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.
About IHV

The Institute of Human Virology (IHV) is the first center in the United States—or 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. IHV was co-founded by Robert Gallo, MD, director of the IHV and co-director of IHV’s Division of Basic Science and Vaccine Development, William Blattner, MD, associate director of the IHV and director of IHV’s Division of Epidemiology and Prevention and Robert Redfield, MD, associate director of the IHV and director of IHV’s Division of Clinical Care and Research.

The Institute, with its various laboratory and patient care facilities, is uniquely housed in a 250,000-square-foot building located in the center of Baltimore and our nation’s HIV/AIDS pandemic. 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 more than 300 employees include 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. IHV’s patient base has grown from just 200 patients to approximately 5,500 in Baltimore and close to 1,000,000 in 7 African and 2 Caribbean nations since 2004.
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 at 410.706.8614 or visit www.ihv.org
Director’s Message

A look at the year

In September 2014, IHV hosted its 16th Annual International Meeting in Baltimore. The Annual Meeting featured themes on HIV cure research; HIV pathogenesis; HIV structural biology, immunology and vaccines; advances in clinical, prevention and public health research, and a cross-cutting session on the molecular and immunological insights from cancer biology and treatment.

Approximately 75 leading virologists and international researchers spoke during the meeting. The gathering included world-renowned scientists from IHV and the National Institutes of Health (NIH), as well as leading African, American, Asian, and European research institutions. Keynote lectures during the 16th Annual International Meeting included Dr. Mark Kaplan, MD from the University of Michigan, who presented the first Reinhard Kurth Memorial Lecture. The Reinhard Kurth Memorial Lecture will continue to be held during IHV’s Annual International Meeting to recognize the outstanding career of IHV’s close friend, Professor Reinhard Kurth, MD. Reinhard co-founded the Global Virus Network (GVN) with William Hall of University College Dublin and me in 2011 and he was a member of the Institute’s Board of Advisors. Reinhard passed away on February 2, 2014 after a long valiant fight against cancer. He was on the frontline of AIDS research having contributed to the understanding of how HIV attacks cells, ultimately leading to disease. He helped pioneer a scientific field that came to be known as endogenous human retrovirology, which focuses on viruses not known to cause disease, but may have important roles in biology. Reinhard, through this cutting-edge research, provided scientists with the tools necessary to study viral sequences contained within the human genome. We look forward to holding this annual Lecture at each of IHV’s Annual International Meetings and honoring our good friend’s legacy.

“Reinhard Kurth was one of the best medical virologists in the world and IHV benefited from his service as a Board of Advisors member. He was able to galvanize investigators from Germany, including from the Robert Koch Institute, the Technical University of Munich and the University of Marburg, to join in the important efforts of the Global Virus Network (GVN) for future medical virologists and for helping policy leaders understand the nature of emerging and reemerging virus infections. He was an invaluable leader of German health sciences, an important advisor to me, and a close, personal friend. His absence will leave a significant hole in my life and that of many others.”—Robert C. Gallo, MD
Additionally, following a vote by senior IHV faculty, IHV awarded annual Lifetime Achievement Awards in 2014 to two distinguished individuals who have had exceptional influence on the science of immunology and care and treatment of HIV. They included:

**2014 IHV Lifetime Achievement Award for Scientific Contributions** — William Paul, MD, Chief of the Laboratory of Immunology at the National Institute of Allergy and Infectious Diseases and former director of the National Institutes of Health Office of AIDS Research. His discoveries and research in immunology have impacted biomedical research greatly. Dr. Paul passed away in September 2015.

**2014 IHV Lifetime Achievement Award for Public Service** — John Martin, PhD, Chief Executive Officer and Chairman of the Board of Gilead, who is a leader in supporting access to life-saving anti-HIV medications that although still under patent have been made widely and affordably available to millions around the world infected with HIV, and for prevention through Pre-exposure drug therapy.

Ambassador Deborah Birx, MD, U.S. Global AIDS Coordinator, also spoke during IHV’s Annual Meeting. She is a world renowned medical expert and leader in the field of HIV/AIDS whose three decade-long career has focused on HIV/AIDS immunology, vaccine research, and global health. As the U.S. Global AIDS Coordinator, Ambassador Birx oversees the implementation of the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), the largest commitment by any nation to combat a single disease in history, as well as all U.S. Government engagement with the Global Fund to Fight AIDS, Tuberculosis and Malaria. IHV is a national leader and recipient of PEPFAR funds providing overseas care to more than 1 million people living with HIV. IHV also provides care to approximately 6,000 Baltimoreans.

**Restructuring**

This past year, I announced a restructuring of the Institute as a result of its continued growth. George Lewis, PhD and I have served as Co-Directors of the Basic Science and Vaccine Development Division; however, we separated the divisions as our vaccine research is involved in a sufficient number of different studies that are extremely translational right now, and that I believe deserve the title of a separate division. Thus, George Lewis became Director of IHV’s Division of Vaccine Research, and I chose not to remain as head of the Basic Science Division any longer, but to remain as overall Director for IHV. I feel it is important to give younger people who have expressed exceptional talent an opportunity to lead the Basic Science Division and thus, named Associate Professor Eric Sundberg, PhD and Professor Wuyuan Lu, PhD as Co-Directors of the Division.

**Basic Science Division**

In the Division of Basic Science, now led by Drs. Sundberg and Lu, nearly two dozen faculty members lead research programs defining the molecular basis of infection and immunity and developing novel therapies and treatments of infectious disease, immune dysregulation, inflammatory disorders and cancer. Approximately 100 scientists, inclusive of faculty, fellows, students and technicians belong to the Division, whose research is supported by a diverse portfolio of federal, state, philanthropic and industrial funds. In this year’s Annual Report, we highlight research from a few junior members of our faculty; senior faculty members will be featured next year.

**Vaccine Research Division**

Over the last year the Division of Vaccine Research, led by Dr. Lewis, has made significant progress in understanding the basis of protective immunity required for a successful HIV-1 vaccine as well as moving an HIV-1 vaccine candidate developed in the institute in collaboration with Profectus Biosciences to a Phase I clinical trial. The first clinical trial of FLSC will be carried out in the institute by the Division of Clinical Care and Research in October 2015 in collaboration with the Division of Vaccine Research and Profectus Biosciences. It is widely agreed that a safe and effective vaccine is the best way to quell the HIV-1 epidemic; however, after over twenty-five years of intensive research, it remains elusive.
Animal Models Division
The Animal Models Division, led by Joseph Bryant, DVM, is in its 20th year as one of the five Divisions here at the Institute that was established for the purpose of developing animal models as it relates to HIV/AIDS and AIDS-associated diseases. Collaborations have resulted in, among other successes, more than 3 patents and most recently the isolation of a small molecule designated as HLBT-001 from a plant (Tillandsia recurvata) that has been shown to have broad anti-cancer properties especially against prostate cancer, B-cell lymphoma, Kaposi Sarcoma, and several others.

Clinical Care and Research Division
The Division of Clinical Care and Research, led by Robert “Bob” Redfield, MD—IHV Associate Director and Director of the Clinical Care and Research Division—continues to develop its tripartite mission of clinical care, clinical research, and medical education, both domestically and around the world. This year, the Division has significantly expanded its clinical research efforts in the area of Hepatitis C therapeutics, solidified IHV’s ambulatory clinical programs at the University of Maryland Medical System’s Midtown campus, and successfully secured multiple post PEPFAR global grants providing advanced medical education, technical assistance, and research capacity in both Sub-Saharan Africa and the Caribbean. The expansion is largely due to the recruitment of Shyam Kottilil, MBBS, PhD, a world-renowned expert in infectious disease, who joined the faculty as Co-Director of IHV’s Clinical Research Unit and as Associate Director for Clinical Research in the Institute’s Division of Clinical Care and Research. Dr. Kottilil has quickly proven himself to be an important addition to both IHV’s scientific and clinical contributions.

Epidemiology and Prevention Division
The Division of Epidemiology and Prevention, headed by IHV Associate Director William “Bill” Blattner, MD this past year, continues to focus its research on three closely related topics: 1) Key and Vulnerable Population Research; 2) Genomic Research in Cancer and Viral Diseases; and 3) Implementation science in HIV Treatment and Care Program. Research training grants from the National Institutes of Health (NIH), Fogarty International Center, and the Centers for Disease Control and Prevention (CDC) support these research efforts. With this funding, the Division works to train the next generation of scientists and epidemiologists, to increase the efficiency of HIV treatment and prevention, and ultimately to prevent a resurgence of the HIV epidemic in Nigeria. Dr. Blattner will retire at the end of January 2016, however, I will continue to draw on his expertise in the future as he will be a special consultant to the Director. Man Charurat, PhD, who is the Deputy Director for the Division, will assume the role of Acting Director and will be vital in advising me and interacting with the other associate scientific directors. It goes without saying that Bill is truly irreplaceable and will be greatly missed.

Financial Overview
Since IHV’s inception, more than $766,000,000 has been generated in externally sponsored revenue. This includes grants from many federal and foundation sponsors for work in basic science, patient clinical care, and international care and treatment. Among the highlights are more than $50M in cumulative funding for our HIV vaccine candidate and several hundred million dollars of support through PEPFAR through which IHV has treated more than one million patients in Africa and the Caribbean. With even more recent grant wins, a new IHV Director of Development (Lori Piccolo) and promising future research, IHV looks to continue its science, health and financial impact on Maryland and the world.

In addition, IHV received a $1 million bequest from long-time board member, The Honorable Robert Keith “Bob” Gray, to establish an endowed distinguished professorship for the Director. Bob was with us at the inception of the Institute, and never wavered in his support and encouragement of all we have accomplished. We could count on him for cogent insights and good strategies for dealing with our challenges and opportunities. To say he will be deeply missed, both personally and professionally, is an understatement.

The Honorable Robert Keith “Bob” Gray, who passed away in April 2014, and Dr. Robert Gallo

Left to Right: Dr. William Blattner and Dr. Man Charurat
IHV Leadership

Robert C. Gallo, MD
Homer & Martha Gudelsky Distinguished Professor in Medicine
Director, Institute of Human Virology
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
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
Professor, Medicine
Professor, Microbiology and Immunology
University of Maryland School of Medicine

George K. Lewis, PhD
Director, Division of Vaccine Research
Institute of Human Virology
Professor, Microbiology and Immunology
University of Maryland School of Medicine

Joseph L. Bryant, DVM
Director, Division of Animal Models
Institute of Human Virology
Professor, Medicine
University of Maryland School of Medicine

Wuyuan Lu, PhD
Co-Director, Division of Basic Science
Institute of Human Virology
Professor, Biochemistry and Molecular Biology
University of Maryland School of Medicine

C. David Pauza, PhD
Associate Director of Faculty Development
Institute of Human Virology
Professor, Medicine
University of Maryland School of Medicine

Eric Sundberg, PhD
Co-Director, Division of Basic Science
Institute of Human Virology
Associate Professor, Medicine
University of Maryland School of Medicine

Dave Wilkins
Chief Operating Officer
Institute of Human Virology
University of Maryland School of Medicine
Basic Science Division
In the Division of Basic Science, nearly two dozen faculty members lead research programs defining the molecular basis of infection and immunity and developing novel therapies and treatments of infectious disease, immune dysregulation, inflammatory disorders and cancer. Approximately 100 scientists, inclusive of faculty, fellows, students and technicians belong to the Division, whose research is supported by a diverse portfolio of federal, state, philanthropic and industrial funds. The Division is organized into five inter-related and inter-disciplinary Research Programs that cover numerous aspects of infection, immunity and inflammation research, including: Structural Biology & Molecular Biophysics; Drug Discovery & Development; Microbial Pathogenesis; Cancer Biology; and Immunity & Inflammation. The Division also houses four scientific core facilities, including the Biosafety Level 3 Facility, Flow Cytometry & Cell Sorting Core, Imaging Core, and mQuant Assay Core. The Division is directed by Drs. Wuyuan Lu and Eric Sundberg. In this year’s Annual Report, we highlight research from a few junior members of our faculty; senior faculty members will be featured next year.

