

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

A fond farewell to Chief Operating Officer Mike Goldrich

Michael Goldrich departed at the turn of this year to take on a senior post at the Beth Israel Deaconess Medical Center where he will serve as vice president of research operations.

This is a great opportunity for Mike – and his family – and we wish them every possible success and happiness in Boston and at the Harvard-affiliated medical center. His achievements here were many and I'd like to take a moment to recognize a few.

Mike joined the Institute very early on and helped make it what it is today. We opened our doors in 1996 and he joined shortly after. From that day forward, we've enjoyed continued success and have grown healthier year by year – administratively, financially and organizationally. We see Mike as a part of the very structure – the foundation – of the Institute.

He brought in a talented staff, from secretarial to budget and finance to public affairs. This took time and, in the midst of all his headaches, he always had time for the scientists. Indeed, that was a major part of his job. Helping the scientists stay happy, yet helping them meet deadlines for grants and other funding sources. In addition to his day-to-day duties within the Institute, Mike acted as the primary liaison with the University of Maryland Biotechnology Institute, of which we are one of five

centers, as well as the University of Maryland School of Medicine and the University of Maryland Medical System. Mike's job was multi-faceted in every sense of the word and he juggled all the pieces effortlessly and courageously. He's helped us stay the course, propelled us forward and known also when to hold us back. His experience and foresight, indeed, have served us well.

I can still hear Mike's favorite phrase when counseling me or others at the IHV: "My opinion, for whatever it's worth..."

Mike, it was always worth a lot.

It is with great happiness then – and sadness – that we bid him a fond farewell as he takes on this new endeavor. We're going to miss Mike greatly and hope that he will always feel that the IHV is a second home – or, should I say, first home.

I should add that Mike, in fact, has become the newest member of our Board of Advisors and, as such, will remain a part of our extended family.

We're happy that he's accepted this advisory post, for it's hard to say goodbye. And, fortunately, we don't have to just yet. Here is to many more memories in the days and years ahead.



Drs. Tony DeVico & Tim Fouts
Institute of Human Virology

PROMISING VACCINE CANDIDATE EMERGES

IDS researchers have developed in the laboratory a candidate vaccine that, for the first time, demonstrates an ability to elicit antibodies that block the infection of multiple HIV strains — an elusive scientific goal that has been pursued for a decade.

The candidate vaccine – still in the early developmental stages at the Institute of Human Virology (IHV) – was described in a report published this August in U.S. Proceedings in the National Academy of Sciences (PNAS), authored by Drs. Timothy Fouts, Anthony DeVico and colleagues at the Institute of Human Virology and Dr. Ranajit Pal and colleagues at Advanced BioScience Laboratories, Inc. (ABL) in Kensington, MD.

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IHV Annual Meeting Highlights

Conference Draws Growing African Contingency

This year's Annual International Meeting of the IHV drew more attendees from the African nations than any other year in the conference's nearly 30-year history.

The AIDS pandemic earlier this year was noted as the deadliest disease in medical history. And though the epidemic knows no bounds, countries in the developing world are hardest hit.

Yvette Felicite Batoula, a journalist from Cameroon, sat through numerous scientific presentations outlining the latest in basic science, clinical and preventative strategies.

She has seen first-hand the destruction that follows in the wake of an HIV diagnosis in her homeland and sees her role as critical in imparting the facts and dispelling the myths of this disease.

"The first problem is that people doubt AIDS exists," she says. "When someone dies, doctors just write that the person died of malaria, for example. So journalists have decided to ask questions. We want to know more about research concerning AIDS and help people know that AIDS exists."

In her country of 14 million, an average 11 percent are HIV-infected. The numbers sky rocket to as much as 30

percent infected in the villages. "There are some villages where you just find little children and old men," she says, adding that there also are few doctors to care for the ill.

Batoula says that she's learning more though her research efforts about treatment regimens more readily available elsewhere, the toxic side effects that accompany them and various dosing



Yvette Felicite Batoula a Cameroon Journalist

options used to offset complications.

She takes this information and communicates it to fellow citizens via African newspaper, television and radio.

