BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

A Common Structural Framework For Rapid Therapeutic Design Against Emerging Pathogens

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Pathogen specific drugs, specifically anti-virals are notoriously difficult to design. This is partially because exploring the breadth of potential variants and systematically developing and assessing a new therapeutic target against every new emerging threat is time consuming and challenging. One of they solutions to therapeutic design is holistic structural assessment of pathogen structure and prediction/evaluation of host interactions. Most emerging viruses evolve from existing classes of organisms, and therefore, it is possible to develop general frameworks for structural biology based interrogation of viral classes.an array of tools are used to achieve this. But traditionally, a given research group specializes in only one or more of those capabilities, whereas the timely integration of these assessments is required to counter an emerging threat- be it natural or engineered. A narrative of how such integration yielded useful information, and the importance of integrating these Capabilities with machine learning and analysis will be discussed.

Since COVID-19 reached pandemic level, the structural biology community has come together to determine the structures of every protein in the SARS-CoV-2 genome. These structures combined with biochemical analysis have revealed the complexity of viral proteins. The virus has a minimized RNA genome by which these viral proteins perform not one but multiple functions, so understanding each protein's multifunctionality requires the determination of the underlying structural mechanisms. These include identification and analysis of the separate functions, and also how the protein converts from one function to another. Hybrid methods analysis, with inputs from multiple modalities, will accelerate determination of SARS-CoV-2 protein mechanisms.

One of the powerful tools to gain such knowledge of the virus is visualization through atomic scale imaging, available through the field of structural biology. Berkeley Lab's infrastructure includes structural biology capabilities (X-ray and electron methods), imaging (IR, fluorescence, chemical mapping), computation/prediction, and protein-protein interaction mapping (X-ray footprinting, mass spectrometry), and the Berkeley Lab Laser Accelerator (BELLA) (based on compact plasma-based accelerators). In addition, X-ray crystallography and cryo-Electron Microscopy (cryo-EM) provide high resolution information for deciphering protein mechanisms. Based on protein structures characterized by these methods, small molecules that could potentially block viral replication can be identified and subsequent high-resolution structures of the proteins with these inhibitors are necessary to improve the protein/ inhibitor affinity for treatment in patients. Structural analysis of antibodies with their antigens can aid in vaccine antigen design and perhaps predict the effectiveness of a vaccine, and can be achieved via the Advanced Light Source (ALS). Other capabilities like Small Angle X-ray Scattering (SAXS) and X-Ray foot printing can be used for further analysis and design development. A snapshot of these technologies and their integration for the development of a framework to combat emerging threats will be presented.