INSTITUTE OF HUMAN VIROLOGY

ANNUAL REPORT 2016

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

About IHV

The Institute of Human Virology (IHV) is the first center in the United States—perhaps the world—to combine the disciplines of basic science, epidemiology and clinical research in a concerted effort to speed the discovery of diagnostics and therapeutics for a wide variety of chronic and deadly viral and immune disorders—most notably HIV, the cause of AIDS. Formed in 1996 as a partnership between the State of Maryland, the City of Baltimore, the University System of Maryland and the University of Maryland Medical System, IHV is an institute of the University of Maryland School of Medicine and is home to some of the most globally-recognized and world-renowned experts in the field of human virology. IHV was co-founded by Robert Gallo, MD, director of the of the IHV, Robert Redfield, MD, associate director of the IHV and director of IHV's Division of Clinical Care and Research and William Blattner, MD, retired since 2016 and formerly associate director of the IHV and director of IHV's Division of Epidemiology and Prevention. IHV is also comprised of an Animal Models Division, Basic Science Division and Vaccine Research Division.

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 hepatitis C virus, human T cell leukemia viruses 1 and 2, human papillomavirus, herpes viruses and cancer research. IHV's patient base has grown from just 200 patients to approximately 6,000 in Baltimore and more than 1,000,000 in 1 Caribbean and 6 African nations.

Contents

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

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.

Robert C. Gallo, MD

Director's Message

A look at the year

In September 2015, IHV hosted its 17th Annual International Meeting in Baltimore. The Annual Meeting was attended by internationally renowned scientists and integrated a multidisciplinary program of basic research including finding a cure for HIV, innovating and guiding development of an effective preventive HIV vaccine, and the study of HIV pathogenesis, hepatitis C and Ebola. Scientists focused on viruses and cancer to inform basic and translational research aimed at developing treatments while clinical research presentations emphasized opportunities to cure hepatitis C with newly available treatments. Global health presentations focused on translating discovery into public health practice.

Approximately 75 leading virologists and international researchers spoke during the meeting while hundreds attended. 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.

Anthony Fauci, MD and Prof. Harald zur Hausen, MD

Additionally, during the meeting, following a vote by senior IHV faculty, IHV awarded annual Lifetime Achievement Awards in 2015 to two distinguished individuals who have had exceptional influence on the science of immunology and care and treatment of HIV. They included:

2015 IHV Lifetime Achievement Award for Scientific Contributions & Public Service—

Anthony Fauci, MD, Director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID). As Director of NIAID for more than 30 years, Dr. Fauci has administered a comprehensive research portfolio targeting the prevention, detection, and treatment of infectious diseases such as HIV/AIDS. He has contributed to the field with his research in immune disease, particularly in Wegener's granulomatosis early in his career, culminating in his work on HIV/AIDS pathogenesis.

2015 IHV Lifetime Achievement Award for Public Service—

Prof. Harald zur Hausen, MD, a virologist and cancer researcher, was the Scientific Director of the German Cancer Research Center from 1983 to 2003. He has pioneered research in papillomaviruses most notably the link between human papillomaviruses (HPV) and cervical cancer. His research helped lead to the development of the HPV vaccine in 2006. In 2008, Prof. zur Hausen was awarded the Nobel Prize in Physiology or Medicine.

During the meeting, Dr. Fauci presented a special lecture entitled "Ending the HIV/AIDS Pandemic: The Convergence of Treatment and Prevention" and Dr. zur Hausen presented the second annual Reinhard Kurth Memorial Lecture entitled "Zoonotic Origin of Some Common Human Cancers and Multiple Sclerosis?"

Dr. zur Hausen presenting the second annual Reinhard Kurth Memorial Lecture

Uniquely at this year's Lifetime Achievement Awards Gala, we premiered a seven-minute film entitled "From Past to Future: Snapshots from the Institute of Human Virology" by Staffan Hildebrand, a Swedish film producer who has been documenting the AIDS pandemic since 1986. The result of his documentation is a unique film archive which highlights the human story of HIV/AIDS all over the world. Hildebrand has worked closely with the Karolinska Institutet during this endeavor. He has closely followed and filmed IHV over the years and his terrific film can be found on the homepage of our website at **www.ihv.org.**

William Blattner, MD and Robert Gallo, MD at the awards gala

One evening during the four-day meeting, we honored IHV Co-founder William Blattner, MD in the wake of his retirement. Dr. Blattner served as head of the IHV Division of Epidemiology and Prevention, Professor of Medicine, and Chief of the Division of Cancer Epidemiology at the University of Maryland, Baltimore. He led the founding of the Institute of Human Virology, Nigeria (IHVN), a key partner in IHV's international outreach. Manhattan

Man Charurat, PhD, shares parting words for William Blattner, MD

Charurat, PhD, Professor of Medicine, assumed the Director role of the IHV Division of Epidemiology and Prevention.

Moving on from our annual meeting, you will find in this year's FY16 annual report that our Divisions continue to advance research and public health locally, nationally and internationally. FY16 is especially memorable as it marks the 20th anniversary of the co-founding of the Institute.

IHV Co-founders William Blattner, MD, Robert C. Gallo, MD, and Robert Redfield, MD

Division of Basic Science

In the Division of Basic Science, co-directed by **Wuyuan Lu, PhD, Professor of Biochemistry and Molecular Biology, and Eric Sundberg, PhD, Professor of Medicine**, 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 µQUANT Assay Core.

Division of Vaccine Research

The Division of Vaccine Research faculty, led by **George K. Lewis, PhD, The Robert C. Gallo, MD Endowed Professorship in Translation Medicine and Professor of Microbiology and Immunology**, is taking a multi-disciplinary approach to developing an HIV-1 vaccine that includes expertise in molecular and cell biology, virology, immunology, and structural biology. The primary goal of the division is to solve four major problems confronting the development of an HIV-1 vaccine; identification of an immunogen that elicits cross-reactive protection, determining the mechanism of cross-reactive protection, increasing the persistence of protective antibody responses, and increasing vaccine efficacy by attenuating vaccine-elicited CD4+ T cell responses that provide increased targets for HIV-1 replication.

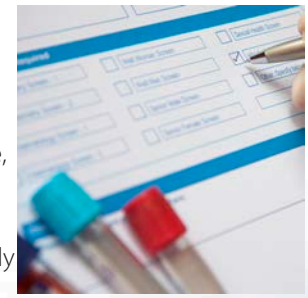
Division of Animal Models

The Animal Models Division, led by **Joseph Bryant, DVM, Associate Professor of Pathology, Director, Animal Models Division and Director, Animal Core Facility**, is in its 20th year as one of the five Divisions established by the Director for the purpose of developing animal models as it relates to HIV/AIDS and AIDS-associated diseases. The Division, also housing the Animal Core, has several interesting collaborations within the Institute, across campus and with external entities as well.

Division of Clinical Care and Research

The Division of Clinical Care and Research, led by **Robert Redfield, MD, The Robert C. Gallo, MD Endowed Professorship in Translation Medicine, Professor of Medicine, IHV Co-founder and Associate Director**, continues to strengthen all three of its interrelated programs of clinical care, clinical research, and medical education, both in the Baltimore and Washington metropolitan areas, and globally. This year, the Division has expanded its Baltimore based ambulatory clinical programs in the management and prevention of HIV infection, and treatment of patients with hepatitis B and C infection under the leadership of Bruce Gilliam, MD, Professor of Medicine. The Division has significantly increased its clinical trial activity under the leadership of Shyam Kottilil, MBBS, PhD, Professor of Medicine, especially in the area of Hepatitis C therapeutics. Finally, under the leadership of Deus Mubangizi, DrPHD, MPH, MBA, Assistant Professor of Medicine, the Division's program in Global Health and Biosecurity continues to secure significant new funding and expand the Institute of Human Virology's global impact.

Division of Epidemiology and Prevention

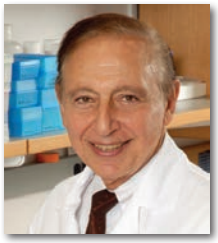


The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS, Professor of Medicine**, integrates the components of research, training and health systems strengthening conceptually through the three-legged stool approach—viewing each leg as necessary to advance science to prevent and treat HIV/AIDS, other infectious diseases, and cancers. The ultimate goal of the Division's population research focus is to have a translational impact on clinical and public health practices. The Division brings together population-based researchers with clinical scientists, educators, healthcare professions and with many external collaborators to carry out its trans-disciplinary research objectives. The Division has 9 faculty members, 6 staff and 2 pre-doctoral candidates with 20 active grants, totaling $85,657,323 of annual funding in 2016. The team of outstanding investigators have been recognized for their research merit and effective public health programs in the area of Prevention and Treatment Research, Pathogenesis Research, Research Training and Health Systems Strengthening.

Financial Overview

When the State of Maryland recruited us to form a cutting-edge, biomedical research institute in 1996, we couldn't predict that our success would be as impactful on the State as has been the case. As the Institute of Human Virology celebrates its 20th Anniversary this year, it continues to generate greater revenue growth. The $80 million that the Institute garnered this year brings IHV's total revenue generated since its inception to $846 million. Concurrently, IHV continues to be an international leader as HIV and other chronic viruses threaten the well-being of millions of people worldwide. In 2016, IHV was awarded more than $180 million in grant funding over the next five years. IHV also made important strides in philanthropic support. This year the Institute was awarded $995,000 in matching funds from the Maryland Department of Business and Economic Development (DBED) as part of the Maryland E-Nnovation Initiative Fund program. The E-Nnovation program is a special fund designed to help the state's research universities recruit and retain top scientists and investigators. The funds, combined with private philanthropy from The Honorable Robert Keith 'Bob' Gray and Stewart Greenebaum, enabled IHV to establish The Robert C. Gallo, MD Endowed Professorships in Translational Medicine. In addition, generous support from IHV's Board of Advisors has led to the creation of the Robert C. Gallo, MD Innovation Fund, a general fund that seeds new lines of life-saving research.

IHV Leadership



Robert C. Gallo, MD

Director, Institute of Human Virology
The Homer & Martha Gudelsky Distinguished Professor in Medicine
University of Maryland School of Medicine

Robert R. Redfield, MD

Associate Director, Director, Division of Clinical Care and Research
Institute of Human Virology
The Robert C. Gallo, MD Endowed Professorship in Translational Medicine
University of Maryland School of Medicine

George K. Lewis, PhD

Director, Division of Vaccine Research
Institute of Human Virology
The Robert C. Gallo, MD Endowed
Professorship in Translational Medicine
University of Maryland School of Medicine

Man E. Charurat, PhD

Director, Division of Epidemiology
and Prevention
Institute of Human Virology
Professor of 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

Joseph L. Bryant, DVM

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

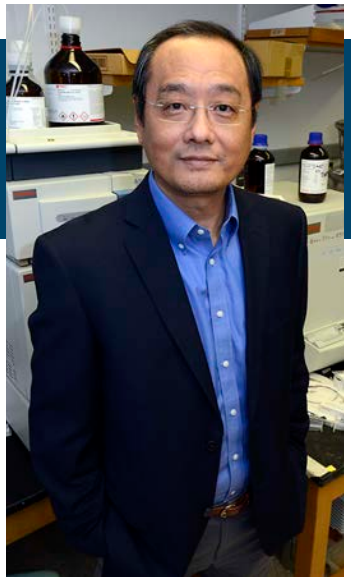
Eric Sundberg, PhD

Co-Director, Division of Basic Science
Institute of Human Virology
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



Wuyuan Lu, PhD

Eric Sundberg, PhD

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 µQUANT Assay Core. The Division is directed by **Wuyuan Lu, PhD**, Professor of Biochemistry and Molecular Biology, and **Eric Sundberg, PhD**, Professor of Medicine. In this year's Annual Report, we highlight research from a few members of our faculty.

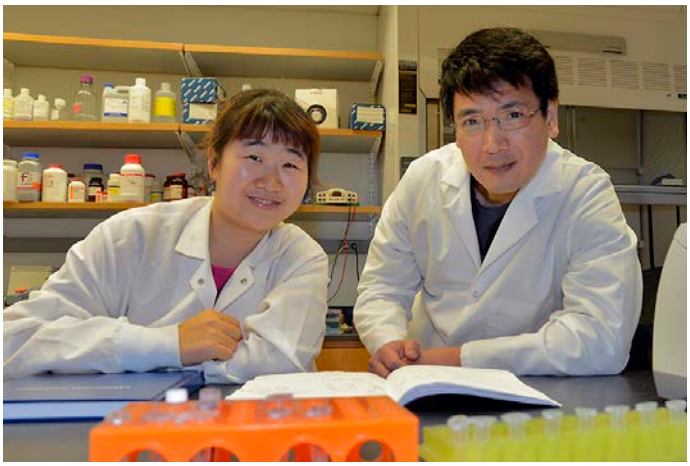
Cheng Laboratory

Hua Cheng, PhD, Associate Professor of Medicine and Microbiology and Immunology, leads a group that focuses on two major areas. One is to investigate the molecular oncogenesis of human T cell leukemia virus type 1 (HTLV-1) that causes adult T cell leukemia-lymphoma (ATL), an aggressive form of hematological malignancy. The other is to develop new cell-based immunotherapy strategies in combating ATL as well as other types of human cancer. The HTLV-1 viral genome encodes two regulatory proteins, Tax and HBZ, which play essential roles in cancer initiation and maintenance. Tax is a unique multi-functional viral protein that regulates both viral and cellular gene expressions, resulting in productive viral replication, enhanced viral infectivity and aberrant T cell proliferation and eventually malignant T cell transformation. A persistent expression of HBZ in all ATL patients suggests its role in the maintenance of T cell malignancy.

Dr. Cheng's team has demonstrated that three factors contribute to HTLV-1 oncogenesis. First, Foxp3, the master regulator of regulatory T cells, appears to assist Tax-mediated transformation of CD4+Foxp3+ Treg cells. Second, in addition to the canonical IκB kinases that regulate NK-κB signaling, the non-canonical IκB kinases including TBK1 and IKKε also play an essential role in promoting T cell survival and proliferation by maintaining the constitutive activity of Stat3. Third, Infection of HTLV-1 interferes with the process of autophagy in order to promote T cell survival and growth. Tax connects the IκB kinase complex to the autophagy molecular complex in increasing autophagic flux by interacting with several cellular factors, such as Beclin1 and Tid1, a molecular chaperone protein.

Recently, Dr. Cheng's team has been developing new immunotherapy methods by exploiting newly established dendritic cell technology. Dendritic cells (DCs) are central in mediating adaptive immunity and are powerful tools for developing cancer vaccine and T cell therapy. Harnessing DCs to prime naïve T lymphocytes could generate viral antigen-specific cytotoxic T lymphocytes (CTLs). It is known that both Tax and HBZ are immunogenic, providing protective immunity against ATLs. Dr. Cheng's team has engineered primary DCs by expressing Tax or a combination of Tax and HBZ in generating viral antigen-specific CTLs, which efficiently kill HTLV-1-transformed T cells in HLA-A2-restricted manner. By extending these findings, Dr. Cheng's team further engineered DCs by expressing common tumor antigens such as hTERT and NY-

Photo left: Yutaka Tagaya, PhD, Head of the Flow Cytometry Core and the Laboratory of Cell Biology, Assistant Professor of Medicine, Division of Basic Science



Long Wu, MS, PhD candidate, and Hua Chang, PhD

EOS-1. By selecting DCs based on the expression of certain molecules, Dr. Cheng's group has been able to develop CTLs with predominant CD3+/CD56+/CD8+ T cell populations, which potently kill a variety of human cancers in non-MHC-restricted manner. Animal studies have demonstrated that these DC-activated CTLs effectively inhibited tumor growth and lung metastasis of human breast and prostate cancer cells in NSG mouse models. Six papers have been published during FY2016, and a patent application related to the dendritic cell technology has been filed.

Fabio Romerio, PhD

Romerio Laboratory

Over the last 12 months, the laboratory of **Fabio Romerio, PhD**, Assistant Professor of Medicine, has shifted its research efforts in the characterization of the antisense gene of HIV-1. The existence of this gene was predicted in the late 1980's, but its role in viral replication remains to be determined and demonstrated. The HIV-1 antisense gene is encoded on the negative strand of the proviral genome, and overlaps the envelope proteins.

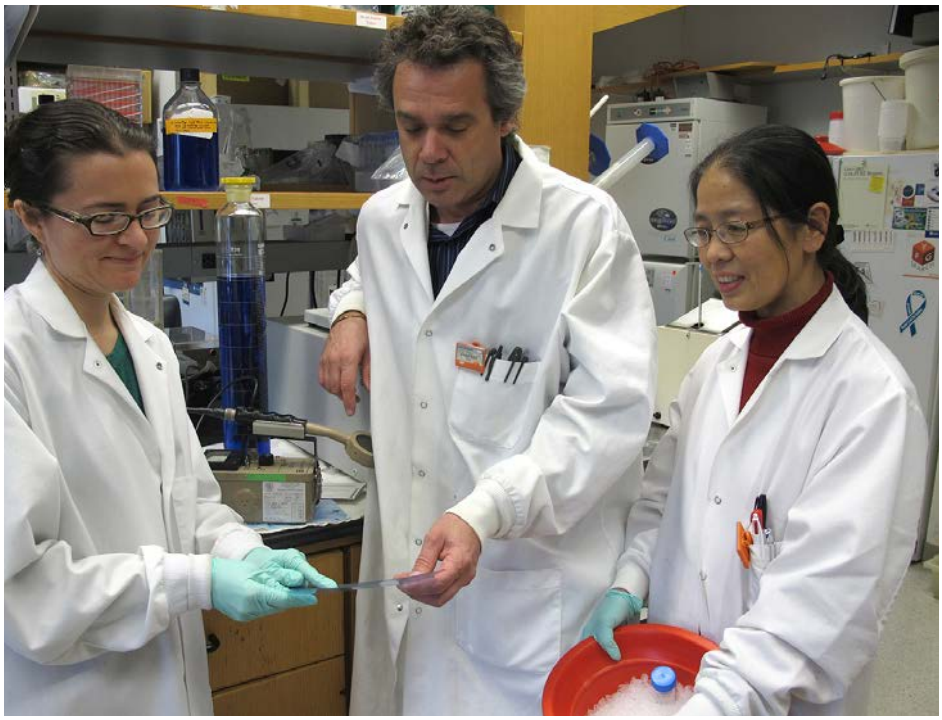
The research in Dr. Romerio's lab focuses on the role of both the transcript and protein that are produced by the HIV-1 antisense gene. Dr. Romerio has shown that the antisense transcript (AST) suppresses viral replication by recruiting a cellular multi-protein complex (termed PRC2) at the HIV-1 5'LTR. PRC2 introduces epigenetic marks that suppress gene expression, thus promoting viral silencing and latency. In addition to further characterizing this biological phenomenon, Dr. Romerio is trying to harness it to develop novel therapeutic approaches to achieve a functional cure for HIV-1 infection.

Additionally, preliminary studies conducted in Dr. Romerio's lab have shown that the HIV-1 antisense protein (ASP) represents a new accessory factor that promotes viral replication. Moreover, Dr. Romerio has shown that ASP associates with the inner leaflet of the nuclear membrane, and is currently focusing his efforts to characterize the role of ASP in the virus lifecycle.

In addition to these studies, the laboratory of Dr. Romerio is also actively involved in developing new methods to quantify the frequency of cells latently infected with HIV-1 in clinical samples. In recent months Dr. Romerio was awarded an R01 research grant from NIAID to utilize immuno-PCR (iPCR) in the context of quantitative viral outgrow assay (QVOA), thus allowing the detection of latently infected cells in clinical samples in a manner that is orders of magnitude more sensitive than current methodologies. More recently, Dr. Romerio has also received R21 funding from NIAID to apply multi-color PrimeFlow RNA technology in the detection of latently infected cells in clinical samples.

Garzino-Demo Laboratory

In the last few years, **Alfreado Garzino-Demo, PhD**, Associate Professor of Microbiology and Immunology, has led his group to identify CD4+CCR6+ T cells as key targets of HIV infection. In the last year, we published a study where we characterized the susceptibility and permissivity of CCR6+Th17 cells to HIV infection. CCR6+Th17cells play a crucial role in AIDS pathogenesis. HIV-1 infection (and its corresponding pathogenic SIV infection model in macaques) inflicts early and severe immune damage by depleting the IL-17-producing subset of CD4+ T helper (Th17) cells in the gut mucosa. Th17 cells, which are not replenished over time, are also likely depleted in the oral mucosa upon SIV/HIV-1 infection. IL-17 up-regulates epithelial cell production of anti-microbial peptides (AMP), including defensins and histatins which have potent activity against bacteria, fungi, and viruses and therefore, Th17 cells play a key role in mucosal barrier protection. Thus, lower levels of Th17 cells in the gut and oral mucosa compromises barrier integrity and allows translocation of microbial products from the intestinal lumen to the systemic circulation. This process triggers chronic immune activation, a strong predictor of progression to AIDS. In contrast, a decline



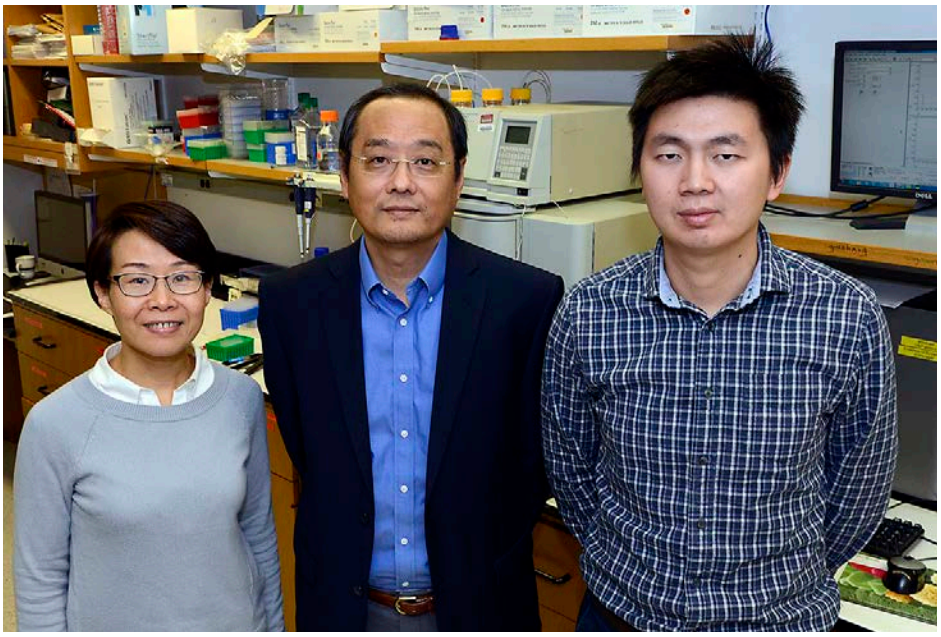
Virginia Carroll, PhD, Alfredo Garzino-Demo, PhD, and, Lingling Sun, MD

of Th17 cells is not observed in HIV-1 long-term non-progressors or in the non-pathogenic SIV infected macaque model. We have shown that expression of the AMP human β-defensin 2 (hBD2) and secretion of histatin-5 (Hst-5) are markedly decreased in the oral mucosa and saliva, respectively, in HIV+ subjects. Based on our findings, we have proposed that the decrease in AMPs expression contributes to increased susceptibility to opportunistic infections. Therefore, based on our findings that β-defensins up-regulate the HIV restriction factor APOBEC3G via CCR6 high levels of hBD2 would make CCR6+ cells, including Th17 cells, less permissive to HIV-1 infection. Based on these combined findings, we hypothesize that depletion of Th17 cells in the oral mucosa due to HIV infection contributes to hBD2 down-regulation in HIV-1 infected patients. This process further aggravates Th17 depletion in a self-perpetuating cycle, hampering immune protection against HIV-1 itself. Subsequently, the depletion of Th17 cells results in decreased production of antimicrobial pep-tides that may help explain why oral manifestations of HIV infection (opportunistic pathogens, such as *C. albicans*, HPV) are still observed even in the era of combination antiretroviral therapy (ART). We are now testing approaches to restore hBD2 levels, or pharmacological interventions to trigger CCR6-mediated up-regulation of APOBEC3G to induce resistance to HIV infection.

