



THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER
ANNOUNCES THE FINAL EXAMINATION OF

ERIC KRISTOPHER DUMAS

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY
GRADUATE COLLEGE
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Tuesday, August 16, 2016 | 10:00 am | Room 109, Biomedical
Research Center, OUHSC

COMMITTEE IN CHARGE: Darise Farris, Ph.D., Chair, Darrin Akins, Ph.D., Dave Dyer, Ph.D.
Madeleine Cunningham, Ph.D., Paul DeAngelis, Ph.D.

Characterization of the Humoral Immune Response to *Bacillus anthracis* After
Vaccination and Cutaneous Infection

Bacillus anthracis is a gram-positive, spore-forming bacterium that is the causative agent of anthrax. Use of *B. anthracis* spores as a biological weapon through the US postal system in 2001 highlighted the need for an improved anthrax vaccine. *B. anthracis* has two major virulence factors, a poly- γ -D-glutamic acid capsule, and a tripartite exotoxin composed of protective antigen (PA), lethal factor (LF) and edema factor (EF). PA and LF combine to form lethal toxin (LT), while PA and EF combine to form edema toxin (ET). The US anthrax vaccine, Anthrax Vaccine Adsorbed (AVA), consists of PA, with only trace amounts of LF and EF, adsorbed to aluminum hydroxide. The UK anthrax vaccine, Anthrax Vaccine precipitated (AVP), consists primarily of PA and LF with detectable amounts of EF, precipitated to aluminum hydroxide. AVA suffers from heterogeneity in PA responsiveness, with evidence of immunodominant, non-neutralizing PA antibodies in

some recipients that is assumed to be genetically determined. Furthermore, studies in animal models have shown that antibodies to alternative targets (LF and EF, for example), contribute to protection, but are missing from the next generation recombinant PA vaccine.

This work tested the hypothesis that heterogeneity in vaccine responsiveness to PA is stochastic, that LF and EF antibodies contribute to toxin neutralization in humans, and that natural infection elicits unique toxin-neutralizing humoral specificities. First, examination of the specificity of PA antibodies during seroconversion to LT neutralization in genetically identical mice revealed that the fine specificity of the humoral response to PA is highly stochastic, indicating that elimination of immunodominance to non-protective epitopes or domains will require their elimination from the vaccine. Second, examination of LF and EF antibodies elicited by AVP vaccination showed that both antibodies can neutralize their respective toxin, but only LF antibodies made an independent and additive contribution to LT neutralization. Finally, the antibody response to natural cutaneous infection in humans was examined. Cutaneous anthrax elicited toxin neutralizing antibodies directed exclusively to conformational epitopes, which differs from vaccine recipients. These data advocate a next-generation anthrax vaccine that presents multiple protective antigens in their natural conformations.