



DISCOVERY



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Summer 2009

A Global Call To Action from HIV Co-Discoverers Robert Gallo and Luc Montagnier

“HIV/AIDS Remains the Number One Global Health Threat”

On Friday, May 8, 2009 HIV co-discoverers Drs. Robert C. Gallo, director of the Institute of Human Virology at the University of Maryland School of Medicine, and Luc A. Montagnier, president of the World Foundation for AIDS Research and Prevention, called on international organizations and governments to immediately implement six objectives to end the HIV/AIDS pandemic. They made the joint announcement at the National Press Club in Washington, D.C., which was preceded by comments from Jeff Crowley, Director of the White House Office of National AIDS Policy.



Montagnier and Gallo during the press conference.

“Globally, many are acting as though HIV and AIDS are no longer the threat they were 25 years ago when the HIV virus was first discovered. However, in fact they remain an unparalleled global health threat, and despite progress in treatment, could worsen unless determined action is taken. We believe the recommendations we are making today are key to reducing and ultimately minimizing the devastation of HIV and AIDS,” said Drs. Gallo and Montagnier.

Global Call to Action:

1. Invest in medical infrastructure and educational outreach programs in U.S. communities most affected by the HIV/AIDS epidemic
2. Promote global development of HIV/AIDS

treatment and control programs along with regional research institutions in developing countries

3. Cultivate and inspire young scientists in the field of human virology

4. Enhance HIV/AIDS education and prevention, especially in countries with high infection rates
5. Support cutting-edge vaccine research and the development of new effective therapies
6. Continue the focus on preventing mother-to-child HIV transmission

“Here we are, 25 years after discovering the cause of AIDS and we still have a major, public health HIV/AIDS crisis,” said Dr. Gallo. “Never in the history of

mankind have we so quickly identified the cause of an epidemic, developed a test for it and begun to develop drug therapy, changing a once-deadly virus to a lifelong condition with

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DIRECTOR'S MESSAGE

Robert C. Gallo, MD

This time around, I wanted to present my Director's message differently. As many of you know our good friend – also an IHV Board of Advisor member – and world-renowned HIV/AIDS patient advocate, Marty Delaney, passed away at the end of January 2009. I had been in touch with Marty since he became sick last fall. I thought sharing my last words to him would be a fitting tribute to my friendship with Marty, and moreover, his lasting legacy beginning in the early days of the HIV/AIDS pandemic.

January 22, 2009

Dear Marty,

You have introduced me at meetings and some events and I have introduced you at others over the past few decades, but now it is time to bare my deepest feelings about you in writing.

You and I met in the mid-1980s at my home in

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Dr. Lai-Xi Wang Inducted into Johns Hopkins Society of Scholars

The Institute of Human Virology's (IHV) Lai-Xi Wang, Ph.D. was inducted Wednesday, May 20, 2009 into the Johns Hopkins Society of Scholars, among the University's distinguished former postdoctoral fellows and junior or visiting faculty from around the world. Established in 1967 these individuals who spent part of their careers at Johns Hopkins have gained marked distinction in their fields of physical, biological, medical, social or engineering sciences of in the humanities and for whom at least five years have elapsed since their last Hopkins affiliation.



Lai-Xi Wang

According to the citation of the induction, "Dr. Wang explored carbohydrate antigens as a target for HIV vaccine, by synthesizing novel oligosaccharide clusters to mimic the antigens on the viral envelope. This work provided important new insights for HIV vaccine design, and propelled him to the forefront of the anti-HIV field. He also developed a highly efficient chemoenzymatic method for making glycoproteins carrying defined oligosaccharides. This opened a new avenue to rapid access to various homogeneous glycoproteins that are essential for probing the structure and function of this class of important biological molecules, and also allows an exciting new opportunity in biotechnology to permits glycoengineering of therapeutic glycoproteins, such as monoclonal antibodies, for enhancing their in vivo efficacy."

Fifteen new members were inducted this year. Dr. Wang is one of the two new members elected by the University's Krieger School of Arts and Sciences.

"I am very happy for Lai-Xi," said Dr. Robert Gallo, Director of IHV. "He is an extraordinary scientist, and we at IHV have been most pleased with his work and relations with colleagues. It's easy to predict that Lai-Xi will continue to be one of our most exciting scientists for the future."

During the time of this prestigious inductions ceremony, the Society presented Dr. Wang a medallion and certificate, followed by dinner in honor of all 2009 inductees and their spouses at the home of President Daniels Nichols House, with honorary degree recipients, Trustees and faculty. On Thursday, May 21, 2009, the new Scholars were recognized during Commencement exercises that morning.

Director's Message, *Continued from page 1*

Bethesda, Maryland. The HIV/AIDS epidemic was in full swing. We approached each other cautiously, kind of like fighters gauging the others style and strength. I knew of you only as a formidable voice for patient advocacy, a "lay person" of uncanny understanding of the science of HIV/AIDS, a force for political change; and the creator of the already renown "Project Inform". I knew you were a leader of what became known as activism for patients as well as for prevention of disease. I knew of you as a leader of a novel movement that brought direct contact and sometimes arguments between the activist and the political leadership and for the first time in medicine brought medical scientists face to face with patients who could effect the pace and thinking of the scientist. I knew you were rather unique in bridging the gap because you were chosen to be an advisor to the Institute of Medicine, the National Academy of Sciences, and the National Institutes of Health. You were the activist, and I a scientist and one who was embroiled in political and media phenomena far beyond his ability to grasp. These things initially added to my wariness of you, but by evening's end of that summer day in Bethesda we began to know each other. You did not lend your friendship easily. It is as if one has to earn it, and not by being "fun to be with" or even by one's intelligence. Rather, it seems to me you had to have an understanding of the core or the soul, if you will, of the person.

Soon we came to trust each other completely. I learned you were far more than a pioneering activist. You were a great and essential teacher for our times. As much as anyone I know you brought simplicity out of complex science and unimaginable politics, and you brought the essence of it all to those in need, namely the patient already infected and those in danger of becoming infected.

I owe you gratitude from two different respects. First, as a scientist I am grateful for your persistence in pushing us to consider practical aspects of our lab research at every step; grateful that you never let us forget the suffering patient; grateful for your often productive and always provocative research questions, formulated by your close association with the epidemic; grateful for leading the cry for support for HIV/AIDS research funding in the earliest and hardest years; grateful for your regular participation at our annual meeting, where you invariably provoked all of us (scientists) to squabble less and produce more;

and grateful for your voice in drowning over-hyped biomedical research claims. Second, at a personal level I am grateful for your invaluable service on the Institute of Human Virology's (IHV) Board of Advisors from its inception in 1996 until now; grateful for your wise advice to me in many facets of this epidemic; grateful for the application of your keen intelligence toward the search for truth; and above all grateful for your friendship in a very difficult period of my life.

I suspect that of all the non-laboratory research contributions to the AIDS field a few activists stand at the top of the list of the contributors. No list is without you, and for me and most of us your name is the top of the top.

