DRUG DEVELOPMENT: SUMMARY OF A CONFERENCE ON OPTIMIZING POSITIVE "HITS" FOR POTENCY AND SAFETY

Executive Summary

The Drug Development Section in the Office of Biodefense Research Affairs in the Division of Microbiology & Infectious Diseases (DMID) at the National Institute of Allergy and Infectious Diseases (NIAID) organized a conference entitled: Optimizing Positive "Hits" for Potency and Safety in Anti-Infective Drug Development." The conference was held on February 7 and 8, 2007 at the Gaithersburg Marriott Washingtonian Center, Gaithersburg, MD. This meeting brought together more than 100 leading researchers from biotechnology and pharmaceutical companies, private research institutes, and academia, as well as program staff from NIAID, the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the United States Food and Drug Administration (U.S. FDA) and the Defense Threat Reduction Agency (DTRA) and provided excellent opportunities to network.

This conference highlighted challenges and opportunities in anti-infective drug development and modern medicinal chemistry approaches to develop safe and potent therapeutics against human pathogens. The conference was organized into two sessions. The first was held on the evening of February 7 and opened with a keynote address on the "Challenges of Antibiotic Drug Development in the 21st Century". The keynote address was followed by a series of short talks from a number of outstanding NIAID-funded investigators on their antibacterial and antiviral therapeutic development projects. In the second session, held the next day, scientific leaders from pharmaceutical, private research institutes and academia communicated their experiences in drug discovery and their current opinions of the best approaches to effectively and efficiently develop anti-infective agents. This session focused on current approaches to optimizing leads for anti-infective therapeutics for target inhibition; absorption, distribution, metabolism, and excretion (ADME) and toxicology; effective pharmacokinetic/pharmacodynamic (PK/PD) profiles for dosing; and reduction in anti-microbial resistance.

The evening session featured several talks focused on small molecule inhibitors of *B. anthracis* toxins, a general approach of inhibiting bacterial folate synthesis pathway and state-of-the-art structure-based design approaches to elucidate bacterial and viral inhibitors. Other talks addressed nucleoside inhibitors of hepatitis virus, cysteine protease inhibitors, replication and siRNA inhibitors of Ebola virus, and DNA synthesis and viral assembly inhibitors of poxvirus. These talks highlighted the diversity of projects for Category A-C pathogens that are in NIAID's translational research and development portfolio.

The second session focused on using different strategies to optimize leads for potency while still retaining good therapeutic properties. There was an interesting presentation about the promise of genomics to accelerate the anti-microbial drug discovery process. While genomics has contributed enormously to the identification of candidate targets, it needs to be followed by more traditional screening approaches such

as *in vitro* bacterial kill and viral neutralization assays. Determining target essentiality is also important to the process of validating targets identified by genome screens. Participants learned that there are a number of antimicrobial drugs to treat infectious diseases that differ from drugs that treat chronic human disease because they do not follow Lipinski's Rule of Five. Therefore, natural products and compounds with less desirable chemical properties may still provide a great source of potential anti-microbial leads and may be valuable for identifying viable drug candidates. Several presentations highlighted the current methods used to optimize active compounds for lower toxicity, higher oral bioavailability, longer half-lives, and reduced resistance. In addition, *in vitro* PK modeling was shown as a valuable approach to model human dosing and to assay the development of drug resistant organisms. There was discussion of the value in using drug cocktails as a more efficient and accurate method to determine drug metabolizing enzyme activity and to predict drug-drug interactions for labeling of drugs. Finally, the importance of studying RNA transcription, protein synthesis, lipid metabolism and cellular entry and permeability as important antimicrobial targets was discussed.

This meeting gave participants an overview of the current challenges and technical opportunities in identifying novel bacterial and viral targets, characterizing and optimizing promising lead compounds, implementing the processes to bring these compounds forward in development, and recognizing the constraints that the current pharmaceutical environment imposes on antimicrobial discovery.