

Discovery

The Newsletter of
the Institute of
Human Virology

FROM LABORATORY TO CLINIC



▶ **ROBERT C. GALLO, M.D.**
Director of the Institute

Message From The Director

The Institute welcomed Lt. Gov. Michael Steele as a visitor in January. As we discussed the state of the current epidemic, we acknowledged historic research and patient care advances over the past two decades.

On the positive side, HIV no longer is a death sentence but a chronic disease that can be successfully managed long term – at least in the developed nations. On the other hand, many patients - even under the best of care - are encountering a resistance to the very drugs that have become life savers. In the developing world, the picture is more dismal.

At the IHV, we are encouraged by the fact that tremendous strides are being made in vaccine development, improved

treatment options and greater global commitment.

The Institute is one of the first recipients of funding support from President Bush's historic Emergency Plan for AIDS Relief and under Dr. Robert Redfield's leadership, our teams will provide care, treatment and counseling to people living with AIDS in Africa, Latin America and the Caribbean. You can read more about this project below.

The IHV last year also launched a national pilot program called the JACQUES Initiative. HIV patients



Dr. Gallo speaks at a press briefing in Annapolis, shown with Claude Allen, Deputy Secretary of Health and Human Services (l) and Maryland Lt. Gov. Michael Steele.

have a difficult task of taking multiple drugs daily and their long-term success depends on strict compliance. By providing patients with direct observation, one-on-one support and instruction, we hope to help them achieve long-term treatment success – several decades of
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IHV awarded historic HRSA grant as part of Emergency Plan for AIDS Relief

The Institute of Human Virology has been awarded an historic grant by the Health Resources and Services Administration to expand the delivery of Anti-Retroviral Therapy (ART) to HIV-

infected persons in Africa, the Caribbean and Latin America as part of the President's Emergency Plan for AIDS Relief.

An estimated \$64 million will be administered to the IHV to provide care, treatment and counseling to people living with AIDS in Africa and other developing countries. This award

represents the largest health care services grant in the history of the University of Maryland School of Medicine and the University of Maryland, Baltimore.

The award is part of a \$335 million five-year grant to five members of a faith-based consortium led by Catholic Relief Services. The consortium also includes the Catholic Medical Mission
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▶ **ROBERT REDFIELD, M.D.,**
*Director of IHV
Clinical Care and
Research Division on
site in Malawi*

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IHV awarded historic HRSA grant, *continued from page 1*

Board, the Futures Group and Interchurch Medical Assistance. The approved budget for year one totals \$24.7 million.

The HRSA grant will enable the consortium, which already has extensive international experience and expertise in the delivery of HIV care, prevention and support efforts, to nearly double the delivery of anti-HIV drugs to HIV-infected persons in parts of Africa, the Caribbean and Latin America. In addition to providing Anti-Retroviral Therapy, the consortium will provide a wide range of support services to people living with HIV/AIDS. These services cover a wide range of prevention and treatment activities, counseling, income generation projects for persons living with HIV/AIDS and care for AIDS orphans.

While the main objective of the consortium is to ensure that people living with HIV/AIDS have access to treatment for HIV and high quality medical care, the program will go far beyond drug procurement and treatment.

"The consortium will expand, on a sustainable basis, the provision of durable therapy to the greatest number of patients in need," says Robert Redfield, MD, professor of medicine, microbiology and immunology at the University of Maryland School of Medi-

cine and director of the IHV's Clinical Care and Research Division. "The program will be based on leading edge medical science, national protocols and programs, and cost-effective deployment of program resources."

One third to one half of healthcare delivery in the developing world is done by faith-based organizations.

"I am especially pleased that Dr. Redfield and School of Medical faculty will provide this necessary care where it is needed most," says Dean Donald E. Wilson. "I hope this is only the beginning of a long and productive relationship with Catholic Relief Services and other faith-based organizations that make up the consortium."

Each of the consortium members currently support quality, effective, and holistic care in the treatment of multiple complex illnesses. Together, they possess the resources to effectively scale up already successful anti-retroviral interventions in response to the global AIDS epidemic.

"What is unique about this partnership," says Ken Hackett, president of CRS, "is that it maximizes the Catholic and mainline Protestant health delivery systems, and the medical and

scientific expertise of the University of Maryland."

This grant is the result of an unprecedented \$15 billion commitment by President Bush and the U.S. Congress to treat 2 million persons with HIV/AIDS, prevent 7 million new infections and provide care and support for 10 million people living with HIV/AIDS, including orphans.

