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DEFENSE OF THE DOCTORAL

DISSERTATION

"Harnessing Machine Learning for Discovery and Optimization of Novel Chemical Tools"

by

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M.D./Ph.D. Program

B.A. 2013, Rutgers University, New Brunswick, NJ

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Wednesday, April 3, 2019
3:00 P.M.
MSB-H609

Abstract

The landscape of drug discovery is ever-changing, and for good reason; with drug-resistant bacterial infections as a global health pandemic, the need for efficacious antibiotics is becoming crucial. Significant challenges in drug discovery include a) discovering the novel chemical tool(s) with activity of interest, and b) optimizing the novel chemical tool(s) to contain the physiochemical properties of a drug-like molecule. Traditionally, executing challenge “a” required tedious plate-based assays that necessitated significant amounts of resources, including time. Even with successful completion of challenge “a” many compounds may never make it into literature due to challenge “b.” Herein, we present the application of naïve Bayesian modeling to identify chemical tools and/or drug discovery entities pertinent to drug-resistant *Staphyloccocus aureus* infections. The quinoline JSF-3151 is predicted by modeling and then empirically demonstrated to be active against in vitro cultured clinical methicillin- and vancomycin-resistant strains while also exhibiting efficacy in a mouse peritonitis model of methicillin-resistant *S. aureus* infection. We highlight the utility of an intrabacterial drug metabolism (IBDM) approach to probe the mechanism by which JSF-3151 is transformed within the bacteria. We also elucidate on a recently discovered mechanism through which *S. aureus* can generate drug-resistance. We further highlight this methodology’s flexibility by addressing challenge “b”. We will discuss our efforts with machine learning models to discover new chemotypes of antibacterial agents against drug-resistant *S. aureus*. We will also discuss how we have used our models to predict for small molecule physiochemical properties such as cytotoxicity and solubility.