In addition, his laboratory collaborated internally (Robert Gallo, MD, The Homer & Martha Gudelsky Distinguished Professor in Medicine and Director of the IHV and, Dr. Wuyuan Lu, Joseph Bryant, DVM, Associate Professor of Pathology and Director of the Division of Animal Models, Mikulas Popovic, MD, Adjunct Professor of Medicine, Man Charurat, PhD, Professor of Medicine and Director of the Division of Epidemiology and Prevention, Sabrina Curreli, PhD, Research Associate of Medicine, and Dr. Fabio Romerio) and externally (Arnaldo Caruso, MD, PhD, Adjunct Professor of Medicine, IHV, University of Brescia, Italy) to characterize the role of the matrix protein of HIV in angiogenesis and HIV-associated lymphoma. Our data (Virginia Carroll, PhD, postdoctoral fellow, and Mark Lafferty, PhD, postdoctoral fellow) shows that several HIV proteins are expressed in a HIV transgenic mouse model of lymphoma developed by Dr. Bryant, but only Matrix/p17 is consistently expressed at high levels even in early disease stages. Microarray analyses of gene expression showed an enrichment of recombination-activating genes (Rag1/2) in mouse lymphoma tissue. When activated human B cells were treated with p17, induction of RAG1 expression was observed in 3 out of 7 donors. Taken together, and in the context of existing literature, our results point at the involvement of p17 in supporting B cell growth and genetic instability.

Lu Laboratory

One of the research areas of **Dr. Wuyuan Lu's** laboratory entails the discovery and development of peptide inhibitors of protein-protein interactions (PPIs) for therapeutic applications. PPIs control all aspects of cellular processes and have emerged as a critically important yet largely unexploited class of intracellular drug targets for disease intervention. Most drug discovery efforts have been focused on small molecules and proteins–the two dominant classes of therapeutics effective against traditional



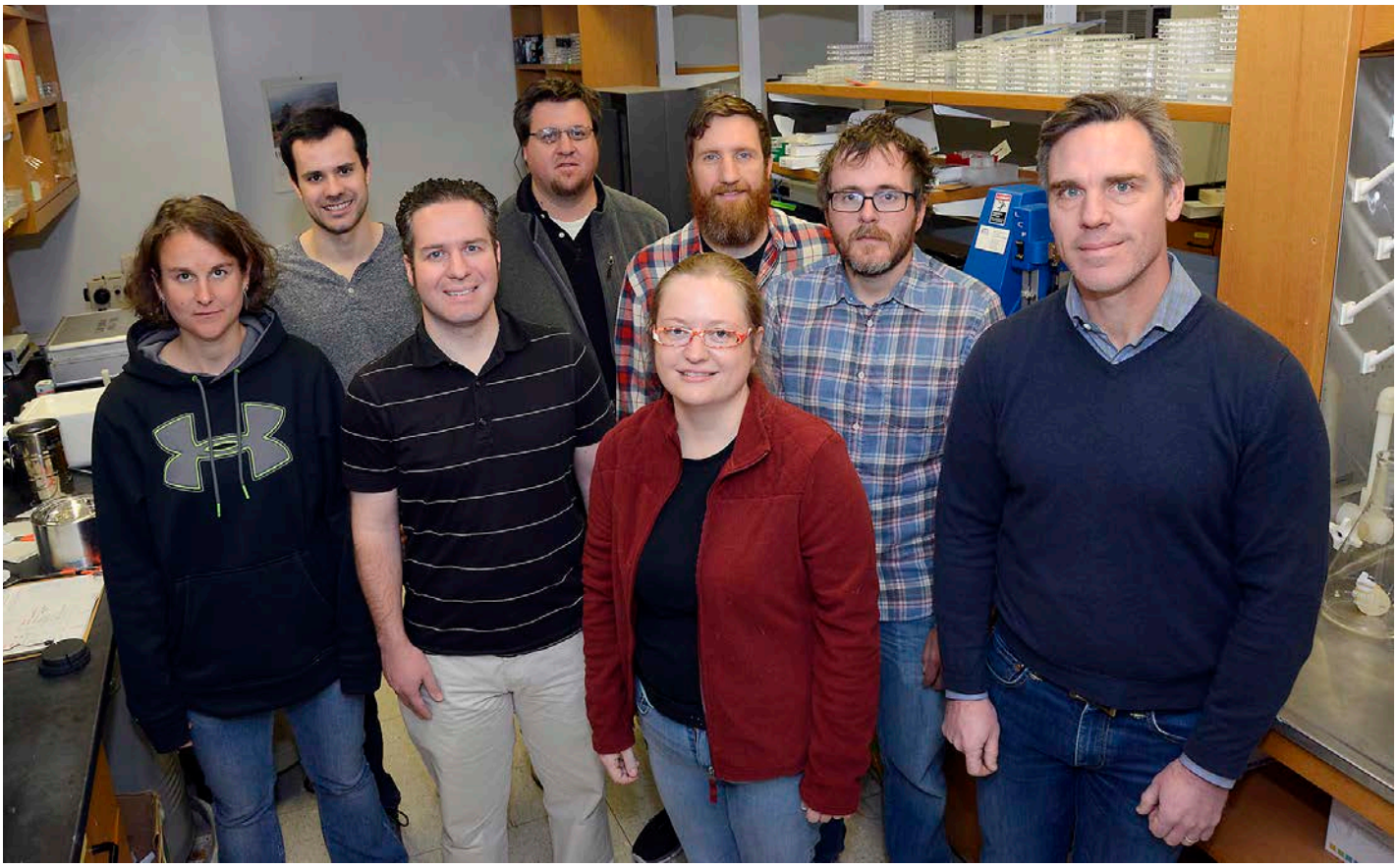
Weirong Yuan, MS, Wuyuan Lu, PhD, and, Xiang Li, PhD student

drug targets such as enzymes, receptors and ion channels, but ineffective in inhibiting intracellular PPIs deemed, traditionally, as "undruggable." Small peptides can be potent and specific inhibitors of PPIs with the potential to capture the best features of both small molecule and protein drugs. However, one devastating pharmacologic limitation of L-peptides is their strong susceptibility to proteolytic degradation in vivo. Toward this end, Dr. Lu and colleagues have discovered a series of proteolytically stable D-peptide inhibitors that potently activate the tumor suppressor protein p53 by antagonizing its negative regulators MDM2 and MDMX. These D-peptide inhibitors of the p53-MDM2/MDMX interactions kill tumor cells in vitro and in vivo, promising a novel class of antitumor agents with unsurpassed pharmacologic properties for clinical use.

Another attractive approach to turning proteolytically degradable L-peptides into drug-like compounds is "hydrocarbon stapling" – a technique developed by Verdine and colleagues of Harvard University that enables side-chain cross-linked and conformationally stabilized helical peptides to actively traverse the cell membrane with improved proteolytic stability and enhanced biological activity. Dr. Lu's laboratory previously discovered and patented one of the most potent L-peptide activators of p53 ever reported, termed PMI, with sub-nanomolar binding affinities for MDM2/MDMX. A hydrocarbon-stapled version of PMI has been designed and mechanistically validated in vitro. A cyclic RGD-linked polymeric micelle vehicle efficiently and specifically delivers stapled PMI to glioblastoma – the most aggressive form of brain cancer. Studies of combination therapy using glioblastoma-bearing nude mice and the standard chemo drug Temozolomide (TMZ) demonstrate that stapled PMI and TMZ are synergistic in prolonging the survival of experimental animals. Remarkably, stapled PMI can dramatically lower TMZ dosage and TMZ-associated toxicity in combination therapy to achieve the same therapeutic efficacy afforded by high-dose chemotherapy alone. Thus, stapled PMI and its derivatives have the potential to become a novel class of powerful activators of p53 for the treatment of a great variety of cancers harboring wild-type p53 and elevated levels of MDM2/MDMX.

Sundberg Laboratory

Dr. Eric Sundberg's research program investigates molecular recognition in infectious diseases in order to define the molecular bases for pathogenesis and immunity, as well as to rationalize the development of novel protein-based therapeutics. Of the many projects currently underway in the laboratory, we have made notable recent progress on the following. First, we are determining the molecular mechanisms by which infection by the bacterium *Helicobacter*



(L-R): Sandra Postel, PhD; Erik Klontz, BS; Kurt Piepenbrink, PhD; Greg Snyder, PhD; Amanda Bowers, MS; Sebastian Gunther, PhD; Daniel Bonsor, PhD; and, Eric Sundberg, PhD

pylori results in gastric cancer, one of the leading causes of cancer mortality globally. *H. pylori* strains that encode genes for a type IV secretion system (T4SS) and an oncoprotein called CagA are most likely to cause malignancies—the T4SS is a molecular machine that injects CagA into host gastric epithelial cells where it dysregulates numerous cell signaling pathways and the apoptotic program. Together with Rainer Haas, PhD, and his group, who are our collaborators at Ludwig-Maximilians-University of Munich in Germany, we have discovered that an adhesin protein on the surface of H. pylori called HopQ must bind to carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) on the surfaces of host epithelial cells to allow translocation of CagA into them. We have characterized HopQ-CEACAM interactions biophysically and are now defining the structural basis by which these proteins interact. These studies are informing our design of novel gastric cancer therapeutics and narrow-spectrum antibiotics that could eliminate H. pylori without destroying the remainder of the gut microbiota, which is being recognized increasingly for its role in maintaining gastrointestinal health. Second, we are investigating the molecular mechanisms by which the IL-1 family of cytokines activate cell signaling events that lead to chronic inflammatory conditions. In particular, we are studying the cytokine IL-33, dysregulated signaling by which is highly correlated to asthma onset and exacerbations. We have recently determined the high-resolution X-ray crystal structure of IL-33 in complex with its cognate receptor ST2 and secondary receptor IL-1RAcP. We are currently defining the molecular basis by which this complex forms and the ways in which it is both similar and different to the complex formed by IL-1 with its cognate receptor IL-1R and the shared secondary receptor IL-1RAcP. Defining these interactions at the atomic level is an essential step towards developing novel inhibitors of the IL-33 signaling pathway that could potentially be used to treat asthma, which we are actively pursuing.

Basic Science Publications

Anton, O. M., S. Vielkind, M. E. Peterson, **Y. Tagaya** and E. O. Long (2015). "NK Cell Proliferation Induced by IL-15 Transpresentation Is Negatively Regulated by Inhibitory Receptors." *J Immunol* 195(10): 4810-4821.

Bardina, S. V., D. Michlmayr, K. W. Hoffman, C. J. Obara, J. Sum, I. F. Charo, **W. Lu**, A. G. Pletnev and J. K. Lim (2015). "Differential Roles of Chemokines CCL2 and CCL7 in Monocytosis and Leukocyte Migration during West Nile Virus Infection." *J Immunol* 195(9): 4306-4318.

Basta, D., **O. Latinovic, M. K. Lafferty, L. Sun**, J. Bryant, **W. Lu**, F. Caccuri, A. Caruso, **R. Gallo** and **A. Garzino-Demo** (2015). "Angiogenic, lymphangiogenic and adipogenic effects of HIV-1 matrix protein p17." *Pathog Dis* 73(8): ftv062.

Bonsor, D. A., D. Beckett and **E. J. Sundberg** (2015). "Structure of the N-terminal dimerization domain of CEACAM7." *Acta Crystallogr F Struct Biol Commun* 71(Pt 9): 1169-1175.

Bonsor, D. A., **S. Gunther, R. Beadenkopf**, D. Beckett and **E. J. Sundberg** (2015). "Diverse oligomeric states of CEACAM IgV domains." *Proc Natl Acad Sci U S A* 112(44): 13561-13566.

Brook, M., G. H. Tomlinson, K. Miles, R. W. Smith, A. G. Rossi, P. S. Hiemstra, E. F. van 't Wout, J. L. Dean, N. K. Gray, **W. Lu** and M. Gray (2016). "Neutrophil-derived alpha defensins control inflammation by inhibiting macrophage mRNA translation." *Proc Natl Acad Sci U S A* 113(16): 4350-4355.

Carroll, V. and **A. Garzino-Demo** (2015). "HIV-associated lymphoma in the era of combination antiretroviral therapy: shifting the immunological landscape." *Pathog Dis* 73(7).

Chauhan, J., S. E. Chen, K. J. Fenstermacher, A. Naser-Tavakolian, **T. Reingewertz**, R. Salmo, C. Lee, E. Williams, M. Raje, **E. Sundberg**, J. J. DeStefano, E. Freire and S. Fletcher (2015). "Synthetic, structural mimetics of the beta-hairpin flap of HIV-1 protease inhibit enzyme function." *Bioorg Med Chem* 23(21): 7095-7109.

Chen, L., **D. Liu**, **Y. Zhang**, **H. Zhang** and **H. Cheng** (2015). "The autophagy molecule Beclin 1 maintains persistent activity of NF-kappaB and Stat3 in HTLV-1-transformed T lymphocytes." *Biochem Biophys Res Commun* 465(4): 739-745.

Chen, L., **D. Liu**, **Y. Zhang**, **H. Zhang** and **H. Cheng** (2015). "Foxp3-dependent transformation of human primary CD4+ T lymphocytes by the retroviral protein tax." *Biochem Biophys Res Commun* 466(3): 523-529.

Chen, X., **N. Gohain**, **C. Zhan**, W. Y. Lu, M. Pazgier and **W. Lu** (2016). "Structural basis of how stress-induced MDMX phosphorylation activates p53." *Oncogene* 35(15): 1919-1925.

Chen, X., L. Tai, J. Gao, J. Qian, M. Zhang, B. Li, C. Xie, L. Lu, **W. Lu** and W. Lu (2015). "A stapled peptide antagonist of MDM2 carried by polymeric micelles sensitizes glioblastoma to temozolomide treatment through p53 activation." *J Control Release* 218: 29-35.

Ding, J., C. Tasker, P. Lespinasse, J. Dai, P. Fitzgerald-Bocarsly, **W. Lu**, D. Heller and T. L. Chang (2015). "Integrin alpha4beta7 Expression Increases HIV Susceptibility in Activated Cervical CD4+ T Cells by an HIV Attachment-Independent Mechanism." *J Acquir Immune Defic Syndr* 69(5): 509-518.

Dolcetti, R., C. Giagulli, W. He, M. Selleri, F. Caccuri, **L. M. Eyzaguirre**, P. Mazzuca, S. Corbellini, F. Campilongo, S. Marsico, E. Giombini, E. Muraro, G. Rozera, P. De Paoli, A. Carbone, M. R. Capobianchi, G. Ippolito, S. Fiorentini, W. A. Blattner, **W. Lu, R. C. Gallo** and A. Caruso (2015). "Role of HIV-1 matrix protein p17 variants in lymphoma pathogenesis." *Proc Natl Acad Sci U S A* 112(46): 14331-14336.

Gounder, A. P., N. D. Myers, P. M. Treuting, B. A. Bromme, S. S. Wilson, M. E. Wiens, **W. Lu**, A. J. Ouellette, K. R. Spindler, W. C. Parks and J. G. Smith (2016). "Defensins Potentiate a Neutralizing Antibody Response to Enteric Viral Infection." *PLoS Pathog* 12(3): e1005474.

Heredia, A., F. Barbault and **E. P. de Leeuw** (2015). "A novel small-molecule inhibitor of HIV-1 entry." *Drug Des Devel Ther* 9: 5469-5478.

Heredia, A., N. Le, R. B. Gartenhaus, E. Sausville, S. Medina-Moreno, **J. C. Zapata**, C. Davis, **R. C. Gallo** and R. R. Redfield (2015). "Targeting of mTOR catalytic site inhibits multiple steps of the HIV-1 lifecycle and suppresses HIV-1 viremia in humanized mice." *Proc Natl Acad Sci U S A* 112(30): 9412-9417.

Iordanskiy, S., R. Van Duyne, G. C. Sampey, C. M. Woodson, K. Fry, M. Saifuddin, J. Guo, Y. Wu, **F. Romerio** and F. Kashanchi (2015). "Therapeutic doses of irradiation activate viral transcription and induce apoptosis in HIV-1 infected cells." *Virology* 485: 1-15.

Koch, K., N. Koch, U. Sandaradura de Silva, N. Jung, J. Schulze zur Wiesch, G. Fatkenheuer, P. Hartmann, **F. Romerio** and C. Lehmann (2015). "Increased Frequency of CD49b/LAG-3(+) Type 1 Regulatory T Cells in HIV-Infected Individuals." *AIDS Res Hum Retroviruses* 31(12): 1238-1246.

Kudryashova, E., **W. Lu** and D. S. Kudryashov (2015). "Defensins versus pathogens: an unfolding story." *Oncotarget* 6(30): 28533-28534.

Latinovic, O. S., S. Medina-Moreno, K. Schneider, **N. Gohain**, **J. Zapata**, M. Pazgier, M. Reitz, **J. Bryant** and R. R. Redfield (2016). "Full Length Single Chain Fc Protein (FLSC IgG1) as a Potent Antiviral Therapy Candidate: Implications for In Vivo Studies." *AIDS Res Hum Retroviruses* 32(2): 178-186.

Latinovic, O. S., J. Zhang, **Y. Tagaya**, A. L. DeVico, T. R. Fouts, K. Schneider, J. R. Lakowicz, A. Heredia and R. R. Redfield (2016). "Synergistic Inhibition of R5 HIV-1 by the Fusion Protein (FLSC) IgG1 Fc and Maraviroc in Primary Cells: Implications for Prevention and Treatment." *Curr HIV Res* 14(1): 24-36.

Latinovic, O. S. and R. R. Redfield (2015). "CCR5-Cellular doorway for HIV-1 Entry." *J Human Virol and Retrovirol* 2(5): 00056.

Latinovic, O. S., S. Medina-Moreno, L. M. Hippler, J. C. Zapata and R. R. Redfield (2016). "Humanized NSG Mouse Models of HIV-1 Infection and Pathogenesis." *J Human Virol and Retrovirol* 3(2): 00087.

Li, J., **C. Lehmann**, **X. Chen**, **F. Romerio** and **W. Lu** (2015). "Total chemical synthesis of human interferon alpha-2b via native chemical ligation." *J Pept Sci* 21(7): 554-560.

Liang, Y., Z. Jie, L. Hou, P. Yi, W. Wang, Z. Kwota, **M. Salvato**, R. de Waal Malefyt, L. Soong and J. Sun (2015). "IL-33 promotes innate IFN-gamma production and modulates dendritic cell response in LCMV-induced hepatitis in mice." *Eur J Immunol* 45(11): 3052-3063.

Basic Science Publications

Massoud, R., Y. Enose-Akahata, **Y. Tagaya**, N. Azimi, A. Basheer and S. Jacobson (2015). "Common gamma-chain blocking peptide reduces in vitro immune activation markers in HTLV-1-associated myelopathy/ tropical spastic paraparesis." *Proc Natl Acad Sci U S A* 112(35): 11030-11035.

Nata, T., A. Basheer, **F. Cocchi**, **R. van Besien**, R. Massoud, S. Jacobson, N. Azimi and **Y. Tagaya** (2015). "Targeting the binding interface on a shared receptor subunit of a cytokine family enables the inhibition of multiple member cytokines with selectable target spectrum." *J Biol Chem* 290(37): 22338-22351.

Niu, G., **H. Zhang**, **D. Liu**, **L. Chen**, C. Belani, H. G. Wang and **H. Cheng** (2015). "Tid1, the Mammalian Homologue of Drosophila Tumor Suppressor Tid56, Mediates Macroautophagy by Interacting with Beclin1-containing Autophagy Protein Complex." *J Biol Chem* 290(29): 18102-18110.

Nolte-'t Hoen E, Cremer T, **Gallo RC** (2016), Margolis LB. Extracellular vesicles and viruses: Are they close relatives? *Proc Natl Acad Sci U S A* 16;113(33):9155-61.

Obata, F., L. M. Hippler, P. Saha, D. M. Jandhyala and **O. S. Latinovic** (2015). "Shiga toxin type-2 (Stx2) induces glutamate release via phosphoinositide 3-kinase (PI3K) pathway in murine neurons." *Front Mol Neurosci* 8: 30.

Pauza, C. D. and **C. Cairo** (2015). "Evolution and function of the TCR Vgamma9 chain repertoire: It's good to be public." *Cell Immunol* 296(1): 22-30.

Perrone, R., E. Butovskaya, S. Lago, **A. Garzino-Demo**, C. Pannecouque, G. Palu and S. N. Richter (2016). "The G-quadruplex-forming aptamer AS1411 potently inhibits HIV-1 attachment to the host cell." *Int J Antimicrob Agents* 47(4): 311-316.

Poonia, B. (2016). "Adoptive transfer of aminobisphonate-expanded Vgamma9Vdelta2+ T cells does not control HIV replication in a humanized mouse model." *Immunotherapy* 8(5): 521-526.

Poonia, B. and S. Kottilil (2016). "Newer therapeutics for hepatitis C." *Ann Transl Med* 4(2): 31.

Radoshitzky, S. R., Y. Bao, M. J. Buchmeier, R. N. Charrel, A. N. Clawson, C. S. Clegg, J. L. DeRisi, S. Emonet, J. P. Gonzalez, J. H. Kuhn, I. S. Lukashevich, C. J. Peters, V. Romanowski, **M. S. Salvato**, M. D. Stenglein and J. C. de la Torre (2015). "Past, present, and future of arenavirus taxonomy." *Arch Virol 160(7): 1851-1874*.

