

Discovery

FROM LABORATORY TO CLINIC



Message From The Director

ROBERT C. GALLO, M.D.

Director of the Institute



The Institute of Human Virology (IHV) has established a facility to assist Nigeria-Africa's most populous nation – in the fight against HIV/AIDS. The new entity, IHV-Nigeria, located in the capital city of Abuja, is an extension of our primary facility in Baltimore, and shares a common mission of care, treatment, training and research.

Nigeria, with an estimated population of nearly 140 million, is widely considered a frontline in efforts to stem the tide of HIV/AIDS in Africa, where the disease has claimed millions of lives. The latest research indicates nearly five percent of Nigerians are infected with HIV, the virus that causes AIDS.

IHV-Nigeria is modeled after IHV-



IHV Research Assistant Cullen Griffith (r) presents Zambian President Levy Mwanawasa (l) with a gift marking the president's visit to the IHV in June. Looking on are Clinical Care and Research Division Director Dr. Robert Redfield, clinical lab manager Joyelle Dominique, and Erin Gover, research assistant.

Baltimore and will be overseen by Dr. William Blattner, the IHV's Director of Epidemiology and Prevention. The

IHV's mission is to provide HIV/AIDS treatment and care, as well as training
(continued on page 2)

Promising Candidates for HIV Vaccines

As someone who has been with the IHV since its inception in 1995, Associate Professor Dr. Anthony DeVico has been at the forefront of a range of major research projects at the Institute. His primary focus has been to study the biochemistry of the HIV envelope and its interactions with the receptors and coreceptors on the surface of host cells. That interest, he points out, "has been a springboard for a number of other lines of investigation, leading to potential ways to block viral infection — such as by vaccines, antiviral drugs, and topical microbicides."

In many cases, the envelope proteins of a virus are good candidates for preparing vaccines against the virus. In the

case of HIV, however, the frequent mutations of its genes lead to so many variations in the viral envelope (gp120) structure that every HIV isolate may look different to the immune system. In other words, a vaccine prepared with an envelope protein from one HIV strain may provide protection against that strain but may fail to protect against other strains.

Some 15 years ago, DeVico and his colleagues thought of a way to circumvent this problem. At the time, it was known that although free HIV gp120 has epitopes (structural features that evoke an immune response) that vary among viral strains, the complex between gp120 and the host cell receptor CD4 exposes a new set of epitopes that are relatively conserved among different HIV strains. So they tested the gp120-CD4 com-

plex in rhesus macaques and found that it elicited antibodies that could neutralize a wide range of HIV isolates.

Those exciting results illuminated a path toward potential HIV vaccines. As DeVico explains, "We took the approach of using an immunogen that looks like the gp120-CD4 complex to generate antibodies to the conserved epitopes. If those antibodies are
(continued on page 3)

inside:

- 3** Using Protein Chemistry to Fight Pathogenic Microbes
- 4** IHV Honors Nobel Prize Recipient Manfred Eigen
- 6** AIDS Vaccine Advocacy Coalition

for caregivers and scientists. In addition IHV will conduct research into HIV/AIDS and related diseases. We are dedicated to the principle that research is essential to developing the best therapies, prevention strategies, and treatment and care approaches. IHV-Nigeria provides a platform for partnerships to effectively engage the best minds in solving research problems.

IHV-Nigeria's care and treatment mission is funded by awards through the University of Maryland Baltimore (UMB) from the Centers for Disease Control (CDC) that total \$22 million through March 2006. Under this program IHV-Nigeria will facilitate treatment of nearly 15,000 Nigerians during the next year at six sites around the country. The funding is part of U.S. President George W. Bush's larger Emergency Plan for AIDS Relief (PEPFAR), a \$15 billion five-year program to fight the spread of HIV/AIDS in 15 countries around the world. IHV previously received a \$64 million, five-year award as a partner with Catholic Relief Services serving nine countries — including Nigeria — through the AIDS Relief Project, managed by Dr. Robert R. Redfield, director of IHV's clinical care and research division.

Project ACTION (AIDS Care and Treatment in Nigeria) is the implementation program for IHV-Nigeria's care and treatment program. According to Project Director Dr. John Farley, a UMB School of Medicine faculty member, ACTION has already enrolled 841

patients, with an additional 1300 to be added by the end of this month. A total of six hospitals geographically dispersed throughout Nigeria have been equipped to support HIV therapy through IHV-Nigeria-initiated laboratory infrastructure upgrades and via training of 274 clinical, laboratory, and technical personnel.

