



INSTITUTE OF HUMAN VIROLOGY

Forging Global Connections and Initiating Global Leadership

2012

ANNUAL REPORT



UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE



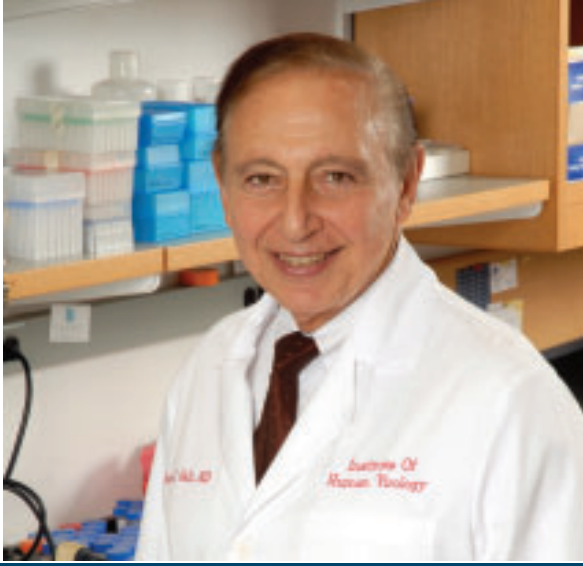
Our Mission

The Institute of Human Virology was established to create and develop a world-class center of excellence focusing on chronic viral diseases, especially HIV/AIDS, and virally-linked cancers. The IHV is dedicated to the discovery, research, treatment and prevention of these diseases. Its unique structure seeks to connect cohesive, multi-disciplinary research and clinical programs so that new treatments are streamlined from discovery to patient. The IHV serves patients locally and the scientific community globally.



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Director's Message

Robert C. Gallo, MD, Director,
Institute of Human Virology and Professor,
Departments of Medicine and Microbiology and Immunology,
University of Maryland School of Medicine

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine continues to experience growth and prosperity despite the challenges our global economy exhibits. The 13th Annual IHV International Meeting, brought back to our hometown of Baltimore, Maryland this year, continues to attract more than 300 scientists, clinicians and pharmaceutical representatives from around the world to explore the latest developments in the fight against HIV/AIDS, viral oncology and other infectious diseases. Prior to the IHV Annual meeting, IHV faculty voted for the prestigious Lifetime Achievement Award in Public Service and Lifetime Achievement Award for Scientific Contributions. The esteemed winners included:

Dr. Bernadine Healy, 2011, recipient of the IHV Lifetime Achievement Award in Public Service:



Dr. Healy's daughters, Marie Loop and Bartlett A.H. Russell, and husband, Dr. Floyd Loop, accepting Dr. Healy's award posthumous on her behalf.

For her distinguished career as a physician, educator, health administrator and the first woman to head the National Institutes of Health (NIH). Known for her honest and courageous leadership and innovative policymaking, Dr. Healy was particularly effective in addressing medical policy and research programs pertaining to women's health. Dr. Healy's family was in attendance and received the Award on behalf of Dr. Healy and a \$2,000 donation

was presented to The Bernadine P. Healy Scholarship at the Cleveland Clinic Lerner College of medicine, Case Western Reserve University.

Dr. Max Essex, 2011, the Mary Woodward Lasker Professor of Health Sciences and Chairman of the Harvard School of Public Health AIDS Initiative, recipient of the IHV Lifetime Achievement Award for Scientific Contributions:



Dr. Robert Gallo and Dr. Max Essex

For his scientific research breakthroughs which was among the first to link animal and human retroviruses with immunosuppressive diseases. In addition to the Award, Dr. Essex was presented a 2004 Boston Red Sox World Champions Autographed Bat. The exemplary science presented at the meeting began with a satellite session focusing on HIV and associated malignancies in developing countries, known as, "Expanding Research Opportunities on the African Continent." The meeting continued with New Agents for Treating Viral Diseases; Mechanisms for Vaccine Protection Against HIV; Evaluation Candidate HIV Vaccines; Interaction of Viruses and Host Cells; Immune Mechanisms Controlling Viral Diseases; Virally-associated Malignancies, and a variety of special lectures on important, emerging topics, including the phenomenon of "AIDS denialists."



National Institute of Allergy and Infectious Diseases (NIAID) Director Dr. Anthony Fauci presenting at last year's prestigious IHV International Annual Meeting.

The Basic Science and Vaccine Development (BSVD) Division saw significant progress in the past year. Central to research and development on our HIV preventive vaccine candidate are two major grants from the Bill & Melinda Gates Foundation. The first of these grants (Gates 1) is in its final year and supports later phase stage preclinical studies and basic research needed to justify transitioning the major HIV preventive vaccine candidate from IHV into clinical development and human trials (Gates 2). These two major grant awards total more than \$42 million. I look forward to working with my colleague and BSVD Co-Division head, Dr. George Lewis and senior IHV researchers, Dr. Anthony DeVico, Dr. David Pauza and IHV Animal Models Division Director, Dr. Joe Bryant. After the completion of phase 1, IHV associate director and head of the Clinical Care and Research Division, Dr. Robert Redfield, and his team will begin clinical trials here in Baltimore. Other faculty in the BSVD Division have been successfully pursuing research in a broad range of research topics encompassing the immunology of persistent viral infections, viral pathogenesis and innovative research on treatment.

The Clinical Care and Research Division, led by Dr. Redfield, launched exciting unique and new collaborations and working partnerships. From the Division's thriving international programs, which have been building strength and growing into new phases of development since 2004, to the continued expansion of clinical outpatient and inpatient services within the University of Maryland School of Medicine, the Clinical Division has initiated some useful and important collaborative projects which have brought new faculty to the Division, as well as sparking growth in existing programs. Dr. Redfield continues to lead programs in Baltimore, Maryland including serving more than 5,000 HIV positive Baltimoreans. Dr. Redfield also oversees and manages programs in Ethiopia, Kenya, Malawi, Nigeria, Rwanda, Tanzania, Uganda, Zambia, Guyana and Haiti.

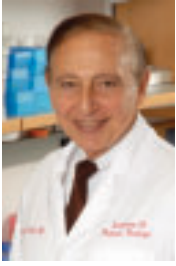
Led by Dr. William Blattner, the Epidemiology and Prevention Division has multiple national and international partners to implement clinical and molecular epidemiologic studies of HIV, virally associated cancer, and their pathogenesis. In the last eight years, the Division

of Epidemiology and Prevention has scaled up research capacity in Nigeria resulting in clinical and laboratory research and training grants. Combined, Dr. Redfield and Dr. Blattner manage programs with more than 750,000 HIV positive Africans in treatment. Specifically, the Division focuses on mother-to-child transmission of HIV, HIV and tuberculosis, emerging resistance to HIV treatment, clinical trials, neurological consequences of HIV infection, cancer epidemiology, and building nursing and pediatric capacity in Nigeria.

IHV Associate Professor and Animal Models Division head, Dr. Joseph Bryant, continued to see growth in research and grants this past year. The Division continues to support BSVD and IHV's HIV preventive vaccine candidate research by studying and hopefully overcoming one of the greatest stumbling blocks to an effective vaccine, namely the sustainability of effective humoral immunity achieved by a candidate vaccine in the face of repeated challenge. The Division also supports a study to investigate the safety, efficacy, and mechanisms of action of Korean Wild Ginseng cambial meristematic cells (DMCs) in the treatment of HIV/AIDS. We believe this technology, in collaboration with Korea's Unhwa Bio Corporation, could contain one or several anti-HIV compounds that can be used alone or in combination with anti-retroviral drug therapy that acts against HIV directly or indirectly. The Division has begun to work closely with Jamaican collaborator, Dr. Henry Lowe and his team, on natural plant products as anti-cancer and anti-HIV compound. Dr. Bryant is also collaborating with Drs. Gallo and Davide Zella on the role of a new Mycoplasma isolated at IHV and the role it plays in Lymphoma, especially in AIDS patients. Lastly, the Division in close collaboration with Dr. Gallo and other IHV senior faculty are preparing for submission of a P01 grant on p17 as it relates to B cell lymphoma. Dr. Bryant's team will play an integral role in the development of the animal model for this project.

In 2012, IHV continued its significant impact on Maryland by generating large amounts of external revenue through grants and contracts. This year saw a major change to the President's Emergency Plan for AIDS Relief (PEPFAR) funding impacting several major Universities' programs, including those at IHV. Whereas, in the past, funding has gone directly to U.S. Universities to implement programs overseas, some countries executed a distinct shift towards funding indigenous organizations instead. However, IHV's increases in basic science research, vaccine research and international institutional strengthening grants offset most of the lost PEPFAR revenue. IHV's major funding sources now include the U.S. National Institutes of Health, the Bill & Melinda Gates Foundation, and the U.S. Centers for Disease Control and Prevention. Additionally, many of the international institutional strengthening grants are subcontracts where an indigenous organization is the prime, increasing our contracting and financial flow challenges. Overall, IHV had a very successful fiscal year, and continues to strategize new revenue opportunities within our mission of fighting chronic viral diseases and cancer.

IHV Leadership



Robert C. Gallo, MD

Director, Co-Director, Division of Basic Science and Vaccine Research, Institute of Human Virology and Professor, Medicine and Professor, Microbiology and Immunology, University of Maryland School of Medicine



William A. Blattner, MD

Associate Director, Director, Division of Epidemiology and Prevention, Institute of Human Virology and Professor, Medicine, University of Maryland School of Medicine



Robert R. Redfield, MD

Associate Director, Director, Division of Clinical Care and Research, Institute of Human Virology and Professor, Medicine and Professor, Microbiology and Immunology, University of Maryland School of Medicine



C. David Pauza, PhD

Associate Director, Institute of Human Virology and Professor, Medicine, University of Maryland School of Medicine



George K. Lewis, PhD

Co-Director, Division of Basic Science and Vaccine Research, Institute of Human Virology and Professor of Microbiology and Immunology, University of Maryland School of Medicine



Joseph L. Bryant, DVM

Director, Division of Animal Models, Institute of Human Virology and Professor, Medicine, University of Maryland School of Medicine



Dave R. Wilkins

Chief Operating Officer
Institute of Human Virology
University of Maryland School of Medicine



About IHV

The Institute of Human Virology (IHV) is the first center in the United States—perhaps the world—to combine the disciplines of basic science, epidemiology and clinical research in a concerted effort to speed the discovery of diagnostics and therapeutics for a wide variety of chronic and deadly viral and immune disorders—most notably HIV, the cause of AIDS.

Formed in 1996 as a partnership between the State of Maryland, the City of Baltimore, the University System of Maryland and the University of Maryland Medical System, IHV is an institute of the University of Maryland School of Medicine and is home to some of the most globally-recognized and world-renowned experts in the field of human virology.

The Institute, with its various laboratory and patient care facilities, is uniquely housed in a 100,000-square-foot building located in the center of Baltimore and our nation's HIV/AIDS epidemic. IHV creates an environment where multidisciplinary research, education and clinical programs work closely together to expedite the scientific understanding of HIV/AIDS pathogenesis and to develop therapeutic interventions to make AIDS and virally-caused cancers manageable, if not curable, diseases.

A particular focus of IHV includes learning how to utilize the body's natural chemistry for its own therapeutic potential and pursuing biologically-based treatment approaches that are less toxic to the body and, often, less costly to the patient and public. IHV also pursues the development of effective therapeutic and preventative vaccines, science's greatest hope in putting an end to the AIDS pandemic.

IHV's approximately 300 employees includes more than 70 faculty whose research efforts are focused in the area of chronic human viral infection and disease. At present, more than 75 percent of the Institute's clinical and research effort is targeted at HIV infection, but also includes the Hepatitis C virus, herpes viruses and cancer research.

The Institute is divided into four major divisions: Basic Science and Vaccine Development, Clinical Care and Research, Epidemiology and Prevention, and Animal Models. To learn more about the Institute and its initiatives, visit www.ihv.org or contact IHV's Director of Public Relations, Nora Grannell at ngrannell@ihv.umaryland.edu.

"The Institute of Human Virology has committed itself to a bold plan that includes clinical product development and basic science research. These twin tracts are driving our vaccine program and may be a future model for development of the Institute."

Dr. Robert Gallo



Dr. Brian Taylor,
Research Supervisor,
 μ QUANT Core Facility

Division of Basic Science and Vaccine Development

The Division of Basic Science and Vaccine Development (BSVD) is the primary engine of discovery for the Institute of Human Virology. Co-directed by Drs. Robert C. Gallo and George Lewis, faculty in this division address a broad range of research topics encompassing the immunology of persistent viral infections, viral pathogenesis, innovative research on treatment, and most importantly, development and testing of preventive HIV vaccines. Investigators in this division are funded by the National Institutes of Health, philanthropic organizations, corporate collaborators and significantly, the Bill & Melinda Gates foundation. FY2012 has been an outstanding year for progress in this division and we are pleased to report here.

