Poster abstract submission

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Poster title

Development of a novel DprE1-targeting lead candidate for NTM-PD treatment

Poster abstract

Nontuberculous mycobacterial pulmonary disease (NTM-PD), primarily caused by Mycobacterium avium (Mav) and Mycobacterium abscessus (Mabs), is a major clinical challenge associated with significant morbidity and mortality. NTMs are recalcitrant pathogens with inherent resistance to many known antibiotics and limited chemotherapeutic options. Current standard-of-care for NTM-PD includes intensive 12-month-minimum multidrug regimens with limited efficacy, high toxicity, frequent treatment failures and high recurrence rates. Hence, there is an urgent unmet need for new, more effective and tolerable antimicrobials that inhibit novel targets in NTMs and enable shorter, safer treatment regimens.

We aim to develop a novel lead candidate for NTM-PD, targeting Decaprenyl phosphoryl-β-D-ribose 2'-epimerase (DprE1), an essential mycobacterial enzyme responsible for biosynthesis of cell wall-forming arabinans, and a promising but unexplored drug target in NTMs. DprE1 is a clinically validated drug target in M. tuberculosis (Mtb), with several covalent (BTZ-043, PBTZ-169) and non-covalent (TBA-7371, OPC-167832) inhibitors under clinical development for tuberculosis treatment. However, most Mtb-active DprE1 inhibitors exhibit poor activity against NTMs, underscoring the need for novel NTM-active DprE1 inhibitors.

Through in vitro phenotypic screening of an in-house small-molecule library of DprE1 inhibitors, we identified FNDR-11016, a novel hit of the Benzimidazole class, potent against Mav (MIC 1 µg/mL) but with

poor activity against Mabs (MIC 32 µg/mL). Focused structural modifications of the hit yielded a series of analogs that are potent and bactericidal against Mav with MIC < 1 µg/mL and maximal kill (Emax) greater than 1 log10 CFU/mL. The front-runner compound, FNDR-11703, exhibits MIC of 0.008 µg/mL against Mav and 0.06 µg/mL against Mabs, favourable kinetic solubility and in vitro metabolic stability. It also demonstrates promising pharmacokinetics in mice via IV and oral routes, with rapid oral absorption (Tmax 0.5 h), moderate oral bioavailability (54.6%), plasma exposures exceeding MIC for at least 12 h, and adequate lung levels. In vitro MIC assays with Mav dprE1 mutants demonstrate a 32-fold increase in MIC, confirming DprE1 as a target. In vivo efficacy studies are currently underway, with the goal to advance FNDR-11703 as a lead candidate with bactericidal activity, improved in vivo pharmacokinetics, and efficacy in murine Mav and Mabs infection models.

Research topic

Small molecule therapeutics