BONE OF CONTENTION

DR. MARK SMELTZER DEDICATES RESEARCH TO THWARTING A DANGEROUS NEMESIS

Despite a close relationship spanning decades, Dr. Mark Smeltzer has not developed fond feelings for his professional protagonist, *Staphylococcus aureus*.

"I am of the personal belief that bacteria do not care about you," Smeltzer said. "They just don't want to die. Most people don't realize that you have a very large number of bacteria living on or in you, mostly on your skin or in your gut, and they live happily there without doing harm and serving some beneficial purposes on your behalf.

"The trouble is when they make their way into places they aren't supposed to be. When that happens, your body has remarkable systems in place to get rid of them. The result is a battle in which the bacteria are trying to 'not die.'

"The result of this battle can have very adverse consequences, and this is what is known as an infection. If we can understand what the bacterium is doing to fight its part of the battle, we can develop therapeutic strategies that prevent it from doing that and tilt the balance in favor of you."

Dr. Mark Smeltzer

Smeltzer, a professor in the Department of Microbiology and Immunology at the University of Arkansas for Medical Sciences (UAMS) and member of the Arkansas Research Alliance (ARA) Academy of Scholars and Fellows, has dedicated his research and professional career to dueling with one such microscopic killer that causes the death of nearly 20,000 Americans every year.

At one point in history, it seemed this threat was neutralized. Before World War II, physicians learned that penicillin could cure Staphylococcus aureus (or staph) infections. However, by the end of the 1940s, the bacteria began to build a stubborn resistance to penicillin. This progression of introducing a new antibiotic — and the bacterium fighting back by developing resistance to the new antibiotic — has continued to the point that many bacterial species, including S. aureus, have now been designated as ESKAPE pathogens (highly virulent and antibiotic resistant bacterial pathogens) owing to the lack of effective antibiotics to treat the infections they cause.

Smeltzer believes addressing this will require a different way of thinking about the problem, and this is what led to his efforts to understand what *Staphylococcus aureus* needs to do to win the battle and "not die." He believes he and his colleagues have uncovered a key weapon that *S. aureus* needs to survive that battle and that he can exploit to clinical advantage.

Smeltzer said this is particularly important in orthopedic infections including those associated with orthopedic implants — fields of medicine whose technology vastly improves lives, and yet all too often are thwarted by an assassin billions of years old. Specifically, the things *Staphylococcus aureus* does to "not die" under these circumstances also render conventional antibiotics almost useless.

Smeltzer and his team at UAMS, which includes Dr. Karen E. Beenken and a long line of graduate students, are working on a far more targeted approach based on understanding what *S. aureus* is doing to survive in the context of complicated orthopedic infections and developing genetic inhibitors (tiny molecules that can prevent the expression of specific genes or alter the function the proteins they encode).

Smeltzer believes such inhibitors could be used to prevent S. aureus from doing what it needs to do to survive this battle and that this would help eliminate staph infections without the specter of bacterial resistance. Having identified what he believes is an important target, Smeltzer is hoping to identify that inhibitor and use it for practical clinical applications.

Another important consideration is the need to get such an inhibitor as well as conventional antibiotics when they are available to the site of the battle without causing collateral damage.

"It isn't often thought of in this way, but antibiotic therapy is chemotherapy, and all chemotherapy has some capacity for off-target adverse effects," Smeltzer said. "Thus, antibiotic resistance is not the inability to kill a given bacterial strain with a given antibiotic, but rather the inability to do so without harming the person you are trying to help."

Orthopedic surgeons often use some form of localized antibiotic delivery to avoid these adverse effects, and the Smeltzer laboratory has also actively investigated methods to optimize such delivery methods. In recent years this led to a collaboration with fellow Academy member Dr. Alex Biris, chief scientist at the Center for Integrative Nanotechnology Sciences at UA Little Rock, who has developed the NuCress™ bone scaffold technology, which promotes healing of large segmental bone breaks.

"Your bone is normally sterile. Your skin is not," Smeltzer said. "Traumatic injury to the bone often includes penetration of the skin, thus introducing bacteria to a place they are not supposed to be. This is when the battle starts, and the consequences can be very serious. To overcome them, you have to both eliminate the bacteria from the bone and repair the damage to the bone."

Smeltzer hopes to utilize technology developed in Arkansas to deliver antibiotics directly to the site of an infection.

Through the NuCress scaffold, Dr. Smeltzer hopes to utilize Dr. Biris' technology to deliver antibiotics directly to the site of infection, thus accomplishing both clinical objectives while at the same time avoiding the unwanted off-target effects. This isn't as easy as dipping the materials into a flask filled with antibiotics and calling it a day.

With the help of an ARA Impact Grant, Smeltzer has developed a process to determine the optimal amount of antibiotics. In simplified terms, he has developed models that look at effectiveness, concentration and the interaction of the two. Think of Biris' bone regeneration scaffold as the "antibiotic delivery vehicle" that allows physicians to apply the antibiotic directly to the site where it is needed most. This simultaneously eradicates infection from contaminated bone while restoring its structural integrity.

However, using this approach to deliver conventional antibiotics is only the tip of the iceberg in terms of the impact Smeltzer's research may have on medicine. He believes that genetic inhibitors, such as the one he is seeking to counter staph infections, can also be incorporated into the bone regeneration scaffold to get an even better therapeutic result, in part by making conventional antibiotics work better. He also believes this approach will lead to an enormous advance in treating all forms of bacterial infections, not just infections related to bone and orthopedic implants and not just infections caused by *Staphylococcus aureus*.

The immediate impact has proven to be of interest to many, including the U.S. Department of Defense (DOD), which views this work as a way of saving lives on the battlefield.

"Traumatic injury to the bone is common on the battlefield due to blast injuries and open fractures," Smeltzer said. "The DOD, Dr. Biris and I share an interest in minimizing the consequences of such injuries and restoring the men and women who serve our country to good health and, hopefully, continued service."

Discovery Economics is a monthly feature highlighting the work of the Arkansas Research Alliance Academy of Scholars and Fellows. Dr. Mark Smeltzer and his collaborator Dr. Alex Biris are members of the Academy. ARA recruits, retainsand focuses strategic research leaders to enhance the state's competitiveness in the knowledge economy and the production of job-creating discoveries and innovation. Learn more at ARalliance.org.