Central to research and development on preventive HIV vaccines are two major grants awarded by the Gates Foundation to Dr. Gallo. The first of these grants (Gates 1) is in its final year and supports later stage preclinical studies and basic research needed to transition the major HIV preventive vaccine candidate from IHV into clinical development and human trials (now funded as Gates 2). These two major grant awards, totaling more than \$42 million, build on two key criteria: 1) durable protection against HIV transmission requires a potent and durable antibody response to the envelope glycoprotein; 2) a conformationally constrained envelope protein (known as Full-Length Single Chain or FLSC) is uniquely capable of presenting key targets for the development of protective antibodies. In pursuit of these objectives, Dr. Gallo created a consortium of researchers involving laboratories at IHV, including its animal testing facilities, clinical testing capacity for human trials, the United States Military HIV Research Program, and Sanofi Aventis, all of which are moving forward in development of the FLSC HIV vaccine.

An important justification for the IHV vaccine program was a large clinical vaccine trial conducted by the United States Military HIV Research Program and Sanofi Aventis, which occurred in Thailand and is known as the "Thai trial." This important clinical study showed that antibody responses to vaccine comprised the protective activity against HIV transmission but raised numerous questions about how these antibodies would perform. "This work stems from the Thai trial," says Dr. Anthony DeVico, "which was predicted to fail because immunogens didn't generate neutralizing antibodies but the trial did not fail. There was protection against HIV transmission, but it wasn't conventional neutralizing antibodies." Thus, a critical



Dr. Joseph Bryant and Dr. Robert Gallo

objective for basic research at IHV is to define the mechanisms for protection with "non-neutralizing antibodies" and learn how to optimize these responses to increase vaccine efficacy.

Dr. Anthony DeVico focuses on understanding the roles for non-neutralizing antibodies in vaccine-induced protection against HIV infection and improving their durability in immunized patients. There is one non-human primate study ongoing and the goal is to prolong the protective antibody response after vaccination, which is a key objective for HIV vaccine development.

There has been in the past year a bigger effort towards understanding antibody-dependent cellular cytotoxicity (ADCC) and Fc-mediated immunity, which is being supported mainly by Dr. George Lewis' Gates grant. "It got into people's heads that protection was certainly due to antibodies, but another kind of antibody that wouldn't register in neutralization assay," says Dr. DeVico. "That generated a lot of interest in ADCC and Fc-mediated immunity that led to the Gates Foundation's interest in putting out these grants, which led to Dr. Lewis' grant."

Research from other institutions focuses on the belief that the best ADCC comes from antibodies that target cells already infected by HIV, which is probably a contributing factor. IHV researchers believe antibodies that attack the virus just as it is attaching and entering a cell, will be equally or more important in developing a successful vaccine. In passive protection studies, IHV researchers found that animals infected before giving an antibody, are not protected. This research proves that antibodies must be present before the time of infection. Dr. DeVico, has been using confocal microscopy to visualize epitope exposure during in

vitro antiviral assays. Some monoclonal antibodies that Drs. George Lewis and Yongjun Guan derived from infected people, will kill cells with attached virions, but it's not always obvious why that happens. We do microscopy to show the relevant epitopes are there and to confirm the mechanism for protection.

There are three major research goals that Dr. George Lewis' group has continued to pursue over the past year. The first includes supporting the development of FLSC immunogen as a vaccine candidate in human trials. That effort is a long-standing collaboration among Institute members and has advanced beyond the basic science level with a planned Phase I clinical trial in 2013-2014. Dr. Lewis' group is supporting that effort by providing transitional continuity from the preclinical studies carried out over the years. In addition, his group is providing key antibody reagents for characterizing the immunogen and for monitoring antibody responses during future vaccine trials. The second major goal includes identifying and characterizing broadly neutralizing antibodies against HIV-1. This work is a team effort with Drs. Yongjun Guan, Marzena Pazgier, Roberta Kamin-Lewis, Mohammad Sajadi, and Anthony DeVico as well as other members of IHV and investigators at other institutions. To date, the group has identified a novel, broadly neutralizing monoclonal antibody that differs in specificity from those isolated by other investigators. Notably, the somatic mutation profile of this antibody is substantially more restricted than existing broadly neutralizing antibodies, making the epitope recognized by this antibody is substantially more restricted than already known broadly neutralizing antibodies, making the epitope recognized by this antibody a strong candidate for rational vaccine design. They have made significant progress in the development of new immunogens based on this epitope.

The third major goal of Dr. Lewis' lab includes defining the role for Fc-mediated effector function in protection against HIV-1. This work is conducted at the IHV as well as with collaborators at other institutions. This effort has led to the identification of non-neutralizing monoclonal antibodies that are extremely potent mediators of Fc-mediated effector function against epitopes that are exposed during viral entry. These antibodies recognize regions of gp120 and gp41 that are obscured in native viral spikes but that become exposed during viral entry. Over the next year, Dr. Lewis' team will pursue further characterization of the monoclonal antibodies in goals two and three by physical-chemical, cell biology, and in vivo approaches including passive immunization in rhesus macaques.

Dr. Lewis' group has achieved five major accomplishments over the past year including:

1. Isolation of novel broadly neutralizing monoclonal antibodies against HIV-1.
2. Identification of new immunogens based on the epitope recognized by our new broadly neutralizing antibodies.
3. Identification of gp120 and gp41 epitopes that are strong targets of Fc-mediated effector function.
4. Characterization at the atomic level of the epitopes recognized by two sets of monoclonal anti-gp120 antibodies that mediate potent Fc-mediated effector function.
5. Development of a new antibody dependent cell mediated cytotoxicity assay format to identify previously uncharacterized responses to epitopes that become exposed during viral entry. This assay is our primary measure of Fc-mediated effector function.

This research provides new information on the range of specificities that mediate protective antibody responses to HIV-1 and provides an avenue to the design of new immunogens as components of an HIV-1 vaccine.

The studies described above identified an epitope target that is the basis for new immunogen designs to elicit broadly neutralizing antibodies. This epitope is unique in that it appears to be transiently exposed during viral entry, showing for the first time, that such structures can be targets of broadly neutralizing antibodies. In addition, these studies show that highly conserved gp120 and gp41 epitopes recognized by non-neutralizing antibodies are very potent targets for Fc-mediated effector function. These epitopes are also exposed selectively during viral entry.

Funding from the first Gates grant on which Dr. Gallo is principal investigator (PI) seeded the monoclonal antibody studies; observations made in that study led



Dr. George Lewis

to a third Gates grant to Dr. Lewis, involving Drs. Guan, DeVico, and Pazgier as project leaders. The broadly neutralizing antibody studies were also supported by two National Institutes of Health (NIH) grants to Dr. Lewis with Drs. Guan, Kamin-Lewis, and DeVico as collaborators. These grants were also seeded by observations made in Dr. Lewis's project on the first Gates grant.

As mentioned in the Director's Message, the Clinical Division, led by IHV Associate Director Dr. Robert R. Redfield has been supporting development of the FLSC immunogen for IHV's first in-house HIV vaccine to be evaluated in a Phase 1 clinical trial that will likely begin in January 2014. There will be a total of 36 people enrolled in the trial. If all goes as scheduled, patients will make 13 visits over 48 weeks to be screened, immunized and give blood for evaluating the strength, magnitude and durability of vaccine response.

For clinical trial approval of a vaccine, scientists must eventually complete 3 test phases; the primary goal of Phase 1 is to test safety of the vaccine. The Phase 1 trial will take place at the IHV and if the vaccination is successful, it will move internationally to a Phase 2 trial that will test the efficacy of the vaccine and ask the question, "What does a full-length single chain do to protection against HIV when included in the same plan used before for the modestly successful Thai trial?"

Vaccine development is more complex in the later stages because one must prove that the immunogen does what it says it does. In the Phase 1 trial, the sole goal is to identify whether there are serious misgivings or problems (with the vaccine product). With IHV's vaccine, one of the biggest concerns is whether or not someone could develop a response against their own CD4 cells, but otherwise, envelope vaccines haven't shown much toxicity in the past and there should not be a problem with this vaccine.

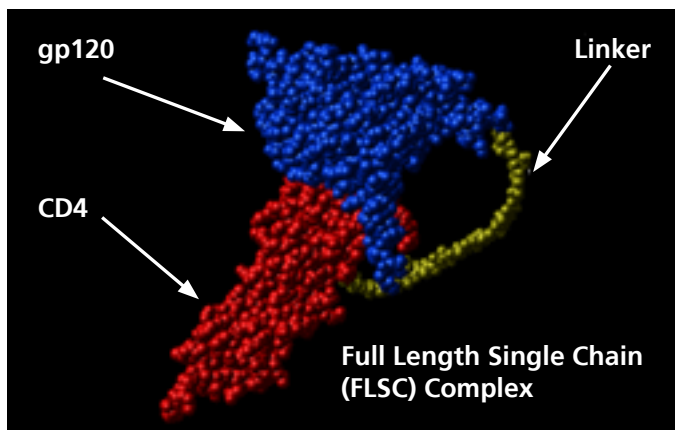
A final vaccine product, before injecting into people, must have animal toxicity studies to demonstrate that there are no safety concerns. The next step is to go into two different studies that look at the stability

and toxicity of the vaccine. This past year has seen the process of developing a human studies protocol, manufacturing the product and getting it ready to go into the toxicity study so the Phase 1 clinical trial can follow in early 2014.

Early-stage vaccine research

In addition to the advanced development and testing program for the Full Length Single Chain HIV vaccine candidate, other early-stage vaccine research efforts are also underway at IHV. In Dr. Maria Salvato's laboratory with funding from the NIH, new adjuvants are being investigated to improve and extend the immune response to HIV vaccines. Adjuvants are compounds (chemical or biological) that are added to elicit stronger responses when injected into people. Distinct from usual adjuvant studies which focus on chemical compositions that can be admixed with proteins or DNA immunogens, Dr. Salvato has focused on co-delivery of important cellular regulatory molecules which may affect the longevity of immune cells. By manipulating pathways controlling cell survival, Dr. Salvato and her colleague Dr. Jiabin Yan have increased and modified the immune responses to HIV vaccine components. This novel approach to improving vaccine efficacy gives us an ability to regulate the relative abundance and function of immune cells capable of increasing or decreasing the immune response to antigen. So far, these studies have been performed in mouse models where it is possible to control carefully the dose of each vaccine component, and to conduct detailed studies on the immune responses. With these results in hand, Dr. Salvato is continuing the pathways for testing HIV vaccine efficacy. Efforts to manipulate cell-signaling pathways are used more commonly in cancer vaccines than in viral vaccines at present. These innovative research studies offer a new look at approaches to manipulating immune responses to HIV and other viral pathogens.

An important challenge to HIV vaccine development is the difficulty of eliciting protective mucosal immune responses. Mucosal surfaces are the primary routes for HIV infection and it has long been believed that strong immune responses at these sites will improve protection against sexually transmitted disease. However, few methods have been successful for delivering protein antigens to mucosal surfaces in a way that elicits strong and durable immunity. Consequently, other investigators have turned to recombinant bacterial or viral vectors capable of immunizing in the mucosa. Dr. C. David Pauza and colleagues' goal was to develop new methods for direct mucosal immunization with protein antigens. Working with Dr. Xiaoping Zhu at the University of Maryland College Park, we developed a new concept for mucosal antigen delivery using mouse models. Taking advantage of a unique molecule on epithelial



cell surfaces, designated Fc receptor neonatal or FcRN, we were able to target HIV structural proteins for transmucosal delivery by linking the virus protein (group-specific antigen or gag) to an Fc sequence obtained from normal human antibody (IgG). The resulting fusion protein, gag-Fc, was delivered to the surface of nasal mucosa and internalized rapidly because it binds FcRN which is a transporting receptor, here pumping the fusion protein across the mucous layer to underlying immune cells. In this way, strong immune responses were developed against gag, and mice were protectively immunized. With new funding from the NIH, Dr. Pauza's group is expanding this program to include HIV envelope glycoprotein antigens (gp120) and testing in both mice and nonhuman primates. The team working on this project includes Dr. Pauza's group, Dr. Xiaoping Zhu from UMCP, and Dr. Lai-Xi Wang from our Institute, who will develop new ways to deliver adjuvants along with the fusion proteins. We are excited about this novel method for antigen delivery and hope to contribute an alternative immunization method that can be considered within the HIV vaccine program.

