Masopust: Vaccination for prevention of HIV

OVERVIEW

The proposed work will test in a NHP SIV vaginal challenge model whether a T cell vaccine could prevent HIV. The vaccination regimen is an alternative vaccination approach that elicits abundant tissue resident virus specific memory CD8 T cells in cervical vaginal tissues. It is a heterologous prime-boost-boost (HPBB) vaccine strategy, employing sequential immunizations with an identical antigen insert expressed by serologically distinct virus vectors, thereby avoiding neutralization of the boosts by the response to the previous vector. Specifically, adult female rhesus macaques will be immunized with recombinant vesicular stomatitis virus (New Jersey serotype, VSV-NJ) and vaccinia virus (VV) vectors that expressed the full gag coding sequence obtained from pCMVgagDX, a high level protein expression construct engineered by codon optimization and inactivation/removal of instability sequences for Rev-independent expression, and human adenovirus serotype 5 also expressing full length Gag.

Preliminary data in Mamu-A*001+ rhesus macaques indicates that this regimen establishes an unprecedented magnitude of Gag-specific memory CD8 T cells (2-12% of CD8+ PBMC remained CM9-specific 16 weeks after the final immunization with the RhAd5 construct. Gag-specific memory CD8 T cells were highly polyfunctional with potent degranulation behavior and were broadly distributed, present in all 29 anatomic compartments sampled. Flow cytometric analyses of Gag-specific memory CD8 T cells in cervix and vagina at 294 days post vaccination showed the induced mucosal memory cells were actually more abundant than the primary effector response during acute infection of unvaccinated animals. The initial Mamu-A*001+ cohort then received a single dose vaginal challenge with SIVmac251, using either 2000 or 8000 TCID50. While all 6 naïve controls were viremic within 7 days after challenge, 5 out of 8 vaccinated animals did not exhibit evidence of systemic infection measured by plasma viremia out to 100 days.

The major goal of this grant is to perform a repeat test of the immunization, measurements of immunogenicity, and a more highly powered assessment of protection in a repeat vaginal low dose SIVmac239 challenge model. A secondary objective for the study is to distinguish if protection occurs by eliminating a detactable transmission, vs. preventing detectable transmission.

Demonstration of this principle could accelerate our prospects for developing a human HIV vaccine by indicating the efficacy of a new class of CD8 T cell vaccines that would complement approaches that attempt to elicit neutralizing antibody.

Grant at a Glance

Principal Investigator
David Masopust, PhD

Grantee Institution
University of Minnesota, Minneapolis, MN USA

Project Title
Vaccination for prevention of HIV

OPPID
1116224

Grant Award
Up to $2.6 million, awarded in November, 2015

Collaborating Institutions
- Oregon Health and Sciences University, Oregon National Primate Research Center, Beaverton, OR USA

The grant is led by David Masopust, from the Department of Microbiology and Immunology at the University of Minnesota. The nonhuman primate model will be conducted at the Oregon Nation Primate Research Center, affiliated with the Oregon Health and Sciences University. The award was made in November 2015, with an anticipated duration of 24 months.