Gallo Honored in Ireland

During an October 20 ceremony in Dublin, IHV Director Dr. Robert C. Gallo was inducted into the Royal College of Physicians of Ireland. The college, founded in 1654, bestowed the honor after hearing an eloquently delivered and often humorous citation by IHV Board of Advisors Member Dr. William Hall, professor of medical microbiology at University College Dublin. While in Ireland, Dr. Gallo also met with medical science students and senior faculty at University College Dublin and, accompanied by Maryland Governor Martin O'Malley, toured the university's Conway Institute of Biomolecular and Biomedical Research. Dr. Gallo was later interviewed by Irish National Radio about his scientific achievements and current developments in HIV/AIDS research. IHV Board of Advisors Member Stewart Greenebaum and his wife Marlene accompanied Dr. and Mrs. Gallo on the Ireland trip.

Dr. William Hall and Dr. Robert C. Gallo

Gates Foundation Grant Will Support IHV Vaccine Research,

Continued from page 1

do this, the virus unfolds a portion of its outer coating, much like a grappling hook. While much of the structure of HIV mutates rapidly and changes shape, this hook remains the same across all strains of HIV. Called gp120, or glycoprotein 120, this hook is the target of the Institute's vaccine.

"Before attaching to a cell, gp120 has a certain shape, and after attachment it has a different shape," said DeVico. "We're targeting gp120 after attachment, because that structure tends to be conserved across the different strains of HIV. It's less of a moving target."

The vaccine is designed to prod the body to generate antibodies that clamp onto gp120 and prevent the virus from infecting white blood cells. In a study published in October in the Proceedings of the National Academy of Sciences, DeVico, Lewis, and their IHV colleagues reported that the vaccine slows HIV infections in monkeys.

> *"It's very important to know under what conditions our vaccine will best work, and this grant lets us do that."*
>
> DR. ANTHONY DEVICO

"While this version of the vaccine did not prevent infection, which is obviously what you eventually want, it did control the infection," said DeVico. "Now we can build on that."

Lewis says that the Institute decided to focus on a vaccine that produces antibodies because "if it's the right kind of antibody in sufficient quantities, it can completely prevent infection." Many other HIV vaccines in development focus instead on stimulating a different kind of immune response, called cell-mediated immunity. But cell-mediated immunity only kicks in after cells have been infected. "It's better to prevent infection, of course, and that's what we're trying to do," said Lewis.

The Gates Foundation grant is funding research that builds on the earlier monkey work. Some experiments are examining the effect of injecting the vaccine directly into muscle. A second set of experiments, led by Pauza, will boost the vaccine with a cholera toxin and study such a strategy prevents HIV infection at the mucous membranes – the most critical route of entry of the virus. The third series of tests will try to identify specifically which antibodies generated by the vaccine most effectively stop HIV from entering white blood cells.

"All three sets of experiments work together to answer questions that arose from the original study," said Lewis. "It's very important to know under which conditions our vaccine will best work, and this grant lets us do that."

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.

Vaccine Enterprise Director Underscores Research Challenges

Dr. Alan Bernstein, the newly appointed executive director of the Global HIV Vaccine Enterprise, came to the AIDS field after a successful career as a cancer researcher and founding director of the Canadian Institutes of Health Research.

As he settles into the Enterprise's new secretariat office in New York, Bernstein hopes to encourage scientists from a variety of fields – especially young scientists – to turn their attention to the quest for an AIDS vaccine.

"We need to encourage not just out-of-the-box thinking but also out-of-the-field thinking," he said. "There's a lot of science going on around vaccinology and immunology that needs to permeate the HIV field."

Bernstein, who became director of the Enterprise in January 2008, has set ambitious goals for the next 12 months.

Among other things, he plans to ask the scientific community to review and update the Enterprise's three-year-old scientific plan; involve more African institutions in AIDS vaccine research; and call on two rising economic powers – China and India – to join the Enterprise by allocating resources that align with the scientific strategic plan.

