A Computational Study of IdeS Inhibitors

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The cysteine protease inhibitor Z-LVG-CHN_2 exhibits antibacterial activity against *Streptococcus pyogenes*. However, it is known that the target of the antibacterial activity is not the primary secreted cysteine protease of *S. pyogenes*. Recently a second secreted cysteine protease has been identified, the Immunoglobulin-G degrading enzyme of *Streptococcus pyogenes* (IdeS). IdeS possesses unusual selectivity for immunoglobulin-G, cleaving both strands of the hinge region. IdeS is also unusual for a secreted protease in that it is secreted in an active form, hinting at intracellular activity as well as the observed extracellular activity.

Multiple peptidic libraries have been synthesized based on the hinge region of IgG, and a number of potential inhibitors have been identified. This work describes docking calculations performed to determine the binding sites and binding mechanisms of the potential inhibitors, as well as to suggest possible ligand modifications to enhance binding. Multiple binding sites have been investigated, as evidence exists for a possible allosteric binding site and there is also speculation that the enzyme is active as a dimer. Our early results indicate the potential inhibitors may plausibly inhibit dimer formation. We have also performed docking calculations on the non-peptidic diversity library available from the NCI.