Dr. Lai-Xi Wang has continued studies in glycobiology as related to HIV vaccine design and antibody effector functions. It is known that



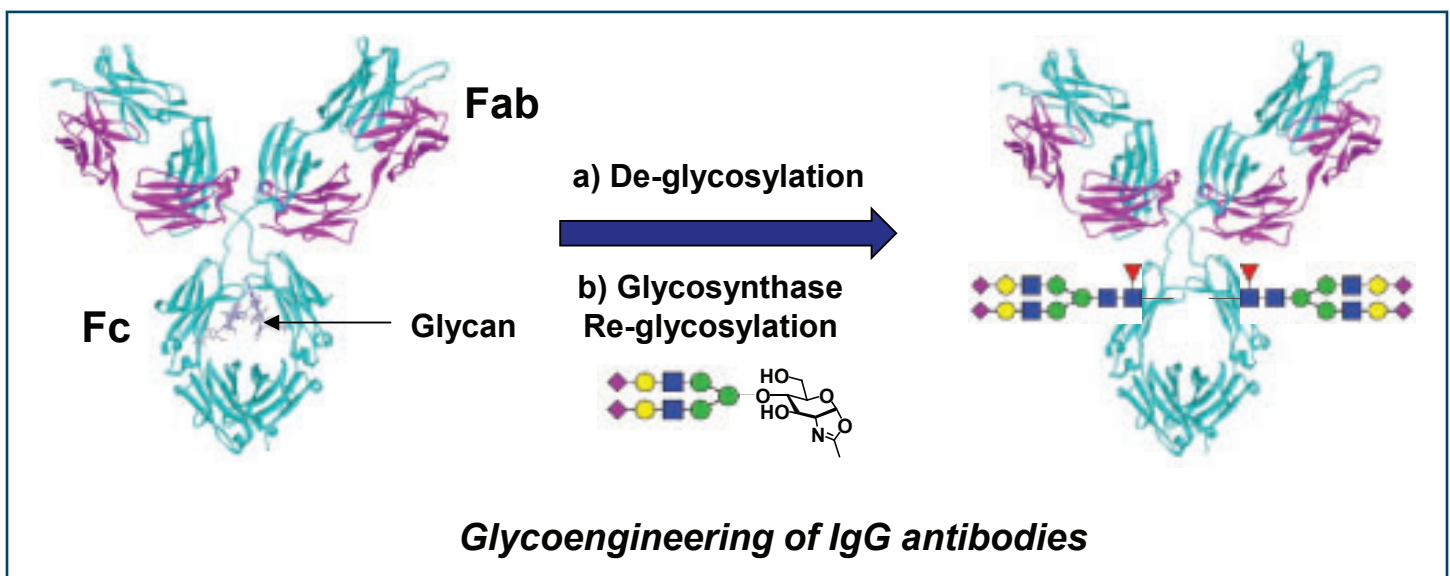
Dr. Lai-Xi Wang

Fc glycosylation of antibodies (the chemical process of adding sugars to the proteinaceous antibody) plays a key role in modulating the effector functions of antibodies, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and anti-inflammatory activity. Nevertheless, commercially available therapeutic IgGs, such as monoclonal antibodies and intravenous immunoglobulin (IVIg), typically exist as mixtures of glycoforms that are not optimal for their respective therapeutic activities.

Dr. Wang's group has developed a highly efficient chemoenzymatic method that permits site-specific remodeling of Fc glycosylation—a two-step enzymatic approach that

includes deglycosylation of the heterogeneous glycans and site-specific enzymatic attachment of now desired glycans. New enzymes and their mutants were discovered to expand the scope of this approach, enabling the production of a series of well-defined antibody glycoforms with enhanced specific effector functions. Toward this end, Wang's approach has been applied successfully to glycoengineering of two important antibodies used in cancer treatment, rituximab and cetuximab, to enhance their ADCC activity, and for the glycosylation remodeling of IVIG to enhance its anti-inflammatory activity. One of the recent publications from his group (*J. Am. Chem. Soc.*, 2012, 134, 12308) was selected for "JACS spotlights" and was highlighted in Faculty of 1000 as a research "of exceptional significance" (<http://f1000.com/717953944>).

Dr. Wang's laboratory is also using a novel chemical approach to characterize the epitopes (antibody recognition sites) of glycan-dependent, broadly neutralizing antibodies such as PG9 and PG16 which were developed elsewhere. In collaboration with Dr. Peter Kwong at NIAID/NIH, Dr. Wang designed and synthesized a series of homogeneous cyclic V1V2 glycopeptides representing a defined portion of the HIV envelope

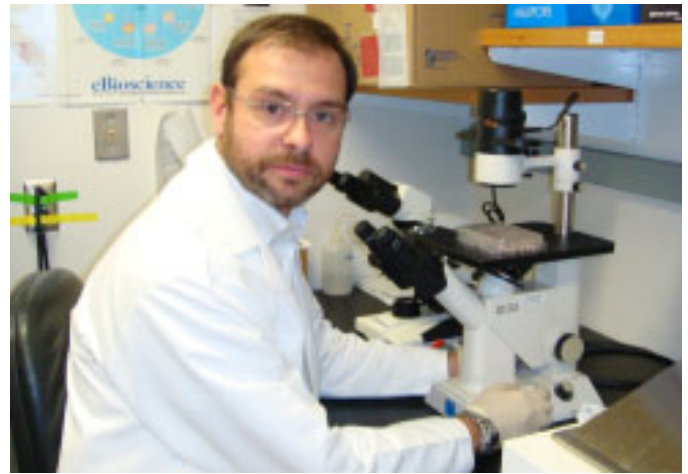


glycoprotein, with well-defined glycans attached at the conserved glycosylation sites (N156 and N160), to recapitulate the true epitopes of PG9 and PG16. Binding studies indicate that the fine structures of N-glycans at both the N156 and N160 sites were critical for antibody recognition. In particular, a complex type sugar at the N156, rather than a high-mannose type glycan (which is less complex), is critical for the high affinity binding of PG9 and PG16 to the antigen, which was not revealed by the X-ray crystallography study of PG9 (Nature, 2011, 480, 336).

These studies provide important insights for HIV-1 vaccine design. In addition, the synthetic HIV-1 V1/V2 glycopeptides will be valuable to serve as coating antigens for detecting glycan-dependent neutralizing antibodies from sera of HIV-infected patients, or those involved in HIV vaccine trials.

Towards A Cure: Research Studies on HIV Restriction Factors and HIV Latency

Studies in the Laboratory of Virus Host Interactions (PI: Dr. Alfredo Garzino-Demo) investigate the impact and mechanistic aspects of human beta-defensins (hBD) 2 and 3, antimicrobial peptides that are produced in mucosae and are known to inhibit HIV. Our data show that hBD2 and 3 inhibit HIV intracellularly, with a mechanism mediated by the antiviral factor APOBEC3G. In particular, we observed that the beta defensins induce APOBEC3G in both resting and activated CD4+ T cells, and in macrophages. The induction is mediated by the chemokine receptor CCR6, which is utilized by hBD2 and 3 possibly to bridge innate and adaptive immune responses. CCR6 is expressed on cells that are of key importance to HIV infection: CD4+CCR5+ T cells, memory T cells, α 4 β 7 cells, immature dendritic cells, macrophages, and Th17 cells. The latter cell type is of particular importance, since Th17 cells are significantly and specifically depleted from the mucosa of HIV infected subjects and of primate animal models of pathogenic SIV infection, but not in non-pathogenic SIV animal models. The depletion of Th17 cells is thought to constitute one of the initial insults to mucosal integrity, leading to immune activation for example by microbial translocation. Protecting Th17 cells, and all CCR6+ cells from infection may limit the damage caused by HIV to the immune system, making defensins (or other molecules that signal through CCR6) candidates for topical microbicides or, that may be used therapeutically in HIV disease. Our NIH-funded studies established the relevance of CCR6 or its ligands to HIV infection, and defined signaling pathways that increase APOBEC3G expression. We now have a greater understanding of how defensins participate in viral immunity, and the important consequences of Th17 changes in disease progression. Dr. Garzeno-Demo's laboratory is also involved in studies on the role of HIV in lymphomagenesis (see next section).

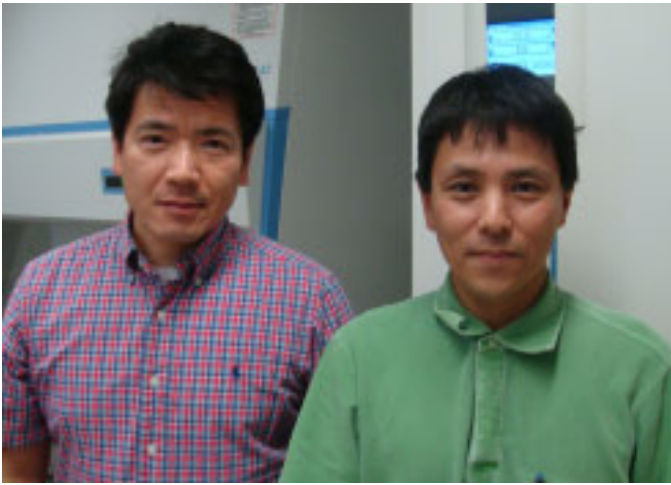


Dr. Fabio Romerio

Eliminating HIV-1 from infected patients is the ultimate therapeutic achievement. Highly active antiretroviral therapy (HAART) in 1996 improved the quality and the expectancy of life for individuals infected with human immunodeficiency virus (HIV)-1. HAART achieves remarkable results in suppressing HIV-1 replication to levels so low that it cannot be detected in blood. However, HAART is not the magic bullet: it is expensive, toxic, and requires strict compliance. More importantly, HAART does not cure HIV-1. A major reason for that failure is that HIV-1 has developed ways of infecting some cells without killing them: it stays within them for long periods of time, hiding from HAART and from the immune system. Researchers at the Institute of Human Virology are studying the nature of these cells, called viral reservoirs: how they are established, how they work, and ultimately how they can be eliminated. Dr. Fabio Romerio is focusing his efforts on CD4+ T cells, which represent the largest viral reservoir in the body. He found a way to produce these cells in the laboratory, and is searching for cell surface biomarkers that can be used to identify these cells and—possibly—as therapeutic targets. Their work revealed that latently infected CD4+ T cells of HIV-1 patients treated with antiretroviral drugs express higher levels of the molecule CD2 on their surface compared to uninfected cells. Dr. Romerio is now testing whether this different behavior can be exploited therapeutically. In addition, he is searching for additional surface molecules that can be used in combination with CD2 to identify with high specificity latently infected CD4+ T cells in patient samples.

Expanding emphasis on Cancer Biology in the IHV

Dr. Yutaka Tagaya, Assistant Professor, is in his second year at IHV. He is expanding his previous immunology projects at the NIH, and expanding his work to include virological aspects affecting intercellular factors that control T cell responses to foreign agents such as infecting human T cell leukemia virus type 1, which was the first known human retrovirus and was discovered

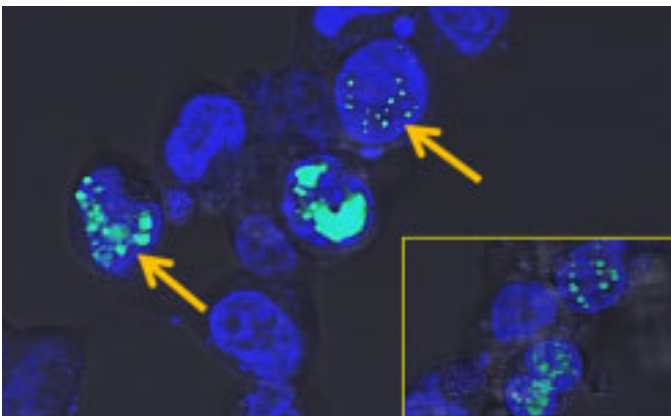


(L to R) Dr. Hua Cheng and Dr. Yutaka Tagaya

in 1980 by Dr. Gallo and colleagues while still at the National Cancer Institute. These factors may have an important role in development of a neurological disease called HAM/TSP that is caused by HTLV-1. HAM/TSP is a group of neurological disease associated with HTLV infection. Additionally, HTLV-1 is the first virus that was shown to directly cause human cancer.

Since last summer, Dr. Tagaya has been developing the program on HTLV, and he collaborates with Dr. Steve Jacobson's group at NIH, which specializes in HAM/TSP. Dr. Tagaya's goals are to understand mechanisms of these neurological diseases and find new therapies. Currently, there is no effective treatment available for HAM/TSP and once signs of neurological degeneration arise there is nothing that can be done.

