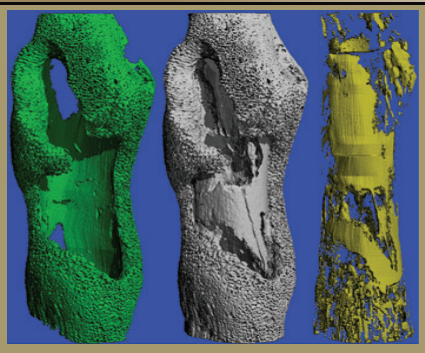
New Molecules Clear Chronic Infections by Disrupting Bacterial Energy Production Pathways

VANDERBILT UNIVERSITY
CTTC Center for Technology Transfer & Commercialization

Summary

New compounds developed at Vanderbilt demonstrate a unique mechanism of broad spectrum activity to stymy antibacterial resistance. The compounds are particularly useful in chronic infections where long term antibiotic therapy fails, because it specifically kills "small colony variants" – the bacteria that have developed resistance mechanisms. These compounds show promise in treating Methicillin-resistant S. aureus (MRSA), Bacillus anthracis (anthrax), and in overcoming difficult-to-treat infections in bone in cystic fibrosis patients. These compounds could be combined with new (and old) antimicrobial drugs to outwit resistant bacterial infections.

Figure 1. '882 inhibits fermenting *S. aureus*. Triplicate cultures of S. aureus were grown in the presence of the indicated additive. After 24 h, cfus were enumerated on tryptic soy agar (TSA) containing 5 mg/mL gentamicin (Gent) and plain TSA with a limit of detection of 100 cfus/mL (minimum y value); #, colonies were not identified above the limit of detection. Shown is the average of three independent experiments. Error bars represent 1 SD from the mean.



James Cassat and colleagues developed micro-CT imaging methods to view staph-infected mouse femur (gray) and to quantitate and view bone formation (green) and bone destruction (yellow).

Osteomyelitis, a debilitating bone infection most frequently caused by Staphylococcus aureus ("staph") bacteria, is particularly challenging to treat.

Now, Vanderbilt microbiologist Eric Skaar, Ph.D., MPH, and colleagues have identified a staph-killing compound that may be an effective treatment for osteomyelitis, and they have developed a new mouse model that will be useful for testing this compound and for generating additional therapeutic strategies.

James Cassat, M.D., Ph.D., a fellow in Pediatric Infectious Diseases who is interested in improving treatments for children with bone infections, led the mouse model studies. Working with colleagues in the Vanderbilt Center for Bone Biology and the Vanderbilt University Institute of Imaging Science, Cassat developed micro-computed tomography (micro-CT) imaging technologies to visualize a surgically introduced bone infection in progress.

"The micro-CT gives excellent resolution images of the damage that's being done to the bone," said Skaar, the Ernest W. Goodpasture Professor of Pathology. "We found that staph is not only destroying bone, but it's also promoting new bone growth. From a therapeutic development standpoint, we think this model is going to allow investigators to test new compounds for efficacy against bone infections caused by staph or any other bacteria that cause osteomyelitis."

- Research News @ Vanderbilt, June 30, 2013

Market and Technology

MRSA infections affect about 5 million people globally, with a mortality rate of 20%. Globally, the therapeutic market to treat these infections is valued at $3.2 billion. MRSA infections are notoriously difficult to treat, in part because the organism adapts readily to different environments to avoid the effect of antibiotic drugs. For example, MRSA can exploit both anaerobic and aerobic energy production. The aminoglycoside class of antibiotics effectively target many aerobically active bacteria, however, a small number of the bacteria within the population can avoid aminoglycoside toxicity by switching over to anaerobic energy production.

MRSA can also adapt by scavenging required nutrients and co-factors, like iron-containing heme, directly from the host. These bacteria must carefully control heme levels by effluxing excess heme, as too much can quickly become toxic and block the ability to switch to anaerobic energy production. Dr. Eric Skaar and colleagues have identified a new method and compounds to simultaneously disrupt these two adaptation strategies (anaerobic energy production and control of heme levels) to wipe out stubborn MRSA infections. The research team discovered and characterized a critical system in Gram-positive bacteria, termed HssRS, that controls the switch to anaerobic energy production in response to heme levels. Medicinal chemistry work has led to the development of small molecule activators of the HssRS system that reduce S. aureus pathogenesis in mouse models of infection.

Intellectual Property Status: A Patent Application has been filed.

CTTC CONTACT:
Karen Rufus
Phone: (615)-322-4295
Fax: (615) 343-4419
Karen.Rufus@vanderbilt.edu

VANDERBILT INVENTORS
Eric Skaar, Laura L. Anzaldi, Gary Sulikowski, Alex Waterson, Paul Reid

VU REFERENCE: VU11161

→ Scan to view other available Vanderbilt technologies.