## REVOLUTIONIZING BIOMEDICAL RESEARCH: INTEGRATING CUTTING-EDGE AI/ML TO UNLEASH INNOVATION IN DRUG DISCOVERY AND THERAPEUTICS DEVELOPMENT

# Mathematical Modeling And In Vitro And Invivo Challenge Models To Identify Optimal Doses Af Drugs Alone And In Combination To Cure The Warfighter Quickly And Suppress Resistance Emergence

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Purpose: Use high dimensional mathematical modeling techniques to protect the warfighter from current and future threats from viruses and bacterial Tier 1 Select agents by identifying a translational pathway from murine treatment model to NHP model to the human.
Objective: Identify dosing regimens that will optimize the effectiveness of antivirals and anti-bacterials and also suppress resistance. This identification will start in in vitro Hollow Fiber Infection Models (HFIM), transitioning to murine systems through target identification. Then, employing PK in NHP challenge models, transition the target profile to this system. If validated the same process will allow identification of the target in humans. With further data on human PK, Monte Carlo simulation will allow identification of a dose and schedule that will attain the target exposure for >90% of patients for optimal therapy and resistance suppression.
Rationale: Viruses and bacterial Tier 1 Select Agents may be intentionally released to cause substantial mortality and morbidity among warfighters. Morbidity may be preferred because of resource utilization. The ability to identify optimal doses/schedules for small molecular weight agents will generate the shortest possible “downtime” after release. Identification of a dose and schedule to suppress resistance will allow these therapeutic interventions to be effective for the foreseeable future.
Relationship to other areas of study: Our laboratory has decades long experience with developing high dimensional mathematical models married to data from preclinical challenge data. This has been supported by a large number of grants from NIAID for nosocomial pathogens, viral pathogens and Mycobacterium tuberculosis. We have more recently used this approach employing DTRA monies for deriving optimal doses and schedules with Tier 1 Select Agents.
Methods: We employ in vitro both a HFIM model and a spinoff model for when we are looking at adherent cells (mostly for viruses) where we can look at the relationship between exposure and response and exposure and resistance suppression. These in vitro systems allow any half-life to be generated, so that murine and NHP challenge systems can be studied. This allows translation to murine challenge and, thence to NHP challenge, terminating in human studies. We have developed models allowing combinations of agents to be studied both in vitro and in vivo (2, 3 and 4 agents).
Preliminary Results: We have used this paradigm to study agents like levofloxacin, moxifloxacin and omadacycline, and LpxC inhibitors in the in vivo setting for Y. pestis, B. anthracis (including a ciprofloxacin-resistant isolate), B. mallei and B. pseudomallei. We have used in vitro PD infection models to prospectively predict the failure of molnupiravir in hospitalized SARS-CoV-2 patients. We have also used these preclinical models and the attendant mathematical analyses to study viruses such as Influenza, Dengue, Hepatitis C and Chikungunya, among others.
Preliminary Conclusions: The combination of high dimensional mathematical models, coupled with both in vitro and in vivo challenge models provides great insight into the optimal dose and schedule for these agents alone and in combination to best protect our warfighters and, importantly, to keep these agents in the armamentarium by suppressing resistance.