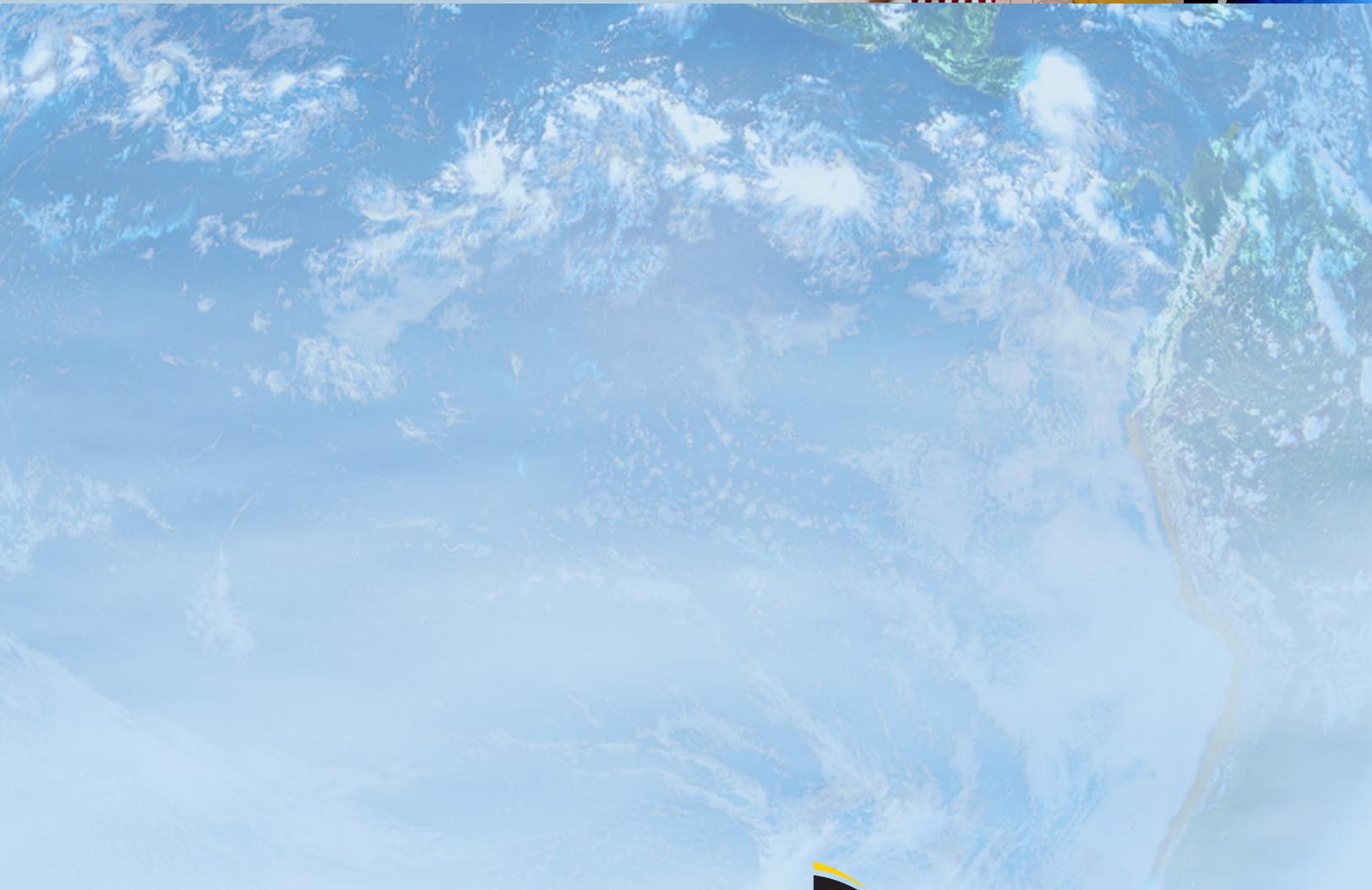


ANNUAL REPORT

2013

Institute of Human Virology



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.

# Contents

Director's Message .....	4-6
IHV Leadership .....	7
About IHV .....	8-9
Division of Basic Science and Vaccine Development.....	10-15
Division of Clinical Care and Research .....	16-19
Division of Epidemiology and Prevention.....	20-24
Global Virus Network (GVN) .....	25
Financials and Related Charts .....	26
IHV Board Memberships .....	27

The Institute of Human Virology is a center at the University of Maryland School of Medicine  
and is affiliated with the University of Maryland Medical Center.

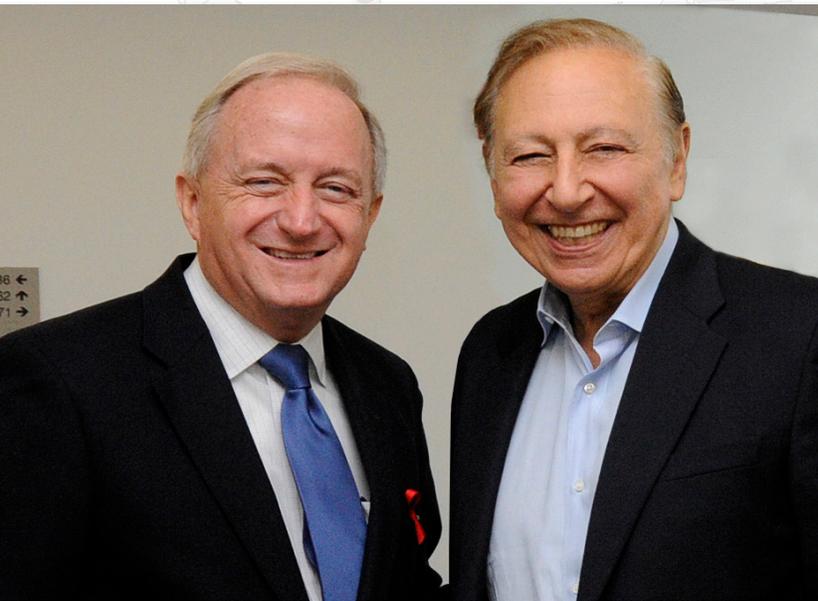
For more information call Nora Grannell 410.706.8614 or visit [www.ihv.org](http://www.ihv.org)

# Director's Message

The Institute of Human Virology at the University of Maryland School of Medicine had a successful and prosperous year in the fiscal year 2013. In October 2012, IHV welcomed a new Board of Advisors Chair, Terry Lierman. Terry is a longtime personal friend and is also renowned on Capitol Hill for his political skills as well as his passionate support of improved healthcare and funding for medical research. Most recently, Terry served as Chief of Staff to U.S. Representative Steny Hoyer (D-MD), also the then Minority Whip of the U.S. House of Representatives. Additionally, making news in October 2012, the IHV hosted its 14th Annual International Meeting in Baltimore, Maryland. The meeting brought together leading virologists and the HIV researchers to discuss breaking scientific advances to allow better treatment and prevention of both HIV and viruses that cause cancer. More than 80 leading virologists and international researchers spoke during the meeting. The gathering included world-renowned scientists from the IHV and the National Institutes of Health (NIH), as well as leading African, American, Asian, European, and Russian research institutions. Keynote lectures during the 14th Annual International Meeting featured Dr. Harold Varmus, Director of the National Cancer Institute, and Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases.



*A Successful and Prosperous  
Year in 2013*



IHV Board Chairman Terry Lierman and IHV Director Dr. Robert Gallo

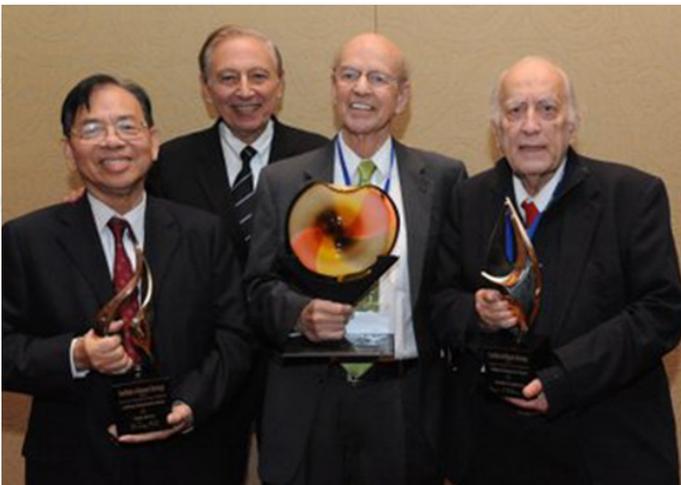
Additionally, following a vote by senior IHV faculty, the IHV awarded annual Lifetime Achievement Awards to three distinguished scientists who have had exceptional influence on the science of HIV and virology. They included:

**2012 IHV Lifetime Achievement Award for Scientific Contributions**—Thomas Waldmann, MD, head of the Cytokine, Immunology and Immunotherapy Section at the National Cancer Institute, for five decades of pioneering contributions to immunology, advances in the understanding of normal and abnormal T-cell biology, and seminal contributions to understanding Human T-Leukemia Virus (HTLV-1);

**2012 IHV Lifetime Achievement Award for Public Service**—Yi Zeng, PhD, Dean of the College of Life Science and Bioengineering at Beijing University of Technology, for a lifetime of leadership in virology and cancer research in China. Dr. Zeng is perhaps best known for discovering the first example of co-carcinogenesis in humans, when the combination of Epstein-Barr virus infection and particular plant products derived common to Southern China caused nasopharyngeal carcinoma; and,

**2012 IHV Lifetime Achievement Award for Excellence in Medical Education**—John Bartlett, MD, Professor at the Johns Hopkins University School of Medicine where he served as the longtime chief of the Infectious Diseases Division and became widely recognized as the world's foremost expert in the treatment of infectious diseases.

**A few of our Division highlights of the year are as follows:** In the Basic Science and Vaccine Development (BSVD) Division, led by Dr. George Lewis and me, we experienced significant progress this past year in our viral oncology, immunology, virology, and HIV-1 vaccine research programs with plans for the IHV HIV vaccine candidate to enter phase 1 clinical trials in 2014.



IHV Lifetime Achievement Award honorees Prof. Yi Zeng, Dr. John Bartlett, and Dr. Thomas Waldmann with Dr. Robert Gallo



(top photo) NCI Director Dr. Harold Varmus and (bottom photo) NIAID Director Dr. Anthony Fauci.

Also of note, Dr. Suzanne Gartner and her team announced that they had identified a new cell derived from a specific type of human macrophage. Dr. Lai-Xi Wang's group has developed a series of cyclic glycopeptides corresponding the V1/V2 domain harboring epitopes recognized by broadly neutralizing mAbs that recognize glycan-dependent epitopes. This work employs a new method developed by Dr. Wang's group to install glycans selectively at predetermined glycosylation sites. This has led to new epitope scaffolds that strongly bind broadly neutralizing mAbs specific for glycan-dependent epitopes, which will be useful for structural and vaccine studies. Also notably, Dr. David Pauza's group has developed Fc-targeted mucosal immunogens for HIV-1 that target neonatal Fc receptor (FcRn). This receptor mediates bidirectional antibody transport across mucosal epithelia and his new IgG-Env fusion proteins can be used to vaccinate mucosally. These studies could lead to strong anti-Env immune responses at mucosal and systemic sites. And, Dr. Wuyan Lu's group used total chemical synthesis to show that a highly conserved salt-bridge in the Dengue Virus 2 capsid protein is essential for the folding and stability of this structural protein. This work provides insight into the role of a fully conserved structural element of the dengue capsid protein C and paves the way for additional functional studies that could lead to new anti-viral drugs for this significant pathogen for which treatments are unavailable.

