

Battling the Omnipresent Predator

by Greg Austin

Humans possess unique talents, which give us an advantage over our environment. When nurses treat our wounds, for example, they disinfect them to destroy bacteria that might party in our bodies. Our immune systems also constantly seek and destroy invading microbes.

However, bacteria are also talented, and the skills of one species, *Pseudomonas aeruginosa*, continue to plague the medical community by thwarting our best efforts to destroy it. *P. aeruginosa* lives and thrives seemingly anywhere: in soil, water, plants and—unfortunately—human tissues. While healthy people can keep it at bay, the ubiquitous bug is ready to pounce on anyone in a weakened state, including burn victims and patients who have cystic fibrosis, a genetic glandular disorder. *P. aeruginosa* plagues intensive care units and cancer wards, and new strains of these bacteria are increasingly resistant to antibiotics.

Revealing how *P. aeruginosa* wreaks havoc on its victims is San Francisco State University Professor Dr. Britta Swanson's talent. She has developed novel strategies to attack this pathogen, new ways to screen for drugs against it, gained insights into its methods of operation and is training her students to further probe its secrets.

Swanson became interested in *Pseudomonas* when she was attending college at Texas Tech University Health Sciences Center in Lubbock, Texas—her husband had a relative who suffered from cystic fibrosis. “That was my initial impetus to get into *Pseudomonas* and learn more about it,” she recalls. “I have a personal connection, and I see how devastating it is.”

P. aeruginosa is a patient predator. It waits for the right opportunity to attack. But unlike tigers or more exotic predators, *P. aeruginosa* is omnipresent. It is all around us, and most disturbingly lives in our hospitals and nursing homes. Its needs are simple—*P. aeruginosa* can even grow in water in which all nutrients have been distilled away. As a result, *P. aeruginosa* is the most common cause of hospital-acquired pneumonia among its class of bacteria, and kills about 60% of its infected victims.

Treating the *P. aeruginosa* illness has always been difficult. Although for decades the antibiotic Tobramycin was the drug of choice to treat *P. aeruginosa* infections, the treatment does not fully eradicate the

disease. Even worse, since only the most resilient bacteria survive after a course of treatment, *Pseudomonas* strains are becoming evermore resistant to drugs. In addition, these bacteria have ways to pump antibiotics out of their systems. Therefore, what little flawed treatment for *P. aeruginosa* we have today is quickly becoming obsolete.

Of the patients who get infected rapidly with *P. aeruginosa*, those whose immune systems are severely compromised run a high risk of even growing this bacteria in their blood. Additionally, patients who have specific long-term illnesses, such as cystic fibrosis, or bronchiectasis, an abnormal permanent dilation of the bronchi, are at high risk for constantly carrying a low level chronic infection of these bacteria in their lungs.

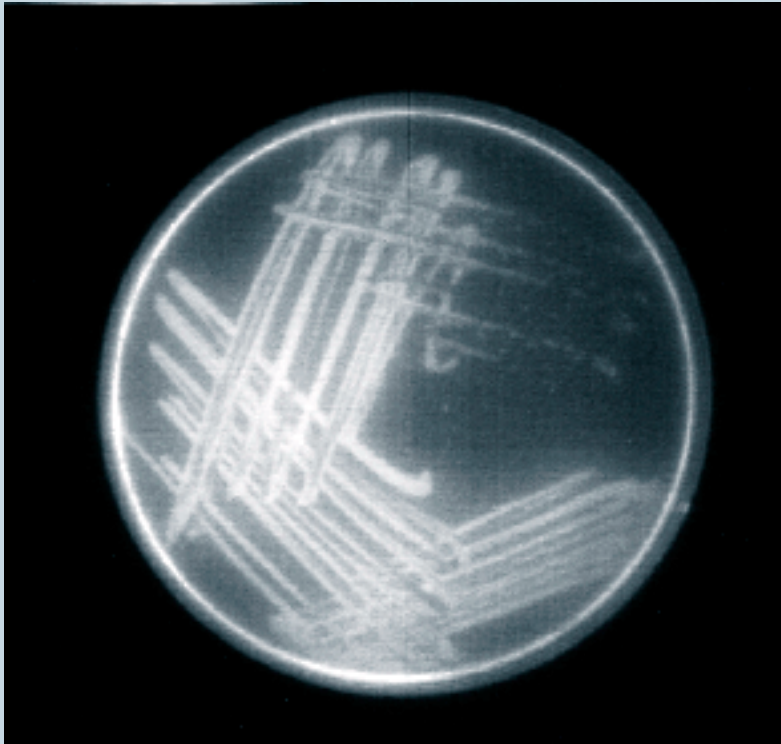
P. aeruginosa can also secrete toxic proteins called exotoxins by five known methods, type I through V. Swanson's team concentrates on the type III secretion system, which the bacteria employ to inject their poisons directly into the cells of the host's body. The vehicle for this lethal injection is a needle complex. The bacteria construct hollow tube-like apparatuses to focus their transfer of exotoxin into a neighboring host cell. These exotoxins help *P. aeruginosa* obtain nutrients and to specifically weaken the white blood cells that the body sends to the site of infection to fight disease.