"People are not educated and I think as a journalist it is my role to educate and inform people of AIDS and about everything researchers are doing to fight AIDS. We also have to change behavior," she says.

Rev. Dr. Charles Abban full-heartedly agrees. President of Miracle Rock Foundation in Ghana, Abban left banking in 1993 to form the AIDS Prevention Foundation that seeks to provide humanitarian as well as spiritual needs of the poor, especially in the rural areas. Foremost are efforts to educate youth on HIV/AIDS, establish clinics that offer counseling, and provide medicines to those infected.

"The HIV/AIDS pandemic has become a serious health development problem," says Abban, "which needs the concerted efforts of all to fight against its continued spread."

Vaccine Candidate, continued from page 1

One of the major challenges in developing an effective AIDS vaccine has long been the fact that HIV, much like the influenza virus, exists as multiple strains that present many different faces to the immune system. The surface of HIV is coated with a protein called gp120 that has chemical features that vary from strain to strain. It has been difficult to find a single vaccine component that is able to generate antibodies that recognize the many forms of gp120 that exist in nature.

The IHV/ABL research team approached the problem by recognizing that all gp120 molecules have a shared characteristic that allows all HIV strains to bind a molecule on human target cells called CD4. Importantly, once gp120 forms a complex with CD4 it undergoes structural and chemical changes that reveal features that are shared by all HIV strains. Taking advantage of this knowledge, the team produced artificial gp120-CD4 complexes that were chemically treated to glue or "crosslink" them together. These complexes were then used to generate antibodies in small animals and monkeys.

"The gp120-CD4 complex has shown a consistent ability to generate antibodies that neutralize a wide range of HIV-1 isolates," says Dr. DeVico, an Assistant Professor at IHV. "The preliminary findings indicate the gp120-CD4 complex might serve as a useful model for HIV vaccine development."

Long the hope of AIDS researchers, it now appears that developing a single HIV vaccine for multiple viruses is indeed an increasingly realistic endeavor.

"From the beginning of the field of HIV/AIDS research, the most important goal was to develop a vaccine that prevents virus infection," says Dr. Gallo. "The difficulties have been many, spanning close to two decades. But this has the potential to bring us a major step forward in that ultimate quest. At the Institute of Human Virology, we will make this our prime effort."

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The Lowly Fat Cell: A New Target and Reservoir for HIV-1?

Dr. France Pietri-Rouxel of the Cochin Institute, Paris and colleagues recently uncovered one of HIV-1's best kept secrets: the virus can enter and replicate within fat tissue. Altering prior assumptions, their discovery impacts future HIV research, and may help explain how HIV evades therapeutic eradication.

Originally working to offset the gaunt facial features associated with lipodystrophy—a condition found in HIV patients after Highly Active Anti-Retroviral Therapy (HAART)—Pietri-Rouxel, Dr. Uriel Hazan, and associates first discovered that fat storage depots from treated patients harbor HIV-1 DNA. Finding HIV DNA denoted that HIV at least partially completes its replication, creating DNA from its RNA genome. “No one ever looked in fat tissue before,” says Pietri-Rouxel.

HIV-1 is known to target immune cells like T lymphocytes and macrophages, gaining entry via a main receptor, CD4, and one of two co-receptors, CXCR4 and CCR5. Pietri-Rouxel and colleagues recently showed that cultured human fat cells also possess the CD4, CXCR4, and CCR5 receptors.

To determine the susceptibility of fat cells to HIV infection, they examined whether HIV-1 could enter and replicate within fat cells, and form infectious particles. Their results supported variable degrees of infection of preadipocytes (immature fat cells) by CXCR4- and CCR5-using HIV strains, low-level viral replication, and weak creation of infectious viral particles.

Next, they looked for HIV receptors in fat tissue sections, removed from humans. “It was very important for us to show HIV receptor expression in sections of human adipose tissue,” says Pietri-Rouxel, “to ensure physiological relevance of our cell culture data.” All three receptors were expressed.