I close this letter with a repeat of what I said in D.C. at

a gathering in your honor, and it is this: if as in sports we had a most valuable player award for an individual's overall contributions to medical health and specifically for contributions to our advances over one of the greatest epidemics in history, it would not be to a scientist, scientist administrator, or political leader. Instead, it would be to an activist from San Francisco, Martin Delaney. Your activism was central to the promotion of the science that led to our advances, and your educational work and administrative leadership in Project Inform led to saving of countless lives.

Those of us at IHV will always carry this memory.

Finally, it was our great pleasure to honor you a few years back with the Institute of Human Virology's second Lifetime Achievement Award for Public Service. We want you now to know that every year we will have the Martin Delaney Lecture at our meeting and that at this May's very special meeting (twenty-five years since the cause of AIDS was shown) there will be a special lecture about you.*

Sincerely,

Bob Gallo

* Delivered on May 9, 2009 by Ms. Brenda Lein and Mr. Mark Herrington.



Delaney lobbying for HIV/AIDS patients rights.

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“HIV/AIDS Remains the Number One Global Health Threat” Continued from page 1

proper medical intervention. It is important for governments and organizations from around the world to come together and combat this collective HIV/AIDS emergency.”

“President Obama is fully committed to the worldwide effort to combat HIV/AIDS, and is equally committed to the effort here at home, where we are facing a serious challenge. With more than 56,000 new infections each year and more than 1.1 million people living with HIV/AIDS in the United States, we continue to have a very serious domestic epidemic. As part of the National HIV/AIDS Strategy development process, we will be developing strategies to lower HIV incidence, get all people living with HIV/AIDS into care, and address health disparities,” said Jeffrey S. Crowley, Director of the White House Office of National AIDS Policy.

“Despite many advances in HIV research from the virus discovery to the antiretroviral therapy, the AIDS epidemic is still spreading and remains a major health problem in many countries,” said Dr. Montagnier. “It is therefore of utmost importance to continue the research to find new ways of treatment and prevention for eradicating the virus infection.”

This global action coincided with the publishing of Dr. Gallo and his colleagues’ four key groundbreaking articles in *Science* magazine, May 4, 1984 Vol 224 (#4648). These four papers proved how the then-new, deadly virus



University of Maryland School of Medicine Dean Albert E. Reece, Crowley, Montagnier and Gallo on May 8, 2009.

was the cause of AIDS. This significant global contribution led to the development of the HIV blood test, thereby diagnosing individuals and helping to control the pandemic, while paving the way for drug and vaccine research initiated at the National Cancer Institute (NCI). These reports followed the publication by Dr. Montagnier and his co-workers who showed the first existence of this new retrovirus and subsequently contributed to demonstrate its causative role in AIDS.”

Drs. Gallo and Montagnier also participated

in a symposium, “25 Years After Discovering HIV as the Cause of AIDS,” co-hosted by the University of Maryland School of Medicine and the National Cancer Institute. The symposium, was held May 9-11, 2009, and looked back at the origins of research on human retroviruses and the 25 years since proving HIV as the cause of AIDS, summarized the accomplishments of a successful research enterprise, and looked ahead to overcoming obstacles in treatment and prevention for the global AIDS epidemic.

Lessons Learned in Vaccine Development

By Stanley A. Plotkin, M.D. (an extract from an article published in the *Journal of the International AIDS Society*, 2009)

We have recently heard many sober pronouncements on the possibility of an HIV vaccine and the cancellation of what was to have been a clinical test of the prime-boost concept. There is no doubt that the results of STEP were disappointing; but HIV is not the only vaccine to experience difficulties. So what lessons can we glean from prior vaccine development?

First, let’s look at an uncomplicated example: the rubella vaccine, one of my personal favorites. This is a live attenuated virus that was isolated

during the 1962-63 rubella pandemic. Why was it successful in giving immunity? Of course the answer is that because neutralizing antibodies to rubella present in the serum and on the mucosa are correlates of protection both in preventing nasopharyngeal implantation and subsequent viremia.

However, things are not always that easy. Paramyxoviruses measles is an example. Live measles virus has been a great success in eliminating the disease, but in the early days there was also a licensed, killed-measles vaccine. Unfortunately, antibodies induced by the killed vaccine were not long-lasting, and when vaccinated children were exposed to wild measles they suffered an atypical

Similarly, a formalin inactivated RSV vaccine was tested in infants, many of whom developed severe respiratory disease after subsequent natural infection with the virus.

The pathogenetic features of these adverse reactions were similar. In both cases the antibodies elicited had either disappeared or were non-protective because they were directed against the wrong protein. Although I will not argue strongly that this type of reaction could also explain the putative enhanced acquisition of HIV in the STEP trial, it at least illustrates the idea that in the absence of functional antibodies, cellular immunity of the

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A Compelling New Mechanism for HIV Cellular Entry

Viruses are generally thought to enter cells by one of two mechanisms: they either fuse directly with the cell's plasma membrane, or they are taken up by the cell in a process called endocytosis, and fuse with compartments called endosomes. While HIV has so far generally been considered to use the first mechanism, evidence for this has been mostly indirect, and it is still not clear exactly how HIV infects cells.

Recent research from IHV sheds new light on the topic. The study, published in the May 1 issue of the journal *Cell*, shows that at least in some cells HIV needs to undergo endocytosis to deliver its contents into the cell. "This is important, definitive work, showing that at least in some cell lines HIV is primarily endocytosed," says Dr. Robert Gallo, Director of the Institute of Human Virology (IHV) at the University of Maryland School of Medicine.

According to Dr. Gregory Melikyan, the IHV researcher who served as senior author on the study, "we were basically interested in the mechanism of fusion between the HIV envelope and cellular membranes. What I realized was that the tools were not in place to answer this question."

Melikyan and his colleagues (Kosuke Miyachi, Yuri Kim, Olga Latinovic and Vladimir Morozov) took two major approaches in their study. In one, they optimized a technique to trap a bacterial enzyme, beta-lactamase, inside the viral particle. They could detect when this enzyme was delivered into the cytosol. They then used 2 inhibitors – a peptide that

inhibited the fusion of the virus to the plasma membrane, and a low-temperature block that inhibited all fusion – to identify where the virus fused.

According to Melikyan, "if all fusion events occur at the cell surface, no matter whether you apply the peptide or the low temperature you will get identical results." What he found, however, was that viruses get quickly taken up in endosomes, where they are protected from the peptide. They then remain there, still susceptible to the low-temperature for a considerable time before they fuse.

This was an unexpected result, and to confirm it Melikyan and his colleagues developed their second approach, a way to directly image fusion of a single viral particle. "We labeled both the envelope membrane and the interior of the virus." If the virus delivers its contents into the cell, the green fluorescent protein used to mark the interior of the virus escapes into the cytosol and disappears. Similarly, when the virus fuses to the plasma membrane, the dye present on the viral envelope disappears. However, this dye

remains visible when the virus fuses with endosomes. So there's a clear-cut difference when the virus fuses at different locations, says Melikyan.

