Award ID:
RP170144

Project Title:
Effective Exploitation Of Structural Data For Oncology

Award Mechanism:
Individual Investigator Research Awards for Computational Biology

Principal Investigator:
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Entity:
Texas A&M Engineering Experiment Station

Lay Summary:

Biotechnology and pharmaceutical industries are taking advantage of genomics and proteomics to identify targets in which one protein interacts with another (protein-protein interactions, PPIs); these are pivotal in many aspects of cancer research. It is relatively easy to validate these targets using “biologicals”, typically humanized monoclonal antibodies (hmAbs). As medicines, however, hmAbs can have drawbacks compared with small molecules designed for the same function; in cancer these are associated with delivery of the drug to the core of the tumor, cost, shelf life, and bioavailability. For these reasons, small molecules tend to be preferred over hmAbs as medicines, all other factors being equal.

Possibly the most important limitation that restricts design and development of small molecules to interfere with PPIs is lack of an established protocol for compound design and optimization; most of the current methods to do this are hit-and-miss, or have poor generality. The PI has a computational method to identify PPIs from hundreds of thousands of possibilities that may be disrupted by a particular type of molecule, then to test analogs of that chemotype to ones with an increased chance of perturbing a particular PPI. In other words, this method, called EKO, is to allow researchers to computationally explore biological diversity of PPIs that fit a specific molecule, and exploring chemical diversity to fit a particular PPI. The current embodiment of EKO requires training to use, and it has only been experimentally confirmed for a couple of illustrative PPIs. This application is to make EKO more user-friendly, and obtain further validation of the value of the approach by addressing a premier PPI target in cancer immunotherapy: PD-1•PD-L1.