In ongoing work with collaborator Jacques Leibowitch, at Hôpital Raymond Poincaré, France, they are now trying to quantify HIV DNA in fat tissue from HIV-infected patients undergoing HAART. “Quantification of HIV DNA in fat tissue, versus peripheral blood cells, will provide important information on whether fat is an HIV-enriched tissue,” says Pietri-Rouxel.

Preliminary results suggest that fat tissue might indeed be an HIV “reservoir.”

Reservoirs are typically body “compartments” where HIV exists, shielded from many anti-viral drugs, by nature of low virus replication



Dr. France Pietri-Rouxel
Cochin Institute, Paris, France

and/or cellular properties. “You have to keep in mind that even if fat cells in humans are poorly infected, fat represents approximately 30 percent of total body mass,” says Pietri-Rouxel.

If fat tissues are HIV reservoirs, therapeutics will need to launch a frontal assault, to improve the effectiveness of current and future drugs and understand the role of scattered fat depots in HIV infection and AIDS progression. The fat cell can no longer be “considered merely a ‘bag of lipids’,” says Pietri-Rouxel. Indeed, a new player may be entering the HIV arena.

Lessons Learned from Natural SIV Hosts: The Evolution of HIV Tolerance

Mark Feinberg, Professor in the Departments of Medicine, and Microbiology and Immunology at Emory University, was always curious about how certain individuals infected with HIV for 20-plus years did not develop AIDS, even without therapy. When most simultaneously infected people were dead, these “long-term non-progressors” were defying the odds. He intended to understand why.

After originally working on the complex, molecular regulation of HIV's life cycle, Feinberg began “probing the equilibrium between host and virus” by working with the “natural” hosts for the virus—African primates, like Sooty Mangabey monkeys.

“These primates are infected with SIV (simian immunodeficiency virus), and exhibit high levels of viral replication, limited lifespan of infected CD4+ T lymphocytes, and lower cellular immune responses, similar to ‘non-natural’ hosts (humans). Yet, Sooty Mangabeys show none of the ‘indirect’ features of HIV disease, like aberrant immune activation,” says Feinberg. They remain healthy.

Humans, and other primates, are less lucky. “HIV is constantly evading their aggressive immune responses,” Feinberg says, “by mutating and infecting critical immunoregulatory cells.” The immune system is “always chasing HIV and is chronically ‘on,’” he claims, which contributes to developing AIDS.

Side effects of this massive immune campaign encompass increased cytokines (immunoregulatory molecules), enhanced programmed cell death (apoptosis), and decreased regenerative capacities of tissues

responsible for replacing T cells lost to direct effects of HIV or SIV.

Searching for mechanisms of natural host resistance, Feinberg hopes to tap into “thousands of years of evolutionary history” between virus and natural host, to discern differences between beneficial and deleterious immune responses, early in HIV infection and afterward. Early responses set the stage for the progression to AIDS. “The immune system is like a vehicle with a limited fuel reserve—if it burns it up at the start, it'll run out of gas early,” he remarks. Somehow, natural host responses evolved into a decision “not to fight, as the best course of action.”

Feinberg strives to understand the genetic bases for host mechanisms arising from alterations within a gene or gene family (genetic polymorphisms). He knows that evolutionary driving forces will “kick in” and adaptive polymorphisms will arise, or “accommodating” host responses, like the Sooty-Mangabeys', may surface. Evolution takes time—yet time is of the essence.

HIV research is also evolving, beyond concepts of AIDS resulting simply from viral depletion of T cells in excess of replacement rates. “AIDS is now seen as a direct and indirect consequence of immune system-mediated damage,” says Feinberg. Research should target virus-host dynamics; vaccines aim to induce “good” immune responses; while therapeutics, previously focused on blocking viral replication, may ultimately modulate deleterious host responses, and, hence, AIDS progression.

News Briefs from the IHV

Could Spinach Help Fight AIDS?

