PRIORITY:

Expanding Basic Discovery Research

Etiology and Pathogenesis

AREA OF EMPHASIS

Etiology and Pathogenesis

FY 2013 RESEARCH PRIORITIES

- Further the understanding of fundamental viral and host mechanisms associated with the acquisition, replication, and persistence of HIV at the cellular and organism level and determinants of disease progression, including intrinsic cellular restrictions, and the mechanisms and role of immune activation and inflammation.
- Identify the sites, mechanisms of persistence, and strategies for eradication of reservoirs of HIV infection.
- Develop novel strategies to treat and prevent HIV using knowledge gained from studies on HIV reservoirs, host mechanisms involved in acquisition and inhibition of HIV infection, and immune activation and inflammation.
- Study the interaction of aging with HIV infection and the mechanisms responsible for the pathogenesis of comorbid conditions such as cardiovascular disease, frailty, and immune dysfunction, including research on the relative contribution of the immune system and immune response to infection on these comorbidities.
- Elucidate the mechanisms associated with the pathogenesis of HIV/AIDS-related coinfections and HIV/AIDS-associated malignancies, and the effect of these conditions on HIV pathogenesis, as well as the impact of HIV on the progression of these diseases.

OBJECTIVE–A: Biology of HIV Transmission

Delineate the viral, host genetic, and immune mechanisms involved in the transmission, establishment, and spread of HIV infection in diverse populations across the spectrum of age, gender, and transmission mechanism in national and international settings.

STRATEGIES

- Determine the role of phenotype/genotype/fitness/generation of HIV variants and dose in various bodily fluids on transmission of cell-free and cell-associated HIV by different routes of transmission.
- Elucidate the genetic complexity, molecular features, and biological characteristics of HIV variants that are transmitted to the naive host.
- Determine the mechanisms by which virus-encoded genes or viral gene products regulate and influence transmission, establishment, and dissemination of HIV infection.
- Determine the cell subsets and tissue types at portals of entry responsible for the acquisition, replication, and dissemination of HIV during the initial stages of infection.
- Delineate the mechanisms and impact of genetic, metagenomic, viral and host epigenetics, and environmental factors on innate, adaptive, and mucosal immune responses that influence HIV replication, transmission, establishment, and dissemination.
- Delineate the mechanisms by which sexually transmitted infections (STIs), other coinfections, and the microbiome (bacterial, fungal, and viral) influence HIV transmission, replication, establishment, and dissemination, and contribute to HIV pathogenesis.
- Evaluate the role and mechanisms of preventing or enhancing HIV transmission, establishment, and spread by soluble factors contained within bodily fluids.
- Investigate the role of immune activation, inflammation, and their mediators in various tissues and organs on the establishment of HIV infection, transmission, and dissemination.
- Use new technology, including computational biology, bioimaging, and high-throughput technology, to advance the understanding of the earliest events in HIV transmission, establishment of foci of infection, and dissemination.
- Develop and perfect animal models of HIV and simian immunodeficiency virus (SIV) infection to facilitate study of HIV transmission and establishment of initial foci of infection.

OBJECTIVE–B: HIV Virology, Viral Pathogenesis, and Viral Persistence

Delineate the viral and host mechanisms associated with HIV replication and dissemination, and those that influence viral setpoint, disease progression, and viral persistence in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Define the molecular mechanisms and pathogen-host interactions underlying infection and replication at the cellular and molecular level, including viral gene products and their interactions with cellular cofactors and host restriction factors.
- Determine the mechanisms of dissemination (within the host) during acute infection; the viral, host, and environmental factors that regulate the establishment of viral setpoint following acute infection; and how viral setpoint influences subsequent disease progression.
- Determine the mechanisms by which infection causes chronic bystander immune cell activation and establishes immune activation setpoint, and how generalized immune activation combined with viral replication affects disease progression.
- Define the sites of infection and replication in the untreated host at the cellular and cell subset level, both anatomically and functionally; how these sites of productive infection are established; and how cell subset targeting determines disease progression or non-progression.
- Define sites and mechanisms of latent/persistent infection in patients on suppressive therapy, and the mechanisms by which reservoirs are established and maintained.
- Define the viral and host polymorphisms and exogenous/environmental factors that regulate virus replication and the development of pathogenesis and disease, and underlying mechanisms responsible.
- Define the co-pathogen and endogenous microbial factors that interact with virus to regulate pathogenesis.
- Further develop and facilitate the use of models to study key features of infection, pathogenesis, and persistence not amenable to study in the human host, such as nonhuman primate models of infection and pathogenesis, including comparative studies of nonpathogenic natural hosts, novel nonprimate animal models, and *ex vivo*, *in vitro*, and theoretical/mathematical models.

