

Discovery



FROM LABORATORY TO CLINIC



ROBERT C. GALLO, M.D.

Director of the Institute

Message From the Director IHV Committed to Translational Research

The Wall Street Journal (Europe edition) in March ran this headline: AIDS Researchers Plan a U.S. Test of Aventis Vaccine. The article highlighted an experimental therapeutic AIDS vaccine available to patients at the Institute of Human Virology.

Many believe important scientific discoveries occur in a moment. Sometimes, that's true. Usually, though, scientific discoveries are not a moment of Eureka!, but rather an accumulation of many, many months or — more often — years of hard work gone unnoticed in quiet laboratory settings. Just as commonly, a scientific “discovery” is the culmination of a series of scientific findings that form a foundation upon which the next is built. This, then, helps form the basis for the basic science linkage to our clinical care program. These collaborative efforts are what truly define the scientific process.

This issue spotlights some of these works in progress and the importance of the Institute's working concept of Lab-to-Clinic. It's a philosophy we espouse because it capitalizes on a teamwork approach designed to cut delays and accelerate the pace of progress. You'll see, too, that it's a philosophy that goes beyond the IHV.

There are two vivid examples. The tat toxoid vaccine referenced in *The Wall Street Journal* was developed by a French pharmaceutical company after many years of scientific research both here at IHV and abroad. An inhibitor of HIV entry developed by Schering-Plough follows more than a decade of

work by researchers at IHV and elsewhere. That work would have moved forward regardless, but these partnerships made it easier — and faster — to streamline the process and speed the pace of discovery.

This approach becomes ever more critical now that HIV/AIDS has been officially recognized as the worst epidemic in medical history. To date, eradication of HIV has not been possible, for many, the currently available drugs can hold HIV at bay. Recently, however, toxicity and drug resistant HIV mutants demand new forms of therapy. Efforts are underway to develop both therapeutic and preventive vaccines — the scientific community's greatest hope in helping to put an end to this raging pandemic.

The actual statistics of those most affected by this disease, both locally and globally, continues to shift — reflective of the nature of the elusive HIV virus itself as it includes more and more demographic subgroups — and excludes none. With this reality, it's increasingly important that we work toward the same goals we've always had with finding new treatment and preventive approaches to HIV/AIDS. We are all in this together, and this increasingly shows in collaborative endeavors worldwide.

IHV OPENS TWO INNOVATIVE TRIALS

Both utilize Institute findings

The Institute of Human Virology leads the way with two promising clinical trials available to patients at fewer than a handful of sites nationwide.

One utilizes a natural compound that can block the HIV virus and halt the progression of AIDS, a Gallo ‘team’ discovery that was hailed by *Science* magazine in 1996 as one of that year's most important scientific breakthroughs.

The Schering-Plough Research Institute is the first to synthetically reproduce this compound — part of a new class of medications called chemokine antagonists — and the Institute of Human Virology is the first of three centers nationwide to offer the experimental drug to HIV patients.

The IHV also is the first — and only — institute in the United States to move forward with another therapeutic AIDS vaccine designed to target and block the biological activity of tat, a protein that is essential for the replication of the HIV virus and ultimate infection.

Both clinical trials incorporate basic science findings credited to Dr. Gallo and faculty at the IHV and also exemplify the

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Lab-to-Clinic: Accelerating Advances in Patient Care

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Institute's mission to hasten scientific progress from bench to bedside, from laboratory setting to actual patient care.

"An underlying research emphasis at IHV is to use the body's natural ability to fend off infection and heal itself and to discover and utilize biological approaches to therapy and treatment that may be less toxic – and less costly – than drugs currently on the market," explains Dr. Robert Redfield, director of the IHV's Division of Clinical Care and Research. "The Schering-Plough compound builds on these significant landmark discoveries – creating a compound that blocks key receptors – or entry points of the virus. It's a new approach designed to actually block the HIV virus from getting into cells in the first place."

IHV will recruit up to 16 volunteers to participate in a 28-day Phase I trial of the oral medication, to be taken twice daily for 10 days. Participants will be hospitalized at the University of Maryland Medical Center for 12 days and will closely monitored. The purpose of a Phase I study is to evaluate the safety, tolerability and possible antiviral effects of the experimental compound.

"Preliminary results have been very promising and it's exciting clinically," says Dr. Redfield. "This new class of med-

ication represents the first alternative treatment option AIDS scientists have seen since the introduction of protease inhibitors in 1996. The creation of chemokine antagonists represents a major milestone in potential treatment and preventive approaches."