The IHV and Thomas Jefferson University (TJU) have been awarded a two-year \$300,000 grant by the National Institute of Allergy and Infectious Diseases to study whether orally administered Tat can help prevent AIDS. Dr. Gallo has long been interested in a Tat vaccine and the IHV has developed a system that shows immunosuppression by the Tat protein, essential to AIDS progression, in mice. TJU, meanwhile, has expertise in gene transfer to plants using plant viruses as vectors. This study combines the two approaches and will express HIV-1 in spinach and following oral administration to mice, analyze systemic and mucosal humoral and cell-mediated reactivity to Tat. Other advantages: Spinach expressing Tat can be grown quickly and economically and is easily produced in foreign countries with no need for refrigeration or medical infrastructure, a potential benefit to those nations already hardest hit by the AIDS epidemic. The principal investigator is Dr. Marvin Reitz.

Anger & AIDS

The Institute of Human Virology has kicked off a two-year study looking at the effects that psychological and spiritual influences may have on the immune systems of patients with HIV and the preventive role they may play in the transmission of the virus that causes AIDS. Stored blood samples from 200 participants will be examined to study progression of disease - or lack thereof - in correlation with reported spiritual attitudes and coping tendencies. Measured throughout the study will be the patient's CD4 cell count, chemokine production and plasma HIV RNA levels. Emotional coping appears consistently in research literature as key among non-medical factors predictive of health outcomes. This will be one of the first scientific studies with empirical data to test these theories. The principal investigator is Dr. Lydia Temoshok.

SAVE THE DATE

**Institute of Human Virology
2003 Annual International
Meeting
September 29-October 3, 2003
Baltimore Waterfront Marriott**

Institute Wins National AACTG Designation

Dr. Robert Redfield, Director of the Institute's Clinical Care and Research Division, has reported that the Institute of Human Virology has been designated by the National Institutes of Health as an official international site of the Adult AIDS Clinical Trials Group, enhancing the IHV's clinical research efforts aimed at developing, testing and refining new drugs and novel therapeutic approaches against HIV/AIDS. The Institute has been awarded a \$750,000 grant to build the infrastructure needs of the program, hire support staff and integrate key IHV investigators into the research agenda of the AACTG.

The Adult AIDS Clinical Trials Group, created in 1987, is the largest HIV clinical trials network in the world and plays a major role in setting standards of care for HIV infection and opportunistic diseases related to HIV/AIDS in the United States and the developed world. A program of the National Institutes of Allergy and Infectious Diseases, Division of AIDS, the AACTG has been pivotal in providing the data necessary for the approval of therapeutic agents, as well as the treatment and prevention strategies, for many opportunistic infections and malignancies. The AACTG is composed of, and directed by, leading clinical scientists in HIV/AIDS therapeutic research.

Epidemiology Division Awarded \$4 Million for Work in Nigeria

The Centers for Disease Control and Prevention has awarded a \$4.4 million Global AIDS Program grant to the IHV's Epidemiology Division to provide technical assistance and scientific expertise to help combat the AIDS epidemic in Nigeria. The Global AIDS Program was established through cooperation of the major industrialized nations to provide funding for increased access to therapy and to enhance prevention efforts in countries hardest hit, particularly sub-Saharan Africa. Nigeria, sub-Saharan Africa's most populous nation, accounts for one in five HIV cases on the continent. IHV investigators will work with CDC and Nigerian colleagues to advance programs in HIV therapeutics and adherence, palliative care, laboratory science, HIV prevention and voluntary testing and counseling. This program will build upon pioneering approaches implemented at the Institute in Baltimore and other international venues.

The Common Flu or Bioterrorism?

The IHV, in collaboration with the Walter Reed Army Institute for Research (WRAIR) and the University of Maryland Medical Center (UMMC), is working to develop rapid diagnostic tools that can distinguish common flu-like viruses from biowarfare pathogens.

