

InvenioIP - Technology Details

Institution: University of Maryland, Baltimore

Docket: AW-2007-003

Title: Antimicrobial Heme Oxygenase Inhibitors and Methods of Use

Summary: Antimicrobials are widely used to treat a variety of infections. However, due to overuse and microbial evolution, many antimicrobials have been rendered ineffective as first-line therapies. The invention relates to a new class of broad-spectrum, small molecule antimicrobials and their use to treat infections. Small molecule inhibitors of an essential enzyme involved in heme utilization by bacterial pathogens were identified using a computer aided drug design screening approach. These compounds inhibit the ability of pathogenic organisms to obtain iron, a necessary requirement for survival and virulence, and they offer potential for the development of a new class of antimicrobial agents with broad-spectrum activity.

Applications: Nearly 2 million patients in the United States get an infection in the hospital each year and about 90,000 of those patients die each year as a result of their infection, up from 13,300 patient deaths in 1992. More than 70 percent of the bacteria that cause hospital-acquired infections are resistant to at least one of the antibiotics most commonly used to treat them. The launches of premium-priced glycopeptides from Pfizer, Theravance/Astellas, and Targanta, as well as next-generation cephalosporins from Johnson & Johnson/Basilea and Cerexa*/Takeda, will take market share from generic vancomycin, the most widely used antibacterial for resistant gram- positive infections. Antibacterial market will experience high turnover as generic erosion of several key antibiotic brands will be partially offset by sales growth of current and novel branded agents. Additionally, the continuous evolution of bacterial pathogens and resulting development of drug resistance creates a constant need for the development of new antibiotics. Despite a lack of significant innovation, it is predicted that antibacterial pipeline represents more than \$3 billion in potential sales by 2015.

Advantages:

- The invention uses small molecules that possess broad-spectrum antimicrobial properties, which can be used to replace existing treatments, supplement existing treatments, or for infections resistant to existing treatments.
- Small molecules have the advantage of cell permeability, blood-brain barrier permeability, not eliciting immune responses, enhanced stability, decreased biomaterial contamination potential, and the capacity for large-scale manufacturing.

State of Development:

- Small molecules possessing antimicrobial properties have been identified.
- Animal studies are currently underway.

R and D Required: • Lead compound optimization.
• Studies are required to demonstrate efficacy and safety prior to use in human subjects.

Licensing Potential: • UM seeks to develop and commercialize by an exclusive or non-exclusive license agreement and/or sponsored research with a company active in the area.

Patent Status: • International Patent Application [PCT/US07/074233](#); Pending. Filed July 24, 2007.

Related Publications: • Furci LM, Lopes P, Eakanunkul S, Zhong S, MacKerell AD Jr, Wilks A. [Inhibition of the bacterial heme oxygenases from Pseudomonas aeruginosa and Neisseria meningitidis: novel antimicrobial targets](#). J Med Chem. 2007 Aug 9;50(16):3804-13.
• Wilks A, Burkhard KA. [Heme and virulence: how bacterial pathogens regulate, transport and utilize heme](#). Nat Prod Rep. 2007 Jun;24(3):511-22.
• Block DR, Lukat-Rodgers GS, Rodgers KR, Wilks A, Bhakta MN, Lansky IB. [Identification of two heme-binding sites in the cytoplasmic heme-trafficking protein PhuS from Pseudomonas aeruginosa and their relevance to function](#). Biochemistry. 2007 Dec 18;46(50):14391-402.
• Rodríguez JC, Zeng Y, Wilks A, Rivera M. [The hydrogen-bonding network in heme oxygenase also functions as a modulator of enzyme dynamics: chaotic motions upon disrupting the H-bond network in heme oxygenase from Pseudomonas aeruginosa](#). J Am Chem Soc. 2007 Sep 26;129(38):11730-42.

Files:

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