Farzan: Preventing HIV-1 transmission with eCD4-Ig

OVERVIEW

There are approximately 35 million people living with HIV-1, 25 million of whom live in sub-Saharan Africa. There are more than 2 million new infections annually. To eradicate HIV-1, we must first stop these new infections, but prophylaxis strategies based on conventional vaccines have largely or wholly failed. These failures are a consequence of two properties of the virus. First, HIV-1 has been selected for generations in the presence of very active immune responses and has developed effective strategies for evading these responses. It is especially adept at evading human antibody responses, integral to most current vaccine approaches. Second, HIV-1 thrives when the immune system is most active. As a result, efforts to enhance an inadequate immune response can in some instances make infection more likely. Effective prophylaxis may therefore require new approaches that do not rely on, and are not limited by, the human immune system. Here we develop one such approach based on a novel entry inhibitor, eCD4-Ig, and an established gene-therapy vector system.

eCD4-Ig is an exceptional HIV-1 entry inhibitor that is on average more potent, and much broader, than the best broadly neutralizing antibodies (bnAbs). eCD4-Ig is potent because it avidly binds both the CD4- and the coreceptor-binding sites of the HIV-1 envelope glycoprotein (Env) trimer. It is broad because it binds only these two conserved, functionally important Env regions. As a result, in laboratory studies, the virus cannot escape eCD4-Ig under conditions where escape from bnAbs is readily observed. Moreover, eCD4-Ig works well in vivo. When an adeno-associated viral (AAV) vector was used to express a rhesus form of eCD4-Ig in four rhesus macaques, these macaques were protected for up to one year from a series of robust intravenous SHIV and SIV challenges. Moreover, AAV-expressed effectively suppressed rebound of an established SHIV infection after cessation of ART. These data raise the possibility that eCD4-Ig can be used to prevent new HIV-1 infections and treat established ones. Here we lay the preclinical foundations for human trials of passively administered eCD4-Ig, and further develop AAV-eCD4-Ig as a candidate HIV-1 vaccine alternative. Work to date has improved the half-life of eCD4-Ig as a protein, improved the potency of eCD4-Ig, and reduced its already low immunogenicity. It has as also shown that AAV-mediate prophylaxis extends to a Tier 3 SIV isolate, SIVmac239, confirming in vivo the exceptional breadth and potency of eCD4-Ig observed in vitro. Control of viral infection after ART cessation further undescores the difficulty of escape from eCD4-Ig in vivo. Studies in the final year will lead to more bioavailable forms of eCD4-Ig, and to more efficient AAV vectors and protocols for expressing eCD4-Ig.

The work is a collaborative effort, led by Michael Farzan, PhD (The Scripps Research Institute); Nancy Schultz-Darken, PhD will oversee the performance of the nonhuman primate studies at the Wisconsin National Primate Research Center. This project will also have extensive engagement by the IAVI Vaccine Product Development Center. The award was received in September, 2015 with an original agreement length of 4 years.

Grant at a Glance

Principal Investigator
Michael Farzan, PhD

Grantee Institution
The Scripps Research Institute, Jupiter, USA

Project Title
Preventing HIV-1 transmission with eCD4-Ig

OPPID
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Grant Award
Up to $5 million, awarded September, 2015

Collaborating Institutions
◊ Wisconsin National Primate Research Center, Madison, USA

RESEARCH OBJECTIVES

1.) Foundations for a clinical evaluation of the safety and efficacy of eCD4-Ig administered as a protein ("foundations for clinical studies"). Sub-aims include:
   a.) Development of a product development plan for eCD4-Ig
   b.) Production of research-grade IgG1 and IgG2 forms of human eCD4-Ig for non-human primate studies
   c.) An assessment in macaques of the pharmacokinetics (PK) and safety of human eCD4-IgG1 and -IgG2, and of their abilities to protect from a SHIV challenge
   d.) An assessment of the PK, safety, and anti-HIV activity of human eCD4-Ig in SHIV infected macaques
   e.) GMP protocols for production of human eCD4-Ig
2.) A comprehensive preclinical evaluation of the feasibility of using AAV-delivered eCD4-Ig as an alternative to an HIV-1 vaccine ("preclinical studies")
   a.) Characterization of the off-target effects of tyrosine-protein sulfotransferase 2, used to enhance eCD4-Ig sulfation
   b.) Development and testing in nonhuman primates of AAV vectors expressing improved eCD4-Ig variants, TPST2, and regulatory elements that regulate or enhance eCD4-Ig expression
   c.) An assessment of AAV-rh-eCD4-Ig-mediated protection from a clade C SHIV and from SIVmac239