"I hope they (China and India) will see the Enterprise as a global effort that they can contribute to," Bernstein said.

Created in 2003 under the leadership of the Bill & Melinda Gates Foundation, the Enterprise is an innovative effort to identify the scientific research needed to develop a safe and effective AIDS vaccine. Similar to the Human Genome Project, it aims to set a clear research agenda and bring together scientists from around the globe to tackle it.

In an interview, Bernstein talked about his new job and the challenges that lie ahead.

Q. *Why did you take the job?*

A. Two things interested me. First, the scientific challenge, which is enormous. Despite all the wonderful science that has gone on over the last 25 years, we still have a ways to go. Second, I was very intrigued by the Enterprise as a model. It's an attempt to bring everyone together – scientists, government, industry and others – and really discuss what's the best scientific approach and then grab the attention of funders.

Q. *What has the Enterprise accomplished so far?*

A. At the organizational level, new countries and funders are subscribing to the plan. Both the Gates Foundation and the National Institutes of Health have made new investments – worth more than half a billion dollars – based on what's in the strategic plan. The European and Developing Countries Clinical Trials Program is expanding trial capacity in Africa. And Canada will contribute $128 million for vaccine research as well as build a pilot vaccine manufacturing plant.

Q. *David Baltimore recently asserted that we are no closer to an AIDS vaccine now than we were 20 years ago. Do you agree?*

A. The headlines did not capture David's tone. I took from what David said that the search for an AIDS vaccine has been and will continue to be a difficult challenge. We need to find ways to address the challenge. But at the end of the day, we will defeat this virus.

Q. *How big a setback was the failure of the Merck Ad5 vaccine?*

A. Although the field is quite despondent, I have a different take. It is naïve to think that every batter is going to hit a home run. Advances in science are slow and incremental. That particular vaccine did not work, but we learned a lot from the STEP trial including the critical value of openness and transparency. The STEP trial set a new high bar in cooperation between industry, public funders, researchers and volunteers.

Q. *What is the role of private industry in the quest for an AIDS vaccine?*

A. We will not have a vaccine without company involvement. Industry has to be at the table. I am now reaching out individually to different companies. For example, one of my interests is adjuvants. We need to start a dialogue to identify conditions that would

Continued on page 4

Institute of Human Virology
725 W. Lombard Street
Baltimore, MD 21201

An institute of

DISCOVERY
LABORATORY • CLINIC • COMMUNITY • WORLD
Spring 2008

Gates Foundation Grant Will Support IHV Vaccine Research

Maryland Governor Martin O'Malley (2nd from left) announced IHV's Gates Foundation Grant at State House in Annapolis. Joining Governor O'Malley and Dr. Gallo are University System of Maryland Chancellor Brit Kirwan (l) and University of Maryland School of Medicine Dean E. Albert Reece (r).

A $15 million grant from the Bill and Melinda Gates Foundation will propel the Institute's HIV vaccine candidate through a series of crucial animal tests over the next five years.

Awarded last summer, the grant provides three years of dedicated funding with an option for an additional two years.

"This grant is a milestone for the institute," said IHV Director Dr. Robert Gallo, who is the principle investigator on the award. "It's going to take us through the next stage of research on our vaccine. I'm deeply proud of the work that's brought us here."

Dr. George Lewis, co-director of the Division of Basic Science and Vaccine Research, and researchers Dr. Anthony DeVico and Dr. David Pauza will lead three sets of experiments to optimize the vaccine.

"We're taking what we've got and figuring out the best way to improve it," said DeVico.

Unlike most other HIV vaccines in development, the Institute's vaccine is designed to neutralize many of the different strains of HIV that circulate worldwide. "Our vaccine focuses on what all strains of HIV have in common, instead of what makes each strain distinct," said Lewis.

