Previous Montaner Lab Projects

Early Innate/Anti-HIV/SIV Response in Exposed Uninfected

Our understanding of early antiviral mechanisms that may reduce HIV-1 or SIV infectivity in the cervico-vaginal compartment in the absence IgG-mediated or CD8 T-cell responses remains incomplete and is the basis for this work. Evidence of resistance to infection in highly HIV-exposed women that remain seronegative (exposed seronegative, ESN) in presence of anti-HIV responses is also supported by nonhuman 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 microenvironment (e.g. intravenous viral challenge). Our preliminary data now shows for the first time that repeated cervicovaginal exposures to SIV in the NHP can result in an increase in innate effector cell infiltrates. These infiltrates include: (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 uninfectious viral exposures in the cervico-vaginal compartment can induce an innate/IgA mechanism mediating a state of reduced mucosal infectivity.

Full text description:
http://projectreporter.nih.gov/project_info_description.cfm?aid=8115636&icde=0

NK/DC cross-talk in HCV clearance and antiviral response

The mechanisms of HCV eradication following IFN/ribavirin therapy in HCV/HIV-1 coinfection or HCV mono-infection remain unclear. The goal of this work is to determine the role of innate immunity effectors in therapy response in HCV and HCV/HIV-1 coinfected subjects by investigating Natural Killer (NK) cell and Dendritic Cell (DC) functionality in relation to level of adaptive T cell responses and therapy-induced HCV suppression. We will test the hypothesis that the sustained functional response of innate effector cells (i.e. Natural Killer cell and Dendritic cell function) to IFN/ribavirin therapy is a determinant of both innate and level of adaptive (HCV-specific) responses and ultimately early and sustained HCV virologic suppression. As a corollary, we hypothesize that innate phenotypes and cell-mediated responses associated with HCV control would be selectively enriched in subjects with documented SVS (independent of HIV-1 infection) as compared to healthy or HIV-1-infected donors without HCV infection.

Full text description:

http://projectreporter.nih.gov/project_info_description.cfm?aid=8131142&icde=0

Collaborations:

Philadelphia FIGHT

The Infectious Disease Division for the University of Pennsylvania

The AIDS Clinic of Drexel University

The National Cancer Institute's Laboratory of Genomic Diversity

The National Cancer Institute's Laboratory of Experimental Immunology

BD Biosciences

Department of Biostatistics of the University of Massachusetts-Amherst

NK cell activation and function in HIV-1 exposed uninfected drug users

Multiply-exposed uninfected IV opioid drug users (EU-IVDU) remaining HIV seronegative are one of very few clinical cohorts where live HIV exposure can be studied in conjunction with epidemiological teams that are studying risk of infection in these subjects. The described seronegative state of subjects known to be at risk of infection via shared needle behavior with persons of unknown status has heightened interest in identifying the mechanism(s) of immune control that may provide resistance to infection in association with HIV exposure and drug use. NK cell activation, increased constitutive degranulation and increased lytic activity, have been proposed in EU-IVDU as a critical feature associated with protection, yet it remains unknown what specific NK membrane protein profiles and functional responses best defines or identifies an NK or DC cell activation program in EU-IVDU. The effects of drug use on NK or PDC activation programs, even in the absence of repeated HIV exposure, are also unknown. We propose to analyze three groups identified by lack of HIV infection (serongative) with different histories of IV opioid drug use.

Full text description:

http://projectreporter.nih.gov/project_info_description.cfm?aid=8044828&icde=0

Collaboration:

University of Pennsylvania School of Medicine, Department of Psychiatry, HIV/AIDS Prevention Research Division

Innate Immunity & HIV Infection - Macrophages

Macrophages constitute an important cellular component of the immune responses against viruses. They serve as antigen presenting cells and also secrete inflammatory mediators to activate innate and adaptive immune cells. Although macrophages from HIV-1 infected patients have not been described to be depleted with disease progression as is the case with CD4 T cells, they exhibit immunological dysfunctions. Following HIV-1 infection, effector functions of macrophages such as phagocytosis, chemotaxis, intracellular killing, inflammatory responses and antigen presentation are impaired. Furthermore, macrophages serve as reservoirs of HIV in chronically infected patients and contribute to approximately one percent of the plasma viral load. Our current work on this area addresses investigation of HIV-specific gene regulation effects on macrophages by analyzing patient-derived monocyte-derived macrophages (MDM) and in vitro infected MDMs.

Full text descriptions:
http://projectreporter.nih.gov/project_info_description.cfm?aid=2330462&icde=0

http://projectreporter.nih.gov/project_info_description.cfm?aid=2650113&icde=0

Collaborations:

Philadelphia FIGHT

CFAR University of Pennsylvania

Interferon-α-2A Immunotherapy for HIV-1 infection

Our long-range goal is to determine if pegylated Interferon-α-2A (Peg-IFN-α2A) can sustain HIV-1 suppression in the absence of Anti-Retroviral Therapy (ART) in infected individuals. We conducted a clinical study to compare two different doses of Roche Pegasys(r) Peg-IFN-α2A, 90 and 180 µg per week, for their ability to maintain viral control when initiated at the time of ART interruption in HIV-infected suppressed patients (VL<50 copies /ml) for 24 weeks or more, as determined by observing >0.5 log difference in viral set-points (delta viral load) obtained at two sequential 12 weeks ART discontinuations, with Peg-IFN-α2A administered only during the second discontinuation. Primary analysis was an "intent to treat" analysis and was address the hypothesis that two different doses of Peg-IFN-α2A (90 and 180 µg/week) would be similarly effective at inhibiting viral replication as defined by <0.5 log difference between the delta viral loads of each experimental arm. Secondary aims evaluated: (1) safety, tolerability and dose-dependent, treatment-associated toxicity, of 50 weekly administrations of Peg-IFN-α2A at 180 or 90 µg/week (in association with ART for the initial 2 weeks, followed by 48 weeks of Peg-IFN-α2A, alone); (2) the potential for PegIFNa2A-mediated (direct and immune-mediated) antiviral activity to extend viral control over a period of 48 weeks after ART interruption; (3) innate immunity outcomes correlated to Peg-IFN-α2A dose and antiviral activity, by monitoring NK and DC subset changes and the ability to maintain/enhance innate immune functions (DC secretory responses, NK antiviral cytotoxic responses); (4) adaptive immunity outcomes correlated to Peg-IFN-α2A dose and antiviral activity by monitoring T-cell subsets changes and the ability to maintain cell-mediated proliferative and cytokine responses against recall antigens (HIV-1 gag p55).