Hua Cheng

Dr. Hua Cheng’s group is investigating how human T cell leukemia virus type 1 (HTLV-1) causes adult T cell leukemia-lymphoma (ATL), an aggressive form of hematological malignancy, and how new therapies can be developed to inhibit disease progression. The HTLV-1 viral genome encodes an oncogenic protein called Tax. Tax is a unique viral protein because it functions to regulate expression of both viral and cellular genes, resulting in productive viral replication, enhanced viral infectivity, aberrant T cell proliferation and malignant transformation of host cells.

Studies conducted in Dr. Cheng’s lab have demonstrated that Tax interferes with the process of autophagy, a cytoprotective cellular mechanism, in order to promote survival and growth of HTLV-1-transformed T lymphocytes. To understand the underlying mechanism, Dr. Cheng’s group discovered that Tax connects the IkB kinase complex to the autophagy molecular complex in increasing autophagic flux. Loss of the autophagy molecules such as Beclin 1 results in the impediment of the activation of NF-kB and Stat3 by Tax and apoptotic death of HTLV-1-transformed T cells, indicating that Tax-deregulated autophagy plays a pivotal role in HTLV-1 oncogenesis. Recently, Dr. Cheng’s team has identified a Tax-interacting cellular protein called Tid1, a mammalian DnaJ protein and molecular chaperone. The study by Dr. Cheng’s team showed that Tid1 is an essential mediator of macroautophagy induced by nutrient deprivation, rramycin and the viral Tax protein. In a mouse model of disease, loss of Tid1 impairs cellular transformation and tumorigenesis mediated by the oncogenic epidermal growth factor receptor (EGFR) or Src tyrosine kinase.

Further studies demonstrated that Tid1 maintains the conformation of the activated EGFR, leading to the persistent activation of the EGFR downstream signaling molecules such as Stat3.

Left to Right: Visiting scientist from Soochow University, China, Limeng Tang, and Dr. Hua Chang

Dr. Cheng’s group has also been developing new therapeutic strategies for treating HTLV-1-associated leukemia. Niclosamide, an FDA-approved drug, has been found to cause degradation of Tax and to induce apoptosis of ATL cells. Further, Dr. Cheng’s team is inventing new immunotherapy methods that can generate highly
potent cytotoxic T lymphocytes and natural killer cells, efficiently killing ATL cells and solid tumor cells. Some of these studies have been published in Journal of Biological chemistry, Oncogene, and Biochemical and Biophysical Research Communications in 2015.

Dr. Olga Latinovic

Dr. Olga Latinovic is developing novel antiviral therapy strategies using various HIV entry inhibitors with a particular focus on developing super-resolution microscopy methods in order to characterize CCR5 conformation changes permissive for HIV-1 entry. Characterizing virus entry related functions of different coreceptor populations may lead to better understanding of their selective targeting by fit HIV-1 virions. In the last two years, Dr. Latinovic established a collaboration with Dr. Tim Fouts from Profectus Biosciences on quantifying the anti-viral effects of their novel and potent entry inhibitors (e.g., anti-CD4 neutralizing antibodies) in a SCID/NOG mouse model. Further collaborative efforts with Dr. Erik de Leeuw on the anti-viral effects of compound 5660386, a novel small molecule inhibitor of HIV-1 entry, resulted in published work in 2015.

Dr. Erik de Leeuw

The innate immune system 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 (AMPs). Dr. de Leeuw’s main research interest is the molecular characterization of the biological activities of antimicrobial peptides called defensins in humans to evaluate their potential as novel therapeutics. Defensins are multifunctional peptides that have antibacterial and antiviral properties. In addition, defensins function in immunity of the human host.

During his time at IHV, Dr. de Leeuw’s work has focused on the functional, structural and anti-microbial aspects of human α-defensins. In collaboration with Dr. Wuyuan Lu’s laboratory, these studies have included the involvement of charge and hydrophobicity on defensin functionality such as bacterial killing, binding to the bacterial toxin anthrax lethal factor, and defensin interactions with host cells. Additional work provided insight into the structural importance of specific residues in defensins involved in their productive processing, folding and proteolytic stability. These studies provided the basis for their finding that α-defensins selectively kill Gram-positive bacteria by targeting Lipid II, an essential component for membrane biogenesis and ideal target for development of antibiotics, a discovery that led to the identification of small molecule inhibitors of Lipid II. These compounds are currently being optimized and examined for their potential as novel, broad-range antibiotic compounds.

In addition to their anti-bacterial properties, defensins act against viruses, including HIV-1. In a combined effort with Drs. Olga Latinovic and Alonso Heredia, Dr. de Leeuw examined the potential of small molecules antimicrobials against HIV-1. In these preliminary studies, lead compounds with activity against primary isolates of the virus have been identified. Current efforts are focused on determination of specificity, efficacy and mechanism-of-action of these compounds.

More recent work is aimed to understand how human α-defensins modulate host immunity. Following his initial observation that human defensins act synergistically with Tumor Necrosis Factor alpha (TNFα), Dr. de Leeuw recently reported on the functional intersection between defensins and the TNF receptor pathway. More detailed studies now suggest that defensins may interact specifically with the Extra Cellular Domain or ECD of TNF receptor 1.

Following the identification of clinically relevant targets for defensins such as Lipid II, viral components or TNF receptor 1, interactions are being validated using biochemical, structural and in vitro cell-based approaches. Together with researchers from the University of Maryland School of Pharmacy, Dr. de Leeuw is identifying and optimizing small molecule drugs against these targets for validation in animal models. The long-term goal of this approach is to evaluate the suitability of lead candidates in our drug development program leading to human clinical trials for broad-spectrum anti-infective or anti-cancer indication.
Greg Snyder

Dr. Snyder’s research interests focus on characterizing the molecular processes underlying host-microbe interactions pertaining to pathogenicity and immune dysregulation. To this end, Dr. Snyder has pursued studies of host-microbe recognition systems of Natural Killer Cell Inhibitory Receptors (KIR), HIV-1 entry and budding, carbohydrate receptors and molecular pattern recognition systems of Toll-Like and Interleukin-1 receptor (TIR) signaling pathways. Dr. Snyder received his training in structural biology, using X-ray crystallography and other biophysical and biochemical techniques as a graduate student at Northwestern University (Evanston, IL) and the Laboratory of Immunogenetics at NIH, NIAID (Rockville, MD) and as a post-doctoral fellow in the Laboratory of Immunology at NIH, NIAID (Bethesda, MD).

In December 2011, Dr. Snyder joined IHV as a Faculty Research Associate in Dr. Eric Sundberg’s laboratory, where he continued with his research on Toll-like and Interleukin-1 receptor signaling pathways and their subsequent subversion by microbial pathogens. In July of 2013, Dr. Snyder was promoted to Assistant Professor as part of an UMB-IHV faculty development initiative for establishment of a research laboratory investigating immune modulation involving host-pathogen interactions, immune dysfunction, autoimmunity and inflammation. The central theme of these investigations is to determine how species identify and respond to pathogenic, benign, and allergic exogenous stimuli.

As a research mentor, Dr. Snyder is committed to the recruitment, development and training of students from diverse backgrounds. The laboratory is currently comprised of postdoctoral fellow Dr. Lindsey Brown, who is the recent recipient of a NIH-NIAID T32 training grant, two undergraduate researchers from University of Maryland College Park and Towson University, a summer student from Dunbar High School and participant in Baltimore City’s Summer BioScience Internship Program, as well as a Nathan Schnaper, a Research intern from Tennessee Technological University. Dr. Snyder is a member of the University of Maryland Marlene and Stewart Greenebaum Cancer Center and holds a joint appointment with the Department of Microbiology and Immunology. The laboratory has obtained independent grant funding from the American Cancer Society and the National Cancer Institute, NIH for investigating innate immune signaling in diffuse large B cell lymphomas.

Yutaka Tagaya

The Tagaya lab has two research goals. One is the development of a new inhibitory peptide that targets multiple cytokines of a family. The immune system utilizes nearly 50 cytokines for its differentiation and functional competence and many of these cytokines form families based on the shared use of their receptor components. Postulating that by targeting the binding interface of family cytokine and shared receptor subunit, Dr. Tagaya showed that multiple cytokines could be inhibited by a single peptide. The concept has been patented and now several peptides have been developed with distinct cytokine target specificities. In collaboration with BIONIZ, LLC (Irvine, CA), which Dr. Tagaya co-founded, he is conducting proof-of-concept studies to show in vivo efficacy, pharmacokinetics, pharmacodynamics, and toxicology using a unique leukemia model that he generated previously (Marks Konczalik et al., PNAS 2000, Sato et al., Blood 2011). Some of these results have been published in a recent paper from the lab (Nata et al., J Biol. Chem. 2015, in press). Dr. Tagaya has also identified several human diseases in which this inhibitory peptide could potentially be used for treatment. One such disease is HAM/TSP (HTLV-1 Associated myelopathy/Tropical
Spastic paraparesis), a progressive myelopathy caused by HTLV-1, which was originally discovered by Dr. Robert Gallo, Director of IHV. Since there is no established treatment for HAM/TSP, this therapeutic approach provides a new hope for patients suffering from this disease. In collaboration with Dr. Steve Jacobson’s group at NINDS/NIH, another recent publication from the Tagaya group (Massoud et al., PNAS, 2015, in press) demonstrates the effective inhibition of pathologic activation of T-lymphocytes from HAM/TSP patients by this peptide inhibitor. BIONIZ is currently preparing to obtain an IND approval for this peptide from the FDA so that this drug can move into clinical trials for treating HAM/TSP patients.

