



# VIRAL PATHOGENESIS

Norman L. Letvin, MD, Chief — The Division of Viral Pathogenesis, directed by Dr. Norman Letvin, is a research division that focuses on elucidating the pathogenesis of AIDS and related opportunistic infections and exploring novel vaccination strategies to protect against HIV-1 infections.

## Highlights

Dr. Raphael Dolin's lab continues to conduct phase I/II clinical studies of candidate HIV-1 vaccines and of vectors related to those vaccines. Much of the work has involved the use of novel adenovirus vectors. Lab members have completed phase I dose escalation studies of Ad26

EnvA and rAdHVR48 EnvA candidate vaccines and a heterologous prime boost study using Ad26 and Ad35 vectors. They have also completed studies of the use of an orthopox vector, Modified Vaccinia Ankara (MVA), in normal subjects and in immunosuppressed patients. The effects of a fusion protein adjuvant, IL-2/Ig, on a DNA HIV vaccine have also been studied in a clinical trial. This trial showed the novel finding that timing of administration of the adjuvant was critical to its potentiating effect.

The Koralnik and Tan labs are studying JC virus (JCV), the etiologic agent of Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disease of the brain occurring in immunosuppressed individuals. These investigators have shown that the cellular immune response, mediated by JCV-specific CD8+ T cells, plays a crucial role in survival from PML. Dr. Igor Koralnik and his colleagues have demonstrated for the first time that JCV may cause demyelinating lesions not only in the white matter but also in the cortical grey matter and infect cortical pyramidal neurons. Dr. Chen Tan and colleagues have recently shown that the bone marrow is a site of JC virus latency.

The Yang, Seaman and Schmitz labs study antibody responses to HIV-1. While broad neutralizing antibody responses are rare in people infected by HIV-1, Dr. Xinzhen Yang has shown that these antibodies target glycan or glycan-dependent epitopes, specifically high-mannose N-linked glycans of HIV-1 glycoproteins. This discovery provides an important lead for future directions of developing anti-HIV-1 vaccines. The lab of Dr. Joern Schmitz studies memory B cells and plasma cells, the cells that produce antibodies. His group is specifically exploring how these cells mature in different anatomical compartments of vaccinated nonhuman primates to shed light on how these immune responses are being generated following HIV vaccination. Dr. Michael Seaman's lab researches the role of antibody-mediated immunity in protection against HIV-1. As a Gates Foundation and NIH supported Pre-Clinical Neutralizing Antibody



Amanda Dabrowski

The Reimann lab engineers antibodies for use as research tools in nonhuman primate models of disease and as interventional agents to treat diseases in humans. Recently lab members have developed and characterized antibodies that block lymphocyte costimulation and are developing these antibodies for preventing rejection of transplanted tissues and for treating autoimmune diseases. One novel antibody has shown promising results in preventing rejection of pancreatic islets in a nonhuman primate model of diabetes and is being evaluated for use in heart and kidney transplantation.

Core Laboratory, these investigators continue to assess the potency and breadth of neutralizing antibodies elicited by candidate HIV-1 vac-

cines currently in development, as well as novel monoclonal antibodies isolated from HIV-1 infected individuals.

## Selected Publications

Baden L, Blattner WA, Morgan C, Huang Y, Defawe OD, Sobiechczyk ME, Kochar N, Tomaras GD, McElrath J, Russell N, Brandariz K, Cardinali M, Graham BS, Barouch DH, Dolin R. Timing of plasmid cytokine (IL-2/Ig) administration impacts HIV-1 vaccine immunogenicity in HIV seronegative subjects. *J Infect Dis* 2011; 204:1541-9.

