OVERVIEW

The goal of this investment is to develop simian-human immunodeficiency viruses (SHIVs) that elicit strain-specific and broadly neutralizing antibodies in rhesus macaques (RMs) as a guide to iterative HIV-1 vaccine development. Historically, models using rhesus macaques and employing challenges with SHIVs have had disappointing outcomes. SHIVs generally failed to elicit broadly neutralizing antibodies (bNAbs) directed against the envelope protein (Env) of HIV-1 and failed to recapitulate the course of antibody evolution seen in naturally infected humans. The hypothesis underlying this grant is that this discrepancy stems from properties of the HIV-1 Envs used in creating the SHIVs, as these have frequently been chosen from strains containing fortuitous mutations that provide for binding to rhesus CD4 (rhCD4), but often at the cost of reduced conformational masking and protection from antibody neutralization.

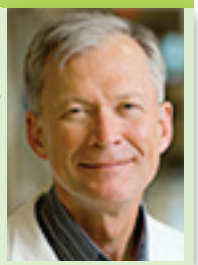
The approach here is to engineer SHIVs from an SIVmac251 vector backbone by inserting the complete tat-rev-vpu-env (gp160) cassettes of transmitted/founder (T/F) or otherwise desirable primary HIV-1 strains, and to modify the Env residue 375 which lines the Phe43 binding cavity and thereby facilitate rhCD4 engagement. Substitutions at Env 375 result in enhanced binding to rhCD4, and SHIVs expressing these modified Envs replicate consistently and persistently in Indian-origin rhesus macaques, eliciting strain-specific, autologous tier 2 neutralizing antibodies similar to those found in humans. The new SHIV design further leads (in some animals) to CD4 T cell decline, immunopathology and AIDS-related death. Importantly, the Envs of all SHIVs tested retained effective conformational masking, tier 2 antibody sensitivity, and antigenicity virtually indistinguishable from their wild type S375 counterparts. This strategy has been elaborated to develop SHIVs containing the BG505 Env gp140, where allelic variants of BG505 Env at codons S375Y/W/H and T332N support efficient virus infection and repli- cation in RM CD4 T cells in vitro and *in vivo*.

This project will test 12 allelic variants of SHIV BG505 for replication in RMs in vivo and will down-select the variants to two: one with a T332N substitution like the variant used to make BG505-SOSIP, and one without a T332N substitution like the variant that infected the human subject who subsequently developed bNAbs. The two SHIV BG505 variants will then be used to infect RMs; then virus-Ab coevolution will be analyzed, including determining strain-specific and bNAb responses, cloning the neutralizing mAbs, and inferring the unmutated common ancestor immunoglobulin receptors (UCA-IgRs). This same experimental strategy will be extended to make additional novel SHIVs including those bearing the Envs of HIV-1 B41 and others that target human V2 bNAb lineage germ line (GL) Ig receptors, including a novel SIVcpz variant MT145. The variants generated under this aim will be down-selected on the basis of in vitro experiments, with three SHIVs advancing to evaluation in the rhesus model.

Grant Leadership

This grant is led by George Shaw, MD, PhD (University of Pennsylvania), with consultation by other CAVD investigators working in the research space centered on anti-Env bNAb development. The award was made in January 2016, with an anticipated duration of 36 months.

Grant at a Glance



Principal Investigator
George Shaw, MD, PhD

Grantee Institution
University of Pennsylvania, Philadelphia, PA USA

Project Title
Novel SHIV Design to Elicit Broadly Neutralizing Antibodies and Guide Iterative Vaccine Development

OPPID
1145046

Grant Award
Up to $3.6 million, awarded in January, 2016

RESEARCH OBJECTIVES

1.) Initial evidence of persistent SHIV replication and strain-specific and heterologous nAb induction in rhesus macaques by new BG505 SHIVs.

2.) Generation of a large volume, high titer BG505-SHIV challenge stock, titrated in rhesus macaques for preclinical challenges.

3.) Optimization of heterologous bnAb induction in the SHIV BG505 infection model, using down-selected variants assessed under objective 1.

4.) Construction and evaluation of additional SHIVs including those bearing Envs of HIV-1 B41 and others that have been shown to bind to human V2 targeted bnAb lineage germline Ig receptors, including a novel SIVcpz variant MT145.

5.) Description of SHIV/Env-Ab co-evolution that leads to bnAb induction in rhesus macaques as a guide for iterative HIV-1 vaccine design.

RESEARCH OUTCOMES

1.) BG505 SHIVs with or without an N332 glycan replicated efficiently in 18 Indian RMs. In each case, strain-specific NAbs developed targeting glycan holes at residues 241/289 or C3/V5. In two RMs, potent bNAbs targeting the V3 high mannose patch, N332 glycan and GDIR motifs developed, thus demonstrated the immunogenic potential of BG505 Env trimer. Rhesus V3 glycan bNAb mAbs are being cloned for use in HIV vaccine design and animal model testing.

2.) BG505.N332 SHIV was grown in primary rhesus CD4 T cells as a challenge stock and used to demonstrate, for the first time, SOSIP-mediated protection from mucosal infection of a primary transmitted/founder Env containing SHIV. “Threshold” titers of serum NAbs required for 50% or 90% clinical protection from mucosal infection of a primary (T/F) virus strain were established in the RM model.

3.) Six primary HIV-1 Envs that bind the UCAs of human V2 apex bNAbs were constructed into SHIVs using the Δ375 strategy. All replicated efficiently in RMs. All six SHIVs elicited V2 apex NAbs with a subset of animals achieving neutralization breadth. bNAbs targeted the V2 apex C strand and were variably depend on N160 and/or N156 interactions, with escape patterns mirroring those observed in humans. Cloning of rhesus V2 apex bNAb mAbs is underway.

4.) The Env of a novel SIVcpz variant MT145 that shows antigenic cross-reactivity to human V2 apex bNAbs and their respective UCAs was constructed into a SHIV and shown to replicate efficiently in RMs, resulting in V2 apex C strand targeted NAbs. This Env has been advanced for human phase 1 testing and preclinical testing in human Ig knockin mice and RMs.