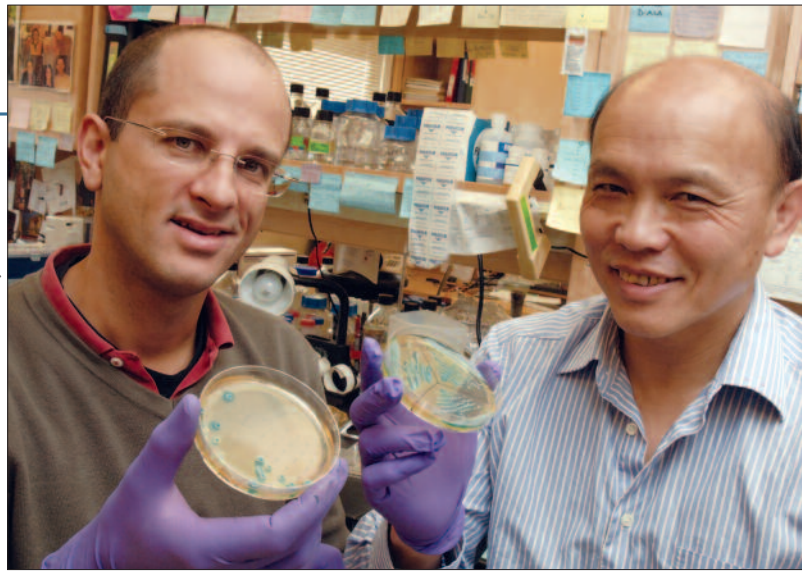
Faculty may have outsmarted staph



JON GILBERT FOX

DMS faculty members Guido Memmi (left) and Ambrose Cheung (right) have figured out a way to distinguish strains of staph infection and better combat them.

It can start out as a small red bump but within days turn deadly. "It" is an infection caused by a tiny bacterium bearing a big name—community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). CA-MRSA is so dangerous in part because it infects otherwise healthy people and is resistant to most antibiotics.

Resistance: "Bacteria, as you know, are smarter than we are," says Guido Memmi, Ph.D., a DMS microbiologist. But in fact, it's Memmi and his collaborator, Ambrose Cheung, M.D., who seem to be outsmarting CA-MRSA. They recently found a way to virtually eliminate its resistance to certain antibiotics. They reported their findings in the November 2008 issue of *Antimicrobial Agents and Chemotherapy*.

Ever since people began using antibiotics to fight *Staph aureus*—starting with penicillin in the 1940s—the bacterium has been mutating into ever more resistant strains. Methicillin, a synthetic form of penicillin, worked for several decades until, in the 1990s, an explosion of methicillin-resistant staph infections showed up in hospitals. Today, strains of MRSA (an acronym that is pronounced "MUR-suh") are generally divided into two categories: hospital-acquired (HA-MRSA) and community-acquired (CA-MRSA), with CA-MRSA being more aggressive and difficult to treat. Drugs do exist to treat both strains, but resistance to those drugs is growing.

Gene: Memmi came to DMS four years ago to work with Cheung, a professor of microbiology and immunology, whose lab has been studying *Staph* for many years. At the time, CA-MRSA was just emerging, says Memmi. So he decided to study the genetics of antibiotic resistance in CA-MRSA. He found that by knocking out a particular gene—and thus the protein it codes for, called PBP4—that CA-MRSA's resistance to certain antibiotics dropped 16-fold, to essentially zero.

Memmi's finding is powerful for a couple of reasons. First, PBP4 is one of several proteins called penicillin-binding proteins (PBPs), which are found in *Staph* cells. (Contrary to their name's implication, however, most of them do not bind to penicillin.) These proteins are important for building the cell walls of the bacteria. Until Memmi's discovery, "the dogma," he says, was that PBP4 was unimportant and resistance was "all about PBP2a." That may have been true for older HA-MRSA strains but doesn't apply to CA-MRSA, he discovered.

The second reason for the finding's importance is that PBP4 can be inactivated by an antibiotic called cefoxitin. That alone isn't enough to stop CA-MRSA, however. Other PBPs must be knocked out, too; fortunately, several of them are susceptible to a synthetic form of penicillin called oxacillin. Memmi found that a mixture of cefoxitin and oxacillin was just the right cocktail to fight the CA-MRSA strains he was working with.

The drug combo worked, killing the deadly bacteria.

But he wasn't content knowing that the drug combination worked in the two lab strains he was using. He wanted to make sure his findings were clinically relevant. So, with the help of Dartmouth pathologist Joseph Schwartzman, M.D., he obtained 300 isolates of MRSA that had been gathered from patients at DHMC.

Tool: Memmi needed to find a way to determine which isolates were of the HA variety and which were CA. He decided to use a genetic approach and in the process discovered four genes specific to CA-MRSA. In essence, he created a new diagnostic tool—a way to quickly diagnose a MRSA infection as HA or CA. (Memmi and Cheung hope to commercialize the tool so doctors anywhere can use it to diagnose MRSA.)

Once Memmi had sorted the HA from the CA isolates, he treated them with cefoxitin and oxacillin. The combo worked on those classified as CA-MRSA, killing the deadly bacteria.

Pipeline: He cautions that the finding is very preliminary. "I don't know if people will ever be treated with cefoxitin and oxacillin," says Memmi. "You still always need a robust clinical study" to determine if a new therapy works. And before a therapy is tested in humans, it needs to be tested in animals. At this point, Memmi and Cheung aren't sure who will conduct those studies. But they hope if the drug combo does turn out to work in humans that it will make its way through the testing pipeline quickly. An interesting twist, adds Memmi, is that "these drugs have been used for 30 years" and are already approved by the Food and Drug Administration.

For decades, *Staph* has been adapting to whatever antibiotics humans have thrown at it. Memmi hopes by understanding the genetics of MRSA's resistance, physicians and researchers can finally stay one step ahead of the superbug. "We have to change the strategy," he says.

JENNIFER DURGIN