using machine learning techniques.

We will initially focus on discovering preclinical drug candidates against infections caused by all eight human herpes viruses (HHVs). This virus family infects billions of humans worldwide every year and is the source of significant mortality in immunocompromised patients. Broad spectrum therapeutics against these key pathogens will benefit the entire global community.

In contrast to other computational efforts, my group has successfuly applied and experimentally verified their predictions of inhibitors to treat herpes, malaria, and dengue. This was accomplished at a fraction of the time, effort, and cost typically required by pharmaceutical companies. Our significant successes thus far attest to the efficacy of our drug discovery technologies.

The Pioneer Award funds will therefore allow us to bridge the gap of discovering computationally predicted lead compounds and demonstrating their preclinical effectiveness for further clinical and therapeutic use. The ultimate goal is to create a comprehensive computational drug discovery pipeline, applicable to any disease, thereby increasing the success rate and reducing the risk, cost, and time associated with traditional drug discovery methods.