Dr. Tagaya is also conducting research on Adult T Cell Leukemia (ATL), which is another disease caused by HTLV-1. He has past experience studying this virus and thought it would be a good way to start a group at the IHV. Last summer an old colleague of Dr. Gallo's from Japan, Dr. Maeda, provided cell lines derived from ATL, for studies in Tagaya's lab. He has been using these cells to find causes for leukemia. Dr. Tagaya is interested in finding a therapy treatment because, like HAM/TSP, ATL is a very difficult to treat in the aggressive form. Fortunately, IHV has decided to expand the emphasis



293T cells expressing HTLV-1 basic leucine zipper factor (N-HBZ GFP-C) on a protein level: O. Latinovic, PhD and Y. Tagaya, PhD MD

on HTLV-1 including the recruitment of Dr. Hua Cheng, who recently joined our staff.

Dr. Sabrina Curreli, Research Associate, works in Dr. Gallo's laboratory and focuses on lymphoma development in association with other infectious agents. Her main project consists of understanding the roles for Mycoplasma infection in lymphomagenesis. This work is done in close collaboration with Dr. Davide Zella from the Basic Science Division, who with Dr. Gallo initiated this study along with Dr. Joseph Bryant, head of the Animal Models Division. In the past year, Dr. Gallo's laboratory (chiefly, Dr. Zella) discovered a strain of Mycoplasma fermentans present in cell cultures during primary isolation of HIV, that induces lymphoma in SCID mice. They are studying the molecular mechanisms for neoplastic transformation and have isolated a protein from Mycoplasma that deregulates the p53 or cancer prevention pathway. This research is relevant because Mycoplasmas are associated with human cancer. However this is the first time that a Mycoplasma tumorigenic protein has been identified. This research could lead to the development of new diagnostic tools and therapeutic approaches in cancer.

Dr. Curreli is also involved in characterizing HIV transgenic mice (with HIV genes inserted into the DNA of mouse cells) that develop pre-B cell leukemia/lymphoma. This project is done in close collaboration with Dr. Joseph Bryant and Dr. Zella, all under Dr. Gallo's supervision. HIV infection is associated with a high incidence of B-cell non-Hodgkin lymphomas and the risk of developing lymphomas is increased approximately 150- to 250-fold among HIV-infected patients compared with the general population. HIV-induced chronic B cell stimulation seems to be critical for lymphomagenesis, however the role for HIV in lymphoma development is not fully understood. This HIV transgenic mouse model is important because it reproduces the high risk for lymphoma seen normally in HIV patients, and is one of a few models for the study of lymphoma development in association with HIV.

This transgenic mouse project is currently tightly connected to a much larger project on the tumorigenic role of HIV p17, which involves numerous scientists at the IHV led by Drs. Gallo, William Blattner, Alfredo Garzino-Demo and Bryant along with collaborators at the Universities of Brescia and Aviano in Italy. These studies are important for understanding the process of lymphomagenesis in HIV infection and could reveal a new tumorigenic role for HIV in lymphoma.

In a recent development, the laboratory has also started to investigate one of the most common AIDS-defining cancers, i.e. B cell lymphoma. In this context, our studies are evaluating an HIV transgenic mouse that has a high incidence of lymphoma, developed by the Animal Model Division. Since this model does not allow for replication of HIV, it is

likely that lymphomagenesis is driven by one HIV protein. One attractive candidate for this role is the p17 Matrix protein of HIV, which has been the focus of a long-term collaboration between our Institute (Drs. Gallo, Garzino-Demo and Romerio) and the University of Brescia (Dr. Arnaldo Caruso). p17 binds to B cells, triggering intracellular signaling (possibly mediated by chemokine receptors CXCR1 and CXCR2, which have been shown to bind p17) and leading to increased clonogenic activity of a B cell line. Based on research performed at the Institute, (Drs. Gallo, Mika Popovic) p17 is detectable in the lymph nodes of HIV infected subjects, even after initiation of antiretroviral therapy, with undetectable HIV RNA signal. Thus it is conceivable that chronic stimulation of signaling in B cells by p17 could initiate or accelerate B cell lymphoma. Preliminary data from our group have shown that p17 is produced in the transgenic animal. We are now studying whether p17, alone or in combination with other HIV proteins, could be the culprit for the increased rates of lymphoma in the transgenic animal model, and have established p17 transgenic mice. Data from these studies will become a component of an institute-wide program project grant (including Drs. Gallo, Blattner, Garzeno-Demo, and Bryant) in collaboration with the University of Brescia (Dr. Arnaldo Caruso) and the oncology center of Aviano, Italy (Dr. Riccardo Dolcetti).

Research on malignant disease in patients with HIV is expanding rapidly at the IHV. Cancer is now a leading cause of death for patients with HIV and the frequency of cancer in that group is rising each year. In the early years of the HIV epidemic, we recognized lymphoma, especially in the central nervous system, Kaposi's sarcoma, and rectal carcinoma as indicators of progression to AIDS. During ensuing years, we are increasingly aware of rapid rises in the incidence of non-AIDS cancers which include a broad spectrum of malignant

diseases. Dr. David Riedel from the Clinical Division has completed a retrospective evaluation of cancer risk among HIV patients in our hospitals and clinics. He noted that patients with a dual diagnosis of HIV and cancer have a very high likelihood of dying from their cancer and importantly, that risk was mitigated by the use of antiretroviral therapy. Since these cancers are of so many different types it is likely that a common mechanism for cancer control is impacted by HIV and dysregulation of this mechanism increases the risk for malignant disease. We believe that HIV effects on tumor immunity are an important part of the puzzle explaining increased cancer risk in our patient populations.

Working with Dr. Redfield and Clinical Division investigators including Drs. David Riedel, Bruce Gilliam and Mohammad Sajadi with funding from the National Cancer



Dr. David Pauza discusses research in his lab.

Institute, Dr. David Pauza's group has characterized the function of gamma delta T cells in numerous patient groups, showing the impact of progressing HIV disease on this critical cell subset that is part of normal tumor immunity. In the past year, they published an important paper on the mechanisms for how HIV infection depletes this T-cell subset (Drs. Haishan Li and Pauza). Since gamma delta T

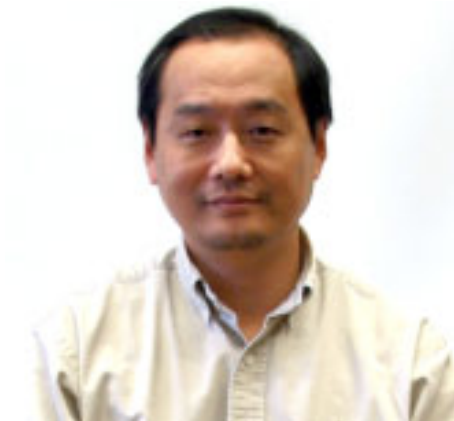
cells cannot be infected directly by HIV, their discovery that viruses and the envelope glycoprotein bind and cause cell killing without infection, was a significant step in understanding the broader effects of HIV on natural tumor immunity. Progressing HIV disease erodes the capacity for tumor cell killing among gamma delta T cells and is an important step for increasing the risk for cancer. More recently, they have begun to explore alternate methods for stimulating gamma delta T cells (Drs. Bhawna Poonia and C. David Pauza) and examined the impact of antiretroviral therapy on recovery of this T-cell subset. These studies lay the groundwork for future interventional clinical trials designed to improve tumor immunity through direct activation of gamma delta T cells in HIV patients. The goal of these studies is to identify new treatment approaches capable of reconstituting key aspects of tumor immunity in HIV disease, which will lower the risk for death and improve clinical management of patients with the difficult dual diagnosis of HIV and cancer.

Lastly, Dr. Zella has been working with Drs. Sabrina Curreli, Alonso Heredia, Eugene Ateh and Joseph Bryant studying the effects of Wild Ginseng on cellular pathways leading to immune-modulation. Wild Ginseng has been demonstrated to activate some cellular pathways leading to an increased immune-activation. The project seeks to better define these pathways in vitro and in vivo.

Structural biology research in the IHV

Dr. Wuyuan Lu has recently been tapped by Xi'an Jiaotong University (XJTU)—a prestigious academic institution in China—to help build a center for translational medicine in the ancient city of Xi'an as an extension of his ongoing biomedical research at IHV. The research center is affiliated with the School of Life Sciences and the Frontier Institute of Science and Technology of XJTU, and forms a strategic alliance with

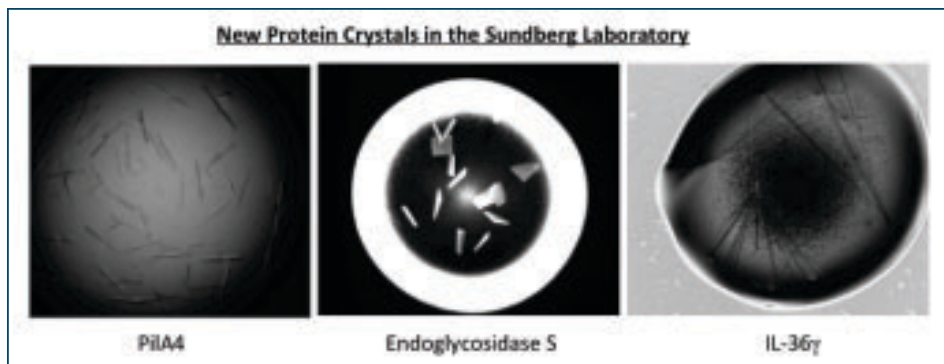
the University's First Affiliated Hospital—the largest hospital in northwest China. The core mission of the center is to support biomedical research aimed at translating basic science discoveries into improved human health in the areas of cancer and infectious disease.



Dr. Wuyuan Lu

Dr. Lu regularly travels to Xi'an for strategic planning consultation that entails the building of the infrastructure of the center, recruitment of its principal investigators, development of curricula for graduate education, and establishment of a multi-disciplinary research program. Discussions are also underway about how to launch a platform in Xi'an to foster close collaborations in basic and clinical research on HIV between the Institute of Human Virology and XJTU. Dr. Lu hopes that his stint in Xi'an will ultimately lead to frequent exchanges of basic scientists, clinicians and graduate students, sponsorship of joint research projects by the U.S. and China, and a greater role for the IHV in leading the global fight against HIV/AIDS.

The major goals of IHV's research in the Laboratory of Chemical Protein Engineering (Lu laboratory) include deciphering the molecular basis of how proteins function, elucidating the structure and function relationships for and mechanisms of action of antimicrobial peptides, and developing novel antitumor and antiviral peptides for the treatment of cancer and infectious disease.



Structural biology has grown rapidly at IHV, including international expansion of Lu's program and the recent arrival of Dr. Eric Sundberg. Having moved his lab to the IHV in April 2011, the period from July 2011 to June 2012 represents the first full year at the Institute for Dr. Sundberg. As such, he has devoted a significant portion of efforts to building the lab, both through the recruitment of personnel and the acquisition of instrumentation. In addition to Dr. Sundberg, the laboratory is now staffed by seven PhD-level scientists and a lab manager. These individuals have brought a wealth of expertise to the laboratory—in structural biology, molecular biophysics, glycobiology and immunology—that is already strengthening the overall research capacity and collaborative enterprise of IHV. In the past year, we have also installed several new major instruments that provide unique research capabilities to



Dr. Eric Sundberg

the IHV community, including an isothermal titration calorimeter for the thermodynamic assessment of

protein-protein interactions and a suite of robotic instruments for the high-throughput crystallization of proteins.

Dr. Sundberg's laboratory has recently grown crystals of several proteins for which X-ray crystal structures will provide significant new insights into three of our newest research projects (see the Figure). These include crystals of: PilA4 (left panel), a *Clostridium difficile* type four pilin protein; Endoglycosidase S (middle panel), an enzyme secreted by *Streptococcus pyogenes* that removes sugar molecules from human antibodies rendering them incapable of activating key innate immune mechanisms; and IL-36 γ (right panel), an interleukin that activates bone marrow-derived dendritic cells and Th1 cells. We are currently collecting X-ray diffraction data on these crystals at synchrotron radiation facilities that will allow us to determine their three-dimensional structures and better understand their biological functions.

In addition to the NIH funding that has supported his research prior to moving to IHV and continues to do so, individuals in the Sundberg laboratory have also been awarded a Fulbright Scholarship, an NIH Postdoctoral Traineeship, and an Alexander von Humboldt Experienced Research Fellowship within the past year.

