Targeting Mip proteins for the development of new antibacterials

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The infectivity and intracellular survival of pathogenic bacteria such as *Chlamydia* and *Legionella* is correlated with a major virulence factor termed macrophage-infectivity potentiator (Mip) [1, 2]. Infections with *Chlamydia* species are responsible for a number of severe medical conditions potentially resulting in infertility, blindness and pneumonia [3], *Legionella* is the etiological agent of Legionnaires' disease [4]. Mip has been shown to possess peptidyl-prolyl-cis/trans-isomerase (PPIase) activity, but *in-vivo* substrates are still unknown. Previously we have determined the crystal structure of Mip from *Legionella pneumophila* to a resolution of 2.4 Å [5]. More recently, the structures of Mip from *L. pneumophila* and *E. coli* in complex with the potent PPIase inhibitors rapamycin [6] and FK506 [7], respectively have been published.

Utilizing available structural information, we developed a pharmacophore model including crucial interactions between the inhibitor molecules and active-site residues of Mip as restraints. Using a subset of the SPECS database [8] of commercially available compounds as a basis, we employed our pharmacophore model to rank ~55,000 compounds and docked the top 500 into the active site of *Legionella* Mip as well as into the active sites of homology models for *C. trachomatis* and *C. pneumoniae* Mip. Interestingly, 38 compounds were found to be common among the top 50 docking solution in all three species. As residues of the active site are well conserved in Mip from *Legionella* and *Chlamydia*, the binding mode of each individual compound was found to be very similar. Based on their chemical structure, the compounds fall into 8 classes. The major class features a central triazole ring and includes 27 out of 38 compounds. The remaining classes include 1-3 compounds each. The identified compounds will be tested for their ability to inhibit the PPIase activity of Mip proteins *in vitro* and for antibacterial efficacy *in vivo*. Furthermore, we aim to determine the three-dimensional structure of corresponding complexes using X-ray crystallography.
References:


8. SPECS Inc. www.specs.net