

A broken autoclave and an innate sense of curiosity have helped a group of researchers shed new light on a ghastly group of common bacteria. Can their work help us squash the superbug?

By Laura Randall

**D**r. George Liu's scientific path seems paved with aha-moments and chance discoveries. Yet, his focused and inspired research on staphylococcus aureus (or 'staph' for short) at Cedars-Sinai has led to a groundbreaking discovery in the area of drug-resistant infections: A compound originally designed to lower cholesterol levels in humans could be used to fight methicillin-resistant staphylococcus aureus, or MRSA.

MRSA conjures up terrifying images—it is often called "superbug" or "flesh-eating bacteria." But behind these headline-making nicknames is a highly contagious strain of bacteria resistant to the penicillin-like drugs that have routinely, and successfully, been used to treat staph infections. Staphylococcus aureus can cause a wide range of health problems, from skin abscesses to life-threatening complications in the lungs, bloodstream, and bones.

Today in the U.S., MRSA is responsible for more deaths per year—nearly 19,000—than the AIDS virus, according



# SUPER

to a 2007 study by the Centers for Disease Control and Prevention. "It's a fascinating story, but also a very frightening one," says George Liu, MD, PhD, who grew up on Africa's Ivory Coast, where malaria was a prominent concern and had a clear influence on his medical career choice. "We are seeing flesh-eating diseases and bone infections that used to be caused by Group B strep, and are now caused by staphylococcus aureus. On top of that, methicillin, which used to be the gold standard for treating staph, is not as effective as it used to be" observes Dr. Liu.

### Staph's retreat

Before focusing on MSRA, Dr. Liu was a research fellow studying Group B strep at the University of San Diego. In 2005, Liu and his colleagues made an unexpected discovery and published a research paper that was widely praised as a major step in developing new agents to fight staphylococcus aureus.

After an intern tasked with washing laboratory equipment mistakenly left traces of bleach on some test tubes, Dr. Liu noticed that the bacteria culture in one of his test tubes wasn't growing as well as the others. Further investigation revealed that the bleach had stripped the culture of its pigment.

"We found that the pigment in the bacteria culture had antioxidant properties, just like the one found in carrots and other brightly colored vegetables," explains Dr. Liu. "So naturally, we asked ourselves whether this golden pigment was what helped the bacteria grow better."

Because staphylococcus aureus is widely known for its yellow color (its name literally means "golden cluster seed"), Liu decided to see if the same thing that had happened with his bacteria culture would happen with staphylococcus aureus. It turned out that it did. "The intern just happened to be a little careless when washing the equipment. At the same time, the autoclave [which



# STAPH

Photograph: Terry Heffernan

sterilizes the tubes after washing] wasn't working well," Liu recalls with a chuckle. "From that discovery, which was pure serendipity, we came all this way."

Liu recalls receiving a phone call from Dr. Eric Oldfield, a professor of chemistry at the University of Illinois who had read about Dr. Liu's findings on staphylococcus aureus. Dr. Oldfield pointed out that the biochemical operation that produces the golden pigment in staphylococcus aureus is similar to the one that makes cholesterol. Intrigued, Liu and researchers from the University of Illinois and the National Taiwan University in Taipei began testing dozens of anti-cholesterol drugs and found that many of them were able to significantly slow the growth of staphylococcus aureus.

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When an anti-cholesterol drug known as BPH-652 was given to staph-infected animal subjects, the result left everyone "shocked and very hopeful," says Dr. Liu. The staph bacterial counts in the animals' kidneys had decreased by 98 percent. When the same drug was tested on human blood, staph bacteria died four times faster than usual.

Also promising, says Dr. Liu, is the discovery that BPH-652 doesn't affect the skin's surface like other antibiotics. He feels that this will likely prevent or minimize resistance that has plagued drugs like methicillin.

Dr. Liu's findings were published in the March 2008 edition of *Science* magazine and earned him the prestigious Young Investigator Award for 2008 from the Pediatric Infectious Diseases Society. He and his colleagues hope to begin clinical trials in humans this year.

### **A widespread infection**

Not long ago, most staph infections were easily treated with traditional antibiotics and targeted vulnerable groups such as the elderly, the sickly, and the very young.





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## The Best Weapon, Hands Down.

The rule is clear: Doctors and nurses are supposed to wash their hands or use a Purell® dispenser before they enter and leave a patient room. For various reasons—not only at Cedars-Sinai but at hospitals everywhere—compliance with this rule falls short of the 100 percent goal. Sometimes, in the rush to get to the next patient, healthcare professionals simply forget to wash their hands. Or they might figure it's not necessary because they were only in a patient's room briefly and didn't touch anything.



Making sure everyone complies with hand-washing guidelines without fail is the goal of a hospital-wide campaign at Cedars-Sinai that involves educating all employees, as well as patients and visitors, about the fact that hand hygiene can, indeed, save lives. New custom-designed kiosks in visitor waiting areas provide Purell® dispensers, masks and tissues and display the message, "The power is in your hands. Please help us protect our patients' health."

Erica Pallys, MD, an infectious disease fellow who helps lead the hospital's hand hygiene task force, says trying to get people to change their routine is a challenge, especially when they can't directly see the results of their actions. "If you don't wash your hands, there is no visible consequence—you don't see that person down the line who could get sick or die. We're making hand hygiene as convenient as possible so that it becomes easy to do the right thing without even thinking about it."

