Picker: Development of Attenuated CMV Vectors for an HIV/AIDS Vaccine

OVERVIEW

In the past decade, we have demonstrated in rhesus models that persistent SIV vaccine vectors based on the ubiquitous β-herpesvirus cytomegalovirus (RhCMV/SIV vectors) elicit and indefinitely maintain systemic high frequency, circulating and tissue-resident effector memory T cell (T_{EM}) responses that can intercept and stringently control a highly pathogenic, AIDS-causing SIV very early, if not immediately, after exposure. Moreover, these responses not only maintain this control over the long term, but actually clear the infection to the degree that protected animals are not distinguishable from non-SIV-exposed animals by state-of-the-art analysis at necropsy.

In addition, we have shown that Rhesus (Rh) CMV vectors can be: 1) used repeatedly in RhCMV+ RM without any inhibition of immunogenicity by pre-existing immunity (a critical feature since the vast majority of people worldwide are naturally CMV-infected in infancy or childhood); 2) programmed to elicit unusually broad CD8+ T cell responses that recognize conventional and/or unconventional epitopes; 3) modified to express multiple vaccine inserts totaling 6 kb or more of exogenous sequence, using endogenous promoters to control insert expression; and 4) significantly attenuated without loss of immunogenicity or efficacy. Our understanding of this system has matured such that we know which CMV genes to manipulate for optimal attenuation (pp71 deletion), or for tuning epitope responses to conventional vs. unconventional presentation (UL128/UL30-mediated "epitope switch mechanism"). Human CMV (HCMV) infection of humans closely resembles RhCMV infection of monkeys, raising the prospect of developing an HCMV-based vaccine platform that recapitulates the biologic properties of our effective RhCMV/SIV vectors. In other funded efforts, we have developed human (HCMV/HIV) homologues of our validated RhCMV/SIV designs as candidate vectors for a prophylactic HIV/AIDS vaccine.

This grant extends these efforts, in two steps. In the first step, we will construct and manufacture (using existing GMP-qualified cell lines) a prototype pp71-deficient HCMV/HIVgag vector for a first-in-man phase 1 clinical trial of an attenuated HCMV vector. This trial is intended to address: 1) confirmation of the safety of pp71-deficient HCMV vector design in humans, 2) confirmation that HCMV-seropositive humans can be super-infected with HCMV-based vectors, 3) determination of the relationship between pp71-deficient HCMV vector dose and immunogenicity, and 4) evaluation of the quantity, quality (effector memory differentiation and function) and durability of the vector-elicited HIVgag-specific T cell responses. The second step, which will occur in parallel with step 1, is the development, validation and production of a 2nd generation vector (or vector set) that is optimized for **safety** (this vector design will include genetic changes in addition to pp71 deletion that will serve as secondary attenuation), **efficacy** (this vector design will have 1 or more vectors with multiple HIV inserts encoding Gag, Pol, and Nef that will be sequence-optimized for cross-reactivity against global M group HIVs and will have optimized CD8+ T cell epitope programming – either conventional or unconventional CD8+ T cell epitopes, as dictated by the presence or absence of UL128-131 genes, or potentially, constitute a vector set with both vector types), and **manufacture** (will have a custom developed GMP-qualified pp71-complementing cell line for efficient manufacture of fully complemented vector). This 2nd generation vector will undergo stringent safety and stability evaluation in the rhesus macaque model.

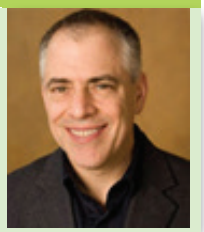
This collaborative effort is lead by Louis Picker, MD (Oregon Health and Sciences University/Vaccine and Gene Therapy Institute), with the participation of Peter Barry, PhD (University of California, Davis, for fetal macaque studies), and Betty Korber, PhD (Los Alamos National Laboratory, for insert designs). It will also leverage the Vaccine Product Development Center. The grant was awarded in July, 2014, with an original agreement length of 5 years.

RESEARCH OBJECTIVES

1.) Performance of a phase 1 clinical trial with a prototype ΔUL82/pp71 HCMV/HIVgag vector [with or without deletion of UL128-130]

2.) Development of a 2nd generation, safety- and efficacy-optimized HCMV/HIV vector set suitable for clinical development as a global prophylactic HIV vaccine

Grant at a Glance



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Grantee Institution
Oregon Health & Science University (OHSU)
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Project Title
Development of Attenuated CMV Vectors for an HIV/AIDS Vaccine

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Grant Award
Up to $25 million, awarded in July, 2014

Collaborating Institutions
- University of California - Davis, Davis, USA
- Los Alamos National Laboratory, Los Alamos, USA