JSF-3285, A Novel KasA Inhibitor for Tuberculosis

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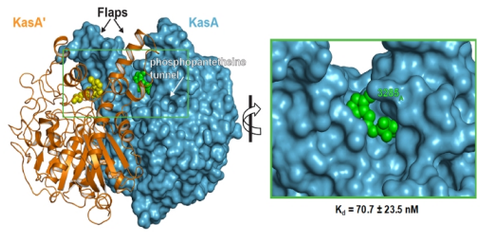
A

Mtb MIC (μM)	Vero cell CC_{50} (μM)	Kinetic Aqueous Solubility (μM)	MLM $t_{1/2}$ (min)	HLM $t_{1/2}$ (min)	Mouse PPB %	Human PPB %	CYP Inhibition for 1A2, 2C9, 2C19, 2D6 & 3A4 (μM)	hERG IC_{50} (μM)
0.20	170	483	28.4	178	68.3	76.5	>50	>50

B



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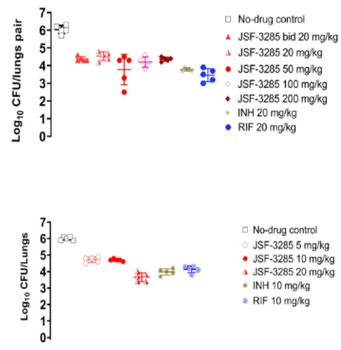

Figure 1. Summary profile of JSF-3285: A) In vitro profile. B) X-ray crystal structure and binding constant for complex with KasA. C) In vivo profile in mouse chronic infection model.

Invention Summary:

New antibacterial drugs that treat multidrug resistant mycobacterium tuberculosis (MDR TB) represent an area of high medical need. The current tuberculosis treatment regimens involve multidrug combinations over an extended period and have associated side effects and toxicities. New TB drugs that reduce side effects and the total length of treatment may result in better patient outcomes.

Through a structure-based drug design program involving >200 compounds, scientists at Rutgers have discovered and developed preclinical candidate JSF-3285. JSF-3285 was generated by optimizing analogues of DG167, a non-patented Glaxo compound. This candidate is a very potent inhibitor of KasA. The KasA enzyme of the M. tuberculosis is known to play a key role in the biosynthesis of the mycolic acid layer of the bacterium's cell wall. This is the same pathway containing InhA which is inhibited by the first line anti-TB drug isoniazid (INH).

The compound (JSF-3285) improves upon the in vitro efficacy profile of DG167 while significantly exhibiting major gains in oral exposure in mice. The compound has exhibited no significant issues regarding mouse toxicity, hERG inhibition, CYP inhibition, Ames mutagenicity, and mouse/human plasma stability and protein binding. Biochemical, biophysical, and genetic (frequency of resistance = 2.7 x 10^{-8} at 16X MIC compound) studies demonstrate it targets KasA (Figure 1B). JSF-3285 is prepared on a multigram scale in three steps with high yield. This gain in pharmacokinetics was evident in potent, bactericidal activity in mouse models of acute and chronic infection down to 5 mg/kg qd po (Figure 1C).

Advantages:

JSF-3285 could be developed and used in combination with currently available/approved therapies for tuberculosis to increase the efficacy and effectiveness of the available solutions.

Market Applications:

Drug treatment of drug-sensitive and/or MDR TB, a next-generation therapeutic strategy for tuberculosis.

Intellectual Property & Development Status:

Patent pending. Available for licensing and/or collaboration.

Direct Link:

http://rutgers.technologypublisher.com/tech?title=JSF-3285%2c_A_Novel_KasA_In hibitor_for_Tuberculosis