BEAT-HIV Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy

We are pleased to announce that the National Institutes of Health (NIH) has awarded nearly $23 million to co-principal investigators Luis J. Montaner, D.V.M., D.Phil., director of the HIV-1 Immunopathogenesis Laboratory at The Wistar Institute Vaccine Center, and James L. Riley, Ph.D., research associate professor at the Perelman School of Medicine at the University of Pennsylvania. The BEAT-HIV Delaney Collaboratory to Cure HIV-1 infection by Combination Immunotherapy is one of six grants awarded by NIH's Martin Delaney Collaboratories to Cure HIV initiative, joining a highly-selective group of U.S.-led teams charged with advancing global efforts to develop a cure for HIV. The five-year award is a partnership of more than 50 leading HIV investigators from The Wistar Institute, the University of Pennsylvania, Philadelphia FIGHT, Rockefeller University, VA San Diego Healthcare System, Johns Hopkins University, the University of Nebraska-Lincoln, and the University of Utah working with government, non-profit, and industry partners to test combinations of several novel immunotherapies under new preclinical research and clinical trials.

The BEAT-HIV Delaney Collaboratory to Cure HIV-1 infection by Combination Immunotherapy has three initial research goals.

- First, identify the best approach to target immunotherapy against replication competent reservoirs by defining the relationship between plasma and tissue clonal expansion, characterize integration sites within blood and tissue, and determine how to maximize viral reactivation of distinct reservoir compartments.
- Second, test clinical strategy combining IFN-α immunotherapy to activate intrinsic/innate responses and ADCC with broadly neutralizing anti-HIV antibodies (both strategies shown to have an effect in humans when used singly); advance preclinical studies on IFN-alpha response, ex vivo combinations with added T-cell-mediated strategies, and develop innovative DNA vaccine delivery systems for sustaining neutralizing antibodies in vivo.
- Third, test clinical strategy that combines two gene therapy vectors to intrinsically protect HIV-specific killer cells by a DCCR5 zinc nuclease given together with a CAR delivering HIV-specificity to CD8 T-cells; advance the preclinical humanized mice platform to test novel combinations of immunotherapy (with/without novel delivery) when administered jointly or in sequence with the objective to recruit maximal intrinsic, innate, and/or adaptive anti-HIV effects.

These objectives are supported by four support teams addressing Clinical, HIV Reservoir Measures, HIV Resistance, and Biostatistics and Data Management. Community Engagement is built upon a 20+year relationship with the local HIV community, CFAR,
and ACTG activity ensuring partnership with target populations. Central administration of resources will ensure maintenance of high impact milestones, study team communications, and yearly goal-oriented resource allocation and/or redistribution as informed by an executive committee, external advisory board, and NIH program.

As a group, we bring diverse expertise and innovation representing the first time that distinct immunotherapy strategies with initial promising results in human trials focused on intrinsic/innate, humoral and adaptive arms of the immune response are actively joined to advance an HIV cure and/or remission under a single common multi-investigator, multi-industry team. The entire team is committed to advance the best outcomes from our collective effort to ultimately develop a strategy to eradicate HIV.

It is anticipated that clinical trials will begin enrolling in early 2018.

Collaborations:

Inovio

Sangamo BioSciences

Merck

Johns Hopkins University

Philadelphia FIGHT

The Rockefeller University

University of Nebraska-Lincoln

University of Pennsylvania

University of Utah

Veterans Medical Research Foundation San Diego - UCSD

BEAT-HIV Study – Currently enrolling
We are currently enrolling participants in the largest HIV Cure-related clinical trial conducted in the United States to date. The purpose of this study is to determine if treatment with pegylated interferon alpha 2b (peg-IFN-α2b) will reduce the amount of integrated HIV DNA in peripheral blood cells and tissues of individuals with chronic HIV infection receiving antiretroviral treatment (ART). A reduction and/or clearance of the latent viral reservoir, i.e. virus that remains dormant in HIV-infected subjects receiving suppressive treatment, is considered essential for HIV eradication. By measuring the changes in integrated proviral HIV DNA, which is considered a surrogate measure of the latent reservoir, the investigators will establish if peg-IFN-α2b treatment should be considered as a component of future viral eradication strategies.

In our recently completed clinical trial (NCT00594880), we demonstrated that treatment with peg-IFN-α2a started on ART resulted in 12 week viral suppression during ART interruption (peg-IFN-α2a monotherapy) in 50% of the subjects, concurrently with activation of intrinsic anti-HIV genes, higher NK responses, and a significant reduction in integrated proviral HIV DNA (a measure of latent reservoir).

Full project description:  

Collaborations:

Philadelphia FIGHT

Infectious Disease Division of the University of Pennsylvania

University of Pennsylvania Center For AIDS Research (CFAR)

Nebraska Center for Virology, University of Nebraska - Lincoln

University of California, San Diego

Merck

Pilot: Use of Peg-Interferon-α2b to reduce latent HIV reservoirs – Enrollment closed
The long-term goal of this research is to evaluate the effect of Peg-IFN-α-2b as an immunotherapy to potentiate eradication strategies against HIV. The short-term goals of this proposal are a) to determine whether Peg-IFN-α-2b can reduce HIV-1 proviral DNA levels in circulating PBMC and GALT in HIV-1-infected individuals who have achieved long-term ART-mediated immune reconstitution, and b) to investigate the role of innate and adaptive immune mechanisms in controlling the size of HIV latent reservoir.