Then something happened that has confounded infectious disease specialists and left many patients and their families frustrated and fearful. Common antibiotic treatments began losing their effectiveness and, through easy outlets like unwashed hands, MRSA started showing up in otherwise healthy groups of people: teenagers, pregnant women, and adults age 20 to 40. In addition, a community-acquired strain of MRSA has been passed among athletes and has spread to nursing homes, schools, and other public places. (Prior to 2000, the infection was largely confined to hospitals.)

"Anybody can get this infection," says Deborah Lehman, MD, associate director of pediatric infectious diseases at Cedars-Sinai.



**A compound originally designed to lower cholesterol levels in humans could be used to effectively fight MRSA.**

Nearly 60 percent of the staphylococcus aureus cultures found in hospitals are methicillin resistant. "Everyone in this field, including pediatricians, has been completely struck by the increasing number of infections we're seeing due to MRSA," notes Dr. Lehman, who is part of a center-wide task force that is working to reduce the number of all drug-resistant organisms at the medical center (see sidebar).

Last year Dr. Liu's laboratory was the recipient of a \$2 million research project grant from NIH to support his ongoing investigative work in the area of staph infections.

His current staff is small, but all of them, Dr. Liu says, display the enthusiasm and curiosity that propelled him to his early findings in this area of research.

"From the get go, we have always said, 'Let's follow our curiosity and see what happens,'" he recalls. "And I think that was what led all the way to these discoveries."

## Staff vs. Staph

**A**n 11-year-old star soccer player with an allergy to antibiotics and a staph infection that destroyed half of his pelvis. A mother-to-be who unknowingly passed an infection onto her newborn, requiring the baby to undergo hours of skin-grafting surgery. A four-year-old boy with a bone infection in his ankle which became so severe that he had to learn how to walk again.

These are a few of the patients who have sought treatment at Cedars-Sinai and other medical centers for the virulent superbug known as methicillin-resistant staphylococcus aureus, or MRSA.

While George Liu, MD, PhD, leads a team of researchers developing new antibiotic treatments for drug-resistant staph infections at the Immunobiology Research Institute (see main article), others at Cedars-Sinai are working to control the problem in real time.

Last year, the Quality Council, the oversight body at Cedars-Sinai, launched an aggressive effort to control not just MRSA, but also all multi-drug-resistant organisms that

may result in hospital-acquired infections.

"Our hospital-acquired infection rates were fairly low and stable," says Michael Langberg, MD,



Dr. George Liu

chief medical officer and senior vice president of medical services at Cedars-Sinai. "But a couple of years ago we became really focused on getting the numbers as close as possible to zero."

The hospital-wide project deployed physicians,



Dr. Michael Langberg

nurses, and clinical and non-clinical staff to tackle five areas designated to help prevent infection and infection transmission:

hand hygiene, decontamination of equipment and the environment, surveillance, contact precautions, and the care and usage of device—or central-line—bundles in patients.

Dr. Langberg admits that zero tolerance is an ambitious goal, but one that task force members are serious about reaching by early 2010. Dr. Langberg, who is co-chair of the Zero Hospital-Acquired Infections Task Force, along with Mark R. Gavens, chief operating officer and senior vice president for

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clinical care services, calls the project’s early observation and study phase “a surprising journey” that has enlightened everyone involved.

“We expected [bacteria] to pop up on elevator buttons, for example, but we also found them on places like privacy screens that had been cleaned and doorknobs in areas that weren’t considered high risk,” he says.

The effort has already led to hospital-wide changes including the introduction of washable microfiber mops, which are more absorbent than conventional loop mops; the replacement of previous privacy curtains with new sturdier ones that stand up to more frequent washings; and the use of fluorescent dye to check a room or surface for contaminants and inform staff before they proceed with cleaning. In addition, the task force has crafted a strict hand-washing policy for all employees. “You go in a room, you leave a room, you wash your hands,” is how Dr. Langberg describes it. The hand-washing policy includes the addition of hand sanitizers not just in healthcare areas, but also in cafeterias and confer-

ence rooms, and at coffee stands. “We believe that hand hygiene is the single greatest intervention we can do to eliminate the acquiring and transmission of infection,” says Langberg.

The task force is also making headway in the area of surveillance. Rekha Murthy, MD, director of hospital epidemiology, heads a group that is responsible for tracking and analyzing hospital-wide data related to infections and how they are contracted. To help prevent the inadvertent



Dr. Rekha Murthy

spread of infection, she has also helped establish a policy that places all incoming patients at high risk for MRSA (such as nursing-home residents) into immediate isolation until their bacteria cultures come back negative.

Dr. Murthy points out that these recent measures build on years of effort at Cedars-Sinai to control the

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spread of MRSA and other infections. What’s unique about the current preventative effort,” she says, “is that it is a wholesale effort that emphasizes rapid response and reaches into every corner of the medical center.”

“The types of individual measures like hand washing are based on Centers for Disease Control guidelines and comparable to what other hospitals are doing,” Dr. Murthy adds. “What I think is unique and groundbreaking here is that all of these are being bundled and rolled out *in toto*, in a comprehensive, full-court press-all, combined with a real focused effort.”

“It all comes down to a common goal,” notes Dr. Langberg, who devotes five to 10 hours a week to the task force. “We realized that if any one of us is a patient coming to the hospital we shouldn’t walk out with a bug we didn’t have. It’s a priority for all of us.”