

# Discovery

The Newsletter of  
the Institute of  
Human Virology

FROM LABORATORY TO CLINIC

## Message From The Director



**ROBERT C. GALLO, M.D.**

*Director of the Institute*

This year marks the 10th Annual International Meeting of the Institute of Human Virology. Attended by several hundred elite scientists from around the world, this meeting is focused almost exclusively on HIV/AIDS and its associated diseases. Of course, as most of you know, this meeting actually dates back to the days before HIV was known. The origins of this meeting, in fact, date back to the discovery in 1980 of the first human retroviruses. The field has taken numerous twists and turns since its earliest detection – with ever-changing mutations of the virus, the effectiveness of newer and better therapeutics and now the increasing incidence of drug resistance.

To celebrate the 10th Anniversary of the International Meeting of the Institute of Human Virology,

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## Impact on Children and Women: Domestic and International Research Perspectives

When treating victims of the HIV/AIDS epidemic, some of the most sensitive issues arise when working to help HIV-infected pregnant women and prevent transmission of the virus to their children. For Dr. Man Charurat, Assistant Professor in the Division of Epidemiology & Prevention at the IHV, the epidemiological study of mother-to-child transmission has been a key research interest since early in his career.

Charurat has been involved with the Women and Infants Transmission Study (WITS). “When the study began in 1989, there was no antiretroviral (ARV) therapy, and the mother-to-child transmission rate in the cohort was around 30%,” he says. “In other words, one HIV-infected woman out of every three transmitted the virus to her infant.

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**ILIA TIKHONOV,**

*Senior Scientist, IHV Basic Science Division*

## Fighting HIV Disease Progression, One Tat at a Time

When Ilia Tikhonov, Senior Scientist in the Basic Science Division of the IHV, began working with Tat, an HIV protein required for viral replication and disease progression, he was fascinated by its potential to provide a truly novel target for a therapeutic HIV vaccine. “Most HIV vaccines are designed to block the activity of a structural protein, located on the outside of the virus,” he states, “but Tat is unique because it functions both within and outside the virus and/or the infected cell, serving as a regulatory protein.”

Tat was first identified as an HIV transcription factor (a protein that activates HIV genes) needed to create multiple copies of functional HIV, soon after initial infection of a cell. Previous work by Robert Gallo, IHV Director, and his collaborator in Paris, Dr. Daniel Zagury, supported Tat’s second

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## Fighting HIV Disease Progression, One Tat at a Time

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role—that of an extracellular protein that helps overcome the defenses of nearby immune cells (“bystanders”) or activates a dormant form of HIV in previously infected cells, awakening the sleeping giant, and promoting disease.

Indeed, Tat can directly activate both viral and cellular transcription in numerous cell types. It may also interact via binding to surface receptors of bystander cells and signaling across the membrane, resulting in lowered immune responses. “Tat’s multiple properties suggest it might be able to remodel its local environment, affecting bystanders and promoting viral spread,” offers Tikhonov.

Paradoxically, the multiple personalities of Tat may make it easier, as well as harder, to decipher how it helps HIV defeat the immune system. “If Tat does all these things, we should have different active sites to target with individual vaccines,” states Tikhonov. However, numerous attempts to generate antibodies against Tat that could afford protection against subsequent HIV infection

(in animal models) met with mixed results, which “lead us to begin thinking Tat might be acting on its own and through induction of secondary factors,” says Tikhonov, “both in our assays and in the body.”

As a first step toward deciphering this puzzle and understanding the structural and functional features of Tat, Tikhonov systematically analyzed antibodies raised against Tat in animals

“We must be able to target both direct and indirect Tat effects to inhibit Tat-mediated pathogenesis with an effective therapeutic vaccine.”