Dr. Erik de Leeuw, Assistant Professor, studies the innate immune system which has evolved as an ancient defense system against infection. Effectors of

innate immunity include a variety of innate immune cells as well as antimicrobial peptides. Dr. de Leeuw focuses his research on one class of antimicrobial peptides in humans, termed defensins, which have been studied for a long time at IHV first in Dr. Lu's group and now by de Leeuw. These versatile peptides act against microbes as well as affect immunity of the host. The overall goal of his research is to determine their therapeutic potential of these peptides and use structural biology to support new drug design. There are currently two projects ongoing that address the functional diversity of these peptides in both arenas. These projects include:

1. Antimicrobial: An ongoing explosion of resistant infections continues to plague global health care. Patients with weakened immunity because of chemotherapy, AIDS or organ transplantation or patients undergoing acute care in hospitals are significantly and increasingly at risk for acquiring opportunistic bacterial infections. In the USA alone, the Centers for Disease Control estimates that ~1.7 million infections per annum occur following hospitalization, with an estimated 99,000 deaths associated. Resistance against commonly used classical antibiotics has emerged in virtually all of bacterial pathogens. In fact, there is no antibiotic currently in clinical use against which resistance has not been reported.

In 2010, Drs. De Leeuw and Lu were among the first to report on the interaction between defensins and Lipid II, an essential component of bacterial cell wall biosynthesis and a validated target for antibiotics. Using a combination of structural, functional and in silico analyses, we have now elucidated the molecular basis for defensin-Lipid II binding (Figure 1). Our long term goal is to use this information to add low molecular weight compounds that are defensin mimetics to the repertoire of antibiotics that target Lipid II as novel therapeutics for the treatment of Gram-positive pathogenic infections.

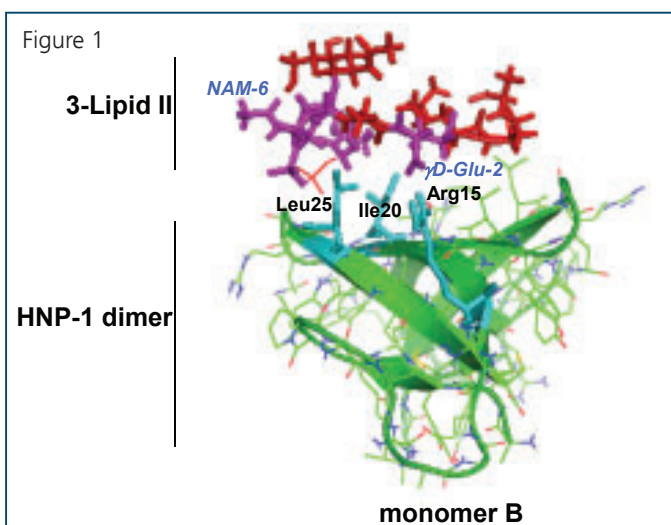
2. Host Immunity: In addition to their major role as natural antibiotics, defensins are increasingly

recognized as signaling molecules in adaptive immunity. Defensins have immunomodulatory properties and affect various cellular processes in cell development, wound healing, fertility and cancer. We initially observed that human defensins act synergistically with Tumor Necrosis Factor alpha (TNF α). TNF α is a key regulator in the immune system with strong proinflammatory and immunomodulatory properties. It is also involved in controlling life or death of target cells and plays a critical role in many acute and chronic inflammatory diseases. TNF α interacts with the extracellular domain of either of two structurally distinct receptors, TNFR1 and TNFR2, activating distinct intracellular signaling pathways and gene transcription. The extracellular domains of TNF receptors are comprised of 3-4 cysteine-rich domains or CRDs. The first of these domains at the extreme N-terminus is termed the Pre Ligand Assembly Domain or PLAD. This domain is involved in pre-assembly of the receptors prior to binding of TNF α . Interestingly, certain viruses produce PLAD-like agonists or antagonists to escape host immunity. Our research suggests that the cellular interactions of human defensins are modulated by the functional expression of TNF α receptors. We further find that human defensins bind to the N-terminal Pre Ligand Assembly Domain of TNF α receptor 1. If validated, this knowledge may provide a crucial first step in our long-term goal to facilitate the rational development of novel, defensin-based therapeutic agonists or antagonists specifically targeting the PLAD domains of TNF receptors.

By obtaining funding from the National Institutes of Health for the work on Lipid II, Dr. de Leeuw achieved an important first step towards research independence. He aims to further establish himself as an independently funded researcher in infectious diseases and cancer at the IHV.

New Cell Discovery

The laboratory of Dr. Suzanne Gartner has identified a new behavior for the human macrophage that explains several features of HIV biology, including how the virus persists within the body indefinitely, how quiescently infected CD4+ T-cells arise, and how the infection leads to depletion of CD4+ T-cells. Her research team found that macrophages cultured from human blood can function as "nurse cells" and in this capacity, generate and release newly formed cells. The new cells released include a previously unknown small cell, termed "self-renewing monocytoic cell" (SRMC) that is highly susceptible to infection with HIV. This small cell can develop into another nurse macrophage that can, in turn, produce another small cell. This nurse macrophage/small cell developmental cycle can continue in culture for several generations, even during continuous production of HIV. Current anti-HIV drugs cannot inhibit HIV maintained through this process, because they act to prevent new infection.

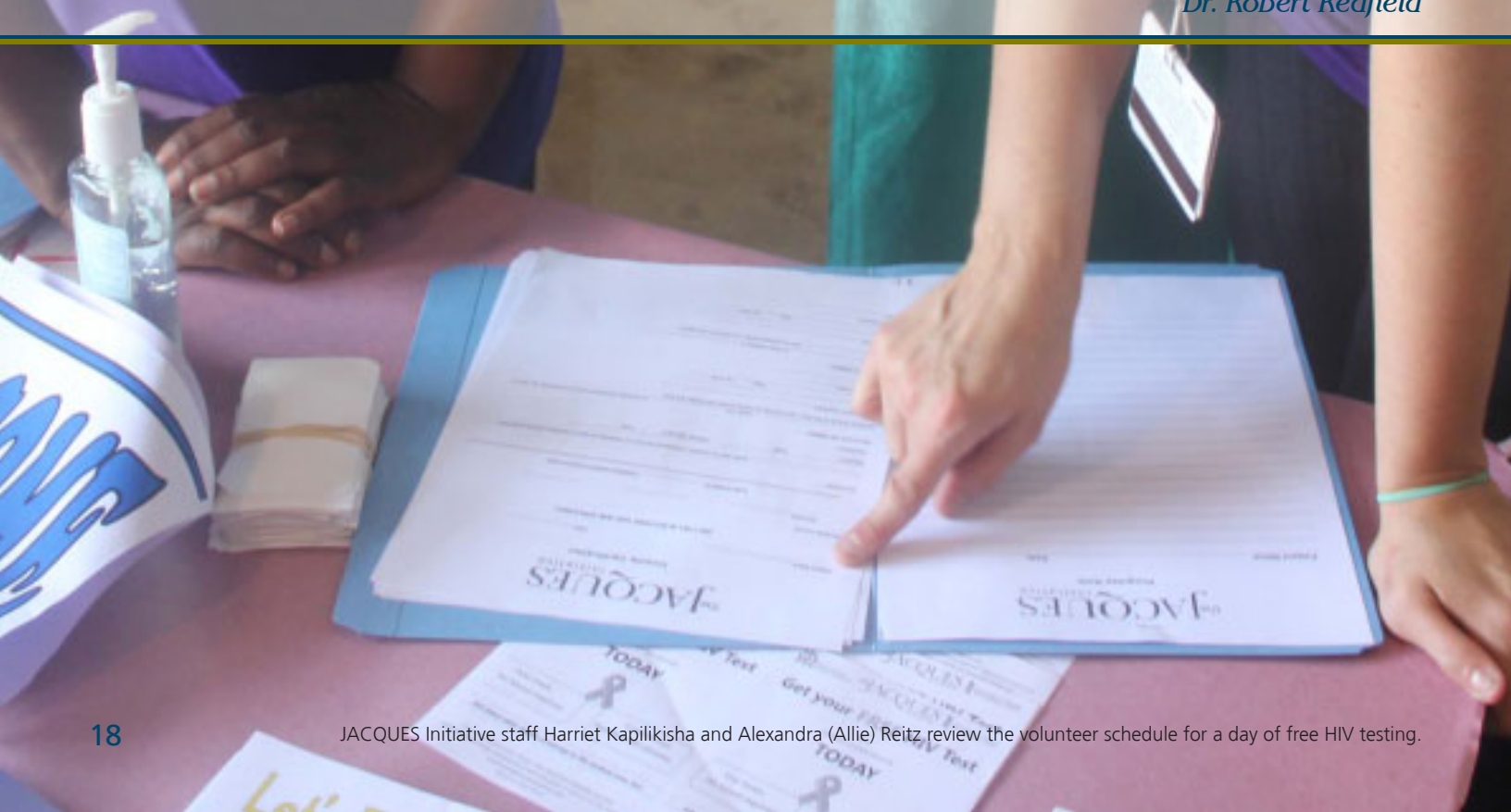


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"This year the Clinical Division has seen tremendous growth and expansion through continued clinical, research, and international collaborations. We received increased international funding, in addition to faculty contributing with new research concepts, and the expansion of clinical care programs."

Dr. Robert Redfield



Clinical Care and Research



Dr. Robert Redfield

There are some exciting new collaborations and working partnerships being developed in the Division of Clinical Care and Research, under the direction of Dr. Robert Redfield. From our thriving international programs, which have been building strength and growing into new phases of development since starting in 2004, to the continued expansion of clinical outpatient and inpatient services within the University of Maryland School of Medicine, the Clinical Division has initiated some useful and important collaborative projects which have brought new faculty to the Division, as well as sparking growth in existing programs.

The Clinical Division has partnered with NIH to launch a **“Bench to Bedside Project”** which will explore a prospective Phase 1 study to assess the safety, tolerability, and anti-fibrogenic



Bench to Bedside Project (L to R) Dr. Kottlil, Dr. Osinusi, and Dr. Talwani
photo credit: Antonio Paterniti

effects of humanized anti-LOXL2 IgG4 antibody in HIV and/or Hepatitis C co-infected patients. This project, spearheaded by Dr. Rohit Talwani (IHV) and Dr. Shyam Kottlil from the Laboratory of Immunoregulation, at the National Institute of Allergy and Infectious Diseases, and the National Institutes of Health, is especially exciting for us, as new therapeutic agents for the treatment of Hepatitis C have been launched in the past year, which we hope will increase the effective management of Hepatitis C, specifically in the HIV/Hep C co-infected population in Baltimore.

CLINICAL RESEARCH

The IHV Clinical Research Unit continues to grow and serve more patients each year. Our ACTG Clinical Research Site (CRS) is enrolling patients in complicated studies to include Hepatitis C trials, naïve studies, and studies for patients with latent TB. We are also enrolling in an investigator initiated pilot study on novel ARV therapy sponsored by Merck, a Hepatitis C study with Vertex using Telaprevir, and a new Gilead Hepatitis B study which will be starting this fall. As our clinical research base has expanded, we also have two ongoing clinical trials operating in Nigeria. The Clinical Division’s Clinical Trials Team in Nigeria, led by Dr. Chidi Nwizu, has been executing two clinical trials over the past three years through sponsorship of the Kirby Institute at the University of South Wales, in Sydney, Australia. One study, the Second Line Study, compares the safety and efficacy of ritonavir boosted lopinavir plus two to three NNRTIs vs. ritonavir boosted lopinavir and raltegravir, in participants virologically failing their first line regimen. This study has enrolled 558 participants and is scheduled to be completed by August 2013. Additionally, the ENCORE study is a study to compare the safety and efficacy of reduced dose efavirenz vs. standard dose

efavirenz plus two NNRTIs. This study has randomized 630 patients on the trial, and is expected to end in July 2013. The success of these two clinical trials being executed in Nigeria lays the groundwork for the IHV Clinical Division to do more clinical research in Nigeria and other African countries.

WESTAT SURVEILLANCE

Under the direction of Dr. Martine Etienne, Dr. Peter Memiah, and Sandra Medina Moreno, the Clinical Division has been collaborating with Westat on a CDC surveillance protocol which will use dried blood spot technology for viral load testing and genotyping in adults and children participating in the Kenyan and Tanzanian antiretroviral therapy programs at our local partner treatment facilities. Fifteen sites have been selected for this surveillance project, which will involve a one-time blood collection for viral load testing and drug resistance testing, if the viral load is > 1,000 copies/mL. This HIV drug resistance genotyping is an essential component of the WHO Global Drug Resistance Prevention and Assessment Strategy. We look forward to observing the outcomes of this important surveillance project in Kenya and Tanzania.

NIH MEPI AWARDS

The IHV Clinical Division received two of the eleven NIH sponsored Medical Education Partnership Initiative (MEPI) grants which were awarded in early FY12 for five years each. One is in partnership with the University of Nairobi (UON), to improve Kenya’s human resource capacity for health and health outcomes by strengthening UON’s medical education training and research capacity. This will be done by developing and implementing a framework for curriculum reform, improving accessibility and the impact of the learning resources in the health sciences library, and creating and monitoring a skills lab, as well as increasing research

capacity through an implementation science fellowship program. We have hosted two MEPI fellows from Kenya on the UMB campus this summer for 6 weeks each and they worked closely with the Clinical Division on developing their research projects. The second NIH MEPI award is in conjunction with the University of Zambia (UNZA). For this award we are partnering with UNZA to improve their capacity to train more health workers, to improve the overall quality of healthcare training at UNZA, and to enhance the Master of Medicine degree programs for physicians in order to ensure that graduates have the capacity to conduct evidence-based research and program evaluation. Both of these NIH sponsored awards are an integral part of the Clinical Division's five phase overall global plan.