Ramachandran, G., P. Gade, P. Tsai, **W. Lu**, D. V. Kalvakolanu, G. M. Rosen and A. S. Cross (2015). "Potential role of autophagy in the bactericidal activity of human PMNs for Bacillus anthracis." *Pathog Dis* 73(9): ftv080.

Shrivastava, S., E. G. Meissner, E. Funk, S. Poonia, V. Shokeen, A. Thakur, **B. Poonia**, S. K. Sarin, N. Trehanpati and S. Kottilil (2016). "Elevated hepatic lipid and interferon stimulated gene expression in HCV GT3 patients relative to non-alcoholic steatohepatitis." *Hepatol Int*.

Taylor, G. H., A. A. Williams and **A. Garzino-Demo** (2016). "Highly active antiretroviral therapy reduces pulmonary IL-8 in HIV-positive women smokers." *Pathog Dis* 74(2).

Taylor, J. K., C. M. Coleman, **S. Postel**, J. M. Sisk, J. G. Bernbaum, T. Venkataraman, **E. J. Sundberg** and M. B. Frieman (2015). "Severe Acute Respiratory Syndrome Coronavirus ORF7a Inhibits Bone Marrow Stromal Antigen 2 Virion Tethering through a Novel Mechanism of Glycosylation Interference." *J Virol* 89(23): 11820-11833.

Valere, K., A. Rapista, E. Eugenin, **W. Lu** and T. L. Chang (2015). "Human Alpha-Defensin HNP1 Increases HIV Traversal of the Epithelial Barrier: A Potential Role in STI-Mediated Enhancement of HIV Transmission." *Viral Immunol* 28(10): 609-615.

Waldhuber, A., **G. A. Snyder**, F. Rommler, C. Cirl, T. Muller, T. S. Xiao, C. Svanborg and T. Miethke (2016). "A Comparative Analysis of the Mechanism of Toll-Like Receptor-Disruption by TIR-Containing Protein C from Uropathogenic Escherichia coli." *Pathogens* 5(1).

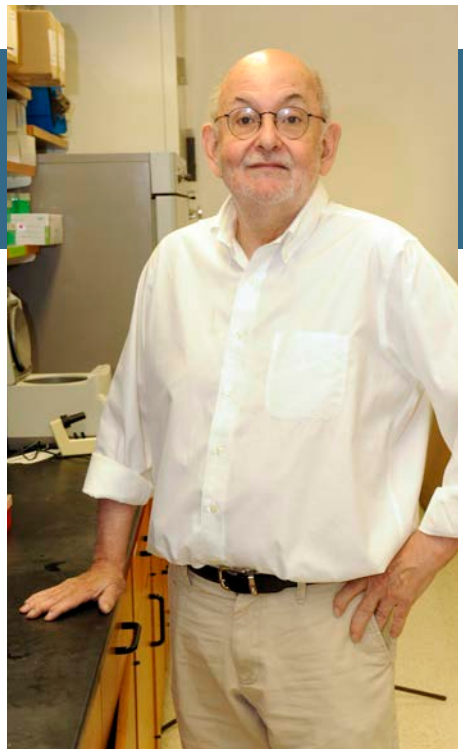
Wang, X., D. K. Shaw, O. S. Sakhon, **G. A. Snyder**, **E. J. Sundberg**, L. Santambrogio, F. S. Sutterwala, J. S. Dumler, K. A. Shirey, D. J. Perkins, K. Richard, A. C. Chagas, E. Calvo, J. Kopecky, M. Kotsyfakis and J. H. Pedra (2016). "The Tick Protein Sialostatin L2 Binds to Annexin A2 and Inhibits NLRC4-Mediated Inflammasome Activation." *Infect Immun* 84(6): 1796-1805.

Xiang, D., Y. Yuan, **L. Chen**, X. Liu, C. Belani and **H. Cheng** (2015). "Niclosamide, an anti-helminthic molecule, downregulates the retroviral oncoprotein Tax and pro-survival Bcl-2 proteins in HTLV-1-transformed T lymphocytes." *Biochem Biophys Res Commun* 464(1): 221-228.

Zhan, C., C. Li, X. Wei, **W. Lu** and W. Lu (2015). "Toxins and derivatives in molecular pharmaceutics: Drug delivery and targeted therapy." *Adv Drug Deliv Rev* 90: 101-118.

Zhao, A., **W. Lu** and **E. de Leeuw** (2015). "Functional synergism of Human Defensin 5 and Human Defensin 6." *Biochem Biophys Res Commun* 467(4): 967-972.

Vaccine Research Division



George K. Lewis, PhD

The Division of Vaccine Research faculty, led by **George K. Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Professor of Microbiology and Immunology, is taking a multidisciplinary approach to developing and HIV-1 vaccine that includes expertise in molecular and cell biology, virology, immunology, and structural biology. The primary goal of the division is to solve four major problems confronting the development of an HIV-1 vaccine; identification of an immunogen that elicits cross-reactive protection, determining the mechanism of cross-reactive protection, increasing the persistence of protective antibody responses, and increasing vaccine efficacy by attenuating vaccine-elicited CD4+ T cell responses that provide increased targets for HIV-1 replication.

The first major problem, development of an immunogen that elicits cross-reactive protection is being pursued via a conformationally constrained vaccine comprised of gp120 linked to the first two domains of CD4 by a flexible peptide spacer that elicits cross-protective immunity against model AIDS viruses in animal models. This immunogen is denoted as the full-length single chain (FLSC) protein. Anthony DeVico, PhD, Professor of Medicine, and his 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, led by Dr. Lewis, 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. DeVico, Tim Fouts, PhD, (Profectus Biosciences),. Robert Gallo, MD, The Homer and Martha Gudelsky Distinguished Professor in Medicine and Dr. 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. 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 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 Robert Redfield, MD, The Robert C. Gallo, MD Endowed Professorships in Translational Medicine, Co-founder, Associate Director, Director, Division of Clinical Care and Research. The Phase I clinical trial also involves Drs. DeVico, Gallo, and Lewis of the Division of Vaccine Research, Bruce Gilliam, MD, Associate Professor of Medicine, Division of Clinical Care and Research, and Dr. Fouts at Profectus Biosciences. Dr. Gilliam is the protocol chair of the Phase I clinical trial. 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 in nearly 20 years.

George Lewis, PhD and Marzena Pazgier, PhD

(L-R): Maria Luisa Visciano, PhD; Robin Flinko; Chiara Orlandi, PhD; William Tolbert, PhD; Anthony DeVico, PhD; George Lewis, PhD; Krishanu Ray, PhD; Marzena Pazgier, PhD; and, Parul Agrawal, PhD

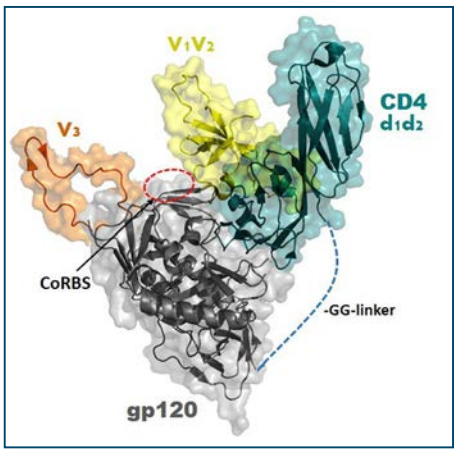
The second major problem, determining the mechanism of cross-reactive protection, is based on the identification of antibody-mediated correlates of protection in animal models immunized with FLSC and challenged with model AIDS viruses. Surprisingly, we found that protection correlates largely with Fc-mediated effector function and not virus neutralization, although passive immunization studies show that neutralizing antibodies can protect in these model systems. This collaboration includes Dr. DeVico, Roberta Kamin-Lewis, PhD, Associate Professor of Microbiology and Immunology, Dr. Lewis, Marzena Pazgier, PhD, Assistant Professor, of Biochemistry and Molecular Biology, Krishanu Ray, PhD, Associate Professor of Biochemistry and Molecular Biology and Mohammad Sajadi, Associate Professor of Medicine, Division of Basic Science. This work was supported initially by a grant from The Bill and Melinda Gates Foundation as well as two R01 grants to Dr. Lewis. More recently, the work is supported by a new collaborative P01 grant with investigators at Duke University, Harvard University, Dartmouth University, Northwestern University, and the University of Pennsylvania. Drs. DeVico, Lewis, Pazgier, and Ray are focusing on physicochemical and cell biology of Fc-mediated effector function for this program. These efforts are also new R01 grants awarded to Drs. Marzena Pazgier and Ray as well as by a R01 and VA Merit Award to Dr. Sajadi.

To determine the mechanism of cross-reactive protection, 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

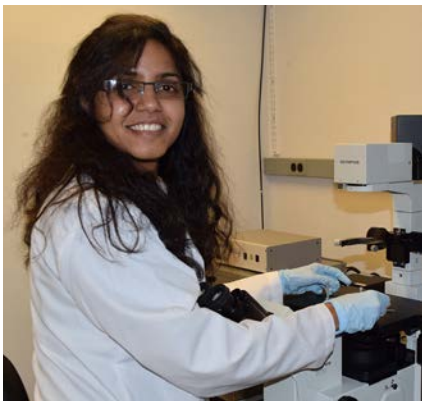
Dr. DeVico's group has developed new tools to characterize target epitopes on free virions, virions entering target cells, and virions budding from infected cells for each type of mAb. This work is leading to an increasingly clear picture of temporal epitope exposure during different phases of the viral 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



Full Length Single Chain



Parul Agrawal, PhD

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 R01 grant and the collaborative P01 grant.

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 R01 and the collaborative P01 grant.

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.

The third and fourth major problems, increasing the persistence of protective antibody responses, and increasing vaccine efficacy by attenuating vaccine-elicited CD4+ T cell responses that provide increased targets for HIV-1 replication, are being pursued via a new P01 grant awarded recently to the IHV. This program is led by Dr. Gallo and includes Drs. DeVico, Lewis, Pazgier, and Wuyuan Lu, PhD, Professor of Biochemistry and Molecular Biology, Co-director, Division of Basic Science, as well as Guido Silvestri, MD at Emory University and Warner Greene, MD, PhD at University of California San Francisco. The program will investigate the cellular and molecular mechanisms underlying poor antibody persistence using the FLSC immunogen in animal models. It will also identify the vaccine elicited CD4+ T cell subsets that compromise antibody-mediated protection against model AIDS viruses in animal models. Both studies will build upon recent studies suggesting that the innate immune environment is altered by HIV-1 exposure and favors infection, which can possibly compromise vaccine efficacy.

Vaccine Research Publications

Chen X, **Gohain N**, Zhan C, Lu WY, **Pazgier M**, Lu W (2016) Structural basis of how stress-induced MDMX phosphorylation activates p53. *Oncogene*, 35(15):1919-25.

Christensen-Quick A, Lafferty M, Sun L, Marchionni L, **DeVico A, Garzino-Demo A.** Human Th17 Cells Lack HIV-Inhibitory RNases and Are Highly Permissive to Productive HIV Infection. *Journal of virology*.2016;90:7833-7847.

DeVico AL, Lewis GK, Gallo RC. Modulating the durability of anti-HIV gp120 antibody responses after vaccination: a comment on Wilson & Karp (2015). Philosophical transactions of the Royal Society of London Series B, *Biological sciences*.2015;370.

Ding S, **Tolbert WD**, Prévost J, Pacheco B, Coutu M, Debbeche O, Xiang SH, **Pazgier M**, Finzi A (2016) A Highly Conserved gp120 Inner Domain Residue Modulates Env Conformation and Trimer Stability, *J Virol*: 90(19):8395-409

Ding S, Veillette M, Coutu M, Prévost J, Scharf L, Bjorkman PJ, Ferrari G, Robinson JE, Stürzel C, Hahn BH, Sauter D, Kirchhoff F, **Lewis GK**, **Pazgier M**, Finzi A (2015) A Highly Conserved Residue of the HIV-1 gp120 Inner Domain Is Important for Antibody-Dependent Cellular Cytotoxicity Responses Mediated by Anti-cluster A Antibodies, *J Virol.*: 90(4):2127-34

Fouts TR, et al. Balance of cellular and humoral immunity determines the level of protection by HIV vaccines in rhesus macaque models of HIV infection. *Proc Natl Acad Sci U S A*.2015.

Gallo RC. Developing a Successful HIV Vaccine. J Infect Dis. 2015 Jul 15;212 Suppl 1:S40-1. doi: 10.1093/infdis/jiv069. PubMed PMID: 26116730; *PubMed Central PMCID:* PMC4574549.

Gohain N, Tolbert WD, Acharya P, Yu L, Liu T, Zhao P, **Orlandi C**, **Visciano ML**, **Kamin-Lewis R**, **Sajadi MM**, Martin L, Robinson JE, Kwong PD, **DeVico AL**, **Ray K**, **Lewis GK**, **Pazgier M** (2015) Cocrystal Structures of Antibody N60-i3 and Antibody JR4 in Complex with gp120 Define More Cluster A Epitopes Involved in Effective Antibody-Dependent Effector Function against HIV-1, *J Virol*: 1;89(17):8840-54.

Gohain N, Tolbert WD, **Orlandi Ch**, Richard J , Ding S, Chen X, Bonsor DA, Sundberg EJ, Lu W, **Ray K**, Finzi A, **Lewis GK**, **Pazgier M** (2016) Molecular basis for epitope recognition by non-neutralizing anti-gp41 antibody F240, *Scientific reports*, Nov 9;6:36685. doi: 10.1038/srep36685

Kaplan G, Roitburd-Berman A, **Lewis GK**, Gershoni JM. Range of CD4-Bound Conformations of HIV-1 gp120, as Defined Using Conditional CD4-Induced Antibodies. *Journal of virology*.2016;90:4481-4493.

Khattar SK, **DeVico AL**, LaBranche CC, Panda A, Montefiori DC, Samal SK. Enhanced Immune Responses to HIV-1 Envelope Elicited by a Vaccine Regimen Consisting of Priming with Newcastle Disease Virus Expressing HIV gp160 and Boosting with gp120 and SOSIP gp140 Proteins. *Journal of virology*.2016;90:1682-1686.

Latinovic OS, et al. Synergistic Inhibition of R5 HIV-1 by the Fusion Protein (FLSC) IgG1 Fc and Maraviroc in Primary Cells: Implications for Prevention and Treatment. Current *HIV research*.2016;14:24-36.

Latinovic OS, Medina-Moreno S, Schneider K, **Gohain N**, Zapata J, **Pazgier M**, Reitz M, Bryant J, Redfield RR (2016) Full Length Single Chain Fc Protein (FLSC IgG1) as a Potent Antiviral Therapy Candidate: Implications for In Vivo Studies, *AIDS Res Hum Retroviruses*: 32(2):178-86

Lewis GK, **Pazgier M**, Evans D, Ferrari G, Bournazos S, Parsons MS, Bernard NF, Finzi A (2016) Beyond Viral Neutralization, *AIDS Res Hum Retroviruses* 2017 Jan 13. doi: 10.1089/AID.2016.0299

Lewis G, **Pazgier M**, **DeVico A** (2016) Survivor's Remorse: Antibody-Mediated Protection Against HIV-1; *Immunological reviews*, in press

Lewis GK, Finzi A, **DeVico AL**, **Pazgier M** (2015) Conformational Masking and Receptor-Dependent Unmasking of Highly Conserved Env Epitopes Recognized by Non-Neutralizing Antibodies That Mediate Potent ADCC against HIV-1, *Viruses*: 18;7(9):5115-32.

Lewis GK. The first 24 h: targeting the window of opportunity for antibody-mediated protection against HIV-1 transmission. Current opinion in *HIV and AIDS*.2016.

Mengistu M, Ray K, **Lewis GK, DeVico AL**. Antigenic properties of the human immunodeficiency virus envelope glycoprotein gp120 on virions bound to target cells. *PLoS pathogens*.2015;11:e1004772.

Prahl A, **Pazgier M**, Alexandratos J, Lubkowski J (2016) Human β-defensin 4 – defensin without the "twist", *Advances in Biochemistry*: 62 (3)

Schmaljohn A, Lewis GK. Cell-targeting antibodies in immunity to Ebola. *Pathogens and disease*.2016;74:ftw021.

Richard J, Pacheco B, Gohain N, Veillette M, Ding S, Alsahafi N, **Tolbert WD**, Prévost J, Chapleau J-P, Coutu M, Jia M, Brassard N, Park J, Courter JR, Melillo B, Martin L, Tremblay C, Hahn BHi, Kaufmanna DE, Wu X, Smith III AS, Sodroski J, **Pazgier M**, Finzi A (2016) Co-receptor Binding Site Antibodies Enable CD4-Mimetics to Expose Conserved Anti-cluster A ADCC Epitopes on HIV-1 Envelope Glycoproteins, *EBioMedicine*:S2352-3964(16)30412-1

Sajadi MM, Farshidpour M, Brown EP, Ouyang X, Seaman MS, **Pazgier M**, Ackerman ME, Robinson H, Tomaras G, Parsons MS, Charurat M, **DeVico AL**, Redfield RR, **Lewis GK** (2016) Lambda light chain bias associated with enhanced binding and function of anti-HIV Env glycoprotein antibodies, *J Infect Dis:* 213(1):156-64.

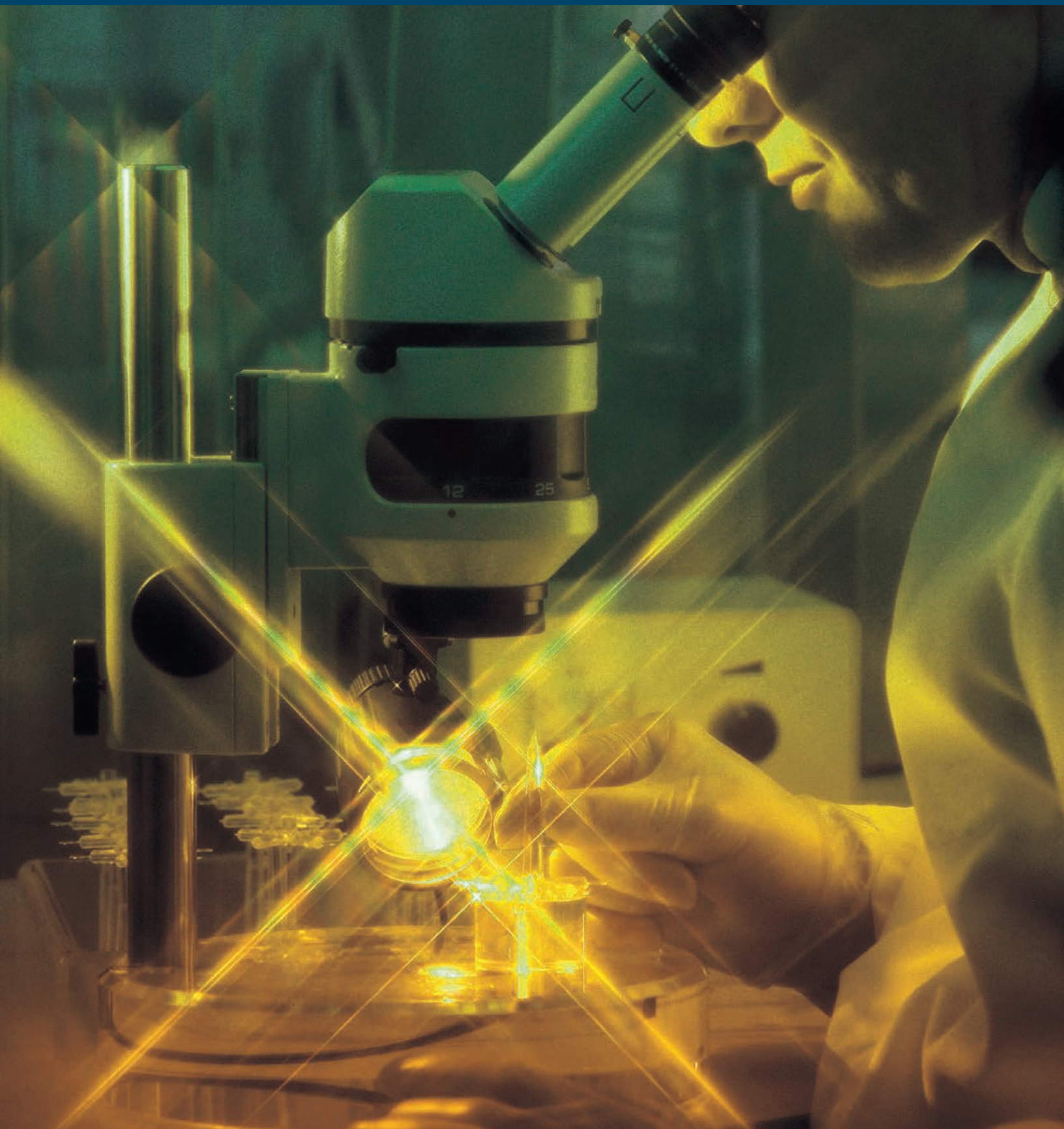
Schwartz JA, et al. An HIV gp120-CD4 Immunogen Does Not Elicit Autoimmune Antibody Responses in Cynomolgus Macaques. *Clinical and vaccine immunology* : CVI.2016;23:618-627.

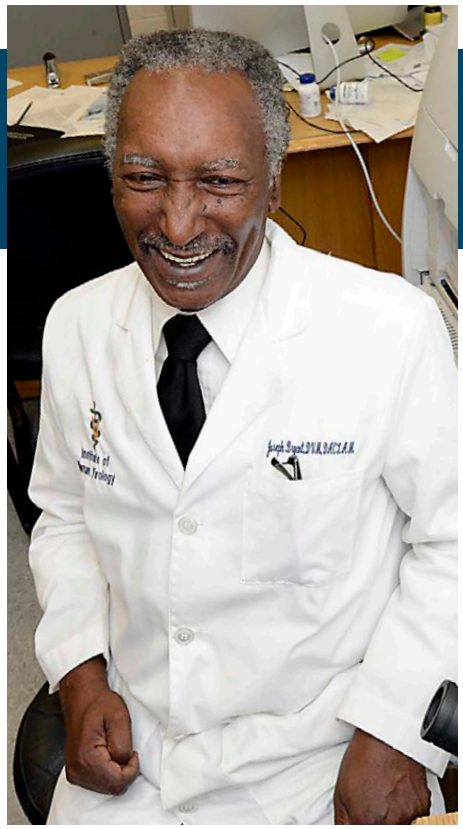
Shen X, et al. Vaccine-Induced Linear Epitope-Specific Antibodies to Simian Immunodeficiency Virus SIVmac239 Envelope Are Distinct from Those Induced to the Human Immunodeficiency Virus Type 1 Envelope in Nonhuman Primates. *Journal of virology*.2015;89:8643-8650.