- ILIA TIKHONOV

and humans. His sophisticated approach revealed almost all antibodies were created against a small segment of Tat, at the beginning of its amino acid chain. Tikhonov then generated a unique, prototypic antibody—one that blocked cellular uptake of Tat as well as Tat’s ability to activate latent HIV (deficient in Tat) within a cell—a property called “transactivation”. However, when cultured cells express Tat, creating culture media possessing transactivation activity, Tikhonov’s antibody could not block this transactivation. “There must be a secondary factor(s) induced in Tat-expressing cells,” he concludes.

Tikhonov’s next step is to uncover the identity and role of these transactivation factors, as well as the relationships between Tat’s structure and function. “We must be able to target both direct and indirect Tat effects,” says Tikhonov, “to inhibit Tat-mediated pathogenesis with an effective therapeutic vaccine.”

## Message from the director, *continued from page 1*

abstracts selected for oral and poster presentation will be published both in the official 2005 meeting program and for the first time also online in *Retrovirology*, an online journal published by BioMed Central. *Retrovirology* is a stringently peer-reviewed journal edited by Kuan-Teh Jeang (USA), Monsef Benkirane (France), Ben Berkhout (the Netherlands), Masahiro Fujii (Japan), Michael Lairmore (USA), Andrew Lever (UK), and Mark Wainberg (Canada) with the assistance of an internationally renowned editorial board.

Highlights of this year’s annual meeting of the IHV will focus on preventive vaccine progress as well as strategies toward an effective vaccine, the escalating trend of drug resistance and new approaches to therapy, subtleties of HIV transmission and, as usual, viral pathogenesis and the immune response to HIV. There will also be special sessions featuring guest speakers, new data and perspectives from a variety of organizations, including pharmaceutical companies, National Institutes of Health, the Gates Foundation and the International AIDS Vaccine Initiative.

As always, I look forward to seeing you all again here in Baltimore. The meeting runs from Aug. 29-Sept. 2. You may register online at [www.ihv.org/meeting](http://www.ihv.org/meeting). Abstracts submissions are due May 23.

**Discovery** is a quarterly newsletter of the Institute of Human Virology. Copies are available upon request.

Please send comments to:

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## Impact of HIV on Children and Women: Domestic and International Research Perspectives

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**DR. MAN CHARURAT**, *Research Assistant Professor in the Division of Epidemiology & Prevention at IHV*

status even to her husband, and this has implications on the uptake of effective prevention strategies. In addition, breast feeding is culturally tied, making it hard to refrain from that activity. Moreover, as certain areas have shortages of clean water, it becomes difficult to prepare formula to feed the baby.

The WITS cohort is now being restructured toward long-term follow-up of infected children. When treatment is unavailable for infected infants, HIV disease progression is bimodal: some infants progress very early on, during the first two years of life, while others survive until later

on, then develop symptoms and die. Charurat says, “One of the key research areas that interests me is to characterize why some infants survive longer and others progress more rapidly. Recent studies done within our division and elsewhere indicate that there are early determinants of disease progression.”

Charurat is further interested in examining how alcohol consumption affects disease progression and management of HIV. Here again, women in the WITS cohort are being studied for the effects of alcohol. “The issue with alcohol is that it’s really along the lines of substance abuse,” he observes. Chronic substance abusers are less likely to take their medications on time; thus, it is important to separate that factor from the biological effects of the substance on HIV disease progression. “Preliminary analysis indicates that daily consumption of alcohol appears to heighten the risk of progression to AIDS,” he adds.

Now, with the development of ARV therapy, the transmission rate in the cohort is no more than 1%.”

In the United States, there were 2,000 cases of vertical transmission in 1990, but only 200 such cases in 2003, according to a recent report. Charurat attributes this dramatic drop to good public health work, including the advocacy of voluntary counseling and testing, routine testing, and availability of ARV. Moreover, the mother is counseled to feed the child with formula rather than breast milk, since the virus can be transmitted through

breast feeding.

Based on the success of this prevention strategy in the United States, Charurat says that “we’re now trying to adapt this model

to high-prevalence areas like sub-Saharan Africa.” Charurat and other IHV faculty members have extended their work to Nigeria, where about 3.6 million people—including about 300,000 children—are infected with HIV.