After looking at thousands of viral particles, "we saw to our surprise that real fusion or content delivery, which is the surrogate of infectivity, occurs only in endosomes," says Melikyan. On the cell surface, HIV seemed to undergo only partial fusion, involving exchange of lipids and activation of fusion proteins, but never completing the content delivery process.

The fact that the virus was unable to infect through the plasma membrane led Melikyan and his colleagues to consider the possibility that HIV might

require cellular co-factors present in the endosomes to complete fusion. In fact, when they tested dynamin, a cellular protein normally involved in endocytosis, they found that it seemed to be necessary for the virus to fuse with endosomes and release its contents into the cytosol.

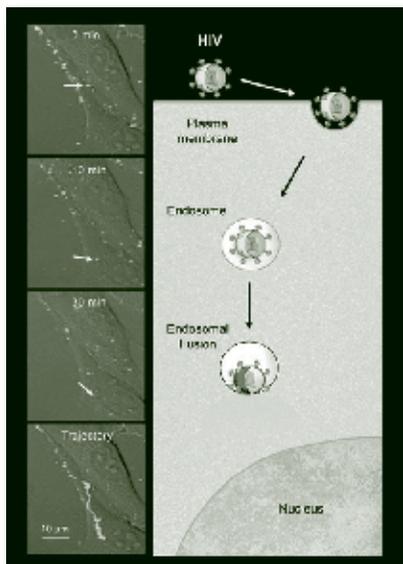
This sets the stage for many future experiments to try to understand the cell biology that is going on, says Melikyan. "We have to try to come up with creative ways of knocking dynamin down and going after dynamin partners, because it may not be directly involved."

The approaches used in the study are also applicable to other viruses. According to Melikyan, "there are indications that for many viruses, depending on cell types, there

is a block for fusion on entry at the (cell) surface."

Another important step would be to repeat the experiments in other cell lines. Melikyan also plans to extend their approach to primary T-cells, the major targets of HIV in human infections.

The study's finding that HIV appears to get quickly endocytosed also has implications for anti-HIV drugs. Gallo points out, "if this proves to be true in primary cells, treatment and vaccine research need to be reevaluated to keep this in mind. This could lead to new approaches." "Once the virus is inside, most inhibitors are not getting to the virus anymore," says Melikyan. His study suggests that some drugs could be more potent if endocytosis was delayed. The fact that the virus appears to spend more time inside the cell also raises the possibility of developing membrane-permeable inhibitors to target the virus in endosomes. Melikyan adds, "of course if dynamin or other cellular partners are involved, then hypothetically speaking one could go after cellular targets like that to minimize infection."



A drawing (right) and images (left) depict the HIV-1 entry route via endocytosis and fusion with an endosomal membrane. A single virus co-labeled with membrane and content markers moves toward the cell nucleus and releases its content into the cytosol. The bottom image shows the virus trajectory.

Grants



Alash'le Abimiku

Alash'le Abimiku, PH.D., Research Assistant Professor, Institute of Human Virology, received a one-year \$268,595 National Institutes of Health agreement in consortium with Vanderbilt University and from the Center for Disease Control for her work entitled, "Implementation of Programs for Prevention, Care and Treatment of HIV/AIDS in the

Federal Republic of Nigeria Under PEPFAR."

Manhattan Charurat, PH.D., Assistant Professor, Institute of Human Virology, received a four-year \$2,867,893 National Institutes of Health grant from the National Institute of Allergy and Infectious Diseases for his work entitled, "Acute HIV Infection and Pregnancy." Also on the grant are key personnel from IHV including William Blattner – other significant contributor, Alash'le Abimiku – co-investigator, and Jean Carr – investigator.



Manhattan Charurat



Wuyuan Lu

Wuyuan Lu, PH.D., Associate Professor, Institute of Human Virology, received a one-year \$45,000 grant from the CRF Program Pilot Grant competition for FY2009 for his work entitled, "Discovery of D-Peptide-Based p53 Activators for Anticancer Therapy," University of Maryland Marlene and Stewart Greenebaum Cancer Center.

Gregory Melikyan, PH.D., Associate Professor, Institute of Human Virology, received a two-year \$375,000 National Institutes of Health grant from the National Institute of Allergy and Infectious Diseases for his work entitled, "Functional Characterization of the Hepatitis C virus E1-E2 Glycoproteins." This funding is supported by the American Recovery and Reinvestment Act of 2009 (stimulus funding).



Gregory Melikyan



Dave Pauza

Dave Pauza, PH.D., Assistant Director, Institute of Human Virology, received a four-year \$1,238,776 National Institutes of Health grant from the National Cancer Institute for his work entitled, "Mechanisms for depleting tumor immunity in AIDS." Also on the grant are key persons: Cristiana Cairo, Investigator (IHV) and Andrei Chapoval, Investigator, Assistant Professor, Department of Otorhinolaryngology-Head and Neck Surgery, SOM.

Board Buzz

Jeff Trammell Joins IHV Board of Advisors

Trammell is president and founder of Trammell and Company, a public affairs consulting firm in Washington, D.C. Previously Trammell served as Senior Managing Director of Hill & Knowlton, an international public affairs/communications firm, from 1988 to 2000, where he oversaw the firm's public affairs practice. He was a senior advisor to Vice President Al Gore during the 2000 presidential campaign and headed business outreach for the Gore campaign, as well as serving as liaison for constituent groups. Trammell served in a similar capacity for the Kerry 2004 presidential campaign.

Trammell worked for a number of years in the U.S. Senate and the U.S. House of Representatives, where he was counsel to the chair of the Subcommittee on Health and Environment of the House Committee on Energy and Commerce. He founded a successful publishing company which produced annual references on Congress and government organizations.

Trammell serves on several boards, including the Board of Visitors of the College of William and Mary, where he is a member of the executive committee. Trammell was the founding chair of the Board of the Thomas Jefferson Public Policy Program at William and Mary and continues as a member of that board. He has served on the board of the Human Rights Campaign, the Gay and Lesbian Victory Fund, which he chaired, and the U.S. Holocaust Memorial Museum advisory board for remembrance of gay and lesbian victims.

He holds a B.A. in American History from William and Mary and a J.D. from Florida State University.



Jeff Trammell

Richard E. Hug Named to BankAnnapolis Board of Directors



Dick Hug

Richard E. Hug, Chairman and CEO of Hug Enterprises, Inc and IHV Board of Advisor member was elected last month to the Board of Directors of BankAnnapolis, a firm specializing in business and real estate investment and consulting.

Hug is well known for his civic involvement and has served as chairman of the Maryland Chamber of Commerce, Maryland Business for Responsible Government, Leadership Maryland, The National Aquarium in Baltimore, the Kennedy Krieger Institute, the United Way of Central Maryland and the Duke University School of the

Environment. Additionally, Hug served on the board of Maryland National Bank from 1986 to 1993.

