Development of Novel Chemical Probes for the Treatment of Lyme Disease

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Lyme disease, caused by the microbial pathogen Borrelia burgdorferi, affects nearly 500,000 people every year in the US, making it the most common vector borne illness. Current treatments for Lyme disease are lacking and it is critical that new therapeutics are developed. Here we examine High temperature protein G (HtpG), a molecular chaperone present in high abundance in Borrelia burgdorferi (Bb). BbHtpG is an ortholog of the 90 kDa Heat shock protein (Hsp90) present in humans, which is a target for several cancers. These proteins utilize ATP hydrolysis to power conformational changes required for client protein folding. The nucleotide binding site located within the N-terminal domain can be targeted by a ligand covalently linked to a photoactivable toxin, allowing for localized targeting of Bb. In this work, known Hsp90 inhibitors were examined using isothermal titration calorimetry to determine binding affinities for BbHtpG to identify promising ligands with selectivity for BbHtpG. Additionally, the co-crystal structure for the N-terminal domain of BbHtpG bound by a high affinity inhibitor, HS-289, in the ATP binding site was determined to 2.3 Å resolution, enabling key structural differences between the ATP binding sites of BbHtpG and Hsp90 to be identified. Chemical fragments that target BbHtpG were discovered by screening fragment libraries with surface plasmon resonance and 19F-NMR, strengthening our understanding of the ATP binding site of BbHtpG. Through this work, novel chemical scaffolds have been identified using fragment-based drug discovery and key structural differences between BbHtpG and Hsp90 have been elucidated by solving crystal structures of BbHtpG. Together these data may facilitate the development of chemical probes that are capable of targeting Bb for the treatment of Lyme disease.