- DR. MAN CHARURAT

to high-prevalence areas like sub-Saharan Africa.” He and Dr. Alash’le Abimiku have extended their work to Nigeria, where about 3.6 million people—including about 300,000 children—are infected with HIV. There are, however, several challenges. One is that the stigma associated with HIV infection may inhibit a woman from divulging her HIV

## Profectus Biosciences Inc. Commences Operations

The IHV has spun off its first company. Profectus Biosciences, Inc. commenced operations in February and will develop and commercialize technologies to reduce the morbidity and mortality caused by human viral diseases and cancers, in particular, by the human immunodeficiency virus (HIV), the causative agent of AIDS. Profectus has exclusively licensed from UMBI certain intellectual property for HIV vaccines and therapeutics developed by scientists at the IHV.

“This initiative is in keeping with our goal of fostering bioscience to meet societal needs and acting as an economic development engine in Maryland’s biotechnology sector,” says Dr. Jennie Hunter-Cevera, president of the University of Maryland Biotechnology Institute, of which the IHV is a center. Profectus is a new tenant at the University of Maryland, Baltimore County’s incubator, techcenter@UMBC. For more information, visit [www.profectusbiosciences.com](http://www.profectusbiosciences.com).

## NIH Awards IHV a \$2 Million Grant to Study Stress and Beta-Chemokines

BALTIMORE, MD – Connections between a “Type C” style of coping with stress and beta-chemokines, key molecules which latch onto and block one of the main HIV co-receptors or doorways by which the dominant HIV strain enters cells, are being investigated in 200 HIV patients followed over 5 years in an outpatient clinic in inner-city Baltimore.



**DR. LYDIA TEMOSHOK, Ph. D.**

The study, Elucidating Biopsychosocial Mediators of HIV Progression, is funded through a highly competitive National Institutes of Health grant awarded to Lydia Temoshok, Ph.D., Professor of Medicine at the University of Maryland School of Medicine, and Director of the Behavioral Medicine Program, Institute of Human Virology, Baltimore.

In collaboration with colleagues in Rome, Dr. Temoshok published a study in 2002 showing that HIV patients exhibiting a strong Type C style of coping with stress (emotionally inexpressive, less able to recognize their own needs and feelings, and thus less able to deal effectively with stressful situations) had faster HIV disease progres-

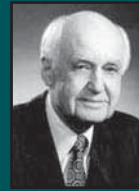
sion 6 and 12 months later. The logical question to address next concerns the potential mediators of this relationship.

Preliminary data by Dr. Temoshok and her IHV colleagues Rebecca L. Wald, Ph.D., Alfredo Garzino-Demo, Ph.D. and Lingling Sun, MD demonstrate a strong and significant relationship in 50 patients between Type C coping and lower production of the two most important beta-chemokines (MIP-1 alpha and MIP-1 beta) which IHV researchers previously found to be associated with a more favorable clinical status in HIV.”

If this strong relationship between Type C coping and dysregulated HIV-specific chemokine production is upheld in the longitudinal study, it suggests that interventions to change maladaptive Type C coping could constitute a safe and effective HIV treatment strategy. The development of synthetic molecules or drugs that mimic the receptor-blocking characteristics of beta-chemokines are a current focus of intense biomedical and pharmaceutical efforts.

The thrust of Dr. Temoshok’s research suggests that behavioral interventions to change maladaptive Type C coping could enhance—naturally and without potential side effects-- the production of the body’s own HIV-protective chemokines.

## Hilleman Honored



IHV Board of Advisors member Maurice Hilleman was honored at a scientific symposium held Jan. 26 in Philadelphia by the American Philosophical Society. Dr. Gallo was

among the speakers at this special event, which also included Dr. Anthony Fauci, Dr. Hilary Koprowski, Dr. Reinhard Kurth, Dr. Adel A.F. Mahmoud, and Dr. Thomas E. Starzl among others, who noted Dr. Hilleman’s legendary contributions to the field of vaccine research. CPI Communications and Eyeline Pictures, in cooperation with the Vaccine Education Center at the Children’s Hospital of Philadelphia, taped the proceedings to be included in a three-part documentary entitled *The Vaccine Makers*, designed to tell the story of modern vaccines.