Dr. Marti Jett's laboratory at the WRAIR monitors blood cell responses to smallpox, anthrax, cholera, plague, endotoxin, and many other lethal agents, by analyzing mRNA changes that occur in the blood cells after they have been exposed to a pathogen or toxin. At the IHV, Dr. Maria Salvato's lab will expose these blood cell cultures to five different viruses that cause flu-like symptoms (influenza, respiratory syncytial virus, parainfluenza virus, rhinovirus, and arenavirus) to determine which genes can discriminate between natural disease and biowarfare agents. To validate laboratory findings, patients with flu-like symptoms are donating blood and nose-wash samples taken while ill and after recovery for correlation with clinical diagnoses. Drs. Dick Kuo and Brian Browne of the UMMC Emergency Department and Dr. Judith Lovchik of the Viral Diagnostics Laboratory are collaborating with the Institute in this endeavor.

Grant Awards

- The Institute will receive a grant totalling \$750,000 (a bridge award) for its work in Maternin and plans a comprehensive reapplication within the next year.
- The National Institute of Allergy and Infectious Diseases has approved a \$400,000 supplement to the IHV's existing program project grant on topical microbicides, bringing the total award to more than \$4 million. The funding will be used to develop a vaginal microbicide designed to prevent the sexual transmission of HIV by targeting and blocking a co-receptor essential for infection.
- The Fondazione Cassa Disparmio Perugia has renewed funding support for the IHV's p17 grant studying interactions of this viral structural protein with mononuclear cells and its potential as an HIV-1 therapeutic vaccine. The total amount is approximately \$200,000 annually, for a period of three years. Principal Investigator is Dr. Mika Popovic.

Spotlight on Mark Kaplan: SAB Member



**Dr. Mark Kaplan, Director
Center for AIDS Research & Treatment
North Shore University Hospital**

For Mark H. Kaplan, MD, FACP, being on the Scientific Advisory Board (SAB) of the Institute of Human Virology (IHV) is “an honor” as well as an opportunity to advance the cause of HIV/AIDS patients.

As founder and Director of the Center for AIDS Research and Treatment at North Shore University Hospital in Manhasset, New York, he spearheads and

undertakes full-time clinical research and practice, and also holds the Jane and Dayton T. Brown Professorial Chair at New York University Medical College. To the IHV, he contributes his virology training and extensive clinical experience in the care of HIV patients.

Kaplan, instrumental early in the discovery of HIV via his recognition of potentially HIV-infected patients, provided blood samples to Robert Gallo which were critical for Gallo’s pioneering discovery of HIV. Kaplan sees his SAB function as providing “patient orientation.” “I keep the focus on major problems of HIV patients, raise clinical questions that haven’t yet been asked, and promote work toward management of opportunistic infections.”

One specific area in which he was empowered “to feel useful” is seen through the outcome of his suggestion for a focus on preventive measures for women. Translating his advice into action, the IHV is now developing vaginal microbicides.

Ever mindful of the HIV patient, Kaplan feels the IHV’s clinical progress is “fantastic.” “Baltimore previously had a neglected

Kaplan sees his SAB function as providing “patient orientation.”

HIV patient sector; the advent of the IHV helped patient care and science, and continues to dramatically improve the community, as well.” Kaplan also feels the patient care model implemented by the IHV’s Clinical Division—essentially “one patient, one primary doctor”—personalizes care and helps patients “navigate the system as well as their disease.”

The existence of the SAB is “a testament to the greatness of these scientists, especially Gallo,” says Kaplan. “Opening yourself to intense, critical peer review is very difficult.” He is continually amazed by the ability “of one man to move ideas forward at the speed of light,” and modestly expresses his gratitude at being part of the process. “When I look back, I can say that at least I tried to help end this scourge of humanity, via clinical samples and clinical vignettes.”

Three Patents Awarded

*Natural compound holds AIDS at bay;
Bacterial vectors facilitate RNA delivery*

U.S. Patent # 6,479,466

Filed: August 2000; Awarded: November 2002.
Inventors: Redfield R.R., Davis C., and A. Heredia.

This patent describes the use of a natural compound known as resveratrol (found in grapes), which can both interrupt the cell cycle and increase the potency of antiretroviral drugs for treatment of HIV infection.

US Patent # 6,500,419

Filed: April, 2000; Awarded: December 2002.
Inventors: Hone D.M., Powell R.J., and G.K. Lewis.

