A Multipronged Approach to Drug Discovery for Protozoan Infections: From Novel Drug Target to PK/PD and Pharmaceutics

Protozoan infections, e.g., human leishmaniasis and sleeping sickness (human African trypanosomiasis [HAT]), are devastating infectious diseases that lack safe and effective treatments. Not only do they threaten the health of millions in endemic countries, thousands of cases (e.g., cutaneous leishmaniasis) have been reported in returning U.S. military personnel from endemic regions, notably Iraq and Afghanistan. Unfortunately, vaccines and preventative chemotherapies are unavailable for leishmaniasis or HAT. Current antileishmanial and antitrypanosomal drugs have limited efficacy, serious side effects, high cost and/or requiring parenteral injection. In an effort to develop new treatments for these infections, we have employed a multipronged approach to drug discovery for human leishmaniasis and HAT. First, we proposed the leishmanial cytochrome P450 (CYP) 5122A1 as a novel drug target and hypothesized its important biochemical role in ergosterol biosynthesis by *Leishmania*. These studies are now supported by a recent NIH R01 grant. Second, working with medicinal chemists and microbiologists, we aimed to better understand pharmacokinetics/pharmacodynamics (PK/PD) of marketed and investigational antileishmanial and antitrypanosomal drugs. For example, aromatic diamidines have potent in vitro antitrypanosomal activities, but they have differential efficacies against second-stage HAT involving the central nervous system (CNS). Our PK/PD studies have shed some light on the factors contributing to their CNS activities. Third, E-cadherin peptide (ECP)-based absorption enhancers have been investigated to improve oral bioavailability and brain uptake of antitrypanosomal eflornithine and pentamidine. In the future, these novel intercellular junction proteins-based absorption enhancers have the potential to achieve oral delivery of peptide- and protein-based biotherapeutics. In summary, our multipronged approach, i.e., target-based, PK/PD optimization and delivery, provides a multifaceted platform that can be leveraged for future drug discovery against protozoan infections and beyond.

Biography (Michael Zhuo Wang, Ph.D.)

Dr. Wang received his BS in Chemistry in 1998 from Peking University (Beijing, China). He completed his PhD in Analytical Chemistry in 2003 from Duke University (Durham, North Carolina, USA) and then postdoctoral studies from University of North Carolina at Chapel Hill, Eshelman School of Pharmacy (Chapel Hill, North Carolina, USA). He is now an Associate Professor (tenured) and Assistant Director of Graduate Studies in the Department of Pharmaceutical Chemistry, School of Pharmacy, University of Kansas (Lawrence, Kansas, USA). He has published more than 40 peer-reviewed papers in reputable journals in the fields of analytical chemistry, pharmaceutical sciences and cancer research, and has served as Grant Reviewer for US National Institute of Health, UK Medical Research Council and Indonesian Science Fund.