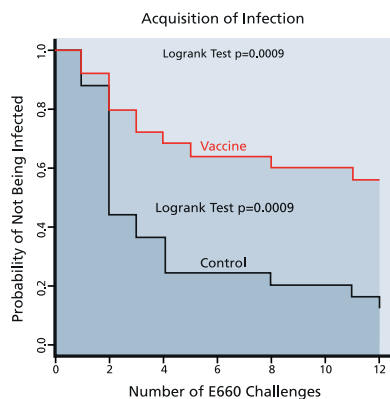
Letvin, NL, Rao SS, Montefiori DC, Seaman MS, Sun Y, Yeh WW, Asmal M, Gelman RS, Lim SY, Shen L, Whitney JB, Seoighe C, Lacerda M, Keating S, Norris PJ, Hudgens MG, Gilbert PB, Buzby AP, Mach LV, Zhang J, Balachandran H, Shaw GM, Schmidt S, Todd JP, Dodson A, Mascola JR, Nabel GJ. Immune and genetic correlates of vaccine protection against SIVsmE660 mucosal infection in rhesus monkeys. *Sci Transl Med* 2011; 3:81ra36.

Yeh WW, Rao SS, Lim SY, Zhang J, Hraber PT, Brassard LM, Luedemann C, Todd JP, Dodson A, Shen L, Buzby AP, Whitney JB, Korber BT, Nabel GJ, Mascola JR, Letvin NL. The TRIM5 gene modulates penile mucosal acquisition of SIV in rhesus monkeys. *J Virol* 2011; 85:10389-98.

Ansari AA, Reimann KA, Mayne AE, Takahashi Y, Stephenson ST, Wang R, Wang X, Li J, Price AA, Little DM, Zaidi M, Lyles R, Villinger F. Blocking of  $\alpha 4 \beta 7$  gut-homing integrin during acute infection leads to decreased plasma and gastrointestinal tissue viral loads in simian immunodeficiency virus-infected rhesus macaques. *J Immunol* 2011; 186:1044-59.

Gheuens S, Bord E, Kesari S, Simpson DM, Gandhi RT, Clifford DB, Berger JR, Ngo L, Koralknik IJ. Role of CD4+ and CD8+ T-cell responses against JC virus in the outcome of patients with progressive multifocal leukoencephalopathy (PML) and PML with immune reconstitution inflammatory syndrome. *J Virol* 2011; 85:7256-63.

Dang X, Bialasiewicz S, Nissen MD, Sloots TP, Koralknik IJ, Tan CS. Infrequent detection of KI, WU and MC polyomavirus in immunosuppressed individuals with or without progressive multifocal leukoencephalopathy. *PLoS One* 2011; 6:e16736.



The Yeh, Santra and Letvin labs make use of nonhuman primate models to explore novel strategies for HIV-1 vaccination. Yeh and colleagues recently developed a novel penile challenge system in monkeys that recapitulates key virologic and immunologic features of mucosal HIV-1 infection. Dr. Santra and colleagues are exploring a series of novel immunogens that have been designed in silico to circumvent the problem for vaccination posed by the genetic diversity of the circulating HIV isolates. Dr. Letvin and his colleagues have shown that protection against infection by AIDS viruses in monkeys can be achieved through vaccination and that this protection is mediated by antibody responses and potentiated by the expression of selected genes.

## Honors and Awards

**Mohammed Asmal, MD, PhD** – Received an Early Career Investigator Award from the HIV Vaccine Trials Network and Center for HIV/AIDS Vaccine Immunology.

**Wendy Yeh, MD** – Received an Early Career Investigator Award from the HIV Vaccine Trials Network and Center for HIV/AIDS Vaccine Immunology, and a Pfizer Young Investigator Award in Vaccine Development from the Infectious Disease Society of America.

**Norman Letvin, MD** – His lab received a Gates Foundation award for work on novel strategies for HIV vaccination, and a seven-year contract from the NIAID to serve as the nonhuman primate core cellular immunology lab for AIDS vaccine research and development.

## Faculty

**Mohammed Asmal, MD, PhD**  
**Raphael Dolin, MD**  
**Igor J. Koralknik, MD**  
**Norman L. Letvin, MD**  
**Sallie R. Permar, MD, PhD**  
**Keith A. Reimann, DVM**  
**Sampa Santra, PhD**  
**Joern E. Schmitz, MD, PhD**  
**Michael S. Seaman, PhD**  
**Chen S. Tan, MD**  
**Xinzhen Yang, PhD**  
**Wendy W. Yeh, MD**