OBJECTIVE–C: HIV Immunopathogenesis

Delineate immunological mechanisms of HIV control, and elucidate the viral and host mechanisms associated with HIV-induced immunopathogenesis, including immune dysfunction, aberrant immune activation, and inflammation.

STRATEGIES

- Delineate the mechanisms by which innate and adaptive immunity, and the effects of genetic or environmental factors on innate and adaptive immunity, influence HIV/SIV replication throughout acute and chronic infection.
- Elucidate mechanisms by which epigenomic modifications of HIV interact with and enable host immune responses to control viral replication, setpoint, spread, and disease progression, and that prevent immune dysfunction, aberrant immune activation, and inflammation.
- Delineate mechanisms responsible for the differences between pathogenic and nonpathogenic infection in humans and nonhuman primates.
- Explore the role of HIV and other common viral coinfections in the development of premature immune senescence in HIV-infected individuals.
- Explore mechanisms of host response to HIV/SIV infection that involve the interface between innate and adaptive immunity.
- Delineate innate and adaptive immune responses to HIV at mucosal surfaces, including the gastrointestinal, genitourinary, and respiratory tracts.
- Elucidate the mechanisms of CD4+ T-cell depletion in the infected host.
- Delineate the pathogenic consequences of HIV infection on leukocyte homeostasis and on the structure and function of primary and secondary lymphoid tissues.
- Examine the role of immune activation, inflammation, and dysfunction/dysregulation in HIV/SIV pathogenesis, and delineate the mechanisms leading to pathological immune activation, immunosenescence, and autoimmunity in HIV/SIV infection.
- Determine the impact of host immunity on viral evolution and fitness, and the influence of viral factors on host immunity.
- Evaluate the extent to which HIV/SIV-related immunopathogenesis can be prevented or reversed by therapeutic interventions.

OBJECTIVE–D: Pathogenesis of Opportunistic Infections and Coinfections

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and significant coinfections in the context of HIV infection in diverse populations across the spectrum of age and gender in national and international settings and the factors that regulate susceptibility to infection or disease that might be targeted for prevention. Priority should be given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals and/or (b) contribute significantly to HIV transmission or acquisition.

STRATEGIES

- Conduct studies of the basic biology of opportunistic and coinfecting pathogens and their interaction with the HIV-infected host.
- Define the relationships in which HIV enhances coinfections and by which coinfections enhance HIV disease progression and the risk of HIV acquisition, including those that are a major cause of morbidity or disease progression (e.g., tuberculosis [TB] and hepatitis C [HCV]) or that contribute to HIV transmission and acquisition (e.g., STIs).
- Identify and elucidate the genetic, metagenomic, viral and host epigenetic, and environmental risk factors, as well as mechanisms of immune dysfunction, associated with the susceptibility to, the development of, and the progression of OIs and coinfections.
- Elucidate the mechanisms of innate and adaptive immune function that mediate protection against OIs and the effect of these mechanisms on HIV infection.
- Study the effects of HIV therapy on the clinical course and manifestation of OIs and coinfections, including pathogenesis of immune reconstitution inflammatory syndrome, and the effect of OI therapy on the clinical course of HIV disease progression.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these infections are altered by antiretroviral therapy (ART).
- Define the molecular and phylogenetic characteristics of major HIV-associated OIs and pathogens, and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine biomarkers and factors associated with clinical response and lack of response to therapeutic interventions and vaccines against OIs and coinfections, and identify basic mechanisms that will provide new targets for the development of vaccines and new treatments for OIs and coinfections that will be effective in HIV-infected individuals.