Full text description:

http://projectreporter.nih.gov/project_info_description.cfm?aid=7006340&icde=0

Collaborations:

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

Drexel Infectious diseases and HIV medicine, Philadelphia, PA

Philadelphia FIGHT, Philadelphia, PA

School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA

TB-related Immune Reconstitution Syndrome

Co-infection with Mycobacterium tuberculosis (MTB) and HIV-1 is a common occurrence in sub-Saharan African Countries. In a significant portion of dual-infected patients initiation of anti-retroviral treatment (ART) results in early onset of clinical and laboratory alterations related to re-acutization of MTB infection, collectively known as Immune Restoration Inflammatory Syndrome (IRIS), the pathogenesis and immune correlates of which are largely unknown at present. We analyzed a cohort of HIVinfected

individuals developing MTB-related IRIS after ART initiation, by measuring adaptive and innate immune functions. Specifically, we tested the hypotheses that: A) innate immune function, as measured by accessory cell activation (antigen presentation and responsiveness to Toll-like receptors (TLR) 2 7/8 and 9 stimulation) and natural killer cell responses (cytotoxic and cytokine secretion) is directly associated with IRIS and is significantly increased in IRIS patients as compared to non-IRIS HIV-infected controls undergoing ART for comparable periods of time: and B) baseline frequency, activation and function of innate immune effectors may predict a future IRIS outcome in MTB/HIV-1 dual-infected subjects.

Full text description:

http://projectreporter.nih.gov/project_info_description.cfm?aid=7167619&icde=0

Collaborations:

Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, SA

Department of Haematology, University of the Witwatersrand, Johannesburg, SA

School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA

Pediatric immune correlates of early anti-HIV therapy

Our studies assessing the effect of HIV infection on innate immune effectors in children indicate that depletion of dendritic cell subsets is associated with progressive infection. We have collaborated with the CHER study group, which recently demonstrated that early ART initiation has a positive effect on mortality and morbidity in perinatally infected children (Link), to assess the immunological correlates of early vs. delayed ART initiation. Our results support the hypothesis that perinatal HIV infection results in a different immune scenario as compared to adults, particularly in regards to the maintenance of naive T cell subsets. this may have important consequences in determining the extent of immune reconstitution on ART in neonates.

Full text description:

http://projectreporter.nih.gov/project_info_description.cfm?aid=6843339&icde=0

Collaborations:

Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, SA

KID-CRU, University of the Stellenbosch, Cape Town, SA

Department of Haematology, University of the Witwatersrand, Johannesburg, SA

The Children's Hospital of Philadelphia, Philadelphia, PA

School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA

Consequences of Intermittent Highly Active Antiretroviral Therapy (HAART)

The Montaner laboratory is investigating whether intermittent HAART can help maintain the benefits of continued therapy while decreasing drug exposure. Although inadequate adherence to HAART may increase the probability of resistant viral mutations, clinical evidence already indicates that complete

removal of HAART does not enhance emergence of resistance to an antiretroviral regimen so that reinitiating the same regimen results in a prompt virologic response. Current research in the laboratory is focused on determining if a series of sequential exposures to viral replication in otherwise chronically suppressed patients under HAART, as a consequence of structured treatment interruptions, can affect the efficacy of therapy, levels of CD4 count and viral load levels upon interruption periods. We are also studying the effect of sequential ART interruption on CD4 count, morbidity and maintenance of Ig titers to neo-antigens.

Full text descriptions:
http://projectreporter.nih.gov/project_info_description.cfm?aid=6213576&icde=0

http://projectreporter.nih.gov/project_info_description.cfm?aid=6696665&icde=0

Collaborations:

Philadephia FIGHT

Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, SA

Thembla Lethu Clinic, Johannesburg, SA

Department of Haematology, University of the Witwatersrand, Johannesburg, SA

School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA

Center for Clinical Epidemiology and Biostatistics from the University of Pennsylvania, Philadelphia, PA

Immune Correlates of Bacterial/Viral Co-infections

The long-range goal of our interest in this area is to determine the factors that predict the manner in which pathogenesis develops during poly-microbial infections. We are addressing the manner in which the developing immune response to a primary infection affects a coincident secondary inflammatory process (co-infection immune response). The short-term goal of this project will be to determine the manner in which BCGassociated inflammation and its modulation of antigen presenting cells affects a new immune response to a vaccine antigen delivered as and inactivated organism vaccine. Taken together, this work seeks to identify innovative targets for increased susceptibility to bacterial/viral co-infections by addressing understudied areas of innate immunity and chronic inflammation as central factors to decreased adaptive responses and protective immunity.

Full text description:

http://projectreporter.nih.gov/project_info_description.cfm?aid=6606309&icde=0

Collaboration:

Center for Clinical Epidemiology and Biostatistics from the University of Pennsylvania, Philadelphia, PA