SOUTHWESTERN NEWS

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UT Southwestern initiating trials in humans for ricin vaccine

DALLAS – Nov. 30, 2004 – A potential vaccine for the deadly toxin ricin, a "Category B" biological agent, will enter the first phase of clinical testing in coming weeks at UT Southwestern Medical Center at Dallas.

The Food and Drug Administration and the UT Southwestern Institutional Review Board have agreed that the trial can go forward in humans.

"This is a safety and immunogenicity trial," said Dr. Ellen Vitetta, director of the Cancer Immunobiology Center at UT Southwestern. "To test the immune response induced by the vaccine, the sera (blood products) from our injected human volunteers will be tested for levels of specific ricin-neutralizing antibodies. These antibodies, in turn, will be evaluated for their ability to protect mice against a lethal ricin challenge. As far as we can tell, the vaccine is completely safe and has no side effects."

Dr. Vitetta's work with ricin received international attention when she and a team of UT Southwestern researchers developed an experimental vaccine for the deadly toxin as an outgrowth of their cancer-therapy work. The translation from discovery to clinical testing has moved rapidly with support from the National Institutes of Health (NIH) and the "incredible efforts of a talented and dedicated group of scientists and research associates," Dr. Vitetta said.

The genetically engineered protein vaccine, RiVax, was developed by Dr. Vitetta and the center's Drs. Victor Ghetie, professor; Joan Smallshaw, assistant professor; and John Schindler, assistant professor and director of the clinical trial.

Ricin, which can be administered in foods and water or sprayed as an aerosol, is extracted from castor beans. There is currently no effective vaccine or treatment for ricin poisoning in humans.

Depending on how the ricin is administered, victims develop fever, nausea and abdominal pain or lung damage before dying within a few days of exposure. There is no antidote after the first few hours of exposure, and because symptoms do not appear until later and often mimic other illnesses, individuals often do not know if they have been exposed until it is too late for treatment, Dr. Vitetta said.

Because castor beans are readily available, public health officials warn that ricin could be used for terrorism. Indeed, ricin has a long history of use in espionage, and there have been several recent incidents involving the toxin in the United States and Europe. The Centers for Disease Control classifies ricin as a

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"Category B" biological agent, which means it is "relatively easy to disseminate."

In creating the new vaccine, Dr. Smallshaw mutated the DNA encoding the active "A" chain of the toxin. She deleted the site in this chain that inhibits the cell's ability to synthesize proteins, as well as the site responsible for inducing vascular leak in the host. UT Southwestern scientists eventually created three genetically distinct non-toxic versions of the ricin A chain, two of which were effective as vaccines in mice. Dr. Vitetta said *E. coli* bacteria are used to produce the A chain protein, making vaccine production inexpensive and safe.

The DNA sequence was identified by Dr. Vitetta's group several years ago in its ongoing efforts to produce safer immunotoxins containing the A chain of ricin. Dr. Vitetta and her colleagues have used such immunotoxins – anti-cancer drugs – as experimental therapy in more than 300 cancer patients.

Injected RiVax protects mice against 10 lethal doses of ricin and has no side effects in mice when given at 100 times the dosage required for an immune response. A similar study in rabbits also showed no side effects, and the animals also produced high levels of ricin-neutralizing antibodies, Dr. Vitetta said.

The pilot phase I trial – to be carried out by Dr. Robert Munford, professor of internal medicine and microbiology – is designed to confirm the vaccine's safety at doses that induce effective antibody levels in healthy humans. DOR BioPharma, Inc. has received an exclusive license for the vaccine and is developing manufacturing processes for the genetically engineered vaccine. DOR is planning to produce a large stockpile for more advanced human clinical testing, product licensing and potential purchases from the U.S. government and other interested parties.

"I am confident that DOR will move the vaccine forward rapidly and effectively after our trial is completed, assuming that the vaccine is safe," Dr. Vitetta said.

"Our future work here at UT Southwestern will focus on how to deliver the vaccine by oral or intranasal routes instead of by injection," she said. "Mucosal immunity is fascinating and extremely important for virtually all types of biothreats because most will be inhaled or ingested. It is important to have immunity at these anatomical sites and not only in the blood. The blood may prevent death but not tissue damage in the lungs, intestine and elsewhere."

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