INTERNATIONAL TRANSITION

The IHV Clinical Division, in partnership with Catholic Relief Services, Catholic Medical Mission Board, Interchurch Medical Assistance, and The Futures Group, joined forces to develop the AIDSRelief Consortium which was awarded PEPFAR funds in 7 African and 2 Caribbean countries in 2004. The IHV was tasked with providing technical assistance for the program from 2004 through 2012, with an additional one year extension in Kenya. During the initial 8 years we received \$187,751,398 in funding, with an additional \$1,369,897 for year 9 in Kenya. Our strategy in developing health capacity over the past 8 years has followed these phases:

- Phase 1 (2004-2009): Emergency Response
- Phase 2 (2004-2009): Country specific health professional capacity development
- Phase 3 (2008-2011): Transition technical assistance programs to national IHV trained technical leaders
- Phase 4 (2009-present): Establish strategic alliances with key in-country institutions and focus in strengthening educational and research capacity



Training African health workers to provide care to their communities.



PACE Symposium with (L to R) Dr. John Bartlett, Dr. Robert Redfield, Dr. Robert Gallo, Professor George Magoha, Professor Kaimeni.

- Phase 5 (2010-present): Conduct funded operational research to define best practices and to develop and implement integrated clinical research programs driven by investigator initiated research proposals

The Clinical Division has worked diligently to establish strong in-country technical teams in order to provide long term assistance with indigenous leaders, which we have succeeded at to date, in all but two countries. Over the past four years we have aligned ourselves with various Ministries of Health, teaching universities, and government entities. These long term plans and capacities were strategically built to transition activities to indigenous organizations as our complete goal. Our international programs have also transitioned over the past few years, from primarily care and treatment programs to programs where we support continuing medical education and develop research projects in partnership with various local indigenous organizations, Ministries of Health, and Universities. Some examples of this successful transition are within the Kenya program where one initial grant is now nine grants and in the Zambia program one grant has now transitioned to four grants. In the Kenya Partnership for Advanced Clinical Education (PACE) grant the IHV team partnered with the University of Nairobi in hosting a very successful symposium in June 2012, which gathered many high level physicians from around the world, to include Dr Robert Gallo.

AIDSRelief was designed with transition to our local partners in mind. Transition actually began in 2009, five years into the PEPFAR award, and each model was developed to suit each country context, yet common threads emerged. The AIDSRelief approach to treatment, systems strengthening, and transition to local ownership are broadly applicable. This model can be used to reach the millions still in need of high quality HIV care and treatment. Transition includes fostering long-term partnerships and targeted capacity strengthening with those health organizations (public and private), who currently deliver AIDSRelief supported HIV care and treatment. The partnership includes the mutual identification of Local Partners

and AIDSRelief roles that optimize the inherent strengths and advantages of each. Transition of the program to the Local Partners is incremental to ensure that the Local Partner has the capacity to support its sites and to maintain uninterrupted quality HIV care and treatment. The transition was planned by AIDSRelief together with the Local Partners, government, and other key stakeholders to increase the sustainability of the HIV care and treatment program, by increasing participation of sites and clients in program management; by strengthening the Local Partners' organizational capacity; by forging a long-term partnership of complementary roles and capacities, and by promoting performance based systems for maintaining quality performance based on clinical outcomes.

GUYANA

In September 2011, the IHV was awarded a new grant by the Centers for Disease Control (CDC) to strengthen medical training within the Republic of Guyana. This is one of our new collaborations which stemmed from our participation in the original PEPFAR grant. The Guyana Partnership for Advanced Clinical Education (GPACE) cooperative agreement, awarded to Dr. Redfield and Dr. Bruce Gilliam, expands on the clinical work and technical assistance IHV has provided to Guyana over the past eight years under PEPFAR. In partnership with the University of Guyana (UG), the Georgetown Public Health Corporation (GPHC), and the Ministry of Health (MOH),

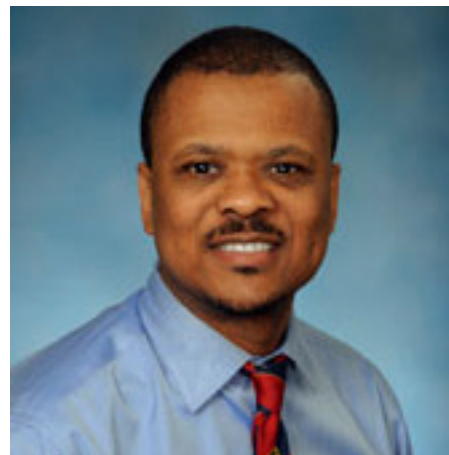


Dr. Adrian Majid

IHV will help establish the first postgraduate training in internal medicine and infectious diseases in Guyana which will be a 3-year program with the inaugural class planned to start in Winter 2012. Over the past year, Dr Gilliam and Dr Adrian Majid have been working with the University of Guyana to improve medical student education through necessary microbiology lab upgrades and equipment, the development of practical lab training, and revisions to the medical student infectious diseases curriculum. Under this grant, we have also provided continuing medical education programs to medical providers, offered technical assistance to programs under the MOH, including the National AIDS Programme, and developed a morbidity and mortality conference at GPHC. This advanced clinical training opportunity allows us to work side by side with the local physicians and trainees in Guyana in order to improve their opportunities for learning and training in internal medicine and infectious diseases.

DOMESTIC CLINICAL

Some of the growth that the Clinical Division has been experiencing is directly related to the continued expansion of the HIV/Infectious Disease clinical services offered to



Dr. Otha Myles

the City of Baltimore. Through the addition of new clinical faculty such as Dr. Otha Myles and Dr. Leonard Sowah over the past 2 years, our reach throughout the School of Medicine, as well as the City of Baltimore has expanded.

Dr. Otha Myles, who became an IHV faculty member in April 2010, was elected as the 136th President of the University of Maryland School of Medicine's Medical Alumni Association for the term of 2011-2012. While Dr. Myles was attending Medical School at Maryland, he started working with the Medical Alumni Association as a medical student member of the advisory board from 1994-1998. Later, he was elected to serve as a member of the Board of Directors, prior to becoming President for this recent one year term. Dr. Myles continues to be highly involved with the SOM and partnering with Dean Reece in creating the "Annual Celebrating Diversity Reception and Dinner", which is a SOM sponsored event held each February.



Dr. Leonard Sowah

Dr. Leonard Sowah came to us from HealthCare for the Homeless in July 2010, and is also currently a member of the Baltimore HIV Planning Council as well as being the current Co-Chair of the Comprehensive Planning Committee. In this position, Dr. Sowah works with other members of the 40 member body to decide on funding allocations for Ryan White Services within HRSA recommended guidelines. Dr. Sowah's involvement in the Baltimore HIV Planning Council offers him the opportunity to interact with local and state government officials, other physicians, and HIV positive patients, in order to contribute to making decisions on the key issues surrounding HIV funding in Maryland.

“The Division of Epidemiology and Prevention continues to engage in a research agenda targeting HIV, TB, and cancer on a global scale through a robust research and training partnership with IHV—Nigeria.”

Dr. William A. Blattner



Epidemiology and Prevention

The Division of Epidemiology and Prevention at the Institute of Human Virology, led by Dr. William Blattner, interacts with IHV's Basic Science Division, the Greenebaum Cancer Center and multiple national and international partners to implement clinical and molecular epidemiologic studies of HIV, virally associated cancer, and their pathogenesis. In the last eight years, the Division of Epidemiology and Prevention has scaled up research capacity in Nigeria resulting in clinical and laboratory research and training grants.

Acute HIV Infection During Pregnancy—

Mother-to-child transmission of HIV in Nigeria, where between 63,000 to 125,000 infants each year acquire HIV, is a major public health challenge. Because current screening algorithms focus on detecting established infection, acute infection cases are not identified by current clinical practices. To study acute HIV infection in pregnancy Dr. Man Charurat was awarded a NIH RO1 as a new investigator for his AVERT study. The AVERT study is focused on advancing understanding of Mother-to-Child-Transmission risks in women who become infected during pregnancy. Because acute HIV infection is associated with exceptional levels of virus and an absent or poorly developed maternal immune response to the virus Dr. Charurat posits that fundamental insights gained from this study will not only establish the frequency of acute infection during pregnancy but also demonstrate the effects on the mother and her infant. Preliminary analysis demonstrates that babies born to acutely infected mothers are at much higher risk of acquiring HIV infection (15% among children of acutely infected mothers versus 3.4% among women with established infection). Among HIV infected women in the cohort 8% acquired infection during pregnancy.

Additionally some attributes of maternal risk such as bacterial infection of the birth canal also contribute to infant and perhaps maternal risk of infection. The unexpectedly high rate of such infections is likely due to husbands having outside sex partners when their spouse becomes pregnant, and it has important public health implications for preventative interventions for couples. Furthermore, because of this high rate more frequent testing of mothers during early pregnancy and subsequently later in pregnancy is suggested, and immediate treatment of the infected mother is recommended. Given the finding that bacterial vaginosis (BV) is associated with HIV acquisition risk promoting screening and treatment for BV represents

an affordable strategy to facilitate prevention of mother-to-child HIV transmission. Collaborative studies with IHV basic scientists are applying cutting edge strategies to understand host and viral factors and their impact on survival growth and development of the infant, and treatment outcome.

Tuberculosis and HIV—Nigeria is not only number 2 in the world for HIV but also ranks 4th for tuberculosis. Building upon the PEPFAR infrastructure for TB diagnostics developed by Dr. Alash'le Abimiku several projects supported by Dr. Blattner's AIDS International Research and Training Program grant from the Fogarty International center have helped to shape understanding of the interaction between HIV and TB. In one project, conducted by Fogarty trainee Dr. Alfred Nwofor, demonstrated the pattern of resistance to anti-TB drugs among patients failing TB treatment as a major source of death among HIV patients. Dr. Nwofor's research formed the basis for



Dr. Nwofor learning the HAIN GenoType MTBDR- plus methodology for studying MDR TB in Nigeria

a PhD thesis from the University of Illorin in Nigeria, part of a "south to south" research training activity. In another project led by Dr. Aliyu Gambo Gumel who recently completed his doctoral degree based on research supported by the Fogarty training grant a broad survey of TB suspect cases documented that 27% were HIV co-infected. HIV co-infection is associated with a high degree of some form of drug resistance. Unexpectedly, a high proportion of cases thought to have classical TB were infected with other species related to classical TB, and these forms of TB organism are more resistant to conventional therapy. HIV patients were also more susceptible to TB related organism that is acquired from the environment.

These findings have major public health significance since many patients thought to be infected with classical TB are infected with related organisms that will not respond to standard TB treatment placing these patients at high risk of death from drug resistant TB. This project is now being extended by current Fogarty trainee, Dr. Jumare, to evaluate the frequency with which family members are at risk for TB (which can be spread unlike HIV by airborne spread). This Mobile Intensified Case Finding for TB/HIV strategy provides a public health outreach strategy to address the community risk posed by TB and to also extend diagnosis of HIV to family members who may have acquired infection either through sexual or mother to child transmission further contributing to the spread of these dual epidemics.

Emerging Resistance to HIV Treatment—

A major threat to the sustainability of expanded treatment access is the emergence of drug resistance to anti-retroviral treatment. A survey conducted by Dr. Blattner, Dr. Mary Ann Etiebet and his team, surveyed 175 clients enrolled on standard PEPFAR treatment for an average of 2 years. Among this cohort over 90% had a mutation to a key drug, non-nucleoside reverse transcriptase inhibitors, one of the two classes of medication available as first line therapy. For the other class, nucleotide reverse transcriptase inhibitors almost half had multiple mutations of whom an additional half now resistant to next generation medications that might be used to “rescue” patients who are failing treatment. A tribute to forward thinking of the IHV team, tenofovir was introduced into the Nigeria program earlier than in most PEPFAR countries with the benefit that those who received this drug as part of the combination were significantly less likely to have multiple drug mutations and were more likely to remain susceptible to drugs to rescue them from treatment failure. These findings have significance for

informing public health strategies for ART regimen sequencing to optimize long-term HIV treatment outcomes in low resource settings.

