National Cancer Institute

# HIV/AIDS Research at the NCI:

## A Record of Sustained Excellence

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

# HIV/AIDS Research at the National Cancer Institute: A Record of Sustained Excellence



*The many common threads between cancer and HIV/AIDS underscore the value of NCI's involvement in HIV/AIDS research.*

— NCI Director John E. Niederhuber, M.D.

## Letter from the Director of the Center for Cancer Research

In 1981, the NIH Clinical Center admitted its first patient with acquired immune deficiency syndrome (AIDS) into the clinical service of the National Cancer Institute's (NCI) Metabolism Branch. Since these earliest days of the deadly epidemic, the NCI has been a leader in AIDS research. NCI intramural scientists were able to quickly apply their expertise in epidemiology, cancer, retroviruses, cell biology, the immune system, and drug development to this public health crisis. Over two decades later, their commitment and contributions remain strong.

The NCI intramural research program (IRP) is a unique nexus for basic, clinical, and translational research. Its mission is to forge a deeper understanding and to develop more effective means for the prevention, diagnosis, and treatment of cancer and AIDS. In pursuit of this goal, dedicated researchers work independently and in multi-disciplinary teams to make discoveries, develop new technologies and approaches, and translate their advances into clinical practice.

The NCI IRP, which includes the Center for Cancer Research (CCR), has a unique ability to integrate multiple scientific disciplines and approaches in support of scientific discovery. Our Centers of Excellence, Faculties, Working Groups, and Programs successfully cut across organizational boundaries to foster collaborative research. The newly formed Center of Excellence in HIV/AIDS and Cancer Virology is one example of this integration.

The NCI IRP collaborates with researchers and clinicians in other NIH institutes, universities, medical centers, and industry. To facilitate a broader, cost-effective AIDS research effort, the NCI intramural program makes many resources developed here available to partners in academic institutions and pharmaceutical companies free of charge. These include: 1) highly purified preparations of HIV and other retroviruses; 2) biological reagents such as purified proteins, antibodies, recombinant DNA vectors and cell lines; 3) natural and synthetic small molecule libraries; 4) highly sensitive methods for HIV detection; and 5) databases, including the HIV Protease Database and the Chemical Structure Lookup Service. Our resource sharing is a critical component of the NCI commitment to speed the development of more effective treatments.

Progress against HIV infection and AIDS, diagnoses once perceived as an automatic death sentence, has been striking. Deaths in the United States have dramatically declined since the 1990s, when effective combination antiretroviral therapy was introduced. In 2005, 17,011 people died of AIDS in the U.S.—about one-third the 51,414 deaths in 1995. But major challenges remain. People now living longer with HIV are facing an increased cumulative risk for AIDS-related as well as other cancers; the pandemic of AIDS and AIDS-associated cancers is a devastating presence in developing countries; and the virus is notorious for outsmarting existing therapies. There is still much to do.

Dr. Robert Wiltrout

After more than two decades of important contributions, it seems fitting to take time to acknowledge and reflect on the current AIDS research effort and the many advances that have already been made within the CCR and NCI IRP, as these achievements serve as the foundation for continued scientific excellence. The research featured on the following pages demonstrates how NCI's investment and sustained commitment to exploration and discovery has led to, and continues to lead to, new approaches and interventions to improve the lives of patients with cancer and HIV/AIDS.

Robert H. Wiltrout, Ph.D.
*Director, Center for Cancer Research*
*National Cancer Institute*
*National Institutes of Health*

# The Early NCI Retrovirus Experience

## A New Virus Revealed

In the years before AIDS appeared as a new disease, investigators in the Laboratory of Tumor Cell Biology, led by Dr. Robert C. Gallo, were searching for cancer-inducing viruses that might be responsible for human tumors. In 1980, the year before the first cases of AIDS were reported, Drs. Bernard Poiesz, Frank Ruscetti, Gallo, and colleagues at NCI discovered and characterized the first human cancer-causing retrovirus, HTLV-1, in a patient with leukemia/lymphoma. Soon after, they identified HTLV-2 as the second human retrovirus.

Retroviruses are unusual. Instead of the normal cellular process of transcribing genetic information from DNA into RNA, they use the enzyme reverse transcriptase to convert their RNA genome into DNA for integration into the host's chromosomal DNA to establish infection.

**1980** First human retrovirus (HTLV-1): T Lymphocyte cell cultures and growth factors

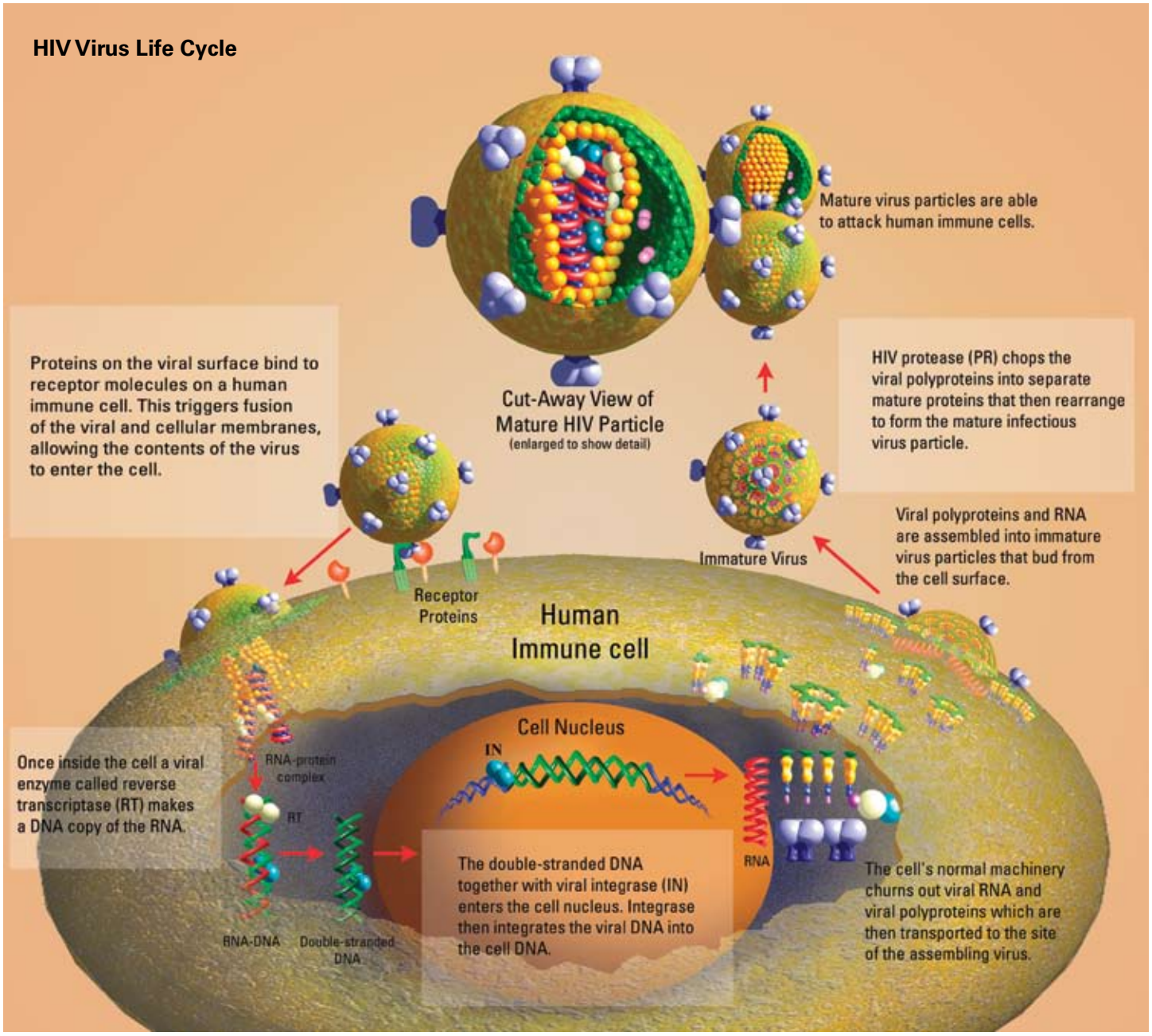
After the first cases of AIDS were reported, Dr. Gallo's group explored the hypothesis that this new disease might also be caused by a human retrovirus, in part because HTLV-1 caused immunodeficiency and cancer. By 1984, they showed that a new retrovirus could frequently be isolated in the blood of patients with AIDS. Drs. Luc Montagnier, Jean-Claude Chermann, and co-workers in France had just reported isolating a retrovirus from the blood of patients with an AIDS prodrome, and subsequent studies showed these to be the same virus, now called HIV (or human immunodeficiency virus). Drs. Gallo, Mikulas Popovic and other colleagues also developed techniques for continuous culture of the new virus in immortalized T lymphocyte cell lines and demonstrated that patients with AIDS had antibodies to this virus. In collaboration with Dr. Larry Arthur at NCI-Frederick, this technology was used to develop a blood test to protect the blood supply.

**1984** HIV-1 demonstrated as causative agent of AIDS: virus cloned and characterized

After these initial discoveries, Dr. Gallo and colleagues including Drs. Flossie Wong-Staal, George Pavlakis, Barbara Felber, Genoveffa Franchini, George Shaw, Beatrice Hahn, Lee Ratner, Mark Feinberg, Suresh Arya, Amanda Fisher, and others defined many key points of the biology of HIV, describing the sequence of the HIV genome, identifying regulatory proteins of HIV, showing that certain strains of HIV could infect macrophages, and elucidating how viral proteins interacted with the host's transcriptional and translational machinery. NCI scientists also helped describe the structures of viral RNAs, as well as critical viral enzymes. Early work by NCI scientists, including Drs. Stephen Oroszlan, Louis Henderson and Alan Rein, also led to the definition of the protein components

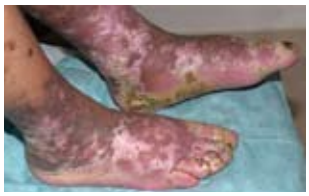
**1984** Large-scale production of HIV-1: development of diagnostic blood tests

From left, Dr. Genoveffa Franchini, Dr. Robert C. Gallo, Dr. Sandra Colombini, and Ershel Richardson discuss their research.