Tolbert WD, **Gohain N**, Veillette M, Chapleau J-P, **Orlandi Ch**, **Visciano ML**, Ebadi T, **DeVico T**, Fouts TR, Finzi A, **Lewis G**, **Pazgier M** (2016) Paring down HIV-1 Env: Design and Structure of an Independent Inner Domain of gp120 that Stably Expresses the A32 Epitope Sub-region of ADCC Epitope Cluster A, *Structure*: 24(5):697-709

Veillette M, Richard J, **Pazgier M**, **Lewis G**, Parsons MS, Finzi A (2016) Role of HIV-1 envelope glycoproteins conformation and accessory proteins on ADCC responses, *Curr HIV Res*: 14(1):9-23

Animal Models Division





Joseph Bryant, DVM

The Animal Models Division, led by **Joseph Bryant, DVM**, Associate Professor of Pathology, Director of the Animal Models Division and Director of the Animal Core Facility, is in its 20th year as one of the five Divisions established by the Director for the purpose of developing animal models as it relates to HIV/AIDS and AIDS-associated diseases. The Animal Core is managed by Mr. Harry Davis who has a staff of five animal care personnel. The Division currently has a staff of two veterinarians responsible for the veterinary care of all animals at the Institute as well as assisting investigators on various scientific endeavors. The Animal Core provides a rich environment for Investigators to conduct HIV and HIV-associated research, and is a state-of-the-art, well-staffed facility that strives to provide a safe, efficient, and cost effective environment for animal experimentation.

THE ANIMAL CORE FACILITY

The Animal Core Facility currently manages twenty animal use protocols for the Institute and the School of Medicine. These protocols include vaccine studies using non-human primates, therapeutic studies using immuno-deficient 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 renowned for its development of animal models, which include:

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 mouse model
5. The HIV-1 transgenic mouse model that develops a b-cell lymphoma similar to that seen AIDS-NHL
6. Humanized mouse models for HIV pathogenesis studies and for therapeutic studies.

The Core provides technical support and technical services. The Animal Core Facility is an Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accredited facility and is a part of the overall animal care and use program here at the medical school. We have over 20,000 square feet of space for housing rodents, primates, and other species if requested.

Collaborative efforts between the Division of Basic Science and Division of Animal Models include the development of Animal Models

Projects include:

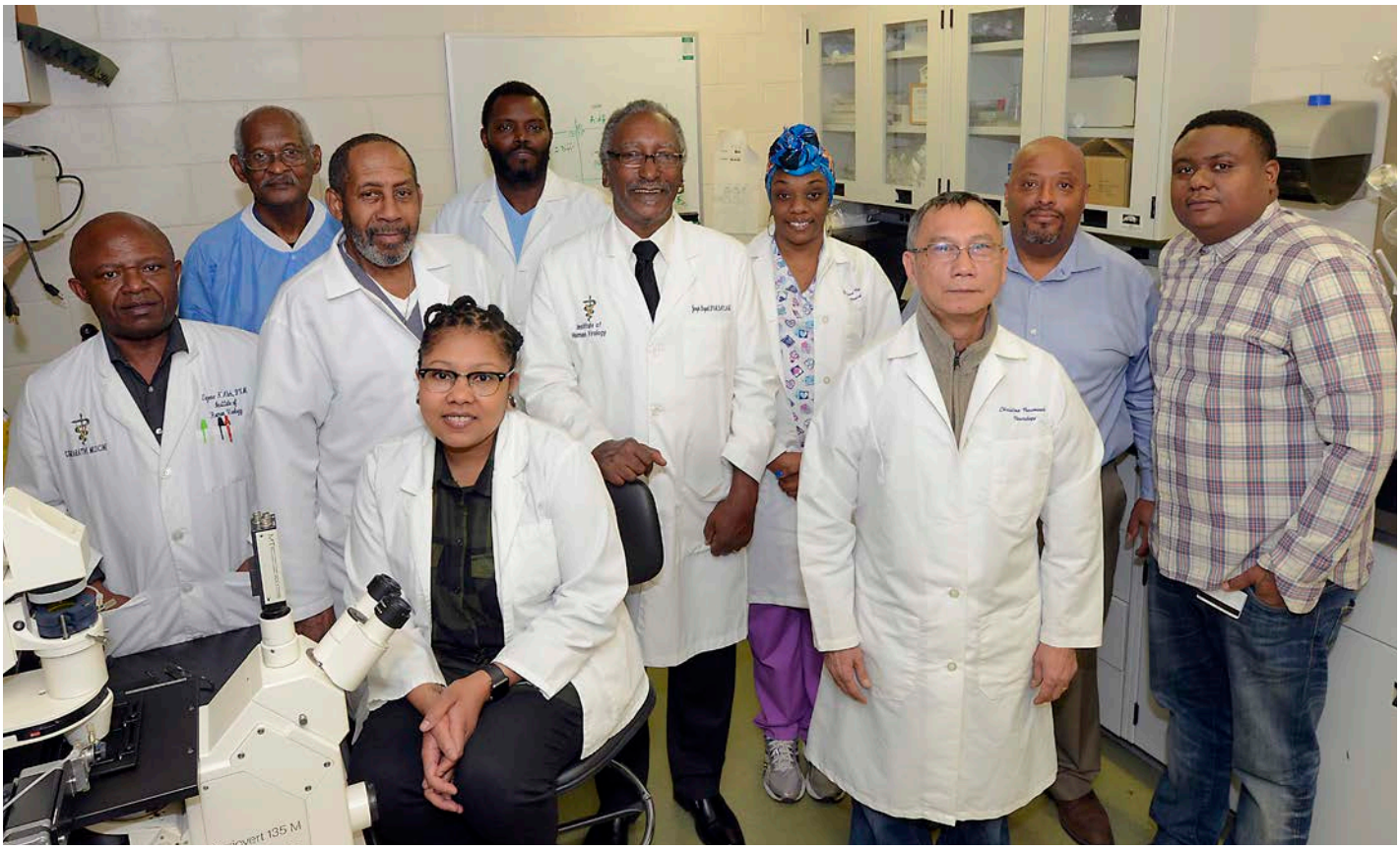
HIV/AIDS Non-Hodgkin Lymphomas

- Pathogenesis Studies
- Development of Animal Models for AIDS/NHL
- HIV-1 matrix protein p17 implicated in virally associated lymphomas
- Mycoplasma and Cancer

Collaborators in the Division of Basic Science

Include:

- **Robert Gallo, MD,** The Homer & Martha Gudelsky Distinguished Professor in Medicine and IHV Director, Divisions of Basic Science and Vaccine Research
- **Davide Zella, PhD,** Assistant Professor of Biochemistry and Molecular Biology, Division of Basic Science
- **Alfredo Garzino-Demo, PhD,** Associate Professor of Microbiology and Immunology, Division of Basic Science
- **Mika Popovic, PhD,** Adjunct Professor of Medicine, Division of Basic Science
- **Olga Latinovic, PhD,** Assistant Professor of Microbiology and Immunology, Division of Basic Science and Clinical Care and Research
- **Virginia Carroll, PhD,** Postdoctoral-fellow, Division of Basic Science
- **Sabrina Currelli, PhD,** Research Associate, Division of Basic Science
- **Fiorenza Cocchi, MD,** Assistant Professor of Medicine, Division of Basic Science
- **Francesca Benedetti, PhD,** Fellow, Division of Basic Science



(L-R): Eugen Ateh, DVM; Albert Hunter; Alfred Dye; Sumiko Williams; John Tripline; Joseph Bryant, DVM; Jabre Ross; Harry Davis; and, Hieu Tran

HIV-1 matrix protein p17 implicated in virally associated lymphomas

Recent studies by the **aforementioned members** of the Division of Basic Science, in collaboration with a team of Italian scientists led by **Arnaldo Caruso, MD, PhD** of University of Brescia Medical School, who is also an Adjunct Professor of Medicine in the Division of Basic Science, suggested 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. The TG26 transgenic mouse model developed in my Division provides a unique platform for the study of lymphoma that develops as a result of HIV-1 gene expression. The connection between HIV-1 p17 and dysregulation of the immune system are intriguing and need to be studied to understand the full consequences of HIV-1 infection. The TG26 mouse model provides unique opportunities for studying the pathogenic effects of HIV-1 gene expression in the absence of active viral replication.

Mycoplasma

Continuing the studies on the relationship between Mycoplasma and cancer, **Davide. Zella, PhD,** and **Robert Gallo, MD,** together with **Sabrina Currelli, PhD, Fiorenza Cocchi, MD, Joseph Bryant, DVM,** and **Francesca Benedetti, PhD,** 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 immune-deficient mice, these data further strengthen the possibility that Mycoplasma could play a role in the first steps of cellular transformation.

Collaborative efforts between the Division of Clinical Care and Research and the Division of Animal Models include the development of Animal Models

Projects include:

- **Alonso Heredia, PhD,** Assistant Professor of Medicine, Division of Clinical Care & Research
- **Olga Latinovic, PhD,** Assistant Professor of Medicine, Division of Clinical Care & Research

Evaluating Treatment with CCR5

Alonso Heredia, PhD and **Olga Latinovic, PhD** is evaluating treatment with a CCR5 antagonist to slow tumor progression in HIV transgenic mice with early states of tobacco-induced non-small cell lung cancer. The Division of Animal Models has recently developed a mouse model for the study of lung cancer in the setting of HIV infection. The mouse model may allow the evaluation of novel treatments for patients with HIV and lung cancer.

Humanized Mice for HIV Studies

Since the **Division of Vaccine Research** developed the Full Length Single Chain Fc protein (FLSC 1IgG1), **Drs. Heredia**

and **Latinovic** are researching this protein as a potent antiviral therapy candidate by identifying implications for in vivo studies in humanized mice.

Other Collaborative efforts with the Animal Models Division

Projects include:

- **Henry Lowe, PhD,** IHV Adjunct Professor of Medicine, Division of Basic Science
- **Walter Royal, MD,** Professor, Department of Neurology
- **Tapas Makar, PhD,** Adjunct Assistant Professor, Department of Neurology
- **Trevor Castor, PhD,** President & Chief Executive Officer at Aphois Corporation

Development of Natural Plants as Anti-Cancer Drugs

Henry Lowe, PhD, IHV Adjunct Professor of Medicine, PhD, Division of Basic Science, from Jamaica is collaborating with the Animal Models Division on a flavonoid from Tillandsia recurvate showing potent anticancer activity against AIDS-defining and non-AIDS defining cancers. The Division's collaborative research has focused on drug discovery from plants resulting in the recent isolation of a very potent anticancer flavonoid (HLBT-1001) from the Jamaican Ball moss (Tillandsia recurvata). HLBT-001 has demonstrated activity in-vitro against ADCs (non-Hodgkin's lymphoma and Kaposi sarcoma) as well as in Non-AIDS Defining Cancers (breast, colon, Hodgkin's Lymphoma, Lung and prostate) with sub-micromolar IC50 concentrations. 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 use of the HIV-1 Transgenic Rat Model Neurological Studies

Walter Royal, MD, Professor in the Department of Neurology at the University of Maryland School of Medicine, is utilizing the HIV-1 transgenic rat model to study the in vivo effects of nicotinamide adenine dinucleotide (NAD) associated in suppressing nervous system inflammation and other neuropathological abnormalities mediated by HIV-1 infection. For these studies, the Division will utilize two transgenic rat models of HIV-1 infection, including a well-established model developed on a wild-type F334 Fisher rat background (the HIV1TgNu+rat), which provides a model of HIV infection in the presence of severe immunodeficiency.

Molecular Studies in the HIV-1 Transgenic Mouse with PCNS Lymphoma

Tapas Makar, PhD, Adjunct Assistant Professor in the Department of Neurology at the University of Maryland School of Medicine, is collaborating with the Division to study HIV primary central nervous system lymphoma (PCNSL) as a malignant diffuse large B cell lymphoma that occurs in 3-5% HIV patients. Animal models have been critical in making progress in understanding of HIV PCNSL pathogenesis and investigating potential therapeutic strategies. The HIV-1 Tg26 mouse model develops PCNSL similar to what is seen in HIV PCNSL. The Division has evaluated the HIV1 Tg mouse model at the molecular level.

Purging Latent AHIV Reservoirs through a Combination HIV Therapeutic

Trevor Castor, PhD, President & Chief Executive Officer at Aphois Corporation. Although combined antiretroviral therapy (cART – combined Antiretroviral Therapy) successfully decreases plasma viremia to undetectable levels, the complete eradication of human immunodeficiency virus type 1 (HIV-1) remains impractical because of the existence of a viral reservoir, mainly in resting memory CD4+ T cells. Various cytokines, protein kinase C (PKC) activators, and histone deacetylase inhibitors (HDACi) have been used as latency-reversing agents (LRAs – Latency Reversing Agents) but their unacceptable side effects or low efficiencies limit their clinical use. Current antiretroviral regimens suppress HIV replication but do not eliminate the virus. Trevor Castor, PhD, President and Chief Executive Officer at Aphois Corporation, is proposing this protocol as a combination therapy approach to activate latent HIV and eliminate the virus reservoirs. Nanosomes delivery can be used to treat animal diseases similar to the ones seen in humans. The animal studies using humanized mouse models are being performed in the Animal Core.

Animal Models Publications

Latinovic OS, Medina-Moreno S, Schneider K, Gohain N, Zapata J, Pazgier M, Reitz M. **Bryant J**, Redfield RR. Full Length Single Chain Fc Protein (FLSC lgG1) as a Potent Antiviral therapy Candidate: Implications for Ain Vivo Studies. *AIDS Res Hum Retroviruses* 2016 Feb; 32(2): 178-86.

Lattova E, **Bryant J**, Skrickova J, Zdrahal Z, Popovic M. Efficient Procedure for N-Glycan Analyses and Detection of Endo H-Like Activity in Human Tumor Specimens. *J Proteome Res*. 2016 Aug 5; 15(8):2777-86.

Basta D. Latinovic O, Lafferty MK, Sun L, **Bryant J**, Lu W, Caccuri F, Caruso A, Gallo R, Garzino-Demo A. Angiogenic, lymphangiogenic and adipogenic effects of HIV-1 matrix protein p17. *Pathog Dis*. 2015 Nov; 73(8):ftv062.

Kawabats S, Heredia A, Gills J, Redfield RR, Dennis PA, **Bryant J**. Impact of HIV on lung tumorigenesis in animal model. *AIDS* 2015 Mar 13;29(a5):633-5.

Mary R. Hannaman, Douglas A. Fitts, Rose M. Doss, David E. Weimstein, **Joseph L. Bryant**. The refined biomimetic NeuroDigm Gel Model of neuropathic pain in a mature rat. F1000 *Research*. Oct., 2016, 5:2516

Clinical Care and Research Division

Robert Redfield, MD

The Division of Clinical Care and Research, led by **Robert Redfield, MD,** Robert C. Gallo, MD Endowed Professorship in Translational Medicine, Co-founder, Associate Director, Director, Division of Clinical Care and Research, continues to strengthen all three of its interrelated programs of clinical care, clinical research, and medical education, both in the Baltimore and Washington metropolitan areas, and globally. This year, the Division has expanded its Baltimore based ambulatory clinical programs in the management and prevention of HIV infection, and treatment of patients with hepatitis B and C infection under the leadership of Bruce Gilliam, MD, Professor of Medicine and Director of the Center for Infectious Diseases. The Division has significantly increased its clinical trial activity under the leadership of Shyam Kottilil, MBBS, PhD, Professor of Medicine, Co-Director of the Clinical Research Unit and Associate Director for Clinical Research, especially in the area of Hepatitis C therapeutics. Finally, under the leadership of Deus Mubangizi, DrPhD, MPH, MBA, Assistant Professor of Medicine and Director of the Center for International Health, Education and Biosecurity, the Division's global health programs continue to secure significant new funding and expand the Institute of Human Virology's impact worldwide.

CLINICAL PROGRAM

To accommodate our expanding ambulatory practice, the Institute of Human Virology and the University of Maryland, Division of Infectious Diseases are merging their outpatient clinical programs into one location at 300 Armory Place on the UMMC Midtown Campus. Our new program will now be known as the University of Maryland Institute of Human Virology Center for Infectious Diseases (IHV CID). The University of Maryland Midtown Campus now serves as the major hub of the Institute of Human Virology's clinical program that allows for synergy between all of its programs and services. The vision for the IHV CID is to serve as the leading center for viral disease and infectious disease treatment, both locally and globally. We strive to ensure access to clinical care, reduce health disparities and stigma, and improve the quality of life for individuals and communities impacted by HIV, Hepatitis B, Hepatitis C, and other infectious diseases. We envision the care delivery model IHV developed in the JACQUES Initiative to be a best practice for caring for individuals with chronic medical illnesses in Baltimore and beyond, which is fully embraced in the expanded IHV CID.

The IHV CID will offer HIV primary medical care, Hepatitis C treatment, special programs targeting HPV infections in patients living with HIV, and general infectious diseases consultation and care. The IHV CID also provides case management, housing assistance, substance abuse treatment, women's health, anal health, HIV prevention through pharmaceutical intervention (including pre-exposure prophylaxis), adolescent transitional care coordination and treatment adherence, nutrition counseling, mental health treatment, and legal and other support services. The unique strengths and resources of all of the IHV's clinical programs are woven upon a shared institutional philosophy of excellence in HIV care, creating a comprehensive, integrated, and innovative model of care delivery. The IHV CID will therefore remain closely linked with the JACQUES Community Outreach Program and the JACQUES Treatment Adherence Center in order to provide supportive, caring services to those most in need.

The IHV Clinic at Midtown and the ID clinic were already located together in 300 Armory Place on the Midtown campus. In July 2016, the JACQUES Initiative Clinic joined these 2 clinics on the Midtown campus. The CID merger will be complete with the move of the Evelyn Jordan Center and the JACQUES Treatment Adherence Center later this year. The new, easily accessible location provides more space for the IHV CID to enhance and expand its already comprehensive services. The IHV CID is open 5 days a week and has the capability to accommodate same day appointments. The University of Maryland Institute of Human Virology Center for Infectious Diseases can be reached at 410-225-8369.

Photo left: A City Uprising event led by IHV's JACQUES Initiative, a program aimed at testing and linkage to care, engages youth of Baltimore City including this young participant pictured with the JACQUES Initiative's Kithia Gray in the event's social media photo booth

Establishment of HIV Pre-exposure Prophylaxis (PreP) Clinic

Also of note, this year the JACQUES program was awarded a 3-year, approximately $1 million grant from the Centers for Disease Control and Prevention to serve as one of 10 Baltimore City Health Department (BCHD) partners in a city-wide demonstration project to implement and evaluate the use of pre-exposure prophylaxis (PrEP) for prevention of HIV transmission in transgender women and young black men who have sex with men. Additionally, this project aims to develop a 'care collaborative' between BCHD, the State of Maryland's Department of Health and Mental Hygiene, local medical clinics, and community partners Patrick Ryscavage, MD, Assistant Professor of Medicine, and Sarah Schmalzle, Assistant Professor of Medicine, are key faculty investigators; Marie Bailey-Kloch, MSW, and Kinicki Hughes have joined the team as Program Manager and Peer Navigator, respectively; and Jeff Weaver, PA is the primary provider in our Partners in Prevention clinic, where PrEP is offered. The JACQUES program namesake, Joe Jacques would be proud of the IHV's JACQUES program's continued commitment to impact of the lives of both those with HIV infection and people presently at risk.

IHV Washington Based Clinical Programs

Since Dr. Kottilil's recruitment to the IHV, our clinical program has expanded to involve Washington, DC. To date, over 8,000 patients with HIV infection, and over 4,000 patients with HCV have been linked to care in one of the IHV supported DC clinics. Sarah Kattakuzhy, MD, Assistant Professor of Medicine, and Elana Rosenthal, MD, Assistant Professor of Medicine, continue to provide the day to day leadership and clinical management, guided by Dr. Kottilil.

New Clinical Programs: Establishment of Clinical Programs in Chronic HBV Infection

During the past year the IHV Hepatitis B and C treatment programs continue to expand driven by Lydia Tang, MB, ChB, Associate Professor of Medicine, Eleanor Wilson, MD, Assistant Professor of Medicine, and Angie Price, NP, both at the Midtown and campus and the Baltimore Veterans Hospital, again guided by the leadership of Dr. Kottilil. Chronic hepatitis B infection in the Baltimore/District of Columbia metropolitan area is mainly defined by a patient population that is not yet engaged in clinical care due to socioeconomic background. The Institute of Human Virology has partnered with the Hepatitis B Initiative of Washington, D.C. (HBI-DC), and the Torture Abolition Survivors Support Coalition (TASSC). Over 5,700 people in the DC-metropolitan area have been screened by HBI-DC, with prevalence rates of 6.4% for hepatitis B. Those who tested positive are linked to care and subsequently referred for further evaluation and treatment. In collaboration, the IHV will establish a clinical program to screen, link, and treat patients with chronic hepatitis B infection and conduct research on immunopathogenesis of HBV persistence aimed to develop therapeutics targeting the cure of HBV chronic infection.

Members of IHV's JACQUES Initiative PreP team led by Patrick Ryscavage, MD (seated far left)

CLINICAL RESEARCH

Clinical Research Unit

The Institute of Human Virology (IHV) Clinical Research Unit (CRU) continues to expand under the leadership of Dr. Shyam Kottilil. The CRU has recently expanded with Jennifer Husson, MD, Assistant Professor of Medicine, and Joel Chua, MD, Assistant Professor of Medicine, joining the team. The multidisciplinary CRU team is comprised of two nurse practitioners, two nurse coordinators, a pharmacist, a regulatory specialist, four study/ research coordinators, and a laboratory technician. During the past year, the CRU has seen significant expansion in novel clinical trials (35 clinical trials, of which 15 are investigator initiated, and 20 are industry sponsored) in the management of viral hepatitis and HIV infections. The CRU aims to support the IHV's goal of advancing research in the field of chronic viral diseases

FLSC Vaccine Trial

Last year, Dr. Bruce Gilliam initiated a Phase 1 randomized, placebo-controlled, modified double-blinded clinical trial designed to evaluate the safety and immunogenicity of a HIV vaccine called FLSC (full length single chain) in healthy volunteers without HIV infection. The preventive FLSC vaccine, as developed by IHV scientists under the leadership of

Members of the newly formed IHV Center for Infectious Diseases led by Bruce Gilliam, MD (not pictured)

Robert Gallo, MD, The Homer & Martha Distinguished Professor in Medicine and Director of the IHV, George Lewis, PhD, The Robert C. Gallo, MD Endowed Professorship in Translation Medicine, Professor of Microbiology and Immunology, and Director of the Division of Vaccine Research, and Anthony DeVico, PhD, Professor of Medicine, and this trial represent true translational impact of IHV on meeting the needs of HIV-infected individuals. Healthy volunteers of 18-45 years of age, and those who have never previously participated in an HIV vaccine trial were immunized with the FLSC vaccine. (Funded by The Bill and Melinda Gates Foundation).