Australian Patent # 750,106

Filed: October, 1998; Awarded: October, 2002.
Inventors: Hone D.M., Powell R.J., and G.K. Lewis.

These two patents describe a method for introducing RNA molecules into eukaryotic cells using bacterial vectors, wherein the RNA mole-

cules are capable of being translated in the eukaryotic cells. The patents provide descriptions of compositions comprising bacterial vectors and nucleic acids that can be introduced into the bacterial vectors in such a manner to enable the delivery of RNA derived from said nucleic acid into eukaryotic cells, wherein the RNA molecules are capable of being translated in the eukaryotic cells. Examples of products the RNA molecule include vaccine antigens, therapeutic agents, immunoregulatory agents or anti-sense RNA molecules or catalytic RNA molecules.

Goldrich Departs IHV; Joins Board of Advisors

Michael Goldrich, chief operating officer of the IHV for the past five years, has announced his departure to assume the role of vice president of research operations at Beth Israel Deaconess Medical Center in Boston.

Mike joined the Institute in 1997 and put into place an outstanding team of administrative and staff support that have allowed the Institute to fulfill the original expectations of when Dr. Gallo and the founding team were first recruited. He also brought to the Institute a balance of science and administration, a sense of stability and business acumen that will continue to serve the Institute well.

Goldrich began his career at the National Institutes of Health (NIH) in Bethesda, Md., more than 30 years ago as a grants management analyst with the National Cancer Institute (NCI). His career includes more than a decade with the NCI as



**Michael Goldrich
New IHV Board Member**

a senior administrator in their laboratory and clinical programs. He then served as Chief Operating Officer for both the National Institute of Allergy and Infectious Diseases and the NIH Clinical Center, responsible for all research-related operations. During his more than 25-year career at NIH he received many honors and recognition for his exceptional skills in strategic planning, administration and financial management. Among the awards Mike received was the Presidential Meritorious Award in 1995.

Goldrich received his BA, magna cum laude, from the University of Maryland and MBA, summa cum laude, from Loyola College.

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.

Cent Gardes Symposium Highlights

*Meeting held Oct. 28-30 in Annecy, France
Highlights reported by Marc Girard,
Director of the Fondation Merieux*

Some 20 researchers presented data on the second day of the XIIIth Cent Gardes Symposium on HIV and AIDS Vaccines, devoted to new vaccinal approaches and clinical trials for both preventive and therapeutic vaccines.

HIV candidate vaccine pipeline is filling
The number of vaccine candidates reaching the diverse stages of clinical trials (I, II and III) is constantly evolving, as **Larry Corey** (*Fred Hutchinson Cancer Research Center, Seattle*) underlined in his review of ongoing research and development of HIV candidate vaccines. There are currently 66 vaccine constructs under development; and 25 vaccine constructs produced under

Good Manufacturing Practice conditions, which are being tested in Phase I clinical trials, which evaluate the safety, tolerance and optimal dose of the vaccine. Five vaccine constructs are in Phase II trials, in which the immune response will be studied. Finally a large phase III trial (to study efficacy) is being run by VaxGen in the United States, Holland, and Thailand, with a vaccine containing recombinant gp120 from subtype B or B/E. Another, associating a canarypox vector and gp120 in a 'prime-boost' protocol should be starting soon in Thailand.

VSV: A promising recombinant vector
John Rose (*Yale University*) reported on attenuated, vesicular stomatitis virus (VSV) as a vector to express HIV genes that can be produced in large quantities in cell lines, has potential to be administered nasally and



Dr. Marc Girard
Director of the Fondation Merieux

which is approaching Phase I clinical trials. The vaccine is being developed with Wyeth.

First clinical results of an anti-Tat vaccine used therapeutically

The HIV regulatory Tat protein plays a critical role in HIV replication and pathogenesis in that it causes immunosuppression and T-cell death, among other effects. Since the presence of anti-Tat antibodies have been associated with reduced disease progression in both seropositive patients and in animal models, it is assumed that inactivated Tat protein immunization could neutralize the effects of extracellular Tat on immune cells.



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