Meanwhile, the Institute's tat toxoid clinical trial utilizes an inactivated form of the protein to induce antibodies against tat. Tat is a protein made by the HIV virus and is essential for the replication of HIV. Tat also is known to act directly on the body's killer T-cells that fight infection, causing them to become inert and leading to their inability to proliferate, thus diminishing the body's immune response against HIV.

It's also been noted that HIV patients who have gone long-term, perhaps for 20 years, without progressing to symptomatic disease often have high levels of Tat antibodies, leading scientists to believe that being able to induce Tat antibodies may result in more and more patients being long-term non-progressors who can live with the HIV virus without succumbing to AIDS.

"We've come to believe that targeting Tat may be an additional arm in the fight against HIV," says Dr. Gallo, "particularly a therapeutic vaccine approach which should be safe, simple and cost effective and potentially applicable for use in developing countries where the AIDS epidemic is at its strongest."

The Institute will be recruiting 32 participants for a five-month study evaluating the safety and efficacy of the tat toxoid vaccine, which will be delivered in a series of intramuscular injections into the shoulder.

Participants will already be on anti-retroviral therapy, which will continue simultaneously throughout the clinical trial, and must have a nondetectable viral load and CD4 cell counts greater than 300.

For more information, call 410-706-2784.

Two clinical trials utilize basic science findings of the Institute.

When HIV Knocks, No One Is Home

Every schoolchild knows that to stop strangers from entering your house, you lock the door and don't answer when they knock. SCH C—a Schering-Plough HIV therapeutic agent in clinical trial at the IHV—belongs to a novel class of antivirals called "entry inhibitors." Designed to deny HIV entrance into immune cells, thus preventing infection, SCH C evolved from basic research discoveries by scientists at the National Institutes of Health (NIH), the Institute, and elsewhere.

Existing anti-viral drugs typically interrupt the HIV life cycle after a cell is infected. But SCH C disrupts HIV fusion with certain immune cells by blocking CCR5, a secondary or "co-receptor" molecule

NIH researcher identifies co-receptor critical to current research.

used in addition to the primary HIV receptor, CD4. Without stable anchoring to CCR5, infection is aborted. CCR5, along with another HIV co-receptor, CXCR4, is actually a receptor for specific chemokines, naturally occurring immune

Tat Toxoid: A Traitor In The Midst

There is a traitor in the midst of the IHV clinical trial of the Aventis-Pasteur Tat toxoid HIV vaccine. The vaccine targets the very molecule that helped create it. Synthesized by HIV-infected immune cells, the Tat protein helps HIV replicate within the cell; yet, outside the cell, Tat suppresses immunity against HIV. Tat toxoid vaccine targets external Tat, by turning traitor on HIV.

The concept, while not novel, is elegant: inactivate a viral toxin to a form that is no longer toxic yet can still elicit strong antibody immune responses. The ingenuity of the vaccine stems from the underlying discoveries of an extracellular Tat form, and Tat's role in immunosuppression.

Novel vaccine uses an elegant approach.

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regulatory molecules. The finding that HIV co-receptors were identical to chemokine receptors is the lineage of SCH C.

In the mid-1990's, NIH's Edward Berger was investigating "why HIV preferentially entered certain human immune cells, but not corresponding mouse cells." CD4, the primary "door" for HIV entry, was already known, but something else was required, such as a co-receptor, to explain how different HIV strains infected different immune cells. Berger's group discovered the first of two such co-receptors. "We called it 'fusin'," says Berger, "because it enabled HIV to fuse with and enter cells." But what was fusin, and how did it work? Comparison of the gene for fusin with known genes suggested it might be a chemokine receptor.

Concurrently, Robert Gallo, then at NIH, and others, were investigating the roles of chemokines in HIV disease. Gallo's group discovered three chemokines capable of suppressing HIV infection of immune T cells. While

chemokines and their receptors were known to exist, their involvement with HIV infection and disease was unknown.

Berger, and others, determined that the other HIV co-receptor was CCR5, the receptor for the chemokines that Gallo's group had identified as HIV suppressors. Soon thereafter, other researchers identified a chemokine that bound to fusin, and fusin was renamed CXCR4. Sub-sequent work revealed that HIV strains present early in an infected person preferentially use CCR5, whereas viruses that use CXCR4 appear later in infection. The mystery was solved.

Blocking CCR5 subsequently became an HIV therapeutic target, primarily because people lacking functional CCR5 genes do not develop HIV, even after prolonged exposure, yet seem otherwise healthy. Blocking CCR5 seemed a relatively safe undertaking. Schering-Plough developed and tested SCH C, a small, synthetic molecule that binds to CCR5. A 28-day clinical trial of the compound, underway at the IHV, will assess safety, tolerability, and anti-viral effects in HIV-infected patients.

