**Screening for Inhibitors of the Proteolytic Complex ClpXP1P2 from *M. tuberculosis***

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Tuberculosis remains one of the leading causes of death from infectious diseases worldwide. *Mycobacterium tuberculosis* (Mtb) has become increasingly resistant to available antibiotics. Therefore, identifying new drug targets and developing selective inhibitors are critical. ClpP1 and ClpP2 are serine proteases that are essential for growth and infectivity of Mtb. Because similar enzymes are not present in the mammalian cytosol, they are attractive drug targets. We have shown that the ClpP1 and ClpP2 proteases function together in Mtb (unlike ClpP proteases in other cells) and have characterized the active 14-subunit ClpP1P2 complex. We have found certain dipeptide derivatives that dramatically stimulate complex formation and enzyme activity against short fluorescent substrates (even in the absence of their associated ATPases). We have also characterized the essential Mtb ATPase complexes, ClpC1 and ClpX, which facilitate protein degradation by ClpP1P2 and are also attractive drug targets. However, no inhibitors of ClpX have been found, nor has any screen for ClpP1P2 inhibitors been reported. Inhibitors of the ATP-dependent protease complex, ClpXP1P2, should be selectively toxic to Mtb, and we have a fluorescent assay appropriate for High Throughput Screens. We now propose to screen for such inhibitors in the small molecule library at HMS's Institute of Chemistry and Cell Biology. When Hits are obtained, we have secondary assays to identify their exact targets in the ClpXP1P2 complex and to test for inhibition of ClpXP1P2 function in bacterial cells and their viability. Hopefully, this work may identify lead compounds for the development of novel treatments for tuberculosis.