Another research focus of the Tagaya lab also has a connection to HTLV-1. He is investigating the virologic and immunologic aspects associated with a fatal T-cell leukemia (Adult T-cell leukemia) caused by HTLV-1, with a particular interest in the involvement of compromised anti-HTLV-1 immunity at the transition of HTLV-1 infected carriers from asymptomatic latency into onset of leukemia. Dr. Tagaya has established a humanized mouse model to study this process in vivo by reconstructing the leukemia and non-leukemic immune cells from ATL patients in severely immune-compromised mice (NSG) mice, in collaboration with the bone marrow transplantation group led by Dr. Aaron Rapoport at the University of Maryland Marlene and Stewart Greenebaum Cancer Center. They have found that anti-HTLV-1 T cells became severely “exhausted” at the end of the latency period, and that the restoration of active anti-HTLV-1 immunity is one of the reasons for the moderately successful outcome of allogeneic stem-cell transplantation which has recently been adopted to treat ATL. Using this mouse model, they are testing whether rejuvenation of anti-HTLV-1 immunity by reversing the T-cell exhaustion may allow the development of novel immunotherapies for treating ATL more successfully.

In addition to laboratory activities, Dr. Tagaya supervises the operation of the IHV Flow Core, which helps IHV researchers with polychromatic flow cytometry and flow-based sorting of non-infected cells and those infected with various human pathogenic viruses (HIV-1, HTLV-1, etc.). Dr. Juan C. Zapata plays a crucial role for the operation of the Flow Core.

**Davide Zella**

Continuing the studies on the relationship between Mycoplasma and cancer, Drs. Zella and Gallo, together with Drs. Curreli, Krishnan, Cocchi, Bryant and a Ph.D. student (F. Benedetti), have found an association between Mycoplasma sequences and certain human cancers. Together with their previous studies, showing that certain strains of mycoplasma induce lymphomas in immunodeficient mice, these data further strengthen the possibility that Mycoplasma could play a role in the first steps of cellular transformation.

**HIV-1 matrix protein p17 implicated in virally associated lymphomas**

Though the incidence of HIV-1 associated malignancies has declined noticeably since the advent of highly active antiretroviral therapy (HAART), this is less so for non-Hodgkin’s lymphoma (NHL), usually of B cell origin, which remains a leading cause of morbidity and mortality in HIV-1 infected individuals. Whereas the mechanisms invoked are generally attributed to immune dysfunction and/or inflammation coupled with transformation initiated by Epstein-Barr virus (EBV), precise molecular events leading to the development and progression of NHL in HIV/AIDS patients have been elusive. In fact, EBV is only implicated in about half the HIV+ NHL cases, and its involvement is limited to initiating events and does not account for full lymphomagenesis. Understanding the molecular mechanisms underlying HIV-1 associated lymphomagenesis is obviously important for both diagnostic and therapeutic interventions of these aggressive cancers. Recent studies by Dr. Gallo and colleagues, in collaboration with a team of Italian scientists led by Dr. Arnaldo Caruso of University of Brescia Medical School, who is also an adjunct professor at the IHV, suggest that the HIV-1 matrix protein p17, a structural protein important for viral assembly and maturation, is the culprit closely associated with lymphoma development in HIV/AIDS patients. This paradigm-shifting discovery built upon their earlier findings that p17 persists in the germinal centers of lymph nodes long after HAART suppression of HIV, and

![Left to Right: Dr. Sabrina Curreli, Dr. Selvi Krishnan, Dr. Davide Zella, Dr. Fiorenza Cocchi, Francesca Benedetti and Dr. Robert Gallo](image-url)
that it promotes angiogenesis and lymphangiogenesis of vascular and lymphatic endothelial cells via the chemokine receptors CXCR1 and CXCR2—a molecular event highly relevant to lymphoma growth, invasion and metastasis. In their recent studies, Gallo et al have identified several dominant variants of p17 from both NHL tissues and plasma of the same HIV+ subjects that not only are pro-angiogenic and pro-lymphangiogenic, but also induce clonogenic growth of transformed B cells via CXCR2-mediated Akt signaling. These growth-promoting effects have been confirmed in murine models of p17-induced angiogenesis, lymphangiogenesis and lymphomagenesis. Extensive biophysical analysis suggests that mutation-induced protein destabilization may trigger a conformational change to p17 that confers its acquired or enhanced ability to productively engage CXCR1/CXCR2 for bioactivity. In light of the fact that HIV-1 associated lymphoma strongly correlates with viral replication and that p17 is prone to mutate, they hypothesize that p17 and certain variants in particular directly contribute to the development and progression of NHL associated with HIV-1 infection.

A manuscript that describes these findings has been accepted for publication in the Proceedings of National Academy of Sciences, USA, and two NIH grant proposals are to be submitted in the coming months that aim to test their hypothesis. It is expected that future studies will gain additional important insights into the structural basis of p17 function as well as p17-induced signaling pathways in promoting lymphomagenesis in HIV/AIDS patients, which, in turn, may lead to the development of diagnostic tools predicting the risk of developing NHL and the discovery of new prevention measures and therapies for HIV-associated NHL.
**Division Faculty Listing and Areas of Research**

**Structural Biology & Molecular Biophysics**
Taking advantage of IHV’s longstanding expertise in analyzing proteins, peptides and their interactions quantitatively and at atomic level resolution, IHV investigators in the Basic Science Division have extensive expertise in protein and peptide structure determination by X-ray crystallography, nuclear magnetic resonance (NMR) and circular dichroism (CD), as well as molecular interaction analysis by surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), fluorescence polarization (FP), fluorescence resonance energy transfer (FRET) and analytical ultracentrifugation (AUC). These studies are critical to defining the molecular bases of pathogenesis and to rationalizing therapeutic development for the entire spectrum of diseases on which IHV researchers work.

Joseph R. Lakowicz, PhD: Associate Member and Professor of Biochemistry and Molecular Biology

Erik de Leeuw, PhD: Assistant Professor of Biochemistry and Molecular Biology

Wuyuan Lu, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Chemical Protein Engineering, Professor of Biochemistry and Molecular Biology

Marzena Pazgier, PhD: Head of the Laboratory of Biomolecular Recognition, Assistant Professor of Biochemistry and Molecular Biology

Greg Snyder, PhD: Assistant Professor of Medicine

Eric Sundberg, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Structural Immunology & Oncology, Associate Professor of Medicine

**Drug Discovery & Development**
A key emphasis in research in the Basic Science Division is the translation of fundamental research to future clinical applications employing the tools of protein, glycoprotein and peptide engineering, including: peptide synthesis using both natural and non-natural amino acids; directed evolution using phage display, mirror-image phage display and yeast display; vaccine subunit design using recombinant protein technologies; and structure-based rational design.

Prakash Chandra, Dphil: Adjunct Professor of Medicine

Hua Cheng, PhD: Associate Professor of Medicine and Microbiology and Immunology

Erik de Leeuw, PhD: Assistant Professor of Biochemistry and Molecular Biology

Alfredo Garzino-Demo, PhD: Head of the Laboratory of Virus Host Interaction, Associate Professor of Microbiology and Immunology

Olga Latinovic, PhD: Head of the Laboratory of Imaging Studies of Pathogens & Cell Interactions and of the Imaging Core, Assistant Professor of Medicine

**Microbial Pathogenesis**
IHV was founded, in part, on an exceptional history of HIV research, a strength that continues to this day. Over the last nearly two decades, pathogenesis research in the Basic Science Division has expanded to encompass a variety of microbes, including Gram-positive and Gram-negative bacteria, Mycoplasma, Histoplasma, HTLV-1, respiratory viruses, hepatitis viruses and hemorrhagic fever viruses. Clinical samples and animal models, as well as genomic, proteomic, and metabolomic profiling are used to characterize diseased and healthy states.

Cristiana Cairo, PhD: Assistant Professor of Medicine

Armando Caruso, MD, PhD: Adjunct Professor of Medicine

Hua Cheng, PhD: Associate Professor of Medicine and Microbiology and Immunology

Fiorenza Cocchi, MD: Laboratory of the Director, Assistant Professor of Medicine

Sabrina Curreli, PhD: Laboratory of the Director, Research Associate of Medicine

Erik de Leeuw, PhD: Assistant Professor of Biochemistry and Molecular Biology

Robert Gallo, MD: IHV Director, Head of the Director's Laboratory, Homer & Martha Gudelsky Distinguished Professor in Medicine and Professor of Microbiology and Immunology

Suzanne Gartner, PhD: Head of the Laboratory of Stem Cell Biology, Associate Professor of Medicine

Alfredo Garzino-Demo, PhD: Head of the Laboratory of Virus Host Interaction, Associate Professor of Microbiology and Immunology

Olga Latinovic, PhD: Head of the Laboratory of Imaging Studies of Pathogens & Cell Interactions and of the Imaging Core, Associate Professor of Microbiology

Haishan Li, PhD: Assistant Professor of Medicine

Yiling Liu, MD: Research Associate of Medicine

Wuyuan Lu, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Chemical Protein Engineering, Professor of Biochemistry and Molecular Biology

Erling Norrby, MD, PhD: Adjunct Professor of Medicine

Fabio Romero, PhD: Head of the Laboratory of HIV-1 Persistence & Immunopathogenesis, Assistant Professor of Medicine

David Pauza, PhD: Head of the Laboratory of T Cells & Viral Pathogenesis, Professor of Medicine

Marzena Pazgier, PhD: Head of the Laboratory of Biomolecular Recognition, Assistant Professor of Biochemistry and Molecular Biology

Guido Poli, MD: Adjunct Professor of Medicine

Bhawna Poonia, PhD: Assistant Professor (P/T) of Medicine

Mikulas Popovic, MD, PhD: Adjunct Professor of Medicine

Marvin Reitz, PhD: Adjunct Professor of Medicine

Maria Salvato, PhD: Head of the Laboratory of Arenavirus Disease & Preventive Vaccines, Professor of Medicine

Greg Snyder, PhD: Assistant Professor of Medicine

Eric Sundberg, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Structural Immunology & Oncology, Associate Professor of Medicine

Yutaka Tagaya, PhD: Head of the Flow Cytometry Core and the Laboratory of Cell Biology, Assistant Professor of Medicine

Juan Zapata, PhD: Research Associate of Medicine

Davide Zella, PhD: Laboratory of the Director, Assistant Professor of Biochemistry and Molecular Biology

Yi Zeng, MD: Adjunct Professor of Medicine
Institute of Human Virology (IHV)

Cancer Biology
IHV cancer research has historically focused on viral oncology, with an emphasis on the pathobiology of HIV/AIDS, its relation to increased risk for malignant disease, and mechanisms explaining this relationship and approaches to prevention. More recently, faculty members in the Basic Science Division have expanded their studies to non-HIV viral oncology, bacterial oncology, dysregulation of apoptosis, and tumor metastasis.

