Pulendran: Protective humoral responses against HIV

OVERVIEW

Developing a vaccine that generates an effective immune response to HIV is a significant challenge. Key issues for current pre-clinical and clinical vaccines include insufficient breadth of neutralizing antibodies and B cell memory responses. The results of the RV144 “Thai trial” are encouraging since the trial is the first demonstration that an immune response can provide some degree of protection against acquisition of HIV infection. The protection, however, declined from approximately 60% after one year to ~31.5% after 3.5 years of the study. Dr. Bali Pulendran hypothesizes that improvements in persistent and broad antibody responses can be generated through the synergistic activation of TLR4 and TLR7/8 on antigen presenting cells using TLR agonists in combination with an appropriate delivery system. Such improvements could make a significant contribution to producing efficacious HIV vaccines.

Dr. Pulendran’s laboratory previously published that PLGA nanoparticle delivery of a vaccine antigen (inactivated influenza) in combination with 2 independent adjuvants that activate TLR4 and TLR7/8, respectively, rather than in combination with a single TLR agonist, enhances virus specific neutralizing antibody titers in mice. Similarly, enhanced neutralizing antibody titers were observed in non-human primates (NHP) for the immunogenic compositions containing both TLR activating adjuvants in combination with PLGA. Studies in mice indicate that a combination of long lived B cell memory responses, T cell help and enhanced germinal center follicle formation contributed to the higher quality and quantity of neutralizing antibodies. For this grant, Dr. Pulendran will seek to recapitulate and extend these findings using HIV envelope (env) antigens in NHP. He will also evaluate an alternative delivery vehicle (PPS) that can be used to delivery antigen and/or TLR ligands and offers different advantages from PLGA with respect to inducing cellular immune responses in mice. Optimal formulation will be selected for NHP studies, including a repeat low dose rectal challenge model to assess efficacy.

The product of this project will be a vaccine platform that incorporates nanoparticle delivery systems with novel adjuvants (GLA and 3M-052) and a relevant clade C HIV env (1086C) together in a realistic immunogenic composition suitable for pre-clinical trials and with a potential for translational Phase I human clinical trials.

The studies outlined in this proposal will be performed at Emory University, La Jolla Institute for Allergy and Infectious Diseases, and École polytechnique fédérale de Lausanne (EPFL) by a highly integrated and experienced team of immunologists, virologists, and veterinarians that have been working collaboratively on this project under the overall direction of Dr. Bali Pulendran.

Grant at a Glance

Principal Investigator
Bali Pulendran, PhD

Grantee Institution
Stanford University
California, USA

Project Title
Programming the magnitude and persistence of protective humoral responses against HIV

OPPID
1040768

Grant Award
Up to $5.9 Million, awarded in August, 2012

Collaborating Institutions
- ◊ École polytechnique fédérale de Lausanne
- ◊ La Jolla Institute of Allergy and Infectious Diseases

RESEARCH OBJECTIVES

1.) Determine if Env (1086C/PLGA/TLR ligand formulations are superior to MF-59 with respect to the magnitude, quality, persistence, and/or breadth of HIV-1 Env specific humoral responses in NHPs.

2.) Define the most optimal delivery vehicle for antigen/TLR ligand based adjuvants for induction of high magnitude and persistent Env specific neutralizing antibodies, systemically and at mucosa in mice and NHPs.

3.) Evaluate the protective efficacy of a HIV vaccine in NHPs, designed from the best formulated TLR ligand based adjuvant, HIV Env immunogen and delivery vehicle, selected from objectives 1 and 2.