Hug is a 1956/1957 graduate of Duke University and began his business career with Koppers Company, Inc., where he was named a corporate vice president in 1973. In 1983, he became President, Chairman and Chief Executive Officer of Environmental Elements Corporation, a firm specializing in air pollution control systems for the utility and industrial markets. After a successful IPO in 1990, the company was listed on the New York Stock Exchange in 1991. Hug retired in 1995, but remained a director, stockholder, and Chairman Emeritus until the company's sale in 2006.

Hug, 74, resides in Arnold with his wife Lois. They have two children and four grandchildren.

Judge Arthur Gajarsa Receives Prestigious Sons of Italy Foundation Honor

IHV Board Member, the Honorable Arthur J. Gajarsa, federal judge for the U.S. Court of Appeals, was one of three honorees during the Sons of Italy Foundation's (SIF) 21st annual National Education & Leadership Awards (NELA) award ceremony. While Gajarsa was honored with the 2009 SIF Lifetime Achievement Award in Jurisprudence and Italian American Leadership, U.S. Vice President Joseph R. Biden was presented the NELA award as the first person not of Italian heritage but a longtime friend of Italian Americans.



Gajarsa receiving his award during the Sons of Italy Foundation's 21st annual National Education & Leadership Awards (NELA) ceremony. Photo by Max Taylor.

Honoring Robert C. Gallo, MD for Historic Contributions to the Science of HIV and AIDS

By Larry Roberts, University of Maryland, School of Medicine



Gallo and Townsend greeting the Honorable Shirley Nathan-Pulliam, Maryland State Delegate, reception before the Gala.

May 4, 2009 was the 25th anniversary of Dr. Robert Gallo and his coworkers four *Science* magazine publications identifying HIV as the cause of AIDS, widely recognized as one of the most important scientific discoveries in history. Dr. Gallo, the director of the Institute of Human Virology at the University of Maryland School of Medicine, and his colleagues proved HIV is the cause of AIDS by isolating and cultivating the retrovirus from many patients with AIDS. Dr. Gallo also led the team that developed the blood test for AIDS, saving countless lives by preventing new infections. The blood test (for antibodies to HIV) was also another important component that linked HIV to AIDS.

To commemorate Dr. Gallo's historic discoveries, the University of Maryland School of Medicine hosted a special scientific symposium and gala, "Celebrating a Visionary's Quest for Discovery" held May 9-11 in Baltimore, Maryland. Dr. Gallo's discovery is shared with Luc Montagnier of the Pasteur Institute in France, who also attended the events.

"The co-discovery is one of the seminal events not only in HIV research but in our understanding of how retroviruses in general cause disease and how they might be thwarted," says Dean E. Albert Reece, MD, PhD, MBA. "We are honored to

be able to recognize Dr. Gallo for this transformative achievement."

The symposium - "25 Years After Discovering HIV as the Cause of AIDS" - reviewed the past, present and future of HIV research, treatment and education. Co-hosted by the School of Medicine and the National Cancer Institute (NCI), the symposium provided an opportunity to recognize the contributions of scientists from a wide range of disciplines. Dr. Gallo said the symposium, held at the Marriott at Camden Yards, inspired young scientists by documenting progress in AIDS research. "The role of scientists at the NCI in the co-discovery of HIV, the development of the HIV blood test and the beginning of anti-retroviral drugs should not be forgotten."

Over the last quarter of a century, AIDS research has eased the suffering caused by the disease and given birth to the field of modern human immunology. Dr. Gallo says around the world, the fight against AIDS has led to unprecedented cooperation and coordination among community leaders, patients, advocates, physicians, scientists and politicians. "AIDS research also had a spin-off affect on society by



The Honorable Kathleen Kennedy, IHV Board of Advisor Chair, emceed the program.

ing a vaccine. The
Lt. Governor Kathleen
Institute of Human



ate and Maryland House Majority Whip, during a



One of seven Gallo “roasters” the evening of May 9, 2009, Dr. Robert Anthony is Gallo’s cousin and close confidante and Chief of Cardiology at St. Mary’s Hospital in their hometown of Waterbury, CT. Other roasters included Dr. John Gershoni, Professor of Cell Research and Immunology at Tel Aviv University; Dr. Max Essex, Chairman of the Harvard School of Public Health AIDS Initiative; Dr. Isaac Witz, Professor Emeritus of Cell Research and Immunology at Tel Aviv University; Dr. Bill Blattner, Associate Director of the IHV; Tim Moynahan, Esquire, Chairman of the Robert C. Gallo Foundation for AIDS & Virus Research and Mr. Stewart Greenebaum, member of the IHV Board of Advisors.



National Institute of Allergies and Infectious Diseases Director Tony Fauci addressing the audience during the symposium.



Dr. Bernadine Healy, U.S. News and World Report reporter and former Director of the National Institutes of Health making opening remarks at the symposium.



University of Maryland School of Medicine Dean Albert E. Reece presented Gallo with a gift of a Brooks Robinson autographed 1966 Baltimore Orioles jersey.



National Cancer Institute Director John Niederhuber making introductory remarks during the symposium.



Drs. Max Essex, Chair of the Harvard AIDS Initiative and IHV Scientific Advisory Board Member, Gallo and Bill Haseltine, Chairman and CEO of Haseltine Associates, Ltd., President of the William A. Haseltine Foundation for Medical Sciences and the Arts and IHV Board of Advisor Member.



Gallo and Dr. Anders Vahlne, Professor of Clinical Virology at the Karolinska Institute, who spoke during the symposium about the history of retroviruses and recently published in May 2009 an article in *Retrovirology* entitled, “A Historical Reflection on the Discovery of Human Retroviruses.”

forging a greater understanding of differences in sexuality, women’s rights, and uniting powerful governments with third world countries.”

Dr. Gallo was recognized for his pioneering research achievements in a special gala. Celebrating a Visionary’s Quest for Discovery: An Evening Honoring Dr. Robert C. Gallo, MD, was held May 9th at the Baltimore Hilton. The gala brought together colleagues, friends, family and the public to thank Dr. Gallo for his historic contributions to AIDS research and his continuing dedication to find-

master of ceremonies was former Maryland
een Kennedy Townsend, who chairs the
n Virology Board of Advisors.