HIV is a retrovirus, belonging to the Lentivirus genus, and, like all retroviruses, replicates by copying its genome RNA into DNA, integrating the DNA into the genetic information of the host cell. Host cell machinery subsequently makes more copies of genome RNA and proteins, which are then assembled into infectious virions. *Figure courtesy of Louis Henderson*

of virus particles, and ongoing studies have continued to establish the roles of these proteins in virus particle assembly and structure. Dr. Marjorie Robert-Guroff and colleagues also described the first neutralizing antibodies that blocked HIV infection and the first HIV escape mutants selected by such antibodies. During this same period, Drs. Gene Shearer, Mario Clerici, and colleagues conducted a number of important studies defining the immunologic perturbations occurring in HIV infection. Subsequently, Dr. Jay Berzofsky and colleagues discovered the first helper and killer T cell epitopes, facilitating work on HIV vaccines to induce cellular immunity.



Kaposi's sarcoma lesions most often develop in the patient's feet because they are often hypoxic (low oxygen). This condition induces replication in KSHV-infected cells.

## Risk Factors

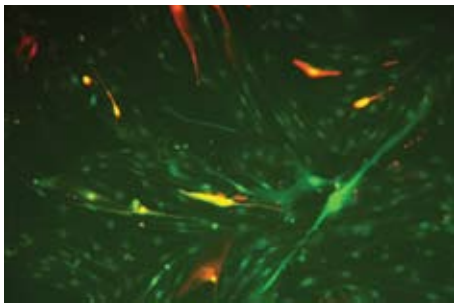
In 1981, clinicians in New York and other coastal cities in the United States began seeing a number of cases of Kaposi's sarcoma (KS) in young men. This disease had previously been extremely rare, occurring mostly in elderly men from Mediterranean countries. This outbreak of KS was one of the first harbingers of the AIDS epidemic.

These observations led Drs. James Goedert, Robert Biggar, and William Blattner, of NCI's Division of Cancer Epidemiology and Genetics (DCEG), to undertake prospective cohort studies of homosexual men. Data and specimens from these studies were important contributions to the 1984 co-discovery of HIV. Through studies of homosexual men, people with hemophilia, injection drug users, laboratory and health care workers, and pregnant women and their offspring, these epidemiologists and their colleagues helped to define the major risk factors for sexual, bloodborne, occupational, and mother-to-infant transmission of HIV. Dr. Biggar's studies in 1984-85 demonstrated the extraordinarily high HIV prevalence in several countries of Africa. Along with Dr. Philip Rosenberg, NCI Biostatistics Branch, and colleagues, DCEG scientists provided data indicating that progression of HIV-related immune deficiency was inexorable and likely to be lethal in most cases, and that the disease progressed at the same rate in homosexual men, people with hemophilia, and all other risk groups.

**1985** Discovery and location of HIV transcriptional activator (tat) protein

**1989** HIV rev protein demonstrated essential for stability and transport of viral mRNA

The team of epidemiologists and statisticians also identified and quantified the prognostic value of CD4+ lymphocyte counts. Drs. Goedert, Biggar, and Thomas O'Brien in the NCI Viral Epidemiology Branch were among the first to apply newly developed quantitative polymerase chain reaction (PCR) methods to help establish the strong relationship between HIV plasma viral load and subsequent risk of AIDS and death.



Human dermal microvascular endothelial cells infected with recombinant Kaposi's sarcoma-associated herpesvirus (KSHV). Green represents latent infection and red represents cells undergoing lytic activation (power 10X). *Figure courtesy of Drs. Paula Velasco and David Davis*

## NCI's Role in Early Advances in HIV/AIDS Research

- co-discovering HIV
- proving HIV as the causal agent of AIDS
- large scale virus culture methods established
- developing first blood test for HIV
- discovering several of the regulatory proteins of HIV
- describing the first antibodies to neutralize HIV
- describing the first neutralization escape mutants of HIV
- discovering the first helper T cell and cytotoxic T cell epitopes of HIV
- describing the first structures of HIV-1 protease and reverse transcriptase

# A Tale of Two Diseases

People infected with HIV face a two-pronged risk—the infection weakens the immune system, leading to AIDS and opportunistic infections—and HIV increases the risk of several cancers, including aggressive B cell lymphomas and primary central nervous system lymphoma. These tumors, as well as cervical cancer, confer a diagnosis of AIDS in HIV-infected individuals. Other tumors are also increased in HIV-infected patients, including Hodgkin's lymphoma, multiple myeloma, lung cancer, and cancers of the liver, lip, and pharynx.

## Treating the Infection

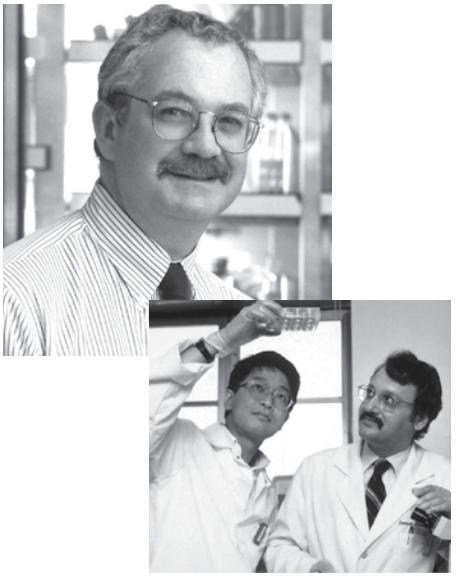
Untreated HIV infection is one of the major root causes of cancer caused by infectious agents. During the early days of the epidemic, most patients with AIDS-associated cancers had extremely low CD4+ T lymphocyte counts and were as likely to die of other complications of advanced AIDS as from the malignancy. Successfully treating these tumors would require effective treatment of the underlying AIDS in addition to treating the tumor itself.

**1985** AZT (zidovudine) blocks HIV-1 infection & clinical trial initiated (approved for treatment of HIV-infected patients in 1987)

And so, in the earliest days of the epidemic, a group of intramural researchers at the NCI turned their attention to developing effective AIDS therapy. Soon after HIV was found to be the cause of AIDS, Drs. Samuel Broder, Hiroaki Mitsuya, and Robert Yarchoan showed that certain nucleoside analogs had activity against HIV in the test tube and rapidly moved to test them in clinical trials in the NIH Clinical Center. Their work yielded the first drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of AIDS: zidovudine (AZT), didanosine (ddI), and zalcitabine (ddC). Dr. Phillip Pizzo and colleagues in the Pediatric Branch conducted some of the initial trials of these drugs in HIV-infected children. Today,

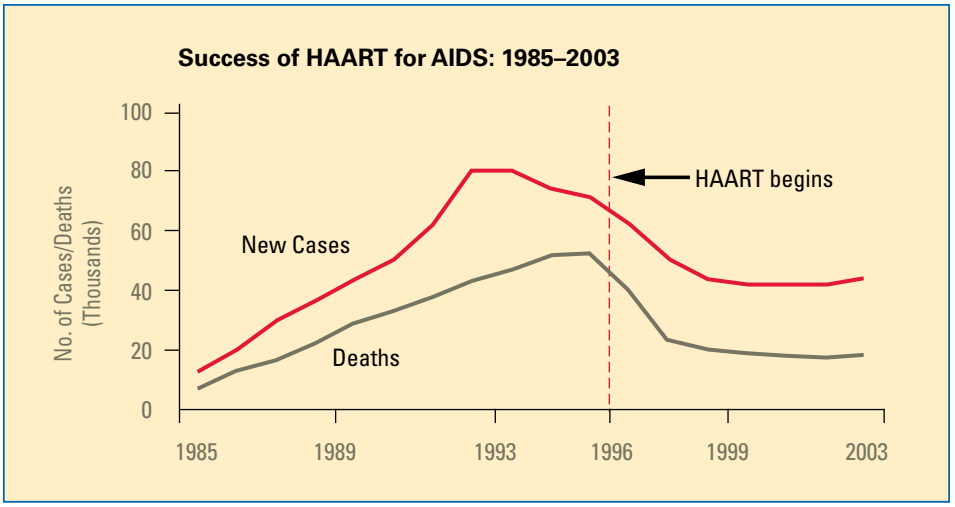
**1991** ddI (didanosine) approved by FDA as second AIDS drug

such drugs, combined with protease (PR) and non-nucleoside reverse transcriptase (RT) inhibitors, form the basis for highly active antiretroviral therapy, or HAART. This therapy reverses the immune suppression caused by HIV infection and markedly extends the lives of HIV-infected patients.



Drs. Robert Yarchoan *(upper left)*, Hiroaki Mitsuya *(above, lower left)*, and Samuel Broder *(above, lower right)*, co-discoverers of AZT and ddI.

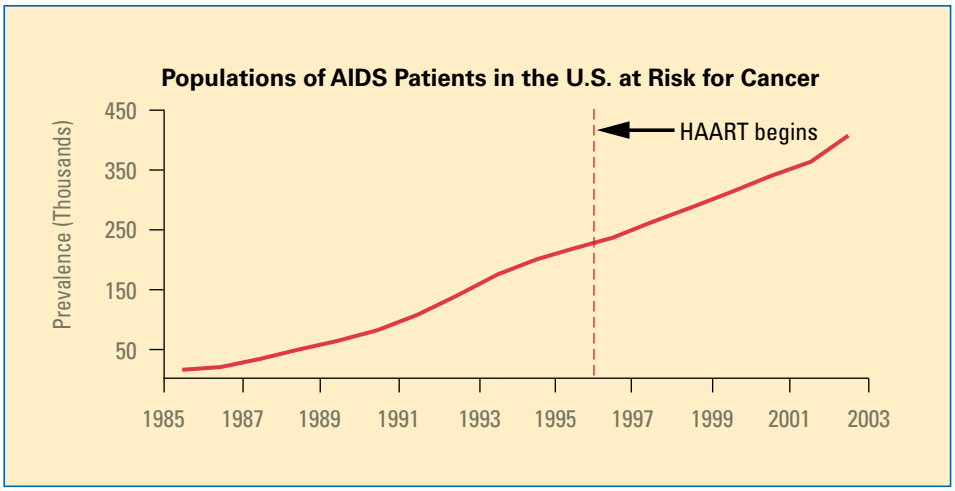
In addition, HAART patients benefit from improved prophylaxis and treatment of opportunistic infections. As a result, advanced AIDS and opportunistic infections have declined dramatically as causes of death in HIV-infected patients, and cancer is emerging as the most common cause of death. Although the risk of developing AIDS-related malignancies that tend to occur in



patients with very low CD4+ T lymphocyte counts has declined, as patients live longer, they have an increasing cumulative risk of developing a variety of other tumors.