Clinical Trials—The goal of creating an international base for clinical trials research for IHV has been achieved through two major accomplishments. First, the IHV team led by Dr. Chris Akolo has been able to activate an NIH sponsored research study to study the benefits of early treatment of HIV patients in the developing world setting. While the potential for reducing morbidity and mortality with antiretroviral therapy (ART) is great, currently available data are insufficient to show the benefits of initiating ART at CD4 cell counts above 500 cells/mm³ and whether these benefits outweigh the risks. The Strategic Timing of AntiRetroviral Treatment (START) study is a multi-country, randomized study funded by the NIH through the INSIGHT network that aims to determine whether immediate initiation of antiretroviral treatment is superior to deferral of ART until the CD4 cell count is below 350 cells/mm³.



Dr. Chris Akolo's START Study—Test and Treat Strategy.

IHV anchors the START study in Nigeria among over 200 sites around the globe. The START study will enroll over 50 volunteers at the IHV site in Nigeria and contribute to an international effort to guide public health policy to optimize benefit to those enrolled in PEPFAR treatment. The START study will also inform the safety of the “test and treat strategy” in the developing world setting.

The second clinical trials achievement is the award to Dr. Alash'le Abimiku of grant funding to support development of a vaccine research trials unit through international funding from the Canadian HIV Vaccine Initiative supported by the Bill & Melinda Gates Foundation.

The vaccine research agenda of this award includes:

1. Building the capacity of the ethical and regulatory government bodies for oversight of the conduct of HIV vaccine trials in Nigeria;
2. Community mobilization and defining risks in a cohort of serodiscordant couples (still a



ACTION register center for HIV testing and educational outreach in Africa.

relevant cohort for vaccine studies in Nigeria as preliminary results shows that 46% reported non-frequent use of condoms while 10% never use condoms. More importantly 58% of their partners, most of whom are on ARVs, had readily detectable viral load levels making it possible for transmission to still occur in this cohort); and

3. International accreditation of the clinical research laboratory through south to south mentoring at the KEMRI/CDC ISO certified laboratory in Kisumu Kenya. A second Canadian Institutes of Health Research multi-country (Canada, Nigeria, and S. Africa) grant exploits the seemingly paradoxical inefficiency of postnatal HIV transmission through exclusive breastfeeding as a human mother-infant model to identify the direct or indirect pathways by which HIV infection is blocked or enabled, and the role of immune activation and mucosal inflammation on transmission

Neurological Consequences of HIV Infection—

In addition to its effects on the immune system and susceptibility to TB and other infections, HIV is also directly toxic to the brain and can cause varying degrees of damage resulting in neurocognitive impairment. In collaboration with the University of California San Diego, and Dr. Walter Royal of the School of Medicine Department of Neurology a prospective cohort study has been implemented with NIH RO1 funding. Over 30 percent of PEPFAR clients demonstrate some form of impairment. Employing state of the art molecular sequencing strategies, the study will target understanding of the features of the virus that cause the impairment as well as provide information on whether the drugs used in the PEPFAR program can reverse any of the damage by lowering the level of virus.



Dr. Alash'le Abimiku's Canadian HIV Vaccine Initiative.



Dr. William Blattner at Otukpo's Commissioning.

CANCER EPIDEMIOLOGY

Viruses and Cancer—Included in the mission of IHV is a focus on cancer research particularly cancers associated with viruses. New insights are emerging about viruses and cancer and it is currently estimated that 20% of cancers worldwide are linked to viruses. The Institute's Viral Oncology Program of the partner Greenebaum Cancer Center is bolstered by the Cancer Epidemiology activities to conduct cancer research. Adopting a molecular epidemiology research strategy strengthened by the international cancer research program established by Dr. Clement Adebamowo and enriched by recruitment of new faculty genetic epidemiologist, Dr. Hongmei Nan, the Division is advancing innovative approaches to link viral exposures to fundamental insights about cancer gene mutations. This research includes targeting understanding of HIV and non-Hodgkin Lymphoma, a study led by Dr. Gallo and engages key collaborators from the Basic Science Division. A longstanding interest of Dr. Blattner, HTLV, the first human retrovirus discovered by Dr. Gallo, is also a focus of emerging research aligned with the strategic recruitment of two new faculty, Dr. Yutaka Tagaya and Dr. Hua Cheng to the Basic Science Division. Partnering with this research team Dr. Hongmei Nan is involved in an exploratory study to identify genetic factors associated with virus-related cancers including HIV-associated B-cell lymphoma and HTLV-1-associated adult T-cell leukemia/lymphoma. Based on the findings, Dr. Nan will explore the interactions between host genetic factors and viral oncogenes. Dr. Adebamowo is leading a major cancer research activity in Nigeria with particular emphasis on establishing a research center through the H3 Africa NIH initiative that seeks to transition state of the art genomics capacity to African laboratories. Already, Dr. Adebamowo has been awarded a project targeting nutritional epidemiology from the Wellcome Trust from the UK and Dr. Alash'le

Abimiku has been funded to develop an international biorepository to support an H3 Africa biorepository. Dr. Adebamowo is focusing on studies of the human papilloma virus associated cervical cancer, a top cancer killer in sub Saharan Africa, a tragedy given that the cancer is preventable. His research targets understanding the interaction between virus, host and genetic determinants of cancer risk. UM-IHV plays a pivotal role in research ethics in Nigeria through the NIH funded West African Bioethics Training Program and its activities including implementation of MSc Bioethics degree at the University of Ibadan which has trained 21 students to date and provided hundreds of short and medium term trainings in addition to establishing and strengthening research ethics committees.



Dr. Clement Adebamowo, trains researchers on cancer registry and HPV detection.

UM-IHV also has a technical collaboration with the Nigerian Federal Ministry of Health and the Nigerian National Health Research Ethics Committee to implement a national system of health research ethics regulation. Through the NIH funded Capacity Development for Research in AIDS Associated Malignancies program (CADRE), UM-IHV works with the Nigerian government to implement the National System of Cancer Registries in Nigeria which now produces incidence data of cancers in Nigeria and develops cancer registration in Nigeria. CADRE also supports the development of clinical trials and epidemiology research capacity in AIDS Associated Cancers in Nigeria. Through CADRE, UM-IHV and the Greenebaum Cancer Center of the University of Maryland School of Medicine, are implementing a Cervical Cancer Screening program; HPV genomics vaginal microbiome and cervical cancer research; and a prospective study of Non-Communicable Diseases (NCD) and HIV infection. Currently, further capacity development in Life-Course Approach to Non-Communicable Diseases (NCD) epidemiology and the use of Case-Method to teach physician-scientists

NCD epidemiology is implemented through the NIH funded Trapping-NCD program.

Building Nursing and Pediatric Capacity in Nigeria

The Division of Epidemiology and Prevention continues to strengthen its partner IHV-Nigeria through training and mentorship. Dr. Nadia Sam-Agudu, an Infectious Disease-trained pediatrician, has been serving full-time as Clinical and Technical Advisor for Pediatric HIV Management and Ms. Emilia Iwu as Nursing Technical Advisor.

Ms. Emilia Iwu's efforts to strengthening the nursing program in Nigeria includes developing capacity of post service nurses through HIV mentoring and training, developing adequate linkage and feedback mechanisms for case management at clinics and hospitals, and engaging Nigerian nurse stakeholders such as Nursing and Midwifery Council of Nigeria (NMCN), Nursing and Midwifery Institutions (including University program), Community Health Practitioners Registration Board of Nigeria (CHRBN), FMOH/SMOH and nurse executives to develop a standardized comprehensive HIV & AIDS nursing curriculum for pre and post service education.



9-month HIV exposed infant being examined by Pediatrics Technical Advisor, Dr. Nadia Sam-Agudu at University of Abuja Teaching Hospital in Gwagwalada.

Dr. Nadia Sam-Agudu has trained and mentored over 350 pediatricians and healthcare workers in the management of pediatric HIV patients and helping establish the 2010 Nigerian Pediatric HIV Guidelines. Dr. Sam-Agudu conducts mentoring visits to both secondary and tertiary-level sites within the PEPFAR network. She has commenced scale up of pediatric provider-initiated testing and counseling (PITC) of HIV. Over 300,000 Nigerian children are estimated to be HIV-infected, yet only 10-15% of them are enrolled in care and treatment programs. PITC efforts are expected to significantly reduce the deficit in diagnosis and ART coverage for infected children.

Furthering IHV's outreach internationally, Dr. Gallo and colleagues established the Global Virus Network (GVN), a global authority and resource for the identification, investigation, and control of viral diseases posing threats to mankind.



The Global Virus Network (GVN)

Many years ago, following his experience with the AIDS virus, Dr. Robert C. Gallo realized that, in the field of medical virology, no one group was responsible for identifying and researching existing and emerging viral threats to human health. After years of prompting, and with backing from co-founders, he started the Global Virus Network to help fill the gap between virus surveillance and public health response, seeking to organize "responsible virologists" with expertise that covers all pathogenic types of human viruses and train new ones.

This past year has seen very rapid growth for the Global Virus Network since its inaugural meeting at the Italian Embassy in March 2011. The organization has been very active in forming its

corporate structure, populating its boards, holding regular international meetings, and introducing itself to the global public health community. Major motion pictures, like "Contagion," and a string of breaking news stories regarding emerging and existing viruses have kept the reasoning behind the establishment of the GVN on the front pages. From Hantavirus and West Nile in the U.S. to Ebola and pandemic influenza in Africa and Asia, stories about the serious viral threats that face mankind grabbed the headlines.

The logic behind formation of the GVN has become evident to many other medical virologists, as evidenced by expansion of the network. New centers have been added to GVN including a Japanese

center, and others have formed including one in Belgium, Holland and France, a Scandinavian-Baltic Center centered in Sweden, the University of Pittsburgh, and the J. Craig Venter Institute, along with substantial reorganization in several centers including Germany, India, and Russia. These positive developments manifest the continued growth and maturation of GVN.

The organization's recent semi-annual meetings have clearly been a highlight of the past year. GVN co-founder, Dr. William Hall, Director of the Irish GVN Center, hosted the second meeting of the GVN in Dublin, Ireland in October 2011 with a stellar program, generous hospitality, concluding with a gala dinner in the home of IHV Board Member, Tom Lynch. The Italian GVN, through Drs. Franco and Luigi Buonaguro, hosted the third meeting of the GVN in Naples, Italy in June 2012 which was equally productive and very well attended. The next GVN meeting will be hosted by IHV in Baltimore. It is being held at the conclusion of the IHV Annual Meeting so GVN delegates who will also be traveling to the city to attend that conference may easily attend both.

One of the greatest benefits the GVN offers its members is the superior network it has created which allows medical virologists to closely interact with their colleagues. This has already paid dividends. For example, the Russian GVN working with Konstantin Chumakov of the U.S. Food & Drug Administration, obtained Bill & Melinda Gates Foundation funding for poliovirus control



Professor Ab Osterhaus discusses engineered influenza viruses at the GVN Naples Meeting.

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The Global Virus Network (GVN) *continued from page 27*

programs in a new collaboration that was initiated because of their interactions via GVN. We also have ongoing communications with the World Health Organization and the U.S. Centers for Disease Control. These arrangements, with official liaisons to each agency, seek to reduce overlap in our missions and create open channels for effective cooperation.

Key accomplishments in program development and financing include substantial base funding for the Dublin and Naples meetings, which was greatly enhanced through local efforts by GVN's Irish and Italian colleagues. In addition, GVN received its first philanthropic program support. GVN members from EU countries have organized into a group led by former EU Parliamentarian, Dr. Umberto Bertazzoni, and are pursuing training and research funds from the EU. This effort was furthered by Dr. Gallo's January visit to the EU Health Directorate in Brussels where he met, along with Dr. William Hall (Dublin), Dr. Arsène Burny (Brussels) and Dr. Reinhard Kurth (Berlin) with officials in the areas of science and technology. Also in Europe, GVN members are developing a proposal for a Strategic Award from the Wellcome Trust in the UK which would be the group's first substantial cooperative research program.

Using their GVN status as a mandate, the Chinese Center is receiving substantial new funding for internal collaboration, scholar exchange and international training programs. They will host the GVN semi-annual meeting in China in the fall of 2013. A large, active, and re-organized German center will host the GVN semi-annual meeting in the spring of 2013 in Munich.

The Network's primary objective of training the next generation of medical virologists has been a constant focus of center directors



Professor Billy Hall leads a panel on virology training programs at the GVN Meeting in Dublin.

worldwide. IHV has hosted three GVN trainees from Italy (Valentina Turri) China (Shaunqing Yu) and Germany (Annica Flemming) so far with great success. There is momentum in this area as GVN has submitted a fellowship funding proposal to the Leir Foundation of New York for support of our first GVN fellows. The GVN centers in the EU are also considering submission of a proposal through the EU Research Area for early-stage trainees in medical virology.