Hepatitis C Clinical Trial Program

Under Dr. Kottilil's leadership, there has been a rapid expansion of the clinical research program focused on novel, investigator initiated clinical trials. In the recent **SYNERGY** trial, they evaluated the impact of adding a third potent drug to LDV/SOF, and tested shortened durations of therapy of 6 weeks, with high cure rates (Kohli et al. The Lancet 2015). Subsequent arms of the SYNERGY study demonstrated limited efficacy of 3 or 4 drug combinations in treating HCV infection in 4 weeks, and modest efficacy of 3 drugs for six weeks (Kattakuzhy S. et al. Annals of Intern Med, Wilson E. et al. Clin Infect Dis 2015).

ASCEND Study

Despite the rapid development of highly effective therapy for hepatitis C, a major restriction of treatment expansion remains the lack of skilled community-based providers available to treat HCV infections. Dr. Sarah Kattakuzhy conducted the ASCEND trial in community clinics in DC. 92.1% of patients receiving care from specialists, 96.7% of patients receiving care from primary care physicians, and 94.9% of patients receiving care from nurse practitioners were cured. This research has the potential to be a genuine game changer for global hepatitis C therapy (funded by NIAID, Gilead Sciences Inc).

RESOLVE Trial

A major clinical dilemma confronting clinicians today is how to treat patients who fail DAA therapies. Dr. Eleanor Wilson sought to investigate the safety, tolerability, and efficacy of treatment with sofosbuvir velpatasvir and GS-9857 (second generation NS3/4A protease inhibitor) in HCV infected patients who have failed previous standard of care combination DAA therapies. This study is funded by Gilead Sciences, as an investigator initiated clinical trial.

Renal Transplant Merck Trial

Dr. Jennifer Husson and Anthony Amoroso, MD, Associate Professor of Medicine, instituted a clinic to manage hepatitis C and HIV in patients undergoing renal transplant. Subsequently, Dr. Husson was awarded an investigator initiated grant from Merck Inc to evaluate clinical and immunologic outcomes of treating HCV using Zepatier, before or after renal transplant.

STOP-CO Clinical Trial

Dr. Redfiled, Dr. Kottilil, and Rolf Barth, MD, Associate Professor of Surgery from the University of Maryland School of Medicine Department of Surgery, along with collaborators from NIH and University of California at San Francisco competed and won a novel U01 grant from the NIH to treat HIV/HCV co-infected patients with sofosbuvir and ledipasvir. This novel grant mechanism is to foster intramural-extramural collaborations, and the IHV team will conduct laboratory experiments to unravel mechanisms associated with HCV clearance.

Members of IHV's Clinical Research Unit led by Shyam Kottilil, MBBS, PhD (pictured first row, center)

MAVERIC

Dr. Lydia Tang is developing a cohort of HIV and HCV co-infected subjects who are being followed for progression of liver fibrosis in order to build upon our existing understanding of CCR5 antagonism in-vivo on the hepatitis C virus, and liver fibrosis. In this recently approved unique study, supported by ViiV Pharmaceuticals, she will augment the ART regimens of participants with maraviroc (CCR5 inhibitor) and follow them prospectively.

CEASE [Citywide Enhanced HIV/AIDS Surveillance and Epidemiology]

In response to the epidemic levels of HIV in Washington, DC and Baltimore, and the high risk of lifetime acquisition of HIV, Dr. Elana Rosenthal and Dr. Sarah Kattakuzhy are conducting the CEASE study, to determine factors associated with HIV acquisition. This NIH funded pilot study will demonstrate how molecular epidemiology can augment traditional surveillance methods to better characterize factors associated with HIV acquisition.

GRAVITY [Geomapping Resistance and Viral Transmission in Risky Populations]

The goal of GRAVITY is to identify newly acquired cases of HIV and HCV in high risk populations, and to better understand characteristics associated with viral transmission in Washington, DC. Drs. Rosenthal and Kattakuzhy have obtained NIH and Gilead Sciences funding to implement HIV and HCV screening programs in those who inject drugs, men who have sex with men, trans individuals, and sex workers.

ANCHOR [A Novel model of Hepatitis C Treatment to Prevent HIV, Initiate Opioid Substitution Therapy, and Reduce Risky Behavior]

ANCHOR will evaluate the efficacy of using HCV direct acting antiviral treatment as an anchor to engage people who inject drugs (PWID) in uptake of HIV prevention strategies including PrEP, opioid substitution therapy, and safer injection practices. This study is funded by a Gilead research grant for 200 courses of HCV therapy (Harvoni) and 200 courses of PrEP).

TIGER [The Initiative for immiGrant Engagement for Recognition of hepatitis B]

TIGER is an innovative project representing an academic—community collaboration between the Institute of Human Virology (IHV) and non-profit organizations. The objective is to enhance community-based hepatitis B, C, and HIV screening and linkage to care in the Baltimore-DC metropolitan area through outreach, education, and free testing.

HIV THERAPY AND ANTI-RETROVIRAL TRIALS

Tenofovir Alafenamide Study

Tenofovir Alafenamide (TAF) a pro drug of tenofovir was developed that has shown similar safety and efficacy to TDF in chronic hepatitis B patients. TOTAL is a study aimed at establishing a real life cohort of urban patients with chronic hepatitis B who will be initiated on TAF.

Hepatotoxicity of ART

In 2015, Dr. Kottilil, in collaboration with Dr. Kenneth E. Sherman from the University of Cincinnati, competed and won a R01 grant from NIAID for evaluating the mechanisms of antiretroviral therapy mediated hepatotoxicity.

Impact of CCR5 Blockade in HIV+ Kidney Transplant Recipients

Dr. Redfield recently won an U01 award from NIAID to use CCR5 blockade in kidney transplant patients to increase renal graft survival.

CLINICAL CARE AND RESEARCH DIVISION LABORATORY-BASED PROGRAMS

The Kottilil Laboratory

The Kottilil Laboratory has launched two targeted research programs: "A Functional Cure Approach to Chronic Hepatitis B infection" and "Hepatitis C Immunology Program". 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. Thus, new therapeutic modalities are needed to achieve eradication of the virus from chronically infected patients in the absence of therapy. The basis of HBV persistence includes viral and host factors. Our ongoing efforts focus on developing novel strategies to achieve sustained cure, or elimination of HBV. These novel approaches include targeting the viral, and or host, factors required for viral persistence, and novel immune-based therapies, including therapeutic vaccines. These efforts are led by Dr. Bhawna Poonia and Dr. Kottilil, and are focused on delineating intrahepatic and peripheral immune responses to HBV antigens that correlates with development of protective immunity. Three separate projects are presently funded by a Framework Research Agreement between Medimmune Inc and IHV, a research grant form Arbutus Pharmaceuticals, and a research grant from Gilead Sciences respectively.

Shyam Kottilil, MBBS, PhD and Angie Price, MSN

Alongside a very active Hepatitis C clinical trial 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. His group recently demonstrated that enhancement of intrahepatic type I interferon expression in patients achieves SVR with DAA therapy. 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, and Bhawna Poonia, PhD, Assistant Professor of Medicine, continue their investigations into determinants of SVR with short duration DAA therapy. Ongoing follow up of a large cohort of patients, Drs. Kottilil and Poonia continue to evaluate the persistence of adaptive immune responses to HCV in patients who achieve SVR, in order to determine long term protection for reinfection in patients with continued high risk behavior. These projects are funded by an investigator initiated clinical research study by Gilead Sciences.

The Redfield Laboratory

In the current era of combined ART patients with HIV are living longer, but increasingly often they necessitate treatment for comorbidities, such as cancer. For example, lung cancer is a major cause of cancer death in patients with HIV. The Redfield Lab continues to explore key host cell pathways as potential therapeutic targets which may help control both HIV and malignancy. One cellular target we are actively investigating is the mammalian target of rapamycin (mTOR), a conserved cellular serine/threonine kinase that forms two complexes in cells, mTORC1, and mTORC2. Recently, the lab has extended this work showing that the mTOR1/mTOR 2 inhibitor (INK128) demonstrated antiviral 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). We are currently evaluating the activity of mTORC-1/2 inhibitors against cancer because the mTOR pathway is often upregulated in cancers common in HIV patients, such as cancers of lung and liver. Our preliminary studies demonstrate that targeting of mTORC-1/2 inhibits the growth of lung cancer and hepatocellular carcinoma tumor xenografts in mice, suggesting these agents may help control both HIV and comorbid cancers in the HIV population.

Another area of active investigation is the targeting of cellular Cyclin-dependent kinase (CDK-9), a cofactor of the HIV Tat protein. We have previously demonstrated that the pharmacological inhibition of CDK9 with Indirubin 3'-monoxime (IM) inhibits HIV transcription in vitro. Our current studies demonstrate that IM inhibits HIV replication in humanized mice, both during acute and chronic infection. Because CDK9 can be dysregulated in cancer cells, we are also pursuing targeting of CDK9 as a potential therapy against both HIV and cancer. We believe that targeting of

Robert R. Redfield, MD and patient

host factors important for HIV replication and for rapid growth of tumor cells may provide novel therapies against both diseases in the growing population of HIV patients with cancer.

The Redfield lab also continues to focus on additional strategies to target CCR5. Earlier work demonstrated that G1 cell cycle agents reduced CCR5 cellular expression, and enhanced antiviral activity of other HIV entry inhibitors to include of a novel molecule development by the Basic Science Division, known as the Full Length Single Chain (FLSC) fusion molecule of a portion of human CD4 and HIV envelope gp120.

Dr. Redfield's lab also continues to investigate potential strategies to overcome resistance to antiretroviral drugs which are critical to ongoing global antiretroviral treatment programs. These include active investigation is to target important pathways in nucleotide biosynthesis and cell cycle. Earlier work demonstrated that a prototype S phase agent Resveratrol and its derivatives enhanced the antiviral activity of nucleotide analogs. Recent work extended these observations "to restore" susceptibility to multi-drug resistant HIV isolates in vitro, as well as in the humanized mouse model. This offers a potential strategy, if resistance to first line antiretroviral therapy in the future becomes a problem limiting the treatment efficacy.

Sajadi Laboratory

Mohammad Sajadi, MD, Associate Professor of Medicine, oversees the NVS cohort, HIV-1 infected individuals who control infection without antiretrovirals. Dr. 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 Drs. George Lewis and Anthony DeVico in the Vaccine Research Division. He has two active grants, an NIH R01 titled, "Discovery of acidic epitopes for HIV-1 broadly neutralizing seroantibodies," and a VA Merit Award titled, "Discovery of acidic epitopes for HIV-1 broadly neutralizing seroantibodies." Dr. Sajadi has developed a novel method to sequence antibodies directly from blood, and is using this technique to study the circulating antibodies that constitute the broad neutralization response in rare individuals with HIV.

Stamatos Laboratory

Nicholas Stamatos, MD, Assistant Professor of Medicine, focused on understanding how modulation of the carbohydrate content of cell surface proteins influences the functional capacity of cells of the immune system. His laboratory continues to study how changes in the polysialic acid (polySia) content of specific cell surface glycoconjugates on monocytes and monocyte-derived dendritic cells and macrophages influences the immune capacity of these cells.

Recently his lab has shown that loss of polySia by peritoneal macrophages enhances phagocytosis of Klebsiella pneumoniae and promotes dendritic cell-induced lymphocyte activation. Current experiments are testing the hypothesis that regulated expression of polysialylated proteins on monocytes, as they differentiate into macrophages and dendritic cells helps direct cell homing, and a well-orchestrated immune response during pulmonary infection with bacterial pathogens.

Dr. Stamatos has previously demonstrated that removal of sialic acid from the surface of peripheral blood mononuclear cells using an exogenous bacterial neuraminidase promoted infection with HIV-1. He hypothesizes that the upregulated sialidase activity in activated lymphocytes is partly responsible for enhanced infection of these cells, and thus, is a potential target for inhibiting infection. In contrast to this work on monomeric sialic acid, we have also found that removal of polySia from a specific protein on the surface of lymphocytes, or in the extracellular milieu markedly inhibits infection. The results from our studies are expected to identify a novel target for treatment of HIV infection and provide a blueprint for down-regulating the expression of polySia or modified protein(s) in activated lymphocytes, as well as in other cells susceptible to infection with HIV-1.

DIVISION OF CLINICAL CARE AND RESEARCH'S CENTER FOR INTERNATIONAL HEALTH, EDUCATION & BIOSECURITY (CIHEB)

Improving Individual Health Outcomes to Impact Population Health

Deus Mubangizi, DrPH, MBA, MPH

The Division of Clinical Care and Research's Center for International Health, Education & Biosecurity continued to prosper under the leadership of Dr. Deus Bazira Mubangizi. Initially this program began as part of the President's Emergency Program for AIDS Relief (PEPFAR), impacting 10 countries in Africa and the Caribbean. Post-PEPFAR, the Global Health and Biosecurity program continues to deliver significant global impact with on-going projects and activities centered on seven countries: Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania, and Zambia. The program continues to provide a wide range of products and services within these resource constrained settings encompassing training and workforce development, capacity building for health services delivery, strengthening of major public health institutions, implementation science, clinical and epidemiological research, and most recently, biosecurity and bio surveillance. In the area of biosecurity, the program significantly scaled up activities under the project "Strengthening Epidemic Response Systems" in Nigeria. This $10 million award, being implemented with the Centers for Disease Control and Prevention under the first phase of the Global Health Security Agenda, aims to enhance systems for monitoring, reporting, and rapidly responding to emerging diseases of global significance, including virally transmitted infections like Ebola, Lassa Fever, and Zika. In the area of global research, internal IHV collaborations between the Divisions of Clinical Care and Research and the Division of Epidemiology enhanced information sharing and cross cutting utilization of research knowledge from clinical and epidemiological studies.

Improving microscopy to support TB management services in Kenya - International Work

The Global Health and Biosecurity program continued to play important roles in strengthening the institutional capacity of National Public Health Laboratories in Haiti and Kenya, and the GHI provided technical assistance for enhanced health service delivery at over 285 facilities in seven countries.

In September 2015, we completed the GHI led Partnership for Advanced Clinical Education (PACE), a six year project implemented in Kenya in collaboration with the Centers for Disease Control and Prevention, the Kenya Ministry of Health, the University of Nairobi, and 6 other national and regional universities and teaching hospitals. PACE has had a tremendous impact on clinical training at pre-service levels, and the enhancement of training faculty capacity in Kenya. PACE succeeded in harmonizing disparate curricula for HIV and infectious diseases into one practice oriented, inter-professional, and integrated curriculum shared across multiple institutions, and better prepared significant numbers of future health workers with practice ready competencies and skills. Of note, these efforts led to the establishment of a two year fellowship in infectious diseases at the University of Nairobi for internal medicine and pediatric residency graduates. This represents the first Sub-Saharan fellowship program in Infectious Diseases, outside of South Africa. With the multiple students and faculty undergoing training through PACE, it joins the ranks of other implemented projects by the Division that have had significant impact on training and workforce development within resource constrained countries. Notable among these are the Guyana Partnership for Advanced Clinical Education (GPACE), which created the first post graduate residency program in medicine and infectious diseases in Guyana, the Haiti Partnership for Institutional Strengthening, which established the first integrated post graduate infectious diseases training program for physicians and nurses in Haiti, and the Zambia Educational Partnership for Advanced Clinical Training (ZEPACT), which is credited with the establishment and continuation of two masters programs in medicine and infectious diseases in Zambia, and has trained over 10% of the country's physician population. These four awards have built on the legacy of the IHV and UMB as a premier training institution and have expanded this legacy abroad. Finally, over the past two years the Division has been successful in securing multiple new 5 year awards ensuring the continuation of this robust program past 2020. These include significant grants in Botswana and Zambia to operationalize HIV treatment as prevention as a strategy to halt the HIV epidemic in these targeted countries, as well as major new grants in Kenya, Tanzania, and Zambia.

Clinical Care and Research Publications

Alexander CS, Pappas G, **Amoroso A**, Lee MC, Brown-Henley Y, Memiah P, O'Neill JF, Dix O, **Redfield RR**, Delva G, **Edozien A**, **Hachaambwa L**, Maro P, **Nwandu A**, Nwizu C, **Obeifune M**, **Oni B**, **Patel D**, **Sheneberger R**, Baribwira C, Kiromera A, Tepper V, Oyebola FO, Kaiza-Kangalwe A, Anthony Loy G, Enejoh V, Nwene E, Stanis-Ezeobi W, Shimabale M, Gashongore I, Etienne-Mesubi M (2015). Implementation of HIV Palliative Care: Interprofessional Education to Improve Patient Outcomes in Resource-Constrained Settings, 2004-2012. *J Pain Symptom Manage*. 50(3):350-61. 2015 Sep.

Aslanabadi A, Ghabili K, Shad K, Khalili M, **Sajadi MM**. On the Emergence of Whooping Cough: Notes from Three Early Epidemics in Persia. *Lancet Infect Dis*. 2015 Dec;15(12):1480-4.

Bagchi S, Patel P, Faramand R, Burrowes S, Hossain M, **Kottilil S**, Miller M, Fantry LE, Redfield RR. Underutilization of Statins for Prevention of Cardiovascular Disease Among Primarily African American HIV-Infected Patients. *J AIDS Clin Res* 2015, 6:9

Bean M, **Tang L**, **Kottilil S**, Beavers KL, Meissner EG. On treatment elevations in hepatic transaminases during HCV treatment with ombitasvir, paritaprevir and dasabuvir. *Open forum for Infect Dis* 2016 doi: 10.1155/2016/6151570.

Bon D, Kohli A, Osinusi A, **Nelson A**, **Kottilil S**, and Herrmann E. A mathematical model of HCV decay kinetics in patients receiving sofosbuvir and ledipasvir *PLoS Comp Biol*. 2016 (in press).

Buckner CM, Kardava L, Zhang X, Gittens K, Justement JS, Kovacs C, McDermott AB, Li Y, **Sajadi MM**, Chun TW, Fauci AS, Moir S. Maintenance of HIV-Specific Memory B-Cell Responses in Elite Controllers Despite Low Viral Burdens. *J Infect Dis*. 2016 Apr 27. pii: jiw163

Chloe Gross, Elizabeth Akoth, Angie Price, Sarah Kattakuzhy, Rachel Silk, Elana Rosenthal. HIV/HCV co-infection: Overcoming barriers to treatment. *JANAC*. 2016 Jul-Aug;27(4):524-9.

Curreli, S., Wong, B.S., **Latinovic, O.**, Konstantopoulos, K. and **Stamatos, N.M.** 2016. Class 3 semaphorins induce F-actin reorganization in human dendritic cells: Role in cell migration (*J. Leukoc. Biol.*, in press)

Doll M, Kleinberg M, Kokh D, **Riedel DJ.** Loss of virologic control and severe Pneumocystis pneumonia in an HIV-infected patient receiving chemotherapy for non-small cell lung cancer. *AIDS Res Hum Retroviruses* 2016;32(1):4-5.

Fisher LH, **Stafford KA**, Fantry LE, **Gilliam BL, Riedel DJ**. Cancer knowledge and opportunities for education among HIV-infected patients in an urban academic medical center. *J Cancer Educ* 2015;30(2):319-26.

Fisher LH, Choi J, Bricker RS, Shere-Wolfe KD, **Saharia K.** A 57-year-old man with dyspnea and cough. *Clin Infect Dis*. 2015; 61: 1026-7.

Hahn K, Kohli A, Sims Z, **Kottilil S**. Durable Sustained Virologic Response after oral directly acting antiviral therapy despite immunosuppressive treatment. *Open Forum Infect Dis* (2015), 2(3):ofv091

Heil E, Hynicka LM, Kottilil S, Tang L. What does the pharmacological future of treating chronic hepatitis C look like. Expert Reviews in Pharmacology (2015), Sep;8(5):605-22.

Heredia A, Le N, Gartenhaus RB, Sausville E, Medina-Moreno S, Zapata JC, Davis C, Gallo RC, Redfield RR. Targeting of mTOR catalytic site inhibits multiple steps of the HIV-1 lifecycle and suppresses HIV-1 viremia in humanized mice. Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):9412-7. doi: 10.1073/pnas.1511144112. Epub 2015 Jul 13.

Jimmerson LC, Urban TJ, Truesdale A, Baouchi-Mokrane F, **Kottilil S**, Meissner EG, Sims Z, Langness JA, Hodara A, Aquilante CL, Kiser JJ. Variant ITPA Phenotypes are Associated with Increased Ribavirin Triphosphate Levels. *J Clin Pharmacol*. 2016 Jun 28. doi: 10.1002/jcph.783.

Kattakuzhy S and **Kottilil S.** HCV Genotype 3 Disease. *Hepatol International* (2016), in press.

Kattakuzhy S, Wilson E, Sidharthan S, Sims Z, McLaughlin M, P**rice A, Silk R, Gross C, Akoth E,** McManus M, **Emmanuel B, Tang L, Nelson A**, Teferi G, Chavez J, Lam B, Mo H, Osinusi A, Polis MA, Masur H, Kohli A, **Kottilil S**. Six-week Combination Directly Acting Anti-HCV Therapy Induces Moderate Rates of Sustained Virologic Response in Patients with Advanced Liver Disease. *Clin Infect Dis.* (2015), 62(4):440-7.

Kawabata S, **Heredia A**, Gills J, **Redfield RR,** Dennis P, **Bryant J.** Impact of HIV on lung tumorigenesis in an animal model. *AIDS* 2015, 29:633-639

Kayumba K, Nsanzimana S, Binagwaho A, Mugwaneza P, Rusine J, Remera E, Koama JB, Ndahindwa V, Johnson P, **Riedel DJ**, Condo J. TRACnet internet and SMS technology improve time to antiretroviral therapy initiation among HIV-infected infants in Rwanda. *Pediatr Infect Dis* J 2016 Mar 30. [Epub ahead of print].

Kohli A., Kapoor R, Sims Z, Nelson A, Sidharthan S, Lam B, Silk R, Kotb C, Gross C, Teferi G, Sugarman K, Pang P, Osinusi A, Polis MA, Rustgi V, Masur H and **Kottilil S.** Ledipasvir and Sofosbuvir for Hepatitis C Genotype 4: A Proof of Concept Phase 2a Cohort Study. *Lancet Infect Dis* (2015), Sep;15(9):1049-54.