Directors Message continued

IHV Associate Professor and Animal Models Division head, Dr. Joseph Bryant, led animal research on lymphoma associated with HIV and primate research on our HIV preventive vaccine candidate.

IHV Associate Director and Director of the Epidemiology and Prevention Division, Dr. William “Bill” Blattner, continued to lead the Institute of Human Virology, Nigeria (IHVN) through funding from the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). IHVN’s impact is best measured in the clinical care, treatment, and prevention services to 944,004 Nigerians who were counseled and tested for HIV; 896,555 mothers who were screened to prevent infections of their babies; 139,857 patients who received antiretroviral therapy; and 32,749 health care workers who were trained.

Dr. Robert “Bob” Redfield, IHV Associate Director and Director of the Clinical Care and Research Division, reported another

successful year, particularly as his team continued to build upon advanced clinical education programs and targeted operational research in their PEPFAR programs in five African and two Caribbean nations. In each of these global locations, we have strong programs providing training, care, and treatment. The Division also provides care and treatment to more than 5,000 Marylanders living with HIV. Dr. Redfield and his team have continued their clinical research mission by maintaining the Division’s NIH funded Clinical Trials Unit (PI, Dr. Charles Davis), and other active trials in both HIV and Hepatitis C therapeutics.

This work collectively brought recognition from our campus colleagues as Bill and Bob were honored this year with the 2012 UMB Entrepreneurs of the Year award.

During FY 2013, IHV’s basic research portfolio, at the heart of our mission, continued to thrive despite severe cuts

to the U.S. National Institutes of Health and U.S. Centers for Disease Control funding levels. The Institute’s overall income continued to be influenced by the U.S. government’s decision to award international HIV care and treatment grants primarily to indigenous institutions as opposed to U.S. universities and institutes. However, as depicted in the Financials Section of this report, a large amount of funding is now going to organizations that the Institute has spun-off both in the U.S. (Profectus Biosciences, Inc.) and in four African nations. The technical assistance that the IHV provides to these organizations brings a great deal of revenue back to the Institute. The IHV continues to augment the world’s ability to fight chronic viral diseases in a meaningful and compelling way.

Participants at IHV’s 14th Annual International Meeting in Baltimore, Maryland.



# 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



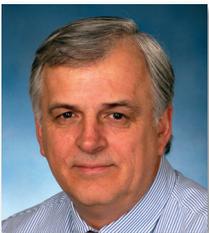
**William A. Blattner, MD**

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



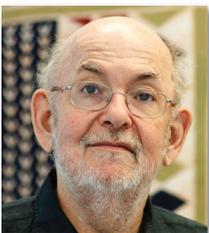
**Robert R. Redfield, MD**

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 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, the 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. The 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 the 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 the public. The IHV also pursues the development of effective therapeutic and preventative vaccines, science's greatest hope in putting an end to the AIDS pandemic.

The 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 Global Virus Network. To learn more about the Institute and its initiatives, visit [www.ihv.org](http://www.ihv.org) or contact IHV's Director of Public Relations, Nora Grannell at [ngrannell@ihv.umaryland.edu](mailto:ngrannell@ihv.umaryland.edu).



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SCHOOL OF MEDICINE



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*“The Institute of Human Virology continues to grow and enhance expertise in HIV, as well as other infectious diseases, including hepatitis viruses and other viruses causing cancer.”*

*Dr. Robert Gallo*

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# Division of Basic Science and Vaccine Development

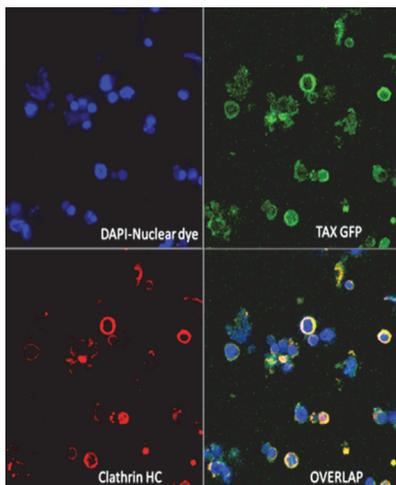
The Division of Basic Science and Vaccine Development faculty, led by Division Directors Drs. Robert Gallo and George Lewis, draws collectively from a wide range of disciplines including molecular and cell biology, virology, immunology, and structural biology to solve problems facing cancer and viral diseases. Significant progress has been made over the last year in our viral oncology, immunology, virology, and HIV-1 vaccine research programs.

## Viral Oncology

The Institute of Human Virology's (IHV) Viral Oncology program studies the etiology and pathogenesis of malignancies caused by virus infections, either by direct transformation by HTLV-1, or by indirect effects of HIV-1 infection, which greatly increases the likelihood that an infected individual will develop a malignancy over their life span, as well as searching for new etiologic infectious agents.

Dr. Hua Cheng's group is studying the oncogenic signaling events mediated by the HTLV-1 transactivator protein, Tax. His group has successfully transformed primary CD4+ T cells with the Tax protein alone to show that part of Tax-mediated transformation involves autophagy. This study was published this year in *The Journal of Biological Chemistry*. Dr. Yutaka Tagaya's group is also studying HTLV-1 oncogenesis but with a different bent. His group has

characterized the transforming effects of HBZ, which is an HTLV-1 encoded basic leucine zipper protein. His group has shown that HBZ can mitigate the cell-intrinsic safeguard mechanism upon clastogenic damage (i.e. UV irradiation, ionizing irradiation, chemical mutagen exposure), which facilitates the survival of mutated cells. His group is testing the hypothesis that this effect contributes to the establishment of heavily mutated progenitor cells in Adult T cell Leukemia, which is caused by HTLV-1.

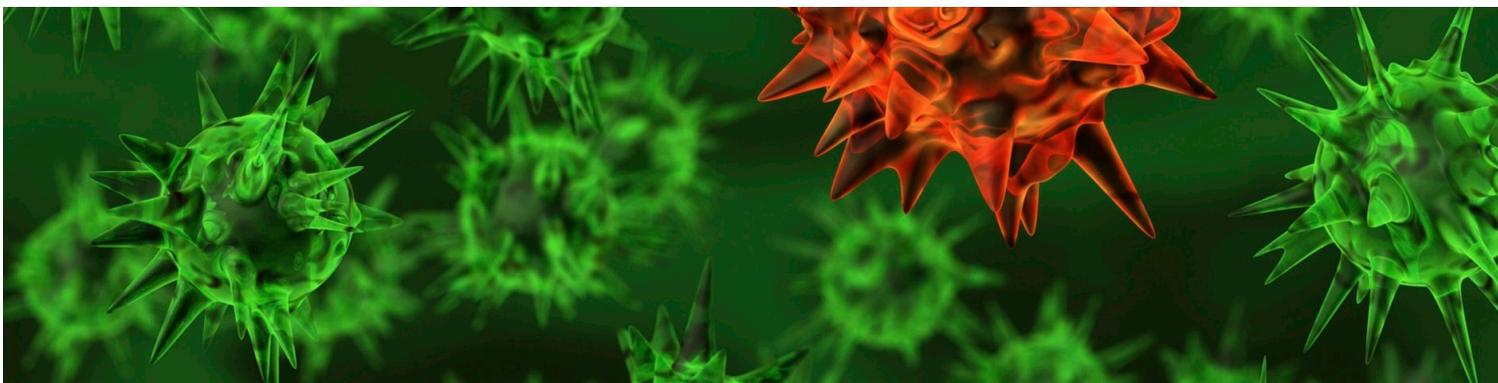


Anti CD3/28 activated CD4+ T cells transfected with TAX GFP/ co-stained with Clathrin HC- mouse monoclonal- Alexa Fluo 555 goat anti mouse IgG2b. Co-localization between TAX and Clathrin (yellow rings): O. Latinovic, PhD and Y. Tagaya, PhD MD

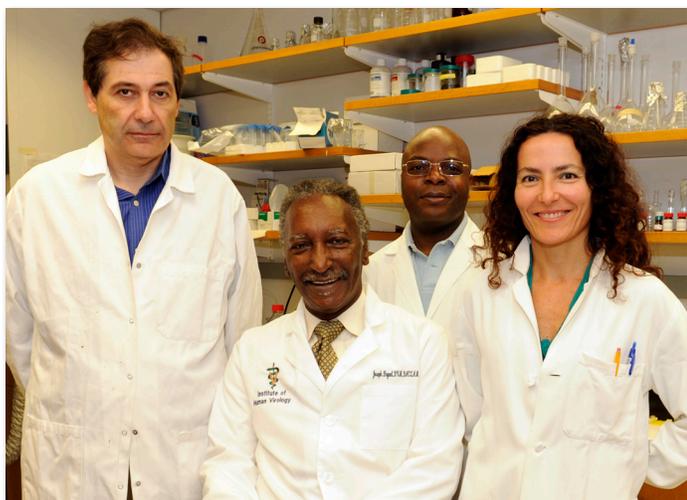
Other investigators of the Viral Oncology Program are studying the mechanism through which HIV-1 infection predisposes to B cell lymphoma. HIV-1 is not a transforming virus and its oncogenic effects are indirect. Dr. Gallo is leading a team comprised of Dr. Wuyuan Lu and Dr. Alfredo Garzino-Demo of the Division of Basic Science and Vaccine Development in collaboration with Dr. Joseph Bryant, Director of the Division of Animal Models and Dr. William Blattner, Director of the Division of Epidemiology and Prevention to determine the role of the HIV-1 structural protein, p17, in the genesis of B cell lymphoma. This research is carried out in collaboration with Prof. Arnaldo Caruso and colleagues at the University of Brescia and Prof. Riccardo Dolcetti of Avano, Italy. This work has led to the identification of B cell lymphomas in HIV-1 transgenic mice. Drs. Curreli, Zella, and Bryant have characterized the tumors that arise spontaneously in these mice as pre-B cell lymphomas, which are similar to some B cell lymphomas that arise in HIV-1 infected people. Dr. Lu's group is studying the structure of p17 and Dr. Garzino-Demo's group is developing new transgenic



(L to R) Drs. Wuyuan Lu, Robert Gallo, and Alfredo Garzino-Demo



mice expressing only p17. These basic science projects are supporting clinical studies of B cell lymphomagenesis by Dr. Blattner and his team.



(L to R) Drs. Davide Zella, Joseph Bryant, Ngeh Toyang, and Sabrina Curreli

Although it is not a virus, Drs. Gallo, Zella, Curreli, and Bryant have discovered that certain strains of human mycoplasma will induce lymphomas in immunodeficient mice. Mycoplasmas are bacteria but they are distinguished from other species by the lack of a cell wall and are the smallest known self-replicating organisms. In addition, they preferentially grow in eukaryotic cells. Studies from this group have shown that primary and secondary tumors from mycoplasma-infected mice harbor mycoplasma DNA sequences and a direct interaction between a mycoplasma protein and p53, impairing its ability to respond to DNA damage and possibly leading to malignant transformation. The studies describe the first causal link between mycoplasma infection and lymphomagenesis.

## Immunology

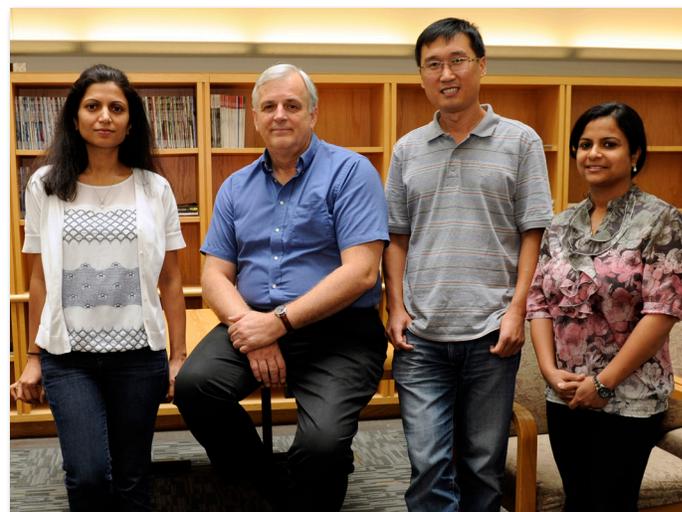
Immunology is comprised of an array of sub-disciplines that have direct bearing on the IHV goal of eradicating infectious diseases and their associated malignancies.