Arnaldo Caruso, MD, PhD: Adjunct Professor of Medicine
Hua Cheng, PhD: Associate Professor of Medicine and Microbiology and Immunology
Sabrina Curreli, PhD: Laboratory of the Director, Research Associate of Medicine
Erik de Leeuw, PhD: Assistant Professor of Biochemistry and Molecular Biology
Robert Gallo, MD: IHV Director, Head of the Director's Laboratory, Homer & Martha Gudelsky Distinguished Professor in Medicine and Professor of Microbiology and Immunology
Suzanne Gartner, PhD: Head of the Laboratory of Stem Cell Biology, Associate Professor of Medicine
Erik de Leeuw, PhD: Assistant Professor of Biochemistry and Molecular Biology
Robert Gallo, MD: IHV Director, Head of the Director's Laboratory, Homer & Martha Gudelsky Distinguished Professor in Medicine and Professor of Microbiology and Immunology
Suzanne Gartner, PhD: Head of the Laboratory of Stem Cell Biology, Associate Professor of Medicine
Erik de Leeuw, PhD: Assistant Professor of Biochemistry and Molecular Biology
Robert Gallo, MD: IHV Director, Head of the Director’s Laboratory, Homer & Martha Gudelsky Distinguished Professor in Medicine and Professor of Microbiology and Immunology

Immunity & Inflammation
IHV researchers conduct fundamental studies on immunity and immune evasion, including acute and chronic human pathogens. They identify the mechanisms for pathogen induction of inflammation and its impacts on chronic viral diseases including HIV and HCV. There exists a critical emphasis on immune checkpoint regulators and their roles in viral immune evasion, as well as immunological studies as part of the HIV Cure strategy including relationships between immune regulation and viral latency or long-term consequences of viral-induced inflammation for comorbidities of HIV. An additional research emphasis lies in cytokine signaling and chronic inflammatory diseases.

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Alfredo Garzino-Demo, PhD: Head of the Laboratory of Virus Host Interaction, Associate Professor of Microbiology and Immunology
Yiling Liu, MD: Research Associate of Medicine
Henry Lowe, PhD: Adjunct Professor of Medicine
Wuyuan Lu, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Chemical Protein Engineering, Professor of Biochemistry and Molecular Biology
David Pauza, PhD: Head of the Laboratory of T Cells & Viral Pathogenesis, Professor of Medicine
Bhawna Poonia, PhD: Assistant Professor (P/T) of Medicine
Haishan Li, PhD: Assistant Professor of Medicine
Wuyuan Lu, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Chemical Protein Engineering, Professor of Biochemistry and Molecular Biology
Fabio Romerio, PhD: Head of the Laboratory of HIV-1 Persistence & Immunopathogenesis, Assistant Professor of Medicine
David Pauza, PhD: Head of the Laboratory of T Cells & Viral Pathogenesis, Professor of Medicine
Bhawna Poonia, PhD: Assistant Professor (P/T) of Medicine
Mikulas Popovic, MD, PhD: Adjunct Professor of Medicine
Marvin Reitz, PhD: Adjunct Professor of Medicine
Maria Salvato, PhD: Head of the Laboratory of Arenavirus Disease & Preventive Vaccines, Professor of Medicine
Greg Snyder, PhD: Assistant Professor of Medicine
Eric Sundberg, PhD: Co-Director, Division of Basic Science, Head of the Laboratory of Structural Immunology & Oncology, Associate Professor of Medicine
Yutaka Tagaya, PhD: Head of the Flow Cytometry Core and the Laboratory of Cell Biology, Assistant Professor, Medicine
Isaac Witz, PhD: Professor (P/T) of Microbiology and Immunology
Juan Zapata, PhD: Research Associate of Medicine
Davide Zella, PhD: Laboratory of the Director, Assistant Professor of Biochemistry and Molecular Biology
Yi Zeng, MD: Adjunct Professor of Medicine
Vaccine Research Division
The FLSC vaccine is a conformationally constrained vaccine, comprised of gp120 linked to the first two domains of CD4 by a flexible peptide spacer that elicits protective immunity against model AIDS viruses in animal models. Dr. Tony DeVico’s group developed the FLSC vaccine concept in the early years of the IHV with the first publication of its physical chemical profile in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research in collaboration with colleagues at Profectus Biosciences. The early years of FLSC development were supported by NIH grants to Division of Vaccine Research Members including Dr. Tony DeVico, Dr. Tim Fouts (now of Profectus Biosciences), Dr. Robert C. Gallo, and Dr. George K. Lewis. The FLSC vaccine concept was licensed to Wyeth Laboratories in 2002 and transferred to Profectus Biosciences in 2004. In 2007, The Bill and Melinda Gates Foundation awarded a large grant to Dr. Robert C. Gallo (Principal Investigator) and his collaborators Drs. DeVico, Lewis, and Fouts to support the advanced preclinical development of FLSC. In April 2011, a consortium of funders led by the Bill and Melinda Gates Foundation and including the Military HIV Research Program as well as the National Institutes of Allergy

The Division of Vaccine Research faculty, led by Dr. George K. Lewis, draws upon a wide spectrum of disciplines including molecular and cell biology, virology, immunology, and structural biology to solve major problems inherent to human viruses with emphasis on HIV-1. Over the last year the division has made significant progress in understanding the basis of protective immunity required for a successful HIV-1 vaccine as well as moving an HIV-1 vaccine candidate developed in the institute in collaboration with Profectus Biosciences to a Phase I clinical trial. This first clinical trial of FLSC will be carried out in the institute by the Division of Clinical Research in collaboration with the Division of Vaccine Research and Profectus Biosciences. It is widely agreed that a safe and effective vaccine is the best way to quell the HIV-1 epidemic; however, after over twenty-five years of intensive research, it remains elusive. IHV investigators have vigorously pursued several AIDS vaccine concepts since the IHV was founded in 1996 with 2015 being a signal year because an institute-developed vaccine, the Full-Length Single Chain (FLSC), developed in the Division of Vaccine Research, has advanced to a Phase I clinical trial. Development of the FLSC vaccine by Institute investigators is an example of the bench to bedside design of the institute by Dr. Robert C. Gallo, IHV Director, Dr. William Blattner, IHV Associate Director, and Dr. Robert R. Redfield, IHV Associate Director, who founded the institute in 1996 to develop new approaches to prevent and treat HIV infections.
and Infectious Disease, NIH, funded an additional grant to the IHV under Dr. Gallo's leadership for continuing support of the clinical development of FLSC for Phase I and Phase 2 clinical trials. The Phase I clinical trial is under way in the Division of Clinical Care and Research, led by Dr. Robert R. Redfield. The Phase I clinical trial also involves Drs. DeVico, Gallo, and Lewis of the Division of Vaccine Research, Dr. Bruce Gilliam of the Division of Clinical Care and Research, and Dr. Tim Fouts at 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 nineteen years ago. It exemplifies the IHV's bench-to-bedside research model and represents the only HIV vaccine candidate to be clinically tested by the University of Maryland, Baltimore (UMB) in nearly 20 years.

In addition to development of the FLSC vaccine, the Division of Vaccine Research members are collaborating on the mechanisms of antibody-mediated protection against HIV-1. The principal goal of this work is to define the relationships among neutralization, Fc-mediated effector function, and protection against HIV-1 transmission. It stems from observations made during the development of the FLSC vaccine that protection in animal models correlates largely with Fc-mediated effector function and not virus neutralization, although passive immunization studies show that neutralizing antibodies can protect in these model systems. This collaboration is led by Dr. George K. Lewis and includes Drs. Tony DeVico, Joseph Lakowicz, Roberta Kamin-Lewis, Meron Meginstu, Marzena Pazgier, Krishanu Ray, and Mohammad Sajadi. This work has been supported by a grant from The Bill and Melinda Gates Foundation as well as two R01 grants to Dr. Lewis. Progress in these projects is leading to independent grant funding to three early stage investigators. Dr. Marzena Pazgier has received a fundable score on a R01 grant from NIAID. Dr. Krishanu Ray received a fundable score on a R01 from NIGMS. Dr. Mohammad Sajadi has received a VA merit review grant and a R01 from NIAID. These grants place these early stage investigators well on the pathway to scientific independence.

Pursuant to our goals, we have identified monoclonal antibodies (mAbs) specific for the HIV-1 envelope glycoprotein (Env) that exhibit a spectrum of biological activities in vitro and in vivo. The in vitro spectrum includes broadly neutralizing mAbs (bnAbs) with modest Fc-mediated effector function, moderately neutralizing mAbs (nAbs) with significant Fc-mediated effector function, and a set of non-neutralizing mAbs (nnAbs) with potent Fc-mediated effector function. This spectrum corresponds to three patterns of protection in vivo against high-dose rectal SHIV challenges. A bnAb that protects completely, a nAb that protects partially, and an nnAb that does not protect. However, the bnAb and nnAb mediated strong post-infection control of viremia. These three patterns define overlapping windows of protection that remain mechanistically undefined in vivo, raising the possibility...
that these windows might be broadened once their mechanisms are understood at the physical chemical level. Accordingly, we have developed new tools to define the mechanism of each pattern of antibody-mediated protection.

Dr. DeVico’s group has developed new tools to characterize target epitopes on free virions, virions entering target cells, and virions budding from infected cells for each type of mAb. This work is leading to an increasingly clear picture of temporal epitope exposure during different phases of the viral replicative cycle that defines windows of opportunity for antibodies to interfere with infection by neutralization, Fc-mediated effector function, or both. This work provides a virological and immunological explanation for the correlates of protection we have linked with the FLSC vaccine strategy. This research involves broad application of several cutting edge technologies, including Fluorescence Correlation Spectroscopy, Fluorescence Resonance Energy Transfer, confocal microscopy and super-resolution microscopy.

Dr. Lewis’s group has developed passive immunization models to evaluate the mechanisms of antibody-mediated protection in vivo. His group is also developing quantitative in vitro models to determine the relative potencies of mAb candidates to be evaluated in passive immunization studies in vivo. This work has led to the identification of “prozones” both in vitro and in vivo for Env specific Fc-mediated effector function. His group is also exploring the mechanism of a novel pattern of mAb synergy in ADCC involving an allosteric effect through which the binding of antigen to the Fab region of a mAb causes a distal conformational change in the Fc-region that leads to increased Fc-receptor binding.

Dr. Pazgier’s group has produced the first atomic level epitope maps for the highly conserved Epitope Cluster A on gp120 that is a hotspot for antibody-cellular cytotoxicity (ADCC). This epitope cluster was implicated as a target of potentially protective antibodies in the RV144 vaccine trial and it is also a similar target for FLSC elicited antibodies in animal models. Dr. Pazgier’s group has also developed a novel “inner-domain” protein that is stabilized in the CD4-bound conformation that expresses Cluster A epitopes with and without the co-expression of V1/V2 epitopes also implicated as protective sites in RV144. This construct has proven useful for additional crystallographic trials, epitope
mapping of immune responses, and eliciting antibodies to epitopes of Cluster A in animal models. She will continue these studies under the aegis of her pending R01.

Dr. Ray’s group has adapted Fluorescence Correlation Spectroscopy and Fluorescence Resonance Energy Transfer to study the interaction of antibodies with Env on virions and in solution. These methods permit the solution-phase characterization of conformational effects that occur after antigen binding leading to increased binding to Fc-receptors. These methods permit co-localization of epitopes to single Env molecules on virions and in solution. He will continue these studies under the aegis of his pending R01.

