

## **Mangrolide A – A Novel Marine-Derived Antibiotic with Activity Against Gram-Negative Pathogens**

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I will present results related to a structurally novel antibiotic termed Mangrolide A, which was isolated from a marine actinomycete from the mangrove swamps in the Bahamas. Structurally, mangrolide A shares similarity to fidaxomicin (®Dificid), which is a clinically approved narrow-spectrum antibiotic used for the treatment of the Gram-positive pathogen *Clostridium difficile*. However, Mangrolide A exhibits potent and selective bactericidal activity against Gram-negative pathogens, including those associated with cystic fibrosis and hospital-acquired pneumonia infections. Mechanism of action studies revealed that Mangrolide interferes with the ribosomal proofreading process, leading to an increased rate of error in protein synthesis. This is the first example of a macrolide glycoside structure displaying the mechanism of action found for aminoglycosides. The frequency of antibiotic-resistant bacteria is currently rising at an alarming rate; therefore, the need to identify new antibiotics has reached a critical level. It is estimated that greater than 1.7 million hospital-acquired bacterial infections occurred in 2008 (4.5 per 1000 patients), resulting in more than 100,000 deaths. The estimated costs on the U.S. health care budget attributed to these infections are \$5 billion annually. Clinicians are increasingly concerned about the threat of Gram-negative pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and the Enterobacteriaceae, the main causes of hospital-acquired pneumonia. In a recent CDC survey 26% of *P. aeruginosa* isolates and 37% of *A. baumannii* hospital-isolates were resistant to the most common antibiotic treatments. While there have been a few approved clinical candidates for Gram-positive pathogens, new treatments for Gram-negative pathogens have stalled in recent decades. **Thus, the need for antibiotics that are effective against Gram-negative infections has become a medical necessity.**