Under this initiative, the consortium's five-year grant will aid 14,900 HIV/AIDS patients in the first year and will increase to 137,600 patients by year five. Nine countries, including South Africa, Nigeria, Kenya, Rwanda, Uganda, Tanzania, Haiti and Guyana, are the proposed recipient countries of ART therapy. They are part of the 14 countries listed in President Bush's Emergency Plan for AIDS Relief.



KEN HACKETT
CRS President

Message from the director, *continued from page 1*

quality health. Even we were surprised by the patient response. Hundreds signed up within weeks, opting to come into the Institute daily in order to better manage their treatment plan.

What we've seen firsthand is a commitment from patients hungry for knowledge – and help. The IHV, in response, is expanding staff to accommodate the needs of this program.

In Baltimore, we have infection rates that rival those of sub-Saharan Africa. If your community is like ours, there remains as much work in the arenas of public awareness and AIDS prevention programs as scientific research and clinical care.

Judging from the reception we've received from our patients here and in Africa, we know they are definitely receptive to the message. We must not let them – or future generations – down. HIV prevention will always be the greatest weapon we have against AIDS. And it will remain so until we discover a cure or develop a vaccine.

I am proud of the work of my colleagues within the Institute and am honored to be on a world-class team that includes all of my colleagues all around the world. I want to thank Lt. Gov. Steele for his focus on the epidemic and the importance of education.

In developing countries, one third to one half of all health care is delivered through faith-based organizations. Here at home, it's just as important to have individuals in direct contact with the public engaged in delivering the important message of prevention.

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A Viral Conspiracy?

Increased Kaposi's Sarcoma Frequency in HIV-1 Infection

HIV-positive patients have an unusually high frequency of Kaposi's sarcoma (KS), a previously rare skin tumor comprised of inflammatory cells (lymphocytes and monocytes) and blood vessel cells (endothelial cells). KS has been directly linked to infection with another virus, human herpesvirus 8 (HHV-8). While an HHV-8 infection does not ensure KS will occur, being HIV-positive gives you up to a 100,000-fold increased risk of developing KS.

Marvin Reitz, Professor in the Basic Science Division of the IHV, became interested in the unusual connection between HIV-1 and HHV-8, especially since simple HIV immunosuppression didn't seem to completely account for it. He began by asking how HHV-8 might cause KS.

Prior research indicated that certain HHV-8 gene product(s) might be secreted by infected cells and influence local, uninfected cells to become tumor-like. One viral protein, encoded by the ORF74 gene, closely resembles a cellular protein (CXCR2) that functions as a receptor for various chemokines (CKs), molecules that modulate immune function. Called vGPCR (viral G protein-coupled receptor), the receptor translates external cell signals, triggered by CK binding, into cascades of intracellular events that ultimately induce synthesis of cellular proteins involved in inflammation, attraction of various immune cells, and blood vessel growth.

Reitz and colleagues created an animal model for KS by producing mice that contained the HHV-8 ORF74 gene throughout their tissues (transgenic mice). A proportion of mice developed KS-like tumors, while vGPCR expression was detected in a minority of tumor and non-tumor cells. When the tumor cells were cultured, most expressed vGPCR and also created very aggressive, KS-like tumors when re-introduced into an immunorepressed strain of mice. "These data strongly suggest that vGPCR plays a major role in KS pathology," says Reitz, "perhaps by

cytokine dysregulation, and has high potential for tumorigenicity (inducing tumors)."

Reitz next investigated vGPCR's potential "collaborative role with HIV-1 in intracellular signaling, [a process] required for tumor development." From previous work in Dr. Gallo's lab, Tat, a HIV-1 protein, was already known to enhance KS cell growth and division and to stimulate expression of specific cellular proteins. Reitz and colleagues wondered whether proteins from both viruses might act in concert to enhance development of KS.

Using either immune cells or blood vessel cells, they first tested whether vGPCR could activate two proteins, NF-AT and NK- β , both known to regulate expression of genes involved with inflammatory responses and blood vessel development. It could. Then, they tested the effect of Tat plus vGPCR, and saw greatly enhanced activation, beyond an additive effect.

Tat had been reported to function directly as a KS growth factor; these results showed it could also work cooperatively with vGPCR. "These results provide the first evidence of collaboration between an HIV-1 protein and an HHV-8 protein," says Reitz, "and support the contribution of vGPCR to KS pathogenesis."

