Gallo: FLSC Phase I & II Clinical Trials

OVERVIEW

Partial efficacy observed in the Phase IIb clinical trial (RV144) in Thailand underscores the need to develop "next generation" regimens that elicit broader and more potent arrays of humoral effector mechanisms against HIV. Protection in RV144 likely involved antiviral antibodies against conserved/functional domains on the HIV envelope glycoprotein, gp120. Accordingly, attempts to expand and enhance such anti-gp120 antibody responses as well as antibodies linked with reduced risk of infection in RV144 are warranted. One practical strategy towards this goal is to build on RV144 via rationally modified ALVAC prime/envelope protein boost regimens. The Institute of Human Virology (IHV) group postulates that the monomeric gp120 protein used in RV144 was likely the most limited component of the vaccine. Such monomers typically elicited only type-specific antibody responses and did not protect against HIV infection in earlier trials. An alternative envelope protein component capable of (1) boosting humoral specificities linked with reduced risk in RV144, and (2) concurrently raising antibodies to conserved gp120 domains linked with protection elsewhere, should boost the protective efficacy of ALVAC prime/protein boost regimens.

The IHV group proposes that a conformationally constrained and stabilized gp120, embodied by a full-length single chain gp120-CD4 complex (FLSC), has properties that will focus immune responses on conserved/functional gp120 domains; thus, optimizing the chances for broad protection against HIV. Five IHV studies in macaques support this concept. In the earliest study, a single chain complex containing rhesus CD4 (rhFLSC, engineered specifically for macaque studies) elicited antibody responses against highly conserved and functional gp120 epitopes and afforded non-sterilizing control of both plasma and tissue viremia following a single high-dose heterologous mucosal challenge with SHIV162P3. A second study showed that such protection depended on vaccine dose. A third study, using multiple low dose virus challenges with SHIV162P3, showed rhFLSC immunization provided an interval of sterilizing protection. A fourth study confirmed the third study. Both studies showed that non-selective T-cell activation diminished the efficacy of FLSC but that ADCC activity against CD4i domains, implicated as affording reduced risk in RV144, increased protective efficacy. A fifth study compared immunization of macaques with the RV144 vaccine versus a regimen that primed with a poxvirus encoding rhFLSC and boosted with rhFLSC protein. This study showed that compared to the RV144-based protocol, the rhFLSC-based strategy elicited statistically superior titers of anti-V1V2 antibodies (a correlate of decreased risk in RV144) and neutralizing antibodies. Overall, these experiments show that vaccination regimens using FLSC (1) will help improve humoral responses linked to reduced risk in human trials; (2) raise responses to highly conserved and functional gp120 epitopes, including ones termed CD4-induced (CD4i), that mediate humoral effector functions correlating with reduced risk in nonhuman primate and human vaccine trials.

The research team seeks to develop the FLSC as a new immunogen that can be used alone or in combination with vCP2438 (due to current unavailability of vCP1521) or related pox vectors to improve upon the efficacy observed in RV144. This program includes production of GMP-grade FLSC; preclinical safety studies; evaluation of safety and immunogenicity for FLSC in a Phase 1 clinical trial; and ancillary studies in rhesus macaques to define how humoral response magnitude, quality and durability elicited by rhFLSC is influenced by combinations with vCP2438 and/or different adjuvant formulations on. In addition, basic studies will compare the antigenicity of vCP2438 versus new poxvirus constructs encoding FLSC. Proposed Phase II clinical studies will be performed in collaboration with investigators at Sanofi-Pasteur and the Military HIV Research Program. These studies will test whether an ALVAC prime/ FLSC boost immunization strategy: (1) elicits a novel combination of humoral immune responses that have been linked with protective efficacy in previous studies; (2) substantially improves the response rates, magnitudes and breadth of humoral responses that correlated with reduced risk in RV144. These characteristics will be established in part by comparisons of Objective 2 with RV144 and with ongoing Phase II/Phase III trials of other envelope-based vaccines. Based on these studies, follow-on Phase 2B and/or Phase 3 clinical trials will be designed to further evaluate the efficacy of vaccine strategies using vCP2438/FLSC prime/boost or FLSC protein alone.

Grant at a Glance

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Project Title
Gallo: FLSC Phase I & II Clinical Trials

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Grant Award
Up to $16.8 million, awarded April, 2011

Collaborating Institutions
- The Institute for Human Virology
- Profectus BioSciences
- Sanofi Pasteur
- The Military HIV Research Program

RESEARCH OBJECTIVES

1.) Preclinical development and Phase I clinical testing of FLSC to identify a safe and immunogenic dose of FLSC/Alum that will be carried into Phase II studies.

2.) Evaluate FLSC in Phase IIa clinical trials in combination with vCP2438.

3.) Determine whether the envelope encoded by ALVAC vCP2438 fortuitously encodes a constrained gp120 immunogen resembling the antigenic character of FLSC. Develop and test versions of ALVAC that express either soluble or membrane-anchored FLSC.

4.) Non-Human Primate studies -

   a.) Establish the immune profiles elicited by a vCP1521 prime, rhFLSC boost vaccine regimen in the rhesus macaque model.

   b.) Evaluate in rhesus macaques the humoral response profiles elicited by rhFLSC formulated in four different adjuvants, including Alum.

PROGRESS

The main aim of this program is to establish that FLSC can be combined with ALVAC to produce a vaccine regimen that (1) elicits a novel combination of humoral immune responses that have been linked with protective efficacy in previous studies; (2) substantially improves the response rates, magnitudes and breadth of humoral responses that correlated with reduced risk in RV144. (Objective 2). Other Objectives were designed to support this goal.

Objective 1 was to prepare and release FLSC clinical trial material, perform the supportive preclinical studies, and demonstrate safety and immunogenicity of the product when formulated in Alum in a Phase 1 clinical trial. Objective 1 accomplishments include; (1) FLSC Drug Substance has been cGMP manufactured and released, yield ~ 1g/L; (2) Al(PO4) formulation (Alum) identified that yields >95% adsorption and has shown stability

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>1 month at 37°C; (3) Alum formulated FLSC drug product has been vialed; (4) ~ 3400 vials at 300 µg/mL of drug product will be available for Phase I clinical testing; (5) ~ 125 g of cGMP manufactured unformulated FLSC [Clinical Grade] has been aliquoted and stored for future studies; (6)

Toxicology/immunotoxicology studies are complete; (7) IND has been filed; (7) IRB approval for the Phase I trial has been obtained; and (8) clinical trial enrollment is complete (60 volunteers), with final dosing to occur January 2018 and final follow up to occur July 2018.

The final configuration (trial design) of Objective 2 has been developed, with strategies and trial sites identified.

Studies in Objective 3 indicate that the CD4-induced A32 domain, a key ADCC target in RV144 and natural HIV infection, is constitutively exposed on the 92TH023 envelope and on the corresponding vCP1521 vaccine construct. This property is shared by FLSC. ALVAC constructs that express either soluble or membrane bound FLSC have been developed and are being characterized immunochemically. Rhesus macaques were immunized with a regimen in which the animals were primed with the ALVAC construct encoding secreted rhFLSC and boosted with rhFLSC. This regimen exhibited superior responses against V1V2 compared to macaques given the RV144 regimen.

Objective 4 to test the immunogenicity of FLSC formulated in different adjuvants has been completed. Overall, Alum was not inferior to alternative adjuvants with respect to quality, quantity or durability of humoral responses. Given such data and established safety profiles, Alum remains the lead adjuvant for Phase II testing.