## Treating the Cancers

Since the development of effective combination antiretroviral treatment began extending the lives of people with HIV, CCR researchers have turned their attention to the AIDS malignancies themselves. Drs. Barbara Ensoli, Shuji Nakamura, and others working with Dr. Gallo investigated the pathogenesis of KS and described the importance of angiogenic factors in this process. In 1995 Dr. Robert Yarchoan and colleagues demonstrated that paclitaxel, an anticancer drug that NCI played a critical role in discovering and developing, is an effective treatment for patients with advanced KS. Paclitaxel is now approved by the FDA as a second-line therapy for KS. More recently, Drs. Yarchoan, Richard Little, and co-workers in the HIV AIDS Malignancy Branch (HAMB) have shown that interleukin-12 (IL-12) has clinical activity in patients with AIDS-associated KS, and a study combining IL-12 and the anticancer drug liposomal doxorubicin in patients with advanced KS is underway.

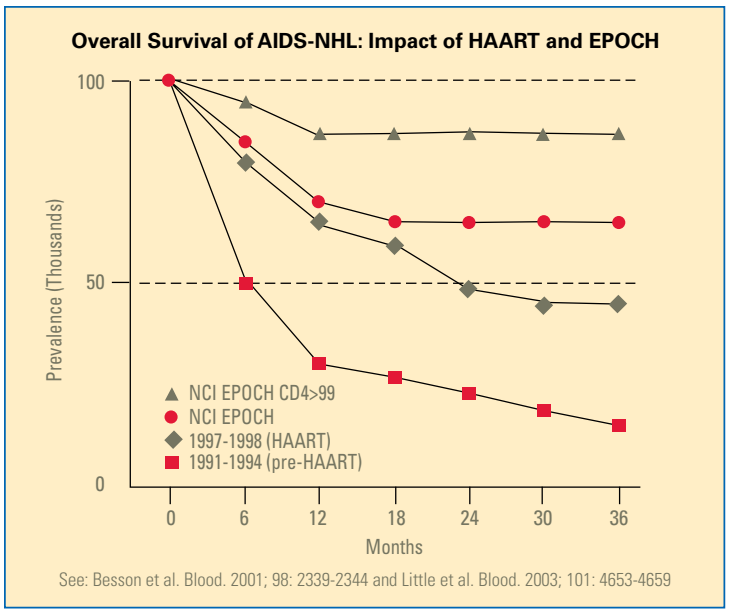



Thanks to progress at the NCI, patients with AIDS-related lymphoma also face a brighter future. During the early days of the epidemic, lymphoma was rapidly fatal, taking patients' lives an average of 4 months after diagnosis. In 2003, CCR's

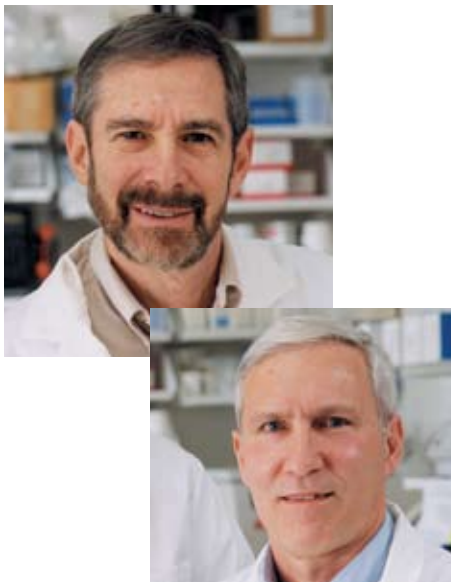
**1995** Paclitaxel active against Kaposi's sarcoma: receives FDA approval in 1997

**2003** EPOCH infusional therapy shown to be highly effective against AIDS lymphoma

Paclitaxel—space filling molecule *(inset, above)*—was originally extracted from the bark of the pacific yew tree (taxus brevifolia). *Source: George McGregor.* Scientists are trying to find alternative ways of producing this compound such as using yew needles. *Source: Dr. Gordon Cragg*




See: Besson et al. Blood. 2001; 98: 2339-2344 and Little et al. Blood. 2003; 101: 4653-4659



Two decades of work by the groups of Douglas Lowy, M.D. *(upper left)* and John Schiller, Ph.D. *(above right),* could help protect millions of women around the world from HPV's cancerous consequences.

Drs. Little and Wyndham Wilson (Metabolism Branch) and colleagues demonstrated that a form of combination chemotherapy called dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) was highly effective against AIDS-related lymphoma. Nearly 75% of patients had a complete response, and more than half were alive and disease free after 4 years. CCR researchers are investigating modifications of this approach to improve responses with less toxicity.

Most AIDS-associated malignancies are caused by DNA viruses such as Epstein-Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV), and human papillomavirus (HPV). HIV-related immunosuppression reduces host resistance to infection and tumor development. Scientists have been studying these viruses, looking for ways to prevent or treat the cancers they cause. Recently, the FDA approved the first vaccine that protects women against HPV infection. This vaccine was based on work that was initiated by Drs. Douglas Lowy and John Schiller in the Laboratory of Cellular Oncology (LCO). Cervical cancer is not only an AIDS-related tumor but also one of the most common tumors caused by an infectious agent. This vaccine may also prevent anal cancer, which has a high incidence rate in AIDS patients.

The HPV vaccine is based on research showing that many copies of a single protein from HPV (the L1 protein) could assemble into hollow spheres called virus-like particles (VLPs). VLPs are not infectious, but cause the body to mount antiviral immune responses. Immunization with these particles stimulated production of antibodies that prevented virus infection in both animals and human volunteers. NCI licensed the technology to Merck and GlaxoSmith-Kline (GSK), both of which have developed HPV vaccines. Both vaccines protect against HPV types 16 and 18, which cause up to 70 percent of all cervical cancers worldwide. Merck's Gardasil®, approved by the FDA in 2006,

**2006** FDA approves the first vaccine to prevent HPV infection

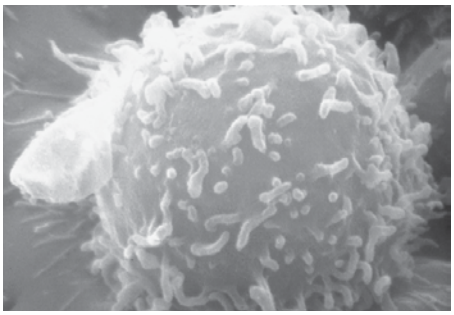
also protects against HPV types 6 and 11, which cause up to 90% of genital warts. In large-scale trials, the VLP vaccines were 100% effective at preventing premalignant cervical changes caused by the virus types in the vaccines. Under the direction of Dr. Allan Hildesheim, the NCI is performing its own testing of the GSK vaccine in Costa Rica, where there is a high rate of cervical cancer.

**2006** Interleukin-12 active against HIV-associated Kaposi's sarcoma

Other CCR investigators are studying the basic biology of KSHV and EBV to identify novel targets for therapy. Dr. Giovanna Tosato, LCO, has identified cytokines produced by KSHV-infected cells that promote development of primary effusion lymphoma, a rare tumor. Dr. Zhi-Ming Zheng in HAMB has been exploring the use of small interfering (si) RNAs to suppress HPV proteins associated with tumor development. Drs. Yarchoan and David A. Davis are developing treatment strategies using pro-drugs activated by viral enzymes that specifically target KSHV-infected cells. HAMB scientists are now conducting a clinical trial of these strategies to treat KSHV-associated multicentric Castleman's disease (MCD). NCI scientists are also adding to our basic understanding of the biology of these viruses. Dr. Denise Whitby of the AIDS Vaccine Program (AVP) has demonstrated the presence of conserved micro-RNA sequences in KSHV isolates. Variation in these sequences, which are believed to help regulate viral gene expression, may correlate with and help explain different disease presentations in KSHV-infected individuals.

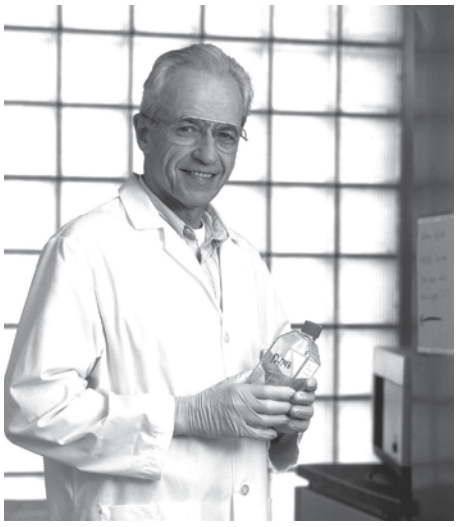
# HIV and the Immune System: How They Interact

The profound immune disruption that is the hallmark of AIDS was clear from evaluation of the earliest patients, and efforts to understand the underlying disease processes that cause this disruption remain an active area of research. HIV preferentially infects cells bearing the CD4 receptor, principally helper T lymphocytes, which play a critical role in orchestrating optimal immune responses. The progressive loss of these cells is a clinically useful marker of disease progression. A key and still largely unanswered question in HIV research is the basis for the overwhelming depletion of CD4+ T cells following viral infection and the profound immune suppression that occurs as disease progresses.



Electron microscopic image of a single human lymphocyte. *Source: Dr. Triche*

Although massive infection of CD4+ T cells occurs during acute infection, direct viral pathogenesis is not believed to be the sole mechanism, in part because the number of HIV-infected CD4+ T cells present at any time in an infected individual is small relative to the cell depletion observed. Therefore, indirect effects caused by immune-mediated mechanisms (immunopathogenesis) likely contribute to the acute and ongoing depletion of these cells. Exposure to virus or viral proteins can result in pathological triggering of many immune system cells, limiting the effectiveness of immune responses by killing the cells, impairing their function, or inducing pathways that suppress antiviral responses.