Reitz envisions treatment of KS "using 'small molecules' that block the receptor and stop intracellular signaling." His future efforts will focus on delineating the signal pathways critical for KS tumor formation, and determining if, and how, they function in actual KS tumors. "Blocking signaling by vGPCR," says Reitz, "may be a way to alter the course of this disease."



MARVIN REITZ
Professor, IHV Basic Science Division



Monkeys Hold Key to Natural HIV-1 Immunity and Novel Immune Function

◀ **JOSEPH SODROSKI**

Professor of Pathology at Dana-Farber Cancer Institute and Harvard Medical School

A Holy Grail long sought by HIV/AIDS researchers are the mechanisms of naturally occurring immunity to HIV-1 infection. Why do some people get infected and not others? Why do some infections progress relatively rapidly toward AIDS while others progress very slowly? Some answers to this question are already known, but another may have just been discovered, quite surprisingly, from studies of monkeys.

Recently, scientists in the laboratory of Joseph Sodroski, Professor of Pathology at Dana-Farber Cancer Institute and Harvard Medical School, showed that a single monkey protein, TRIM5alpha, can prevent HIV from establishing an infection within monkey cells. While humans were also found to possess TRIM5alpha, it is much less efficient at combating HIV. The implications for basic HIV research as well as treatment and prevention strategies are huge.

“We know for years that HIV couldn’t infect monkeys. That’s been the whole problem with creating a viable primate model for HIV,” says Sodroski. While monkeys are susceptible to infection by SIV (the Simian Immunodeficiency Virus), translating study results from monkeys to humans has been very difficult. “Now,” says Sodroski, “we have cells that actively make a novel HIV

resistance factor that provides a major block to HIV replication. We can better understand the pathogenesis (disease progression) of HIV and how to model treatment.”

Essentially, TRIM5alpha blocks a very early stage of HIV infection. The components of HIV that allow it to replicate within a cell are encapsulated by an inner protein coat, or capsid, which must be shed within the infected cell before HIV can copy itself. “While HIV can still get through the front door (i.e., enter the cell),” Sodroski explains, “TRIM5alpha prevents it from taking off its coat.”

Although evidence already shows that TRIM5alpha binds to the viral capsid, Sodroski intends to learn exactly how this protein accomplishes its task. “Up to now, even the mechanism of viral uncoating was a mystery,” he says. Somehow, TRIM5alpha may help “target the capsid for destruction,” Sodroski hypothesizes.

So what promise may TRIM5alpha offer for HIV treatment and/or preven-

tion? “We now have the ability to study individual human variation in HIV infectivity and TRIM5alpha function,” Sodroski says. “Once we understand this, we may be able to enhance TRIM5alpha function, either via small drug therapies or increased protein expression.” It is also possible that manipulating TRIM5alpha could lead to a vaccine that prevents HIV transmission, but Sodroski feels this would be much further in the future.

An additional boon offered by this discovery may well prove much broader in scope. Sodroski and colleagues showed that TRIM5alpha is located in cellular compartments called cytoplasmic bodies, of previously unknown function, and that TRIM5alpha is a member of a larger family of TRIM proteins. “TRIM5alpha may exemplify a new, intracellular arm of the immune system,” Sodroski remarks, “one where TRIM proteins ‘scout around’ for infectious agents within the cell. We’ll be working towards answers to these questions for years to come.”

World Famous Immunologist Visits

Nobel Prize winner Dr. Rolf Zinkernagel met with researchers at the IHV on April 12 and gave a formal lecture at the University of Maryland School of Medicine.

Zinkernagel, along with Dr. Peter Doherty, was awarded the Nobel Prize in 1996 for the discovery of how the immune system recognizes virus-infected cells.

They studied the responses of different strains of mice to viruses and found that white blood cells from one mouse strain can only detect and kill the virus infected cells of another mouse strain if the two mouse strains carried the same transplantation antigens.

This principle of simultaneous recognition of both self and foreign molecules

has since constituted a foundation for the further understanding of the specificity of the cellular immune system. From the seemingly simple observation Doherty and Zinkernagel, and subsequently a whole generation of immunologists, were able to find new solutions to a series of fundamental immunological problems.

