COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Optimizing Combination Therapy With Antivirals And Host-targeting Agents To Protect The Warfighter From Viral Threats

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Purpose: Protect the warfighter from current and future viral threats via small molecules with broad-spectrum and/or host-targeting activity alone and in combination.

Objective: Identify promising antiviral and host-targeting agents against viral threats and design innovative regimens that will maximize effectiveness and prevent resistance. These regimens can be used therapeutically or prophylactically following exposure, allowing the warfighter to remain on duty or return to duty quickly.

Rationale: Viral diseases are distributed globally and are associated with severe human illness, resulting in high morbidity and mortality rates. Consequently viruses pose a significant threat to warfighters around the world. These viral infections are associated with a lack of military readiness, resulting in mission impairment and failure, as well as significant medical costs. Currently, there are no antiviral therapies available for the treatment or prevention of many viral threats, representing a major therapeutic gap for military personnel and operations.

Relationship to other areas of study: This research is related to the Integrating Cutting-edge AI/ML to Unleash Innovation in Drug Discovery and Therapeutic Development. Our approach and resulting data can be used with conjunction of AI/ML to make predictions for optimizing clinical trial design and predicting treatment outcomes. Moreover, new drugs discovered using these platforms can be experimentally assessed/validated in our laboratory.

Methods: We employ in vitro pharmacodynamic (PD) infection models in which any desired concentration-time profile (i.e. pharmacokinetic (PK)) can be simulated. This allows for the ability to mimic the correct human exposure, peak and trough concentrations, and time above a threshold for any compound. The PK can be simulated for monotherapy or combination therapy of two drugs in this in vitro system. The in vitro simulation of human PK profiles in combination with serial sampling provides a more accurate representation of the likely behavior of the desired antiviral in man regarding effectiveness and resistance prevention. Additionally, PD models allow one to assess the influence of dosing interval on viral inhibition and resistance suppression for each agent.

Preliminary Results: We have used in vitro PD infection models to prospectively predict the failure of molnupiravir in hospitalized SARS-CoV-2 patients. We are currently investigating alternative dosing strategies with molnupiravir, including combination therapy with a host-targeting agent, to develop an effective regimen for people with severe COIVD-19. We have found that the combination of molnupiravir and host-targeting compound quickly drives infectious virus to extinction and this suppression is maintained over time. These results were not achieved with monotherapy. We have used PD models to evaluated combination therapy against many other viruses which have all been published.

Preliminary Conclusions: In vitro PD models can provide valuable information regarding dose-response relationships for antivirals and host-targeting agents, as mono- and combination therapy, against viruses that pose significant threats to warfighters. This information can be used to design protocols for human clinical trials and bring a prophylaxis/treatment to the warfighter faster. We have the ability to perform studies with flaviviruses, alphaviruses, influenza, and Hantaviruses, to name a few, all of which serve as major threats to military operations.