When HIV infects a white blood cell, it first docks with a receptor on the cell's surface. To

Continued on page 5

DIRECTOR'S MESSAGE

Robert C. Gallo, MD

A Major Malfunction in Vaccine Research

When the space shuttle Challenger exploded in 1986, NASA called it a "major malfunction." The field of HIV research suffered an equally disastrous, though less obvious and infinitely less publicized, catastrophe last September. Interim data from a large, expensive vaccine trial, the STEP trial, co-sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and Merck, showed that the vaccine employing an adenovirus vector with HIV genes had failed. Not only did the vaccine offer no protection from HIV, it apparently increased the risk of infection in recipients who had previously been exposed to adenoviruses similar to the vaccine vector. Even less visible has been a similar failure of a related trial in South Africa. Early commentaries suggest that the vaccines used in South Africa were also prone to enhancing risk of infection. Remarkably, another adenovirus-based vaccine, albeit in a different form and having different HIV content, is under discussion and NIAID may go forward in testing it.

The consequences of these failures are now

Continued on page 3

Big Grant Wins Strengthen IHV Program in Nigeria

Recent grant wins totaling $49 million from the President's Emergency Plan for AIDS Relief (PEPFAR) will allow IHV to continue providing care and treatment for people living with HIV/AIDS in Nigeria, a country with 380,000 new HIV infections per year.

"There is a huge need here," said IHV Associate Director Dr. William A. Blattner, who heads the affiliated IHV-Nigeria in Abuja, Nigeria. "Our goal is to provide quality care and treatment in a sophisticated clinical structure, while implementing the largest and most complex public health program ever."

Using a comprehensive care model, integrated laboratory services and 24 clinical care sites, the team headed by Blattner has tested more than 220,000 Nigerians, with approximately 50,000 Nigerians now receiving antiretroviral treatment. Four mobile outreach units have been initiated to reach high-risk groups, including commercial sex workers (where the HIV prevalence rate is 50%), motorcycle taxi drivers and young mothers in antenatal clinics. IHV-Nigeria also employs innovative solutions to Nigeria's HIV/AIDS epidemic — mobile tuberculosis programs, six regional virology labs with advanced laboratory techniques including polymerase chain reaction, genetic sequencing, and a Biological Safety Level 3 laboratory to address the problem of drug-resistant tuberculosis.

While providing direct patient care, the IHV program found a high proportion of patients who are suspected of failing treatment previously because of poor medication adherence. The program is evaluating treatment failure by regimen with the expanded use of viral load testing and training Nigerian physicians on second-line therapy regimens. Efforts are being made to identify the best practices for patient adherence.

The Nigeria effort emphasizes the need for partnerships with the Government of Nigeria and the country's established medical institutions. Through physician and laboratory staff training, IHV-Nigeria is helping Nigeria develop its own ability to combat the country's HIV/AIDS epidemic.

IHV Director Dr. Robert C. Gallo, who visited Nigeria in late 2005, said, "the work being done now in Nigeria is extraordinary. We are very proud of our Nigerian staff and of Dr. William Blattner."

IHV-Nigeria's Emily Umaru, a public health nurse and social worker, speaks with a group of Nigerians living with HIV/AIDS.

AIDSRelief Project Treats 100,000th Patient

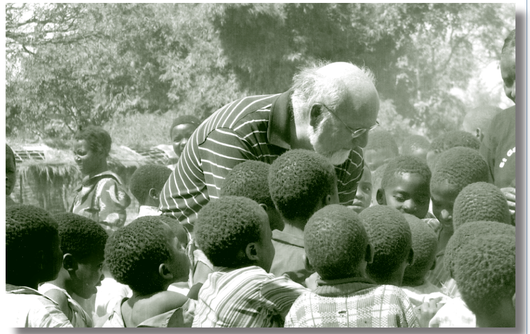
IHV's AIDSRelief project celebrated the 100,000th person on antiretroviral treatment during a ceremony held on March 7 at Catholic Relief Services' headquarters in Baltimore. IHV and Catholic Relief Services have been partners in the AIDSRelief consortium since the project's inception in 2004. The project also provides care to more than 250,000 people.