There has also been substantial progress in the corporate evolution of GVN. The organization has recently begun to expand its governing structure and is adding valuable members to its two boards: Corporate and Scientific Leadership. GVN has solicited names from its members and interest has been strong. The coming year will populate these three with an influential group that spans science, industry, and government. The group continues to search for the right match with U.S. governmental agencies and NGOs appropriate for support of GVN's goals and objectives and has recently made progress in this area. Finally, the organization continues its pursuit of support from major international foundations involved in global health issues as well as individual philanthropists who have

an interest and a means to help GVN succeed in its mission.

As part of GVN outreach and visibility efforts, Dr. Gallo and representatives of the group have, over the past year, met with Dr. Raj Shah, Administrator of USAID, Dr. Bill Colglazier, Chief S&T Advisor to the Secretary of State, and Dr. John Holdren, Assistant to the President for Science and Technology. In addition to these personal meetings, Dr. Gallo and leaders of the organization have been interviewed in major publications and presented on the GVN at international symposia. An example would be Dr. Gallo's presentation of the GVN concept to major international policy makers at the Institute on Science for Global Policy conference in Edinburgh, Scotland last October.

Overall, there are many reasons to be highly enthusiastic about the progress and promise of GVN. In less than two years, much has already been accomplished. GVN has proven to be an enhancement to IHV's overall research and training programs and, under Dr. Gallo's leadership, a major contribution to public health and international visibility for the Institute.

New Cell Discovery

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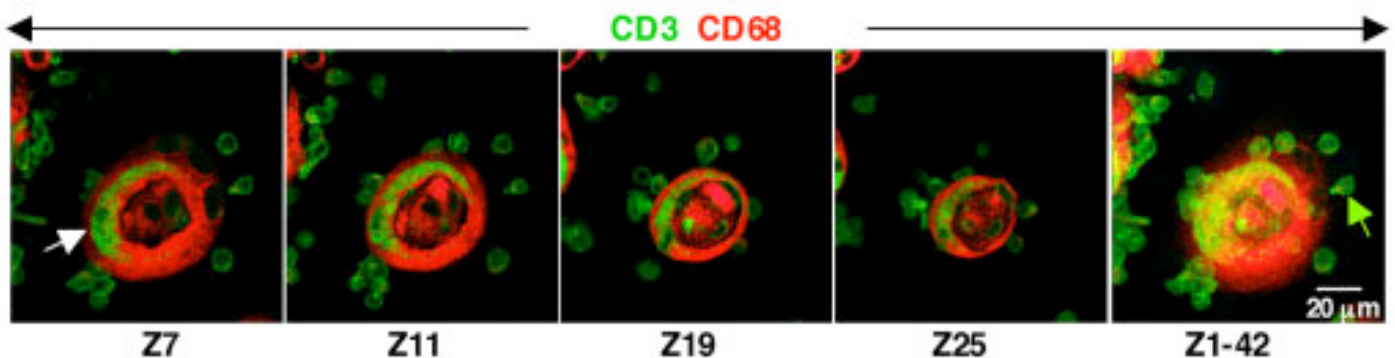
Dr. Suzanne Gartner

The nurse macrophage/small cell cycle does not require infection of new cells and for this reason, it may help to explain, along with latently infected long-lived cells, how “wildtype” HIV strains—those lacking drug resistance mutations—

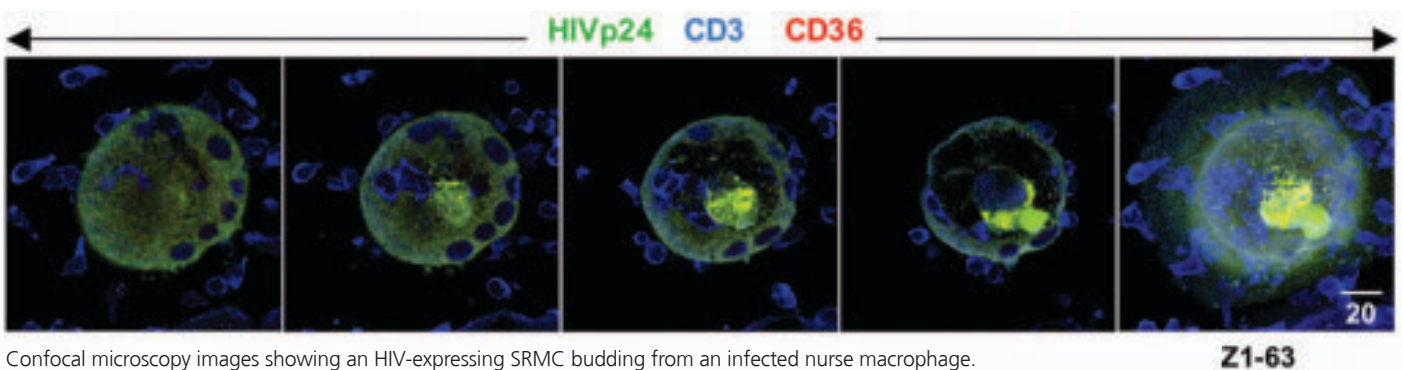
are maintained within the body during years of uninterrupted anti-HIV therapy. The researchers emphasize that although working with HIV led them to recognize nurse macrophage behavior, all of the phenomena observed can be seen in uninfected, as well as HIV-infected macrophage cultures.

Amazingly, nurse macrophages can also produce CD4+ T-cells, which are released as resting cells. These cells are a specific subtype of CD4+ T-cells, the subtype preferentially targeted by HIV. The researchers observed a dramatic decline in T-cell production in HIV-infected macrophage cultures, as well as release of resting CD4+ T-cells that contained HIV DNA, but were not producing the virus. These findings suggest that nurse macrophages may represent a source of latently infected CD4+ T-cells, and that compromise of nurse macrophage

production of CD4+ T-cells, brought about by HIV infection, may contribute to the CD4+ T-cell decline that characterizes AIDS. Dr. Gartner notes, “Thus far, the experiments have been performed using macrophages obtained from blood, and then cultured in the laboratory. We are now trying to determine if these phenomena are operational *in vivo*—within the human body.” Dr. Gallo adds, “The concept that a cell can be produced within another cell, a ‘mother’ cell, is new at least in human biology—and thought-provoking, and it makes sense that a virus would exploit this process as a survival strategy. Of course, the phenomena must be documented directly in patients, but it is likely that these concepts will ultimately impact several fields. In fact, this observation *in vitro* does demonstrate that at least some macrophages have a capacity never before described.”



Confocal microscopy images showing T-cell production within a human nurse macrophage. Images are from an uninfected culture. T-cells are identifiable by staining with CD3 (green color) and macrophages are identifiable by staining with CD68 (red color). Z refers to Z-stack level; lower numbers correspond to levels closer to the bottom of the cell, where it attaches to the culture plate. The far right panel shows the entire cell as a composite of Z-stack levels 1-42. In the first 4 panels, green-colored T-cells can be seen deep within the macrophage. Free CD3 antigen is also apparent (white arrow), and a T-cell can be seen being released at the surface of the macrophage (green arrow).

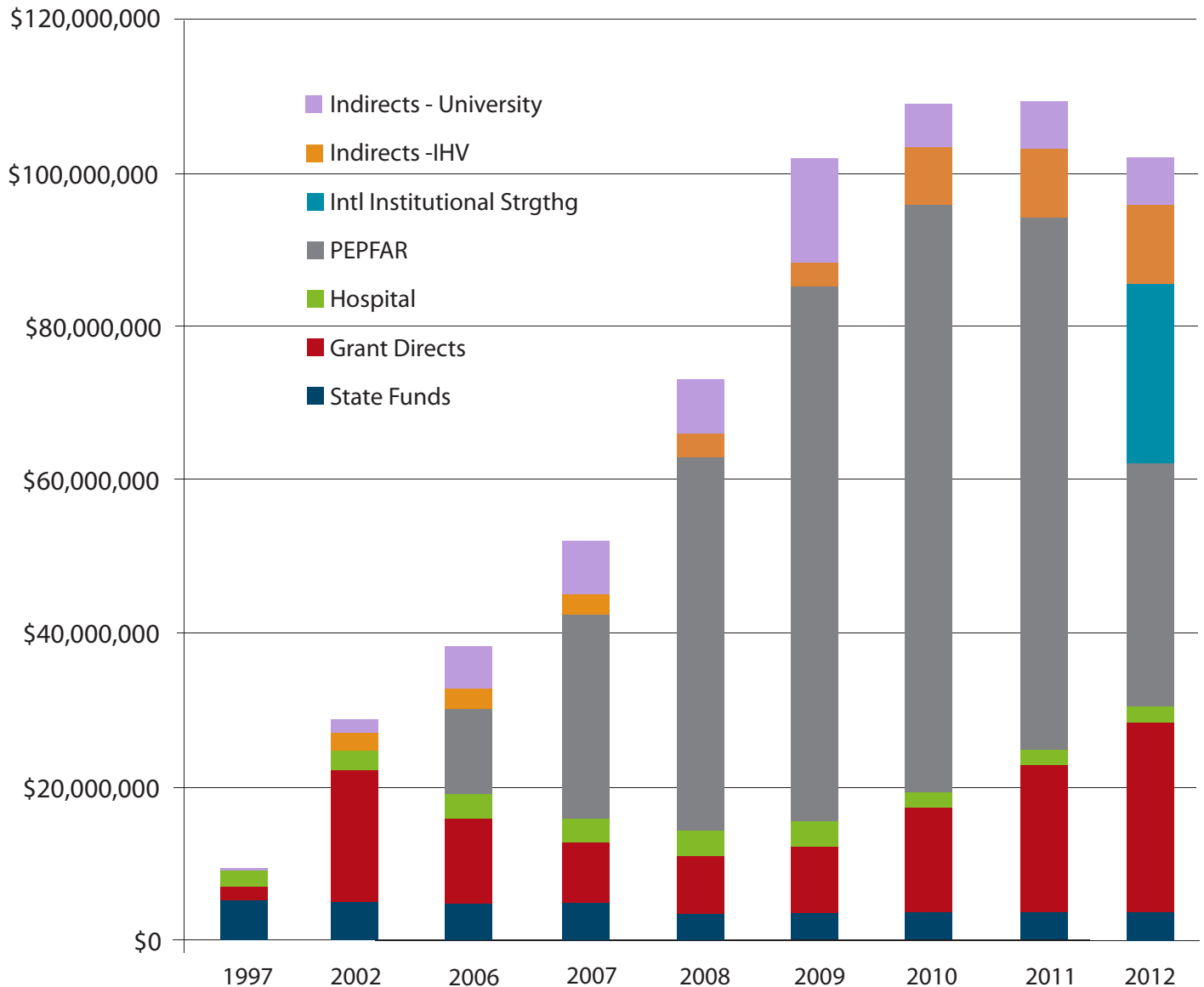


Confocal microscopy images showing an HIV-expressing SRMC budding from an infected nurse macrophage. CD3 (blue) is a T-cell marker, and CD36 (red) is a macrophage marker. The yellow color indicates colocalization of the HIV protein p24, with CD36. A small CD36+ cell (SRMC) can be seen budding from the center of the large macrophage. Blue-colored T-cells can be seen within the macrophage, and in close association with its surface. Although these T-cells are within an HIV-expressing nurse macrophage that is releasing a virus-expressing SRMC, they, themselves, are not expressing the virus (HIVp24). This suggests that infected nurse macrophages may produce and release latently infected T-cells. The far right panel is a composite of Z-stack levels 1-63, and shows the nurse macrophage in its entirety.

Financials and Related Charts

Budgeted Revenues: Distribution by Funding Sources

In 2012, the Institute of Human Virology (IHV) continued its significant impact on Maryland by generating large amounts of external revenue through grants and contracts. This year saw a major change to the President's Emergency Plan for AIDS Relief (PEPFAR) funding impacting several major Universities' programs, including those at IHV. Whereas, in the past, funding has gone directly to U.S. Universities to implement programs overseas, some countries executed a distinct shift towards funding indigenous organizations instead. However, IHV's increases in basic science research, vaccine research and international institutional strengthening grants offset most of the lost PEPFAR revenue. IHV's major funding sources now include the U.S. National Institutes of Health, the Bill & Melinda Gates Foundation, and the U.S. Centers for Disease Control and Prevention. Additionally, many of the international institutional strengthening grants are subcontracts where an indigenous organization is the prime, increasing our contracting and financial flow challenges. Overall, IHV had a very successful fiscal year, and continues to strategize new revenue opportunities within our mission of fighting chronic viral diseases and cancer.



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725 West Lombard Street | Baltimore, Maryland 21201-1009
410.706.8614 | 410.706.1952 fax | www.ihv.org



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