Dr. Gene Shearer

Dr. Gene Shearer and colleagues in the Experimental Immunology Branch have shown that the balance between protective and pathogenic effects of IFN-α produced by plasmacytoid dendritic cells (pDC) activated by noninfectious HIV particles may be tipped in favor of pathogenesis in HIV infection. The high proportion of non-infectious HIV particles present can trigger IFN-α-induced apoptosis of HIV-exposed but uninfected CD4+ T-cells. Exposure of pDC to non-infectious HIV can also upregulate the immunosuppressive, tryptophan-catabolizing enzyme, indoleamine 2,3-dioxygenase (IDO). Culture of these pDC with CD4+ T cells results in CD4+ T cell suppression. High IDO expression *in vivo* is often associated with accumulation of regulatory T cells (Tregs) in lymphoid tissues. These immunopathogenic mechanisms can be blocked by small molecules that inhibit HIV-CD4 binding, suggesting a potential use for inhibition of both HIV infection and immunopathogenesis.

**1985** Identification of antibodies that block HIV infection

**1987** Identification of Helper T cell epitopes in HIV proteins

Mechanisms of depletion of uninfected CD4+ T cells are also being explored by Dr. Robert Blumenthal and colleagues of the CCR Nanobiology Program, revealing both mechanisms of HIV-induced bystander apoptosis and strategies to circumvent it. The group has provided the first direct evidence that HIV-1 gp41-mediated hemifusion of infected with uninfected cells is required and sufficient for apoptosis of these bystander T cells. Furthermore, such apoptosis is not dependent on virus replication but on the phenotype of the Env glycoprotein associated with the virus. Mechanistic studies show that Env-mediated apoptosis can be prevented by using the PR inhibitor nelfinavir and the fusion inhibitor enfuvirtide. This work may have

important implications for HIV-1-infected individuals treated with enfuvirtide and/or nelfinavir. Dr Frank Maldarelli, HIV DRP, is exploring the applicability of these findings in a clinical setting.

**1988** Demonstration that cytotoxic T lymphocytes (CTL) are important in HIV infection

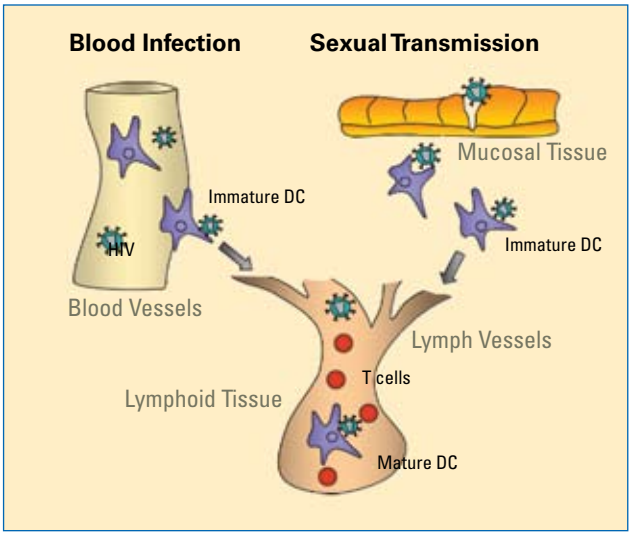
Other CCR scientists including Drs. Thomas Waldmann (Metabolism Branch), Francis Ruscetti (Laboratory of Experimental Immunology), and Joost Oppenheim (Laboratory of Molecular Immunoregulation), have played a role in the discovery and characterization of immune system components such as natural killer (NK) cells and NK-T cells, as well as immune modulatory cytokines such as IL-2, IL-7, IL-15, and TGF-β. Contributions of CCR immunologists have stimulated the investigation of additional pathways of how HIV harms the immune system and laid the groundwork for designing preventive and therapeutic strategies.

Virus-specific CD8+ cytotoxic T lymphocytes (CTLs) play a role in controlling viral replication. Dr. Berzofsky and colleagues have studied the impact of antigen specificity, receptor avidity, and anatomic localization on the effectiveness of CD8+ T cells in controlling infection, demonstrating the importance of local mucosal immunity. However, despite a detectable frequency of virus-specific CTLs during the chronic phase, the virus is never completely eradicated. In the absence of drug treatment, control of viremia during

Dr. Claes Ohlen

the chronic phase is eventually lost and infected individuals develop AIDS. It is not known why all infected cells are not killed by the immune system and why the infection is consequently never cleared, but mechanisms may include: (1) latently infected cells hiding from the immune system through lack of viral replication; (2) infected cells persisting in tissues where T cells normally do not traffic; (3) mutations in the viral genome leading to viral escape from the T cells; and (4) an insufficient number of virus-specific CTL limiting the viral control.

Dr. Claes Ohlen of the AIDS Vaccine Program (AVP) is evaluating the impact of adoptive transfer of large numbers of cloned autologous virus-specific CD8+ CTL on acute and chronic infection in experiments in non-human primates. These studies aim to characterize the potential maximum efficacy of CD8+ CTLs as an effector mechanism for preventive or therapeutic vaccines. His aim is to better characterize the immunobiology of HIV-specific CTL in infected hosts and to lay the foundation for subsequent vaccine studies using adoptive T cell transfer in macaque models.




While HIV is well known for its destruction of CD4+ T helper lymphocytes, other immune cell types such as dendritic cells and macrophages are also thought to play key roles in viral pathogenesis and spread. Dendritic cells act as immune sentinels, capturing invading pathogens in the blood and mucosal surfaces to process as antigens and later present to CD4+ T cells. However a sizable proportion of HIV that is sequestered by dendritic cells escapes degradation and exploits the interaction with T cells to facilitate its spread. *Figure courtesy of Dr. Vineet KewalRamani*

# Susceptibility to Infection, AIDS, and Related Diseases

Not everyone responds to HIV in the same way. Although most HIV-infected individuals develop AIDS within 10 years, some take only a few years, while as many as 5% remain relatively healthy for 15 years or more. NCI scientists are trying to decipher which genes are associated with progression or non-progression to AIDS and viral-induced cancers.

Dr. James Goedert in the Division of Cancer Epidemiology and Genetics (DCEG) with other intramural and extramural collaborators discovered in 1987 that progression was slower in younger than in older people with hemophilia. Looking closely at AIDS-defining malignancies, Drs. Goedert, Robert Biggar, Charles Rabkin, Eric Engels, Sam Mbulaiteye, and their DCEG colleagues conducted a number of epidemiologic studies exploring the relationship between infection with Kaposi's sarcoma associated herpesvirus (KSHV), also called human herpesvirus-8 (HHV-8), and KS. This group also showed that KS risk is reduced with cigarette smoking, for reasons yet unknown. In recent years, using data from DCEG's HIV/AIDS cancer match and other sources, they showed that use of HAART greatly reduced the risk of KS and of some types of non-Hodgkin's lymphoma (NHL), particularly in the brain. Paradoxically, HAART use appears to increase the risk of Hodgkin's lymphoma.

Over the past decade, NCI scientists have identified variations in numerous host genes or gene families that affect the rate of disease progression and even susceptibility to HIV infection itself. CCR researchers are exploiting these results to block HIV in several ways.

Genes containing variants that affect outcome of HIV exposure are involved in either the viral replication cycle or the innate/acquired immune response to the virus. Although some of these genetic effects are pronounced, most are weak and detectable only in large cohorts that are well-defined with regard to clinical parameters. Using a candidate gene approach, NCI scientists have identified multiple host genetic effects on HIV infection or

**1992** Host cell proteins incorporated into HIV-1 shown to have functional significance

the rate of disease progression after infection. The chemokine receptors CCR5 and CXCR4 are major cellular co-receptors for HIV. NCI investigator Dr. Michael Dean and others in the Laboratory of Genomic

Dr. Mary Carrington

**1997** Mutant CCR5 receptor linked to less rapid progression to AIDS

Diversity (LGD) were among the first to identify a deletion in the CCR5 gene *(CCR5Δ32)* that protects against infection in individuals homozygous for the mutation. CCR researchers also helped show that heterozygotes for this variant, while not protected against infection, progress to AIDS more slowly than individuals homozygous for wild type *CCR5*.

This finding represents the first major success in identifying a genetic variant that affects HIV infection and has contributed to the development of two treatments for HIV infection: CCR5 antagonists, the first of which was recently approved by the FDA and monoclonal antibodies against the CCR5 co-receptor. Furthermore, *CCR5Δ32* has subsequently been shown to influence susceptibility to other diseases, including smallpox and West Nile virus-associated encephalitis.

Particularly strong genetic associations with HIV disease progression have involved variation in the highly variable *HLA* class I genes, which influence resistance/susceptibility to AIDS through both acquired and innate immune responses. These genes code for cell-surface proteins that present foreign peptides to the immune system.

