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Researchers Developing Radically Different Screening Tool to Answer Public Health Threat of Drug-resistant Bacteria

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MERCED - Amid international concern about the public health threat of drug-resistant *Staphylococcus aurea* bacteria, researchers at the University of California, Merced, have filed for a patent on a powerful new screening tool that could someday answer widespread calls for universal staph screenings before patients are admitted to hospitals.

"Universal screening is not possible right now," said Professor Miriam Barlow of UC Merced's School of Natural Sciences. "The standard means for identifying drug-resistant staph is a two-step process that requires several days. Obviously hospitals can't make patients wait that long to be admitted.

"Our screening method is being developed with the aim of accomplishing a screening in six hours or less."

M2IDF at a Glance

Barlow and her colleagues, professors Matthew Meyer of the School of Natural Sciences and Shawn Newsam of the School of Engineering, are developing what they call the Microcalorimetry Microorganism Infectious Disease Analyzer (M2IDF), a machine that measures how bacterial cells respond to heat as a way of identifying the bacteria and determining whether they are resistant to antibiotics.

"We're melting the cells, the same way ice melts," Barlow explained. "When compounds are melting, they absorb heat at different rates. Chemical differences in different strains of bacteria make them absorb different amounts of heat at different times. These differences are the basis for identifying bacteria."

Experiments and testing continue at UC Merced with the aim of bringing M2IDF to the market. The professors involved are seeking industrial partners for its development. Their patent application was filed Jan. 3.

The Grave Threat of Resistant Staph

Barlow and her colleagues believe that resistant staph (Multiply Resistant *Staphylococcus aureus*, or MRSA) is a public health threat comparable in scope to AIDS. Antibiotic resistant pathogenic bacteria have been increasing in frequency and global spread for years. Hospital-acquired infections have long been a major source of resistant bacteria, but now those hospital-acquired infections are moving from hospitals into the community and posing an increasingly serious public health threat.

Barlow also said that MRSA is only the first of what will be many antibiotic resistant organisms that will spread from hospitals to the community.

Current Screening and Treatment Procedure

The standard means for identifying MRSA and other resistant bacteria is a two step process that requires several days.

- Material from the site of infection must be cultured for 2-3 days in order to identify the organism that is responsible for the infection.
- The isolated organism must be tested for susceptibility to a panel of antibiotics that are commonly effective against that organism, a process that requires another 1-2 days.

During the assessment period the patient is usually treated with an antibiotic that the physician hopes will be effective. When the infectious organism is resistant to that antibiotic the patient suffers as the infection often becomes more severe. With luck, in 2-5 days an effective antibiotic can be identified and administered.

Radical New Screening Tool: M2IDF Analyzer

Professors at UC Merced are developing their new staph screening tool, the M2IDF, with the aim of reducing the time required for identification of the organism and determining antibiotic resistance from the current 3-5 days to a matter of six hours or less. This rapid identification will permit early intervention with an effective antibiotic, providing a significant savings in risk to the patient, duration of hospital stay and cost of treatment.

Every time an ineffective antibiotic is administered, especially in a hospital setting, the population of resistant organisms increases and the problem of worldwide antibiotic resistance becomes a little more severe. By reducing the use of ineffective antibiotics the M2IDF will reduce the spread of resistance and prolong the use of antibiotics as an effective means of infectious disease therapy.

Future Development and Availability of M2IDF

The M2IDF is currently at an early stage of development in the laboratories of Barlow, Meyer and Newsam at UC Merced.

The M2IDF measures bacterial metabolism to determine what concentrations of antibiotics are lethal to microbes. It identifies bacteria by measuring variations during heat-stimulated denaturation of cellular components - the melting process Barlow described.

So far, the research team has used standard microcalorimeters and limited their experiments to known organisms grown one at a time in separate cultures. The effectiveness of the M2IDF approach has been demonstrated under controlled laboratory conditions.

Continued development of the M2IDF will involve four stages.

1. Continued experiments with a wide variety of infectious bacteria to determine the accuracy with which the M2IDF can distinguish infectious organisms and determine antibiotic susceptibility from monocultures. That will be followed by similar experiments on mixed cultures. During this period we will assess the limitations of the approach. How complex a mixture of organisms can the M2IDF handle? What is the limitation of sensitivity? How many cells are required for an accurate analysis?
2. Assessing the capability of the system when dealing with clinical samples from infection sites, including a variety of bodily materials in addition to the infectious organisms themselves. How do those materials affect the sensitivity and reliability of the testing? Will a brief period of culture be required before analysis, or can the method be applied directly to some clinical samples? During this period the team plans to develop a library of response profiles of an increasingly wide variety of pathogens. They also anticipate moving from being able to distinguish *Pseudomonas* from *Staphylococcus* toward being able to distinguish *Pseudomonas aeruginosa* (another common and dangerous hospital-spread bacterium) from *Pseudomonas fluorescens* (a generally harmless relative used to produce antibiotics, protect plants from fungi and even make yogurt).
3. Current microcalorimeters are capable of analyzing only one sample at a time. The team will have to design a machine to perform high-

throughput analysis, handling dozens of samples a day. This stage will require partnering with a medical engineering and instrumentation company. During this period an integrated collaboration with the medical engineering firm is very likely to result in increased sensitivity and increased resolution.

4. Finally, a prototype high-throughput M2IDF instrument will have to be refined and turned into a well-designed, user-friendly, reliable instrument that can be provided at a reasonable cost to hospitals.

Barlow, Meyer and Newsam are actively seeking industrial partners for the continued development of the M2IDF technology. With the right partner or partners, they hope to bring the M2IDF to the market in about six years.

About the Researchers

All three professors are members of the founding faculty at UC Merced. Barlow is an expert in microbial evolution and antibiotic resistance, and Meyer is optimizing the chemical aspects of the M2IDF process. Newsam, who is developing algorithms to analyze the output from the instrument, recently won the Presidential Early Career Award for Scientists and Engineers based on his highly interdisciplinary research in computer vision.

Biomedical Research at UC Merced

The growing program in biomedical research at UC Merced is a vital component of an innovative medical education program planned leading to a future medical school to begin educating doctors in Merced in 2013. For more information, please see <http://med.ucmerced.edu>.

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