

APPENDIX M-1-A. SCIENTIFIC ABSTRACT FOR PROTOCOL B004

A Phase 1 Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of a Multiantigen HIV (HIV-MAG) plasmid DNA (pDNA) Vaccine co-administered with Recombinant Human IL-12 pDNA (GENEVAX[®] IL-12) followed or preceded by Recombinant Ad35-GRIN/ENV HIV Vaccine in HIV-Uninfected, Healthy Volunteers

SHORT TITLE FOR THE STUDY:

Prime boost study of HIV-1 Multi-Antigen pDNA Vaccine +/- IL-12 pDNA given intramuscularly by *in vivo* Electroporation (IM/EP) and Ad35-GRIN/ENV given IM

The protocol submitted for review will evaluate the safety, tolerability and immunogenicity of a fixed dose of the Profectus' HIV-1 multi-antigen plasmids (HIV-MAG pDNA) with or without human IL-12 pDNA when delivered by IM/EP followed or preceded by recombinant adenovirus vector (Ad35-GRIN/ENV).

The HIV-MAG pDNA vaccine consists of two plasmid DNA expression vectors, ProfectusVax HIV-1 gag/pol and ProfectusVax HIV-1 nef/tat/vif, env. ProfectusVax HIV-1 gag/pol is a 7,487 base pair plasmid expressing an HIV-1 clade B gag/pol fusion under the control of a human CMV (HCMV) promoter and bovine growth hormone polyadenylation (polyA) signal. ProfectusVax HIV-1 nef/tat/vif, env is a 8,750 base pair dual promoter plasmid expressing (i) an HIV-1 clade B nef/tat/vif fusion under the control of a HCMV promoter and an SV40 polyA signal; and (ii) a HIV-1 clade B primary isolate env gp160 under the control of a simian CMV (SCMV) promoter and bovine growth hormone polyA signal.

The vaccine will be administered with a 3rd expression plasmid, namely IL-12 pDNA (GENEVAX[®] IL-12) as molecular adjuvant in order to augment the immune response to the vaccine. GENEVAX[®] IL-12 is a dual-promoter expression vector encoding the human IL-12 p35 and p40 genes and is 6,259 bp in size. The IL-12 p35 subunit is expressed under control of the human cytomegalovirus (HCMV) immediate early promoter and SV40 polyA signal, while the IL-12 p40 subunit is expressed under control of the simian cytomegalovirus (SCMV) promoter and bovine growth hormone (BGH) polyA signal.

The vaccine with or without IL-12 pDNA will be delivered intramuscularly by *in vivo* electroporation (IM/EP) using the TriGrid[™] Delivery System (TDS-IM) developed by Ichor Medical Systems, Inc.

Currently, a Phase I study (ACTG5281) evaluating the safety and immunogenicity of Profectus' HIV-MAG pDNA vaccine plus IL-12 pDNA (GENEVAX[®] IL-12) when delivered with and without *in vivo* EP in HIV-infected subjects stable on HAART is ongoing in the US. GENEVAX[®] IL-12 is tested at 3 dosage levels up to 1000mcg per administration. That study was reviewed and approved by the RAC (RAC Protocol 1004-1038).

Several HIV-1 pDNA vaccines expressing antigens similar to HIV-MAG have been tested in Phase 1 clinical studies in combination with GENEVAX[®] IL-12 pDNA. The NIH sponsored

clinical trials (HVTN 060, 063, 070) in which different candidate HIV-1 pDNA vaccines co-administered with the GENEVAX[®] IL-12 given intramuscularly (IM) by needle injection were tested in approximately 250 healthy HIV-uninfected adults. No major safety concerns have been noted in these studies. Currently, a Phase I study (HVTN 080) is ongoing, where GENEVAX[®] IL-12 (at 1000mcg per administration) is co-administered with a similar HIV-1 pDNA vaccine pDNA in 48 healthy adults. Delivery is intramuscularly by INOVIO's Celectra[®] electroporation device. Enrolment is complete. No safety concerns have been raised.

The IAVI Ad35-GRIN/ENV vaccine consists of 2 co-formulated vectors: a recombinant replication-incompetent Adenovirus serotype 35 vector containing HIV-1 subtype A *gag*, *reverse transcriptase*, *integrase* and *nef* gene sequences (fusion protein, GRIN) and a recombinant replication-incompetent Adenovirus serotype 35 expressing HIV-1 subtype A gp140 *env* gene (ENV). IAVI's Ad35-based vectors are currently being studied in 3 Phase 1 trials with a total enrolment of ~400 individuals, mostly in Africa.

Following entry into the target cells, the HIV-1 gene products will be expressed without the production of infectious adenovirus (Ad35) and without integration into the host genome. These gene products can be produced in cells that are not actively dividing.

IAVI collaborated with the Aaron Diamond Research Center, New York, NY on the first clinical trial of electroporated DNA in healthy volunteers, using a similar HIV-1 DNA vaccine construct (Vasan S, Hurley A, Schlesinger SJ, et al; *In Vivo* Electroporation Enhances the Immunogenicity of an HIV-1 DNA Vaccine Candidate in Healthy Volunteers. Plos ONE May 2011, Vol 6, Issue 5, e19252).