## IHV Welcomes Trujillo

J. Roberto Trujillo, M.D., Sc.D., has joined the IHV as an Assistant Professor and Director of Latin Research in Virology and Neurosciences. He was formerly with the National Institutes of Health, National Institute of Neurological Disorders and Stroke, Laboratory of Molecular Medicine and Neuroscience. After completing his M.D. from Universidad Autonomia del Estado de Mexico and Baylor College of Medicine, Trujillo finished his Doctorate of Science training at Harvard University under the direction of Dr. Max Essex. Dr. Trujillo is also the founder of the Pan American Society for Neurovirology, he developed the headquarters for the association in Monterey, Mexico and instituted the society’s Scientific Program for the Americas. His research interests include molecular neurovirology, neuroscience and infectious diseases, and HIV-1 neurotropism regulation.



## Spotlight: Ron Brown Scholar Recounts Summer

Nelson Mandela recently said, "we are called to join the war against HIV/AIDS". I took up his call for action this past summer as an intern at the Institute of Human Virology, a research center dedicated to understanding and developing treatments for fighting HIV. The molecular mechanism of HIV infection has always been one of my scientific interests and I have always been eager to aid in researching possible ways to curb the HIV/AIDS epidemic. When Mr. Mallory informed me that the Institute of Human Virology was interested in hosting Ron Brown Scholars as summer interns, I knew that this would be the perfect opportunity for me to gain experience in HIV research.

I was drawn to the Institute of Human Virology because of its multilevel approach to the HIV/AIDS epidemic. Located in Baltimore, MD, an area with one of the largest rates of HIV infection in the United States, the Institute of Human Virology is dedicated to conducting basic science research to better understand the HIV virus, developing vaccinations for HIV and delivering these treatments discovered at the laboratory bench to the bedside of HIV/AIDS patients. All of the facilities necessary for accomplishing these goals are located within the Institute of Human Virology. I thought that this was a unique

approach to helping to solve the HIV/AIDS epidemic and I wanted to be part of the experience.

After visiting the Institute of Human Virology and learning about their different divisions of research, I decided to intern in Dr. David Pauza's laboratory in the Basic Science division. I worked with researchers studying the TAT protein, a candidate target protein for an HIV vaccination. There is still much to discover about the TAT protein and its exact role in cells infected with HIV, but the prospects for its use in fighting HIV infection are great. My role in the lab was to assist in experiments aimed at dissecting the exact function of the TAT protein by determining whether TAT protein made in cells manipulated to express TAT can be exported from these cells and cause the transactivation of cells infected with TAT deficient HIV.

In working with TAT researchers to unravel the secrets of the TAT protein, I learned how to use many different laboratory tools in molecular biology to decipher the TAT protein's interactions. I had the opportunity to perform many of the laboratory techniques that I was taught in my biology classes. It is one thing to learn the basis of these techniques in class but to actually use them to seek the answers to research questions forced me to understand and execute these techniques on another dimension. I especially enjoyed

learning how to design experiments to test a hypothesis and further one's knowledge. The best part of this internship was experiencing the ups and downs of

research and learning that research is a continuous process that requires patience and dedication.

As I reflect on my summer intern experience, I am most grateful for the opportunity to experience biomedical research on a disease that has ravaged our world. I enjoyed becoming familiar with the challenges of medical research and at the same time I was inspired by researchers who knew that their work was needed to save the lives of millions across the globe. My summer at the Institute of Human Virology has motivated me to continue my quest to become a researcher with the goal of furthering our understanding and treatment of HIV/AIDS. With recent advances in HIV research and the promise of future developments in treatment, I believe that the global community can recover from the devastation of the HIV/AIDS epidemic.



