MRSA researchers identify new class of drugs effective against superbug

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(Medical Xpress)—In two separate studies, researchers at The Ohio State University Wexner Medical Center have discovered a new class of treatment against methicillin-resistant Staphylococcus aureus (MRSA) as well as evidence of a growing need to quickly genotype individual strains of the organism most commonly referred to as the "superbug."

"The public is most familiar with the dramatic progression of skin infections caused by MRSA, but MRSA is responsible for a range of difficult to treat illnesses," noted Dr. Kurt B. Stevenson, an infectious disease expert at Ohio State, and primary investigator of one of the studies following the transmission of MRSA infections in communities. "While we've seen a decrease in the number of MRSA cases, identifying new drug treatments and tracking methods will be critical to stopping these infections before they can start."

Cancer treatment search leads scientists to MRSA killer, immune booster

In the August issue of Bioorganic and Medicinal Chemistry, researchers detail the results of a study that began 10 years ago, when Ching-Shih Chen, professor of medicinal chemistry at Ohio State College of Pharmacy, and a team of researchers were creating a library of anti-cancer agents built around he scaffold of the molecules of celecoxib, a popular arthritis treatment in a family of drugs known as cyclooxygenase-2 (COX-2) inhibitors. This effort yielded OSU-03012

(AR12), a compound that is currently in a Phase I clinical trial as anticancer agent at the OSU Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

After observing how OSU-03012 acted within breast cancer cells, Hao-Chieh Chiu, a then postdoctoral researcher in Chen's laboratory, realized that the derivatives were suppressing a mechanism that bacteria use to take over their host cells. Chiu decided, with the support of Dr. Chen, to focus his research on testing this compound library against a variety of bacteria.

"When these compounds showed anti-bacterial activity against Salmonella and Francisella, we began testing efficacy against a variety of pathogenic bacteria, including Staphylococcus aureus, Enterococcus, and Streptococcus," said Chiu, who is now an assistant professor at the Department of Clinical Laboratory Sciences and Medical Biotechnology at National Taiwan University. "It became clear that these analogues had a unique anti-bacterial activity, and they appeared to be most potent against Staph aureus and other MRSA strains."

The researchers narrowed the library down to a single agent (dubbed "compound 46") and moved to testing in MRSA-infected mice. Published in the August issue of *Bioorganic and Medicinal Chemistry*, the authors report that an intraperitoneal administration of compound 46 resulted in increased survival in MRSA-infected mice versus untreated mice.

"It was particularly gratifying to see that these compounds, originally designed as anticancer agents, work as a novel class of anti-bacterial agents based on the same principle in bacterial cells," said Chen.

The researchers are hopeful that this early work will ultimately provide insights on the development of a treatment for antibiotic resistant

infectious diseases. The team is already working with scientists at the Ohio State Center for Microbial Interface Biology, led by Dr. Larry Schlesinger, to use this technology to develop novel agents against tuberculosis, another public health threat facing similar issues with drug resistance.

MRSA DNA tells scientists where it's been – and where it might go next

Investigators in the Division of Infectious Diseases at the Ohio State College of Medicine have created a statewide "roadmap" of MRSA infections that is helping them better predict how – and where – MRSA will spread.

The team, funded by the Centers for Disease Control and Prevention (CDC), used diverse methods from geographic analysis to molecular genotyping to track more than 1,000 MRSA cases from the Wexner Medical Center and community hospitals across Ohio. Experts say using a variety of tracking methods is essential to stopping infections before they start.

"With data from different sources, we've markedly improved our understanding of how MRSA is acquired and then spread among healthcare facilities. For example, we identified a very rare strain in the US, ST-239, which originated in Asia, spread to hospitals in Western Europe, and was introduced to Ohio sometime in the past two decades. It's that level of knowledge that will help us change the course of transmission," said Stevenson, whose research on ST-239 and its presence in healthcare facilities was just published online in the October issue of Emergent Infectious Diseases.

Stevenson's team has also applied these tracking methods to bloodstream

isolates from hospitals in Franklin County, Ohio, as well as skin and soft tissue infections among patients receiving primary care in a variety of settings. The results not only demonstrated the value of rapid molecular typing in examining the distribution and transmission of individual MRSA strains, but showed that particular strains tended to cluster in specific places.

"These studies have demonstrated that specific molecular types of MRSA are linked to specific types of infections, or even specific settings. For instance, there are strains that tend to colonize catheters, strains that are more commonly found in nursing homes," said Shu-hua Wang, assistant professor of infectious disease. "As we understand why certain MRSA strains behave as they do, more targeted interventions for prevention and treatment can be tested."

Stevenson is hopeful that technology will someday provide a quick and inexpensive on-site genomic analysis of MRSA. In anticipation of that day, the team is using the "roadmap" data to create a MRSA molecular library that provides a detailed background on individual strains, including its drug resistance, weaknesses, and most likely source of transmission.

"We're envisioning a future where every patient admitted into a hospital will get a rapid, strain-specific MRSA test and within minutes, a doctor will know exactly what protocol to follow to stop the patient from getting sick, and stop the bacteria from spreading," said Stevenson.

Both the drug development and community tracking studies were funded by the Ohio State Center for Clinical and Translational Science with a goal of increasing the MRSA knowledge-base from both a basic science "bench" perspective, as well as using real-time data from infected communities to determine how the virulent bacteria spreads.