Dr. Sajadi’s group has developed new methods for the isolation of human mAbs based on a combination of proteomics and deep sequencing and is applying it to isolate new bnAbs from HIV-1 infected volunteers. Serum antibodies are fractionated by affinity chromatography and isoelectric focusing to identify fractions enriched for specific biological activities, including neutralization breadth, Fc-mediated effector function, or both. The enriched protein fractions are sequenced and the variable region sequences matched against DNA sequences obtained by deep sequencing from the same individual. His group has developed an algorithm to rapidly pair VH and VL sequences to reconstitute the specificity and biological activities found in the serum antibodies from HIV-1 infected volunteers. This novel approach has led to the identification of a number of new bnAbs that are under characterization. He will continue this work under the aegis of his VA merit award and R01 grants.
Dr. Joseph Bryant is an Associate Professor and Director of the Animal Models Division at the Institute of Human Virology, he is also Director of the Animal Core Facility at the Institute. The Core is managed by Mr. Harry Davis and he has a staff of 5 animal care personnel. The Division is in its 20th year as one of the five Divisions here at the Institute that was established by the Director of IHV for the purpose of developing animal models as it relates to HIV/AIDS and AIDS-associated diseases. The Division currently has a staff of 2 veterinarians responsible for the veterinary care of all animals at the Institute. The veterinarians also assist investigators at the Institute on various scientific endeavors. The Animal Models Division has 1 Ph.D. scientist, and 3 technicians working on various scientific endeavors.

The Division over the years has provided research assistance to all investigators using animals at the Institute. We are currently overseeing 10 animal protocols as collaborators and/or support technical services. These protocols include vaccine studies using non-human primates, therapeutic studies using immunodeficient mice, and working with investigators using transgenic and knockout mice. The Division provides for translation of basic biomedical knowledge for prevention or new treatments, which often requires the use of animals as models or as a means of testing therapeutics and/or vaccines.

The Division is known for its development of animal models. They include the following: 1) The HIV-1 transgenic mouse model; 2) The HIV-1 transgenic rat model; 3) The HIV-1 transgenic nude rat model; 4) The HIV-1 transgenic nude mice; 5) The HIV-1 transgenic mouse model that develops a b-cell lymphoma similar to that seen AIDS-NHL; and 6) Humanized mouse models for HIV pathogenesis studies and for therapeutic studies.

Over the past 5 years we have worked very closely with Dr. Henry Lowe from Jamaica who is an Adjunct Professor here at the Institute on the isolation of anti-cancer agents from natural plants from Jamaica. This collaborative effort has resulted in over 3 patents and most recently we have isolated a small molecule designated as HLBT-001 from a plant (Tillandsia recurvata) that has been shown to have broad anti-cancer properties especially against prostate cancer, B-cell lymphoma, Kaposi Sarcoma, and several others.
The Division of Clinical Care and Research continues to develop its tripartite mission of clinical care, clinical research, and medical education, both domestically and around the world. This year, the Division has significantly expanded its clinical research efforts in the area of Hepatitis C therapeutics, solidified IHV’s ambulatory clinical programs at the University of Maryland Medical System’s Midtown campus, and successfully secured multiple post PEPFAR global grants providing advanced medical education, technical assistance, and research capacity in both Sub-Saharan Africa and the Caribbean.

Over the past year the Division leadership structure has been enhanced. Dr. Bruce Gilliam serves as the Director of the Division’s Comprehensive Clinical Programs. Dr. Shyamasundaran Kottilil serves as the Director of the Division’s Clinical Research Program. Dr. Deus Mubangizi serves as the Director of the Division’s extensive Global Health Program. These individuals lead and ensure the continued growth and success of each of these important components of the Division.

Dr. Bruce Gilliam joined the IHV in 2000. Dr. Gilliam received his medical degree from Jefferson Medical College, completed a residency in Internal Medicine at the University of California, Davis Medical Center, and completed a fellowship in Infectious Diseases at the University of North Carolina, Chapel Hill. Since joining the IHV, Dr. Gilliam served in leadership roles for the University of Maryland Global Health Initiatives Corporation, and is the central figure responsible for the success of the Division’s Global Health program today.

**CLINICAL PROGRAM**

The IHV continues to provide state of the art, high quality care to the citizens of Maryland, and beyond. With more than 5,000 patients in our clinics, the IHV continues to identify unmet patient needs and expanded services to address them. The IHV provides comprehensive ambulatory care services to patients living with HIV on the Midtown campus at the Primary Care Clinic, directed by Dr. Mariam Khambaty, the JACQUES Clinic directed by Dr. Patrick Ryscavage, and the Infectious Diseases Clinic directed by Dr. Janaki Kuruppu. The IHV also has maintained a strong clinical presence on the downtown
IHV’s HIV Preventive Vaccine entered Phase 1 first in Man trial
IHV’s Drs. Gallo, Lewis, and DeVico and Profectus Biosciences’ Dr. Tim Fouts have developed a novel vaccine candidate known as full length single chain (FLSC). Unlike other previous vaccines, this vaccine mimics the conserved transitional state that forms when HIV binds to CD4. The clinical development program is jointly funded by the Gates Foundation, the US Army, and the NIH. The first in man trial is now IRB approved, and will start enrolling volunteers in the fall of 2015, with Dr. Bruce Gilliam serving as the Principal Investigator. The primary objective of this phase 1 study is to assess the safety and immunogenicity of this candidate vaccine.

Hepatitis C Clinical Program
Since Dr. Kottilil’s recruitment, the hepatitis C clinical program has expanded to involve District of Columbia sub-specialty clinics, Midtown campus clinics, the Evelyn Jordan clinic, the UMSOM Methadone Treatment Center, and the Center for Addiction Medicine Clinics, the Veteran’s Affairs Medical Center Clinics. At these locations, Dr. Lydia Tang, Dr. Eleanor Wilson, and Angie Price, NP, are embedded within established primary care, HIV, substance abuse and specialty clinics, bringing hepatitis care to a high-risk population.

To date, the DC Partnership For AIDS Progress (DC PFAP) project has linked over 4,000 hepatitis patients to care.

New Fibroscan Services offered at IHV’s Midtown Clinic
The IHV acquired a Fibroscan machine at Midtown this year and now provides this painless procedure for all patients with hepatitis requiring assessment of the degree of their liver fibrosis. Under the leadership of Dr. Mariam Khambaty, two nurse practitioners, Angie Price and Hazel Jones Parker, the IHV Midtown Clinic provides fibroscan evaluations for patients with liver disease. The IHV providers at the Baltimore VA also have a Fibroscan machine for assessment of liver fibrosis in our veterans. State of the art treatment is provided in all of these clinics and IHV providers continue to work with policymakers and insurers to attempt to provide access to Hepatitis C Virus (HCV) treatment for all of those in need of it.

New IHV Clinical Initiatives at Midtown: Enhanced HIV and HCV program for diagnosis and linkage to care, Anal Health Clinic, and Pre Exposure Prophylaxis (PrEP) Clinic
The IHV was awarded funding from Gilead Sciences’ FOCUS program to support routine HIV and Hepatitis C testing and linkage to care in the inpatient setting at the UMMC Midtown Campus. The project is led by the JACQUES Initiative, which provides “linkage to care navigation” services for patients identified with HIV and HCV.

In January 2015, the IHV opened an Anal Health clinic at Midtown to address the increased needs of patients with HIV and HPV co-infection by providing education, screening for anal dysplasia, and high resolution anoscopy.

The IHV also established pre-exposure prophylaxis services linked with the Baltimore City Health Department. The IHV clinics at Midtown, the Baltimore VA, and the Evelyn Jordan Center are now providing pre-exposure prophylaxis (PrEP) services to individuals at high risk of acquiring HIV.

CLINICAL RESEARCH
Clinical Research Unit
The Institute’s Clinical Research Unit (CRU) continues to expand. Drs. Charles Davis, Bruce Gilliam, and Shyam Kottilil, serve as the unit’s Co-Directors. Dr. Davis oversees the unit’s HIV related therapeutic intervention trials and cohort studies; Dr. Shyam Kottilil oversees the research efforts in HBV and HCV, and Dr. Bruce Gilliam oversees the unit’s preventive and therapeutic HIV related vaccine trials.

With the successes of highly active antiretroviral therapy, the direction of HIV treatment has switched from the goal of just attaining viral suppression to the goal of sustaining viral suppression with the least impact on each individual’s metabolic profile (i.e., the lowest toxicity). The CRU recently completed a pilot trial evaluating the novel combination of Raltegravir, an integrase inhibitor, with Maraviroc, a CCR5 antagonist, in antiretroviral naïve patients. This regimen has limited metabolic toxicity, and may even have a positive impact on an individual’s risk of co-morbidities. Similarly, the IHV participated in a trial evaluating a new formulation of Tenofovir, called Tenofovir Alafenamide, which has the potential to have less bone and renal toxicities. The CRU also conducted several trials evaluating a new NNRTI, Doravirine, being developed by Merck, which is active against mutation commonly conferring resistance to Efavirenz and Nevirapine.

The IHV is also evaluating new agents for the management of patients with these highly resistant strains. The first is a Phase 3 study evaluating BMS-663068 an attachment inhibitors which binds to gp120 to prevent attachment of HIV to the cell. Another new agent under investigation, Ibaluzimab, is a monoclonal antibody that binds to domain 2 of the CD4 receptor to block viral entry.
Hepatitis C Clinical Trials

Under Dr. Kottilil’s leadership, there has been a rapid expansion of the clinical research program focused on novel, investigator initiated clinical trials. In 2012, Dr. Kottilil conducted the first FDA approved single center clinical trial in the US that used a DAA without concurrent IFN to treat HCV infection in the USA (Osinusi A. et al, JAMA 2013). This study contributed to the FDA labeling of this regimen as an alternative to interferon-based therapy and was the first IFN-free clinical trial for HCV GT-1 patients conducted in the US.

Dr. Kottilil’s team also conducted the first interferon and ribavirin free clinical trial for HIV/HCV co-infected subjects. Fifty HIV GT-1 treatment naive, non-cirrhotic subjects with stable HIV disease were treated with LDV/SOF (90mg/400mg) once daily for 12 weeks in an open-label, single center study. Forty-nine participants (98%) achieved SVR (Osinusi et al. JAMA 2015; Tang and Kottilil. The LANCET HIV 2015).

Industry-sponsored larger clinical trials demonstrated that most HCV-infected patients are cured with 12 weeks of DAA therapy. In the SYNERGY trial, Kottilil and his team evaluated the value of a third potent DAA to LDV/SOF and tested whether shortened durations of therapy were efficacious. 19 of 20 patients treated for 6 weeks with the three-drug regimen LDV/SOF plus GS-9669 (a non-nucleoside NS5B inhibitor) achieved SVR12, with 1 patient relapsing 2 weeks after completing therapy. 19 of 20 patients treated with the three drug combination of LDV/SOF plus GS-9451 (a NS3 protease inhibitor) for 6 weeks, achieved SVR12. In this landmark trial, we demonstrated that two different three-drug regimens administered for only 6 weeks resulted in a high cure rate for HCV infection (Kohli et al. The LANCET 2015).

