New UCSD Program to Fight Drug-Resistant Bacteria

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In response to the major public health threat posed by antibiotic-resistant bacteria, researchers at the University of California, San Diego (UCSD) are launching a new program to develop novel antibiotics – from initial discovery, through development and testing, to clinical trials.

"UCSD is uniquely positioned to provide all of the necessary expertise to fight this urgent medical problem," said UCSD Chancellor Marye Anne Fox. "UCSD researchers in medicine, pharmaceutical sciences, medicinal chemistry and oceanography will combine their expertise to explore potential new antibiotic drug discoveries."

The program brings together researchers from UCSD's School of Medicine, Skaggs School of Pharmacy and Pharmaceutical Sciences, the Department of Chemistry and Biochemistry and Scripps Institution of Oceanography to harness what might prove to be the world's most important untapped drug resource – the ocean.

William Fenical, Ph.D, professor of oceanography and pharmaceutical sciences and director of Scripps's Center for Marine Biotechnology and Biomedicine, and colleagues at Scripps are working on the isolation and characterization of potent substances from the sea – discovering novel drug-producing microbes.

Fenical's research team has discovered at least 13 new groups of microbes which are adapted to live in the world's oceans. Many of these new bacteria are found in deep- ocean sediments, a habitat that had never been conceived as a resource in previous drug discovery programs.

"In laboratory culture, these new bacteria produce an amazing diversity of structurally unprecedented and highly bioactive molecules with the potential to contribute successfully to the treatment of infectious diseases," said Fenical.

Victor Nizet, M.D., is an associate professor of pediatrics in the Division of Infectious Diseases at UCSD's School of Medicine. He and other researchers in the School of Medicine possess expertise in developing innovative strategies from antibiotic resistant microbes. Nizet and his colleagues use molecular and cellular approaches to study the disease-causing properties of

bacterial pathogens, as well as the mechanisms human immune systems can use to defend against infection.

"In recent years, the problem of antibiotic resistance has greatly accelerated," said Nizet. "The problem is no longer restricted to the hospital setting, as more and more infections acquired out in the community are being produced by drug-resistant strains."

The Problem of Antimicrobial Resistance

According to Center for Disease Control statistics published in Spring 2006:

- → Nearly 2 million patients in the United States get an infection in the hospital each year
- → About 90,000 of those patients die each year as a result of their infection, up from 13,300 patient deaths in 1992
- → More than 70 percent of the bacteria that cause hospital-acquired infections are resistant to at least one of the antibiotics most commonly used to treat them
- → People infected with antibiotic-resistant organisms are more likely to have longer hospital stays and require treatment with second- or third-choice medicines that may be less effective, more toxic, and more expensive

Staphylococcus aureus or "staph" is the leading cause of human infections in the skin, deep tissues, bones and joints. Staph especially flourishes in the hospital setting, producing bloodstream and surgical wound infections. The spread of antibiotic resistant strains of staph, referred to as methicillin-resistant *Staphylococcus aureus,* or MRSA, has reached epidemic proportions in both hospital and community settings and poses a major threat to the public health.

"The crisis is compounded because many of the world's largest pharmaceutical companies have abandoned antibiotic development efforts," said Nizet. He said there is serious concern that the pipeline of new medications is insufficient, failing to keep up with evolving bacteria resistance. "Some resistant species are only one or two steps away from being medically untreatable," he said.

UCSD's Plan of Attack: Discovering and Developing New Medicines

Scripps researchers are working to purify diverse chemicals found in marine sources and test for their ability to kill drug-resistant species like MRSA, fielding novel compounds with anti-microbial activity. They collaborate with chemists such as UCSD's Mike VanNieuwenhze, assistant professor of chemistry and biochemistry, who uses his experience to understand how antibiotics work, then chemically modifies them to enhance activity and minimize toxicity.

The project also utilizes researchers in the Skaggs School of Pharmacy and Pharmaceutical Sciences, building on faculty expertise in pharmaceutical chemistry for synthesizing lead drugs and characterizing natural products; pharmacokinetics – the processes by which a drug is absorbed, distributed, metabolized, and eliminated by the body – and pharmacogenetics – the study of how the actions of and reactions to drugs vary with the patient's genes.

"With newly recruited faculty in pharmaceutical chemistry, coupled with long-standing expertise in pharmacology and chemistry, UCSD is well positioned to contribute to this and other critical areas of drug development," said Palmer Taylor, Ph.D., dean of the Skaggs School and Associate Vice Chancellor of Health Sciences at UCSD.

Plans are underway for a new division, based in the School of Medicine's Department of Pediatrics and led by Nizet, who will also hold a joint appointment at the Skaggs School. The division, with a major focus on the development of new antibiotics, hopes to recruit several new faculty members to work in the area of novel antibiotics in coming years.

The UCSD researchers' aim is not to simply kill bacteria, but to develop more pathogen-specific drugs that possess fewer side effects. They are also looking at ways in which medicines can work to boost the body's own immune system's ability to kill bacteria, especially in patients with compromised immune systems.

"Through discoveries made at UCSD, we understand many specific virulence factors that allow bacteria to cause disease," said Nizet. "We believe the next generation of antibiotics will include products that disarm bacteria by neutralizing their virulence factors. In that way, the pathogens may be rendered harmless, without such a strong stimulus for resistance."

"By linking Scripps's marine drug discovery program with the expertise in the Schools of Medicine and Pharmaceutical Sciences, UCSD is in a unique and unprecedented position to discover and develop new medicines for the future," said Fenical.

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