

Division of Viral Pathogenesis



Norman L. Letvin, MD,
Chief

● Overview

The Division of Viral Pathogenesis is a research-based division that explores the immune control of human immunodeficiency virus, related nonhuman primate immunodeficiency viruses, and other viruses that affect immunosuppressed individuals. The Division is particularly interested in developing a vaccine against the human immunodeficiency virus (HIV-1).

● Research Activities

Research Funding • AY'07

Federal Direct.....	11,758,775
Federal Indirect.....	6,030,003
Other Direct.....	5,537,575
Other Indirect.....	551,105

Dr. Dan Barouch's laboratory focuses on the development of novel vector-based HIV-1 vaccine strategies. The laboratory is currently engaged in the construction and evaluation of novel serotype and chimeric adenovirus vector-based vaccines for HIV-1. The group will advance a series of these novel adenovirus vectors into clinical trials supported by funding from both NIH and Gates Foundation vaccine development programs.

Dr. Raphael Dolin's and Dr. Michael Seaman's laboratory provides support for phase I/II human clinical vaccine studies as a Site Affiliated Laboratory (SAL) for the Harvard HIV-1 Vaccine Trial Unit of the HIV-1 Vaccine Trials Network (HVTN) as well as for NIAID/DMID sponsored clinical trials studying the use of Modified Vaccinia Ankara (MVA) as a novel vaccine against smallpox. The laboratory

also performs analyses of antibody immunity elicited by these candidate vaccines. Finally, the laboratory is a Pre-Clinical Neutralizing Antibody Core Laboratory and Acute Infection Specimen Acquisition Laboratory for the Global HIV/AIDS Vaccine Enterprise (GHAVE) funded by the Bill and Melinda Gates Foundation.

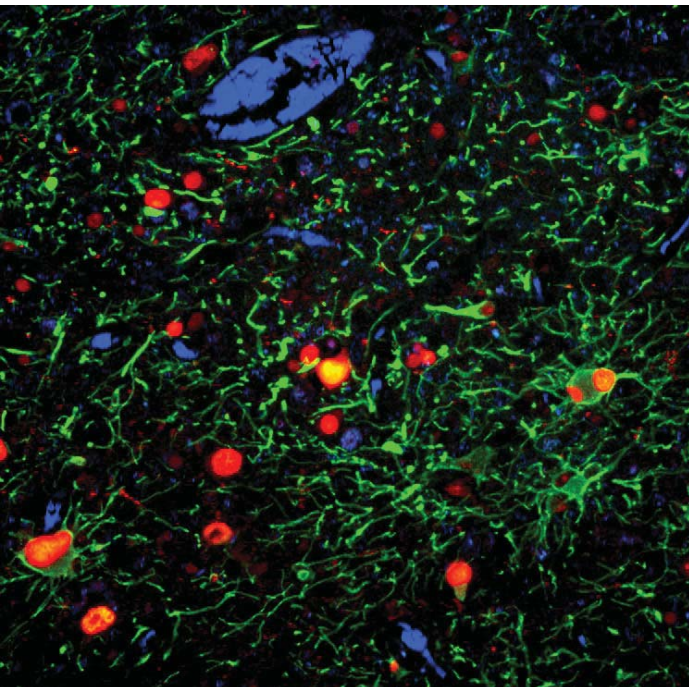
Dr. Igor Koralnik leads the HIV/Neurology Center, and his work focuses on the pathogenesis of JC virus in Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disease of the brain that occurs in immunosuppressed individuals with AIDS, persons with leukemias, and organ transplants. The laboratory has characterized a JC virus variant with a novel tropism to granule cell neurons, and also studies the immune response to another human polyomavirus, BKV, which is a cause of kidney disease in renal transplant recipients.

Dr. Keith Reimann's laboratory engineers recombinant antibodies and fusion proteins for use as therapeutics and as research reagents in a wide variety of nonhuman primate disease models. Dr. Sampa Santra is involved in evaluating the efficacy of candidate HIV-1 vaccines in nonhuman primates. The candidate vaccines that are being studied in nonhuman primates have unique immunogens to address the problem of extensive genetic diversity of HIV-1.