Dr. David Pauza and Dr. Haishan Li have shown that the HIV-1 envelope glycoprotein (Env) triggers the signaling kinase, p38 MAPK, after it binds to the CCR5 co-receptor on the CD4+ T cell surface, which up-regulates caspase proteins leading to cell death. In contrast, during productive infection of CD4+ T cells by HIV-1, Env binding to CD4 activates Akt kinase that shuts off the p38 MAPK signaling pathway, which counters this death signal. Thus, HIV-1 has evolved to target memory CD4+ T cells that express CCR5

but it has adapted through binding to CD4 to avoid cell death that would decrease yields of infectious virus. In addition, they have shown in CCR5 negative CD4+ T cells that Akt activation by Env binding to CD4 triggers the expression of cell surface markers indicative of a T follicular helper phenotype (Tfh). Tfh cells play a key role in providing help to B cells to become memory cells or antibody secreting cells. This activation might be key to the known accumulation of large numbers of Tfh in lymph nodes during active HIV-1 infection and it could also be the underlying factor leading to polyclonal B cell activation and hypergammaglobulinemia that is a well known element in AIDS pathogenesis. This work has led to the possibility of using kinase inhibitors as potential adjunct therapies for HIV-1 disease, especially for infected individuals that are refractor to conventional anti-retroviral therapy, or for HIV-1 associated malignancies.

Dr. Cristiana Cairo, in collaboration with Dr. Pauza, has been investigating the role of  $V\gamma V\delta 2$  cells in the context of neonatal and infant immunity. Studies in Cameroon suggested that prenatal exposure to placental malaria causes depletion of pathogen reactive  $V\gamma V\delta 2$  cells in the fetus leading to poor responses by this important subset in neonates. Dr. Cairo has obtained a new R01 grant to pursue these studies.

Dr. Bhwana Poonia and Dr. Pauza have shown that CD56 expression is significantly reduced on CD8+ T lymphocytes during HIV-1 infection in humans. CD56 defines the subset of CD8+ T cells that have effector memory properties including potent cytolytic activity.

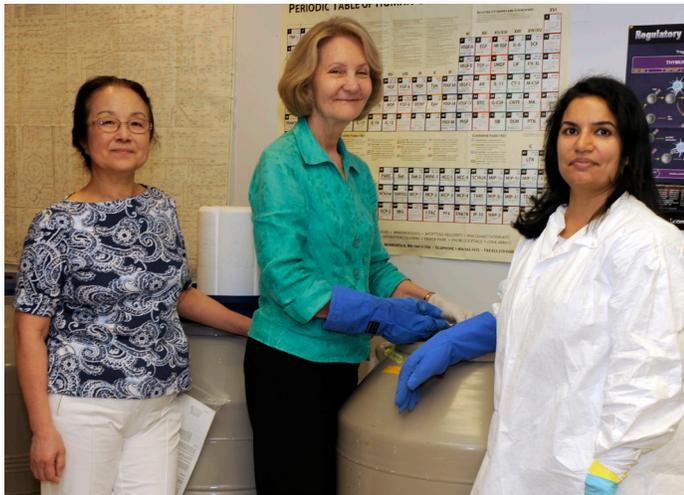


(L to R) Drs. Bhawna Poonia, Dave Pauza, Haishan Li, and Suchita Chaudhry

Thus, HIV-1 infection down-regulates the CD8+ T cell subset that mediates Class I MHC-restricted killing of infected target cells. They have shown that the CD8+ CD56+ subset is not restored in HIV-1 infected individuals for whom their viral loads are suppressed by anti-retroviral therapy. By contrast, elite controllers, which are HIV-1 infected individuals that control viral loads spontaneously, have the normal complement of this subset, which might contribute significantly to this autologous control of viral replication. Strategies to restore this subset in HIV-1 infected individuals are being explored as a potential tool in efforts to cure HIV-1.

Dr. Maria Salvato's laboratory profiles innate and acquired responses to arenavirus infections. She took advantage of SIV-infected monkeys leftover from a vaccine study by the Pauza laboratory to show that they could support an attenuated Lassa fever vaccine. The monkeys developed excellent immune responses against Lassa virus and never developed signs of arenavirus disease. Graduate student Juan Carlos Zapata reported on this work as part of his PhD thesis, received from the University Autonoma, Medellin, Colombia.

Dr. Suzanne Gartner's laboratory is continuing investigations of multi-lineage differentiation potential of novel small cells produced by nurse macrophages, which was published in PLoS One recently. A particular focus is the question of whether the nurse cells can generate erythroid progenitors and CD34+ hematopoietic stem cells. In addition, Dr. Gartner's group has continued the characterization of steps leading to the production of CD4+ T cells from then nurse macrophages. Studies are continuing in humans, based on observations that nurse macrophages and their novel monocytoid progeny reside in human bone marrow.



While Dr. Yiling Liu (left) looks on, Dr. Suzanne Gartner (center) retrieves a specimen from liquid nitrogen for Dr. Jennifer Bharucha (right), a member of Dr. Alfredo Garzino-Demo's laboratory. The three researchers study HIV infection in macrophages, particularly within brain and bone marrow. Drs. Gartner and Liu have worked together on this problem for more than 20 years.

Dr. Erik de Leeuw's laboratory is investigating the anti-microbial effects of defensins, which are a class of anti-microbial peptides with activities on bacteria and HIV-1. Dr. Leeuw's studies are focusing on the role of defensins as signaling molecules that connect the innate and adaptive immune systems. In this regard, his group has shown that defensins interact synergistically with TNF- $\alpha$ , which is a key regulator in the immune system with strong proinflammatory and immunomodulatory properties. It

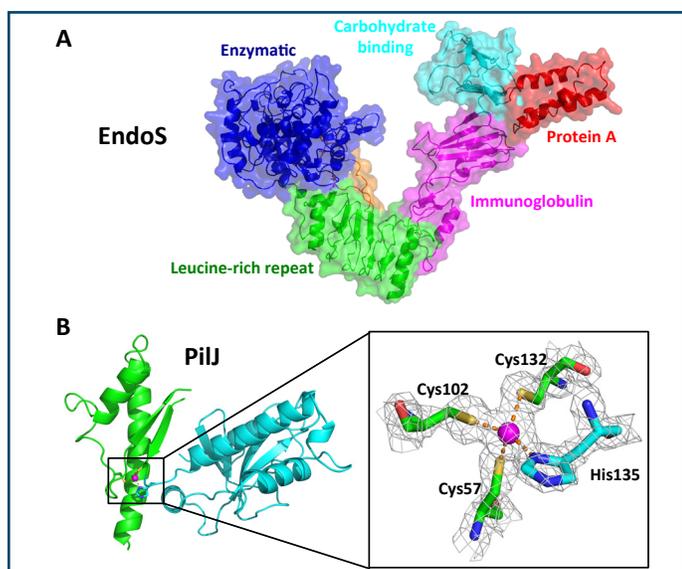


Dr. Erik de Leeuw

plays significant roles in many acute and chronic inflammatory diseases. Human  $\alpha$ -defensin 5 (HD-5) induces cell death of T cell lines in vitro, as well as inhibiting the growth of lymphoma cells in immunodeficient mice. HD-5 mediated killing depends on the functional expression of TNF- $\alpha$  receptors. Studies of signaling pathways lead to the novel hypothesis that HD-5 binds to the extracellular domain of TNF receptor 1. If this hypothesis is confirmed, it will serve as the basis for the rational development of defensin-based agonists or antagonists that specifically target the extracellular domain of TNF receptor 1. Such drugs could be used to treat inflammatory diseases as well as malignancies.

Dr. Wuyuan Lu's laboratory continues to use multi-disciplinary approaches to elucidate the molecular basis of how antibacterial and antiviral peptides function in innate immunity. His team has contributed to a paradigm-shifting discovery (Chu et al. 2012 Science 337:477) that describes a novel mode of antibacterial action for the human enteric  $\alpha$ -defensin 6 (HD6) highly expressed by secretory Paneth cells of the small intestine. Defects in Paneth cells and reduced expression of enteric  $\alpha$ -defensins are linked to ileal Crohn's disease—a chronic inflammatory disorder of the small intestine. Paradoxically, however, HD6 shows little bactericidal and membranolytic activities in vitro despite the fact that HD6 fully protects against bacterial invasion in HD6+/- transgenic mice challenged with the enteric pathogen *S. Typhimurium*. Extensive biochemical, biophysical, and structural studies reveal that HD6 forms structured nanonets to entrap enteric bacterial pathogens (instead of directly killing them), and protect against bacterial invasion of the intestinal epithelium.

Dr. Eric Sundberg's group investigates molecular recognition in infectious diseases as a path to rationalizing novel therapeutic approaches to microbial pathogenesis, chronic inflammatory diseases, and infectious causes of cancer. Dr. Sundberg's group is elucidating the molecular basis of effector functions of antibodies with the goal of manipulating these functions for specific therapeutic purposes. In collaboration with Dr. Lai-Xi Wang, Dr. Sundberg's group has determined the crystal structure of Endoglycosidase S (**Figure, Panel A**), a large enzyme that removes sugars specifically from IgG. This enzyme is used extensively for glycan engineering. The structure provides novel information on the catalysis mechanism of this enzyme that will be useful in further tailoring its activity. Dr. Sundberg's group has developed hyper-glycosylated antibodies that bind selectively to activating Fc receptors, which could greatly enhance the in vivo activity of



therapeutic antibodies while providing a basis for next-generation vaccines. In collaboration with Dr. Michael Donnenberg in the Department of Medicine, Dr. Sundberg's group recently determined the first X-ray crystal structure of a Type IV pilin protein (**Figure, Panel B**) from the gram-positive bacterium, *Clostridium difficile*, which causes antibiotic resistant infections with significant morbidity and mortality. Type IV pilin proteins are important for bacterial colonization and virulence and, as such, it is a novel target for drug or vaccine intervention. The new structural information will be used to guide drug and vaccine development.

## Virology

Fundamental virology remains a mainstay in HIV-1 research providing new windows on therapeutic targets and several investigators are pursuing different strategies to prevent or abrogate HIV-1 infection.

Dr. Alfredo Garzino-Demo's group focuses on the anti-HIV-1 activities of  $\beta$ -defensins with emphasis on signaling activity initiated by the binding of  $\beta$ -defensins to the chemokine receptor, CCR6. This interaction leads to the activation of APOBEC3G, a cytidine-deaminase that is involved in the innate resistance to HIV-1 infection. Thus,  $\beta$ -defensins indirectly affect HIV-1 replication through the activation of this potent innate anti-viral pathway. Dr. Garzino-Demo's group is also investigating the role of  $\beta$ -defensins and the CCR6 signaling pathway in the protection



(Back Row) Drs. Kurt Piepenbrink, Greg Snyder, Eric Sundberg, and (Front Row) Drs. Tali Reingewertz, Sandra Postel, Sebastian Gunther, and Beatriz Trastoy-Bello

of Th17 cells from HIV-1 infection. This subset is massively and selectively lost in the gut mucosa of humans infected with HIV-1 and rhesus macaques infected with SIV.