The combination of a high mutation rate and rapid replication enables HIV to adapt in patients with HIV infection, in most cases regardless of *HLA* genotype. Nevertheless, specific types of *HLA* have been

### Genes That Affect HIV-1 Infection and AIDS Progression

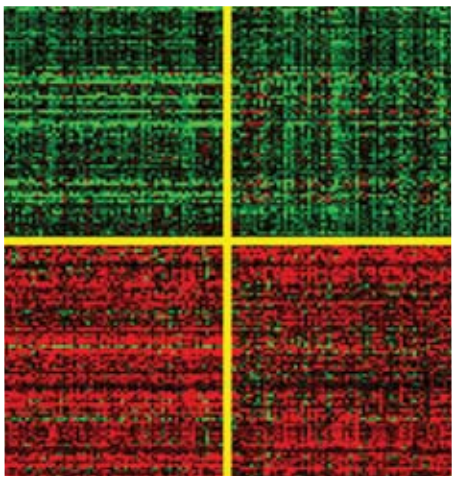
| Gene | Genotype | Effect |
|---|---|---|
| CCR5 | Δ32/Δ32 | Prevent infection |
| CCR5 | +/Δ32 | Delay AIDS |
| CCR2 | +/64I | Delay AIDS |
| RANTES | -403A/-28G | Delay AIDS |
| HLA | HLA- A,-B,-C homozygosity | Accelerate AIDS |
| HLA | B*35P*x* | Accelerate AIDS |
| HLA | B*57, B*27, B*w*4 | Delay AIDS |
| KIR/HLA | KIR3DS1/HLA-B B*w*4-80I | Delay AIDS |
| IL-10 | -592A | Accelerate AIDS |
| APOBEC3G | 186R | Accelerate AIDS |
| DC-SIGN | -336C | Susceptibility to infection |
| TSG101 | HapC | Accelerate AIDS |
| CUL5 | Cluster II haplotypes | More rapid CD4+ T cell loss |

identified that confer relative increases in protection from or susceptibility to progression to AIDS in HIV-infected individuals. In some cases, functional work involving HIV antigen presentation by the HLA gene products has explained the genetic associations observed with the corresponding genes. Recently, several investigators have shown that HLA class I gene products interact with the highly variable killer cell immunoglobin-like receptors (KIRs), which participate in controlling both natural killer cells and a subset of T cells. Investigators in Dr. Mary Carrington's laboratory showed that specific combinations of HLA gene products and KIRs interact synergistically in defense against HIV. Ongoing multi-disciplinary collaborations with investigators at Harvard University and the CCR Cancer Inflammation Program aim to understand how these combinations work.

Variants in other host immune response genes also are associated with disease progression. One such gene is *APOBEC3G*, which encodes a protein that inhibits viral replication. The HIV protein Vif suppresses APOBEC3G protein activity by inducing its degradation. The observation that a variant of *APOBEC3G* is associated with more rapid progression to AIDS supports developing inhibitors that block Vif-promoted degradation of this antiviral cellular protein. Complementary studies by Dr. David Derse, HIV Drug Resistance Program (DRP), are also investigating the role of APOBEC3G in restricting HTLV-1 infection.

**1996 – 2002** Role of MHC and KIR in determining outcome of HIV infection deciphered

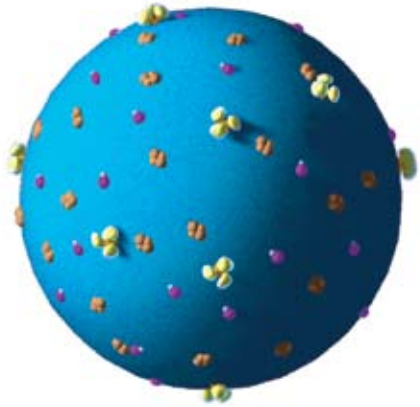
In the last decade, LGD scientists have described 18 host genetic variants (AIDS restriction genes) that influence the outcome of HIV exposure and infection, discoveries that have led to novel salvage therapy design and implementation. Researchers under the direction of Dr. Stephen O'Brien have proposed a dense single nucleotide polymorphism scan across the entire human genome to search for all gene variants that regulate a person's response to HIV/AIDS. The goal of this approach is to identify regulatory host genetic factors required for HIV infection and AIDS progression that can serve as new targets for therapeutic development and even genetic factoring in clinical trials of AIDS vaccines and drugs.



Microarray analysis can be used to group genes that are expressed at normal levels (green) or overexpressed (red) in individuals that are susceptible to HIV infection, AIDS, or related diseases.

# Outsmarting a Formidable Foe: Viral Diversity and Drug Resistance

A major challenge in treating HIV is the virus's ability to mutate and become resistant to therapies. The virus is also adept at living within minute reservoirs in the body at levels undetectable by standard assays. CCR scientists are addressing both of these issues with highly sensitive assays and novel animal models of disease.



Depiction of an HIV viral particle courtesy of Dr. Louis Henderson

## HIV Variation

Like all viruses, HIV can generate genetic diversity by mutation when it replicates, as well as by recombination between genetically distinct viruses. Using model cell culture systems, Drs. Vinay Pathak and Wei-Shau Hu, HIV DRP, have found that the rate of recombination depends on the balance between the production of viral DNA and the destruction of viral RNA. The odds of recombination depend on a perfect match between genetically distinct viruses in one region of the RNA genome —even one base difference between viruses can greatly reduce the likelihood that they will recombine.

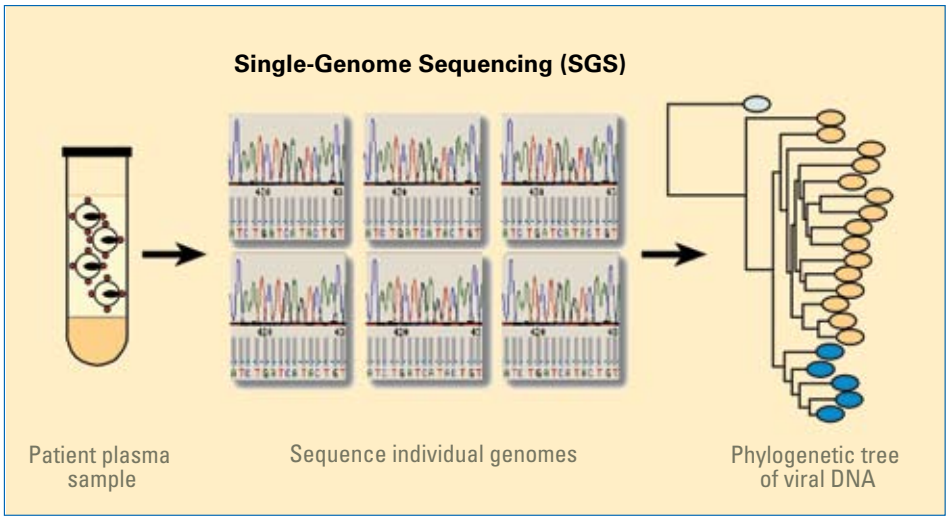
CCR scientists also have developed sensitive tools for assessing the genetic variation within HIV populations. When first infected, most patients have only a single HIV strain or clone. In contrast, studies by the group of Dr. Sarah Palmer, HIV DRP, indicate that individuals infected with HIV for long periods have a complex mixture of closely related but genetically distinct viruses (called a quasispecies), and that recombination among these viruses contributes substantially to this diversity. Through mutation and selection, this clonal virus population rapidly becomes diverse. Occasionally, an individual is infected with two or more viruses from the same quasispecies. In these cases, there is rapid recombination and mutation, leading to a much more diverse viral population. DRP researchers are investigating how this diversity affects disease course and the efficacy of antiviral therapy.

## HIV Assays

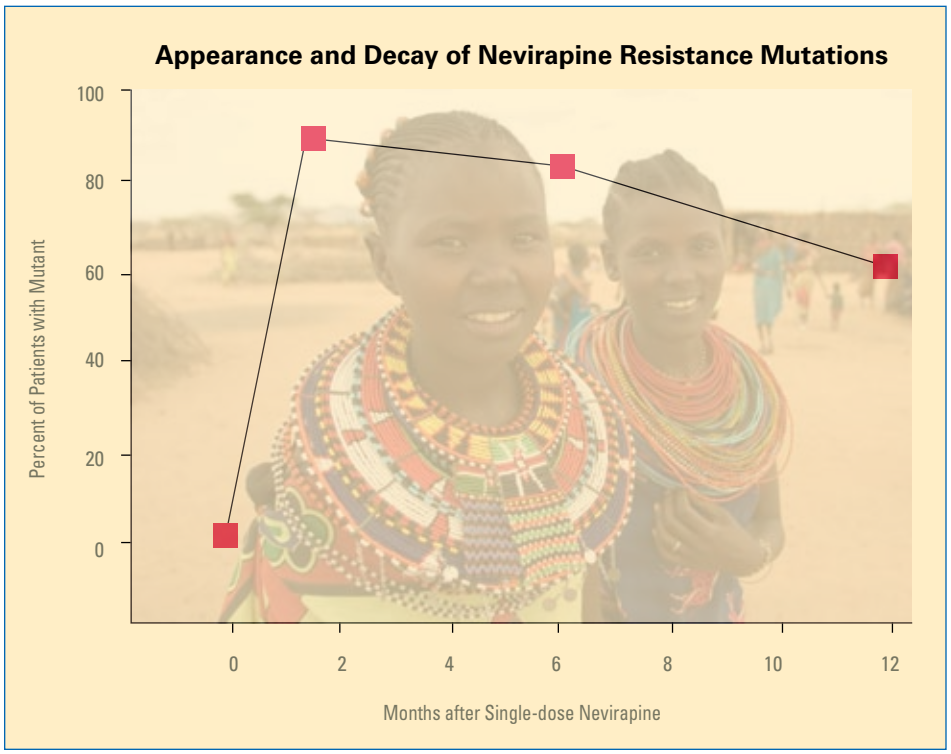
Therapy that reduces HIV to levels undetectable by standard "ultrasensitive" assays (less than 50 copies of virus RNA, or less than 25 viral particles, per milliliter of blood) can potentially prolong disease-free life indefinitely, as long as these low levels are maintained. HAART does not cure the infection. If therapy is interrupted, even after many years, residual virus replicates and viral RNA levels increase. Occasionally, therapy fails due to the appearance of resistant virus.

**2001** Mechanistic basis of AZT resistance reported

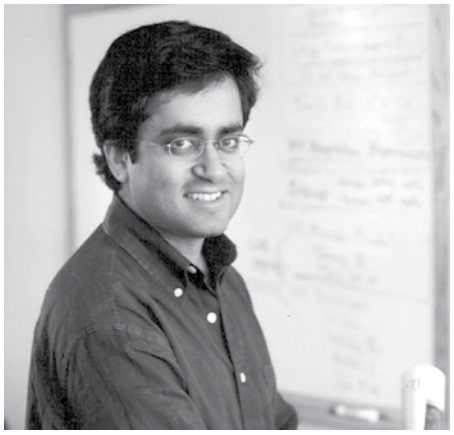
In collaboration with Dr. John Coffin of Tufts University, Dr. Palmer's group has developed an HIV assay that is 100 times more sensitive than the "ultrasensitive" assay in general use. A large study using this assay found that about 80% of patients on




Detecting HIV quasispecies through single genome sequencing. cDNA produced from plasma HIV RNA is diluted to a single copy. From 11 to 50 single genomes are sequenced per sample and phylogenetic analyses are performed. *Figure courtesy of Dr. Sarah Palmer*




long-term suppression therapy can sustain very low levels of virus (averaging around 2 viral particles per milliliter of blood) for 7 years or more. Initial experiments suggest that the detected virus is not a result of replicating virus that somehow escapes from the antiviral drugs. Rather, this reservoir comes from cells that were infected



Dr. Vineet KewalRamani

**2005** Ultrasensitive assays developed to detect patient virus and drug resistance

before the initiation of therapy and that have persisted for many years. This virus is the most likely source of the rekindled infection when therapy is halted.