Dr. Joern Schmitz's laboratory studies the immunopathogenesis of AIDS in nonhuman primates. His group studies AIDS virus replication and pathogenesis in the African green monkey (AGM), a species that is naturally infected with an AIDS virus but does not develop disease. He and his colleagues are evaluating the role of B lymphocytes in containing infection with HIV-1. Finally his group is evaluating novel gene-therapy treatments for AIDS in nonhuman primate models.

Dr. Xinzhen Yang's laboratory studies the role of HIV-1 envelope in viral entry. In particular, his laboratory is interested in how antibodies block viral infection and what kind of neutralizing antibody responses are produced *in vivo* during the course of HIV-1 infections, issues of central importance in the development of an effective HIV vaccine.

Dr. Norman Letvin's laboratory uses nonhuman primate models to study the role of cellular immunity in controlling HIV spread. Much of this work focuses on the generation of cellular immune responses through vaccination and the extent of protection conferred by vaccination. His laboratory is part of the NIH-funded Center for HIV/AIDS Vaccine Immunology (CHAVI), the NIH Vaccine Research Center, and the Gates Foundation funded Collaboration for AIDS Vaccine Development.



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• C virus infection of astrocytes in the brain of a patient with Progressive Multifocal Leukoencephalopathy (PML) – Christian Wuethrich, PhD, Instructor of Neurology HMS; Igor J. Koralnik, MD, Associate Professor of Neurology, and Director, HIV/Neurology Center, BIDMC.

● Awards and Honors

Dr. Michael Seaman received the 2008 HIV Vaccine Trials Network (HVTN) Citizenship Award, Dr. Igor Koralnik was elected to the American Society for Clinical Investigation (ASCI), and Dr. Norman Letvin became an elected Fellow of the American Academy for the Advancement of Science (AAAS).

● Faculty

Dan Barouch, MD, PhD	Sampa Santra, PhD
Raphael Dolin, MD	Joern Schmitz, MD, PhD
Igor Koralnik, MD	Michael Seaman, PhD
Norman Letvin, MD	Xinzhen Yang, PhD
Keith Reimann, DVM	

● Selected Publications

Lima MA, Marzocchetti A, Autissier P, Tompkins T, Chen Y, Gordon J, Clifford DB, Gandhi RT, Venna N, Berger JR, Koralnik IJ. Frequency and phenotype of JC virus-specific CD8⁺ T lymphocytes in the peripheral blood of patients with progressive multifocal leukoencephalopathy. *J Virol* 2007; 81:3361-8.

Dang X, Wuethrich C, Axthelm M, Koralnik IJ. Productive SV40 infection of neurons in immunosuppressed rhesus monkeys. *J Neuropath Exp Neurol* 2008; 67:784-792.

Chen Y, Trofe J, Gordon J, Autissier P, Woodle ES, Koralnik IJ. BKV and JCV large T antigen-specific CD8⁺ T cell response in HLA A*0201⁺ kidney transplant recipients with polyomavirus nephropathy and patients with progressive multifocal leukoencephalopathy. *J Clin Virol* 2008; 42:198-202.

Veazey RS, Acierno PM, McEvers KJ, Baumeister SHC, Foster GJ, Rett MD, Newberg MH, Kuroda MJ, Williams K, Kim E-Y, Wolinsky SM, Rieber EP, Piatak M, Lifson JD, Montefiori DC, Brown CR, Hirsch VH, and Schmitz JE. Increased loss of CCR5⁺ CD45RA⁻ CD4⁺ T cells in CD8⁺ lymphocyte-depleted sim-

ian immunodeficiency virus-infected rhesus monkeys. *J Virol* 2008; 82:5618-5630.

Zahn R, Hermann FG, Kim E-Y, Wolinsky S, Rett M, Johnson RP, Villinger F, von Laer D, Schmitz JE. Human and non human primate immunodeficiency virus entry is efficiently inhibited by cell surface-expressed gp41-derived peptides. *Hum Gene Ther* 2008; 15:1210-1222.

