Novel Small Molecule Inhibitors of Borrelia burgdorferi

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Lyme disease is the most commonly reported vector-borne illness and the third most frequently reported Notifiable Infectious Disease in the United States. Early treatment with front-line antibiotics typically eradicates symptomatology and the causative agent (*Borrelia burgdorferi*), however, in a small percentage of patients, symptoms persist for extended periods after treatment, an occurrence collectively referred to as post-treatment Lyme disease syndrome (PTLDS). While the exact cause of PTLDS remains unknown, in vitro modeling indicates that *Borrelia* species are capable of forming slow-growing 'persister' cells that are resistant to killing by frontline antibiotics. DNA synthesis and transcription appear to be essential for maintaining *Borrelia's* persistent state during in vitro growth, making nucleotide acquisition pathways attractive targets for small molecule inhibitors. *Borrelia* has lost its ability to synthesize purine nucleotides de novo, and therefore must salvage them from its external environment. This is particularly critical in the mammalian host where the abundance of guanine in blood and tissue is very low. Inosine-5'-monophosphate dehydrogenase (IMPDH) or GuaB, allows for the conversion of adenine and hypoxanthine-based nucleotides into xanthosine monophosphate and eventually guanosine monophosphate (GMP). While *B. burgdorferi* IMPDH deletion strains are capable of colonizing adult ticks, they are severely attenuated in larval ticks and completely incapable of survival in mouse infection models. In this study, we screened a collection of IMPDH inhibitors for their ability to attenuate the growth *B. burgdorferi* strain B31 in vitro. Actively growing *B. burgdorferi* cultures were treated with compounds [100uM] for four days, bacterial cells were examined by light microscopy for morphological changes and serial dilutions were plated for colony forming unit counts. We identified a single compound capable of reducing the growth of *B. burgdorferi* strain B31. We plan on validating the inhibitory nature of this compound on the *Borrelia* IMPDH enzyme. We also plan on developing and screening structural analogues of this inhibitor for antibacterial activity in *B. burgdorferi*. Identification and characterization of a small molecule inhibitor against *B. burgdorferi* growth can potentially lead to the development of new therapeutics against *B. burgdorferi* infection.