

Project Title: Global Consequences of Interruption of Microbial Autoinducer Signaling

Institution and State: Boise State University, Idaho

Background: There has been a dramatic rise in the past two decades in antibiotic resistant microbes that cause human and animal disease, and thus there exists a continual need to develop new antimicrobial drugs. A novel drug target is to interrupt the way bacteria communicate with each other. Bacterial systems of communication (termed “autoinducer signaling” or “quorum sensing”) is required for bacteria to coordinate their attachment to surfaces (make biofilms) and to produce disease-causing substances (virulence factors). Bacteria communicate with each other by producing small molecules....a bacterial chemical language. Targeting antibiotics to destroy these small molecules may be a novel way to reduce or stop bacteria from causing disease. Targeting bacterial communication will also increase microbial sensitivity to host immune responses and reduce resistance to standard antibiotics. Our research focuses on the bacterial enzyme Methylthioadenosine / S-adenosylhomocysteine nucleosidase (MTN) which is critical for bacterial communication because it forms autoinducer-2 molecules. Interruption of MTN activity has broad impacts on bacterial metabolism, and ultimately decreases the ability of bacteria to make biofilms and attach to mammalian cells.

Advance: Our studies show that inhibitors of MTN have unique effects. For bacteria like the Lyme disease-causing *Borrelia burgdorferi*, MTN inhibitors are cytotoxic agents and interrupt nutrient salvage pathways necessary for bacterial survival (Cornell et al, 2009). For *E. coli* that can cause diarrhea, the loss of MTN decreased bacterial replication, biofilm formation, and bacterial attachment to mammalian cells. The underlying mechanism of these effects may include the ability of the bacteria to form vitamins required for their metabolism (Parveen & Cornell, 2010). Our work uses sophisticated equipment including liquid chromatography coupled mass spectrometry to examine the proteins of MTN deficient bacteria. Recent findings suggest that antibiotics targeting MTN may make bacterial cells more susceptible to other standard antibiotics. Ultimately, this means that the development of a new class of antibiotics, the MTN inhibitors, will be useful in treating drug-resistant bacterial infections.

How NCRR Grant Enabled Advance: Summer student support provided by the Idaho INBRE-1 project (2004-2008) was used to develop much of the initial data that went into the project outlined in INBRE-2 (2009-present). INBRE-2 has provided technical salary support for a technician to work on the project, summer salary support for the project mentor (Cornell), graduate student stipend for a Master’s student, and supply money to buy necessary equipment and reagents. The support from INBRE-2 was critical for developing the data that went into a recent NIH R15 application that is now under review. In addition, the INBRE project was a major component of our successful NSF MRI application (PI Cornell) that supported the purchase of a \$500,000 state of the art LC/MS instrument used for proteomic and metabolomic studies. Improvement to our facilities also made us more competitive for a successful \$940,000 Dept. of Defense grant application to develop a vaccine for West Nile Virus (PI Cornell). NCRR support has led directly to two publications of our work, and we have four additional manuscripts that we are either under review or have planned submissions in early 2012.

Public Health Impact Statement: Our work is relevant to public health, since it describes a potential target for novel antibiotic development, and helps explain how drugs acting on this target will work. This is important for public health, since current antibiotics are increasing becoming obsolete due to the emergence of widespread drug resistance.

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Cornell KA, Primus S, Martinez JA, Parveen N. Assessment of methylthioadenosine/S-adenosylhomocysteine nucleosidases of *Borrelia burgdorferi* as targets for novel antimicrobials using a novel high-throughput method. J Antimicrob Chemother. 2009 Jun;63(6):1163-72. Epub 2009 Apr 17. PMID:19376840 PMCID: PMC2734086

Parveen N, Cornell KA. Methylthioadenosine/S-adenosylhomocysteine nucleosidase, a critical enzyme for bacterial metabolism. Mol Microbiol. 2011 Jan;79(1):7-20. doi: 10.1111/j.1365-2958.2010.07455.x. Epub 2010 Nov 18. PMID:21166890 PMCID: PMC3057356 [Available on 2012/1/1]