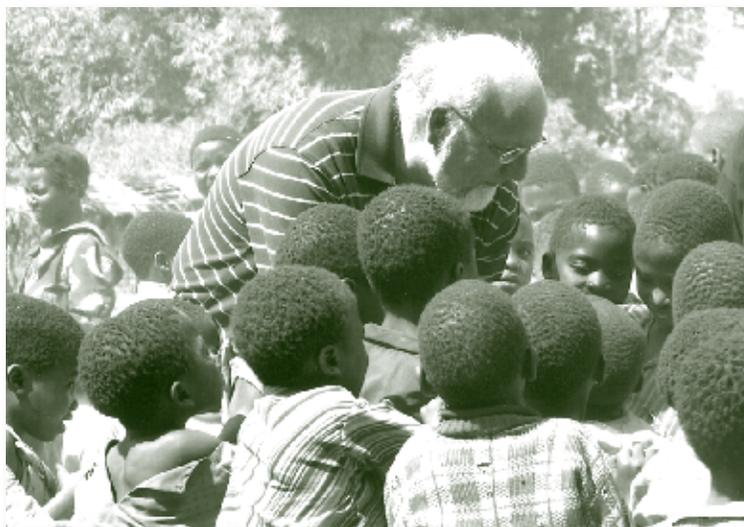
Townsend,
ed the Gala

IHV – Providing Aids Relief Services Worldwide

Through the President's Emergency Plan for AIDS Relief (PEPFAR) funding, the Institute of Human Virology (IHV) of the University of Maryland School of Medicine (SOM) is having an enormous, global impact on those suffering from HIV and AIDS. Catholic Relief Services partners with IHV SOM, Catholic Medical Mission Board, Interchurch Medical Assistance and Futures Group to collectively form AIDSRelief Consortium. In 2004, AIDSRelief was awarded a competitive five-year PEPFAR grant from the U.S. Health and Human Services (HHS) to provide HIV care and antiretroviral therapy (ART) in the following nine countries: South Africa, Zambia, Nigeria, Kenya, Rwanda, Uganda, Tanzania, Haiti, and Guyana. AIDSRelief is one of two major PEPFAR grants IHV SOM implements and is led by Dr. Robert Redfield, Co-Director of IHV and Professor of Medicine, and Microbiology and Immunology at the School of Medicine.

At the close of year five of the grant, AIDSRelief is proud to reflect on its accomplishments in "Providing Treatment and Restoring Hope," the program's mantra. It has made remarkable progress improving the quality of life for people living with HIV around the world, while scaling up access to services. Most importantly, this work has been conducted in a context which supports country programs' National Treatment Plans and strengthens and empowers local healthcare systems. As of November 30, 2008, AIDSRelief is providing 141,669 patients with ART and has enrolled 382,189 patients in HIV care and treatment at 187 local partner treatment facilities in the aforementioned nine African and Caribbean nations. AIDSRelief's strong focus on a comprehensive continuum of care from health institution to community and household has continued to demonstrate a low level of patients lost to follow-up care at 5.33%, while cumulative mortality remains around 8.1%. Recently this grant was renewed through 2013.

"Dr. Redfield's program has been extremely successful in assisting these PEPFAR countries in therapy, education and training," said Dr.



Dr. Robert Redfield greeting children in Africa

Robert Gallo, Director of IHV and Professor of Medicine and Microbiology and Immunology at the School of Medicine. "AIDSRelief's significant contributions, including care and therapies for more than 350,000 HIV-positive Africans and Caribbeans, are historical legacies for IHV and the School of Medicine."

AIDSRelief strives to achieve durable viral suppression through first line regimens. Programs that demonstrate durable therapeutic outcomes are more cost-effective over the long run, as fewer patients require more expensive second-line and salvage regimens or costly diagnostic testing. Maintaining maximum HIV viral suppression is the basic treatment goal of ART upon which all other outcomes rest – including immune restoration, decreased morbidity attributed to opportunistic infections, AIDS-related mortality, quality of life, and long-term costs of care. Results from AIDSRelief's second-round patient-level outcomes indicate high levels of "on treatment" viral suppression including Kenya at 94.6%, Zambia at 92.4%, Nigeria at 86.2% and Rwanda at 89.3%.

"I have been enormously privileged to work with an outstanding group of deeply committed health professionals to share the experience and capacity of IHV SOM globally and contribute to the impact and success of our nation's global health programs," said Dr. Redfield.

IHV SOM's role in the Consortium is to impart years of work in HIV/AIDS to physicians,

nurses, adherence specialists, laboratory technicians and communities in resource limited settings in Africa and the Caribbean. IHV SOM is responsible for the medical and clinical outcomes of AIDSRelief including clinical capacity building, AIDSRelief's medical curriculum, quality assurance and quality improvement in addition to laboratory procurement, installation and training. IHV SOM physicians work closely with local partners for drug regimen supply chain management through evidenced based forecasting and regimen selection.

The goal of IHV SOM AIDSRelief is to provide care and treatment for HIV patients and their families through supportive care delivery models which are sustainable and which can be replicated or scaled-up relatively easily. A program implemented successfully through IHV SOM in Baltimore known as the JACQUES Initiative has served as a model for IHV SOM's programs in Africa and the Caribbean. IHV SOM has been successful both locally and now globally in developing and building upon the JACQUES Initiative's programs that has translated a non-traditional model of care energizing people living with HIV into an effective community-based health delivery system. This scalable model, which is not limited to the traditional healthcare workforce, includes ART adherence and treatment support using people living with HIV infection as treatment guardians and treatment specialists to form a strong and expanded community of health network.

As AIDSRelief enters the sixth year of operations under the newly reauthorized Lantos-Hyde Act of 2009, the program will continue building local capacity with the goal of preparing and graduating local partners who are ready to operate independently. IHV SOM continues to play a critical role in medical education and curriculum development to a cadre of highly trained group of local doctors, nurses, community health workers, laboratorial specialists and other healthcare professionals to optimize sustainable health intervention.

Vigil Focuses Attention on HIV/AIDS Impact



Candlelight by Antonio Paterniti

By: Rosia Scalia, University of Maryland, Baltimore

It started with a candlelight vigil to raise awareness about the devastating impact of the HIV/AIDS epidemic on women and girls. It ended with the shocking news that a volunteer who took the rapid test that evening screened positive for the virus. Staff at the JACQUES Initiative, part of the University of Maryland School of Medicine's Institute of Human Virology (IHV), will treat her. Named in honor of a patient advocate who espoused education, research, and informed decision making, the JACQUES Initiative monitors prescription medication and provides drug addiction counseling, help with housing, insurance, job search training, and the like.

The vigil—a community event associated with the interdisciplinary course *Women: The Changing Face of HIV/AIDS*—was organized by six Master's of Social Work degree students and their two Maternal and Child Health (MCH) doctoral fellow advisors. “Through their efforts, these women have brought our campus together with the community, illuminating how HIV/AIDS impacts women throughout our community, state, nation, and world,” said Edward Pecukonis, PhD, MSW, an associate professor at the School of Social Work who directs the School's Maternal and Child Health educational program. Doctoral students Shauna Acquavita, LCSW-C, BCD, and Maya Gibbons, MSW, provided guidance to the six MCH scholars—Kerri Agee, Caitlin Johnson, Erin Penniston, Jessica Porto, Kate Wasserman,

and Kim Weingarten—who organized both the course and the vigil.

