Towards a Combination Antiviral Therapy for Flu: An Interdisciplinary Drug Discovery Effort

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A pandemic outbreak of a highly pathogenic influenza virus such as the avian H5N1 or H7N9 strain could potentially kill millions of people before new vaccines become available. Since current antiviral drugs are losing their effectiveness as resistant virus strains emerge, new anti-influenza drugs are urgently needed. The influenza polymerase is conserved and essential for viral propagation, so inhibitors of it can potentially block any influenza virus. Additionally, by inhibiting multiple components of the polymerase, a combination therapy can be developed to help prevent viral resistance. A multidisciplinary approach combining crystallography, computational chemistry, and biology was used to quickly and efficiently find inhibitors to different polymerase components. Co-crystallography and solvent mapping was performed to identify more potent inhibitors of the PA endonuclease with fragment-based drug discovery. A docking-based virtual screen followed by biological validation was used to find new cap-binding inhibitors of the PB2 subunit. A viral transcription assay showed that inhibitors of PA and PB2 had better effects when used together than either alone. Thus, I have identified a number of new influenza polymerase inhibitors showing potential for development into real flu medicine and a possible combination therapy to avoid drug resistance. Co-crystallography and docking studies also provide valuable information for further drug design and optimization. Therefore, these discoveries will help combat influenza and save lives.

Awards Won:

First Award of $5,000