This study, 600 HCV genotype 1 mono-infected, and HCV/HIV co-infected patients initiated treatment with ledipasvir and sofosbuvir for 8-24 weeks, based on the medication labeling instructions, and participants are assigned to treatment either by an ID or hepatology specialist, a primary care provider, or a nurse practitioner and followed for both immediate (SVR12) and long term (comorbidity disease, cirrhoshepatocellular carcinoma, transplantation, and mortality) outcomes over a 10 year study period using an existing electronic database.

RESCUE Trial Awarded to Kottilil team

Another major clinical dilemma confronting clinicians today is how to treat patients who fail DAA therapies. As of yet, the ideal re-treatment strategy and predictors of response in these patients have not yet been determined. The RESCUE trial is an investigator initiated trial (funded by Gilead Sciences) that will test the safety, tolerability, and efficacy of treatment with sofosbuvir (an approved NS5B inhibitor), GS-5816 (second generation NSSA inhibitor) and
GS-9857 (second generation NS3/4A protease inhibitor) in HCV infected patients with early and advanced liver disease who have failed previous combination DAA therapies.

Recently, the IHV also received an NCI contract award to develop a pilot project to evaluate precision medicine model for treatment of hepatitis C using DAA. This study will utilize baseline predictors to enrich for good prognostic factors for achieving SVR for short duration therapy for HCV at the Baltimore Veteran’s Affairs Medical Center, and UMB clinics. The objective is to develop a predictive model that can precisely enrich for patients for 100% SVR with DAA therapy.

Dr. Kottilil’s team, with collaborators from NIH and UCSF were awarded a novel U01 grant from the NIH to treat HIV/HCV co-infected patients with sofosbuvir and ledipasvir (STOP-CO trial $ 725,000/year for 3 years). This grant mechanism is to foster intramural-extramural collaborations, and enhance the utility of NIH Clinical Center resources. The IHV team will conduct laboratory experiments to unravel mechanisms associated with impaired intrahepatic immunity that is associated with HCV clearance (SVR) as a result of DAA therapy.

Furthermore, recently Dr. Redfield and his team won an R01 award from NIAID to use CCR5 blockade in kidney transplant patients. This grant will test the novel concept of using blockade of CCR5 receptor to interfere with cellular chemotaxis and increase graft survival in kidney transplant recipients.

**LAB RESEARCH**

**HIV Related Research**

Dr. Mohammad Sajadi’s lab is currently focused on humoral immunity in the NVS cohort and other HIV-infected individuals with broadly neutralizing antibodies, and also works closely with the Vaccine Research Division. Dr. Sajadi is a recipient of the 2014-2015 Passano Foundation Clinician-Investigator award. He is also a recent recipient of a NIH R01 titled, “Discovery of acidic epitopes for HIV-1 broadly neutralizing seraantibodies,” and a VA Merit Award entitled, “Discovery of acidic epitopes for HIV-1 broadly neutralizing seraantibodies.” In the past year, Dr. Sajadi has developed a novel method to sequence antibodies directly from blood, and will use this technique to study the circulating antibodies in subjects with HIV-1 broad neutralizing antibodies.

To overcome HIV resistance to approved antiretrovirals, the Redfield lab is targeting host proteins that HIV necessitates in its lifecycle. The lab continues to focus on strategies to target CCR5, a key co-receptor for HIV cellular attachment. Earlier work demonstrated that G1 cell cycle agents reduced CCR5 cellular expression, and enhanced antiviral activity of other HIV entry inhibitors. More recently the lab has extended this work to assessing the antiviral activity of a novel molecule developed by the Vaccine Research Division, Full Length Single Chain (FLSC), a fusion molecule of a portion of human CD4 and HIV envelope gp120. The antiviral activity of FLSC is further enhanced by forming a FLSC IgG1 form of the fusion protein. (Latinovic et al, AIDS Research and Retroviruses 2015). Earlier work demonstrated that a prototype S phase agent Resveratrol enhanced antiviral activity of nucleotide analogs. Recent work extended these observations to resveratrol derivatives which demonstrated greater bio-availability affirming ability of combination of these derivatives to “restore” susceptibility to multi-drug resistant HIV isolates in vitro, as well as in the humanized mouse model. (Heredia et al. JID 2013, and AIDS 2014.)

The Redfield lab has also shown that Cyclin-dependent-kinase 9 (CDK9) and Mammalian target of Rapamycin (mTOR), are cellular proteins targets for inhibiting HIV in vitro. We have demonstrated that targeting these proteins in a pre-clinical animal model (humanized mice) suppresses HIV in vivo. Recently, we extended this work showing that the mTOR1/mTOR 2 inhibitor (INK128) demonstrated antiviral viral activity for both CCR5 and CXCR4 strains of HIV, working by both reducing CCR5 expression, as well as inhibiting both basal and induced transcription of HIV genes (Heredia et al. PNAS 2015).

**Kottilil Laboratory—Eradication of Chronic Hepatitis B infection**

Although suppression of HBV replication is achieved in the majority of patients with currently available newer antivirals, discontinuation of therapy prior to hepatitis B surface antigen loss or seroconversion is associated with relapse of HBV, in the majority of cases. The basis of HBV persistence includes viral and host factors. Kottilil’s lab efforts focus on developing novel strategies to achieve sustained cure, or elimination of HBV. These efforts are led by Dr. Bhawna Poonia and Dr. Kottilil, and are funded by a Framework Research Agreement between Medimmune Inc and IHV ($560,700).

**Hepatitis C Immunology Program**

Dr. Kottilil has a highly productive
translational/bench research portfolio focused on unraveling biological correlates of protective immunity to hepatitis C virus in patients undergoing DAA therapy. In this regard, his group recently demonstrated that enhancement of intrahepatic type I interferon expression in patients achieves SVR with DAA therapy (Meissner et al. J clin Invest 2014). Furthermore, adaptive immune responses, precisely interferon gamma producing T cells to HCV antigens, were augmented by DAA therapy in patients with SVR, suggesting a role for innate and adaptive immune responses in HCV clearance with non-immune based DAA therapy. Using the samples collected from various clinical trials conducted by Dr. Kottilil, he and Dr. Poonia continue their investigations into determinants of SVR with short duration DAA therapy funded as an investigator initiated study by Gilead Sciences.

**HIV Co-Morbidity Cohort Research**

Dr. Ryscavage’s research interests focus largely on the care of young adults in adult HIV care. He identified a cohort of approximately 120 adults with perinatally-acquired HIV infection and examined patterns of HIV and non-HIV-associated illness among this cohort.

Dr. Shashwatee Bagchi’s research interest is in the cardiovascular complications of HIV-infected individuals. Preliminary data from that study has identified hepatitis C co-infection as a risk factor for developing accelerated coronary heart disease (CHD), and women appear to have greater CHD events than men in our HIV population.

This year Dr. Riedel received the 2015 Passano Foundation Clinician-Investigator Award to expand a prospective cohort of HIV patients with cancer, with the goal to develop and implement strategies to improve patient outcomes. Preliminary data has shown improved virologic control in patients co-managed in IHV’s cancer HIV clinic with Oncology.

Dr. Carla Alexander, in collaboration with Victoria Raveis, PhD, of New York University, was awarded a 3-year $2.1 million comparative effectiveness research contract from the Patient Centered Outcomes Research Institute (PCORI) in Washington, DC. The Care and Support Access (CASA) study is for HIV+ young men who have sex with men (yMMSM), which is the implementation of a palliative approach with HIV treatment, which evolved from Dr. Alexander’s experience in teaching HIV care and treatment in nine countries funded by PEPFAR.

**GLOBAL HEALTH INITIATIVE:**

**Bridging the Gap between Science and Practice**

The Global Health Initiative (GHI) under the leadership of Dr. Deus Bazira Mubangizi has active programs in seven countries: Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania, and Zambia. This year the Global Health Initiative has received funding from CDC for three new major programs in Kenya, Zambia, and Botswana. While Kenya and Zambia have been countries of operation for the IHV since 2004, this is the first time the IHV has worked in Botswana. The program, the Botswana-University of Maryland School of Medicine Health Initiative – BUHMMI, is purposed to enhance capacity of the Government of Botswana’s HIV response toward epidemic control. The 5 year program started in April 2015. Botswana is the first country in the world with real promise to control the HIV epidemic, and Dr. Mubangizi’s team is thrilled to be the main partner of the Government of Botswana and its people, in helping to make that historical milestone a reality.

Similarly in Zambia, the IHV/UMB was funded in December 2014 by CDC to implement a 5 year program titled “Stop Mother and Child HIV Transmission” (SMACHT), whose overarching goal is to ensure an AIDS-free era in Zambia, by ensuring that every child born, irrespective of the sero-status of the mother, is born HIV-free. This program, led by Dr. Robb Sheneberger as PI, will build upon previous and ongoing work in Zambia focusing on health workforce development by training present and future health care leaders through in-service, specialty, and sub-specialty training in internal medicine and infectious diseases.

Kenya, which is home to the largest portfolio of programs under the IHV’s Global Health Initiative, recently received new funding to implement a 5-year program titled, “BORESHA MAABARA”, which is Swahili for “improve laboratory services”. The program’s goal is to provide technical assistance to achieve and sustain reliable, quality assured laboratory services in the country, and to increase access and support to lab services for surveillance, prevention, treatment and care of HIV, TB, and related opportunistic diseases. The BORESHA MAABARA program is the premier national lab support initiative to the Ministry of Health in Kenya.

The GHI continues to grow and has provided opportunities for more faculty to assume Principal Investigator roles. Currently active PIs include: Dr. Anthony Amoroso, Dr. Deus Mubangizi, Dr. Sylvia Ojoo, Dr. Devang Patel, Dr. David Riedel, Dr. Robert Redfield, and Dr. Robb Sheneberger.

Left to Right: Dr. Shash Bagchi, Dr. Patrick Ryscavage, and Dr. David Riedel
Epidemiology and Prevention Division
The Division of Epidemiology and Prevention continues to focus its research on three closely related topics: 1) Key and Vulnerable Population Research; 2) Genomic Research in Cancer and Viral Diseases; and 3) Implementation science in HIV Treatment and Care Program. Research training grants from the National Institutes of Health (NIH), Fogarty International Center, and the Centers for Disease Control and Prevention (CDC) support these research efforts. With this funding, the Division of Epidemiology and Prevention works to train the next generation of scientists and epidemiologists, to increase the efficiency of HIV treatment and prevention, and ultimately to prevent a resurgence of the HIV epidemic in Nigeria. The Division’s faculty implements 21 research and training grants from the NIH and the World Health Organization (WHO) with an annual direct funding of $7.82M and four implementation grants from the CDC at an annual direct funding of $66M.

**Dr. Blattner’s Retirement**

William A. Blattner, MD, a pioneer in the epidemiological studies of human retroviruses, is retiring January 31, 2016. In his career, Dr. Blattner has made seminal contributions to the field of HIV/AIDS research, including understanding the cause of AIDS, its transmission, and methods of infection prevention. His discoveries have had a major impact on controlling and treating HIV on an international scale, greatly improving the human condition for millions.

