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# *Abstract*

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| **Project Title:** | Screening for Inhibitors of the Mevalonate Pathway in Streptococcus Pneumoniae |

***Abstract:*** *DESCRIPTION (provided by applicant):* Streptococcus pneumonia (SP) takes the lives of nearly 4000 people daily, the majority of whom are children below the age of five. The organism's ability to evolve resistance mechanisms has produced strains capable of tolerating our "last line of defense" antibiotics. This laboratory recently discovered that diphosphomevalonate (DPM), an intermediate in the mevalonate pathway, is a potent allosteric inhibitor of the SP mevalonate kinase (MK), and that it does not inhibit the human isozyme. The mevalonate pathway is essential for survival of the organism in mouse lung. DPM and the allosteric site offer a lead compound and target that provide an opportunity to develop a new class of antibiotics that could help eradicate this disease. Our preliminary data demonstrate that compounds based on these principles are capable of killing infectious SP in rich media. We are hoping to expand our repertoire of lead compounds by working together with the Molecular Libraries Screening Centers Network (MLSCN) to screen roughly 150,000 potential inhibitors against each of the three SP enzymes that comprise the mevalonate pathway. These enzymes are members of the GHMP kinase protein superfamily, whose biomedical relevance extends to both orphan diseases and cataract formation. We have determined the structures two of the three enzymes in the pathway, and have an excellent structural model for the third. We have just received word that that our recently submitted RO1 on the mevalonate pathway project (which will fund a protein functionalist, a high resolution NMR spectroscopist, an X-ray crystallographer and a synthetic chemist) will be funded for five years beginning April 2006; hence, we are well positioned to take advantage of the opportunities provided by the MLSCN screens.

***Thesaurus Terms:*** Streptococcus pneumonia, SP, diphosphomevalonate, DPM, mevalonate pathway, allosteric inhibitor, mevalonate kinase, MK, Molecular Libraries Screening Centers Network, MLSCN, GHMP kinase protein, NMR

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