

Population Dynamics Virtual Seminar



Bree Aldridge
Tufts University

21.05.21 - 3:30 pm GMT

Design of combination therapies for tuberculosis

TB remains a major cause of death worldwide. The standard drug regimen is six months of combination therapy with four antibiotics. TB requires multidrug treatment because the bacteria occupy lesions that present resident bacteria to different microenvironments, creating a spectrum of drug susceptibilities. We critically need shorter and more effective multidrug regimens using a new set of antibiotics that are active against drug-resistant strains. We aim to realize the vast combination space's potential by prioritizing combinations from systematic *in vitro* measurement and computation. We used our efficient drug combination measurement technique (DiaMOND) to comprehensively measure drug interactions and combination potencies in *in vitro* models that emulate the lesion microenvironment to (1) predict treatment outcomes in animals based on *in vitro* data and classifiers trained using machine learning and (2) validate *in vitro* models for standard use in drug response studies for TB. We established a practical pipeline to predict whether combinations were better than the standard of care or not in mouse models using signatures of *in vitro* DiaMOND measurement. Our approach is broadly generalizable to other disease systems that require combination therapy.

Suggested Readings: *Systematic measurement of combination drug landscapes to predict in vivo treatment outcomes for tuberculosis* - Jonah Larkins-Ford, Talia Greenstein, Nhi Van, Yonatan N. Degefu, Michaela C. Olson, Artem Sokolov, Bree B. Aldridge - bioRxiv 2021.02.03.429579 - <https://doi.org/10.1101/2021.02.03.429579>

Morphological profiling of tubercle bacilli identifies drug pathways of action - Trever C. Smith, Krista M. Pullen, Michaela C. Olson, Morgan E. McNellis, Ian Richardson, Sophia Hu, Jonah Larkins-Ford, Xin Wang, Joel S. Freundlich, D. Michael Ando, Bree B. Aldridge - Proceedings of the National Academy of Sciences Aug 2020, 117 (31) 18744-18753; DOI: 10.1073/pnas.2002738117 - <https://www.pnas.org/content/117/31/18744.abstract>