Weill Cornell Medicine

Whole Cell Active Inhibitors of Mycobacterium Tuberculosis Lipoamide Dehydrogenase

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Background & Unmet Need

- Tuberculosis (TB) infected 10 M and killed 1.5 M people in 2018, and remains a worldwide health crisis due to rising drug resistance
- The BPaL regimen (bedaquiline, pretomanid, and linezolid) received FDA approval in 2019 and is the first regimen in decades to feature novel MOAs
- However, there is a need to develop additional inhibitor classes to novel targets, to sustain the TB drug pipeline and shorten and diversify drug regimens
- Lipoamide dehydrogenase (Lpd) is a promising therapeutic target but has yet to be chemically validated
- Mtb lacking Lpd fails to grow on carbohydrates as a sole carbon source and connect establish TB infection in mice
- **Unmet Need:** Novel classes of Mtb inhibitors targeted unexplored targets such as Lpd

Technology Overview

- **The Technology:** Improved sulfonamide-based Lpd inhibitors that exhibit acceptable Mtb permeability and phenocopy *lpd* genetic deletion *in vitro*
- Through an extensive structure-activity relationship (SAR) campaign, compound **13** emerged as the lead candidate with the lowest minimum inhibitory concentration (MIC) and highest pyruvate fold increase
- Compound **13** was shown to be a potent, time-dependent, slowly dissociating inhibitor of Mtb Lpd
- **PoC Data:** Compound **13** selectively kills Mtb under nitrosative stress and inhibits the growth of Mtb inside mouse bone marrow-derived macrophages (BMDM)
- NB: Compound **13** not tested for efficacy in TB mouse model due to high susceptibility to mouse microsomal metabolism
- Development of next-generation analogs is ongoing

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Developed in collaboration with the Tri-I TDI

Patents:
PCT Application Filed

Publications:
Ginn et al. *ACS Infect Dis.* 2021.

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Technology Applications

- Treatment and prevention of Mtb infection
- Inclusion in combination regimens to combat Mtb resistance

Technology Advantages

- Highly selective for mycobacterial Lpd over the human enzyme, reducing risk of off-target effects
- Compound **13** is a slowly-dissociating inhibitor of Mtb Lpd
- No toxicity to mouse bone marrow-derived macrophages (BMDM) and HEPG2 cells was observed below 100μM

Supporting Data / Figures

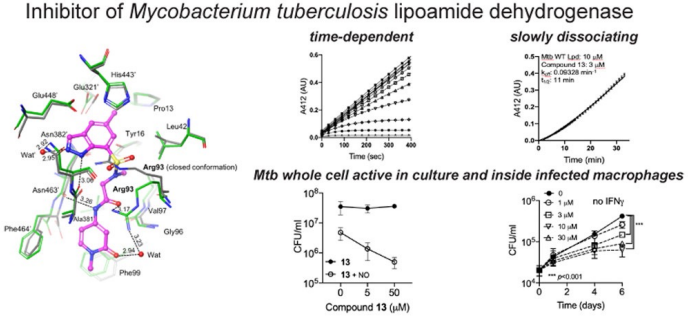

Figure 1: Compound **13** is a potent, time-dependent slowly dissociating inhibitor of Mtb Lpd. Compound **13** selectively kills Mtb under nitrosative stress and inhibits the growth of Mtb inside mouse bone marrow-derived macrophages (BMDM).

The Tri-I TDI has produced an extensive preclinical data package that is available under CDA

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