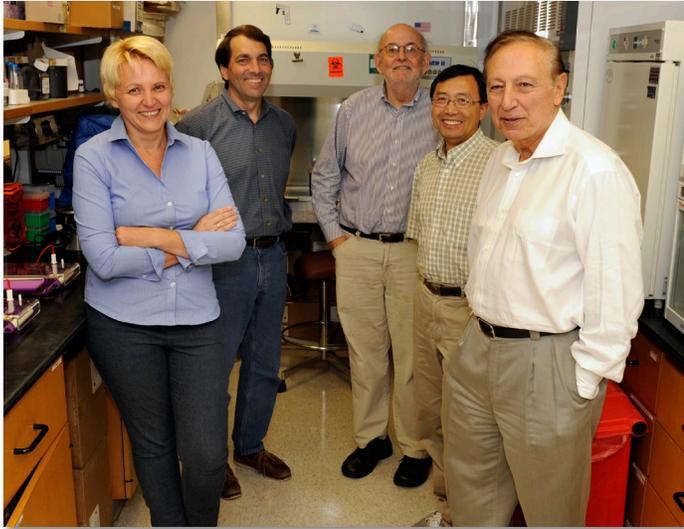
Dr. Fabio Romero's group investigates the basic biology of the CD4+ T cell reservoir for HIV-1. This work is significant in that the reservoir is refractory to anti-retroviral drugs and any attempt to cure HIV-1 must include reservoir eradication. Dr. Romero's group has used an in vitro reservoir model to show that reservoir CD4+ T cells have high levels of CD2. This enables enrichment of the reservoir population although it is still heterogeneous in phenotype. Additional studies are being carried out to identify more cell surface molecules that are expressed selectively on reservoir cells. Identification of the ultimate phenotype of reservoir CD4+ T cells will be important to ultimately curing HIV-1.

Dr. Olga Latinovic is studying the synergistic effects of two molecules that inhibit HIV-1 infection in vitro. The first molecule is Maraviroc, a FDA-approved drug that binds to CCR5 and blocks HIV-1 entry. The second molecule is FLSC-IgG1, which is a chimeric protein comprised of CD4-triggered gp120 fused to the heavy chain of IgG1 developed in the IHV by Dr. Tony DeVico who collaborates on this work. FLSC-IgG1 also binds to CCR5 but with a different mechanism than Maraviroc. Synergistic in vitro inhibition of HIV-1 infection is observed when these two molecules are combined. New imaging methods to define the mechanisms of inhibition at the single cell level have been developed with Dr. Joseph Lakowicz, and an in vivo model for therapy by this drug combination have been developed in collaboration with Dr. Robert Redfield.

Drs. Romero and Latinovic organize the IHV Journal Club that meets twice a month. After hors d'oeuvres and beverages, Journal Club can become a lively discussion of current publications.

Dr. Joseph Lakowicz is developing new methods to quantify protein-protein interactions using intrinsic fluorescence that occurs from all proteins with novel photonic structures. This approach is being developed in collaboration with Dr. Tony DeVico and it will lead to a label free method for high-throughput screening of biological molecules. The approach is being developed for rapid screening of monoclonal antibodies. Dr. Lakowicz is also collaborating with Dr. Latinovic where they have developed a method based on plasmonic substrates to directly identify HIV-1 secreting cells in vitro. Finally, Dr. Lakowicz is collaborating with Dr. DeVico and Dr. Lewis on the development of a method to directly quantify the binding of antibody to HIV-1 virions in solution. This method employs Fluorescence Correlation Spectroscopy and it directly quantifies the binding of antibodies to virions, obviating the inherent problems encountered with typical plate capture assays. This information is being used to define epitope exposure throughout the HIV-1 replicative cycle.

Dr. Wuyuan Lu's laboratory previously discovered several proteolysis-resistant D-peptide activators of the tumor suppressor protein p53 for anticancer therapy. More recently his team has developed a highly sensitive fluorescence polarization assay that is being automated for high throughput screening for small molecule inhibitors of HIV-1 assembly and maturation. The proof of concept is based on the notion that dimerization of the C-terminal domain of the HIV-1 capsid protein or CTD, is critically important for the assembly of both immature and mature viral particles. CTD dimerization inhibitors thus are expected to abrogate HIV



(L to R) Drs. Marzena Pazgier, Anthony DeVico, George Lewis, Yongjun Guan, and Robert Gallo

assembly and maturation, promising a novel class of therapeutic agents for the treatment of HIV-1 infection. Of note, his laboratory, in collaboration with Dr. Marzena Pazgier, has also unveiled the structural basis of redox-controlled HIV-1 capsid assembly and disassembly by demonstrating that formation or reduction of the highly conserved disulfide bond between Cys198 and Cys218 in the HIV-1 capsid protein significantly impacts the ability of CTD to dimerize. Their findings explain why an extracellular environment stabilizes a circulating virus while an intracellular environment favors its uncoating.

## Vaccine

A safe and effective vaccine is widely viewed as the best way to quell the HIV-1 epidemic; however, after over twenty-five years of intensive research, it remains elusive. IHV investigators are actively pursuing several vaccine strategies with a lead vaccine candidate now poised for a Phase I clinical trial.

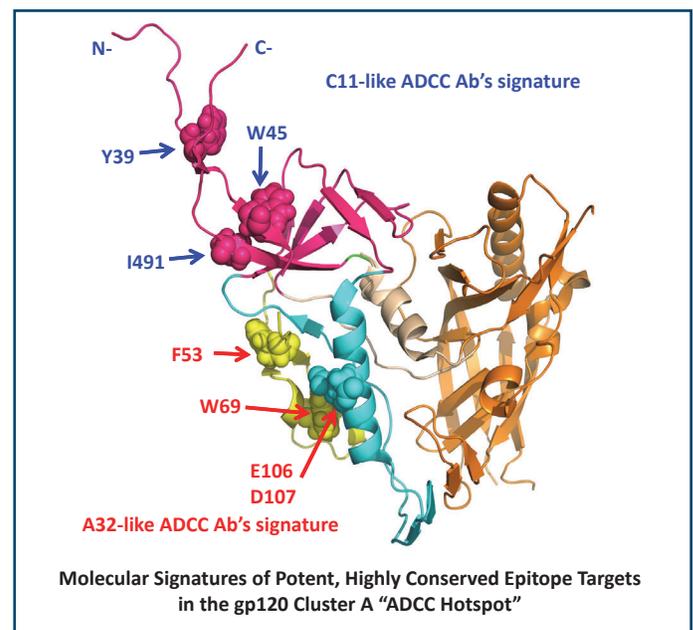
Dr. Gallo is leading a program to evaluate a conformationally constrained vaccine denoted as FLSC (Full Length Single Chain) in a Phase I Clinical Trial to be conducted in IHV's clinic in Baltimore. The Bill and Melinda Gates Foundation and the U.S. Military HIV Research Program support this study and it involves members of the Institute including Dr. Tony DeVico, in whose group FLSC was originally developed, Dr. George K. Lewis who is Co-Principal Investigator, Dr. David Pauza and Dr. Joseph Bryant, who are responsible for primate studies for the program, and Dr. Bruce Gilliam and Dr. Robert Redfield, Director of the Division of Clinical Care and Research, who are responsible for the Phase I Clinical Trial. The project also includes collaboration with former IHV member Dr. Timothy Fouts, who is also a co-inventor of the vaccine, and is currently of the Baltimore based Profectus Biosciences. This program represents the cumulative efforts of a large group of investigators who were brought together by Dr. Gallo to work on an HIV-1 vaccine when the IHV was established seventeen years ago. It is emblematic of the original design of the IHV to go from bench to bedside inside a single institution. FLSC is a conformationally constrained fusion protein of gp120 and CD4 that stably exposes highly conserved epitopes that are targets of protective antibodies.

A number of challenge studies in non-human primates carried out over the years show that FLSC elicits protective responses in rhesus macaques against a model AIDS virus SHIV162p3. These studies have identified serological correlates of this protection in addition to identifying protein and adjuvant compositions that are key to protection. These key preclinical studies set the stage for the first evaluation of FLSC in humans scheduled for 2014.

In addition to his involvement in the development of FLSC, Dr. Lewis also leads a group of IHV collaborators in a program to understand the basis of antibody-mediated protection against HIV-1. This program is funded by the Bill and Melinda Gates Foundation and involves extensive collaborations among IHV members, Dr. Yongjun Guan, Dr. Tony DeVico, Dr. Marzena Pazgier each of whom leads key projects of the program. This program tests the hypothesis that non-neutralizing antibodies that exhibit potent Fc-mediated effector function can protect rhesus macaques against SHIV162p3.

Dr. Youngjun Guan's group has isolated, produced, and characterized a large number of mAbs from an HIV-1 infection cohort established by Dr. Mohammad Sajadi and Dr. Robert Redfield in the Division of Clinical Care and Research. In addition, his group has isolated mAbs from rhesus macaques infected with SHIV162p3 as a part of ongoing FLSC protection studies by Drs. DeVico and Lewis. This work has led to the identification of an epitope "hotspot" on Env recognized by non-neutralizing mAbs that mediate potent antibody dependent cell mediated cytotoxicity (ADCC), which is a major Fc-mediated effector function. They include highly conserved epitopes in gp120 and gp41. These epitopes map to regions that control the interaction between gp120 and gp41 in virus assembly and their dissociation during viral entry. The first results from these studies were published in PNAS earlier this year. These mAbs will be evaluated in passive immunization studies in the next year.

Dr. Guan's group has also isolated a new broadly neutralizing mAb that recognizes a unique epitope that is a template for next-generation HIV-1 vaccine design in the IHV.

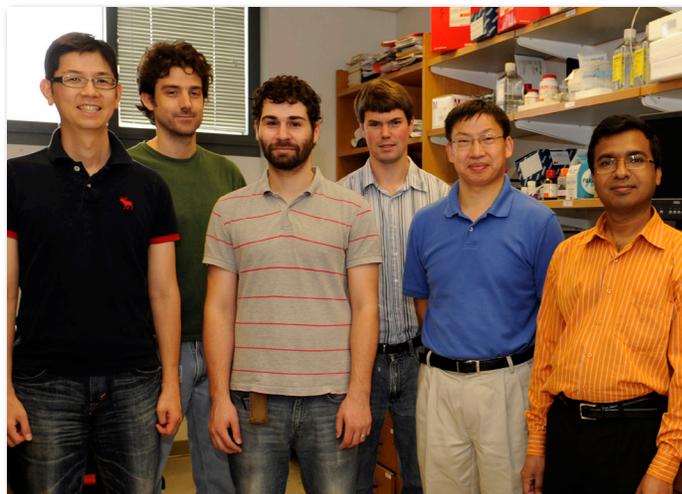


Dr. Tony DeVico's group has developed state of the art methods to quantify epitope exposure on free virions in solution and at the virion-cell surface interface during viral entry. These studies use the new mAbs identified by Dr. Guan's group as well as standard mAbs used by the field for epitope characterization. Epitope exposure on free virions is determined by the fluorescence correlation spectroscopy method described earlier in the collaboration with Dr. Joseph Lakowicz. Epitope exposure at the virion-cell interface is determined by single viral particle imaging using conventional confocal microscopy as well as by super resolution microscopy. Information from these studies is being used in conjunction with a new ADCC assay developed in Dr. Lewis' group using target cells sensitized with entering virions to determine the relationship between epitope exposure and ADCC activity. These studies indicate that factors other than just epitope exposure dictate differences in potencies among mAbs that mediate ADCC.