“The success of the evening was not only about the number of people who showed up for the vigil, but who signed up to volunteer with our Initiative and who agreed to get tested,” said Derek Spencer, MS, CRNP, executive director of the JACQUES Initiative. “Additionally, I want to thank IHV's Board of Advisor Member Fred Cannon, Senior Vice President of BMI, for helping to enlist The Marcus Johnson Project's support for entertainment during the event.”

Nearly 200 people from across the city gathered on campus for the event, including Delta Psi Theta Sorority Sisters, students from Roland Park Country School and Steuart Hill Academic Academy, leaders from the city's faith communities, government officials, front-line health care workers, HIV/AIDS patients, and medical researchers.

“Having awareness without being engaged is criminal. We want to raise awareness and engage people. We want to help people become engaged in dealing with the problem, a call to action,” Spencer said.

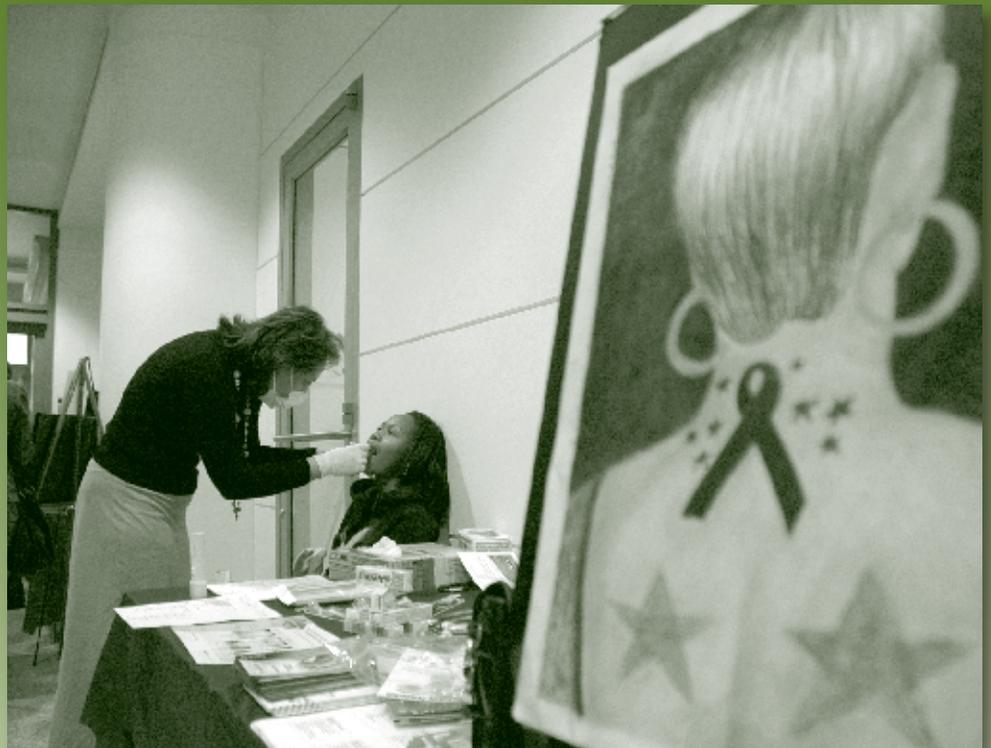
Three women who serve on the front lines of HIV/AIDS treatment were honored: Dorcas Baker, RN, BSN, ACRN, MA, who organized the

first HIV Over Fifty conference at Johns Hopkins University in 2002 and who volunteers services to improve the lives of African-Americans; Debbie Rock, MSW, the founder and executive director of the LIGHT Health and Wellness Comprehensive Services, Inc., which serves families and children impacted by health and social issues such as HIV/AIDS and substance abuse; and the Rev. Debra Hickman, MDiv, co-founder, president, and CEO of Sisters Together and Reaching Inc. (STAR), a faith-based, nonprofit organization that provides spiritual support, direct services, and prevention education to HIV/AIDS infected and affected men and women.

Wasserman was also honored for her work conceptualizing and organizing the vigil due to her passion for raising awareness about the virus on campus.

Angela Wakhweya, MD, MSs, deputy director of the Maryland AIDS Administration, discussed the epidemiology of the virus' impact on women and girls, saying that everyone must embrace the triple Ts: Talk, Testing, and Treatment.

“We must talk consistently and constantly about where we are with the epidemic,” Wakhweya said. “We must urge people to be tested, at least once a year and twice a year if they are at risk, and we must be able to treat early, before AIDS sets in.”



Members of the public participate in IHV's free HIV testing during the event. Photo by Antonio Paterniti.

Longtime Gallo Colleague Popovic Enters Semi-Retirement



Mika Popovic

In 1973, the universe of retrovirus researchers was small, and those interested in the possibility of human retroviruses were really very small. So when two of them, Robert Gallo and Mika Popovic, collided at a cancer meeting in Oslo they did what was natural – they gabbed about their mutual interest at a pub. “It was mid-summer, one of the longest days of the year, and at 10 p.m. it was nice and warm and there was sunshine, and we were outside drinking beer

and talking about retroviruses,” remembers Popovic, who is semi-retiring from his position as Professor at IHV. “I was looking for some evidence that a human retrovirus can be involved with various cancers, and Bob Gallo was interested in the same thing. That was our first contact.”

At the time Popovic was a post-doctoral fellow in a cancer lab in Sweden. A few years earlier he had finished an M.D. in his native Czechoslovakia, but after a year working at a hospital Popovic decided to pursue a research career instead. So he enrolled in a Ph.D. program and met his mentor, Jan Svoboda, a noted Czech virologist with a keen interest in avian (chicken) retroviruses. Popovic adopted that interest, and ran with it.

In 1979, that interest paid off when Gallo invited Popovic to work in his lab at the National Cancer Institute. By 1980 Gallo and his co-workers had discovered and isolated the human T cell leukemia lymphotropic virus 1 (HTLV-1), the first known human retrovirus. Then Popovic, Gallo et al. plus independent workers in Japan, showed it was the cause of adult T cell leukemia. Later it was shown by Antoine Gessaine and Guy de Thé of France to cause a fatal neurological disease as well. “He joined us after we discovered HTLV-1, and Mika did a marvelous job on the next step of that work, the biological part,” says Gallo. Specifically, Popovic along with Isao Miyoshi in Japan showed that the virus transformed certain immune cells (CD4 T cells), immortalizing them (ie the cells grew forever). He also obtained many more isolates of HTLV-1.

Popovic’s next major contribution arrived in 1984, as co-author on four *Science* papers that outlined HIV as the cause of AIDS. Popovic was the lead author on one of the papers, which described how to culture HIV and grow large amounts of it, a critical step in developing reagents to test the blood supply for HIV, a key concern at the time.

“My main contribution was that I succeeded in showing that HIV could be isolated and grown in sufficient amounts in cell lines,” says Popovic.

