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Researchers put potent staph killer to the test, hope for new drug treatment

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(PhysOrg.com) -- Standard antibiotics, and even those reserved for the most defiant infections, are fighting an uphill battle against the evolutionary ingenuity of bacterial defenses. Staphylococci, and especially methicillin-resistant Staphylococcus aureus (MRSA), is a particular scourge in hospitals, and is increasingly infecting people outside of health care settings. But a promising new MRSA killer — a genetically engineered enzyme first created at Rockefeller — is now being tested in human skin cells and will soon advance to trials in a new animal model, the minipig. The enzyme has been recently been shown to target and kill MRSA in mice with greater efficiency than the only approved topical treatment for such infections, a drug called mupirocin. Researchers say the work is steadily advancing through stages that could lead to the development of a frontline drug to fight MRSA, which costs hospitals billions of dollars a year.

“It’s the start of a new class of drugs,” says Mina Pastagia, a clinical scholar in Vincent Fischetti’s Laboratory of Bacterial Pathogenesis and Immunology, who is leading the current research. “We’re starting from scratch, and it looks promising.”

The work stems from the genetic engineering of a lysin, a protein derived from viruses that have been infecting bacteria for billions of years, by a team of researchers in Fischetti’s lab. Nature produces countless lysins that can fight staph, but when they are recombinantly produced in the laboratory they are often insoluble or have low activity. Lysins have two basic parts. One, the binding region, recognizes the

target bacteria and latches hold. The second bores holes through the bacterium's cell wall, killing the organism. The Fischetti teams tried combinations of these two parts from about two dozen naturally occurring lysins and came up with a chimera that is easy to produce, soluble, and very active. This new creation — named chimeric lysin for staphylococci or ClyS — retained the power to kill MRSA, and was especially effective in a mouse model when used in combination with oxacillin, an antibiotic that is powerless against MRSA on its own. "The fact that lysins work synergistically with antibiotics to increase their effectiveness, particularly those to which bacteria are resistant, will enable 'shelved' antibiotics to be reinstated, increasing our antibiotic armamentarium to these pathogens" says Fischetti.

Having shown the power of ClyS in vitro, researchers next tried the chimera on mice infected by MRSA. Again, the synthetic lysin proved potent, clearing up the infections, and the researchers published the results in April 2010 in Antimicrobial Agents and Chemotherapy. The latest research, published in February in the same journal, focused on a topical model and showed not only that ClyS could work, but that it worked about 10 times better than the only other topical antibiotic on the market — mupirocin. Led by Pastagia, scientists from Fischetti's lab and James Kreuger's Laboratory of Investigative Dermatology developed an ointment containing ClyS, which they tested on mice infected with multiple strains of MRSA, including the most potent found in hospitals. They found it killed an order of magnitude more MRSA bacteria than did mupirocin, and it did so quickly, without generating any resistance either from the bacteria itself or from antibodies produced by the mice in response to the ointment.

The ability of bacteria to rapidly evolve defenses against antibiotics is one of the biggest challenges to developing effective new drugs. "This was key," says Pastagia, "because about 15 to 20 percent of patients develop resistance to mupirocin." Unlike the lysin ClyS, a chimeric

phage enzyme that drills a hole in the bacterium's cell wall and kills quickly, mupirocin interferes with the bacteria's ability to make proteins, a slower process. The speed, efficiency and method with which ClyS kills MRSA could be a major tactical advantage in the arms race against increasingly sophisticated bacteria, Pastagia says.

MRSA is known to colonize humans, particularly in the nose, throat and skin, which makes them carriers of this pathogen. This can lead to the infection of a carrier's wounds or spread to other individuals with open sores. In the hospital, doctors sometimes swab the noses of at-risk surgical patients and treat those positive for MRSA with mupirocin prior to surgery in order to decrease the risk of infection. Mupirocin can also be used to treat superficial MRSA skin infections. The resistance rate for mupirocin has been on the rise, however, and microbiology labs do not always test for resistance to it, leading to ineffective MRSA treatment. Dr. Pastagia and her colleagues hope to find a more effective alternative in the form of lysin therapy.

Now Pastagia, who is also an instructor of clinical investigation at Rockefeller's Center for Clinical and Translational Science, has launched a trial to study the impact of ClyS on the cells of human patients with psoriasis, a disease of the skin and one of humanity's oldest, affecting about two percent of Americans. Cells from psoriatic lesions are frequently infected with staph, which potentially spread and worsen the condition. Pastagia harvested cells from 25 patients and is performing histological and other experiments to determine the effects ClyS has on them in hopes that it may have therapeutic effects. Preliminary results are promising, she says, and she hopes to publish them within the next year.

After the auspicious early performance of ClyS, the researchers contacted officials with the U.S. Food and Drug Administration last year for guidance on the best way to fast-track the drug development process.

The in vitro results were strong, as were those in mice, but they were told that before a full-fledged clinical trial in humans would be possible the researchers would have to show topical ClyS' effectiveness in another animal, more closely related to human skin. The regulators suggested minipigs, smaller versions of the familiar domesticated variety, first bred for research in Europe. Rockefeller's Comparative Bioscience Center, which primarily houses the mice and rats used in university research, is adapting the facility to accommodate the small pigs, which are expected to arrive in April, Pastagia says. She plans to conduct experiments similar to those done in mice, both to test for the efficacy of ClyS and its toxicity — whether it has any adverse effects on the minipigs apart from the desired salutary ones. There were no obvious side effects on the mice treated in earlier experiments, Pastagia says.

If the results are strong, the researchers could move on to a clinical trial on human patients at Rockefeller's hospital. The ability to do the work at Rockefeller would save the considerable expense of outsourcing such trials to other facilities, Pastagia says.

"This is a very exciting project for me," she says. "I used to be a pharmacist — I was compounding then — thereafter I became a physician with a focus on infectious diseases. This project brings all of my training together. I would love to see research at the bench all the way through to a treatment that can help a lot of people."

More information: *Antimicrobial Agents and Chemotherapy* 55: 738–744 (Ferbruary 2011). A novel chimeric lysin shows superiority to mupirocin for skin decolonization of methicillin-resistant and -sensitive Staphylococcus aureus strains. Mina Pastagia, et al. aac.asm.org/cgi/content/abstract/55/2/738