Dr. Blattner’s research in HIV began in 1981 during his 22-year tenure at the National Cancer Institute (NCI). With colleague Robert C. Gallo, MD, Dr. Blattner defined the link between the first human retrovirus, HTLV-1, and adult T-cell leukemia/lymphoma. He was an important member of Dr. Gallo’s research team when the AIDS virus was discovered, and contributed to studies that established HIV as the cause of AIDS and described its transmission and prevention. Further, Dr. Blattner wrote the first peer-reviewed paper that analyzed the sensitivity and specificity of the HIV blood test.

In 1995, Dr. Blattner left the NCI for the University of Maryland, where he co-founded the Institute of Human Virology (IHV) with Drs. Gallo and Robert R. Redfield. With the IHV mission of integrating basic, clinical and population research to advance the pace of discovery from bench to bedside and public health practice, Dr. Blattner’s research provided insight into the pathogenesis of acute HIV infection and mother-to-child transmission of HIV. With a $293 million funding from the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), Dr. Blattner led one of the earliest and largest response to combat HIV in Nigeria, the AIDS in Care and Treatment in Nigeria (ACTION) Program that screened over 3 million for HIV, served 1.3 million at risk mothers and babies, cared for 267,000 and treated 166,000 HIV...
Key and Vulnerable Population Research

Drs. Charurat and Blattner lead the TRUST Study, an NIH-sponsored large R01 implementation science research grant investigating optimal strategies for addressing gaps in treatment and prevention among men who have sex with men (MSM) in Nigeria. The study has enrolled over 1300 MSM at the clinics in Abuja and Lagos. Study findings have made significant impacts. MSM are disproportionately impacted by HIV in Nigeria with HIV prevalence of 45%, 10 fold higher than in the general population. By using a “test and treat” approach, Drs. Charurat and Blattner have shown that respondent driven sampling provides accurate data which can be used to target ARV-based prevention (Baral et al., JAIDS 2015, Mar 1;68 Suppl 2:S107-13). More importantly, this work demonstrated that the majority of individuals engaged in treatment as prevention (TasP) can be retained in care after 18 months of follow-up (Charurat et al., JAIDS 2015, Mar 1;68 Suppl 2:S114-23). These findings have critical implications for improving rates of diagnosis and treatment, and the ability to monitor response to treatment.

A key factor associated with engagement in TasP includes disclosure of sexual orientation to health care providers. Unfortunately, such open disclosure and the ensuing access to prevention services was negatively impacted by the anti-gay law that was passed 10 months after the start of the study. Recently published in Lancet HIV, (Schwartz et al, Lancet HIV 2015, HIV. 2015 Jul 1;2(7):e299-e306), we found that both fear of seeking health care and avoidance of health care among MSM have increased following the passage of the Nigerian Same-Sex Marriage Prohibition Act. Reports of “fear of seeking health care” increased nearly 3-fold during the months after passage of this law, highlighting the need for patient advocates in both the healthcare and legislative domains. This year, Drs. Charurat and Blattner were awarded a new 5-year NIH-sponsored R01 to investigate the use of pre-exposure prophylaxis (PrEP) in this population to prevent forward transmission. This new funding will also investigate the interpersonal, network and structural barriers and characterize HIV transmission networks using phylodynamic epidemiology.
With the new goal of PEPFAR (PEPFAR 3.0) to “do the right thing at the right place and the right time” and the global response to fast track towards the 90-90-90 goal by 2020, there is a need to identify and target neglected and hard-to-reach populations. Drs. Blattner, Charurat, and Rebecca Nowak collaborated with Dr. Nicaise Ndembi of the Institute of Human Virology Nigeria, Dr. Gustavo Kijak of the U.S. Military HIV Research Program, and Dr. Erik Volz of the Imperial College U.K. to study the patterns and linkages among and between key and general populations. A cutting edge approach, phylodynamic analysis, integrates sequence data on the virus (a form of “molecular clock”) and epidemiological data to document patterns of transmission and trends over time. For this analysis HIV-1 pol sequences from 5 different risk groups were analyzed and examined. A paraphyletic relationship was observed between the MSM and general population, highlighting interconnections that are targets for impactful intervention. To estimate transmission rates within and between MSM and the general population, they developed a dynamic infectious disease model that accounted for stage of infection, sex, risk group, and variable force of infection through time. The analysis showed that incidence of HIV infection has increased in MSM populations despite the overall decline in incidence recently in the general Nigerian population. By targeting the interconnected networks of HIV, particularly focused on providing treatment and prevention services to high-risk groups cost effective impacts on the HIV epidemic can be achieved. One such effort is illustrated through Dr. Helen Omuh, a post-graduate Nigerian trainee whose Master's degree was supported by the Division of Epidemiology and Prevention. Dr. Omuh is working to engage women partners of MSM into HIV care and to enhance our understanding of how HIV transmission occurs across sexual networks. These studies highlight the innovative approaches employed by the Division of Epidemiology and Prevention to catalyze interventions tailored to prevent forward transmission in high-risk populations.

Genomic Research in Cancer and Viral Diseases

Dr. Clement Adebamowo assumes Dr. Blattner’s role of Associate Director for Population Science at the University of Maryland Greenebaum Comprehensive Cancer Center and will lead genomic research in cancer and viral diseases in the Division. In his new role, Dr. Adebamowo will work closely with the faculty of IHV and the leaders of the University of Maryland Greenebaum Cancer Center (UMGCC) Population Science Program, led by Drs. Joanne Dorgan and Cheryl Holt, to expand overall population science cancer research at UMB.

Dr. Adebamowo is PI of the African Collaborative Center for Microbiome and Genomics Research (ACCME), a grant funded through the NIH - Human Heredity and Health in Africa (H3 Africa). The ACCME grant is a multi-country, multi-institutional collaborative research involving the IHVN, IHV, and CIDRZ - based in Zambia. The ACCME aims to implement research programs to characterize the human microbiome and its role in health and disease. Specifically, ACCME links and leverages existing funded research and program activities at the collaborating institutions to study the interaction between vaginal microbiome, host genetic factors and molecular variants of Human Papilloma Virus (HPV), This research determines correlates of viral persistence in the causal pathway of cervical cancer, a major cause of preventable mortality on the African continent. Recent studies by the investigative team employ bacterial culture-independent, “clone and sequence approach” with 16S ribosomal RNA gene technologies. Through these experiments, they have documented the complexity of vaginal microbiome and classified consistent microbial groupings that provide new insight into relationship between the vaginal microbiome and cervical cancer pathogenesis.

Dr. Alash'le Abimiku leads another NIH H3Africa award to IHVN, the IHVN H3 Biorepository, which will use three biorepository facilities in Nigeria to study genomics and environmental determinants of common diseases. The biorepository network functions at International Society for Biological and Environmental Repository (ISBER) international standards, and supports multiple H3Africa investigators in the West African region. The biorepository already offers a broad...
range of services from specimen collection to shipment, including training and mentoring in pre-analytical, analytical, and post analytical processes.

Through seed funding awarded from the MPower and the UM SOM Department of Epidemiology and Public Health, Dr. Rebecca Nowak, who was recently promoted to Assistant Professor, investigates the epidemiology of human papillomavirus (HPV), the virus etiologically linked to anogenital cancers, in those at high risk for HIV. Her pilot cross-sectional study is one of the first to evaluate the prevalence of anal high-risk HPV in a young cohort of HIV-positive and HIV-negative MSM in sub-Saharan Africa (90% prevalence vs. 41%, p<0.001). In multivariate analyses, HIV infection was associated with a 2-fold increased prevalence of anal high-risk HPV. Other independent risk factors included more than 10 years since anal sexual debut and concurrent relationships with men. She is currently evaluating the role of the rectal microbiome as a mediator in the relationship between HIV and high-risk anal HPV.

MARGIN is an NIH funded genomic research study, led by Dr. Charurat that focuses on HIV-exposed and uninfected infants. This project grew from the observation that about 15% of all newborn babies in sub-Saharan Africa are exposed to HIV but remain uninfected; these exposed, uninfected infants are at risk for early life development abnormalities including subnormal growth or weight gain and increased risk for adverse clinical outcomes. In collaboration with the Institute for Genome Sciences, preliminary data using 454 pyrosequencing of 16S rRNA on vaginal samples from 21 months (11 HIV-infected and 10 uninfected) revealed the composition of vaginal microbiota is altered among those with HIV infection. The next phase of the study is to understand the shift in the vaginal microbiome in HIV-infected women, and more importantly for HIV-infected mothers, how the shift in maternal microbiome can influence the development of infant gut microbiome.

Implementation Science and HIV Care and Treatment Program

Dr. Patrick Dakum leads the Institute of Human Virology Nigeria (IHVN), a key partner of the CDC PEPFAR program and the Global Fund program to fight AIDS, Tuberculosis and malaria. Through this funding, IHVN provides comprehensive HIV Prevention, Care and Treatment in ten states in the Federal Republic of Nigeria. IHVN also addressed multi-drug resistant TB prevention and control. Its malaria program supports diagnosis and case management in 5 States in the Federal Republic of Nigeria. High impact is achieved through 109 laboratories and testing centers that are based at comprehensive semi-automated labs in 23 referral hospitals, 34 local hospitals and 44 large primary health centers; and basic HIV testing and hematological testing in 163 community centers in 10 of Nigeria’s 36 states including the Federal Capital Territory. In addition, IHVN developed 8 viral molecular laboratories for HIV viral load and pediatric detection, 5 regional training centers, 5 mobile laboratories, one national TB reference laboratory, and a molecular sequencing laboratory. There is also continued focus on scaling up pediatric HIV treatment through strategies such as Provider-Initiated Testing and Counselling and tracking of HIV-positive infants infected through mother-to-child transmission.

The transition to the WHO recommendations for lifelong ART for pregnant women with HIV requires a major paradigm shift from “PMTCT” to comprehensive maternal-infant HIV care that promises benefits for the mother and infant. Many countries have not effectively implemented even basic short-term programs to prevent transmission to children, and Nigeria alone contributes 23% of all newly infected infants in the world. The MoMent study (PI Dr. Nadia Sam-Agudu, Assistant Professor) examines the impact of structured peer counseling and support on uptake of services and retention among PMTCT clients in rural areas. As featured recently in JAIDS 2014 Nov 1;67 Suppl 2:S132-8, this study found that the financial cost of transportation, low confidence in the healthcare system, poor provider attitudes, and intense community-level HIV stigma are significant barriers to PMTCT uptake and retention in Nigeria. Mentor Mothers were found to be highly acceptable among stakeholders including pregnant women and women of childbearing age.