Entry inhibitors may hold the key to HIV prevention.



Edward A. Berger, Ph.D.
NIAID, National Institutes of Health

Tat's extracellular existence was uncovered in the early 1990's by Robert Gallo and colleagues, while working with endothelial cells (cells that comprise blood vessels) from



Daniel Zagury, M.D., Ph.D.
NEOVACS

Kaposi's sarcoma, an endothelial tumor associated with skin lesions in AIDS patients. That Tat was an immunosuppressor, to be targeted for a vaccine, was discovered in the mid-1990's by Daniel Zagury, then at the Pierre and Marie Curie Institute in Paris.

Zagury wanted to know why an HIV coat protein (env) could trigger a high immune cell response only in healthy, uninfected people, and not in HIV-positive people. "The obvious difference between the two groups was the presence of HIV itself," he says. He began searching for an HIV-produced factor that could trigger immunosuppression.

On learning about Gallo's extracellular Tat, and after study-

ing other candidates, Zagury pursued a functional role for Tat. Using native Tat to treat macrophage and dendritic cells, the first cells usually infected by HIV, he saw "a huge production of alpha-IFN (alpha-IFN)"—an immunoregulatory molecule involved in the normal process of turning off the immune system—similar to the high alpha-IFN levels found in HIV patients. Tat also paralyzed immune T cells. If he treated immune cells with antibodies against both Tat and alpha-IFN, effectively preventing Tat and alpha-IFN from working, he prevented immunosuppression. Zagury now began working on Tat toxoid vaccine.

Studying inactivated Tat in animals, he aimed for "strongly neutralizing antibodies against native Tat, and minimal toxicity, especially to the immune system." Ultimately successful, his Tat toxoid patent was licensed to Aventis-Pasteur, who developed it into the Tat toxoid vaccine being tested for safety and immune response at the Institute of Human Virology.

Zagury feels "Tat toxoid vaccine can be most effective as a therapeutic vaccine early in HIV infection," although it could conceivably be used "in combination with an alpha-IFN vaccine for late stage infection." Gallo, too, is excited to see Tat toxoid enter the clinic, expressing delight that "our early research helped form the basis for these novel vaccines."

News Briefs from the IHV

Two Notable Awards & One Gallo Day

Dr. Gallo on April 29 was the recipient of this year's Thomas P. Infusion Award, presented by the Lautenberg Research Center for General and Tumor Immunology. Dr. Gallo on May 22 received the 2002 National Education & Leadership Award, presented by the Sons of Italy Foundation (SIF) at a black-tie gala in Washington, D.C. The SIF is the philanthropic arm of the Order Sons of Italy in America, the nation's largest and longest existing organization representing men and women of Italian heritage. In recognition of this honor, Dr. Gallo's hometown of Waterbury, CT hosted a celebration on April 26 with Mayor Michael Jarjuro presenting the scientist with a key to the city and Gov. John G. Rowland also declared Friday "Dr. Robert Gallo Day in Connecticut."

International Conference Update

This year's seventh annual International Meeting of the Institute of Human Virology will be held September 9-13 at the Baltimore Waterfront Marriott. The theme: Cures for Tomorrow from Research Today. More than 600 leading scientists from around the world are expected to attend. For more information, visit www.ihv.org.

In the News

The Wall Street Journal Europe, 3/15, "AIDS Researchers Plan a U.S. Test of Aventis Vaccine"

Washington Techway, 3/4, "Designer Rats; Through Genetic Engineering, Scientists Gather Another Tool for Understanding AIDS" (available at www.washtech.com)

American Medical News, 2/25, "Directly Observed Therapy May Help Baltimore's HIV-infected Patients Follow a Complex Treatment Regimen" (available at www.ama-assn.org)

The Baltimore Afro American, 2/23, "Educate Yourself About HIV Vaccines"

AIDS Pioneers Join Forces

Dr. Robert Gallo and Dr. Luc Montagnier have joined together in a global research endeavor designed to speed the discovery of AIDS vaccines. Created under the auspices of UNESCO, the Program for International Viral Collaboration will be co-directed by the two pioneering scientists. The World Foundation for AIDS Research and Prevention will provide leadership in developing resources to sponsor and fund an international research network involving research laboratories in Baltimore, Rome, Montreal, Nigeria, Cameroon, the Ivory Coast and other sites in Africa, Central America and Asia.