The project was recently announced at the Maryland State Capitol by Lieutenant Governor Michael Steele. Dr. Donald Wilson, Dean of the University of Maryland School of Medicine, noted at the event that "health challenges related to HIV/AIDS in Nigeria mirror those in the City of Baltimore, so there is much to be learned and much to be shared."

The research and research training mission of IHV-Nigeria is powered by funding from the Centers for Disease Control, the National Institutes of Health Fogarty International Center, and, in collaboration with Harvard School of Public Health, by the Bill and Melinda Gates Foundation, totaling \$3.7 million in addition to PEPFAR funding. Central to the research training mission of IHV-Nigeria is an NIH Fogarty Center-sponsored grant that provides cutting edge research training to select Nigerian scientists. Three recent Nigerian Fogarty trainees are engaged in vaccine development, drug discovery, and drug resistance pattern research on Nigerian isolates of the virus; one trainee is named as a co-inventor on a patent disclosure. IHV-Nigeria research studies are focused on preventing HIV infection of children born of HIV infected mothers — powered by funding from a collaboration with Harvard School of Public Health and the Bill and Melinda Gates Foundation — and on acute HIV infection, through funding from CDC.

"The success of our trainees in advancing science is notable," states Dr. Abdulsalami Nasidi, the Director for Special Projects for the Federal Ministry of Health in Abuja, "but for science to advance to the next level in Africa, advanced facilities are needed." To this

end IHV through IHV-Nigeria envisions a public-private partnership to build a research facility in Nigeria that will promote a common ground for mutual scientific advancement in the discovery process. I will be traveling to Nigeria later this year to dedicate new IHV-Nigeria facilities and to chair a special scientific symposium on HIV/AIDS featuring presentations by Nigerian scientists.

We were also honored to recently meet with Zambia's President Levy Mwanawasa, share some of the work we have underway in Africa, and hear as well his personal perspective on the situation in Zambia. We are more and more encouraged and excited at the potential for growing partnerships between the scientific community and those leaders whose citizens are most affected by HIV.



▲ At a press briefing in Annapolis from l to r are Maryland Lt. Gov. Michael Steele; O.I. Udoh, deputy chief, Nigerian Embassy; Dr. William Blattner, Director of Epidemiology and Prevention at the IHV; and Dr. Bruce Jarrell, senior associate dean for Academic Affairs at the University of Maryland School of Medicine.

Dr. Gallo, working with Dr. Blattner and Dr. Abimiku, has been involved in Nigeria since 1991, when he developed the country's first dedicated HIV laboratory. In his honor, a state-of-the-art clinical and research laboratory structure at the Plateau State Human Virology Research Center was unveiled by the Nigerian government as "Gallo House" during the building dedication a year ago. According to Dr. Abimiku, a new training laboratory was implemented to provide ongoing training and quality control to ensure that HIV therapy is being safely delivered.

Discovery is a quarterly newsletter of the Institute of Human Virology. Copies are available upon request. Please send comments to:

Gwen Newman

Institute of Human Virology
725 W. Lombard Street, Baltimore, MD 21201
phone: 410.706.4616 fax: 410.706.1952
email: newmang@umbi.umd.edu

Editor: Gwen Newman
Writers: Elizabeth McKenna
Dinshaw Dadachanji
Copy Editor: Elizabeth Bamford
Staff Photographer: Risa Davis
Design: Graphic Solutions

Using Protein Chemistry to Fight Pathogenic Microbes



DR. WUYUAN LU,
IHV Associate Professor

Pathogenic microbes occur in such a wide variety and employ so many different molecular weapons that the fight against them is a daunting task. Fortunately, our bodies are equipped with a host of defense mechanisms, but, as we know, they are not always adequate to combat infection.

Given this situation, Dr. Wuyuan Lu, an Assistant Professor who joined the IHV faculty in 2000, is using his expertise in protein chemistry to help lead

the battle against pathogenic microbes on several fronts.

Lu is currently directing a research team to study an array of proteins, including (1) antimicrobial proteins, such as human defensins and psoriasin, (2) viral proteins, such as the HIV-1 matrix protein and the HTLV-1 protease, and (3) survivin, an anti-apoptotic protein expressed by tumor cells. His goals are to obtain the detailed structures of these proteins, to identify their functional sites, and to elucidate their mechanisms of action. The knowledge gained from these studies should provide insights into designing therapies for a range of diseases.

Lu's research group employs a solid-phase peptide synthesis technique that enables them to produce long, complex peptide sequences at high yield and purity. In addition, they can stitch peptides together to produce large proteins, using a method called native chemical ligation. Lu attributes these techniques to his former mentor, Dr. Stephen Kent. He lauds the post-doctoral researchers in his lab—particularly, Dr. Zhibin Wu, Dr. Xiangqun Li, and Dr. Erik de Leeuw—for their rapid

progress and high-quality work.