The CDC funded Nigerian Alliance for Health Systems Strengthening (NAHSS) award provides technical assistance to the Government of Nigeria to implement a national program for HIV/AIDS clinical quality improvement called NigeriaQUAL. Since the inception in 2012, Drs. Blattner and Charurat have guided the implementation of NigeriaQUAL assessments, data analysis and evidenced-based interventions to improve the quality of care in over 500 treatment sites throughout the 12 US government supported PEPFAR states in Nigeria. By strengthening the medical system from the bottom up, the goal of NAHSS is to promote a sustainable program of quality improvement at the local, state and federal governments, US PEPFAR HIV/AIDS legacy in Nigeria.
Clinical Research

There is a growing portfolio of research funding awarded directly to IHVN. Dr. Abimiku, Professor, is the Nigerian PI for a study of breast milk from HIV-infected and uninfected women funded by the Canadian Institutes of Health. The Nigerian site has completed 90% of its enrollment target of 300 HIV+ mothers and their infants. The mother-infant pairs are followed for 18 months and include 11 study visits when breast milk, blood and stool are collected from the mother and saliva, blood, stool collected from infants. In addition to insights about barriers to program uptake the study also has a basic science component, to investigate levels of soluble Toll-Like Receptor 2 (sTLR2) in breast milk from HIV-infected women. Since sTLR2 binds to HIV-1 proteins TLR2 regulates the chemokine receptor 5 expression an important entry molecule for the HIV virus. TLR2 could have benefits in helping reduce transmission of HIV from mother to child through breast feeding.

IHVN is the only Nigerian site in the NIH-sponsored Strategic Timing of AntiRetroviral Treatment (START) Study led by Dr. Ernest Ekong, IHVN Director of Clinical Services. This multi-country, randomized study was designed to determine whether early treatment at high CD4 level had benefit. In May 2015, NIH un-blinded the study after finding that AIDS events, serious non-AIDS events, and deaths were significantly reduced in the early treatment group. The impact of these results were aptly summarized by Dr. Anthony S. Fauci, Director of NIAID, who concluded that “together with data from previous studies showing that antiretroviral treatment reduced the risk of HIV transmission to uninfected sexual partners, these findings support offering treatment to everyone with HIV. These findings have global implications for the treatment of HIV.”

The Correlates of Monocyte-Associated Virus in HIV Neurocognitive Impairment (NeuroAID study), co-led by Dr. Walter Royal, Professor of Medicine at UMSOM, and Dr. Blattner completed its final follow up. This study showed that about 25% of the HIV-1 infected treatment naïve participants had evidence of mild neurocognitive impairment. They further identified key immune markers—soluble CD14 (sCD14), monocyte chemoattractant protein 1 (MCP-1), and neopterin—that correlated with the severity of impairment. Recently, this work was presented by Dr. Jibreel Jumare, a Fogarty trainee and PhD candidate, at the 2015 Meeting of the International Society for Neurovirology. These results provide insight into the vital role of monocyte activation in the pathogenesis of HIV-associated neurocognitive disorders. A follow up R01 study is planned to help identify specific diagnostic and prognostic biomarkers and to support the development of therapeutic and preventative interventions.

Research Training

Since 1998 the Division has been a leader in implementing research training in Nigeria and has been responsible for developing IHVN and its newly established International Research Center of Excellence into a major research player in Africa as measured by its $7.5M annual research budget. The infrastructure of IHVN has provided UM-IHV AITRP trainees a platform for conducting impactful research projects. To date, UM-AITRP Fogarty Trainees have published 377 peer-reviewed papers, 24 trainees completed advanced degrees (PhD and Masters), 36 underwent post-doctoral trainings at the IHV and the University of Maryland Baltimore, and almost 2,000 trainees attended in-country short courses like biostatistics and research ethics.

As PEPFAR transitions into a more supportive role, sustainability depends on the development of human resources that will implement HIV prevention, care and treatment programs with the support of their government and existing infrastructure. By collaborating with key government institutions in Nigeria tasked with regulating training Institutions, Dr. Abimiku was instrumental in the Division’s effort to update the National HIV/AIDS Laboratory Guideline in partnership with the Association of Public Health Laboratories, USA. This updated guideline in turn has informed the curricula of 19 universities and 47 colleges of health technology offering medical laboratory science. To date, the grant has built the capacity of 140 faculty members from these academic centers in adult learning principles, Good Clinical and Laboratory Practice, Quality Management System and advanced HIV/TB molecular techniques; and trained 139 interns and 1910 professional laboratory personnel.

Dr. Clement Adebamowo is the PI of the West African Bioethics Research Ethics Training and Capacity Building Program in Nigeria. In the last six years, the grant has developed a health research ethics system for Nigeria and other West African countries. The program works closely with the Nigerian National Health Research Ethics Committee to elevate the standard of research ethics review in Nigeria, implement electronic-ethics review, establish new ethics committees, and strengthen existing IRB. The program offers face-to-face training in Responsible Conduct of Research (RCR) that meets current NIH requirements and provides training in ethics issues related to data management and data privacy, biosafety and biosecurity in addition to standard trainings in informed consent and the Nigerian National Code for Health Research Ethics. In addition to bioethics, Dr. Adebamowo is the PI for the NIH training grant entitled: The Training Program in Nigeria for Non-Communicable Disease (NCD) Research. This grant uses a combination of short, medium and long term training programs, to develop capacity in Nigeria for NCD research.
IHV: A Global Virus Network (GVN) Center of Excellence

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a Center of Excellence of the Global Virus Network with a major role in its formation and subsequent continued success it experiences today. Since the HIV/AIDS outbreak of the early 1980’s, it has been the goal of IHV Director Robert Gallo, MD 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.

GVN was officially co-founded in 2011 at the Italian Embassy in Washington, D.C. by Dr. Gallo, who also serves as GVN’s Scientific Director, and his colleagues William Hall, MD, PhD, and the late 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 as well as a member of the IHV Board of Advisors. Dr. Kurth was 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 in addition to serving as a member of the IHV Board of Advisors. At the inaugural meeting in DC, attendees from more than a dozen countries affirmed and ratified GVN’s goals and objectives. Since that day, meeting GVN was incorporated by the U.S. government as a non-profit, 501(c)(3) organization. In 2012, GVN appointed Sharon Hrynkow, PhD as President of the GVN. Its members represent expertise covering every class of human virus, and comprise more than 20 countries. GVN has held subsequent meetings in Ireland, Italy, USA, Germany, Russia, Sweden, Grenada, and Estonia. In May 2015, GVN held a very successful meeting in Beijing, China hosted by Yi Zeng, MD of China’s Centers for Disease Control at Beijing University of Technology where IHV was well represented. In particular, this past year has been a pivotal one for GVN, including the election of finance and business leader N. Scott Fine as Chairman of the Board of Directors—he has been very active and passionate in his service to GVN and his commitment to its success.

As Ebola made headlines and GVN researchers led much of the scientific advances in Ebola research, GVN leadership including its Scientific Director, Dr. Gallo, provided written testimony to the Senate Appropriations Committee on the U.S. government response to Ebola. They urged all partners “to support training of local medical virologists—who could work in trusting relationships with colleagues worldwide — as an essential component of the global safety net against pandemics.” The testimony was followed up with an op-ed co-authored by Mr. Fine and Drs. Hrynkow, Gallo and Diane Griffin, MD, PhD, Director of the GVN Center of Excellence at Johns Hopkins Bloomberg School of Public Health, published in the Baltimore Sun similarly encouraging national and global public policymakers, business leaders and academic leaders to increase support for the training of the next generation of medical virologists as part of comprehensive pandemic preparedness plans.

GVN and its partners, including IHV Board Member Harry Huge’s Foundation (the Harry and Reba Huge Foundation), convened in June the 2nd Regional Scandinavian-Baltic Conference on emerging viral threats which included approximately 100 participants from Sweden, Estonia, Latvia, Lithuania, Ukraine, Russia, and the U.S., including the IHV. Such regional conferences provide unique opportunities for junior researchers to interact with prolific virologists of the GVN, including Dr. Gallo. They also offer virologists working on different viruses, vectors, and vaccines the chance to learn about the current research of their colleagues and to develop new collaborations and scientific exchanges.

This past year, GVN formed a task force of international experts on Human T-cell Lymphotropic (Leukemia) Virus-1 (HTLV-1), which was discovered by Dr. Gallo in 1980 and is the first known human retrovirus, and only known human leukemia virus. The mission of the HTLV-1 Task Force is to help speed the discovery of drugs that will stop virus transmission and progression from infection to disease (both leukemia and sometimes the development of a fatal neurological disease mimicking multiple sclerosis); and to educate the public about this and related viruses, the diseases...
they cause, and how to prevent their spread. The Task Force consists of experts from 11 countries and is led by Dr. Gallo, Luc Willems, PhD (Research Director, National Fund for Scientific Research at University of Liège, Belgium) and Hideki Hasegawa, MD, PhD (Director, Department of Pathology, National Institute of Infectious Diseases, Japan). As he leads the task force, Dr. Gallo draws on expertise from other IHV researchers such as Yutaka Tagaya, PhD and Hua Cheng, PhD.

This summer, GVN held its prestigious 2nd Annual Short Course in Medical Virology in Baltimore, MD. The impressive one week intensive course covers the basic, translational, and clinical aspects of viruses that pose the greatest threats to human health. Lecturers included medical virologists drawn from across GVN’s Centers of Excellence globally making for an impressive program that reviewed state-of-the-art aspects of research on a wide array of viruses, and included hands-on laboratory and clinical components. IHV hosted many meetings and provided an array of experts to speak to participants throughout the week. IHV faculty and staff supporting the important event included Robert Gallo, MD; Marv Reitz, PhD; Alfredo Garzino-Demo, PhD; Shyam Kotttil, MBBS, PhD; Patrick Ryscavage, MD; Yutaka Tagaya, PhD; Bruce Gilliam, MD; and, Nora Grannell. Burgeoning medical virologists were encouraged to participate in deep discussions and interaction with medical virology leaders in addition to meeting with policymakers and leaders in Washington DC.

IHV faculty and staff contribute time generously to the GVN throughout the year, including most notably Dave Wilkins and Nora Grannell, who also serves as GVN’s PR Director on a part-time basis, and IHV faculty, Robert Redfield, MD; William Blattner, MD; Dave Pauza, PhD; Maria Salvato, PhD; Mangalasseril Sarnagadharan, PhD; and, Alash’le Abimiku, MON, PhD.
Since IHV’s inception, more than $766,000,000 has been generated in externally sponsored revenue. This includes grants from many federal and foundation sponsors for work in basic science, patient clinical care, and international care and treatment. Among the highlights are more than $50M in cumulative funding for our HIV vaccine candidate and several hundred million dollars of support through U.S. President’s Emergency Plan For AIDS Relief (PEPFAR) through which IHV has treated more than one million patients in Africa and the Caribbean. In addition, IHV received a $1 million bequest from long-time board member, The Honorable Robert Keith “Bob” Gray, to establish an endowed distinguished professorship to honor his special friendship with Dr. Gallo. With even more recent grant wins, a new IHV Director of Development (Lori Piccolo) and promising future research, IHV looks to continue its science, health and financial impact on Maryland and the world.

If you would like to make a gift to support IHV, please visit our website at www.ihv.org or contact Lori Piccolo at 410-706-1388, lpiccolo@ihv.umaryland.edu.
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