Dr. Marzena Pazgier's group is determining the epitope footprints for mAbs isolated by Dr. Guan's group that exhibit potent ADCC activity. Her group has used X-ray crystallography to solve co-crystal structures for three anti-gp120 mAbs that mediate potent ADCC. These mAbs recognize structures associated with the mobile regions of gp120 that communicate CD4-induced conformational changes to gp41 during viral entry. These studies are being used in conjunction with mutagenesis data from Dr. Guan's group to define epitope signature sequences at the atomic level. Most importantly, the epitope footprint defined for these mAbs falls into the region of gp120 that was implicated in the RV144 vaccine trial as a target of potentially protective antibodies that mediate ADCC.

In addition to his involvement in the development of FLSC as a vaccine, Dr. Lewis' group is investigating the physical-chemical basis for ADCC. Studies are underway to determine the molecular basis of the bell-shaped dose-response curves seen in ADCC assays. These studies employ the information from the projects led by Drs. Guan, DeVico, and Pazgier in addition to flow cytometric methods to quantify the degree to which multivalent mAb binding and Fc orientation determine the binding of immune complexes on target cells to Fc receptors on effector cells. These interactions are major elements controlling ADCC potency *in vitro*. In addition, his group is testing the hypothesis that these effects determine the protective potency of mAbs in passive immunization studies in non-human primates. These studies will be carried over the next year using a passive immunization model developed in collaboration with Dr. DeVico and the broadly neutralizing mAb developed by Dr. Guan.

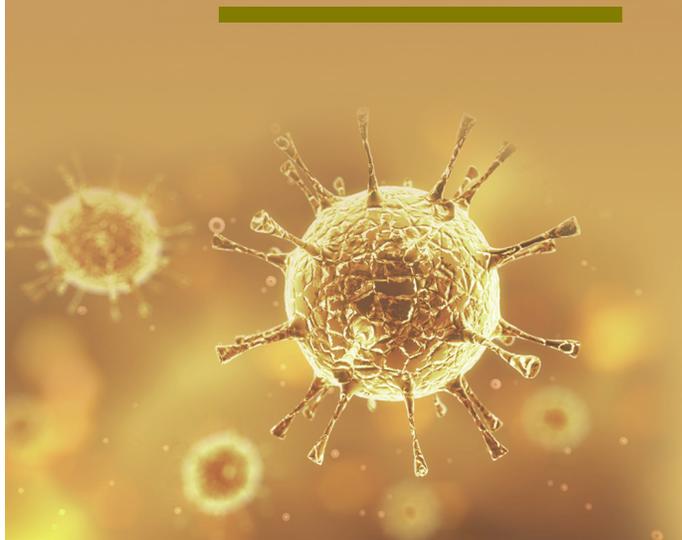
Dr. Lai-Xi Wang's group is investigating carbohydrate scaffolds as potential HIV-1 vaccine candidates. His group has developed a series of cyclic glycopeptides corresponding the V1/V2 domain harboring epitopes recognized by broadly neutralizing mAbs that recognize glycan-dependent epitopes. Antibodies targeting V1V2 were also one of the correlates of protection in the RV144 trial. This work employs a new method developed by Dr. Wang's group to install glycans selectively at predetermined glycosylation sites. This has led to new epitope scaffolds that strongly bind broadly neutralizing mAbs specific for glycan-dependent epitopes. This pioneering work, mainly carried out by postdoctoral fellow Mohammed Amin, was recently published in *Nature Chemical Biology* (Amin et al; 2013). Further, Dr. Wang's group is using these glycosylation methods to improve the functional activity of monoclonal antibodies that mediate ADCC. This work should lead eventually to more potent therapeutic mAbs and possibly new vaccine candidates.



(L to R) Drs. Takahiro Yamaguchi, Joseph Lomino, John Giddens, Christian Toonstra, Lai-Xi Wang, and Mohammed Amin.

Dr. David Pauza's group is developing Fc-targeted mucosal immunogens for HIV-1. These immunogens bind the neonatal Fc receptor (FcRn) that mediates bidirectional antibody transport across mucosal epithelia. His group has developed IgG-Env and IgG-Gag fusion proteins that can be used to vaccinate mucosally. This work involves collaborations with Drs. Sundberg, Salvato, Wang, and Bryant of the IHV.

*“Basic Science is the foundation  
for everything—without it,  
there would be no  
drug therapy or vaccines”*





# Division of Clinical Care and Research

The Division of Clinical Care and Research continues to develop its tripartite mission: clinical care, clinical research, and medical education, both domestically and around the world. Our clinical program continues to grow with the recent opening of the UMMS Mid Town Campus (formerly Maryland General Hospital), and will serve at this site to expand both ambulatory and acute HIV and Hepatitis clinical activities. Our laboratory based clinical research program continues to focus on targeting host cell pathways and novel approaches for therapy of chronic viral diseases. The Clinical Research Unit has also expanded its hepatitis therapeutic research activities establishing a strong intramural partnership with NIH. Finally, the division's medical education activity is on a solid foundation, both domestically and abroad.

## Laboratory Research

The focus of laboratory based research efforts within the Division of Clinical Care and Research continue in the area of targeting host cell pathways as potential primary therapeutic targets, as well as a strategy to enhance the activity of a FDA approved anti-HIV agent.

Dr. Alonso Heredia's research focuses on inhibiting HIV by targeting host cellular proteins. One main advantage of this strategy is that HIV resistance may not develop as rapidly as on strategies that target viral proteins. Dr Gallo's seminal studies on inhibition of HIV with hydroxyurea provided proof-of-concept for the targeting of cellular factors in HIV therapeutics. Together with Dr. Redfield, Dr Heredia has shown and published effective inhibition of HIV and enhancement of antiretrovirals by targeting cellular inosine monophosphate dehydrogenase with Mycophenolic acid, NFKB with Vitamin E, CDK9 with Indirubin derivatives, CCR5 with drug-induced CCR5 ligands and CCR5 antibodies. Recent work demonstrated that Resveratrol (a polyphenol in grapes, berries, and other fruits) enhances HIV inhibition by tenofovir and emtricitabine, the two most widely prescribed antiretrovirals in HIV therapy. In addition, Resveratrol sensitizes tenofovir- and emtricitabine-resistant primary isolates of HIV-1 from clades B and C. We are currently evaluating the efficacy of these approaches in preclinical animal models. (Heredia A, Davis CD, Reitz MS, Jr., Le NM, Wainberg MA, Foulke JS, Wang LX, and Redfield RR. Targeting of the Purine Biosynthesis Host Cell Pathway Enhances the Activity of Tenofovir Against Sensitive and Drug-Resistant HIV-1. *J Infect Dis.* 2013 Aug 27. Epub ahead of print).

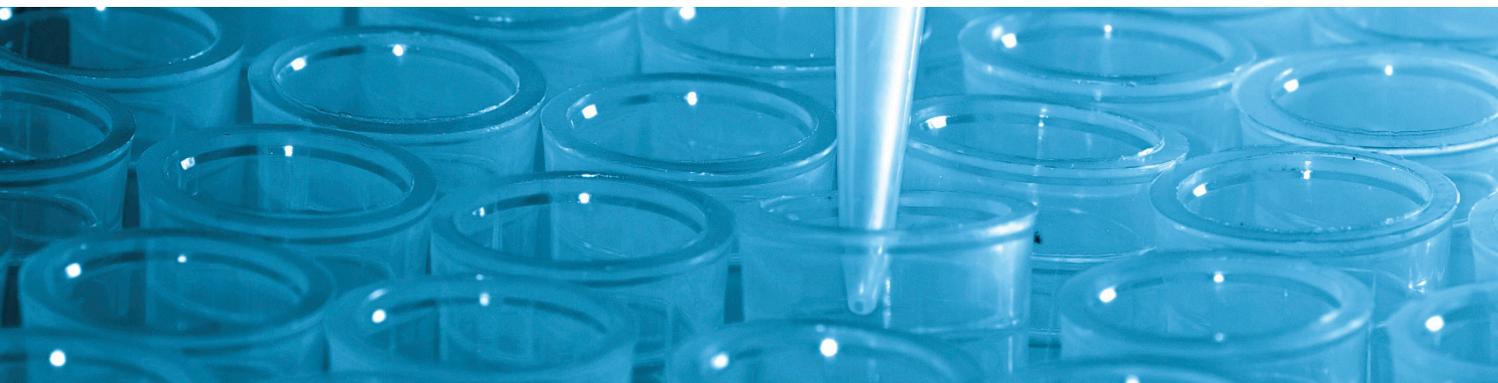


Dr. Alonso Heredia

Dr. Olga Latinovic, Assistant Professor, has been working closely with Dr. Robert R. Redfield on HIV entry inhibition since joining the IHV. Her main research project focuses on the CCR5 molecule, a major co-receptor in HIV entry, by directly targeting and reducing its expression. She is developing different combination approaches to enhance potency and decrease side effects of HIV-1 entry inhibitors, as well as to overcome and prevent resistance. One of Dr Latinovic's ongoing projects is related to the role of statins and CCR5 expression levels. Dr. Latinovic is currently evaluating the clinically approved CCR5 antagonist, Maraviroc (Pfizer, 2007), in combination with a fusion protein (FLSC-IgG1) containing gp120, the D1 and D2 domains of human CD4, and the hinge-CH2-CH3 region of human IgG1 fusion protein, originally developed by Drs. Vu, Fouts, and DeVico. The two reagents bind distinct domains of CCR5, and both have relatively high anti-viral activities that strongly synergize when tested with different cell types, including primary CD4+ T cells. Based on these data, Drs. Latinovic and Redfield believe that the FLSC IgG1-Maraviroc has a substantial therapeutic potential. They are currently using this combination of reagents in a humanized SCID/NOG mouse model experiments in collaboration with Dr. Bryant, and research staff: E. Ateh, S. Medina-Moreno, K. Schneider, and J. Zapata.



Dr. Olga Latinovic



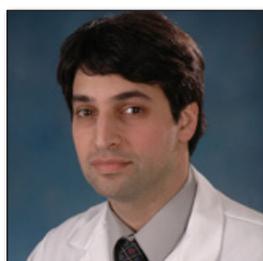
Dr. Nicholas Stamatou's research is directed toward understanding how modulation of the carbohydrate content of cell surface proteins and lipids influences the functional capacity of cells of the immune system. Two main projects in the laboratory are focused on elucidating the role of sialic acid (N-acetylneuraminic acid) in regulating the responses of peripheral blood mononuclear cells (PBMCs) to infectious agents and inflammatory stimuli. Given its terminal location on glycans and its hydrophilic and electro-negative features, sialic acid plays an important role in regulating cellular interactions with ligands, microbes and neighboring cells and in controlling cellular activation, differentiation, transformation and migration. His lab has shown that permissive infection of PBMCs with HIV-1 is enhanced after removal of sialic acid from the cell or virus surface, as well as demonstrating that desialylation of glycoconjugates on the surface of purified human monocytes activates cells, stimulates production of cytokines (e.g. IL-12p40, TNF $\alpha$ , and IL-6). The relevance of these findings is supported by the marked increase in endogenous sialidase activity in activated lymphocytes, and in monocytes during differentiation into either macrophages or dendritic cells, and by the inhibition of cytokine production, and infectivity of HIV-1 when the sialidase activity of these cells is inhibited by sialic acid analogs or specific anti-sialidase antibodies. We have implicated two endogenous sialidases (Neu1 and Neu3) in these processes and suggest that each may be a potential target for therapeutic agents during infectious and inflammatory conditions.



Dr. Nicholas Stamatou

Dr. Mohammad Sajadi oversees the NVS cohort, HIV-1 infected patients who control viral replication in the absence of HIV therapy. Dr. Sajadi has been studying the NVS and other HIV patients with low viral loads a model to study HIV humoral immunity. Working with the Division of Basic Science and Vaccine Research, the team has identified a large panel of HIV monoclonal antibodies that have neutralizing and/or ADCC activity.