## The Evolution of Resistance

Treatment of HIV-positive pregnant women with a single dose of the RT inhibitor nevirapine is quite effective at preventing viral transmission to their newborns, and has been important in preventing the spread of HIV in Africa. However, this treatment also leads to the rapid generation of resistant virus in these women. A CCR-developed assay revealed that a large majority of treated pregnant women have detectable mutations that cause this resistance. The HIV DRP's Dr. Frank Maldarelli is measuring the effect of these mutations on subsequent therapy using the same inhibitors.

**2007** Monkey model for HIV resistance evolution developed

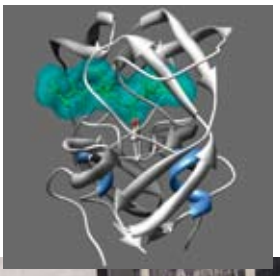
Evolution of HIV drug resistance is difficult to follow in patients with the kind of detail necessary to fully understand this important process. Carefully designed studies in experimental animals are necessary, but the model virus, simian immunodeficiency virus (SIV), is not sensitive to many commonly used anti-HIV drugs such as the RT inhibitor efavirenz. For this reason, the group of CCR investigator Dr. Vineet KewalRamani, HIV DRP, has developed an HIV-SIV hybrid virus that causes disease in monkeys and is fully sensitive to efavirenz and other RT inhibitors. Studies of virus replication in infected monkeys treated with such drugs and using the highly sensitive assays developed in the DRP are beginning to reveal important details of the way in which resistance mutations can arise and spread through a viral quasispecies. These studies will help in the design of therapeutic and preventive approaches to HIV infection with a lower chance of failure from the appearance of drug-resistant virus.

# Better Ways to Find Better Drugs

Since initial testing of AZT, ddI, and ddC, NCI researchers continue to search for new anti-HIV drugs. Multi-disciplinary collaborations are exploring the structures of viral proteins, the interaction of these proteins with antiviral drugs, and, finally, testing natural products that exhibit strong inhibition of HIV.

## Structural Biology

Detailed structures of HIV proteins are important for understanding their function in virus replication as well as their interaction with antiviral drugs. Knowledge gained through this process is also critical to the development of improved therapeutics and understanding the mechanisms by which HIV acquires resistance. CCR scientists Dr. Alexander Wlodawer, Macromolecular Crystallography Laboratory (MCL), and Dr. Stephen Hughes, HIV DRP, have played a key role in elucidating the structures of the enzymes PR, RT, and integrase (IN), that are essential for HIV replication.

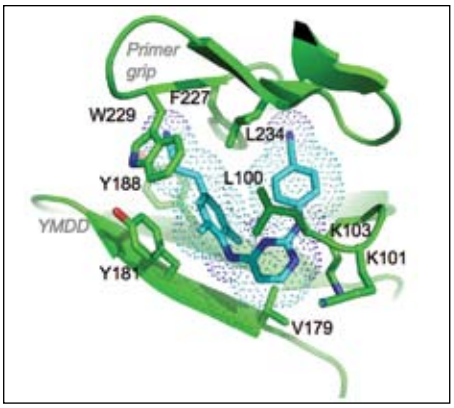


Structure of PR with the inhibitor ritonavir in cyan (right) from Dr. Alexander Wlodawer (below)

In 1989, the Wlodawer group reported the first structure of HIV-1 PR bound to a substrate-based inhibitor and since then has provided important information on drug-resistant variants of this enzyme. At the same time, his group has studied the related enzymes of Rous sarcoma, feline immunodeficiency, and human T-cell leukemia viruses. The MCL also established and maintains the HIV Protease Database which is available online to researchers, educators, and students.

**1989** Structure of an inhibitor bound to HIV-1 protease solved

Subsequently Dr. Hughes' group, together with Dr. Edward Arnold, Rutgers University, published in 1993 the first high-resolution structure of HIV-1 RT containing double-stranded DNA. This long-standing collaboration has made important contributions to our understanding of the structural and biochemical basis for the action of, and resistance to, RT inhibitors. For example, they showed that mutations conferring resistance to AZT create a binding site for the energy molecule ATP on HIV RT. Bound ATP mediates a reaction promoting DNA synthesis in reverse. This leads to removal of the drug from the growing DNA chain which allows viral DNA synthesis (and viral replication) to continue.



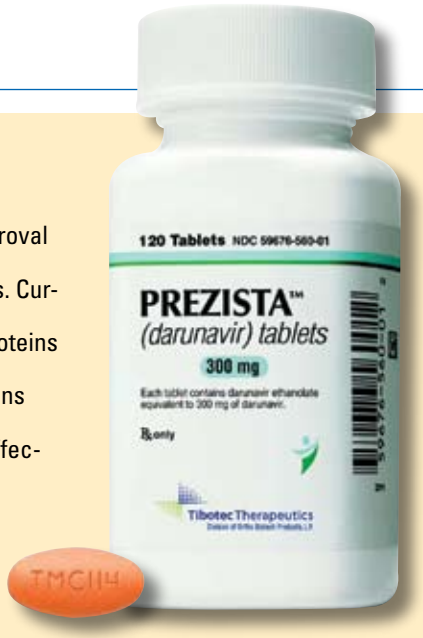

Structure of HIV-1 RT (green) bound to the inhibitor TMC278-rilpivirine (blue). *Figure courtesy of Drs. Kalyan Das and Edward Arnold, Rutgers University*

Several drugs interrupt reverse transcription by mimicking nucleotides and inserting themselves into viral DNA, rendering it useless. However, the ribonuclease H (RNase H) activity of reverse transcriptase—which removes viral RNA from RNA-DNA duplexes—is also essential for viral DNA synthesis, but has received little attention as an antiviral target. CCR scientists Drs. Stuart Le Grice, HIV DRP, and John Beutler, Barry O'Keefe, and Kirk Gustafson, Molecular Targets Development Program (MTDP), have identified several classes of RNase H inhibitors. In collaboration with extramural scientists in the United Kingdom and the United States, co-crystals of HIV RT with two inhibitors have been obtained, providing an important platform for lead optimization.

The CCR Laboratories of Molecular Pharmacology (LMP) and Medicinal

**1993** Structure of HIV-1 reverse transcriptase bound to double-stranded DNA solved

Darunavir (Prezista®), a novel PR inhibitor developed by Dr. Hiroaki Mitsuya, HAMB, and Purdue University scientists, was granted accelerated FDA approval in 2006 for treatment of AIDS patients failing to respond to existing therapies. Current PR inhibitors bind at the active site and prevent release of structural proteins from larger precursors, resulting in non-infectious virions. However, mutations can easily change the structure of the active site, rendering such drugs ineffective. Darunavir's advantage is that it binds tightly to portions of PR that change little, even with viral mutations that render PR insensitive to other inhibitors.



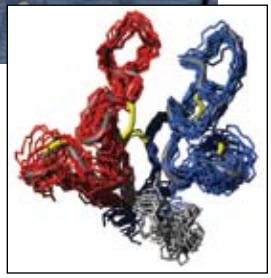

**1997** Cyanovirin-N identified as HIV-1 entry inhibitor

Chemistry (LMC) have been instrumental in drug discovery and structural biology. The LMP-LMC collaboration is among the world's most productive for the discovery of inhibitors of the HIV IN. Most current drug regimens block either RT or PR. Dr. Yves Pommier's group (LMP) was among the first to evaluate IN inhibitors, providing mechanistic clues for developing drugs presently undergoing clinical trials. Dr. Pommier's group also has contributed novel biochemical assays to probe IN-DNA-drug interactions. Lastly, the first crystal structures for the catalytic core domain of IN containing divalent metal were reported by the Wlodawer group, while an MCL-LMP collaboration provided the first high-resolution structure of an IN inhibitor bound to the enzyme.

## Taking Advantage of Nature's Products

MTDP and Natural Products Branch researchers have isolated several anti-HIV agents from natural product extracts. Working with industrial and academic partners, potent analogs have been developed and tested in animal models, and some have moved into clinical studies.

Cyanovirin and scytovirin, isolated from the blue-green algae *Nostoc ellisosporum* and *Scytonema varium*, respectively, act against a broad spectrum of laboratory and clinical HIV strains. Both block replication by binding to specific carbohydrate groups on the viral envelope glycoprotein. In collaboration among IRP groups, the structures of both inhibitors have been obtained using nuclear magnetic resonance imaging and x-ray diffraction. Collaborative studies have also shown that cyanovirin controls replication in a macaque-based anti-SIV topical microbicide model system. Griffithsin, derived from a red algae, *Griffithsia sp.*, is extremely potent against both HIV-1 and HIV-2. Griffithsin functions similar to cyanovirin and scytovirin, but has a greater number of carbohydrate binding sites, which may explain its enhanced potency.