Three immediate opportunities utilize concepts developed at the IHV:

- A novel oral vaccine delivery system utilizing Salmonella bacteria to more economically deliver a greater number of viral genes in order to stimulate an immune response in humans.
- A vaccine targeting tat, a molecule that the HIV virus uses to paralyze the immune system's response to the virus.
- IHV scientists also have developed a novel vaccine that generates the broadest HIV immune response seen to date, blocking infection by diverse strains of HIV in laboratory experiments.

\$300,000 Grant Aims to Study HIV in Nigerian Army

The U.S. Navy has awarded a \$300,000 grant to the Institute to study HIV in the Nigerian Army. The one-year grant aims to establish baseline data on HIV seroprevalence in the Nigerian Army and to identify specific high-risk behavior associated with the spread of HIV in the Nigerian Army - information that is critical for the design of appropriate intervention programs. Like other countries, a number of factors place the Nigerian military at high risk of contracting HIV, namely Nigeria's participation in United Nation's peacekeeping missions in countries with high HIV infection rates that further exposes them to the virus while they themselves transmit HIV to the general population. Not much is known on the epidemiology of HIV in the Nigerian military or the factors fueling the epidemic. The long-term goal is to establish an effective voluntary counseling and testing service and a prototype HIV surveillance system specifically for the Nigerian Army. This study, funded by the U.S. Navy as part of its Department of Defense program on HIV/AIDS prevention program, also will include family members of army personnel.

Ninth Patent Awarded

A patent has been awarded to David Hone, R.W. Crowley and George Lewis for non-pyrogenic derivatives of lipid A. This patent provides a novel vaccine adjuvant comprising lipopolysaccharide (LPS) antagonist. The broadest patent claims protect the commercial rights to compositions comprising purified lipopolysaccharides (LPS) from *E. coli* DhtrB1 and DmsbB mutant strains that a) Stimulate b-chemokine secretion from mononuclear cells; b) Induce reduced levels of proinflammatory cytokines including at least one cytokine selected from the group consisting of IL-1b, IL-6 and TNF; and c) Suppress replication of HIV-1 in mononuclear cells.

Education Program Targets Teens

In observance of World Vaccine Awareness Day on May 18, the Institute on Friday, May 17 hosted an educational event for local high school students emphasizing the importance of vaccine research. Students learned more about HIV/AIDS prevention efforts, toured the Institute laboratories and met with Dr. Gallo and fellow IHV scientists to learn how they can help put an end to the global AIDS epidemic.

KO8 Grant Awarded

The NIH's National Institutes of Heart, Lung and Blood has approved a three-year \$350,000 KO8 training grant to support the basic research of Nicholas Stamatou in the role of sialidase in the pathogenesis of HIV-1.

Spotlight on Timothy C. Moynahan: IHV Board Member



Tim Moynahan, owner of the Connecticut law firm Moynahan, Ruskin, Mascolo & Minella, committed to the Institute of Human Virology (IHV) Advisory Board in 2000, willingly signing on to something he considered “much bigger than myself.”

In keeping with his 37 years experience as a civil and criminal trial lawyer, he is on the Board of Governors of Connecticut trial lawyers. He also is a partner with Unisphere, a \$100 million

international science and technology company that brings technical, business, and financial expertise to the assistance of private-sector commercialization endeavors with public-sector investments, primarily in government-sponsored research and development.

Not surprisingly, for the last 10 years he has engaged in what he terms “entrepreneurial law.” “I forge alliances, find money, and create partnerships,” he says, “and that’s the facet of my experience that is most brought to bear for the IHV.”

When approached by Robert Gallo, Director of the IHV, to apply his expertise on its behalf, Moynahan thought there was no better vehicle than sitting on the IHV Board. “I can learn about the nature and potential of the research, in-depth, to better help the IHV form strategic alliances, advance its business causes, and help locate funding sources and benefactors,” he states. Moynahan sees his business focus, namely,

network building and negotiations, as the means to accomplish these goals. “I have several ‘streams of influence’ that I’m working on, hoping they will converge to an outpouring of benefits for the IHV,” he says, enthusiastically.

Moynahan is inspired by his perception of the quality and level of commitment of IHV researchers and clinicians, especially Gallo. “In the annals of our lifetime,” Moynahan says, “he is a major contributor to the quality of life.”

Accordingly, Moynahan has high expectations of those he admires and champions. “I expect them to achieve their greatness and objectives,” he emphasizes. As for himself, he hopes that when he looks back on his Board work he “can say I was part of the team, and maybe made some contribution that moved things incrementally towards accomplishing something wonderful.”

New Board Members

The Institute of Human Virology welcomes U.S. Circuit Judge Arthur J. Gajarsa and Maryland State Treasurer Nancy K. Kopp to its Board of Advisors.

