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"Unraveling the Spectrum of Amide Hydrolysis in *Mycobacterium tuberculosis* to Develop Novel Pyrazinoic Acid Prodrugs for the Treatment of Pyrazinamide-Resistance Tuberculosis."

By

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M.D./Ph.D. Program
B.A., Biology, 2017, Columbia University, New York, NY

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Department of Medicine
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Monday, March 31, 2025
12:00 P.M.
ICPH Auditorium, Zoom

Join Zoom presentation:
https://rutgers.zoom.us/j/7759110171?pwd=ekVrdDJGSlY2MTZ2MGZ3aDNVQUwzZz09
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ABSTRACT

Tuberculosis (TB) is a global health crisis. As the leading cause of death due to infectious disease, it claims 1.5 million lives a year. Although TB can be treated, the curative regimen is lengthy and complex. As a result, drug-resistant *Mycobacterium tuberculosis* (Mtb) is steadily increasing. Novel therapeutics that decrease treatment duration and increase barriers to resistance are essential for disease eradication. Several first- and second-line antituberculars are prodrugs that are metabolized inside Mtb. Prodrugs can be designed to contain hydrophobic moieties that allow them to pass through the markedly lipid-rich environment of the Mtb cell envelope and deliver Mtb-active polar moieties inside the bacterium. Many of these Mtb prodrugs are activated by non-essential enzymes. Pyrazinamide (PZA) is a key first-line antitubercular drug due to its treatment-shortening capacity. It is activated to pyrazinoic acid (POA) by the non-essential amidase PncA, and the vast majority of PZA resistance is caused by mutations in *pncA*. We have identified several other non-essential Mtb amidases that activate amide antituberculars. In this work, we show that this non-essentiality can be harnessed to develop prodrugs with increased barriers to resistance. We developed a novel prodrug design platform to generate amide compounds that can pass through the Mtb capsule and release antitubercular amines or carboxylic acids that are active within Mtb. After identifying over 200 structures that undergo amide hydrolysis in Mtb, we linked POA to select amine metabolites released from these parent compounds. The resulting POA-conjugates were activated by non-PncA amidases, retaining POA-like activity in PZA-resistant strains and restoring the activity of a first-line antitubercular critical for shorter TB regimens. We also elucidated the mechanisms of action and activation of our most promising POA-conjugate, PT-260, to show that it parallels POA activity and is likely activated by two amidases, necessitating more than one mutation for loss of drug activation. Our metabolism-centered approach introduces a novel framework for TB prodrug discovery that can be applied to other classes of enzymes and their small molecule substrates.