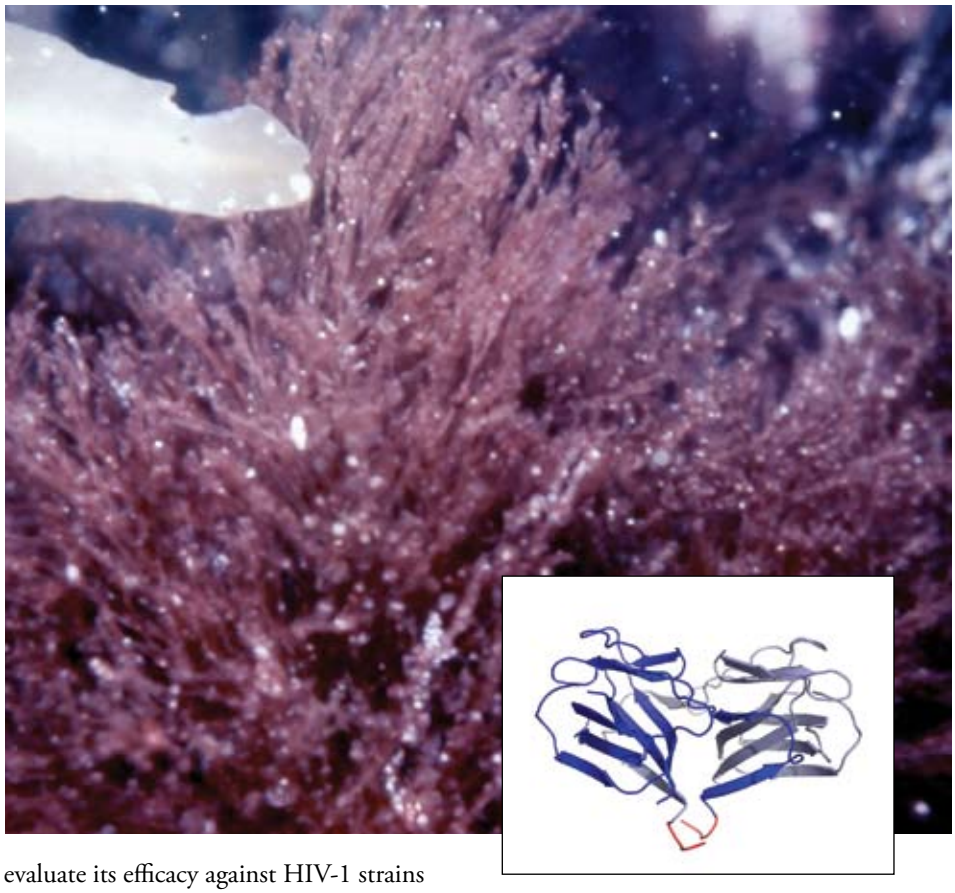


NMR Structure of Scytovirin *(right)* from Dr. R. Andrew Byrd *(above)*

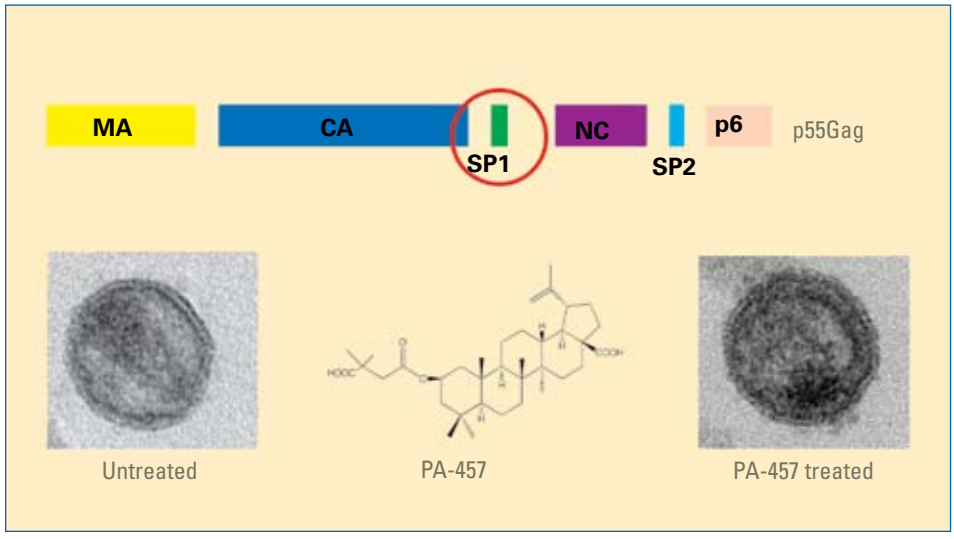
Dr. Eric Freed

A constant challenge to HIV therapy is developing therapeutics that are effective against drug-resistant virus. Following a collaborative venture between HIV DRP researcher Dr. Eric Freed and Panacos Pharmaceuticals, Gaithersburg, MD., clinical trials are underway for bevirimat, a derivative of betulinic acid originally extracted from a Taiwanese herb. Bevirimat induces changes in HIV by interfering with proteolytic processing of the gag precursor polypeptide into structural proteins, leading to defective virus particles. Bevirimat is also effective against drug-resistant HIV-1 strains. Results from clinical studies suggest that resistance to bevirimat does not emerge as rapidly as resistance to other antivirals. Dr. Freed's group plans to define bevirimat resistance more precisely and to evaluate its efficacy against HIV-1 strains resistant to PR inhibitors. If further clinical testing is encouraging, an application for FDA approval is scheduled for 2008.

**2006** FDA approves the HIV protease inhibitor Darunavir (Prezista)



*Griffithsia sp.*, the red algae from which griffithsin was isolated. *Photograph and structure courtesy of Dr. David Newman and Dr. Alexander Wlodawer, respectively*




Bevirimat blocks the cleavage of SP1 from the c-terminus of CA, disrupting virus maturation. *Figure courtesy of Dr. Catharine Adamson*

# Looking Ahead: Vaccines to Prevent Infection

Vaccines are undoubtedly the most effective method for controlling viral infections and epidemics. However, HIV presents unique challenges. The virus integrates into the DNA of an infected host cell, ensuring that infection persists for the life of that cell. This property of integration also allows the virus to exist in a latent state, hidden from the immune system, thus favoring its persistence. In addition, just as the virus mutates to become resistant to drugs, the continuous selection of variants in the face of immune responses leads to enormous diversity in HIV strains, both worldwide and even within a given infected individual over time.

To achieve meaningful protection, a vaccine must therefore elicit broad, cross-reactive immune responses capable of protecting against multiple variants. A further challenge is the fact that the HIV envelope glycoprotein is extensively masked with sugars and shows extensive variation; epitopes that are targets of broadly neutralizing antibodies are sequestered and not easily recognized by the immune system. With these issues in mind, NCI researchers are exploring several vaccine strategies designed to elicit the required cellular (T cells) and humoral (antibody) immunity prior to infection.

## DNA Vaccines

Drs. George Pavlakis and Barbara Felber, Vaccine Branch (VB), are working to enhance cellular immune responses by developing DNA vaccines with genes designed for high-level production of HIV proteins, combined with DNA for cytokines as molecular adjuvants, to induce strong antiviral immune responses. Dr. Jay Berzofsky, VB, has shown that long-lived, high-avidity cytotoxic T lymphocytes (CTLs) can control HIV viremia, and that development of such CTLs can be enhanced by IL-15. Together these researchers are exploring a vaccine strategy in which DNAs encoding both IL-15 and HIV genes are co-administered, eliciting the potent cellular immunity needed to maintain low viral burdens. Synthetic HIV protein fragments (peptides) are also being used together with IL-15 and other molecules, which regulate immune responses in order to increase vaccine potency.

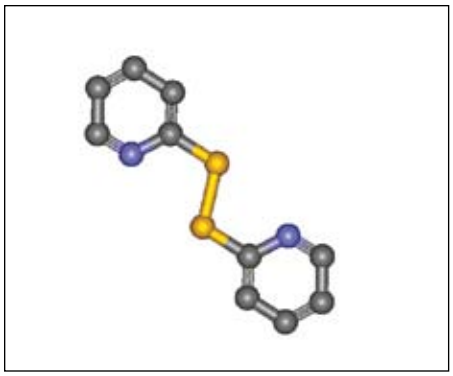
**1993** NC protein targeted for chemical inactivation of HIV-1 as vaccine candidate

Dr. George Pavlakis

Vaccines offer the hope of an effective means to control HIV infection.

## Neutralizing Antibodies

Dr. Dimiter Dimitrov, CCR Nanobiology Program has identified several unique cross-reactive antibodies against HIV-1 and other viruses including SARS CoV, Hendra, and Nipah viruses, and used molecular engineering to optimize these



Structure of aldrithiol-2, a chemical treatment which covalently modifies internal, but not surface, HIV proteins. *Figure courtesy of Dr. Michal Legiewicz*

antibodies. A comparative analysis of the sequences of these antibodies suggested a novel challenge in the development of an efficacious HIV vaccine—lack or limited availability of B cells with appropriate receptors. Dr. Dimitrov's group has also developed one of the most potent and broadly cross-reactive antibodies against the HIV-1 envelope glycoprotein. Commercial development of this antibody is underway.

## Novel Whole Inactivated Vaccines

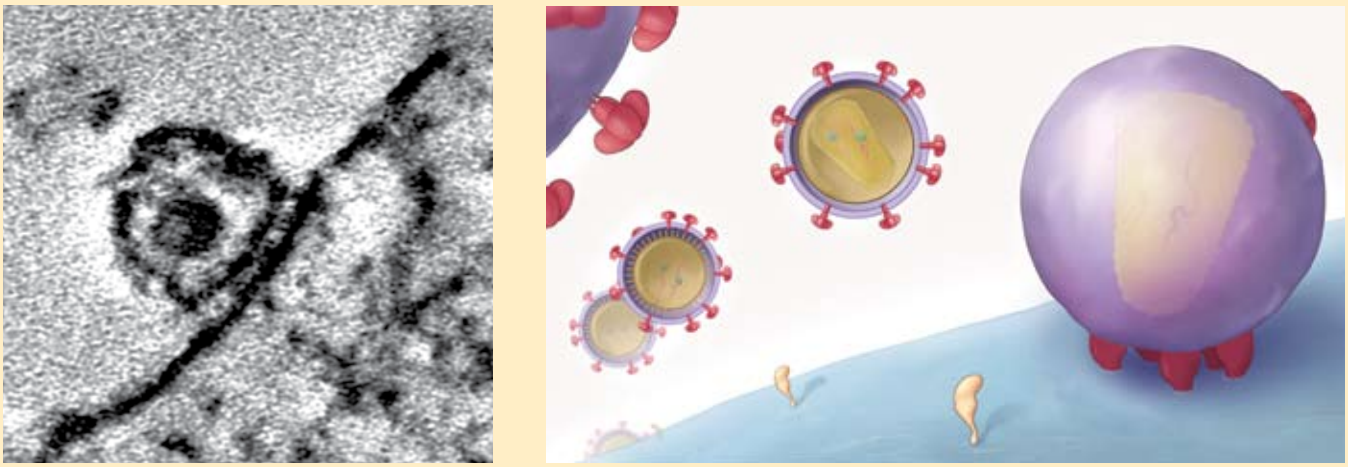
Dr. Jeffrey Lifson and colleagues in the AVP have developed a novel procedure to render HIV-1 noninfectious. This strategy arose from basic studies by Drs. Lou Henderson, Rob Gorelick, Larry Arthur, and Elena Chertova showing that viral replication depends on highly conserved sequences in certain sections of the nucleocapsid (NC) protein encoded by the HIV gag gene. Exploiting the intrinsic chemistry of retroviruses, the group developed specific chemical treatments that preferentially covalently modify interior proteins of the virus (including NC), eliminating infectivity. In contrast to conventional methods of viral inactivation, this approach leaves the

**1997** Replication-competent adenoviral vector vaccines protect chimpanzees from HIV infection

**2002** Systemic immunization with poxvirus vaccine induces mucosal T cell responses

immunologically important viral envelope glycoproteins structurally and functionally intact. These inactivated virions are being used extensively as reagents in immunologic assays and studies of basic viral biology, while CCR scientists are exploring their potential as vaccine immunogens in non-human primate models.