OBJECTIVE–E: Pathogenesis of Metabolic and Body Composition Change

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic disorders, body composition changes, nutritional status, endocrine dysfunction, oral health, gastrointestinal disorders, skin, muscle, and bone disorders, pulmonary disorders, nephropathy, hematologic disorders, and cardiovascular disease in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Define the mechanisms underlying alterations in metabolism, body composition, nutritional status, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, renal, bone, skeletal muscle, oral, gastrointestinal, pulmonary, hematologic, and skin diseases or manifestations to determine:
  - the effects of antiviral therapies and suppression of virus replication, viral setpoint, episodic viremia, and sites of viral reservoirs;
  - the influence of disease stages, including the degree of initial immunosuppression and immune reconstitution, residual immune dysfunction, lymph nodes disarray, and inflammation;
  - the contributions of individual virologic and host factors, including host genetic variation;
  - the contributions of OIs, nonopportunistic infections, hormonal dysregulation, and other consequences of HIV infection;
  - the role of diet, nonopportunistic infections, and nutritional status on malabsorption, malnutrition, immune status and exacerbation of metabolic disorders, steatosis, comorbidities, and HIV pathogenesis;
  - the influence of hormones on HIV pathogenesis; and
  - the impact of pharmacokinetics, pharmacogenomics, and drug–drug interactions.
- Study the impact of HIV on an aging population, including the implications of HIV infection for physical function and for cardiovascular, pulmonary, metabolic, bone, skeletal muscle, skin, oral, and renal diseases.
- Define the relationship between natural aging and HIV-induced pathological changes in multiple organ systems both without and on treatment.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, nutritional status, growth and development, diabetes, and bone, skeletal muscle, skin, renal, pulmonary, oral, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, physical function, impaired growth and development, diabetes, and bone, skeletal muscle, skin, renal, pulmonary, and atherosclerotic cardiovascular disease.
- Study the influence of the gut microbiome and other microbiota in conjunction with metabolic abnormalities, body composition changes, and cardiovascular and pulmonary disease associated with HIV infection.
- Integrate studies of these disorders and disease into ongoing and planned treatment trials and observational studies.

OBJECTIVE–F: Pathogenesis of Malignancies

Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of AIDS-defining and other HIV-related malignancies in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Elucidate the mechanisms by which HIV infection and its treatment enhance the development of various AIDS-defining malignancies, non-AIDS-defining malignancies, preneoplastic lesions, and other hyperproliferative conditions.
- Identify the mechanisms by which immune dysfunction (including inflammatory changes), oncogenes, suppressor genes, carcinogens, environmental factors, and non-HIV viral and other microbial organisms, genes, and proteins contribute to the development of cancer and preneoplastic lesions and hyperproliferative conditions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Conduct studies on the biology of opportunistic pathogens that are the principal etiologic agents for HIV-associated malignancies (e.g., Kaposi's sarcoma-associated herpesvirus), and investigate their interaction with the host and the mechanisms by which they cause malignancy in HIV-infected populations.
- Address the impact of HIV infection and prior therapy on the pathogenesis and treatment of common non-AIDS-related cancers (e.g., breast, colon, lung, prostate, liver, and skin) that may emerge in the aging HIV-infected population.
- Explore the mechanisms involved in the shifts in the spectrum on both AIDS-defining and emerging non-AIDS-defining malignancies that are occurring in HIV-infected individuals whose lives are extended by ART treatment. Conduct studies on how the interplay of HIV infection, host factors, and aging (including natural aging and premature aging that may be caused by HIV) enhance the development of these cancers.
- Elucidate the pathogenic mechanisms of AIDS-defining and other HIV-related tumors that arise in HIV-infected patients, including genetic changes, by comparing these tumors to similar tumors that arise in HIV-uninfected patients.
- Identify basic mechanisms that will facilitate the development of effective therapies and preventive measures (including vaccines) for AIDS-defining and other HIV-associated tumors.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected patients.

OBJECTIVE–G: Pathogenesis of Neurological Disease

Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Define the neurobiological, immunological, and molecular basis of HIV- or ART-associated neurological and neurobehavioral dysfunction, including neurocognitive impairment, peripheral neuropathies, chronic pain, and sleep disorders.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease, including the role of central nervous system (CNS) drug penetration.
- Explore the relationship of virologic, host, pharmacogenetic, and environmental factors (including substance abuse) to susceptibility of HIV-associated neurological and neurobehavioral dysfunction or neuropathogenesis.
- Explore the role of viral and host genetic factors in HIV neuropathogenesis.
- Investigate the mechanisms and determinants of HIV neuroinvasion (e.g., via blood-brain barrier), spread, persistence, and latency within the CNS.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment as well as its functional consequences.
- Delineate the role of OIs, coinfections, metabolic disorders, vascular disease, or other organ-specific disease or treatment complications in HIV-associated neurologic and neurobehavioral dysfunction.
- Define the roles of innate and adaptive immunity in the control of HIV, OIs, and coinfections in the CNS.
- Investigate the pathophysiology of HIV-associated CNS disease in the asymptomatic, acute, and early stages of infection.
- Identify aspects of HIV infection that uniquely influence or interact with the developing nervous system or the processes of neurocognitive decline with aging or aging-related diseases.
- Employ therapies that effectively suppress HIV replication and/or stimulate neuroprotection to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.
- Determine the mechanisms regulating the changing/fluctuating symptomatology of HIV-associated nervous system disease in the current era of ART.
- Define the impact of treatment drugs (including antiretroviral, TB, and HCV therapeutics) and other environmental factors (alcohol, smoking, substance abuse, and nutrition) on HIV-associated neuropathogenesis and peripheral neuropathy.