Dr. Sajadi is also working on a project to directly sequence antibody from patient plasma, as well as studying the common characteristics of antibodies that mediate the neutralization response in chronic



Dr. Mohammad Sajadi

HIV infection (Sajadi MM, Lewis GK, Seaman MS, Guan Y, Redfield RR, DeVico AL. Signature biochemical properties of broadly cross-reactive HIV-1 neutralizing antibodies in human plasma. *J Virol.* 2012 May; 86(9):5014-25. PMID: PMC3347347). Dr. Sajadi is also studying the interaction between HIV and HCV infection in the NVS. Despite control of HIV infection, those NVS with HCV have lower CD4 cell counts and higher levels of immune activation than NVS without HCV. Furthermore, NVS with HCV have lower naïve cell proportions (CD4 and CD8) compared to NVS without HCV or normal controls, suggesting altered T-cell homeostasis caused by HCV co-infection. (Sajadi MM, Redfield RR, Talwani R.

Altered T cell subsets in HIV-1 natural viral suppressors (elite controllers) with Hepatitis C infection. *AIDS.* 2013 May 8.)

### Clinical Research

Dr. David Riedel's work is focused on HIV infection and cancer. He has recently established a cohort of patients with HIV infection and cancer, and recently published the clinical experience of 470 patients highlighting the high cancer related mortality in patients with HIV and cancer co-morbidity. (Riedel DJ, Mwanji EIW, Fantry LE, Alexander C, Hossain MB, Pauza CD, Redfield RR, Gilliam BL. High cancer-related mortality in an urban, predominantly African-American, HIV-infected population. *AIDS* 2013;27:1109-1117). New strategies are needed for HIV-infected patients to reduce the risk of cancer, to identify cancers earlier, and to improve treatment outcomes.

Antiretroviral therapy is highly successful in inducing sustained HIV suppression, however regimens today rely on the use of nucleoside/tide analogs and protease inhibitors. Both classes have the potential to induce clinically relevant toxicities that may enhance underlying HIV comorbidities. Currently NRTI's are the main backbone of antiretroviral therapy, however recent work has shown an effect of NRTIs on telomerase activity which may link the long-term use of these drugs directly to the process of accelerated aging, providing a possible mechanism for some of the various co-morbidities (including cancer risk) associated with long-term HIV infection. Dr. Gilliam designed and implemented a novel study using Raltegravir and Maraviroc



Dr. David Riedel



Dr. Bruce Gilliam

in Combination for the Treatment of Antiretroviral Naïve HIV-1 Infected Patients as a proof of concept of a NRTI/PI sparing regimen. This is a 48 week, open-label, pilot study in 7 volunteers who had CD4 counts >350 and HIV viral loads of >5,000 copies/ml. The study documented rapid and sustained HIV viral suppression. Three patients have completed the study so far and remained non-detectable at the week 48 final visit. Based on these results, Dr. Riedel has developed a follow-up protocol in 30 volunteers, which is designed to de-intensify patients with ARV induced HIV suppression to an integrase and CCR5 antagonist regimen. Telomerase length and telomerase activity will be measured before and after starting this new regimen to determine whether these drugs may have a lesser impact on these critical cellular functions.

### Hepatitis Therapeutic Clinical Trials

Significant new developments in the treatment of HCV are progressing. Under the leadership of Dr. Rohit Talwani, the Institute's Clinical Trials program evaluating new direct acting antiviral (DDA) drugs against HCV, continues to grow and build upon the recently established collaborations with Dr. Shyam Kottlilil from the Laboratory of Immunoregulation at the National Institute of Allergy and Infectious Disease at NIH. These trials include the use of anti HCV DDA without the use of interferon which represents a major milestone in HCV treatment.

Dr. Anuolowapo Osinusi (working under the direction of Dr. Kottlilil) and Dr. Talwani recently successfully completed a phase 2 trial of Sofosbuvir and weight based ribavirin to be published in JAMA later this year. The Division is excited to also welcome Dr Osinusi as a new faculty member this fall.

This effort also includes two joint NIH funded bench to bedside clinical collaborative proposals to investigate a novel therapeutic targeting CCR5 or lysyl oxidase 2 molecule for treatment of HCV induced liver inflammation and fibrosis in patients with significant liver fibrosis. In addition, building on the multi-centered observations for NIH funded "Kidney and Liver Transplantation in People with HIV" program, the NIH IHV collaboration recently added sub-study funding to identify viral, host, clinical, and donor factors associated with spontaneous clearance of HCV and SVRs in HIV infected liver transplant recipients.

We also have three young faculty who trained at NIH and have recently joined the IHV faculty. Dr Paul Saleeb completed medical school at the University of Texas Southwestern, did his internal medicine residency at Georgetown and his fellowship at NIH, under the mentorship of Dr Steven Holland in the Laboratory of Clinical Infectious Diseases.



Dr. Rohit Talwani

Dr Kapil Saharia went to Duke University for medical school, Yale University for internal medicine residency, and the University of Maryland for his infectious diseases fellowship, before spending 2 years at NIH in Dr Richard Koup's Immunology Laboratory.

Dr Anu Osinusi completed medical school at the University of Ibadan in Nigeria, her internal medicine residency at Rush University in Chicago, and her infectious diseases fellowship at the University of Maryland before joining the Laboratory of Immunoregulation at the NIH.

### Clinical Program

The Division of Clinical Care and Research continues to provide clinical care to patients living with HIV and Hepatitis. This activity includes several ambulatory clinics to include the Evelyn Jordan Center (directed by Dr. Lori Fantry), the Family Center Clinic at Midtown Campus (directed by Dr. Mariam Khambaty), the JACQUES Clinic at the Institute of Human Virology (directed by Derek Spencer), the HIV/ID clinic at the Baltimore VA (directed by Dr. Anthony Amoroso), and the Hepatitis Clinic at the Baltimore VA (directed by Dr. Rohit Talwani). In addition, IHV faculty continue to provide acute care for patients admitted to the University Hospital. Working together, we continue to try to provide quality clinical services to improve the lives of those we are privileged to serve.

### Preparing the Future

One of the key new initiatives from the Clinical Division, spearheaded by Derek Spencer, Director of the JACQUES Program, is Preparing the Future (PTF). New HIV infections are discovered each day in the United States, and through this new program, PTF, students from the University of Maryland's Graduate School and six professional schools have the opportunity to work as a team to offer HIV testing and linkage to care to Baltimore citizens. PTF already has trained more than 450 students and health care providers with the needed communication skills to test and counsel HIV patients. Preparing the Future is designed as a model for the nation and is supported by a grant from Gilead Sciences' HIV FOCUS Program, for the JACQUES Initiative (JI). A central component of PTF brings together teams of graduate students from the University's dentistry, law, medicine, nursing, pharmacy, and social work schools to identify new infections of HIV and increase access to care for people living with HIV, aimed at addressing the goals of the National HIV/AIDS Strategy (NHAS).

Throughout the 2012-2013 academic year, inter-professional teams of students and faculty advisors have been discussing and managing patient cases at designated HIV testing sites, such as Community, a Walgreens Pharmacy on Baltimore's busy downtown Howard Street. The trainees learn the role of the pharmacist, how to test, checking in patients and helping them with paperwork, and providing results and counseling to the clients.

Another objective of PTF is to educate residents, nurses, and support staff in an effort to operationalize routine testing as an integrated model for screening. With the support of many people, ranging from chief residents, interns, nurses, social workers, information technology, phlebotomy, lab services, and finance administrators, the project has succeeded.



Dr. Paul Saleeb



Dr. Kapil Saharia



Dr. Anu Osinusi



Drs. Thomas Macharia and Jennifer Husson participate in a Preparing the Future training session.

## Medical Education

The Clinical Division is deeply involved in the training of medical students, medical residents, and fellows in Infectious Diseases. Dr. Devang Patel provides oversight for the microbiology component of the second year medical students' Host Defenses course which involves many of the faculty within the Clinical Division, as teachers. In addition, faculty provide bedside teaching in both the inpatient and outpatient setting to medical students and residents. Dr. Bruce Gilliam is the Director of the Infectious Diseases Fellowship Program which has grown to 7 fellows per year. The IHV clinical faculty also provide a significant component for the physicians engaged in training our infectious disease fellows.

In addition to our domestic medical educational activity, the Clinical Care and Research Division continues to provide training in HIV care and treatment as part of our International Physicians Exchange Program (IPEP). In March 2013, we hosted seven physicians from various countries such as Russia, Tanzania, Haiti, Rwanda, Kenya, and Zambia for a three week extensive clinical training and education program.

In addition to hosting the IPEP Program, the Division of Clinical Care and Research has developed strong in-country partnerships with key medical schools, and has established CDC and NIH funded training programs in infectious diseases in Africa and the Caribbean. Our key partners include the University of Notre Dame, Haiti, the University of Guyana and the Georgetown Public Hospital Center, the University of Nairobi, the University of Rwanda, the University of Zambia, and the Zambia Teaching Hospital. We are actively

continuing our ongoing medical education programs in Guyana, Haiti, and Zambia. Our Haiti program is in its third formal class with a total of 27 trainees so far. Three of the first class of trainees from 2011, are now junior faculty who are training the 2013 class. In Guyana, we started with our first class of 7 trainees in January 2013, and are well on our way to establishing a three year internal medicine/infectious diseases training program at Georgetown Public Hospital, in partnership with the Ministry of Health and the University of Guyana. In Zambia, we are in year 5 of training local physicians and have educated 25 thus far, to include the National ART Coordinator of the Ministry of Health, the Medical Directors of the Zambian Army, Zesco (the main electricity company in Zambia), the Mining Company, CHRESO University, and the Pearl of Health Hospital.

## IHV-UON Collaboration: Unit of Clinical Infectious Diseases and ID Fellowship Program

Over the past 5 years the Clinical Care and Research Division has developed a strong partnership with the University of Nairobi in Kenya, to include securing multiple joint

grants from the US Government. One example is a 5 year CDC funded grant entitled "Partnership for Advanced Clinical Education", where we revised the HIV related curriculum for medical schools, nursing schools, and laboratory technician training institutions throughout Kenya.

Now the Clinical Division of IHV is working with the University of Nairobi (UoN) to establish a Unit of Clinical Infectious Diseases (UCID), as well as the country's first post-graduate fellowship program in Infectious Diseases. With IHV's support, 7 UoN faculty are completing a three month clinical preceptorship in Baltimore (5 from medicine, 1 from pediatrics, and 1 from clinical microbiology). Dr Marybeth Maritim and Dr Judith Kwasa, pictured here with Dr Redfield (left to right), will be key faculty in the new fellowship program. IHV faculty will rotate in Kenya to provide clinical teaching and develop the ID service along with them. The UoN UCID will be a resource for the Kenyan Ministry of Health, and will also establish a research agenda to inform national and global policies and practices, with collaborative research projects between the UoN and IHV faculty.



(L to R) Dr Marybeth Maritim and Dr Judith Kwasa, pictured here with Dr Redfield



# Division of Epidemiology and Prevention

The Division of Epidemiology and Prevention continues its global research and international capacity building focus in partnership with the Institute of Human Virology, Nigeria, a center of excellence located in Abuja Nigeria. On behalf of a dedicated team of faculty and staff Dr. Blattner received the University's 2012 Entrepreneur of the Year award in recognition of \$240 million in funding since 2004 that has touched the lives of over one million in Nigeria and laid the foundation for a robust research infrastructure.