**KORYSE WOODROOFFE**

## HIV and Burma

Burma, like several other southeast Asia countries is in the midst of rising HIV infection. The country - bordering Thailand and China and under military rule - has not been the topic of much discussion in the HIV world, though there are programs addressing the epidemic. Dr. Gallo recently returned from five days in Burma, where he met with representatives from the World Health Organization and Burmese health representatives who want to better understand the significance of HIV on the population and people of Burma. Meetings were held in three cities and included health officials as well as laboratory centers. Dr. Gallo had the opportunity to speak to the diplomatic and business communities as well as health and technology groups. The event was organized by France's oil company, Total, which wants to establish programs to help HIV patients in the communities it serves.



**CHINA COLLABORATION** -- Alan Yu of CK Life Sciences Int'l, Inc., in Hong Kong, Dr. Yu Wang, who heads China's Centers for Disease Control & Prevention and Dr. Robert Gallo have partnered to form a research institute in Beijing.

**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.

## In Memoriam -- Thomas J. Matthews, Ph.D.

On December 20, 2004, the community of AIDS researchers lost one of its brightest and most innovative investigators with the untimely death of Tom Matthews at age 59. Recognized not only for his integrity, dedication and valuable scientific contributions, but also for his friendly and outgoing demeanor, Tom was well respected and especially well liked by the extended family of HIV-1 scientists who were fortunate to be among his many collaborators and friends.

Raised in Evergreen, Colorado, Tom received his Ph.D. in Biochemistry from the University of Missouri. Following post-doctoral studies in Roland Rueckert's picornavirus laboratory at the University of Wisconsin, he made his way to Duke University Medical Center and the laboratory of Dani Bolognesi. There, his initial projects were focused on the use of MuLV antigens as model tumor-associated antigens in formulating novel passive immunotherapy strategies for cancer. In 1984, following much prodding from Dr. Gallo (then at the NCI), Dani and his laboratory group turned their attention toward the AIDS virus, and Tom began his work aimed at understanding the mechanism of HIV-1 neutralization. His strong commitment to vaccine-related research resulted in the

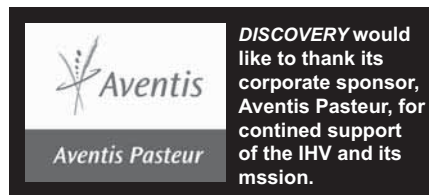
pivotal description of the principal neutralization domain (PND) of HIV-1 located within the V3 loop of gp120. It was around this time that Bob Gallo began referring to Tom as 'Kid Matthews,' owing to Tom's youthful appearance and recalling the name of a boxer Bob had once followed. Tom quickly became an active participant at Bob's annual LTCB (and eventually IHV) meetings as well as in numerous vaccine sessions at AIDS conferences.

Tom's many insights into HIV-1 neutralization formed the basis of our current understanding of this important potential correlate of protection. In fact, it was Tom's extensive search for potential vaccine determinants within the viral envelope that led to his discovery that a peptide (DP-178) representing a specific region in gp41 was extremely potent in blocking the process of virus entry into susceptible host cells. This finding formed the basis for the development of a whole new class of antiretroviral compounds – the fusion inhibitors. To explore the therapeutic potential of DP-178 and its derivatives, Tom and Dani founded the biopharmaceutical company Trimeris, Inc., that was responsible for bringing the lead T-20 compound, Fuzeon, (generic, enfuvirtide), to licensure. Despite

this rapid-fire string of successes, Tom remained forever humble about his important discovery, taking greatest pride when hearing directly from HIV-infected patients on how Fuzeon had significantly improved their lives.

Those of us who knew Tom as a friend and colleague will miss him greatly, and will cherish the memories of his infectious laughter, kind spirit, and generous nature. But it is most important that he be remembered as a dedicated scientist with the highest integrity who wanted to make a difference through his contributions. He had the uncanny ability to 'think outside of the box' long before it was fashionable (or even prudent) to do so. His memory will serve as an inspiration to us all.

-- Written by Kent J. Weinhold, Ph.D.,  
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