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OPTIKA, A New High Content Drug Combination Kill Kinetic Assay

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Abstract:
Tuberculosis (TB) is one of the top 10 causes of death worldwide. Recently, treatment shortening from 6 to 4 months for drug-susceptible (DS) TB has been announced by WHO. Moreover, FDA approved the combination of bedaquiline, pretomanid and linezolid (BPaL) for 6 months XDR-TB treatment. This new evidence suggests that new anti-TB compounds progressing into clinical trials have the potential to make shorter, simpler regimens. Understanding how to develop such regimens remains a challenge.Traditional methods used to develop drug combinations involve a first step of empirical phenotypic screening for *in vitro* synergies [checkerboard assays (CBA) or, more recently described, DiaMOND]. A fundamental limitation of such approaches is their dependence on the Fractional Inhibitory Concentration Index (FICI, a measurement of growth inhibition) as the metric of drug activity, which requires secondary validation by time-kill assays (TKA), the gold-standard *in vitro* proxy.TKAs are the most valuable *in vitro* pharmacokinetics and pharmacodynamics assays, and the basis of pharmacometric modelling of antimicrobial drug action. However, compared to the fixed endpoint for CBA or DiaMOND, TKAs rely on CFU enumeration at different time points, requiring large culture volumes and, when using *Mycobacterium tuberculosis*, have a limited throughput that is linked to the technical operator's capacity (ca. 30 samples). This creates a barrier to validate interactions of more than 3 drugs per experiment due to the large number of possible combinations.In this context, we developed a new methodology named **OPTIKA (Optimized Time Kill Assays)** that dramatically increases traditional TKA capacity, and allows for facile and dynamic interrogation of drug interactions with a CFU-free methodology. OPTIKA is based on the CARA assay and replaces the use of CFU with a resazurin-based fluorescence readout in a 96-well plate format. This technique has been optimized to robustly analyse up to 770 unique conditions (in

quadruplicate: 3080 samples) at the time and allows data to be delivered after 10 days, almost 2 weeks earlier than traditional CFU-based methods. OPTIKA can play a critical role in initiatives such as the ERA4TB consortium, which aims to evaluate the efficacy of novel anti-TB drug combinations as well as new molecules to progress through the drug development pipeline. In this presentation, we will describe the development of OPTIKA and how our combination data compare to previously performed CBA and DiaMOND assays.

Acknowledgments/ References:

Sub-track (Complete): AAR02 Antibiotic Agents: Mechanisms of Action and Resistance
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