## Most Vulnerable Population Studies

With a population of about 162.5 million people and an HIV prevalence rate of 4.1%, Nigeria has the second highest HIV burden in the world. This is not, however, the full picture. The drivers of the epidemic, including men who have sex with men (MSM) and female

commercial sex workers, account for 47% of the new infections. With the increasing global accessibility of Anti-Retroviral Therapy (ART), rising evidence for the support of Treatment as Prevention, and lack of evidence to shape care services for the most at risk population driving the infection, Dr. William Blattner's NIH funded Network-Based Recruitment of MSM into HCT, Care, Treatment and Prevention Services at Trusted Community-based Venues" (TRUST) study is engaging MSM's in HIV care and treatment and collecting social and behavioral data through applying biological and network theory tools to inform best practices and inform vaccine research.

The study is on track to recruit 1200 participants; 600 from Abuja and 600 from Lagos. The study team, led by Dr. Man Charurat, Associate Professor, uses a Respondent-Driven Sampling method to recruit participants. In the initial year of the study, over 400 MSM participants have been enrolled in a clinic in Abuja, and of these study participants, over 40% were found to be HIV positive. In line with the concept of Treatment as Prevention, all who have tested positive for HIV are either on ART, or in treatment preparation for ART.

With 1.7 million women in childbearing years infected with HIV in Nigeria and the country accounting for 23% of newly infected infants in the world, Dr. Man Charurat's NIH funded Acute HIV Infection and Pregnancy (AVERT) study has uncovered significant findings. The study shows higher than expected HIV transmission rates from mother to child for mothers that are newly infected with HIV. Despite the availability of HAART and PMTCT prophylaxis, transmission rates are significantly higher for mothers who newly acquired HIV infection during pregnancy (15%) versus those with established HIV during pregnancy (3.4%). This points to the importance of instituting repeat HIV testing throughout pregnancy. Furthermore, the study's characterization of the quasi-species of the virus in transmitted and non-transmitted mother-infant pairs has led to additional questions regarding infants exposed but not infected by the HIV virus. Infants exposed but uninfected with the HIV virus are at a much higher risk for early life development abnormalities



Dr. Charurat has been working with vulnerable populations in Nigeria for more than a decade.



IHVN Chief Executive Officer, Dr. Patrick Dakum, undertakes community advocacy.

including growth faltering, higher morbidities, increased risk for infant diarrhea, and higher mortality.

### HIV's Impact on the Brain

The Correlates of Monocyte-Associated Virus in HIV Neurocognitive Impairment study investigates the impacts of HIV on brain function. This NIH funded grant is led by Drs. William Blattner and Walter Royal (Department of Neurology). The study has enrolled 200 HIV positive persons prior to initiation of anti-HIV therapy. At baseline an extensive battery of neuropsychological tests is administered to gain a detailed profile of how the different domains of brain function are impacted by HIV infection. Among these 200 subjects almost one third show evidence of impairment that is often not clinically apparent. Given that HIV patients with therapy can now live a normal lifespan, understanding the implications of this chronic damage to the brain is important. The focus of the study is on understanding the characteristics of the virus taken to the brain by monocytes that is associated with brain impairment. As a prospective longitudinal cohort study, the



Dr. Blattner with NeuroAids Study Team in Abuja.

impacts of treatment, as well as the further deterioration in brain function, are a key focus. Analyses of monocyte-associated HIV DNA viral load, HIV-1 viral quasispecies both in the plasma and HIV DNA, and identification of plasma markers are currently in progress.

### H3 Africa

Dr. Clement Adebamowo was just awarded an NIH funded African Collaborative Center for Microbiome and Genomics Research (ACCME), part of the Wellcome Trust and NIH funded H3Africa initiative, which is set up at the IHVN and is currently engaged in integrative epidemiology of cervical cancer that is exploring the host and viral genomics and epigenomics, somatic cervical cancer genomics as part of NIH led Cancer Genome Atlas mapping project (TCGA), vaginal microenvironment—innate immunity and vaginal microbiota, as well as detailed risk factor characterization of prevalent and persistent HPV infection.

Dr. Alash'le Abimiku, Associate Professor, was awarded an H3 Africa Biorepository grant. This award is foundational to future research to study the role of the genome in human health and viral diseases. The biorepository will support multiple genomic research partners by providing reliable sample processing, secure storage and shipment, and accessible clinical and epidemiological data to achieve best science.

### Preventing Babies from Becoming HIV Infected

Dr. Nadia Sam-Agudu, Assistant Professor and ID Pediatrician, is the Principal Investigator for The Impact of Mentor Mother Programs on Prevention of Mother to Child Transmission (PMTCT) Service Uptake and Retention at Primary Healthcare Facilities in Nigeria (MoMent) study. This four year implementation research study,

sponsored by the Canadian International Development Agency and WHO, identifies and trains Mentor Mothers, women who are HIV-positive and successfully completed PMTCT services at least once, to act as guides and a support system for other, less experienced HIV-positive mothers. The premise of the study is to evaluate the impact of Mentor Mothers on PMTCT outcomes for the HIV-positive mother and exposed infant. Outcomes include measuring drug adherence, early infant HIV diagnosis, attending appointments, retention in the program, and ultimately, rate of HIV transmission to the infant.



Dr. Alash'le Abimiku explaining the operations of the biorepository laboratory at IHVN to NIH program officers during a site visit.

### HIV Protective Immune Responses

With funding from the Bill and Melinda Gates Canadian HIV Vaccine Initiative and Canadian Health Research Institutes, Dr. Abimiku leads the Nigerian team in a multicountry team grant involving Canada, South Africa, and Nigeria to use two natural models to document risks and protective immune responses in HIV exposed uninfected partners of

serodiscordant couples and infants of HIV infected mothers. These models provide unique opportunities to understand modes of natural protection, as well as immune activation providing critical information to HIV vaccine development especially relevant for developing countries with high HIV prevalence and high disease burden constantly activating and challenging the immune system. For instance the association of innate antiviral and mucosal immunologic factors in breast milk on lowering mother to child transmission of HIV via breastfeeding, represents a novel and important human model for understanding the identity of molecules and immune responses that correlate with protection. Such comprehensive immunologic studies that simultaneously consider maternal, breast milk and infant factors and the biological and immunological processes that are involved with transmission are necessary to exploit the seemingly paradoxical inefficiency of postnatal HIV transmission through exclusive breastfeeding which is promoted in developing countries.

### Capacity Building In Nigeria

Strengthening Health Human Resources in Nigeria Group (SHaRING) is led by Dr. Alash'le Abimiku. In the last 9 years, with the support of a CDC PEPFAR award, Dr. Abimiku has developed over 200 PEPFAR laboratories/testing centers in Nigeria, 11 PCR laboratories which diagnose 75% of the HIV-exposed infants and five regional training laboratories which have trained over 6,000 laboratory workers in basic to advanced laboratory skills. Additionally, Dr. Abimiku has developed a molecular sequencing laboratory and a national certified biosafety level 3 TB reference laboratory. For this \$5 million SHaRING grant award, Dr. Abimiku is responsible for pre and in-service laboratory health human resources development for the PEPFAR program including HIV/AIDS and co-infection laboratory training; integrated and comprehensive national laboratory curriculums; and auxiliary lab support services including biorepository, supply chain management, and equipment maintenance and repair. To achieve these goals, SHaRING will strengthen universities and institutions for HIV/AIDS and co-infection training, establish Continuing Medical Laboratory Education training, and accreditation of Nigerian laboratories.



Dr. Nadia Sam-Agudu examines an HIV positive infant.

## The Growth of the Institute of Human Virology, Nigeria (IHVN)



Mr. Mensah, Dr. Blattner, Dr. Patrick Dakum, and Mr. Hayes visit the proposed site for IHVN's future research center near Abuja.

The Institute of Human Virology, Nigeria (IHVN) was established in 2004 by the Institute of Human Virology (IHV) of the University of Maryland School of Medicine to create a center of excellence to support PEPFAR implementation and its research program. In 2010, IHVN was transitioned from a UMB affiliate to an independent indigenous Nigerian organization with an independent board. In the same year, IHVN received its first direct award from CDC in the amount of \$435,000 and two sub-awards totaling \$1.4 million from Global Fund principal recipients (National Malaria Control Program and National Agency for the Control of AIDS). Subsequently, IHVN's direct grant portfolio has grown to about \$35 million, \$68 million, and about \$75 million in 2011, 2012, and 2013 respectively. As the grant portfolio of IHVN grew in absolute dollar terms, the sources of funding also became more diverse under the leadership of CEO, Dr. Patrick Dakum.

Through the strong collaboration with IHV/UMB faculty, IHVN sources of funding now include CDC, NIH, GHRI (Canada), Global Fund, Wellcome Trust (UK), UMB and others. IHVN's staff

strength has also grown from 20 in 2004 to over 400 in 2013. IHVN's growth has been facilitated by the strong technical support from IHV/UMB; a sound and focused corporate strategy led by a highly competent, diverse and intensely engaged board; a highly technical and professional staff led by a well-qualified, internationally-exposed, culturally-competent management, and a robust corporate operations department led by Mr. Charles Mensah, IHV Managing Director.

In its short years in existence, IHVN has developed a world-class diagnostic and research infrastructure in Nigeria to facilitate the training, treatment, and research activities of its collaborating faculty. This infrastructure includes high capacity molecular labs; a high capacity Gene Sequencing lab; BSL2 and BSL3 labs; training labs, and multi-media training centers, including a clinical training center. IHV-Nigeria has been an essential resource in the current research and research training through NIH and CDC funding to the parent IHV. To mark its 10th anniversary, IHVN proposes to consolidate its resources by commissioning an international research center and corporate office complex in 2014.



Mrs. Joyce Johnson, Director of Health Programs, has been instrumental in the success of the Nigeria Program.

### Strengthening Pre-Service Health Professionals Capacity

**(SPEARHEAD)** grant, led by Dr. Clement Adebamowo, is a Human Resources for Health Capacity Development grant from the United States CDC, which aims to build the capacity of Nigeria pre-service health care workers to respond to the HIV/AIDS epidemic through the provision of internationally-accredited training to community health workers, midwives, nurses, public health physicians, and clinicians. This \$5 million grant has completed a comprehensive review and modernization of the HIV/AIDS curriculum of the training institutions that are engaged in producing this cadre of health care workers for Nigeria. Within this first year of the grant, a series of Train the Trainers programs is being implemented to build the capacity of Master Trainers in Nigeria who will return to their institutions to train other Master Trainers; collectively they will train and mentor the students enrolled in the institutions.

### Capacity Development for Research into AIDS Associated Malignancies (CADRE)

is an NIH funded training grant to Dr. Clement Adebamowo to build the capacity of Nigerian researchers to conduct AIDS Associated Malignancy Research. Since it was awarded to the University of Maryland 3 years ago, CADRE has trained 6 pre-doctoral and 18 post-doctoral trainees. These trainings have contributed to the resuscitation of cancer registration in Nigeria with the formation of the Nigerian System of Cancer Registries. After a more than 30 year absence, Nigerian cancer registration data is now being collated as part of the World Health Organization Cancer in Five Continents publication. So far 3 papers on cancer registration in Nigeria have been published and 7 more are in various states of publication. Another outcome of this grant is the conduct of research training on vaginal microbiome, high risk Human Papilloma Virus infection and risk of cervical cancer. This training generated the pilot data that led to the successful competition for a \$4.25 million H3Africa NIH grant that establishes a collaboration between the University of Maryland's Institute of Human Virology and Institute of Genome Sciences, as well as collaborators in the United Kingdom, Zambia, and Nigeria. CADRE is also supporting the development of clinical trials capacity at the National Hospital, Abuja, Nigeria in order to qualify this site as an international site for AIDS Associated Malignancies research.



Drs. Adebamowo and Parham discussing cervical cancer with NIH team visiting Nigeria.



Dr. Chris Akolo training research study teams.