Funded by the President's Emergency Plan for AIDS Relief (PEPFAR), the project is active in Guyana; Haiti; Kenya; Nigeria; Rwanda; Tanzania; Uganda and Zambia. IHV clinical staff provide the lion's share of technical expertise in training local physicians and nurses in HIV/AIDS care and treatment and in improving clinical sites.

Speaking to a standing-room only crowd, Dr. Robert Gallo praised IHV's more than 100 clinical staff working in Baltimore and at sites across Africa and in the Caribbean, singling out AIDSRelief Principal Investigator and IHV Associate Director Dr. Robert Redfield and AIDSRelief Senior Project Director Dr. Anthony Amoroso. He noted that the IHV Scientific Advisory Board had recently described IHV's PEPFAR contributions as "historic", and looked ahead to another celebration that would be held to mark "when there is no HIV".

Dr. Redfield spoke about PEPFAR alleviating disparities in HIV/AIDS care and treatment between the developed world and developing countries, especially in Africa. "In the United States", he said, "people living with HIV/AIDS can take medication and live a normal lifespan. In Africa, people with HIV/AIDS are dead within five years unless they're treated."

AIDSRelief is projected to continue at least through 2013, with anticipated funding to IHV in excess of $120 million. Other AIDSRelief consortium partners are the Catholic Medical Mission Board; Interchurch Medical Assistance; and Futures Group.



IHV Associate Director Dr. Robert Redfield on a Recent Visit to Africa

Director's Message, A Major Malfunction in Vaccine Research

Continued from page 1

reverberating through the field. Already, some drug companies have stopped vaccine development. Others are questioning any vaccine that relies solely on cell-mediated immunity – the approach of the STEP vaccine - rather than the generation of appropriate antibodies against the virus coupled with cell mediated immunity.

While failures are an unavoidable reality of grand scientific endeavors, the fallout from the STEP trial presents an opportunity to re-evaluate the entire HIV vaccine development process. We do not need a witch hunt directed at NIH's NIAID. NIH, including NIAID, has many highly competent and dedicated administrative leaders, but taking a lesson from the Challenger would be a correct move. The intense scrutiny of NASA after the Challenger disaster led to positive changes in the way the space agency does business. Similar analyses are now needed for the government's HIV vaccine efforts.

Like Challenger's leaky O-ring, there were early signals that the STEP vaccine was doomed. The vaccine development process has concentrated too much power in the hands of a few administrators and others outside NIH who have clear conflicts of interest. Often these individuals have little or no experience in retrovirology. We need a more open process that puts a premium on accountability, creativity, and fresh points of view. This should include transparency in decision making and exclude people with conflicts of interest.

I am calling for an independent review process by objective observers to examine the events leading up to the STEP trial. The panel should be composed of people who are not involved in HIV vaccine research but who would have access to leading HIV experts. It should examine how and why pre-clinical data showing that the STEP vaccine did not work in monkeys was overlooked. Such an investigation would be analogous to what NASA did after the Challenger accident.

The panel should also thoroughly inspect the administrative machinery that greenlights vaccine candidates. The process NIH has recently used to prioritize vaccine candidates is murky, and as I already implied, some non-NIH decision makers have clear conflicts of interest. The process should instead be guided by open scientific peer review with the same conflict of interest rules employed during normal grant evaluations.

Another concern for the panel: Examining the "feed the pipeline" mentality of the vaccine clinical trials network. Countless millions of dollars have been spent building a global network of vaccine trials sites, but the capacity of this network has outstripped the number of suitable vaccine candidates. Subsequently, vaccines that offer little or no chance of success are hurried into clinical trials simply to fill the pipeline. This short-minded approach diverts resources from basic research, discovery and the development of other vaccines that have a better chance of stopping HIV. Careful thought should be given to markedly reducing the number of sites engaged in vaccine trials. Finally, I hope NIAID will cease funding large pharmaceutical companies to conduct trials that end in predictable failure. NIH's mission should focus on biomedical research and discovery and not on serving as a cash cow for the pharmaceutical industry.