Most recently, Dr. Sriram Subramaniam, of CCR's Laboratory of Cell Biology, working with Dr. Lifson, used advanced 3-D electron microscopy to examine the initial interactions between HIV and susceptible host cells, identifying a consistent structure, named the "entry claw," that appears to consist of molecules on the surface of the virus interacting with receptors on the host cell membrane. Further study



Contact of HIV-1 with T cells. Electron tomographic analysis *(left)* reveals the architecture of the virus-cell contact region which forms an "entry claw" as shown in the schematic *(right). Figure courtesy of Dr. Sriram Subramaniam*

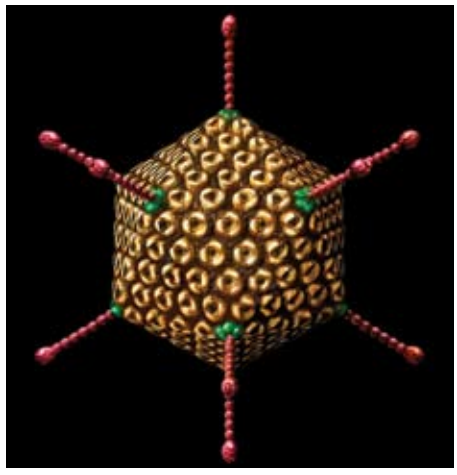
Marjorie Robert-Guroff, Ph.D. The pill she is holding is a prototype version of the adenovirus-based HIV vaccine.

of this structure should offer important clues for designing improved anti-HIV therapies aimed at blocking virus-target cell interactions.

2005 Mucosal vaccine delays virus dissemination from the mucosal site of transmission in a non-human primate model

## Live Vector Vaccines

Poxviruses have been exploited extensively as vaccine vehicles. Dr. Genoveffa Franchini, VB, has advanced this approach to prevent infection as well as for therapy. Dr. Franchini has demonstrated protective efficacy of two vaccines in non-human primates infected with SIV and HIV using naturally attenuated (or weakened) canarypox and molecularly attenuated vaccinia (cowpox) virus vectors. Immunization of SIV-infected macaques in combination with suppressive antiviral therapy followed by cessation of the drug regimens led to prolonged intervals of low virus levels.



Adenovirus Graphic *© Russell Kightley, Russell Kightley Media, Canberra, Australia*

As HIV is primarily a sexually transmitted disease, vaccines must induce potent immunity at rectal and genital sites. The Vaccine Branch's Dr. Marjorie Robert-Guroff uses adenovirus (Ad) vectors for vaccine development. These vectors infect the epithelial cells lining the airways and gastrointestinal tract, inducing mucosal and systemic immune responses. A comparative study of replicating and non-replicating adenovirus vectors in non-human primates established that replicating Ad-HIV recombinants more effectively primed antibody responses and elicited more potent and persistent cellular immunity. A combination regimen involving initial Ad-recombinant administration followed by immunization with HIV envelope protein induced broadly reactive, functional antibodies that neutralized a spectrum of HIV clade B isolates, the type found in the United States. The antibodies also mediated antibody-dependent cellular cytotoxicity, killing cells infected with the more diverse HIV strains present worldwide.

In preclinical studies, the replicating Ad-based strategy has elicited potent, durable protection against HIV isolates and virulent SIV. As a first test in humans, a phase I trial of this strategy in HIV-negative volunteers will be conducted at the NIH Clinical Center in collaboration with the National Institute of Allergy and Infectious Diseases.

# Center of Excellence: Bringing It All Together

Although this brochure captures only a limited number of seminal contributions made by former and current NCI researchers, it nonetheless highlights an uninterrupted, institutional investment in retrovirus biology for more than three decades, with particular emphasis on combating HIV infection. While we can be proud of these achievements, the sobering fact remains that the number of newly HIV-infected adults and children rose globally from ~3.9 million in 2004 to ~4.3 million in 2006, and the number of deaths from ~2.7 million to ~2.9 million over the same period. The initial successes of highly active antiretroviral therapy (HAART) are also being threatened by the rapid emergence of drug-resistant virus, placing a constant demand for the continuous development of alternative and more effective therapeutic and immunological interventions.

Recent evidence also suggests that the increased life expectancy of HIV-infected individuals on HAART may enhance their cumulative risk of developing both AIDS-defining and non-defining cancers (such as lung cancer, Hodgkin's lymphoma, and anal carcinoma). In addition to the important role of these pathogens in the global HIV/AIDS epidemic, approximately one in every five human cancers is caused by infectious agents, with an estimate of 1.9 million cases per year worldwide. Of these, approximately 70% are caused by viruses such as human papilloma virus, type B and C hepatitis viruses, Epstein-Barr virus, and human T-cell leukemia virus.

As part of an NCI response to these formidable problems, the Center for Cancer Research has established the Center of Excellence in HIV/AIDS and Cancer Virology (CEHCV). As one of several new Centers, the CEHCV will coordinate existing structures and areas of expertise across the NCI-Frederick and Bethesda campuses as a means of rapidly communicating advances in the discovery, development, and delivery of antiviral and immunologic approaches for prevention and treatment of HIV infection, AIDS-related malignancies, and cancer-associated viral diseases. The CEHCV will also be challenged to lead new initiatives, projects, and collaborations, thereby positioning the IRP to play a significant role in interdisciplinary and multi-disciplinary translational research.

A strong research program within the NCI should also seek to nurture partnerships and take advantage of complementary expertise of researchers across the NIH and within the extramural community. The CEHCV endorses NCI's longstanding commitment to making reagents and resources available, both nationally and internationally, as a means of diversifying the strategies that can be applied to these devastating diseases and of facilitating further efforts in this area.

Dr. Stuart Le Grice

Finally, continuing the outstanding quality of basic and clinical research within the NCI requires a commitment to mentoring junior colleagues at all levels. In my opinion, the strongest testament to our personal accomplishments as scientists is how well we have prepared the next generation for the challenges ahead. In the current, highly competitive funding environment, our involvement and support will be crucial to their success. Participation of CEHCV members in events planned for the coming years will be essential to such endeavors, and I am confident that we can rise to these challenges.

Stuart F. J. Le Grice, Ph.D.
*Head, Center of Excellence in HIV/AIDS and Cancer Virology*
*National Cancer Institute*
*National Institutes of Health*

***Center of Excellence in***
**HIV/AIDS and Cancer Virology**


## Training Opportunities within the Center of Excellence in HIV/AIDS and Cancer Virology

The CEHCV is committed to supporting and training the next generation of HIV/AIDS and cancer virology researchers, helping launch careers in science, and enabling established investigators to pursue investigator-initiated research. The CEHCV works to create a high-quality research environment for scientists and clinicians. Training young investigators to address complex scientific questions through collaboration and multi-disciplinary approaches is a major goal of the CEHCV. Trainees at the CEHCV have the unique opportunity to learn from experts with world-class reputations in basic virology, biochemistry, structural biology, genetics, drug discovery and development, antiviral resistance, vaccine development, and epidemiology in one of the world's leading scientific institutions. Current openings for postdoctoral fellows, staff scientists and research fellows in any CEHCV laboratory in the CCR can be found online at *http://ccr.cancer.gov/careers/positions.asp* while other opportunities within the NCI can be found at *http://www.cancer.gov/researchandfunding/intramural.*

### Organizational Investments of the NCI

1987 Established AIDS Vaccine Program at Frederick Cancer Research and Development Center

1993 HIV/AIDS Cancer Match established

1995 Established AIDS Malignancy Consortium to develop approach for the management of cancers in HIV-positive individuals

1995 Linked AIDS data and Cancer Registries

1995 Established AIDS Cancer Specimen Resource to distribute tissues from AIDS patients for basic, translational, and epidemiological research

1996 Established intramural HIV and AIDS Malignancy Branch

1997 Established the HIV Drug Resistance Program at NCI-Frederick

2005 Established Office of AIDS Malignancy Program at the NCI

2007 Established Center of Excellence in HIV/AIDS and Cancer Virology

## The Center of Excellence in HIV/AIDS and Cancer Virology

The CEHCV is composed of members from across the NCI's different branches, laboratories, and programs. Current research is being conducted in the areas of AIDS malignancies, HIV virology and molecular pathogenesis, immunology/immunopathology, vaccines and immunotherapy, epidemiology, drug development/resistance, and cancer virology.

## Our Mission

The mission of the Center of Excellence in HIV/AIDS and Cancer Virology (CEHCV) is to facilitate and rapidly communicate advances in the discovery, development, and delivery of antiviral and immunologic approaches for the prevention and treatment of HIV infection, AIDS-related malignancies, and cancer-associated viral diseases.

For more information on the CEHCV, the CCR, or NCI please visit:
http://ccr.ncifcrf.gov/initiatives/CEHIV/
http://ccr.cancer.gov/
http://www.cancer.gov/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