Wu, who joined Lu's lab in November 2000, focused his early efforts on synthesizing defensins, a group of small cationic proteins produced by various cell types, including epithelial cells and neutrophils. He explains that his main challenge was to find a way to get each primary amino acid sequence to fold into the correct three-dimensional shape. Having crossed that hurdle, he has prepared various defensins and their analogs and is investigating their structure-function relationships. He has also synthesized survivin and the HIV-1 matrix protein and is involved in designing novel ligands to interfere with the function of survivin.

Li came to Lu's group in July 2004 and has since been working on two projects. First, he synthesized the HTLV-1 protease and its substrates. He is now participating in a collaboration to study the protease structure and to design an inhibitor that targets the enzyme and blocks HTLV-1 replication. Second, he has synthesized psoriasin—a protein made by skin cells—that was recently reported to kill *E. coli*. The plan is to clarify how the structure of psoriasin is related to its function and to understand its mechanism of action.

De Leeuw, who joined Lu's team a few months back, is investigating the use of human α -defensin 5 as a therapeutic agent in treating Crohn's disease, a chronic condition that includes inflammation of the gut. Recent evidence suggests that this disease is accompanied by a reduced expression of α -defensins 5 and 6 by Paneth cells in the intestines. He is involved in developing a liposome-based oral vaccine that helps restore normal defensin levels in the intestinal epithelium.

So how does a protein biophysical chemist feel about being surrounded by cell biologists, molecular biologists, virologists, immunologists, and clinicians at the IHV? "It has been a blessing," says Lu. Complimenting Dr. Robert Gallo, Director of the IHV, for being a "charismatic cheerleader," he adds that "the support I have been receiving from Gallo and a lot of my other colleagues is really important for any success."

Promising Candidates for HIV Vaccines, *continued from page 1*

present at a high enough titer in a vaccinated individual, they may protect the person from HIV infection."

At that stage, notes DeVico, they needed an efficient system that would coexpress both proteins, preferably bound to each other. So in 2000, he and Dr. Timothy Fouts, then his postdoctoral associate, designed a synthetic gene incorporating the gp120 sequence at one end and a segment of the CD4 sequence at the other. Expression of that gene produces a single polypeptide chain, labeled "full length single chain" (FLSC). This chain folds into a structure closely resembling the natural gp120-CD4 complex, and, like the complex, it can raise antibodies that cross-react with various HIV-1 isolates. FLSC therefore appears to be an excellent vaccine candidate.

There is, however, one concern about using FLSC. Because it contains a human protein sequence (CD4), it could, theoretically, evoke an autoimmune response. Fortunately, other investigators have found that people injected with milligram quantities of CD4 have not developed autoimmune responses. Nonetheless, to provide an alternative, DeVico's team is testing a newer

polypeptide in which gp120 is linked to a scorpion toxin derivative (in a nontoxic form) that mimics the characteristics of CD4. This construct is called "single-chain M9."

The technology for preparing and testing these promising vaccine candidates has now been licensed to Profectus Biosciences, Inc., a company that recently spun off from research at the IHV. DeVico observes that, if things keep going well, "FLSC will continue toward phase I clinical trials, while single-chain M9 still needs some improvements before it is ready."



JOHN VU & DR. TONY DEVICO,
*Graduate Research Assistant
& IHV Associate Professor*

IHV Honors Nobel Prize Recipient Manfred Eigen

This year's International Annual Meeting of the Institute of Human Virology will honor German physicist Manfred Eigen as recipient of its Lifetime Achievement Award, reserved for senior scientists who have made remarkable contributions to the world at large, within the scientific field and to those at the IHV.

Eigen, 78, is a co-recipient of the Nobel Prize in Chemistry awarded in 1967 for his work with extremely rapid chemical reactions and is the recipient of



MANFRED EIGEN

numerous prestigious awards recognizing legendary contributions throughout his career. His scientific interests have ranged from the thermodynamic properties of water and aqueous solutions and the theory of electrolytes, through thermal conductivity and sound absorption, to fast ionic reactions.

In the early '50s, Eigen began his work on fast ionic reactions in solution and in subsequent years developed a series of measuring techniques involving times down to the order of a nanosecond. Eigen was able to study many extremely fast chemical reactions by a variety of methods that he introduced and which are called relaxation techniques. These involve the application of bursts of energy to a solution that briefly destroy its equilibrium before a new equilibrium is reached. Eigen studied what happened to the solution in the extremely brief interval between the two equilibria by means of absorption spectroscopy. Among specific topics thus investigated were the rate of hydrogen ion formation through dissociation in water, diffusion-controlled protolytic reactions, and the kinetics of keto-enol tautomerism.