**The Training Program in Nigeria for Non-Communicable Disease Research (TRAPING—NCD)**, also led by Dr. Clement Adebamowo, is an NIH funded grant designed to train African researchers in modern life course epidemiology methods for research in Non-Communicable Diseases. This grant, which started in 2011, has provided training to 4 post-doctoral trainees and 6 pre-doctoral trainees to date, and has provided training that led to the development of a prospective cohort of twin and multiple births in Nigeria—the country with the reputed highest twinning rate in the world. This important resource links this grant with the CADRE Epigenetics Laboratory for exploration of epigenetics factors that affect growth, development and behavior. The Traping-NCD grant has also supported the development of infrastructure for successful conduct of nutrition epidemiology research in Nigeria through training to develop food frequency questionnaires, food diary and algorithms for conversion of FFQ data to nutrients and the use of the NIH/NCI ASA24 software for dietary recall. Another linkage to the CADRE grant provides Traping-NCD trainees training on epigenetics and molecular biology of breast cancer.

**The West African Bioethics Training program**, also directed by Dr. Clement Adebamowo, has been continuously funded since 2005 by NIH. This training grant is designed to provide modern international research ethics training to biomedical researchers in West Africa. Since inception, this program has trained 25 bioethicists to earn a Master's Degree in research ethics at the University of Ibadan, Nigeria. Over 4,000 researchers have received short term trainings, 21 research ethics committees have been newly established or strengthened and several research projects have been conducted in ethics of genomics research – a strategic focus of the training program. In addition, the program serves as a technical consultant to the Nigerian government and lead with the provision of ethics regulatory guidelines, research ethics consultation to federal and state governments in Nigeria and development of additional research ethics codes and sub-codes

**The University of Maryland, Institute of Human Virology AIDS International Training and Research Program (UM-IHV AITRP)**, led by Dr. William Blattner, enters its 14th year of research training having supported 26 masters level and doctoral degree students, five post-doctoral students, 30 short-term trainings in Baltimore, and 96 courses and workshops. With Nigeria having the second highest

burden of HIV in the world and the fifth in tuberculosis, coupled with the infusion of the President's Plan for AIDS Relief and a growing research enterprise, the UM-IHV AITRP affords a unique opportunity to advance research training to build the research capacity in Nigeria and at the Institute of Human Virology-Nigeria (IHVN). The grant focuses on addressing key research areas of public health importance as identified by the Federal Government of Nigeria: TB and HIV, Public Health Scale-up, Prevention of mother-to-child HIV transmission and Pediatric HIV, Neurological, Mental Health and Behavioral research, Advanced Laboratory research, and HIV Treatment, ARV response, and Resistance.

Dr. William Blattner is also the Principal Investigator of the University of Maryland led **Nigerian Alliance for Health Systems Strengthening project (NAHSS)** funded by the Center for Disease Control to provide technical support to the Federal Ministry of Health towards the development of the National Quality Improvement program (NigeriaQual). Since inception of the NAHSS project in October 2012, more than 400 persons drawn from USAID, CDC, DoD, PEPFAR and Global Fund implementing partners in Nigeria, Multidisciplinary Planning teams from 6 States in Nigeria and the Federal Ministry of Health have been successfully trained on NigeriaQual implementation. A major milestone of the NAHSS project is the implementation of the first-ever National data collection for NigeriaQual. More than 130 treatment sites in Nigeria supported by USAID, CDC and DoD partners participated in the NigeriaQual data collection cycle in July 2013.



Sharing Laboratory Resources.

# IHV Supports



GVN Co-Founder and Scientific Director, Dr. Robert Gallo, GVN Board of Director Member and Executive Director of The World Academy of Sciences (TWAS) Dr. Romain Murenzi, and GVN President Dr. Sharon Hrynkow.

Since 2010, the Institute of Human Virology (IHV) at the University of Maryland School of Medicine, led by Dr. Robert Gallo, has been working to create, develop, and launch the Global Virus Network (GVN). Since the HIV/AIDS outbreak of the early 1980's, it has been Dr. Gallo's goal to promote a global collaborative network to overcome gaps in research during the earliest phases of viral epidemics and to ensure that sufficient numbers of medical virologists are trained to meet these challenges.

The GVN was officially co-founded in 2011 at the Italian Embassy in Washington, D.C. by Dr. Gallo and his colleagues William Hall, MD, PhD, and Reinhard Kurth, MD. Dr. Hall is Chair of Medical Microbiology and Director of the Centre for Research in Infectious Diseases at University College Dublin's (UCD) School of Medicine and Medical Science in Dublin, Ireland, and Dr. Kurth is the former Director of the Paul Ehrlich Institute and the Robert Koch Institute and Chairman of the Foundation Council at Ernst Schering Foundation in Berlin, Germany. At the inaugural meeting in DC, attendees from more than a dozen countries affirmed and ratified GVN's goals and objectives. Since that three day meeting, the GVN worked to become incorporated as a non-profit, 501(c)(3) organization, and this status was granted by the US government in March 2013. GVN members represent expertise covering every class of human virus, and come from more than 20 countries. GVN has held

subsequent meetings in Ireland, Italy, Baltimore, Maryland, Germany, and Russia. In 2012, the GVN Board of Directors elected Kathleen Kennedy Townsend, former Lt. Governor of Maryland and IHV Board Member, to serve as the GVN Board's second Chairperson. The Board also appointed Dr. Sharon Hrynkow to serve as the first GVN president. Between October 2012 and June 2013, the GVN Board added 15 new members and two advisors, including business leaders, non-profit organization leaders, public health and virology leaders, among others. The GVN opened new offices across the street from the IHV at the UMB BioPark, expanded its staff from one-full time professional, Robert Karrs, to include a range of volunteers (IT web lead Dr. Florence Haseltine, who was instrumental in the launch of GVN's website) and pro bono professional services for accounting (Heymann Suissa and Stone) and legal (Greenberg Traurig, thanks to IHV Board Member Robert Charrow). In July 2013, the Board of Directors elected its third Chairman, G. Steven Burrill, also CEO of Burrill & Co.

The IHV continues to support the GVN as it continues to mature as an independent organization. Dr. Gallo is an active Scientific Director for GVN, and he continues to host strategy meetings every two weeks. These meetings benefit from input from a range of IHV staff, notably Dave Wilkins, and Nora Grannell, who also serves as GVN's PR Director on a part-time basis, and IHV faculty, Drs. Robert Redfield, Bill Blattner, Dave Pauza, Maria Salvato, Yongjun Guan, Mangalasseril Sarngadharan, and Alash'le Abimiku. This past year, the GVN Fall 2012 meeting was hosted by the IHV in Baltimore, Maryland. The spring 2013 GVN meeting was hosted by the Technical University of Munich under the leadership of Dr. Ulrike Protzer and with support from foundations and private sector groups.

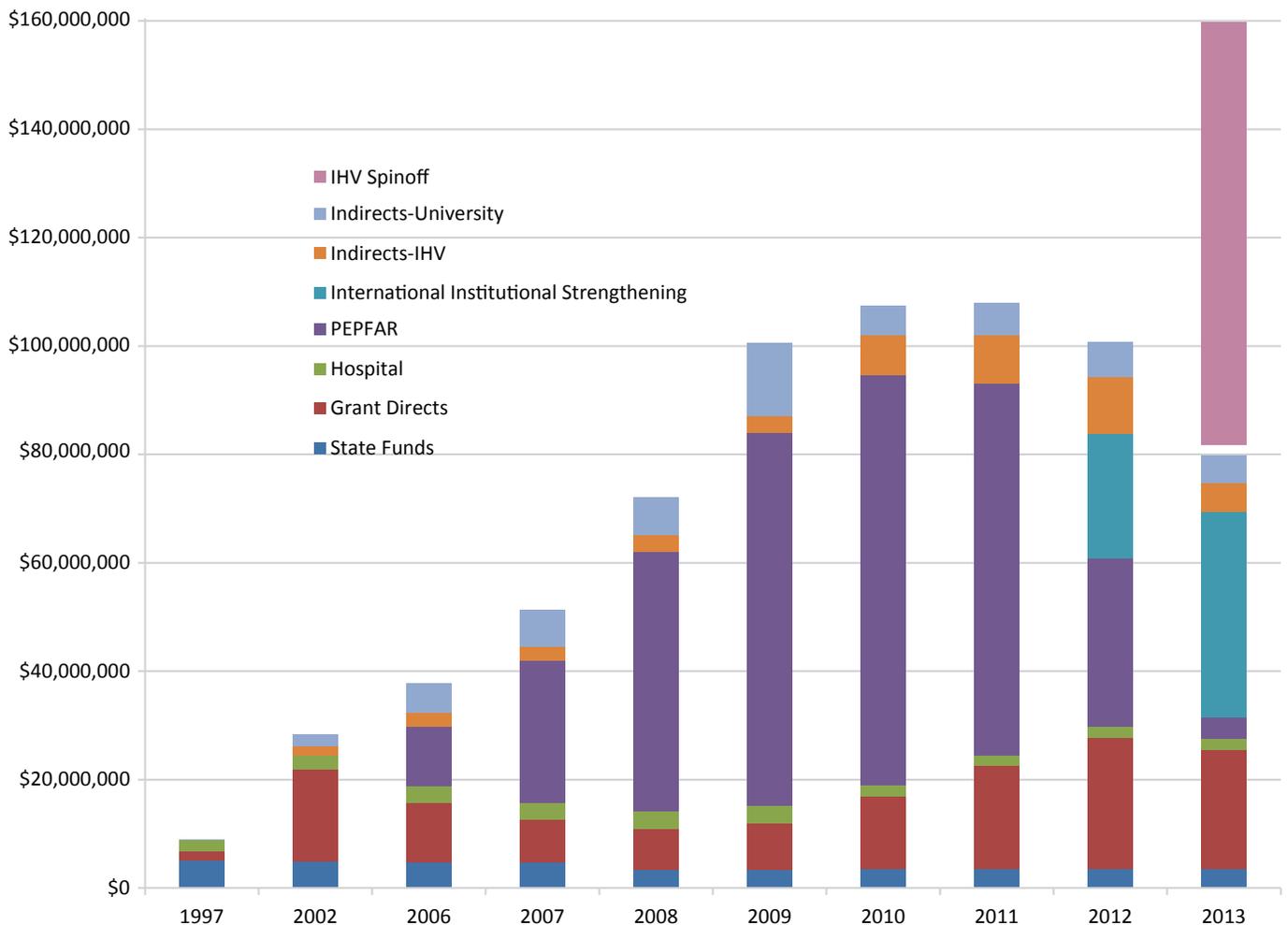


# Financials and Related Charts

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine continues to be funded for research, clinical care, and epidemiology at a level that makes it one of the largest research institutes in America, if not the world.

The IHV's success in driving basic research, vaccine development, clinical trials, patient care, and international institutional strengthening in the fields of HIV and other chronic viral diseases, positions the Institute as a successful model in the research community. IHV has also been able to provide significant financial support to the new Global Virus Network (GVN), established to organize the world's top virus researchers.

During FY 2013, IHV's basic research portfolio, at the heart of our mission, continued to thrive despite severe cuts to the U.S. National Institutes of Health (NIH) and U.S. Centers for Disease Control (CDC) funding levels. The Institute's overall income continued to be influenced by the U.S. government's decision to award international HIV care and treatment grants primarily to indigenous institutions as opposed to U.S. universities and institutes. However, the graph below depicts the large amount of funding now going to organizations that the Institute has spun-off both in the U.S. (Profectus Biosciences, Inc.) and in four African nations. The technical assistance that the IHV provides to these organizations brings a great deal of revenue back to the Institute. The IHV continues to augment the world's ability to fight chronic viral diseases in a meaningful and compelling way.



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