Gajarsa, who currently sits on the U.S. Court of Appeals for the Federal Circuit, brings a wealth of experience in patents, trademarks and intellectual property. Kopp, a representative in the Maryland House of Delegates since 1975, is a nationally-recognized leader in education and fiscal management.

Gajarsa has a masters of economics degree, began his career as a patent examiner with the U.S. Patent and Trademark Office, served as a law clerk for Judge Joseph McGarraghy on the United States District Court for the District of Columbia and worked as an attorney in the Department of Defense specializing in defense systems analysis and intellectual property rights.

He was nominated for appointment in April 1996 by President Clinton and was confirmed by the Senate the following year. He and his wife, Melanie, have five children and reside in Potomac, Md.

Kopp holds a masters degree in government and has a 27-year legislative career where she was a senior member of the powerful House Appropriations Committee, most



Nancy K. Kopp
MD State Treasurer



Arthur J. Gajarsa
US Circuit Judge

recently chairing its Subcommittee on Education and Economic Development. Kopp, Speaker Pro-tem of the House of Delegates from 1991-93, also served as President of the Women’s Caucus of the Maryland Legislature in 1996-97.

During her service in the House, Treasurer Kopp was often called upon to chair commissions dealing with a variety of subjects, including the State Superintendent of Schools’ Task Force on Dropout Prevention, Intervention and Recovery and was Vice-Chair of the Task Force on the Reorganization and Funding of the University of Maryland. She and her husband, Robert, have two children and reside in Bethesda, MD.

Dr. Barry Bloom Visits

Barry Bloom, Professor of Immunology and Infectious Diseases, and Dean, Harvard School of Public Health, was a participant in the IHV’s Distinguished Lecture Series with a presentation entitled “Economic and Political Impact of Infectious Diseases.”

Dr. Bloom has been extensively involved with the World Health Organization for more than 30 years, is a member of the WHO Advisory Committee on Health Research and has chaired



the WHO Committees on Leprosy Research and Tuberculosis Research, and the Scientific and Technical Advisory Committee of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

Dr. Bloom currently serves on the U.S. AIDS Vaccine Research Committee, the Scientific Advisory Board of the National Center for Infectious Diseases of the Centers for Disease Control and Prevention, and the National Advisory Board of the Fogarty International Center at the National Institutes of Health.

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 viral 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.

DID YOU KNOW:

In the Institute's short, five-year history:

●IHV staff has grown from 50 to more than 200 and the IHV's total budget has increased from several million dollars in 1996 to more than \$25 million today. There has been a corresponding increase in sponsored research, from \$2 million to more than \$15 million. Trial related sponsored research has grown to \$4 million -- an indication of the confidence that major pharmaceutical and biotech companies have in the Institute.

●The Institute has been awarded nine patents — for the development and use of transgenic rats, finding small proteins that kill tumor cells, chemokines that inhibit HIV infection, bacterial delivery systems for DNA vaccines and the development of new immune “boosters” to augment vaccines.

●Research advances have included the discovery of Maternin, a naturally-occurring substance produced in pregnant women that, in animals, has been shown to inhibit tumor growth and to promote the generation of blood cells from precursors.

●The IHV has positioned itself as one of the world's premier research and development operations. Its scientists have identified new anti-HIV suppressive factors and have pioneered a novel oral vaccine delivery system that uses attenuated salmonella bacteria to more efficiently deliver a greater number of viral genes in order to stimulate a vaccine response. Basic vaccinologists also have engineered a vaccine that generates the broadest HIV-neutralizing antibody responses achieved to date. These technologies offer the potential for a single vaccine that may be effective against a broad range of HIV strains.

●The Institute of Human Virology was selected as one of nine centers worldwide to become one of the HIV Vaccine Trials Units of the NIAID/NIH sponsored HIV Vaccine Trials Network.

●Clinical investigators are actively studying use of a natural product, called Resveratrol, to improve the efficacy of current antiretroviral treatment.

●The Institute has established vaccine research infrastructure in Trinidad and Tobago and is conducting the first vaccine trial in that country. A longstanding research infrastructure in Nigeria is further being developed through a joint initiative with the Harvard School of Public Health, funded by the Bill and Melinda Gates Foundation.

●The IHV clinical research unit has conducted more than 30 intervention trials investigating new treatments for HIV, HCV and HPV infection. In addition, four Institute discoveries have already been advanced from bench-to-bed-side.

●Among the 2,500 patients currently receiving care through the IHV's Clinical Care Program, 700-800 are uninsured and underinsured, thus the Institute is serving those at greatest risk and in greatest need.

	DISCOVERY would like to thank its corporate sponsor, Aventis Pasteur, for continued support of the IHV and its mission.
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