Collaborations:

Philadelphia FIGHT
The Infectious Disease Division for the University of Pennsylvania
CFAR University of Pennsylvania

Early innate/IgA anti-HIV/SIV response in exposed uninfected

Our understanding of early anti-viral mechanisms in the cervico-vaginal compartment that may reduce HIV-1 or SIV infectivity in the absence IgG-mediated or CD8 T-cell responses remains incomplete and is the basis for this work. Evidence for resistance to infection in highly HIV-exposed women that remain seronegative (exposed sero-negative, ESN) in presence of anti-HIV responses is also supported by non-human primate (NHP) models where repeated low-dose cervico-vaginal challenges in Rhesus macaques can result in a refractory state that can only be overcome by increased infectious doses or by-pass of the mucosal micro-environment (e.g. intravenous viral challenge). Our preliminary data now shows for the first time that repeated cervico-vaginal exposures to SIV in the NHP can result in an increase in innate effector cell infiltrates including (1) plasmacytoid dendritic cells expressing IFN-a as a potential inductive factor associated with the local increase in tissue APOBEC 3G expression, and (2) CD68 macrophages infiltrates among Fc-receptor bearing cells. We will test the hypothesis that uninfected viral exposures in the female cervico-vaginal compartment can induce an innate/IgA mechanism mediating a state of reduced mucosal infectivity.

Full text description:
Innate Immunity & HIV-1 Infection - Dendritic Cells and Natural Killer Cells

The absence of clear immune correlates for protection against HIV-1 highlight the critical need to identify new pathways of host-resistance from infection. The overall goal of this R21 proposal is to identify novel mechanism(s) of protection in a cohort of HIV-exposed individuals who remain sero-negative (HESN) despite many years of high-risk behavior and exposure. Previous studies of HESN subjects exposed to HIV-1 through IV-drug use and needle-sharing (HESN-IDU) have identified several potential innate and intrinsic mechanisms of protection, including heightened Natural Killer (NK) cell function and increased resistance of CD4+ T cells to HIV-1 infection. Our preliminary data now provide the basis to test an innovative model for how these innate and intrinsic mechanisms of resistance may cooperate to provide a sustained barrier against HIV-1 infection in HESN-IDU subjects. We propose to investigate potential immune mechanisms of resistance from infection including phenotypic and functional characterization the innate (NK cells), adaptive (CD4+ T cells) and intrinsic (Tetherin, APOBEC) host anti-viral response. Together, this proposal will test if high-risk needle-sharing activity in protected HESN-IDU subjects triggers an anti-viral environment involving Interferon and/or S100 proteins that can augment NK activity against virally infected cells and increase CD4+ T cell resistance to HIV-1.
Collaborations:

Infectious Disease Division of the University of Pennsylvania Hospital, Philadelphia, PA

Philadelphia FIGHT

BD Biosciences

HIV-1 Patient Partnership Program

With long-standing commitment from Philadelphia FIGHT (a community-based HIV-1 primary care provider) and the University of Pennsylvania along with the support of Henry S. Miller, Jr. and Ken Nimblett, the Herbert Kean, M.D. Family Endowment, and the Robert I. Jacobs Fund of The Philadelphia Foundation, the HIV-1 Patient Partnership Program was established to provide clinical material for basic research and to sponsor the Jonathan Lax Memorial Lecture.

Research with clinical material obtained from this program is focused on mechanisms of AIDS immunopathology. This collaborative link, between our research team and over 5000 HIV-1 patients in the Philadelphia region, has led to the largest HIV Cure clinical trial to date – the BEAT-HIV Study.

The Jonathan Lax Lecture honors the memory of Jonathan Lax, a businessman, inventor, teacher, and one of the best known AIDS activists in Philadelphia's community-based clinical research network, where he volunteered with many groups to try and speed the drug approval process. He left funds to start a clinic - today called the Jonathan Lax Center - that is now the largest provider of AIDS care, independent of a patient’s ability to pay, in Philadelphia. The Lax Lecture is a public lecture held in June of each year at The Wistar Institute, where leading international HIV scientists interact with local researchers, clinicians, and patient advocates. Previous speakers include NIAID Director...
Anthony Fauci, Partners In Health Founder and Harvard Professor Paul Farmer, Project Inform Founder Martin Delaney, and 2008 Nobel Laureate Françoise Barré-Sinoussi.

The Montaner laboratory makes its research accountable to the patient community through community advisory board (CAB) review and community representation on Data Safety Monitoring Boards for actively enrolling studies. In addition, we provide community-focused research seminars at Philadelphia’s AIDS Education Month and the annual Lax Lecture, so that community members and other interested individuals are informed about the outcomes of patient-supported research.

**Collaborations:**

- Philadelphia FIGHT
- The Philadelphia Foundation