Kohli, A, **Kattakuzhy S.**, Sidharthan S., **Nelson A**, McLaughlin M., Seamon C, **Wilson E**, Meissner EG, Sims Z, **Silk R.**; **Gross C, Tang L, Price A**, Jolley TA, **Emmanuel B**, Proschan M.;Teferi G, Chavez J, Abbott S, Osinusi A, Mo H, Polis MA, Masur H, **Kottilil S.** Four-week Directly Acting Anti-HCV Regimens in HCV Genotype-1 Patients without Cirrhosis: A Phase 2a Cohort Study. *Annals of Intern Med* (2015), in press.

Kottilil S. AASLD/IDSA HCV Guidance Panel. Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected with Hepatitis C Virus. *Hepatology* (2015), Sep;62(3):932-54.

Latinovic O, Redfield RR. CCR5: A Cellular Doorway for HIV-1 Entry. *Journal of Human Virology and Retrovirology* 2015, 2 (5):00056

Latinovic OS, Medina Moreno S, Hippler LM, Zapata JC, Redfield RR. Humanized NSG Mouse Models of HIV-1 Infection and Pathogenesis. *J Hum Virol Retrovirol* 2016, 3 (2):00087

Latinovic O, Zhang J, **Tagaya Y, DeVico A**, Fouts T, Schneider K, **Lakowicz J, Heredia A, Redfield RR.** Synergistic Inhibition of R5 HIV-1 by the Fusion Protein (FLSC) Igg1 Fc and Maraviroc in Primary Cells: Implications for Prevention and Treatment. *Current HIV Research*, 2016, 14

Liu F, Fan X, Auclair S, Ferguson M, Sun J, Soong L, Hou W, **Redfield RR**, Birx D, Ratto-Kim S, Robb M, Kim J, Michael N, Hu H. Sequential Dysfunction and Progressive Depletion of Candida albicans-Specific CD4 T *Cell Response in HIV-1 Infection. PLOS Path* 12(6): e1005663

Majumdar A, **Gilliam BL.** Grazoprevir, *Drugs Fut* 2016 41(2): 85-109.

Makuza JD, Nsanzimana S, Muhimpundu A, Pace LE, Ntaganira J, **Riedel DJ.** Prevalence and risk factors for cervical cancer and pre-cancerous lesions in Rwanda. *Pan Afr Med* J 2015;22:26.

Meissner EG, Decalf J, Casrouge A, Masur H, **Kottilil S.** Albert ML, Duffy D. Dynamic Changes of Post-translationally Modified Forms of CXCL10 and Soluble DPP4 in HCV Subjects Receiving Interferon-free Therapy. *PLOS ONE* (2015), Jul 16;10(7):e0133236.

Meissner EG, Kohli A, Virtaneva K, Sturdevant D, Martens C, Porcella SF, McHutchison JG, Masur H, **Kottilil S.** Favorable response to HCV treatment with directly acting antivirals correlates with changes in hepatic interferon gene expression independent of cirrhosis. (2015), *J Hep* (in press).

Meissner EG, McLaughlin M, Matthews L, Gharib AM, Wood BJ, Levy E, Sinkus R, Virtaneva K, Sturdevant D, Martens C, Porcella SF, Goodman ZD, Kanwar B, Myers R, Subramanian M, Hadigan C, Masur H, Kleiner DE, Heller T, **Kottilil S,** Kovacs JA, Morse CG. Simtuzumab treatment of advanced liver fibrosis in HIV and HCV-infected adults: Results of a 6-month open-label safety trial. 2016 *Liver Int.*

Mutagoma M, Kayitesi C, Gwiza A, Ruton H, Korelos A, Gupta N, Balisanga H, **Riedel DJ,** Nsanzimana S. Estimation of the size of the female sex worker population in Rwanda using three different methods. *Int J STD AIDS* 2015:26(11):810-4.

Mutagoma M, Ndahimana J, Kayirangwa E, Dahourou AG, Balisanga H, DeVos JR, McAlister D, Yang C, Bertagnolio S, Riedel DJ, Nsanzimana S. Prevalence of transmitted HIV-1 drug resistance among young adults attending HIV counseling and testing clinics in Kigali, Rwanda. Antivir Ther 2015 Oct 11. [Epub ahead of print]

Mutagoma M, Balisanga H, Remera E, Gupta N, Malamba SS, **Riedel DJ,** Nsanzimana S. Ten-year trends of syphilis in sero-surveillance of pregnant women in Rwanda and correlates of syphilis-HIV co-infection. *Int J STD AIDS* 2015 Dec 21 [Epub ahead of print].

Mutagoma M, Remera E, Sebuhoro D, Kanter S, **Riedel DJ**, Nsanzimana S. The prevalence of syphilis infection and its associated factors in the general population of Rwanda: a national household-based survey. *J Sex Transm Dis*, 2016;2016:4980417.

Ndahimana JA, **Riedel DJ**, Muhayimpundu R, Nsanzimana S, Niyibizi G, Mutaganzwa E, Mulindabigwi A, Baribwira C, Kiromera A, Jagodzinski LL, Peel SA, **Redfield RR**. HIV drug resistance mutations among patients failing second line antiretroviral therapy in Rwanda. Antiviral Therapy 2015; 10.3851/IMP3005

Ndahimana JD, **Riedel DJ**, Mwumvaneza M, Sebuhoro D, Uwimbabazi JC, Kubwimana M, Mugabo J, Mulindabigwi A, Kirk C, Kanters S, Forrest JI, Jagodzinski LL, Peel SA, Ribakare M, **Redfield RR**, Nsanzimana S. Drug resistance mutations after the first 12 months on antiretroviral therapy and determinants of virologic failure in Rwanda. *Trop Med Int Health* 2016 Apr 28. [Epub ahead of print].

O'Brien T, Feld J, **Kottilil S**, and Pfieffer R. Precision medicine for hepatitis C. *Clinical Infect Dis* (2016), in press.

O'Brien TR, Feld JJ, **Kottilil S**, Pfeiffer RM. No scientific basis to restrict 8 weeks of treatment with Ledipasvir/Sofosbuvir to patients with HCV RNA <6,000.000 IU/ml. *Hepatology* (2015), 63(1):28-30

Clinical Care and Research Publications

O'Connell RJ, Excler J-L, Polonis VR, Ratto-Kim S, Cox J, Jagodzinski LL, Liu M, Wieczorek L, McNeil JG, El-Habib R, Michael NL, **Gilliam BL**, Paris R, VanCott TC, Tomaras GD, Birx DL, Robb ML, Kim JH. Safety and Immunogenicity of a randomized Phase I prime-boost trial with ALVAC-HIV(vCP205) and Oligomeric gp160 MN/LAI-2 Adjuvanted in Alum or Polyphosphazene. *J Infect Dis* 2016 Jun 15;213(12):1946-54.

Oliver WD, Heil EL, Gonzales JP, Mehrotra S, Robinett K, **Saleeb P**, et al. Ceftolozane-tazobactam pharmacokinetics in a critically ill patient on continuous venovenous hemofiltration. *Antimicrobial Agents and Chemotherapy* 2016, 60(3): 1899-1901.

Papudesu C and **Kottilil S, Bagchi S.** Grazoprevir-Elbasvir for treatment of HCV Infection Hepatol. *Intern* (2016), in press

Petersen T, Townsend K, Gordon LA, Sidharthan S, **Silk R, Nelson A**, **Gross C,** Calderon M, Proschan M, Osinusi A, Polis MA, Masur H, **Kottilil S**, and Kohli A. High adherence to directly acting antiviral therapy in inner city HCV infected patients. *Hepatol International* (2015), 10(2):310-9.

Petersen P, Lee YJ, Osinusi A, Amorosa V, Wang C, Kang M, Matining R, Zhang X, Dou D, Umbleja T, **Kottilil S** and Peters MG. Interferon Stimulated Gene Expression in HIV/HCV Co-infected Patients treated with Nitazoxanide/Peginterferon Alfa-2a and Ribavirin *AIDS Res Hum Retr* (2016), in press.

Poonia B and **Kottilil S.** Newer therapeutics for hepatitis C Annals Transl Med 2016, 4(2):31.

Price A, Gross C, Akoth E, Wilson E, Osinusi A. and **Kottilil S.** Supervised ART interruption to allow HCV therapy with DAAs in HIV/HCV coinfected subjects *Open Forum for Infect Dis* 2016.(in press)

Ramay F, **Amoroso A,** von Rosenvinge E, **Saharia K.** Fecal Microbiota Transplantation for Treatment of Severe, Recurrent, and Refractory Clostridium difficile Infection in a Severely Immunocompromised Patient. *Infectious Diseases in Clinical Practice.* 2015. Epub.

Riedel DJ, Rositch AF, **Redfield RR, Blattner WA.** HIV-associated lymphoma subtype distribution, immunophenotypes and survival in an urban clinic population. Leukemia and Lymphoma, 2015 June 19: 1-7

Riedel DJ, Rositch AF, **Redfield RR.** Patterns of HIV viremia and viral suppression before diagnosis of non-AIDS defining cancers in HIV infected individuals. *Infect Agent Cancer.* Nov 2015, 10:38

Riedel DJ, Cox ER, Stafford KA, Gilliam BL. Clinical presentation and outcomes of prostate cancer in an urban cohort of predominantly African-American, HIV-infected patients. *Urology* 2015;85(2):415-22.

Riedel DJ, **Tang LS**, Rositch AF. The role of viral co-infection in HIV-associated non-AIDS related cancers. *Curr HIV/AIDS Rep* 2015; 12(3):362-72.

Riedel DJ, Rositch AF, **Redfield RR**. Patterns of HIV viremia and viral suppression before diagnosis of non-AIDS-defining cancers in HIV-infected individuals. *Infect Agent Cancer* 2015;10:38.

Roland ME, Barin B, Huprikar S, Murphy B, Hanto DW, Blumberg E, Olthoff K, Simon D, Hardy WD, Beatty G, Stock PG, HIVTR Study Team (**Davis CE** et al). Survival in HIV-positive transplant recipients compared with transplant candidates and with HIV-negative controls. *AIDS* 2016 Jan 28:30 (3):435-44.

Rosenthal E, Polis MA, **Kottilil S**. Sofosbuvir and Ledipasvir for HIV/HCV Coinfection. Exp Opin on Pharmacotherapy (2016), 17(5):743-9.

Rosenthal E, Kottilil S and Graham C. Cost effectiveness of DAA therapy; hard choices. Infections and Cancer 2016 (in press).

Rosenthal ES, Graham C. Price and Affordability of Direct-Acting Antiviral Regimens for Hepatitis C Virus. Infectious Agents and Cancer. 2016 May 16;11:24.

Rower J, Meissner E, Jimmerson L, Osinusi A Sims Z, Petersen T, Bushman L, Wolfe P, McHutchison JG, **Kottilil S**, Kiser J. Serum and Cellular Ribavirin Pharmacokinetic and Concentration-Effect Analysis in HCV Patients Receiving Sofosbuvir plus Ribavirin. J Antimicro Chemotherapy (2015) Aug;70(8):2322-9.

Ryscavage P, Macharia T, **Patel D, Palmeiro R**, Tepper V. Linkage to and retention in care following healthcare transition from pediatric to adult HIV care. AIDS Care. 2016 May;28(5)561-5.

Sajadi MM, Farshidpour M, Brown E, **Ouyang X**, Seaman M, **Pazgier M**, Ackerman M, Robinson H, Tomaras G, Parsons M, **Charurat M, DeVico A, Redfield RR, Lewis G.** γ Light Chain Bias Associated with Enhanced Binding and Function of Anti-HIV Env Glycoprotein Antibodies. *JID* 2016:213 (1 January) 213:156-164

Schmalzle SA, Buchwald UK, **Gilliam BL, Riedel DJ.** Cryptococcus neoformans Infection in Malignancy. *Mycoses* 2016 March 2.

Sehgal R, Patra S, David P, Vyas A, Khanam A, Hissar S, Chibber G, **Kottilil S**, Maiwall R, Sarin SK, Trehanpati N. Imapired monocyte and macrophage functions and defective TLR signaling in hepatitis E virus infected pregnant women with acute liver failure. *Hepatology* (2015), 62(6):1683-96.

Shrivastava S, Meissner EG, Funk E, Poonia S, Shokeen V, Thakur A, **Kottilil S**, Sarin SK, Trehanpati N. Elevated hepatic lipid and interferon stimulated gene expression in patients infected with hepatitis C virus genotype-3 relative to patients with non-alcoholic steatohepatitis (NASH). *Hepatol Intern* (2016), in press.

So-Armah KA, Tate JP, Chang CH, Butt AA, Gerschenson M, Gibert CL, Leaf D, Rimland D, Rodriguez-Barradas MC, Budoff MJ, Samet JH, Kuller LH, Deeks SG, Crothers KA, Tracy RP, Crane HM, **Sajadi MM**, Tindle HA, Justice AC, Freiberg MS; **Sowah LA**, Buchwald UK, **Riedel DJ, Gilliam BL, Khambaty M,** Fantry L, Spencer DE, **Weaver J, Taylor G, Skoglund M, Amoroso A, Redfield RR.** Anal Cancer Screening in an Urban HIV Clinic: Provider Perceptions and Practice. *J Int Assoc Provid AIDS Care* 2015 Nov-Dec;14(6):497-504.

Squarre D, Kabongo I, Munyeme M, Mumba C, Mwasinga W, **Hachaambwa L**, Sugimoto C, Namangala B. Human African Trypanosomiasis in the Kafue National Park, Zambia. *PLoS Negl Trop Dis.* 2016 May 19;10(5):e0004567. doi: 10.1371/*journal*. pntd.0004567. 2016 May 19.

Tang L and **Kottilil S.** Treatment of HCV in HIV-infected patients: no longer a challenge? *The LANCET HIV* (2015), 2(8): e308-9.

Tang L, Heil E, **Kottilil. S**, Dual Sofosbuvir and ribavirin therapy for hepatitis C infection. *Expert Rev in Gastro Hepatol.* (2015), in press.

Tang L, Ward H, **Wilson E, Kottilil S.** Treatment of HBV: an update. *Future Microbiology*, (2015), in press.

Tang L, Marcell L, **Kottilil S**. Sherman KE. Extra hepatic manifestations of hepatitis C infection. *Infections and Cancer* 2016, 23;11:29.

Tang L, Masur J, **Nelson A**, Osinusi A, Kohli A, Polis MA, and **Kottilil S**,Baseline Mental Health Disease and Hepatitis C: Impact on Sustained Virologic Response and Adherence with Interferon-Free Therapy. W. *J Gastroenterology* (In press)

Taremi M, Kleinberg ME, Wang EW, **Gilliam BL, Ryscavage PA**. Galactomannan antigen detection using bronchial wash and bronchoalveolar lavage in patients with hematologic malignancies. *Ann Clin Microbiol Antimicrob* 2015 Nov 14;14(1):50.

Theisen-Toupal J, **Rosenthal ES,** Rowley CF. Reimagining long-term antibiotics for persons who inject drugs: time to shift the status quo? *J Hosp Med*. 2016 Apr 4.

Townsend K, Petersen T, Gordon LA, Kohli A, **Nelson A,** Seamon C, **Gross C,** Tang L, Osinusi A, Polis MA, Masur H, **Kottilil S.** Effect of HIV co-infection on adherence to a 12-week regimen of regimen of hepatitis C virus therapy with ledipasvir and sofosbuvir. *AIDS* (2015), 30(2):261-6.

Townsend K, Meissner EG, Sidharthan S, Sampson M, Remaley A, Kohli A, Osinusi A, Masur H and **Kottilil S**. Interferon free of HCV in HIV infected subjects results in increased serum LDL levels. *Aids Hum Retr* (2015), 32(5):456-62.

Trehanpati N, **Kottilil S**, Patra S, Vasudevan M, Sehgal R, Daivid P, Vyas A, Khosla R, Khanam A, Kumar G, Hissar S, Ramakrishna G, Sarin SK. miRNA Signatures indicate Acute Liver Failure in hepatitis E infected pregnant females. *Nature Scientific reports* (2016) in press.

Wilson EM, Kattakuzhy S, Sidharathan S, Sims Z, **Tang L**, McLaughlin M, **Price A, Nelson A, Silk R, Gross C, Akoth E**, Mo H, Subramanian GM, Pang PS, McHutchison JG, Osinusi A, Masur H, Kohli A and **Kottilil S**. Successful retreatment of chronic hepatitis C genotype-1 infection with ledipasvir and sofosbuvir after initial short course therapy with direct acting antiviral regimens. *The Clin Infect Dis,* (2015) 62(3):280-8.

Wilson EM and **Kottilil S.** The implications for clinical laboratories of the new drug therapies for hepatitis C. *Clin Microb Rev.* (2015), in press

Wilson EM and **Kottilil S.** Eradication strategies for HBV. *Clin Infect Dis* (supplement) (2015), 62 Suppl 4:S318-25

Wilson, E, KH Hullsiek, I Sereti and JV Baker. "Reply to Bandera et al," *JID* (2015); 212(5):841-2.

The VACS Project Team. Do Biomarkers of Inflammation, Monocyte Activation and Altered Coagulation Explain Excess Mortality Between HIV Infected and Uninfected People? *J Acquir Immune Defic Syndr.* 2016 Feb 13.

Epidemiology and Prevention Division

Man Charurate, PhD, MHS

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, integrates the components of research, training and health systems strengthening conceptually through the three-legged stool approach – viewing each leg as necessary to advance science to prevent and treat HIV/AIDS, other infectious diseases, and cancers. The ultimate goal of the Division's population research focus is to have a translational impact on clinical and public health practices. The Division brings together population-based researchers with clinical scientists, educators, healthcare professions and with many external collaborators to carry out its trans-disciplinary research objectives. The Division has 9 faculty members, 6 staff and 2 pre-doctoral candidates with 20 active grants, totaling $85,657,323 of annual funding in 2016. The team of outstanding investigators have been recognized for their research merit and effective public health programs in the area of Prevention and Treatment Research, Pathogenesis Research, Research Training and Health Systems Strengthening.

PREVENTION AND TREATMENT RESEARCH

High-risk men and women and HIV-exposed children are the focus of many of the Division's studies designed to improve lives through science-driven change. The TRUST/Building TRUST, ADAPT and MoMent studies involve research to prevent and treat HIV.

TRUST and Building TRUST Research Studies

52.2% of the Men-having-Sex-with-Men (MSM) tested in our studies in Abuja and Lagos are infected with HIV. Engaging and retaining them in care has been a major aim for the past 3 years. In 2014 an anti-homosexuality law was signed into law where the punishment for homosexuality is up to 14 years in jail further discouraging many MSM from getting tested for HIV or seeking treatment. This year the TRUST and Building TRUST studies (1R01MH099001, R01A1209143, PI: Charurat, Professor) continued to test and provide HIV care to MSM in Nigeria. Even though the MSM's in Nigeria, represent less than 2% of the population, a very high percent of new infections can be attributed to this group. The Division's molecular epidemiology work, using phylodynamic analysis of HIV sequences and dynamic infectious disease modeling, has estimated that

Trust and Building Trust Study

Photo Left: IHV-Nigeria organizes HIV prevention outreach

9.1% of transmissions in the general population can be attributed to the MSM population in Nigeria. Analysis also shows that providing universal treatment to key populations, such as the MSM, is cost-effective and highly impactful. This ongoing study is continuing to characterize the HIV transmission network as it relates to sexual networks, community and the individual. The one-stop MSM clinic in Abuja is also investigating the impact of Pre-Exposure Prophylaxis (PrEP) for its high-risk HIV-negative MSM. PrEP is designed to prevent HIV infections by taking a prophylaxis pill every day to prevent the virus from establishing a permanent infection.

HIV Care for Adolescent Transition—ADAPT

ADAPT study

A newly funded NIH study this year, The Adolescent to Adult Patient-centered HIV Transition (ADAPT), (R01HD089866 PI: Charurat/ Tepper/Ekong), is a randomized trial of innovative interventions targeting the major drivers of loss to follow up in the ART continuum of care cascade among adolescents. One of the distinct challenges faced by emerging adults with HIV is the transition of their care from their long-term pediatric HIV provider to treatment within an adult HIV program. While conceptually the transition from pediatric to adult care may seem straightforward, the reality is that the transition often is a very difficult process. The consequences of an unsuccessful transition can be catastrophic. The ADAPT study is designed to inform strategies for transition services in resource-limited settings; examine the developmental, clinical, and other factors that predict a successful transition; and gain fundamental insight on implementation barriers among African adolescents through the application of the ego-network defined social support that will inform targets for structured intervention. The finding from this study will guide institution of best practices for transitioning adolescents in Nigeria and other countries lower and middle income countries with similar challenges and potential for high impact.

MoMent study

PMTCT service uptake and retention—MoMent

Nigeria accounted for almost 30% of global new child HIV infections in 2015. The transmission of HIV from HIV-positive mothers to their babies during pregnancy, labor and delivery or breastfeeding can be reduced to below 5% with effective interventions. However, many women in Nigeria are unable to fully benefit from available services due to lack of support and counseling both at the facility and in the community. The INSPIRE Mother-Mentor (MoMent) study (PI: Nadia Sam-Agudu, MD, Assistant Professor of Epidemiology and Prevention) investigates the impact of a structured, supervised peer counseling intervention on uptake of Prevention-of-Mother-to-child-Transmission services and retention in care among HIV-infected mothers and HIV-exposed babies in rural North-Central Nigeria. The MoMent study is the first to prospectively evaluate the impact of peer counseling on PMTCT outcomes in West Africa. The MoMent study is the first to assess the impact of peer counseling within PMTCT programs in West Africa. This WHO and Canadian government-supported study involves 20 Primary Healthcare Centers, and has completed enrollment. Analysis of early outcomes is ongoing. The final follow-up is expected to be completed in 2017.

PATHOGENESIS RESEARCH

Implementing research programs to characterize the human microbiome and its role in health and disease pathogenesis is another major focus of the Division. The MARGIN, ACCME and Anal Cancer study are all involved in understanding the biological mechanisms that lead to specific diseases or outcomes.

Microbiome, growth development—MARGIN

ADAPT study

The Microbiome and Health Outcomes among HIV-exposed Uninfected Infants (MARGIN, R01DE025174, PI: Charurat) just completed the second year of the study. Uninfected infants born to HIV infected mother have developmental abnormalities including growth faltering, higher morbidities, and increased risk for infant diarrhea. MARGIN is investigating the infant's altered gut microbiota and the association between these clinical outcomes. 127 mother and infants have been enrolled in the study, and we have observed similarities between the mother's vaginal microbiota and infant's meconium suggesting inheritance of maternal microbiota very early in life.