During the Rogers Commission hearings on Challenger, physicist Richard Feynman said that "reality must take precedence over public relations, for nature cannot be fooled." His words ring true for HIV vaccine research today. Now is the time to pause and re-focus our efforts, because the field simply can't afford another major malfunction.

Discovery is published quarterly.
Complimentary copies are available upon request.

Questions/Comments?
Contact: Tim McCoy, tmccoy@ihv.umaryland.edu
Editor: Tim McCoy
Writers: Brian Vastag and Tim McCoy
Design: Graphic Solutions

IHV Community News

New Members Strengthen IHV Advisory Boards

John P. Coale

John P. Coale joins IHV's Board of Advisors as a leading advocate for social and institutional reform. The Washington, DC-based lawyer successfully advocated for victims of the Union Carbide accident in Bhopal, India, and forced major changes in the tobacco industry when he played a key role in obtaining billions of dollars in payments from tobacco companies. An active supporter of Democratic Party causes, he is married to Greta Van Susteren, host of Fox News' On the Record program.

Lynda Dee

Lynda Dee becomes a member of the Board of Advisors while also serving as president of AIDS Action Baltimore, a position she has held since 1987. A lawyer, she has been an outspoken advocate for patients' rights and has served on numerous local, state and national committees, including the CDC HIV Entry Inhibitor Planning Committee and Panel. She was a founding member of Baltimore's Chase-Brexton Clinic, a leading healthcare provider to communities affected by HIV/AIDS.

Richard E. Hug

Richard E. Hug joins the Board of Advisors as a former member of the University System of Maryland Board of Regents. He was previously president, chairman and CEO of the publicly listed Koppers Company, Inc. Politically active in recent years, he was finance chair for the 2002 and 2006 campaigns of former Maryland Governor Robert Ehrlich and the Maryland finance chair for the 2000 and 2004 Bush for President campaigns.

Kathleen E. Squires

Kathleen E. Squires is the newest member of IHV's Scientific Advisory Board. She is professor of medicine and director of the Division of Infectious Diseases and Environmental Medicine at Jefferson Medical College. Dr. Squires previously served as associate chief of HIV in the Division of Infectious Diseases at the Keck School of Medicine and director of HIV/AIDS Women's Activities in the 1917 Clinic at the University of Alabama at Birmingham. She is a member of the AIDS Clinical Studies and Epidemiology Study Section at the National Institute of Allergy and Infectious Diseases.

Dr. Cybele Garcia Recognized

Dr. Cybele Carina Garcia, a postdoctoral researcher from Argentina working at IHV with Dr. Igor Lukashevich, was recently awarded a $25,000 Gorgas Memorial Institute Research Award for her work to develop recombinant vaccines against Argentinean and Bolivian hemorrhagic fevers. The Gorgas Memorial Institute fosters research and training in tropical diseases through collaboration between young scientists in research institutions in the Americas and the United States.

Cybele Garcia

Vaccine Enterprise Director Underscores Research Challenges

Continued from page 6

be acceptable to both industry and academic researchers to encourage access to adjuvants.

Q. *Do you see any realistic hope for a vaccine that would prevent infection by eliciting broadly neutralizing antibodies to HIV?*

A. Although we've had a couple strategies that have not worked, I don't think we should throw the baby out with the bathwater. In addition, we don't yet know whether a prime-boost strategy might work. There are some experiments going on now to make much better antigens to combine neutralizing antibodies and smarter strategies to elicit more robust cellular responses.

Q. *What novel AIDS vaccine concepts will the Enterprise explore?*

A. I've been struck by a few things. First, the importance of mucosal immunity. Second, recent observations that a subset of T-helper cells disappear after infection. Are they important? Can we exploit that? I don't know. Third, genomics is another obvious area. Elledge's group has identified human genes that are required for HIV infection. Could they be targets not only for drug development but also for vaccine development? Fourth, what are the true in vivo correlates of immune protection? These are just some early impressions of areas for further research. And I think young investigators need to be actively encouraged to enter the HIV vaccine field.