Adjuvanted Nanolipoprotein Particles for Use in Enhancing the Protective Efficacy of *Francisella tularensis* Membrane Protein Antigens

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Biological weapons, and concerns over their use, often are perceived as modern inventions. However, biological weapons have been used for hundreds of years. Some of the earliest recorded biological weapons date back to 1346, when the bodies of plague victims were catapulted over city walls by invading armies causing devastating epidemics. As a result of the anthrax letter attacks of 2001, there have been heightened concerns about our nation’s preparedness for and capability to respond to intentional biological releases. Governmental agencies, including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Department of Agriculture (USDA) have assembled a list of Select Agents and Toxins, which could be used as biological weapons and have the potential to pose severe threats to both human and animal health. A subset of these Select Agents, the so-called “dirty dozen,” have been designated as Tier 1 agents, indicating that they present the greatest risk for deliberate misuse with severe public health consequences, mass casualties, and devastating economic impacts. One of these Tier 1 Agents is the Ebola virus, which we hear about daily due to the current West Africa epidemic. A lesser-known Tier 1 Agent is *Francisella tularensis*, the causative agent of tularemia. *F. tularensis* is one of the most deadly bacterial pathogens known, with the ability to infect humans via multiple infection routes (inhalation, ingestion, mucosal exposure, skin infections, etc.), low infectious dose (less than 10 bacteria), environmental stability, ease of aerosolization, and ability to cause severe disease and death in 5 to 6 days. Despite all of these concerns and decades of research, there is no FDA-approved vaccine against tularemia.

To address this major gap in public health preparedness, Dr. Jason Huntley, Assistant Professor of Medical Microbiology and Immunology, recently was awarded a 3 year grant from the U.S. Department of Defense to develop and test new recombinant protein vaccine formulations for their ability to protect animals against aerosolized *F. tularensis*. The rationale for this vaccine development project comes from previous studies in the Huntley laboratory studying *F. tularensis* outer membrane proteins (OMPs). Bacterial OMPs are arguably some of the most important molecules to study, given their surface exposure, known roles in disease (e.g., host cell attachment and invasion), and ability to induce strong immune responses. Dr. Huntley and colleagues previously published a study demonstrating that purified OMPs could protect mice against pulmonary *F. tularensis* infection. More recent studies in the Huntley laboratory have demonstrated that *F. tularensis* changes its surface OMP profile during animal infection, with unique subsets of OMPs expressed in different organs at different times during infection. The Huntley laboratory also has used high-throughput technologies such as immunoproteome microarrays to identify which OMPs stimulate the strongest immune responses (Figure 1). Together, these preliminary studies have helped prioritize which OMPs should be tested as vaccine candidates.
Over the next three years, the Huntley laboratory will overexpress and purify large quantities of approximately 15 recombinant *F. tularensis* OMPs from *E. coli*. Following purification, the Huntley laboratory will examine antibody (e.g., isotype and titer) and T cell (e.g., proliferation and cytokine release) responses to each purified OMP. The most immunogenic OMPs will be sent to Dr. Huntley’s collaborators at Lawrence Livermore National Laboratory in Livermore, California for incorporation into nanolipoprotein particles (NLPs). NLPs are discoid-shaped membrane bilayers that will be tested as a novel vaccine delivery platform (Figure 2). NLPs are safe to use in animals, extremely small (10-25 nm), and spontaneously self-assemble with scaffold protein and various lipids. An added advantage of NLPs is that they can be assembled to contain a wide range of adjuvants. Dr. Huntley and his colleagues will be testing at least two new adjuvants in this project, including monophosphoryl lipid A (MPLA) and CpG oligonucleotides. Following NLP:OMP assembly, vaccine safety and efficacy will be tested in a rat pulmonary infection model. After the first series of vaccine studies, the most protective individual NLP:OMP vaccines will be combined and tested as multi-valent vaccines.

In summary, the goal of this newly funded grant is to develop and test novel vaccine formulations against tularemia. The approach by Dr. Huntley and his colleagues has many advantages over previous studies: 1. Surface-exposed proteins, such as OMPs, are the most recognized targets by the immune system during the early stages of infection, therefore pre-existing immunity to OMPs likely will block the initial infection process; 2. NLPs are a novel vaccine delivery platform that stabilizes, protects, and allows for timed-release of OMPs and adjuvants to enhance immune stimulation; 3. This project will provide new information about the repertoire of immune responses needed for protection against *F. tularensis*. Together, these results will lead to future development of a safe and effective tularemia vaccine for humans.
The first annual Research Excellence Award honors UTMC clinical research coordinators who exemplify excellence in knowledge, skills, and values of the profession. The Jacobson Center for Clinical and Translational Research (JCCTR) established the award that was presented to two coordinators for their outstanding performance last month.

**Stephanie Smiddy**, has been working as a CRC in the Department of Medicine Division of Rheumatology, Obstetrics and Gynecology and Oncology for the last six years.

"It is an honor to be chosen as a recipient of the first annual Research Excellence Award from the JCCTR. It is very gratifying to know that my hard work was acknowledged and valued. I truly appreciate this award and recognition!"

**Jennifer Gilmore**, is a CRC for the Department of Medicine who has been running clinical trials for General Internal Medicine for over 14 years.

"Thank you so much for the 2014 Research Excellence Award, it was very unexpected and I am honored. It is wonderful to be able to represent this amazing group of coordinators!"

We congratulate these award recipients, who continue to inspire us with their commitment to research excellence!

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**Clinical Research Coordinators Pass Certification Exam**

Congratulations to Stephanie Smiddy & Chris Eisenhauer for passing the Certified Clinical Research Coordinator (CCRC) exam administered by the Association of Clinical Research Professionals (ACRP) in September.

ACRP Certification is the formal recognition of clinical research professionals who have demonstrated the knowledge, skills, and abilities to perform ethical and responsible clinical research based on international standards. The CCRC designation promotes professionalism in clinical research by validating competence and dedication to quality standards and is a mark of excellence.

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Fatty liver disease: a new epidemic, a new concern

12:00 - 1:00 PM, 1035 Collier Building

To be presented by:
Dr. Sonia Najjar, Ph.D., Professor, Director, Cntr for Diabetes & Endocrine Research
Dr. Thomas Sodeman, M.D., Professor, Chief, Gastroenterology and Hepatology
Lunch will be provided

**New clinical trials**

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Dr. Atallah – Anesthesiology

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