Gallo says the paper “was a technical breakthrough that made the development of the blood test quite rapid and easy. It was a major advance. Mika is the first author because as Gallo notes “his along with my technicians were the hands that were wet. It took a lot of experimentation to get that to succeed.” Gallo points out that the blood test was not only essential for saving the blood supply and protecting people in need of donor blood from being infected with HIV contaminated blood, its use also became a major factor in showing HIV was the cause of AIDS. Further, by knowing people were infected long before they developed AIDS, education of infected people could begin, and when treatment became available, physicians could know who to treat years in advance of clinical signs of AIDS. In addition, the cell culture system enabled scientists to test drugs against HIV and so contributed to the pioneering work of anti-HIV drug development by former

National Cancer Institute Director Sam Broder and his co-workers.

The blood test became available by February 1984 in the Gallo lab, and its application was made available to industrialized countries through larger companies – first by Abbott and later others.

During that critical work with HIV, in 1983, Popovic was granted political asylum in the U.S. When he arrived in the U.S. in 1979, he had planned to return to Czechoslovakia after a few years. “I was already established over in Czechoslovakia, I was head of the department,” he says. But political turmoil in Czechoslovakia – the Soviet Union still had sway at that time – left Popovic with few choices. So he stayed in the U.S., not returning to his homeland until after the Berlin Wall fell – the first of several visits since.

He joined IHV at its inception in 1996, and has continued contributing to the understanding of HIV and other retroviruses. In particular, he’s helped explain why lymphomas occur frequently in HIV-infected individuals.

Although Popovic is semi-retired, he still has his hands in three projects. First, he is looking for retroviruses in lung cancers that form in non-smokers. His second ongoing project involves searching for HIV proteins in the blood of patients taking highly active retroviral therapy. “The work is not finished but it looks like, yes, the patients do have circulating viral proteins” even though they have no detectable viral RNA in their blood, Popovic says. For the third project, Popovic is collaborating with researchers in Michigan, Sweden and Germany to search for microbial agents that might trigger sarcoidosis and other diseases characterized by granulomas.

To keep up his lab work, Popovic draws inspiration from his former mentor, whom he visited recently in Prague. At 75, Jan Svoboda still spends time in the laboratory, writes, and publishes his research. “If he can work so actively at 75, I should still work at 68,” says Popovic.

When he’s not working, Popovic plans to garden, fish, and read books on history, a favorite subject.

“In late 1970, the field of human retrovirology as an area of research was thought to be maintained only by a ‘political skill’ of a few researchers and human retroviruses were termed as ‘human rumor’ viruses,” said Popovic. “However, it is very difficult to imagine that in early 1980’s the field of human retrovirology could have been developed so rapidly without Bob Gallo’s outstanding knowledge and expertise in the field as well as without his extraordinary capacity and skill to maintain a well supported Laboratory of Tumor Cell Biology (NCI) with outstanding researchers working in this field in a highly competitive NIH environment. One should take in consideration that in 1982, when the AIDS epidemic started in this country, vast majority of retrovirologists moved into other areas of research, mainly into the field of oncogenes, and the NIAID laboratory for retroviruses was focused on studies of human endogenous retroviral sequences instead of exogenous retroviruses. Without discussions, at the beginning of the AIDS epidemic, the best prepared laboratory to face this new epidemic and find effective solutions was Bob Gallo’s laboratory.”

“During my work in Bob Gallo’s laboratory which encompasses almost three decades, I faced with Bob Gallo ‘good time’ and ‘bad time,’” continued Popovic. “A reporter, Malcolm Gladwell, who covered science and medicine for *The Washington Post* magazine described my work with Bob Gallo as follows: *In retrospect, it was the purest of good fortune that a year before the AIDS retrovirus surfaced in the West, these two men [Bob Gallo and Mika Popovic] with their passionate, shared interest in this obscure field linked up at the world’s most important research institution. When others around the world were looking for fungi or bacteria or chemicals as the cause of AIDS...*,” Popovic recalled.

Memory B Cells Reveal Early Response to HIV

Natural HIV suppressors – people who contract HIV but whose immune systems control the infection – often have low levels of anti-HIV antibodies in their blood. That finding has puzzled researchers. New research led by IHV’s Co-Director of Division of Basic Science and Vaccine Research, George Lewis, concludes that such



George Lewis

individuals did, at some point, generate antibodies that targeted HIV.

“My hunch is, the antibodies we found do contribute to

control of HIV in these individuals, but they’re probably not the whole story,” said Lewis. The research was published in the March 10 *Proceedings of the National Academy of Sciences*.

Three natural viral suppressors who had been infected with HIV for 5, 13, and 17 years were studied. None of the volunteers had ever received anti-retroviral therapy, yet their blood levels of HIV remained very low.

Lewis and his colleagues (Yongjun Guan, Mohammad M. Sajadi, Roberta Kamin-Lewis, Timothy R. Fouts, Anthony Dimitrov, Zhixin Zhang, Robert R. Redfield, Anthony L. DeVico and Robert C. Gallo) found that the three volunteers also carried very low concentrations of anti-HIV antibodies in their blood. “We knew that suppressors already made antibodies to the envelope protein because they had low levels of them in the circulation. So we researched the memory pool to find specificities that were not in the serum,” said Lewis.

“Memory B cells are just what you’d expect,” said IHV Director Robert Gallo. “They’re like a library of the pathogens we’ve previously been

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From Bad Fall, to Great Spring

Last fall and the early days of the New Year were challenging ones for IHV's Director, Dr. Robert C. Gallo. It began with the "un-noble Nobel" decision as reported in the press, included a battle in South Africa with typhoid fever and ended in his good friend, Marty Delaney's passing.

However, this past spring was quite another story. On March 12, Gallo received the Governor's International Leadership Award, the most esteemed international award bestowed by Maryland, recognizing decades of sustained and exemplary global leadership of those providing a significant positive impact on Maryland and its global footprint. "I am privileged to honor Dr. Gallo and the Institute for Human Virology for their dedication in resolving some of the most challenging medical problems facing people worldwide, and helping to find a vaccine that can help thousands of people affected by the HIV/AIDS epidemic," said Governor Martin O'Malley.

On March 26, Gallo was in Ocho Rios, Jamaica to receive two awards including an honorary degree of doctor of science from the University of Technology (UTech), and the Sir Allister McIntyre Distinguished Award from the University of West Indies (UWI's) University Diabetes Outreach Programme.

On April 14, Gallo was in Ireland to receive the James Joyce award from the Literary and Historical Society at the University College Dublin for his role "in identifying the Human Immunodeficiency Virus as the infectious agent responsible for AIDS." The Society further noted Dr. Gallo's team "worked to grow the virus in an immortalized cell line leading to his development of a blood test for HIV and the ability to screen donated blood for this virus." Gallo was the first scientist to receive this prestigious award. Past years diverse recipients have included Nobel laureates FW DeKlerk, John Hume and Seamus Heaney as well as Noam Chomsky, JK Rowling and last year, Will Ferrell.