To explore the importance of the type III secretion system in real infections, Swanson and eight other associates from University of California, San Francisco Medical Center conducted studies at Moffitt-Long Hospital, University of California, San Francisco Medical Center to determine the ability of *P. aeruginosa* strains expressing the type III secretion system to sicken and kill patients versus strains that do not express the type III system. During a ten-month period, *P. aeruginosa* cultures were collected from the lower respiratory tract and blood of 108 patients.

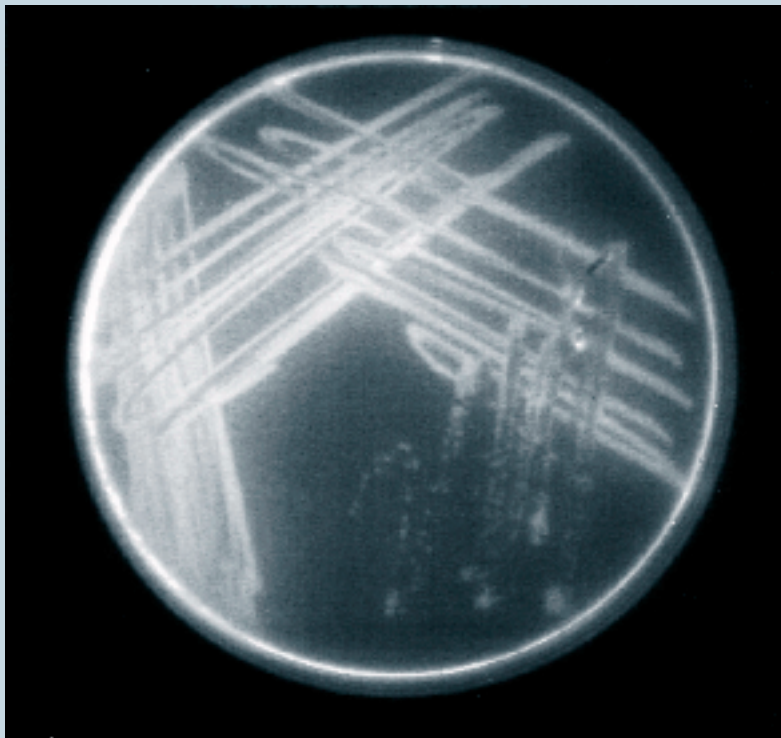
The researchers demonstrated that



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The plates at left are streaked with a laboratory strain of *Pseudomonas aeruginosa*. This organism has been modified so that we can monitor the expression of the type III secretion system (TTSS). It contains a bioluminescence gene located proximal to TTSS genes. When the TTSS is activated, *Pseudomonas* will bioluminesce (glow like a firefly) and we can measure and record the level of activation.



more people die of *P. aeruginosa* infections when the bacteria use the type III secretion system. Among patients with *P. aeruginosa*, those infected with strains that expressed at least one type III protein had a mortality rate of 21%, compared to those infected with strains that did not, whose mortality rate was 3%. This implies that the function of the type III system correlates directly with sickness and death. Swanson's lab is interested in understanding the proteins and mechanisms involved in activating the system. For example, her team of undergraduate and graduate students are studying whether the needle complex acts a sensor. They suspect the complex itself may detect contact with a white blood cell, or other target, and then trigger the pumping of toxin.

Finding chemicals that interfere with the type III system could pave the way toward the development of new drugs to treat the infection. However, besides new drugs designed to inhibit the bacteria once an infection has developed, Swanson is interested in drugs that follow the old adage: An ounce of prevention is worth a pound of cure.



The graduate student pictured at left is Tanya Gannon. She finished her thesis work summer 2005.

Tanya utilizes the luminescent bacteria in a 96-well tissue culture plate containing human epithelial cells. Using this high-throughput technique, she can monitor the activity of several different genes that make up the type III secretion system. She compares the activity of TTSS genes expressed from the wild-type strain to the activity expressed in a mutant strain.



“The biggest problem is that we have all these drugs to try to kill off bacteria,” Swanson remarks, “but the most important part of trying to treat infection is to block that very first, first step of attachment and colonization.” So, bacterial adhesion and how to prevent it is one of Swanson’s research interests. *P. aeruginosa* adheres and colonizes by binding to specific carbohydrate residues on the surface of

the lungs, which are lined with epithelial cells. Swanson developed a rapid, sensitive and reproducible method for screening agents that inhibit the bacteria’s adhesion, a system ideal for testing potential new drugs.

Because the field is so broad, and there is little time for one individual to explore all of the potential leads toward developing a treatment for *Pseudomonas*, Swanson

enjoys teaching. Her students learn cutting edge microbiological techniques involved in dissecting the type III secretion system. Sewing the seeds of education is one way to ensure that someone else can help continue these investigations. As the next generation of the microbes evolve and adapt new talents for survival and advantage, the next generation of microbiologists, some led by Swanson, will prepare for their arrival. ❖