OVERVIEW

HIV is a worldwide problem impacting people in all countries, but particularly Southern Africa and other developing regions. An HIV vaccine represents one of our best hopes in combatting this epidemic. Current immunization strategies, including those supported by the CAVD, are increasingly targeting precise B cell specificities to mimic neutralizing antibody responses generated during natural infection, in an effort to maximize the potency of the vaccine-elicited Ab response. An understanding of the frequencies and affinities of human naive B cell specificities capable of immunogen recognition in unimmunized individuals can aid in immunogen design and inform decision-making for advancement of promising immunogens to clinical trials. Immunogen-specific human naive B cell repertoire analysis is a platform for accelerating iterative immunogen design and immunogen advancement along the clinical development pipeline. This investment will be used to improve the efficiency of a platform to accelerate HIV vaccine immunogen design.

This investment is primarily to support equipment purchase and personnel in activities that underlay BMGF efforts to elicit broadly neutralizing antibodies using germline targeting (GT) approaches. Briefly, the premise of these efforts is that investigators can design immunogens that will target rare precursor B cells, activate and expand them, and then use additional immunogens to shepherd these responses via germinal center somatic hypermutation and affinity maturation to elicit broadly neutralizing antibodies. An understanding of the human B cell specificities capable of immunogen recognition in unimmunized individuals can aid in immunogen design and inform decision making for clinical advancement to vaccine trials. Identifying and isolating these rare human naive B cells by cell sorting is key to determine their frequencies and affinities for CAVD-supported potential vaccine candidates that depend on germline-targeting or rational protein design vaccine strategies for HIV, or other pathogens.

The Crotty lab was the first in the world to succeed in sorting human epitope-specific naive B cells specific for a candidate HIV vaccine immunogen, which helped support the decision to advance eOD-GT8 60mers to Phase 1 clinical trials. Identifying human epitope-specific naive B cells specific for new candidate HIV vaccine immunogens with conventional flow cytometry instruments is extraordinarily difficult, due to the rarity and low affinity of the cells, resulting in major signal-to-noise challenges. The S6 Symphony instrument helps overcome signal-to-noise limitations of conventional cell sorters, allowing for more accurate identification and isolation of epitope-specific precursor naive B cells, which has important implications for vaccine immunogen design and the selection of immunogens for advancement to clinical trials. In summary, immunogen-specific human naive B cell repertoire analysis will accelerate the immunogen design of CD4-binding site and V2-apex immunogens and will provide information useful for decision making on immunogen advancement along the clinical development pipeline.

RESEARCH OBJECTIVES

1.) Obtain a BD S6 Symphony instrument at LJI and validate its use for improved characterization of the human naive B cell repertoire specific for the eOD-GT8 immunogen.

2.) Characterize the human naive B cell repertoire to novel CD4-binding site and V2-apex candidate immunogens to feed back into the iterative immunogen design cycle.

Grant at a Glance

Principal Investigator
Shane Crotty, Ph.D.

Grantee Institution
La Jolla Institute for Immunology, USA

Project Title
Improving the efficiency of identification of epitope-specific precursor naive B cells in the human B cell repertoire

OPPID
1203211

Grant Award
Up to $599,999.00 awarded in August 2018