Dr. Zinkernagel’s current research interests include vaccine efficacy, the nature of T cell memory, auto-immunity, and the development of cell-mediated immunity, all of which are primary research interests at the IHV and UMSOM. Zinkernagel’s lecture was sponsored by the Department of Microbiology and Immunology and co-sponsored by the Institute.

Spotlight: Nancy Kopp, IHV Advisory Board Member

From her vantage point of more than a quarter century of public service, State Treasurer Nancy Kopp brings considerable insight not only to the people and legislature of Maryland but to the IHV as well.

Treasurer since February 2002, Kopp served previously as a Delegate to the Maryland General Assembly for 27 years. Her role as chair of the House Appropriations Sub-Committee on Education and Economic Development, in particular, resulted in her intimate involvement with educational, financial, and fiscal issues, and bolstered her commitment to each. "My role as Treasurer is to ensure that Maryland maintains its outstanding reputation as, to quote the late Delegate Pete Rawlings, 'a socially responsible and fiscally prudent state'," she declares.

Similarly, Kopp is dedicated to promoting the continuing success of the IHV. A long-term champion of the University of Maryland, Kopp was

instrumental in encouraging the concept of the IHV among her legislative peers, and raising their awareness of the benefits it would afford to Maryland at large and to the communities it could serve. "I viewed this as a unique opportunity for Maryland to be the site of an outstanding, multidisciplinary center, focused on the worst epidemic in human history [HIV/AIDS]," Kopp states emphatically.

Watching the evolution of the IHV, Kopp felt and continues to feel that her greatest role as a Board member is to "ensure continued viability. I believe that education is the engine of social and economic development," Kopp says. "Being on the IHV Board, and involved with the Legislature, allows me to strengthen academic and applied research for the benefit of the State, and I find that immensely rewarding."

While still seeing room for the IHV to grow through enhanced technology transfer (changing an idea or product from research into an application), Kopp



NANCY KOPP
IHV
Advisory
Board
Member

delights in its "already outstanding progress, in such a short amount of time." She hopes to help the IHV grow even stronger and to continue telling the tale of its accomplishments.

Kopp feels the IHV has tremendous potential to answer significant questions in both basic science and health care. "I'd like to feel that my years spent educating my fellow politicians and the citizens of Maryland about the IHV will have made a significant difference," she says.

Gallo Inducted into Inventors Hall of Fame

Dr. Robert C. Gallo, a founder and director of the IHV, was inducted into the National Inventors Hall of Fame on May 1. Also honored was Prof. Luc Montagnier, former director of the Centre National de la Recherche Scientifique and co-founder of the World Foundation for AIDS Research and Prevention in Paris.

Gallo and Luc Montagnier in 1983-84 isolated and identified HIV, a discovery that made it possible to diagnose and better control the disease.

The not-for-profit National Inventors Hall of Fame is the premiere organization in the U.S. dedicated to honoring and fostering creativity and invention. Each year a new class of inventors is inducted into the Hall of Fame in recognition of their patented inventions that make human, social, and economic progress possible. Founded in 1973 by the U.S. Patent and Trademark Office and the National Council of Intellectual Property Law Association, the Hall's permanent home is Akron, Ohio, where the inventors in the hall are honored and from where it administers its national programs.



FARLEY CLEGHORN
Director, Center
for HIV/AIDS

Cleghorn to Direct HIV/AIDS Center

Farley Cleghorn, M.D., M.P.H., has assumed the post of Director, Center for HIV/AIDS, at the Futures Group International, a health services development and research organization based in Washington, D.C. The HIV/AIDS Center is the largest center within the organization, with more than 200 employees. The center oversees prevention, therapeutic and monitoring/evaluation programs as well as epidemic

forecasting/modeling studies in more than 35 countries worldwide.

Cleghorn, who served as deputy director of the IHV's Epidemiology & Prevention, will retain an adjunct appointment at the Institute.

IHV Awards

The Institute of Human Virology has been awarded \$1.6 million by the National Institutes of Health (Department of Health and Human Services) to study the pathogenesis of Lassa fever virus. LAS is a deadly arenavirus carried by rodents and sometimes transmitted to man with lethal consequences, most notably in West Africa.

"The sizeable disease burden and the possibility that LAS virus can be used as a biological warfare agent make a strong case for effective vaccine development," says Igor Lukashevich, the study's Principal Investigator.

The IHV also is the recipient of a \$222,000 grant awarded by the National Institute on Alcohol Abuse and Alcoholism to study whether alcohol consumption accelerates the progression of HIV infection and affects pregnancy outcomes among HIV-infected women.

