798. The Role of Whole-Genome Sequencing in Characterizing the Mechanism of Action of Anti-Tuberculosis Compounds: Demonstrated With Para-Amino Salicylic Acid and Its Analogue

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Session: 70. Tuberculosis and Other Mycobacterial Infections
Thursday, October 4, 2018: 12:30 PM

Background. Para-aminosalicylic acid (PAS) was one of the first antibiotics to be used against tuberculosis (TB) and it is still one of the last remaining drugs available to treat extensively drug-resistant (XDR) disease. Despite being on the market for decades, the mechanism of action of PAS is not completely understood yet. Sixteen new compounds against *Mycobacterium tuberculosis* were created in the laboratory as salicylate analogues (based on their chemical structures) and their antimycobacterial activity had never been tested before. The main aim of this project was to test the activity of these new analogues and to understand their mechanism of action (including PAS).

Methods. The compounds were tested using three different methods (spot culture, resazurin, and MGIT system). Additionally, resistant mutants were created against PAS and the most promising analogue; whole-genome sequencing (WGS) was performed to understand their mechanism of action.

Results. One compound in particular, AD25a, showed the lowest critical concentration (0.04 μg/mL) among the salicylate analogues. The WGS analysis identified a total of 28 single nucleotide polymorphisms (SNPs) in the AD25a-resistant mutants and 40 SNPs in the PAS-resistant mutants (when compared with the reference strain H37Rv). The SNPs identified in the AD25a and PAS-resistant mutants did not overlap. The genes *rrs*, *rrl* and *folC* were mostly involved in the PAS-resistant mutants.

Conclusion. The complete difference in the mutation profiles suggests that AD25a has a mechanism of action different to that of PAS, despite AD25a being synthesized as a salicylate analogue. WGS analysis of PAS-resistant mutants has also provided some interesting results. In particular, all our PAS mutants showed mutations in the *rrs* and *rrl* genes (16S and 23S RNA genes, respectively). These mutations should affect the ribosomes and the overall synthesis of proteins. This highlights a new potential mechanism of resistance for PAS that has never been observed before.

Disclosures. **All authors:** No reported disclosures.