After his trip to Ireland, Gallo traveled directly to Naples, Italy where he was presented The Public Health Medal Award by the Governor of Campania,



Evening of the Dan David Prize ceremony on May 17, 2009. From right to left: First row: Prof. Andrew E. Lange, Prof Paul Richards, Prof. Robert C. Gallo, Mr. Ron Huldai Mayor City of Tel Aviv-Jaffa, Prof. Zvi Galil President Tel Aviv University, Mr. Gianni Alemanno Mayor of Rome, Mr. Dan David, Prof. Paolo de Bernardis, Prof. Dani Leviatan Rector Tel Aviv University. Sitting: Mr. Shimon Peres President of the State of Israel, Mr. Tony Blair. Standing in front: Mrs. Gabi David.

The Honorable Antonio Bassolino. Gallo received this Medal on April 16 for "his discovery and pioneering fundamental studies on human retroviruses and their role in oncology and immunodeficiency."

Gallo was in New York to receive an Honorary Doctor of Science at Mount Sinai School of Medicine's Commencement on May 14. He then flew directly to Tel Aviv, Israel where he was presented on May 17 with the international Dan David Prize, named after global businessman and philanthropist Dan David. Annually, the Dan David Prize awards three prizes of US\$1 million each for outstanding achievement and in turn, the laureates donate 10% of their prize money towards 20 doctoral and postdoctoral scholarships.

The Dan David Prize chooses winners "in the Past, Present and Future Time Dimensions." Gallo was chosen in the Future Dimension "for his research of the HIV and T cell leukemia viruses and especially for the development of a robust, simple blood test to detect the HIV virus, the importance of which for the epidemiology of this huge pandemic cannot be overestimated." Fellow recipients included Past Dimension winners Paolo de Bernardis (University La Sapienza, Rome, Italy), Andrew Lange (Caltech, USA) and Paul Richards (UC Berkeley, USA) for their research and data presented in 2000 which provided the first undisputed evidence that the Universe has a flat geometry and Present Dimension winner former Prime Minister of Great Britain Tony Blair for international leadership in engineering agreements and forging lasting solutions to areas in conflict.

Memory B Cells Reveal Early Response to HIV,

Continued from page 10

exposed to."

Each memory B cell produces antibodies against a single target, and after an infection clears, memory B cells lie in wait. And they can wait a long time. A paper published in *Nature* last year found memory B cells specific for the 1918 flu in nonagenarian survivors of that pandemic. Antibodies generated by those B cells neutralized the 1918 virus.

Lewis wanted to know if antibodies generated by the natural HIV suppressors were capable of neutralizing the virus. "We'd like to know what the specificity of B cells are. These are people who are controlling infection and we think they made some antibody responses early on that have smoldered down because there isn't a [viral] load," said Lewis.

So after isolating the HIV-specific memory B cells from the three volunteers, the team determined what part of the virus they targeted. "Some of the monoclonal antibodies we've isolated look interesting, and we can now transfer them into animals and see if they block model HIV viruses from infecting the animals," said Lewis.

The antibodies Lewis and his colleagues recovered from the memory B cells of the three volunteers attack various sites on the HIV envelope protein. Some block the HIV co-receptor, where HIV locks onto CD4 immune cells after binding with them.

However, he added that it's impossible to know how many of these antibodies the 3 individuals had made in the past. The experiments do show conclusively, though, that the volunteers did make antibodies that targeted the HIV envelope protein.

"It's a very important piece of work," said Gallo. He points to vaccine trials where researchers failed to find anti-envelope antibodies in the blood of the volunteers. It may be that those volunteers generated such antibodies, but that the antibodies quickly vanished from the blood. "You may see a negative antibody result, when in fact the antibodies were very important for controlling the disease early on," said Gallo. "In that way, this study helps indirectly with vaccine development."

“The week in Israel with my family and friends, was the best week of my life.”

ROBERT GALLO

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a world-class center of excellence focusing on chronic viral diseases, most notably HIV/AIDS, and virally linked cancers. IHV is dedicated to fundamental and clinical research leading to improved treatment and prevention of these diseases. Our unique structure connects cohesive, multidisciplinary research and clinical programs to streamline new treatments from discovery to patient. IHV serves the global scientific community and treats patients at clinics in Maryland, across Africa and in the Caribbean.

Lessons Learned in Vaccine Development Continued from page 3

wrong type can enhance--rather than diminish--susceptibility.

Another type of contretemps occurred with the first licensed rotavirus vaccine. Although protective, it caused intussusception (intestinal invagination) in some patients. This happened because the supposedly attenuated simian vector retained pathogenicity for the infant intestine, causing diarrhea and fever. The point is that the choice of a supposedly attenuated vector is a key issue, and that the wrong choice of vector brings safety problems.

Another lesson is that correlates of immunity may be complex, and antibody and cellular immunity are often collaborative. This point can be illustrated with reference to cytomegalovirus. As in HIV, super infection may occur in previously infected individuals, but the course of secondary infection is much less pathogenic than in non-immune subjects. Antibody to CMV alone may protect against primary infection, but if infection occurs, cellular immunity is critical in controlling it.

Nevertheless, two vaccines in development have shown moderate ability to prevent or modify CMV infection. Thus, the fact that super infection has been demonstrated in some already HIV infected people does not necessarily rule out a role for

immunity in controlling disease after infection.

The last agent I would like to discuss is hepatitis C, because there are many similarities between it and HIV. Although Hep C is a flavivirus, it shares a number of properties with HIV. Interestingly, patients who resolve acute Hep C infections have higher levels of neutralizing antibodies early in infection than do those who go on to chronic infection. Antibodies do not help when they develop late in chronic infection. On the other hand, cellular immunity developing late in infection does stop chronic viremia. Although a crucial difference between the two viruses is the lack of integration by Hep C in contrast to HIV, nevertheless I think it is instructive to see that a chronic infection can be counteracted by standard immune responses.

So what can be said about immune protection against HIV? In general, innate immune responses are clearly valuable both immediately after infection and as adjuvants to adaptive immune responses. The question is do they have memory?

I doubt that we can escape totally from having to make multivalent or regional HIV vaccines. Indeed, recent reports suggest that multivalent HIV envelopes give broad neutralizing responses.

If high levels of antibody are necessary for protection, and as HIV spreads from the site of

implantation within several days, effector B cells must be in the circulation and producing antibody at the time of exposure. Thus, booster doses of an AIDS vaccine will be necessary to maintain protective levels of antibody. Indeed, booster doses are commonly needed for vaccines, even for some that are highly efficacious.

This may be an inconvenient truth, but the use of adjuvants might also help. The new adjuvants now available in vaccinology are legion and they increase breadth as well as height of antibody responses.

The lessons of vaccinology that are likely to apply to HIV are that antibody and effector cells on the mucosa are needed to prevent implantation, that high levels of antibody are required to prevent or modulate viremia, and that both CD4 and CD8 cells are needed to kill cells once they are infected.

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