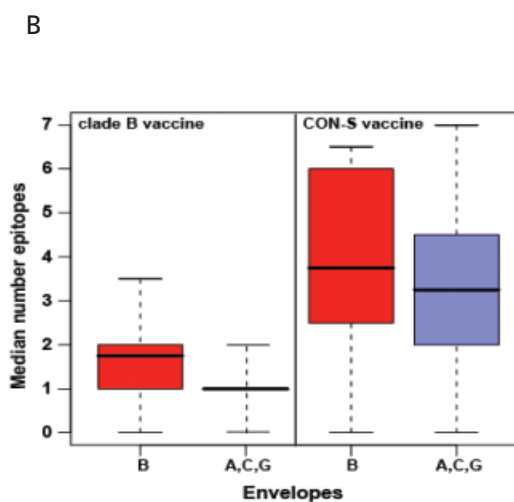
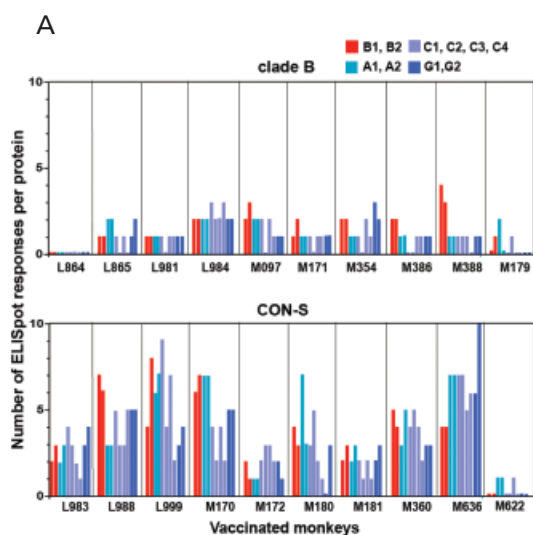
Santra S, Korber BT, Muldoon M, Barouch DH, Nabel GJ, Gao F, Hahn BH, Haynes BF, Letvin NL. A centralized gene-based HIV-1 vaccine elicits broad cross-clade cellular immune responses in rhesus monkeys. *Proc Natl Acad Sci U S A* 2008; 105:10489-94.

Yang X, Lipchina I, Lifton M, Wang L, Sodroski J. Antibody binding in proximity to the receptor/glycoprotein complex leads to a basal level of virus neutralization. *J Virol* 2007; 81:8809-8813.

Choi EI, Reimann KA, Letvin NL. *In vivo* natural killer cell depletion during primary simian immunodeficiency virus infection in rhesus monkeys. *J Virol* 2008; 82:6758-61.

Kaufman DR, Goudsmit J, Holterman L, Ewald BA, Denholtz M, Devoy C, Giri A, Grandpre LE, Heraud JM, Franchini G, Seaman MS, Havenga MJ, Barouch DH. Differential antigen requirements for protection against systemic and intranasal vaccinia virus challenges in mice. *J Virol* 2008; 82:6829-37.

Liu J, Kjekken R, Mathiesen I, Barouch DH. Recruitment of antigen-presenting cells to the site of inoculation and augmentation of human immunodeficiency virus type 1 DNA vaccine immunogenicity by *in vivo* electroporation. *J Virol* 2008; 82:5643-9.



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- Vaccination with consensus envelope (CON-S) induced magnitude and breadth of T cell responses: Peripheral Blood Mononuclear Cells (PBMC) from vaccinated monkeys were assessed for their recognition of specific epitopes of each of the 10 indicator envelope proteins. (A) Number of epitopes recognized of each individual indicator envelope protein by PBMCs of vaccinated monkeys. The CON-S-vaccinated monkeys generated responses to more epitopes than did the clade B-vaccinated monkeys ($p < 0.00002$). (B) Median number and IR of epitopes recognized from clade B envelope proteins and non-clade B envelope proteins by PBMCs of each group of vaccinated monkeys. The CON-S-immunized monkeys generated responses to more non-clade B envelope epitopes than the clade B-immunized monkeys ($p < 0.00047$).