"The importance of this research is highlighted by the rapidly increasing rates of HIV infection among urban minority women and the fact that AIDS is now the leading cause of death among minority women of child-bearing age. Our proposal has implications for catalyzing key improvements in prevention and treatment strategies and reducing the spread of HIV/AIDS in women and their infants," says Principal Investigator M. Charurat.

The study will examine the influence of alcohol consumption on clinical, virological and immunological markers of HIV-1 disease progression; determine the relationship between alcohol consumption and adherence to antiretroviral medications and patient outcomes; determine whether alcohol use and in-utero exposure to antiretroviral therapy are associated with adverse pregnancy outcomes; and examine the joint effects of maternal alcohol use and antiretroviral therapies on pregnancy outcomes including mother-to-child transmission of HIV.

THE INSTITUTE OF HUMAN VIROLOGY (IHV) at the University of Maryland was established to create and develop a world-class center of excellence focusing on chronic diseases and virally linked cancers. The IHV is dedicated to discovery, research, treatment, and prevention of these diseases and cancers. Its unique structure seeks to connect cohesive, multidisciplinary research and clinical programs so that new treatments are streamlined from discovery to patient. The IHV serves patients locally and the scientific community globally.

American Attitudes and Perceptions Affect Our Search for An HIV Vaccine

It is not news that racial and ethnic minority participation in HIV preventive vaccine trials has been very low compared to their participation in treatment clinical trials.

The little research that does exist shows some startling insight into the challenges we face in ensuring that HIV preventive vaccine trials are reflective of those communities in the United States most affected by the AIDS epidemic – African Americans, Latinos, and men who have sex with men (MSM).

For example, in a 2003 NIH-funded survey of Americans attitudes about vaccine research, 48% of African Americans, 28% of Latinos, 13% of men who have sex with men (MSM), and 20% of the general population believed that there was already a vaccine to prevent HIV but that it was being kept a secret. The survey also showed:

- 77% of African Americans, 55% of Latinos, and 70% of MSMs mistakenly believed or did not know whether a person could get HIV/AIDS from the vaccines being tested;
- In a sub-sample, 61% of African Americans, 60% Latinos, and 42% of MSM believe an HIV preventive vaccine will benefit both HIV positive and negative individuals;
- 62% of African Americans, 77% of Latinos, and 70% of MSM believe a vaccine is the best hope for controlling the AIDS epidemic.

Development of vaccines to prevent HIV infection requires the full support and involvement of HIV-affected communities, prevention providers and treatment advocates. The real challenge is to promote HIV prevention,

care, treatment, and research through community and/or group level approaches focusing on individuals and communities in a meaningful and culturally relevant manner.

The NIAID survey showed a need for key messages that would help clarify misinformation and misperceptions about vaccine research and lead to a more supportive environment for that research. In response, NIAID developed several key messages including:

- There is not an HIV vaccine currently available;
- HIV vaccines being tested in humans do not contain HIV; therefore they cannot cause HIV infection;
- Individuals who volunteer for an HIV preventive vaccine trial must be HIV negative;
- The best long-term hope for controlling the AIDS epidemic is the development of safe, effective, and affordable preventive HIV vaccines;
- Diverse populations must be included in clinical trials (e.g., whites, African Americans, American Indian/Alaska Native, Asian/Pacific Islander, Hispanics, men who have sex with men); and
- A comprehensive approach to vaccine research includes the partnerships of prevention and care and treatment providers.

As part of NIAID's efforts to create this supportive environment, its Division of AIDS created a national HIV Vaccine Communications Campaign. The Campaign reaches out to community-based and national organizations, AIDS service organizations, community

leaders, scientists, researchers, and others for guidance, direction and input into how to share these key messages. For the first time in 2003, the Campaign awarded sub-contracts to numerous local and national groups to incorporate these key messages into their day-to-day programs and activities. A major component of the Campaign is its annual HIV Vaccine Awareness Day, May 18th. Through bilingual print and radio ads and local events, Americans will be asked to wear their red AIDS ribbon upside down to form a "V" for vaccines and the vision for a world with AIDS. The Campaign has developed a tool kit with fact sheets, talking points, and media tools for use by organizations interested in helping to support the search for a vaccine. The tool kit can be found at: <http://www.aidsinfo.nih.gov/other/vaccineday2004.asp>

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