The candidate HIV-MAG pDNA vaccine, adjuvanted by the plasmid GENEVAX[®] IL-12, is intended to elicit robust and long-lived env-, gag-, pol-, nef-, tat- and vif-specific CD4⁺ and CD8⁺ T cell responses. It is hypothesized that the cytokine-enhanced multi-antigen pDNA vaccine when delivered via *in vivo* EP will induce HIV-specific CD4⁺ and CD8⁺ responses in a majority of vaccine recipients and these responses will be of greater magnitude and breadth when pIL-12 is included, compared to the responses seen following immunization without IL-12 and given intramuscularly by standard needle injection. The study will compare two doses of pIL-12. The electroporated HIV-1 DNA vaccine and IL-12 pDNA adjuvant introduce genes that will be expressed transiently; they are not intended to modify a person's genetic material in a permanent or heritable way.

The primary rationale for the proposed trial is based on a challenge study conducted by IAVI with Simian Immunodeficiency Virus (SIV) in non-human primates (NHP) with a regimen consisting of multigenic SIV DNA plasmid(s) co-administered with or without p IL-12, injected intramuscularly by *in vivo* electroporation (IM/EP) as a prime, followed by a recombinant vector Adenovirus 5 (rAd5) SIV vaccine as boost. Following repeated intra-rectal challenge with a low dose of SIVmac239, a 4-log reduction in SIV set-point virus load was observed in macaques that received plasmid IL-12 with SIV DNA priming, compared to naive controls ($p \leq 0.01$); moreover, 5 of 6 macaques controlled viremia to very low or undetectable levels. SIV DNA plasmid co-delivered with plasmid IL-12 by IM/EP induced a greater frequency and broader repertoire of multifunctional T cells which were associated with greater control of SIV replication, compared to the responses detected in animals that did not receive plasmid IL-12 on

DNA priming. The proposed clinical study will attempt to replicate, in humans, the immune responses seen in non-human primates (NHP) that had a 4-log reduction in SIV viral load following SIVmac239 challenge.

The IAVI B004 prime-boost study will test five regimens each involving sequential administration of Profectus' HIV-MAG IM by *in vivo* electroporation and IAVI's Ad35-GRIN/ENV. Seventy five healthy, HIV-uninfected volunteers will be enrolled into 5 groups of 15 subjects each, in a ratio of 12 vaccine and 3 placebo recipients (Table 1). Randomization will be across groups. Blinding is with respect to vaccine (HIV-MAG pDNA +/- IL-12, Ad35-GRIN/ENV) versus placebo and to dosage of IL-12 pDNA, but not to schedule, number of vaccinations administered and delivery method.

Table 1: Study Design

		Months 0, 1, 2	Month 6
Study Groups	N vaccine / placebo	Prime Vaccine (dosage, delivery)	Boost Vaccine (dosage, delivery)
1	12/3	HIV-MAG (3,000mcg) (IM/EP*)	Ad35-GRIN/ENV (2x10 ¹⁰ vp***, IM**)
2	12/3	HIV-MAG (3,000mcg) + GENEVAX®IL-12 (100mcg) (IM/EP)	Ad35-GRIN/ENV (2x10 ¹⁰ vp, IM)
3	12/3	HIV-MAG (3,000mcg) + GENEVAX®IL-12 (1000mcg) (IM/EP)	Ad35-GRIN/ENV (2x10 ¹⁰ vp, IM)
		Month 0	Month 4
4	12/3	HIV-MAG (3,000mcg) + GENEVAX®IL-12 (1000mcg) (IM/EP)	Ad35-GRIN/ENV (2x10 ¹⁰ vp, IM)
5	12/3	Ad35-GRIN/ENV (2x10 ¹⁰ vp, IM)	HIV-MAG (3,000mcg) + GENEVAX®IL-12 (1000mcg) (IM/EP)
Total	75 (60/15)		

*IM/EP=intramuscular by *in vivo* electroporation

**IM=intramuscularly

*** vp=viral particles

IAVI B004 is a Phase 1 HIV vaccine study, with the ultimate goal of identifying a vaccine to prevent HIV infection. IAVI's primary focus is on a preventive HIV vaccine for Africa, and like most of their studies, this will be conducted at three sites in Africa, all of which have previously conducted Phase 1 trials of preventive HIV vaccine candidates in healthy volunteers at low risk for HIV infection. The lead site, Projet San Francisco in Kigali, Rwanda, is affiliated with Emory University, Atlanta. For each site proposed, the Ethics Committee has a Federal Wide Assurance (FWA), and, for a previous planned study, received a favorable review by the Division of AIDS operational team. Both PSF Kigali and KAVI-Nairobi have previously conducted at least one IND study.

The study will be conducted under BB-IND # 14770 which has been allowed to proceed by the US Food and Drug Administration.