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Modified PAS analogues making PAS great again

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Tuberculosis (TB) is one of the deadliest infectious disease resulting in nearly 1.5 million deaths annually and infecting nearly one-quarter of the population. Para-aminosalicylic acid (PAS), an important second-line agent for treating drug-resistant mycobacteria, has low bioavailability and rapid clearance that necessitate high daily doses of up to 12 grams/day, which in turn causes severe gastrointestinal disturbances by disruption of gut microbiota and host epithelial cells. In this project we aim to improve the bioavailability of PAS, while retaining its anti-mycobacterial activity. We have developed a series of prodrugs that substantially increase the oral bioavailability, which prevents intestinal accumulation as well as undesirable bioactivation by the gut microbiome to non-natural folate species that exhibit cytotoxicity. The conceptually simple prodrug approach does not address the intrinsic rapid clearance of PAS by N-acetyltransferase (NAT); thus, we have also designed analogues of the PAS scaffold to lower clearance of PAS enzymes by sterically blocking N-acetylation and electronic deactivation of the para-amino group. Combination of these dual approaches together may provide a next-generation PAS drug with substantially higher oral exposure to prevent adverse reactions and development of resistance.

Biography

Pooja has completed her Bachelors' from Bombay College of Pharmacy, India and her Masters' at from Creighton University, Nebraska. She is currently pursuing her PhD at the University of Minnesota under the guidance of Dr. Courtney Aldrich. She is actively involved with a number of student groups and enjoys networking.

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