Division of Viral Pathogenesis

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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.

Research Activities

Dr. 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. Dolin's and Dr. 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. 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 occurring in immunosuppressed individuals with AIDS, leukemias, and organ transplant recipients. 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. Reimann's laboratory has a well-established program to develop new recombinant antibodies and fusion proteins for use as research reagents supporting multi-disciplinary use of nonhuman primate models.

Research Funding • AY'07

Federal Direct	17,585,683
Federal Indirect	6,480,458
Other Direct	3,325,468
Other Indirect	224,193

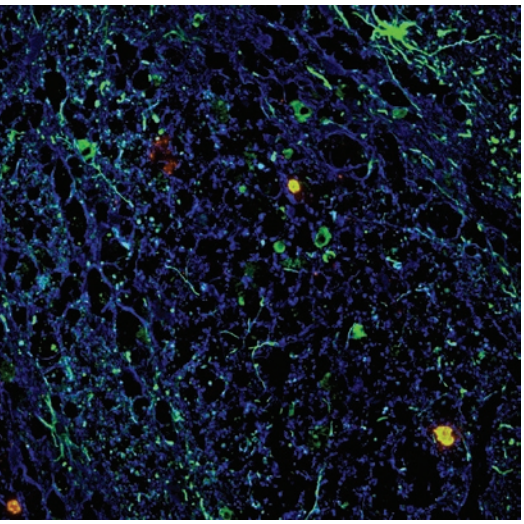
Dr. Santra evaluates novel vaccine strategies in nonhuman primate models, focusing on the assessment of novel strategies for generating cellular immune responses.

Dr. 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. Finally his group is evaluating novel gene-therapy treatments for AIDS in nonhuman primate models.

Dr. Williams's laboratory focuses on central nervous system disease caused by HIV and SIV infection. This work aims to define the role of monocyte subsets, macrophages, and

CD8+ T lymphocytes in controlling infection, pathogenesis, and traffic of virus to the brain.

Dr. 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, an issue of central importance in the development of an effective HIV vaccine.



Presence of JCV-infected glial cells in the brain of an HIV+ patient with Progressive Multifocal Leukoencephalopathy. Triple immunofluorescence staining with anti poliomavirus, anti CNPase and anti GFAP abs reveals a few JCV-infected oligodendrocytes (yellow-red) in an demyelinated area as well as debris of an JCV-infected glial cell (red). JCV-free oligodendrocytes and myelin are stained in green while astrocytes are blue.

Dr. 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.

Selected Publications

Chen Y, Trofe J, Gordon J, Du Pasquier RA, Roy-Chaudhury P, Kuroda MJ, Woodle ES, Khalili K, Koralnik IJ. Interplay of cellular and humoral immune responses against BK virus in kidney transplant recipients with polyomavirus nephropathy. *J Virol* 2006; 80:3495-3505.

Greenland JR, Geiben R, Ghosh S, Pastor WA, Letvin NL. Plasmid DNA vaccine-elicited cellular immune responses limit *in vivo* vaccine antigen expression through Fas-mediated apoptosis. *J Immunol* 2007; 78:5652-8.

Letvin NL, Mascola JR, Sun Y, Gorgone DA, Buzby AP, Xu L, Yang ZY, Chakrabarti B, Rao SS, Schmitz JE, Montefiori DC, Barker BR, Bookstein FL, Nabel GJ. Preserved CD4+ central memory T cells and survival in vaccinated SIV-challenged monkeys. *Science* 2006; 213:1530-3.

Manuel ER, Charini WA, Sen P, Peyerl FW, Kuroda MJ, Schmitz JE, Autissier P, Sheeter DA, Torbett BE, Letvin NL. Contribution of T-cell receptor repertoire breadth to the dominance of epitope-specific CD8+ T lymphocyte responses. *J Virol* 2006; 80:12032-40.

Roberts DM, Nanda A, Havenga MJ, Abbink P, Lynch DM, Ewald BA, Liu J, Thorner AR, Swanson PE, Gorgone DA, Lifton MA, Lemckert AA, Holterman L, Chen B, Dilraj A, Carville A, Mansfield KG, Goudsmit J, Barouch DH. Hexon-chimaeric adenovirus serotype 5 vectors circumvent pre-existing anti-vector immunity. *Nature* 2006; 441:239-43.

Santra S, Sun Y, Parvani JG, Philippon V, Wyand MS, Manson K, Gomez-Yafal A, Mazzara G, Panicali D, Markham PD, Montefiori DC, Letvin NL. Heterologous prime/boost immunization of rhesus monkeys by using diverse poxvirus vectors. *J Virol* 2007; 81:8563-70.

Seaman MS, Leblanc DF, Grandpre LE, Bartman MT, Montefiori DC, Letvin NL, Mascola JR. Standardized assessment of NAb responses elicited in rhesus monkeys immunized with single- or multi-clade HIV-1 envelope immunogens. *Virology* 2007; 367:175-86.

Sun Y, Schmitz JE, Buzby AP, Barker BR, Rao SS, Xu L, Yang ZY, Mascola JR, Nabel GJ, Letvin NL. Virus-specific cellular immune correlates of survival in vaccinated monkeys after simian immunodeficiency virus challenge. *J Virol* 2006; 80:10950-6.

Thorner AR, Lemckert AA, Goudsmit J, Lynch DM, Ewald BA, Denholtz M, Havenga MJ, Barouch DH. Immunogenicity of heterologous recombinant adenovirus prime-boost vaccine regimens is enhanced by circumventing vector cross-reactivity. *J Virol* 2006; 80:12009-16.

Yang X, Lipchina I, Cocklin S, Chaiken I, Sodroski J. Antibody binding is a dominant determinant of the efficiency of human immunodeficiency virus type 1 neutralization. *J Virol* 2006; 80:11404-11408.

Faculty

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