Eigen was particularly interested in proton reactions: together with Dr. Leo De Maeyer he was the first to determine the neutralization rate and found the anomalous conduction characteristics of protons in ice crystals. The development of the theory of relaxation of multi stage processes was followed by studies on metal complex reactions, in which the fast reactions of a large number of metal ions were investigated in relation to their position in the periodic table. Around 1960 the emphasis in his work shifted towards physical-organic chemistry. The individual steps of a series of reaction mechanisms were elucidated, and a general theory of acid-base catalysis was verified experimentally.

NCI's von Eschenbach to Give IHV's Annual Greenebaum Lecture



Andrew C. von Eschenbach, M.D., Director of the National Cancer Institute, will give the Second Annual Stewart and Marlene Greenebaum Lecture on Oct. 3.

von Eschenbach is the 12th NCI director since the creation of the NCI in 1938 and formerly was with the University of Texas, M.D. Anderson Cancer Center, where he was director of the Genitourinary Cancer Center and director of the Prostate Cancer Research Program. von Eschenbach also served as vice president for academic affairs at M.D. Anderson and as executive vice president and chief academic officer, leading a faculty of almost 1,000 cancer researchers and clinicians.

A native of Philadelphia, von Eschenbach earned his medical degree from Georgetown University in Washington, D.C., in 1967. He completed residencies in general surgery and urology at Pennsylvania Hospital in Philadelphia, then was an instructor in urology at the University of Pennsylvania School of Medicine. He served as a lieutenant commander in the U.S. Navy Medical Corps. von Eschenbach went to M.D. Anderson for a fellowship in urologic oncology in 1976 and was invited to join the faculty the following year.

von Eschenbach has contributed more than 200 articles, books, and chapters to the scientific literature. He is an editorial board member of four leading journals and serves on the board for the National Coalition for Cancer Research. He was a founding member and leader of the National Dialogue on Cancer and, prior to his appointment as NCI director, was president-elect of the American Cancer Society.



Dr. Gallo was recently honored with the Golden Medal of the MM Foundation, presented by the King and Queen of Spain, and the Ellis Island Medal of Honor, awarded by the National Ethnic Coalition of Organizations Foundation, Inc.

Spotlight: Sten Vermund, IHV Scientific Advisory Board Member



Sten Vermund, Professor of Epidemiology, Medicine, Pediatrics, and Nutrition Sciences, and Director of the Sparkman Center for Global Health, School of Public Health, at the University of Alabama, Birmingham (UAB), has long been a champion of bringing together medicine, laboratory science, and epidemiology for preventing and treating infectious diseases. He brings this commitment to his future appointment as the first Amos Christie Chair in Global Health and director of the Institute for Global

Health at Vanderbilt University, as well as to the IHV.

Vermund complemented his M.D. from Albert Einstein College of Medicine with degrees earned in both Community Health in Developing Countries and Public Health from two prestigious London Schools, as well as a Ph.D. in Epidemiology from Columbia University. Prior to his 11 years at UAB, Vermund served six years as a Branch Chief at the National Institutes of Health (NIH), firstly of Epidemiology in the AIDS Program, and then of Vaccine Trials and Epidemiology in the Division of AIDS.

The late 1980s saw Vermund's pivotal clinical trial among the first to elucidate the high risk posed to HIV-positive women of cervical cancer attributable to co-infection with human papilloma virus (HPV). "This discovery gave me great personal satisfaction, primarily because it sounded the alarm for the special needs of women living with HIV, and nurtured

the seed for addressing women's health and AIDS at the NIH," a then neglected area.

More recently, via his role with the AIDS International Training and Research Program, sponsored by the Fogarty International Center, Vermund interfaces with numerous Asian and African countries, fostering the knowledge required to frame and execute prevention and treatment programs. Vermund and key UAB colleagues grew their Zambia program into a "multi-million dollar (per year) center for HIV prevention trials."

Although formally affiliated with the Board for under three years, Vermund's ties to IHV leadership hark back over a decade. He has seen the IHV make "substantial progress, growing a vibrant program in Baltimore and overseas, from scratch." Currently, he interacts most with William Blattner, Director of the Epidemiology and Prevention Division, collaborating on "modeling infectious diseases, making projections regarding epidemics, and vaccine trials preparedness."

