

# Immune Response to Vaccination with the Licensed Anthrax Vaccine AVA

IRB# 2004-031

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## Synopsis:

The recent, intentional dissemination of *Bacillus anthracis* caused significant morbidity and mortality, as well as widespread and costly disruption of essential public services. The resulting re-evaluation of current methods for the prevention and treatment of anthrax has revealed significant gaps in our knowledge of the basic immunobiology of this disease, and highlighted the need to develop methodologies for establishing vaccine efficacy in the absence of clinical trials.

The research described in this proposal will define the molecular and structural characteristics of the protective antibody response elicited by the currently licensed human anthrax vaccine. Methods of repertoire cloning recently developed in our laboratory will be used to establish at the molecular level the structural diversity, variable gene usage, and somatic maturational history of the human antibody repertoire specific for the protective antigen (PA) of *B. anthracis*. The extent to which different individuals utilize the same immunoglobulin variable gene products to bind specific epitopes on the antigen will be determined. Through sequence analysis, the degree to which responding antibody clones have undergone somatic maturation will be ascertained. Clonally derived PA-specific binding domains will be expressed *in vitro*, the subset capable of blocking PA functional activity identified, and affinity and valence requirements for functionality established. Cloned antibody binding domains will be used to define the PA-associated antigenic epitopes recognized by the human immune response, and to pinpoint those PA-associated epitopes that elicit neutralizing antibodies.

Our findings will be crucial for the rational design of PA subunit vaccines, and will aid in establishing *in vitro* correlates of protective immunity to *B. anthracis* infection. In addition, the antibodies isolated will constitute a panel of fully human monoclonal binding domains with potential for therapeutic use as passive immunogens.