SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS RECEIVE $15.1 MILLION IN FEDERAL GRANTS TO STUDY BIOTHREATS

DALLAS – Oct. 6, 2003 – Researchers at UT Southwestern Medical Center at Dallas have been awarded $15.1 million in grants from the National Institutes of Health to study anthrax, ricin, plague, tularemia and Lassa fever – all pathogens that can be used as biological weapons.

The largest of the grants is a 4½-year, $8.7 million award to study tularemia, a deadly infection caused by the bacterium *Francisella tularensis* that is easier to use as a weapon than anthrax. Dr. Michael Norgard, chairman of microbiology at UT Southwestern, will lead a team of six researchers in five separate projects analyzing the external environment of the bacterium and identifying how it reacts with target host cells.

Other research groups at UT Southwestern will work to develop a vaccine for ricin, engineer antibodies against anthrax, develop new drugs to treat Lassa fever, and identify the method by which the organism that causes plague blocks the body's innate immune response, resulting in proliferation of the pathogen.

The grants were awarded by the NIH's National Institute of Allergy and Infectious Diseases.

"Embarrassingly little information is known about the organism that causes tularemia," said Dr. Norgard. "Our work will be rooted in basic science, with the goal of moving toward things that could have more practical use in the biodefense effort, such as treatments, vaccines, diagnostics, and novel intervention strategies."

Francisella tularensis was one of several biological weapons stockpiled by the U.S. military in the late 1960s, and destroyed by 1973. Fifty to 100 incidences of tularemia occur naturally in the U.S. each year, most often in farmers, veterinarians and hunters. The illness can be transmitted through a bite from an infected animal, such as a mouse, squirrel or rabbit, or by direct contact with the animal's tissues or fluids. It can also be transmitted through ingestion of

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contaminated food, water, or soil; or by inhaling infective aerosols. It is one of the most infectious of the known pathogenic bacteria; examining an open culture plate can cause exposure.

"It's a very dangerous organism to work with, and that's why so little is known about it," Dr. Norgard said.

Tularemia is classified by the U.S. government as a Category A biothreat, the highest classification. Aerosol dissemination of the *F. tularensis* bacteria in a populated area would result, within three to five days, in sudden onset of a bacterial infection in a large number of people. Symptoms begin abruptly one to 10 days after exposure and include headache, chills, nausea, vomiting, high fever and severe exhaustion. Extreme weakness, recurring chills and drenching sweats follow. Within 24 to 48 hours, an inflamed blister appears at the infection site and rapidly forms into an ulcer. Without antibiotic treatment, the infection can lead to respiratory failure, shock and death.

Dr. Ellen Vitetta, director of UT Southwestern's Cancer Immunobiology Center, received a 3½-year, $2.5 million grant to lead a team of four investigators in developing a vaccine for ricin and for initiating clinical trials. Dr. Vitetta and her team have already developed an experimental vaccine for the deadly toxin as an outgrowth of their cancer-therapy work.

Ricin, a toxin derived from castor beans, can be administered in foods and water or sprayed as an aerosol. A small dose can produce flu-like symptoms and result in death within a few days. It has been used as a biological weapon in several countries.

Dr. Vitetta expects to initiate tests in mice against airborne ricin as early as the first quarter of 2004, when UT Southwestern is slated to complete a planned biosafety level 3 facility.

"We are currently optimizing production, formulation and storage of the vaccine," Dr. Vitetta said. "We will then gather all the data to file an IND (investigational new drug) application with the Food and Drug Administration. We hope to start field trials of the intramuscular vaccine in the spring of 2004."

Ricin is classified as a Category B biothreat.

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Dr. Philip Thorpe, professor of pharmacology, was awarded a 4 ½-year, $1.68 million grant to develop broad-spectrum drugs to treat Lassa fever, an acute viral illness found in West Africa. Lassa fever, a Category A biothreat, occurs naturally in rodents and is transmitted to humans by contaminated materials or person-to-person contact. It is mild or has no observable symptoms in about 80 percent of people infected, with the remaining 20 percent having a severe multisystem disease. During an epidemic of Lassa fever, up to 50 percent of hospitalized patients with the illness would die.

"We are developing drugs to use against Lassa fever that operate on a new principle in virology," Dr. Thorpe said. "They exploit the fact that viruses coat themselves with an outer membrane where some of the lipids are inside-out. The drugs direct our immune responses to the inside-out components of the viral membrane, or envelope."

These drugs potentially could be effective against numerous viruses that have similar outer membranes, including smallpox.

Dr. Sally Ward, professor of microbiology and a professor in the Center for Immunology and the Cancer Immunobiology Center, received a 4½-year, $1.5 million grant to engineer antibodies targeting anthrax, an infectious disease caused by the spore-forming bacterium *Bacillus anthracis*.

Anthrax is No. 1 on the nation's list of potential bioterrorism threats – a Category A. Aerosol dissemination of anthrax spores can travel several miles and remain potent. The aerosol cloud would be colorless, odorless and invisible, and people indoors would receive the same amount of exposure as those outdoors. Inhalation anthrax is the most deadly of the three types. Initial symptoms resemble a common cold. In most cases, these symptoms progress to severe breathing problems, shock and death. The other two types are cutaneous, or skin, anthrax and gastrointestinal anthrax. Cutaneous anthrax is caused by handling products from infected animals and leads to a skin infection that develops into a painless ulcer with a characteristic black area in the center. About 20 percent of untreated cases of skin anthrax result in death.

Dr. Kim Orth, assistant professor of molecular biology, was awarded a 4½-year,

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$800,000 grant to study the pathogenic factor *Yop J* – a protein produced by *Yersinia*, which is the bacterium that causes plague.

"When you are infected with plague, the bacteria doesn't want the body to know it's there, and one of the tools it uses is this molecule, *Yop J*," Dr. Orth said. "The cells that are essential for recognizing that you're being infected are killed, so your body doesn't know you are infected, and the bacteria can survive and proliferate, resulting in the painful death of an untreated host."

The bacterium that causes plague, a Category A biothreat, thrives in the rodent and flea ecosystem. It is transmitted to humans through fleabites and can cause death within less than a week. The illness is marked by fever, extreme exhaustion, and a painful, swollen lymph node that is often hot to the touch. Plague can be treated with antibiotics if it is caught in time. About a dozen Americans are infected with plague each year. The last known outbreak occurred in India in the 1990s.

These grants come on the heels of substantial NIH grants awarded earlier this month for the creation of eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research. The UT Medical Branch in Galveston was named as one of the eight centers. UT Southwestern will partner with UTMB to oversee two of the six core areas of research assigned to the Texas region: a pathogen expression center overseen by Dr. Stephen Johnston, director of UT Southwestern's Center for Biomedical Inventions and professor of biochemistry and internal medicine; and a biocomputation center led by Dr. Harold "Skip" Garner, professor of biochemistry and internal medicine.

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