Current Montaner Lab Projects

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

The National Institutes of Health (NIH) 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-select 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 70 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.

**AMOHI Consortium**

**ART (Antiretroviral Therapy) ● Medications for Opioid Use Disorder (MOUD) ● Opioids ● HIV Infection**

Two five-year, NIH-funded projects will study the effect of medications for opioid use disorder (MOUD) in HIV-1-infected opioid users who receive antiretroviral therapy (ART). These studies will provide evidence of the impact of methadone maintenance therapy, when compared to naltrexone or buprenorphine.

The first five-year grant supports an international trial conducted between the U.S., Vietnam and France, in collaboration with the Vietnam Ministry of Health, the University of Pennsylvania, IMEA (a French-led initiative to expand access to HIV/hepatitis prevention and treatment services), the Pasteur Institute, and industry partner Alkermes, plc. The goal of this three-arm randomized trial is to evaluate the impact of long-term opioid receptor stimulation or blockage with MOUDs on immune reconstitution in HIV-infected people who inject drugs and are initiating ART. Early preliminary data suggest that chronic opioid receptor engagement by an opioid receptor agonist while on ART may result in increased immune activation and inflammation associated with increased levels of persistent HIV, when compared to a full opioid receptor antagonist. To verify this hypothesis, the study will assess recovery outcomes and adherence to therapy 48 weeks after initiation of ART in 225 participants with OUD who receive either methadone (opioid receptor agonist), extended-release naltrexone (antagonist) or buprenorphine (partial agonist).

The second grant includes a single visit study in collaboration with University of Pennsylvania, Jonathan Lax Treatment Center, and the Icahn School of Medicine at Mount Sinai, among others. This study will assess the preliminary observation that greater myeloid activation and HIV persistence is present in people receiving opioid receptor agonists when compared to people treated with opioid receptor antagonist naltrexone.

Blood and tissue samples from individuals living with HIV who are receiving ART and treatment with different MOUDs will be used to study the mechanisms that regulate persistent immune activation and residual HIV expression.

**Development of Novel Small Molecule Rb Protein Modulator for Ovarian Cancer Immunotherapy**

According to NCI statistics, ovarian cancer represents 1.3% of all cancers, and more than 21,000 women are diagnosed every year in the US. An estimated one woman in 75 will develop ovarian cancer during her lifetime. Although many therapeutic approaches have been tested, including surgery, radiation, chemotherapy, and immunotherapy, ovarian cancer remains extremely difficult to treat, and novel therapeutic strategies are needed. This project, funded in part by the Department of Defense, is based on our discovery of a novel small molecule, AP-3-84, that may increase antitumor immune responses and could benefit ovarian cancer patients by providing novel therapies to lower tumor burden and improve overall survival.
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 patients and other stakeholders 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.

Humanized Mouse Program

Absent direct clinical trials in humans, animal models of HIV infection are the best platform to explore novel preclinical anti-HIV strategies. Animal models for HIV infection include nonhuman primates and humanized mice. The humanized mouse system has been developed to model HIV infection in humans, response to antiretroviral therapy (ART) and novel cure interventions, as well as study viral rebound after therapy interruption. Humanized mice have emerged as a model that can be used for high-volume screening, yet the suboptimal immune differentiation that occurs in this model has raised concern on its ability to fully reflect all aspects of the immune response in humans.

The new WistarHu HIV-infected, ART suppressed mouse platform will be used for Wistar-based discovery of strategies against HIV based on changes in viral measures on ART or effects of ART interruption [Analytical Therapy Interruptions (ATIs)] on viral load rebound. Using this new platform, we will establish ART formulations, HIV infection, HIV suppression and characterize changes on immune reconstitution, persistent HIV measures and microbial translocation after ART and during an ATI. We will also determine the relationship between residual activation, mechanism of antiviral control or reactivation, and viral measures on ART or during ATIs.
Immunity & HIV-1 Infection - Dendritic Cells and Natural Killer Cells

The absence of clear immune correlates for protection against HIV-1 highlights the critical need to identify new pathways of host resistance to 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 seronegative (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 to infection including phenotypic and functional characterization of the innate (NK cells), adaptive (CD4+ T cells) and intrinsic (Tetherin, APOBEC) host antiviral response. This proposal will test if high-risk needle-sharing activity in protected HESN-IDU subjects triggers an antiviral 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.

Full text descriptions:

BEAT-HIV Study – No Longer 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, concurrent 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:
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.