Alash'le Abimiku, MON, PhD

Innate Factors and Immune Responses In HIV Exposed Infants—INFANT STUDY

The INFANT study is a Canadian Institute of Health Research team grant linking investigators in Canada, South Africa, and Nigeria (Nigeria PI: Alash'le Abimiku, MON, PhD, Professor of Medicine) to use two observational cohort of mothers living with HIV and their HIV-exposed uninfected infants in Nigeria and South Africa to understand the innate and adaptive immune responses and drivers of infection. A total of 680 mother-infant pairs were recruited into the study with 490 pairs with HIV+ mothers on HAART and 190 controls pairs with HIV- mothers. Preliminary data shows that over a 2-year study period, only 2 infants were infected despite the infants being exclusively breast fed for the first few months of life with quite a few mothers not being virologically suppressed. The overall incidence of HIV-infection so far was 0.5/100 person-years (95% CI:0.06-1.81).

The African Collaborative Center for Microbiome and Genomics Research

ACCME study

The African Collaborative Center for Microbiome and Genomics Research (ACCME) (5U54HG006947 PI: Clement Adebamowo, MD, Professor of Epidemiology and Prevention) study is funded through the NIH - Human Heredity and Health in Africa (H3 Africa). The ACCME study aims to investigate the interaction between vaginal microbiome, host genetic factors and molecular variants of Human Papilloma Virus (HPV). This research is designed to determine correlates of viral persistence in the causal pathway of cervical cancer, a major cause of preventable mortality in African. ACCME includes both a scientific and training plan focused on understanding the associations between high risk HPV infection, vaginal microenvironment, HPV genomics, germline and somatic mutations in the etiology of cervical cancer. The ACCME center is designed to implement projects including Epidemiology and Biomarker Discovery of Persistent high risk HPV (hrHPV) infection and Cervical Cancer in African women at risk of cervical cancer; Discovery of Biomarkers of the association between the Vaginal Microenvironment and persistent high risk HPV (hrHPV) infection and the Gene Discovery of Risks of persistent hrHPV infection (hrHPV), cervical cytokines, patterns and stability of vaginal microbiome and CIN2+ Project.

Faculty Q&A with Nowak—High Resolution Anoscopy—the first of its kind in Nigeria


Faculty Q&A group

As a member of the Division of Epidemiology and Prevention, Rebecca Nowak, PhD, Assistant Professor of Epidemiology and Prevention, recently received an early-stage NCI award entitled: "UMB TRUST-ANAL CANCER STUDY"(3P30CA134274-08S4). As the lead investigator, she is implementing this study in Nigeria. The study compares persistence of anal human papillomavirus (HPV), a strong risk factor for pre-cancer, between HIV-positive men who have sex with men (MSM) and HIV-negative MSM in Nigeria. She will explore the diversity and composition of anal microbiota and its relationship to persistence of high-risk HPV among HIV-positive and HIV-negative MSM. In addition, she is developing one of the first anal cancer screening programs in sub-Saharan Africa using high resolution anoscopy (HRA) to support a cohort study of HPV pathogenesis and anal cancer disease progression.

We sat down with Dr. Nowak to learn a little bit more about the anal cancer in Nigeria and HRA.

Why focus on anal cancer? I have been working in research involving HIV+ and HIV- Men-who-have-Sex-with-Men since I joined IHV. This cohort of individuals have many of the risk factors for developing anal cancer.

What are the risk factors for anal cancer? Some of the risk factors include: HIV infection, receptive anal intercourse, multiple sex partners, anal warts, HPV infection, and smoking.

Suppose you have these risk factors, what should you do? Share you symptoms with your doctor. He/she may recommend that you get screened for anal cancer. Identifying anal cancer in its early stages can improve your five year survival from 30% to 80%.

What does the screening involve? First your physician will ask you about your anal symptoms, such as itching, bleeding, discharge, or pain and probably perform a digital rectal exam. If necessary, the physician will then examine using High Resolution Anoscopy (HRA). HRA uses a lighted magnifying scope to identify diseases in the folds of the lower rectum and anus. If lesions are found, a biopsy will be performed to determine if the lesion or growth in cancerous and a treatment plan is initiated.

RESEARCH TRAINING AND HEALTH SYSTEMS STRENGTHENING

Training the next generation of global health researchers and preparing a health care workforce to achieve an AIDS free generation, malaria elimination, and TB control are integral to the Division's mission. We are striving to achieve these goals through infrastructure development, research training programs, and improving the HIV/AIDS, TB and malaria service delivery in Nigeria.

IHV-Nigeria International Research Center of Excellence (IRCE)

In 2016, the IHV-Nigeria International Research Center of Excellence (IRCE) was created to provide an enabling environment for creative thinking and innovation in science to address global health priorities. Under the leadership of Dr. Alash'le Abimiku, IRCE is creating a platform for the implementation of research and clinical trials at international standards while fostering collaborations and synergism between Nigeria's finest researchers and their counterparts at international research institutions and universities. A regulatory structure is being developed to ensure that research is conducted under the highest scientific and ethical standards. IRCE, with the technical support of IHV, has developed a sophisticated research laboratory structure including a genomic laboratory, biorepository, BL-3 and molecular TB laboratory, and a WHO accredited viral sequencing laboratory, all structures to facilitate technical assistance and training by the Global Virus Network (GVN) in disease surveillance and containment of outbreaks.

IHVN H3Africa Biorepository (I-HAB)


IHVN Biorepository (I-HAB)

The NIH funded IHVN's H3Africa biorepository (4UH3HG007008, PI: Abimiku) is one of three regional biorepositories established to store and distribute high quality valuable biological specimens and data gathered from 25 research projects across 27 African countries involving over 500 investigators and about 75,000 study participants that make up the H3Africa consortium. Using internationally accepted guidelines such as the International Society for Biological and Environmental Repositories (ISBER), I-HAB ensures access to high quality samples and data while using Laboratory Information Systems (LIMS), which automates sample management for efficient storage, retrieval, and chain-of-custody.


EPI-Nigeria

Fogarty International Center—EPI-Nigeria

In 2016, the Division of Epidemiology and Prevention was awarded a National Institutes of Health Fogarty International Center, Epidemiology Research Training for Public Health Impact (Epi-Nigeria) grant (D43TW010051 PI: Charurat/ Abimiku). To train the next generation of population-based researchers, EPI-Nigeria offers a distance, mentored research training program to acquire a Master of Science in Health Sciences (MSHS) with a concentration in Implementation and Dissemination Research Science through the UMB Graduate School for Nigerian trainees. In addition, a PhD in Epidemiology is also offered which requires the Nigerian trainee to spend two years in Baltimore, Maryland at the UMB before returning home to complete their dissertation research. The goal of this Fogarty research training program is to offer trainees a quality on-line Master degree program in Implementation and Dissemination Science Research or a PhD in Epidemiology to build in-country capacity to study methods and interventions that will translate into everyday clinical and public health practice to improve lives. Enrollment into this Fogarty Training program will begin in January 2017.

West African Bioethics Training

The West African Bioethics Training grant (R25TW007091 PI: Adebamowo) at the Center for Bioethics and Research has trained 41 Master degree students in bioethics since 2006. This bioethics training program in Nigeria has helped establish the Nigerian research ethics regulatory environment. It has provided over 14,000 research ethics trainings in Nigeria, partly through its collaboration with the Collaborative Institutional Training Initiative (CITI), formerly of University of Miami but now a program of Biomedical Research Alliance of New York (BRANY), and through collaboration with the Nigerian National Health Research Ethics Committee and local research institutions and universities.

Interview with Patrick Dakum


Patrick Dakum, MBBS, MPH

We sat down with Patrick Dakum, MBBS, MPH, Assistant Professor of Epidemiology and Prevention, Nigerian public health physician, and Institute of Human Virology Nigeria Chief Executive Officer, to discuss the Institute of Human Virology Nigeria (IHV-Nigeria).

Please describe IHV-Nigeria. IHV-Nigeria was established in 2004 as a local non-governmental organizational affiliate of IHV in Nigeria to help address the HIV/AIDS epidemic. Through technical assistance from IHV and infrastructure development, IHV-Nigeria has expanded into otherinfectious diseases and non-communicable diseases including, cancer, tuberculosis, malaria and other diseases.

What is the mission of IHV-Nigeria? IHV-Nigeria is dedicated to becoming a Public Health and Research Center of Excellence in providing health service implementation, capacity building, and research, and ensuring equitable access to individuals and communities through innovative and evidence-based strategies.

What impact has IHV-Nigeria's public health implementation programs had in Nigeria? IHV-Nigeria now offers Anti-retroviral Treatment (ART) services in 312 facilities, PMTCT services in 593 facilities, tuberculosis services in 161 facilities and HIV Counseling and Testing Services in 601 facilities under its PEPFAR project. Also, through funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria, IHV-Nigeria is offering Drug Resistant-TB services at 16 treatment centers, HIV/AIDS services at 46 ART and 164 PMTCT facilities and malaria prevention, care and treatment services at 1785 facilities. All these facilities and treatment centers comprise of primary, secondary and tertiary health centers in twenty two of the 32 states in Nigeria. The Technical Working group for IHV-Nigeria's HIV, TB and malaria public health implementation programs are made up of the expert faculty from the IHV Division of Epidemiology and Prevention and department leads from IHV-Nigeria. In partnership, we have had made significant impacts on the health system, communities and individuals in Nigeria. The Division's faculty have help write National Guidelines for adult and paediatric HIV care and treatment, implemented community ART initiatives, and commenced ARV therapy for over 280,000 HIV infected Nigerians.


HIV Prevention

HIV Prevention, Care and Treatment Programs

IHV-Nigeria, in partnership with IHV for technical assistance and training, has a robust HIV/AIDS care and treatment program focusing on anti-retroviral treatment for adult and children (including pregnant women), laboratory diagnosis and key populations. We provide

services in the area of care and support, prevention of mother-to-child transmission of HIV clinical services, HIV counseling and testing, support to orphans and vulnerable children, training and research. Achievements made in prevention, treatment and care since 2004 are below:

Cummulative Achievements in HIV/AIDS from 2004–2016			
	PEPFAR	Global Fund	Total
Individuals counseled, tested and recieced results	5,232,574	1,008,364	**6,240,938**
Pregnant women counseled, tested and recieced results	2,299,189	560,792	**2859,981**
Pregnant women confirmed positive	73,973	9,103	**83,078**
Clients cumulatively enrolled in the HIV Care program	344,665	71,948	**416,613**
Clients cumulatively initiated on ART	230,218	42,988	**273,206**
Paediatric clients cumulatively initiated (Subset of ART above)	14,366	2,387	**16,753**
Pregnant women provided ARV prophylaxis	64,228	7,055	**71,283**

Man Charurat, PhD, MHS

Technical Assistance in Viral load Scale Up and Global Health Security Agenda

As one of the African Society of Laboratory Medicine (ASLM), the IHVN under the leadership of Dr. Abimiku currently supports Uganda and Kenya on viral load scale up; and three West African countries (Nigeria, Ghana, and Gambia) in mapping and servicing biosafety hoods as part of the global security agenda.

Recognized for her champion for laboratory quality and her involvement in the ASLM Board for the last 5 years, Dr. Abimiku was recently elected chair of the Board of Directors at the African Society for Laboratory Medicine Her commitment to African research and publications and her passion for strengthening laboratory medicine in Africa is unmatched.

TB and Malaria Prevention, Care and Treatment Programs

66,499 Nigerians have been treated for TB through the IHV-Nigeria Global Funds program and 1,583 have been diagnosed and treated for drug-resistant tuberculosis. 1,028 healthcare service providers have also received training in drug-resistant -TB management. The diagnosis and treatment of multi-drug resistant TB was possible through IHV's foresight in building and maintaining a Bio-Safety Level 3 laboratory in Nigeria, in 2010. This was one of the first BL3 laboratories in Africa at the time.


Testing for TB and Malaria

In addition to TB, IHV-Nigeria supports malaria prevention and treatment through distribution of insecticide-treated nets and Artemisin in Combination therapy for malaria prevention and treatment in Kogi, Jigawa, Katsina and Benue States. Over 4.88 million insecticide treated nets have been distributed and 7.9 million people have received artemisin in combination therapy treatment for malaria in the 1,785 facilities being supported by the IHV-Nigeria Global Funds program. Finally, molecular surveillance of drug resistant malaria commenced in 2016.

Nigerian Alliance for Health System Strengthening—HIV/AIDS Clinical Quality Improvement

Through the CDC-supported Nigerian Alliance for Health System Strengthening (NAHSS) project (1U2GH000656, PI: Charurat), the Division of Epidemiology and Prevention is involved in providing the Presidents Emergency Plan for AIDS Relief (PEPFAR) technical assistance to the Government of Nigeria through the implementation of a national quality management program for HIV care and treatment programs in Nigeria. NigeriaQUAL, the quality management program, builds upon the framework of performance measurement (data), quality improvement (problem identification, prioritization, and implementation of change), and a quality management structure (quality improvement teams at the site, local, state and federal level) to elevate the HIV care in the government system. The program outcomes are quality HIV care and prevention at the site level, saving lives and prevent new infection, and provide the government with data-driven evidence to make smart investments for controlling the epidemic.

SHIELD—a CDC new award

In August 2016, the Division was awarded a 5-year $7 million CDC grant titled: Strengthening HIV Field Epidemiology, Infectious Disease Surveillance, and Lab Diagnostic (SHIELD, U2GH001976, PI: Charurat) Program. SHIELD, which will be conducted jointly with the IHV's Division of Clinical Care and Research, will be supporting the Nigeria Field Epidemiology and Laboratory Training Program (NFELTP) mission as well as evaluating the National test-and-treat strategy and community ART initiatives in Nigeria.

Epidemiology and Prevention Publications

Abimiku A, Timperi R, Blattner W. Laboratory Innovation Towards Quality Program Sustainability. *Curr HIV/AIDS Rep.* 2016 Aug;13(4):202-8.

Abubakar A, **Ndembi N,** Ogbanufe O, Inalegwu A, Wilson S, Ebagua I, Peters S, Chime C, **Dakum P, Abimiku AG**. Improved Performance of COBAS AmpliPrep/COBAS TaqMan Version 2.0 Assay Over Amplicor Monitor Version 1.5 in the Quantification of HIV-1 RNA Viral Load in Abuja, Nigeria. *Curr HIV Res***.** 2015;13(4):262-7.

Adebamowo SN, Adeyemo AA, Tekola-Ayele F, Doumatey AP, Bentley AR, Chen G, Zhou J, Shriner D, Fasanmade OA, Okafor G, Eghan B Jr, Agyenim-Boateng K, Adeleye J, Balogun W, Amoah AG, Owusu S, Acheampong J, Johnson T, Oli J, **Adebamowo CA**, Rotimi CN. Impact of Type 2 Diabetes on Impaired Kidney Function in Sub-Saharan African Populations. *Front Endocrinol* (Lausanne). 2016 May 30;7:50.

Adeyemo AA, Tekola-Ayele F, Doumatey AP, Bentley AR, Chen G, Huang H, Zhou J, Shriner D, Fasanmade O, Okafor G, Eghan B Jr, Agyenim-Boateng K, Adeleye J, Balogun W, Elkahloun A, Chandrasekharappa S, Owusu S, Amoah A, Acheampong J, Johnson T, Oli J, **Adebamowo C,** Collins F, Dunston G, Rotimi CN. Evaluation of Genome Wide Association Study Associated Type 2 Diabetes Susceptibility Loci in Sub Saharan Africans. *Front Genet*. 2015 Nov 24;6:335.

Al-Mujtaba M, Cornelius LJ, Galadanci H, Erekaha S, Okundaye JN, Adeyemi OA, **Sam-Agudu NA.** Evaluating Religious Influences on the Utilization of Maternal Health Services among Muslim and Christian Women in North-Central Nigeria. *Biomed Res Int*. 2016;2016:3645415.

Avong YK, van Wyk B, Njab J, **Abimiku AG, Ndembi N**, Okuma J, Ogbanufe O, **Ekong E, Dakum P, Blattner WA.** Adherence to Anti-Retroviral Therapy in North Central Nigeria. *Curr HIV Res*. 2015;13(4):268-78.

Chiwanga FS, Njelekela MA, Diamond MB, Bajunirwe F, Guwatudde D, Nankya-Mutyoba J, Kalyesubula R, **Adebamowo C,** Ajayi I, Reid TG, Volmink J, Laurence C, Adami HO, Holmes MD, Dalal S. Urban and rural prevalence of diabetes and pre-diabetes and risk factors associated with diabetes in Tanzania and Uganda. *Glob Health Action*. 2016 May 23;9:31440.

Coker M, Etiebet MA, Chang H, Awwal G, Jumare J, Musa BM, Babashani M, Habib AG, **Dakum P, Abimiku AG, Charurat ME**, Blattner WA, Eng M, **Ndembi N.** Socio-Demographic and Adherence Factors Associated with Viral Load Suppression in HIV-Infected Adults Initiating Therapy in Northern Nigeria: A Randomized Controlled Trial of a Peer Support Intervention. *Curr HIV Res*. 2015;13(4):279-85.

Dareng EO, Jedy-Agba E, Bamisaye P, Isa Modibbo F, Oyeneyin LO, Adewole AS, Olaniyan OB, **Dakum PS**, Pharoah PD, **Adebamowo CA.** Influence of Spirituality and Modesty on Acceptance of Self-Sampling for Cervical Cancer Screening. *PLoS One*. 2015 Nov 3;10(11):e0141679.

de Souza JA, Hunt B, Asirwa FC, **Adebamowo C,** Lopes G. Global Health Equity: Cancer Care Outcome Disparities in High-, Middle-, and Low-Income Countries. J Clin Oncol. 2016 Jan 1;34(1):6-13. doi: 10.1200/JCO.2015.62.2860. *Epub* 2015 Nov 17. Review.

Ezeanolue EE, Powell BJ, Patel D, Olutola A, Obiefune M, **Dakum P,** Okonkwo P, Gobir B, Akinmurele T, Nwandu A, Torpey K, Oyeledum B, Aina M, Eyo A, Oleribe O, Ibanga I, Oko J, Anyaike C, Idoko J, Aliyu MH, Sturke R, Watts H, Siberry G; Nigeria Implementation Science Alliance. Identifying and Prioritizing Implementation Barriers, Gaps, and Strategies Through the Nigeria Implementation *Science Alliance*: Getting to Zero in the Prevention of Mother-to-Child Transmission of HIV. J Acquir Immune Defic Syndr. 2016 Aug 1;72 Suppl 2:S161-6.

Ezeanolue EE, Nwizu C, Greene GS, Amusu O, Chukwuka C, **Ndembi N,** Smith RM, Chiller T, Pharr J, Kozel TR. Brief Report: Geographical Variation in Prevalence of Cryptococcal Antigenemia Among HIV-Infected, Treatment-Naive Patients in Nigeria: A Multicenter Cross-Sectional Study. *J Acquir Immune Defic Syndr.* 2016 Sep 1;73(1):117-21.

Fantry LE, **Nowak RG**, Fisher LH, Cullen NR, Yimgang DP, Stafford KA, Riedel DJ, Kang M, Innis EK, Riner A, Wang EW, **Charurat ME.** Colonoscopy Findings in HIV-Infected Men and Women from an Urban U.S. Cohort Compared with Non-HIV-Infected Men and Women. *AIDS Res Hum Retroviruses*. 2016 Sep;32(9):860-7.

Folayan MO, Cáceres CF, **Sam-Agudu NA,** Odetoyinbo M, Stockman JK, Harrison A. Psychological Stressors and Coping Strategies Used by Adolescents Living with and Not Living with Hiv Infection in Nigeria. *AIDS Behav*. 2016 Sep 7. [Epub ahead of print]

Guwatudde D, Nankya-Mutyoba J, Kalyesubula R, Laurence C, **Adebamowo C,** Ajayi I, Bajunirwe F, Njelekela M, Chiwanga FS, Reid T, Volmink J, Adami HO, Holmes MD, Dalal S. The burden of hypertension in sub-Saharan Africa: a four-country cross sectional study. BMC Public Health. 2015 Dec 5;15:1211.

Huo D, Feng Y, Haddad S, Zheng Y, Yao S, Han YJ, Ogundiran TO, **Adebamowo C,** Ojengbede O, Falusi AG, Zheng W, Blot W, Cai Q, Signorello L, John EM, Bernstein L, Hu JJ, Ziegler RG, Nyante S, Bandera EV, Ingles SA, Press MF, Deming SL, Rodriguez-Gil JL, Nathanson KL, Domchek SM, Rebbeck TR, Ruiz-Narváez EA, Sucheston-Campbell LE, Bensen JT, Simon MS, Hennis A, Nemesure B, Leske MC, Ambs S, Chen LS, Qian F, Gamazon ER, Lunetta KL, Cox NJ, Chanock SJ, Kolonel LN, Olshan AF, Ambrosone CB, Olopade OI, Palmer JR, Haiman CA. Genome-wide Association Studies in Women of African Ancestry Identified 3q26.21 as a Novel Susceptibility Locus for Estrogen Receptor Negative Breast Cancer. *Hum Mol Genet*. 2016 Sep 4. pii: ddw305. [Epub ahead of print]

Inalegwu A, Phillips S, Datir R, Chime C, Ozumba P, Peters S, Ogbanufe O, Mensah C, **Abimiku A, Dakum P, Ndembi N.** Active tracking of rejected dried blood samples in a large program in Nigeria. *World J Virol*. 2016 May 12;5(2):73-81.

Isa Modibbo F, Dareng E, Bamisaye P, Jedy-Agba E, Adewole A, Oyeneyin L, Olaniyan O, **Adebamowo C.** Qualitative study of barriers to cervical cancer screening among Nigerian women. *BMJ Open*. 2016 Jan 11;6(1):e008533.

Jaquet A, Odutola M, Ekouevi DK, Tanon A, Oga E, Akakpo J, **Charurat M,** Zannou MD, Eholie SP, Sasco AJ, Bissagnene E, **Adebamowo C,** Dabis F; IeDEA West Africa Collaboration. Cancer and HIV infection in referral hospitals from four West African countries. *Cancer Epidemiol*. 2015 Dec;39(6):1060-5.

Jaquet A, Odutola M, Ekouevi DK, Tanon A, Oga E, Akakpo J, **Charurat M**, Zannou MD, Eholie SP, Sasco AJ, Bissagnene E, **Adebamowo C,** Dabis F; IeDEA West Africa Collaboration. Cancer and HIV infection in referral hospitals from four West African countries. *Cancer Epidemiol*. 2015 Dec;39(6):1060-5.

Jedy-Agba EE, Oga EA, Odutola M, Abdullahi YM, Popoola A, Achara P, Afolayan E, Banjo AA, Ekanem IO, Erinomo O, Ezeome E, Igbinoba F, Obiorah C, Ogunbiyi O, Omonisi A, Osime C, Ukah C, Osinubi P, Hassan R, Blattner W, **Dakum P, Adebamowo CA**. Developing National Cancer Registration in Developing Countries - Case Study of the Nigerian National System of Cancer Registries. *Front Public Health*. 2015 Jul 30;3:186.