"I like to think I'm helping the IHV gain some perspective regarding their international service enterprise (doing clinical and community work overseas), drawing from my own experiences," says Vermund. "They won't lose their research mission by broadening their focus to international service; they'll ultimately broaden their research focus as well." In his view, the relatively recent foray of the IHV into the international clinical arena will involve it in "new and tremendous activities that integrate the clinic with research, as a model for partnership."

IHV Extends Condolences Vaccine Pioneer, Beloved BOA Member Maurice Hilleman Passes Away at 85

The man credited with saving more lives than any other scientist in the past century passed away this April in Philadelphia. Maurice R. Hilleman was Director of the Merck Institute for Vaccinology and Adjunct Professor of Pediatrics at the School of Medicine, University of Pennsylvania.

"One can say without hyperbole that Maurice changed the world with his extraordinary contributions in so many disciplines: virology, epidemiology, immunology, cancer research and vaccinology," said Dr. Anthony S. Fauci, a friend and director of the National Institute of Allergy and Infectious Diseases.

Much of modern preventive medicine is based on Hilleman's work, and his

contributions helped extend human life expectancy and improve the economies of many countries. Dr. Hilleman and his



MAURICE HILLEMAN

team at Merck & Co. developed about three dozen experimental and licensed animal and human vaccines, including 8 of the 14 routinely given to young children in the U.S. today. His work is credited by scientists for virtually wiping out many of the dreaded and deadly childhood diseases that remained common just 40 years ago. His MMR vaccine protects children against three different diseases - measles, mumps and rubella. Ironically, his death came less than one month

after the Centers for Disease Control and Prevention announced that rubella had been eliminated as a health threat in the U.S.



Moynahan Honored

IHV Board of Advisors member and Connecticut-based attorney Tim Moynahan was recently named Man of the Year by Yeshiva Gedolah of Waterbury. A dinner and awards ceremony was held June 6 in New York where Tim accepted this award. Moynahan, a life-long Waterbury resident, is a principal of Moynahan, Minnella, and Tindall LLC. He is also president of the Connecticut chapter of the Ireland Chamber of Commerce in the United States and is affiliated with The Palace Theater in Waterbury, the Connecticut Trial Lawyers Association and the Waterbury Chamber of Commerce.

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.

AIDS Vaccine Advocacy Coalition

The number of people living with HIV/AIDS now approaches 40 million worldwide, and over 3 million people died of AIDS in 2004 alone. Each day 14,000 more men, women and children get infected—95% of them in developing countries.

Against this background though, one important statistic is too easily forgotten: Even in the most affected regions of the world, the vast majority of people have not acquired HIV. Providing people—especially youth—with access to the information, tools and support to remain HIV-free is an enormous challenge. Today's AIDS prevention efforts must be expanded, so they can reach more places and more people. A massive scale-up of access to treatment for infected people is also critical.

But the unbroken spread of the epidemic reminds us that we must add new tools, and a safe, effective AIDS vaccine remains the world's best chance to curb the relentless epidemic. And the search for a vaccine does not have to come at the expense of our immediate response. Testing vaccines requires that we do all the other key things anyway – delivering the best possible risk-reduction counseling and prevention tools; ensuring confidential, voluntary counseling

and testing; and providing referral to comprehensive treatment. Prevention, testing, treatment and trials.

While scientific issues remain a great challenge, without an increased sense of urgency and expanded community and public involvement, a vaccine is far less likely to bring the AIDS epidemic under control in our lifetimes.

To marshal and sustain public involvement in the global AIDS vaccine efforts, communities need information that not only educates but also suggests how people can play an active role. As the global effort to develop an AIDS vaccine scales up, the need for information geared to lay readers is growing quickly.

To address this need, the AIDS Vaccine Advocacy Coalition (AVAC) produced the AIDS Vaccine Handbook as a collection of easy-to-read, lively essays written by people involved in research and advocacy from around the globe. Edited by science-journalist Patricia Kahn, the Handbook provides an overview of the key scientific, policy, social, ethical and economic challenges involved in the vaccine effort, and of the diverse experience gained around the world over the past two decades. The essays are written by

people involved in this work in many different ways in many parts of the world.

Founded in 1995, the non-profit AVAC uses education, policy analysis and advocacy to accelerate the ethical development and global delivery of vaccines against HIV/AIDS. AVAC is committed to translating and communicating this long, complex web of activities to a wider constituency and to ensuring that the rights and interest of trial participants, eventual vaccine users and communities are fully represented and respected in the process.

The handbook is available electronically at www.avac.org and can be ordered at www.amazon.com. Copies are available free of charge to community organizations by sending an email request to handbook@avac.org.



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

a center of