Jatau B, Avong Y, Ogundahunsi O, Shah S, Tayler Smith K, Van den Bergh R, Zachariah R, van Griensven J, **Ekong E**, **Dakum P.** Procurement and Supply Management System for MDR-TB in Nigeria: Are the Early Warning Targets for Drug Stock Outs and Over Stock of Drugs Being Achieved? PLoS One. 2015 Jun 22;10(6):e0128500. doi: 10.1371/journal.pone.0128500. eCollection 2015. PubMed PMID: 26098673; *PubMed Central PMCID*: PMC4476751.

Love RR, Hossain SM, Hussain MM, Mostafa MG, Laudico AV, Siguan SS, **Adebamowo C**, Sun JZ, Fei F, Shao ZM, Liu Y, Akram Hussain SM, Zhang B, Cheng L, Panigaro S, Walta F, Chuan JH, Mirasol-Lumague MR, Yip CH, Navarro NS Jr, Huang CS, Lu YS, Ferdousy T, Salim R, Akhter C, Nahar S, Uy G, Young GS, Hade EM, Jarjoura D.Luteal versus follicular phase surgical oophorectomy plus tamoxifen in premenopausal women with metastatic hormone receptor-positive breast cancer. *Eur J Cancer.* 2016 Jun;60:107-16.

Mahande MJ, Phimemon RN, **Ramadhani HO.** Factors associated with changes in uptake of HIV testing among young women (aged 15-24) in Tanzania from 2003 to 2012. *Infect Dis Poverty*. 2016 Sep 6;5(1):92.

Mukamal KJ, Clowry CM, Murray MM, Hendriks HF, Rimm EB, Sink KM, Adebamowo CA, Dragsted LO, Lapinski PS, Lazo M, Krystal JH. Moderate Alcohol Consumption and Chronic Disease: The Case for a Long-Term Trial. *Alcohol Clin Exp Res*. 2016 Sep 30.

Ndembi N. Adherence to Antiretroviral Therapy, Retention in Care and HIV Drug Resistance in Nigeria. *Curr HIV Res*. 2015;13(4):260-1.

Epidemiology and Prevention Publications

Nowak RG, Gravitt PE, He X, Ketende S, Dauda W, Omuh H, Blattner WA, **Charurat ME**; TRUST Study Group. Prevalence of Anal High-Risk Human Papillomavirus Infections Among HIV-Positive and HIV-Negative Men Who Have Sex With Men in Nigeria. *Sex Transm Dis*. 2016 Apr;43(4):243-8.

Nwofor AC, Nyamngee A, Nwabuisi C, Iwakun M, Gidado M, Mensah C, **Dakum P**, Agbede OO, Ndembi N, Blattner WA, **Abimiku AG**. Performance of Genotype MTBDRplus in the Detection of Resistance to Rifampicin and Isoniazid Among Clinical Mycobacteria Isolates in Ilorin, Nigeria. *Curr HIV Res*. 2015;13(4):308-14.

Obuku AE, Bugembe DL, Musinguzi K, Watera C, Serwanga J, **Ndembi N**, Levin J, Kaleebu P, Pala P. Macrophage Inflammatory Protein-1 Beta and Interferon Gamma Responses in Ugandans with HIV-1 Acute/Early Infections. *AIDS Res Hum Retroviruses*. 2016 Mar;32(3):237-46.

Oga EA, Brown JP, Brown C, Dareng E, Adekanmbi V, Odutola M, Olaniyan O, Offiong R, Obende K, Adewole AS, Peter A, **Dakum P, Adebamowo C**. Recurrence of cervical intraepithelial lesions after thermo-coagulation in HIV-positive and HIV-negative Nigerian women. *BMC Womens Health*. 2016 May 11;16:25.

Oga EA, Schumaker LM, Alabi BS, Obaseki D, Umana A, Bassey IA, Ebughe G, Oluwole O, Akeredolu T, Adebamowo SN, **Dakum P**, Cullen K, **Adebamowo CA**. Paucity of HPV-Related Head and Neck Cancers (HNC) in Nigeria. *PLoS One*. 2016 Apr 6;11(4):e0152828.

Onovo AA, Nta IE, Onah AA, Okolo CA, Aliyu A, **Dakum P**, Atobatele AO, Gado P. Partner HIV serostatus disclosure and determinants of serodiscordance among prevention of mother to child transmission clients in Nigeria. *BMC Public Health*. 2015 Aug 28;15:827.

Osawe S, Okpokoro E, Datiri R, Choji G, Okolo F, Datong P, **Abimiku A**. Development of a prospective cohort of HIV Exposed Sero-Negative (HESN) individuals in Jos Nigeria. *BMC Infect Dis*. 2016 Jul 22;16:352.

Peprah E, Wiley K, Troyer J, Adebamowo SN, Adu D, Mayosi BM, Ramsay M, Motala AA, **Adebamowo C**, Ovbiagele B, Owolabi M; H3Africa Cardiovascular Diseases Working Group and as members of the H3Africa Consortium. Building a Platform to Enable NCD Research to Address Population Health in Africa: CVD Working Group Discussion at the Sixth H3Africa Consortium Meeting in Zambia. *Glob Heart*. 2016 Mar;11(1):165-70.

Pharr JR, Obiefune MC, Ezeanolue CO, Osuji A, Ogidi AG, Gbadamosi S, Patel D, Iwelunmor J, Yang W, Ogedegbe G, Ehiri JE, **Sam-Agudu NA**, Ezeanolue EE. Linkage to Care, Early Infant Diagnosis, and Perinatal Transmission Among Infants Born to HIV-Infected Nigerian Mothers: Evidence From the Healthy Beginning Initiative. J Acquir Immune *Defic Syndr*. 2016 Aug 1;72 Suppl 2:S154-60.

Ramadhani HO, Muiruri C, Maro VP, Omondi M, Mushi JB, Lirhunde ES, Bartlett JA. Association of knowledge on ART line of treatment, scarcity of treatment options and adherence. *BMC Health Serv Res*. 2016 Jul 15;16:265.

Ramadhani HO, Bartlett JA, Thielman NM, Pence BW, Kimani SM, Maro VP, Mwako MS, Masaki LJ, Mmbando CE, Minja MG, Lirhunde ES, Miller WC. The Effect of Switching to Second-Line Antiretroviral Therapy on the Risk of Opportunistic Infections Among Patients Infected With Human Immunodeficiency Virus in Northern Tanzania. *Open Forum Infect Dis*. 2016 Jan 29;3(1):ofw018.

Rhee SY, Jordan MR, Raizes E, Chua A, Parkin N, Kantor R, Van Zyl GU, Mukui I, Hosseinipour MC, Frenkel LM, **Ndembi N**, Hamers RL, Rinke de Wit TF, Wallis CL, Gupta RK, Fokam J, Zeh C, Schapiro JM, Carmona S, Katzenstein D, Tang M, Aghokeng AF, De Oliveira T, Wensing AM, Gallant JE, Wainberg MA, Richman DD, Fitzgibbon JE, Schito M, Bertagnolio S, Yang C, Shafer RW. HIV-1 Drug Resistance Mutations: Potential Applications for Point-of-Care Genotypic Resistance Testing. *PLoS One*. 2015 Dec 30;10(12):e0145772.

Rodriguez-Hart C, Liu H, **Nowak RG**, Orazulike I, Zorowitz S, Crowell TA, Baral SD, Blattner W, **Charurat M**. Serosorting and Sexual Risk for HIV Infection at the Ego-Alter Dyadic Level: An Egocentric Sexual Network Study Among MSM in Nigeria. *AIDS Behav*. 2016 Feb 24. [Epub ahead of print]

Royal W 3rd, Cherner M, Burdo TH, Umlauf A, Letendre SL, Jumare J, **Abimiku A**, Alabi P, Alkali N, Bwala S, Okwuasaba K, Eyzaguirre LM, Akolo C, Guo M, Williams KC, Blattner WA. Associations between Cognition, Gender and Monocyte Activation among HIV Infected Individuals in Nigeria. *PLoS One*. 2016 Feb 1;11(2):e0147182.

Sajadi MM, Farshidpour M, Brown EP, Ouyang X, Seaman MS, Pazgier M, Ackerman ME, Robinson H, Tomaras G, Parsons MS, **Charurat M**, DeVico AL, Redfield RR, Lewis GK. λ Light Chain Bias Associated With Enhanced Binding and Function of Anti-HIV Env Glycoprotein Antibodies. *J Infect Dis*. 2016 Jan 1;213(1):156-64.

Sam-Agudu NA, Folayan MO, Ezeanolue EE. Seeking wider access to HIV testing for adolescents in sub-Saharan Africa. *Pediatr Res*. 2016 Jun;79(6):838-45.

Schwartz SR, **Nowak RG**, Orazulike I, Keshinro B, Ake J, Kennedy S, Njoku O, Blattner WA, **Charurat ME**, Baral SD; TRUST Study Group. The immediate eff ect of the Same-Sex Marriage Prohibition Act on stigma, discrimination, and engagement on HIV prevention and treatment services in men who have sex with men in Nigeria: analysis of prospective data from the TRUST cohort. *Lancet HIV*. 2015 Jul;2(7):e299-306.

Stahlman S, **Nowak RG**, Liu H, Crowell TA, Ketende S, Blattner WA, **Charurat ME**, Baral SD; TRUST/RV368 Study Group. Online Sex-Seeking Among Men who have Sex with Men in Nigeria: Implications for Online Intervention. *AIDS Behav*. 2016 May 27. [Epub ahead of print]

Stahlman S, Sanchez TH, Sullivan PS, Ketende S, Lyons C, **Charurat ME**, Drame FM, Diouf D, Ezouatchi R, Kouanda S, Anato S, Mothopeng T, Mnisi Z, Baral SD. The Prevalence of Sexual Behavior Stigma Affecting Gay Men and Other Men Who Have Sex with Men Across Sub-Saharan Africa and in the United States. *JMIR Public HealthSurveill*. 2016 Jul 26;2(2):e35.

Tekola-Ayele F, Doumatey AP, Shriner D, Bentley AR, Chen G, Zhou J, Fasanmade O, Johnson T, Oli J, Okafor G, Eghan BA Jr, Agyenim-Boateng K, **Adebamowo C**, Amoah A, Acheampong J, Adeyemo A, Rotimi CN. Genome-wide association study identifiesAfrican-ancestry specific variants for metabolic syndrome. *Mol Genet Metab*. 2015 Dec;116(4):305-13.

Ugoji C, Okere N, **Dakum P**, Ake-Uzoigwe R, Igboelina D, **Ndembi N**, **Ekong E**, Charurat M, Blattner WA. Correlates of Patient Retention in HIV Care and Treatment Programs in Nigeria. *Curr HIV Res*. 2015;13(4):300-7.

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 Professor of Microbiology at the University College Dublin (UCD) in Dublin, Ireland. 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 three-day meeting, GVN was incorporated by the U.S. government as a non-profit, 501(c)(3) organization. This past year, GVN moved its headquarters to the IHV. Its members represent expertise covering every class of human virus, and currently comprise virologists from 38 Centers of Excellence and 6 Affiliates in 25 countries, and its numbers continue to grow. GVN has held subsequent meetings in Ireland, Italy, USA, Germany, Russia, Sweden, Grenada, Estonia and China. GVN held a very successful meeting in Sapporo, Japan in Fall 2016 in partnership with the Japanese Society of Virology, the National Institute of Infectious Diseases (NIID) in Tokyo, Japan and the Research Center for Zoonosis Control (CZC) at Hokkaido University where IHV was well represented. The GVN also announced the election of prominent drug discoverer, virologist, and entrepreneur, Raymond Schinazi, PhD, Hon DSc, to GVN's executive committee and the reappointment of esteemed lawyer Tim Moynahan, Esq as Chairman of GVN's Board of Directors.

Meeting participants, many of whom are not pictured here, gather for a photo during the international meeting of the GVN Meeting in Sapporo, Japan

Participants of this year's 3rd Annual GVN Short Course are pictured with Robert Gallo, MD in his office in Baltimore, Maryland

As Zika dominated international headlines this year, in February 2016 GVN announced the formation of the GVN Zika Task Force chaired by Scott Weaver, PhD, who is director of the University of Texas Medical Branch's Institute for Human Infections and Immunity and scientific director of the Galveston National Laboratory, a GVN Center of Excellence. The GVN Zika Task force fills a gap identified by leading scientists to catalyze urgent international collaborative research. Subsequently, Allergan plc (NYSE: AGN), a leading global pharmaceutical company committed to the research and development of new treatments for infectious diseases, donated $100K to the GVN Zika Task Force to establish an international serum bank of collected blood donations from individuals after confirmed infection with the Zika virus.

In May 2016, GVN announced Dr. Weaver, as the inaugural recipient of the GVN Robert C. Gallo Award for Scientific Excellence for his leadership in the GVN, as well as his exceptional public health virology research. Moving forward, the honor will be presented at the annual meeting. Thus, during this year's meeting in Sapporo, Japan, Ab Osterhaus, DVM, PhD, Director of the University of Veterinary Medicine Hannover in Hannover, Germany, a GVN Center of Excellence, was presented with the second GVN Robert C. Gallo Award for Scientific Excellence and Leadership for his pioneering contributions in influenza and coronavirus research as well as his contributions to advancing the GVN mission. Dr. Osterhaus has discovered more than 50 new viruses in humans and animals. His knowledge has, amongst others, helped the World Health Organization to effectively combat outbreaks of SARS and pandemic Influenza. He is a member of the Royal Dutch Academy of Sciences and was awarded the Royal decoration of Commander in the order of the Dutch Lion.

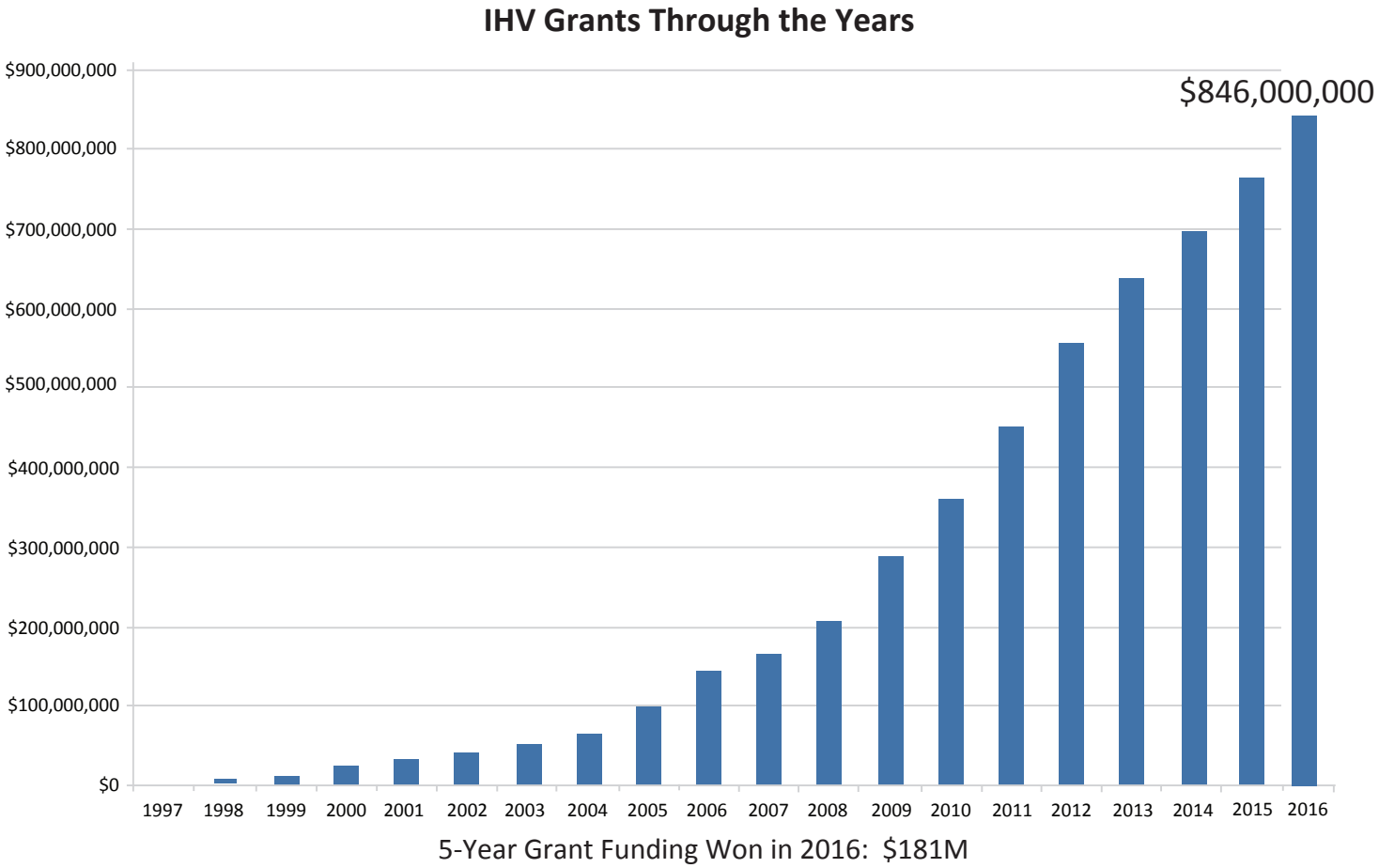
This summer, GVN held its 3rd Annual Short Course in Medical Virology in Baltimore, Maryland. The one-week intensive course covers the basic, translational, and clinical aspects of viruses that pose the greatest threats to human health. Lecturers included medical virologists drawn from across GVN's Centers of Excellence globally making for an impressive program that reviewed state-of-the-art aspects of research on a wide array of viruses. 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; Shyam Kottilil, MBBS, PhD; Patrick Ryscavage, MD; Yutaka Tagaya, PhD; Bruce Gilliam, MD; Alan Schmaljohn, PhD; George Lewis, PhD, and, Niel Constantine, PhD, MT(ASCP). Burgeoning medical virologists were encouraged to participate in deep discussions and interaction with medical virology leaders in addition to meeting with policymakers and leaders at the National Institutes of Health in Bethesda, Maryland.

IHV faculty and staff contributed time generously to the GVN throughout the year, including most notably Robert Gallo, MD, who serves as Scientific Director of the GVN, Dave Wilkins, who oversees GVN's finances, and Nora Grannell, who serves as GVN's PR Director. Other contributors include Robert Redfield, MD; George Lewis, PhD; Shyam Kottilil, MBBS, PhD; Man Charurat, PhD; Yutaka Tagaya, PhD, Alash'le Abimiku, MON, PhD, and, Joyce Johnson.

Financial Overview

When the State of Maryland recruited Robert Gallo, MD, Robert Redfield, MD, and William Blattner, MD to form a cutting-edge, biomedical research institute in 1996, no one predicted that their success would be as impactful on the State as has been the case. As the Institute of Human Virology celebrates its 20th Anniversary this year, it continues to generate greater revenue growth. The $80 million that the Institute garnered this year brings IHV's total revenue generated since its inception to $846 million. Concurrently, IHV continues to be an international leader as HIV and other chronic viruses threaten the well-being of millions of people worldwide. In 2016, IHV was awarded more than $180 million in grant funding over the next five years.

IHV also made important strides in philanthropic support. This year the Institute was awarded $995,000 in matching funds from the Maryland Department of Business and Economic Development (DBED) as part of the Maryland E-Nnovation Initiative Fund program. The E-Nnovation program is a special fund designed to help the state's research universities recruit and retain top scientists and investigators. The funds, combined with private philanthropy from The Honorable Robert Keith 'Bob' Gray and Stewart Greenebaum, enabled IHV to establish The Robert C. Gallo, MD Endowed Professorships in Translational Medicine. In addition, generous support from IHV's Board of Advisors has led to the creation of the Robert C. Gallo, MD Innovation Fund, a general fund that seeds new lines of life-saving research.



IHV BOARD OF ADVISORS

Terry Lierman, Chair
Summit Global Ventures

Peter Angelos
The Law Offices of Peter Angelos

Robert Charrow, Esquire
Greenberg Traurig LLP

Barbara Culliton
Science Journalist and Policy Consultant

The Honorable Elijah Cummings
U.S. House of Representatives

John Evans
Evans Telecommunications

The Honorable Arthur Gajarsa
WilmerHale

Michael Greenebaum
Greenebaum Enterprises.

Harry Huge
Harry Huge Law Firm LLP

Mark H. Kaplan, MD
University of Michigan Health System

Sheilah A. Kast
On the Record, WYPR

John R. Kelly
Kelly & Associates Insurance Group (KELLY)

Willliam E. Kirwan, PhD
University System of Maryland

The Honorable Nancy Kopp
Maryland State Treasurer

John McHutchison, MD
Gilead Sciences, Inc.

Charles Modica, JD
St. George's University

Timothy Moynahan, Esquire
The Moynahan Law Firm, LLC

Franco Nuschese
Georgetown Entertainment Group

Joseph Pagano, MD
University of North Carolina

Peter Palese, PhD
Mount Sinai School of Medicine

James Pinkerton
RATE Coalition

Ellen Ratner
Talk Radio News Service

The Honorable Kathleen Kennedy Townsend
Retired Lt. Governor of Maryland

Guangqi Tian
Sino Invest Ltd

Jeffrey Trammell
Trammell and Company

Lenny Wilkens
NBA Hall of Fame Coach and Player

The Honorable R. James Woolsey Jr.
Lux Capital Management

Steven Wozencraft
John O'Donnell Associates, LLC

Stewart Greenebaum, *Honorary*

The Honorable Ernest F. Hollings, *Honorary*

Ray Lewis, *Honorary*

Princess Chulabhorn Mahidol, *Honorary*

SCIENTIFIC ADVISORY BOARD

Joseph Pagano, MD, Chair
University of North Carolina

Edward Berger, PhD
National Institute of Allergy and Infectious Diseases (NIAID)/ National Institutes of Health (NIH)

Willi K. Born, PhD
National Jewish Health

William DeGrado, PhD
University of California, San Fancisco

Max Essex, DVM, PhD
Harvard AIDS Institute

Warner C. Greene, MD, PhD
Gladstone Institute of Virology and Immunology

Mark H. Kaplan, MD
University of Michigan Health System

Michel Klein, MD
VaxiBio, Inc.

Douglas Nixon, MD, PhD
The George Washington University

Erling C. J. Norrby, MD, PhD
The Royal Swedish Academy of Sciences

Micheal S. Saag, MD
University of Alabama at Birmingham Center for AIDS Research

Erica Ollmann Saphire, PhD
The Scripps Research Institute

Mario Stevenson, PhD
University of Miami

Sten Vermund, PhD
Vanderbilt University

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

INSTITUTE OF HUMAN VIROLOGY

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE