INSTITUTE OF HUMAN VIROLOGY

ANNUAL REPORT

2017

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 a Basic Science Division, Vaccine Research Division, and four Scientific Core Facilities.

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.

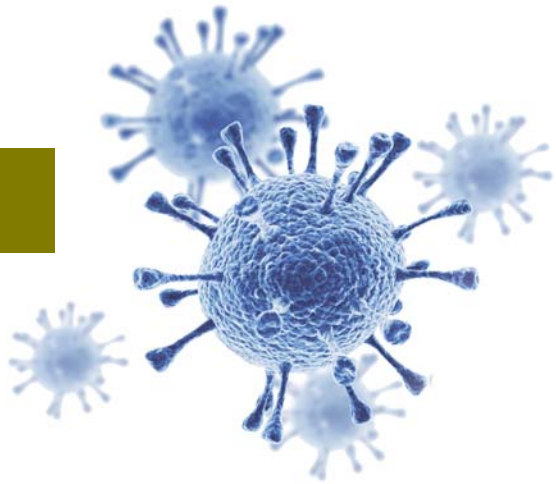
IHV's more than 300 employees include 70 faculty whose research efforts are focused in the area of chronic human viral infection and disease. At present, more than 75 percent of the Institute's clinical and research effort is targeted at HIV infection, but also includes hepatitis C virus, human T cell 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.

Our Mission

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

Contents

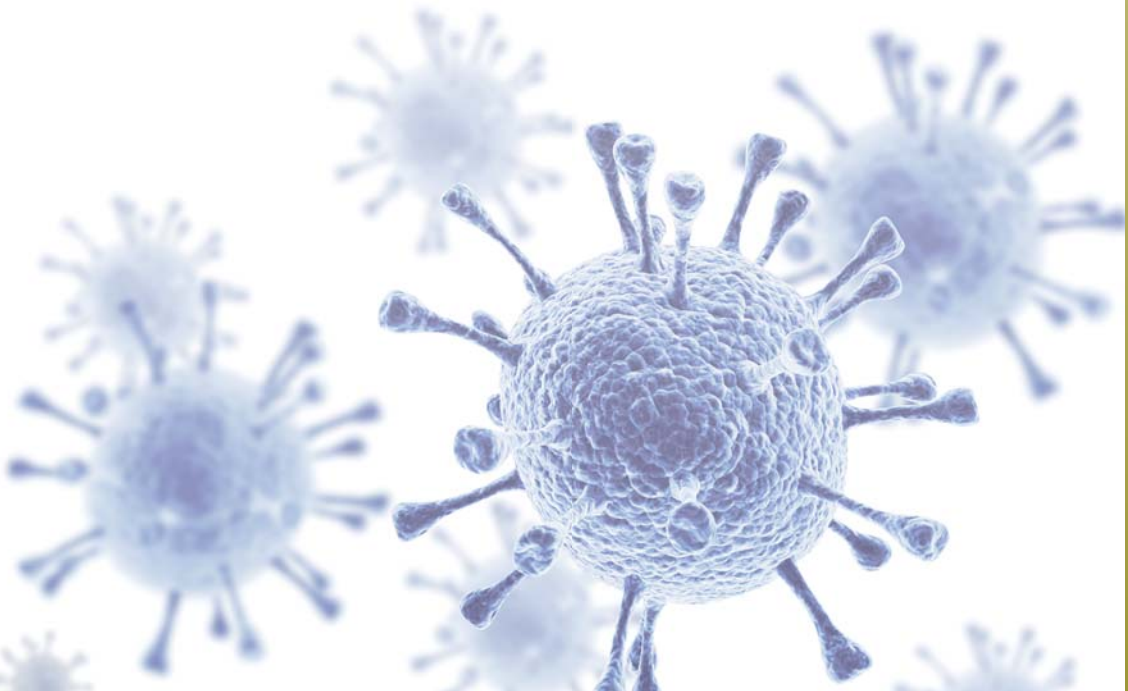
The Institute of Human Virology is a center at the University of Maryland School of Medicine and is affiliated with the University of Maryland Medical Center.
For more information call Nora Samaranayake at 410.706.8614 or visit www.ihv.org



"The future of the IHV lies in the next generation, and it is incumbent on us to be certain that we create the proper scientific environment that stimulates young people's medical scientific interest to be part of IHV's journey."

Robert Gallo, MD,

on the occasion of his 80th birthday celebration



Director's Message

Robert C. Gallo, MD

The Institute of Human Virology at the University of Maryland School of Medicine had an interesting past year.

In September 2016, IHV hosted its 18th Annual International Meeting at the Four Seasons Hotel in Baltimore. The Annual Meeting was attended by internationally renowned scientists and integrated a multidisciplinary program of basic and translational research including HIV "cure" research, emerging concepts in cancer therapy, preventative and therapeutic vaccines, immunology and viral pathogenesis, cancer and stem cells research, infectious agents causing cancer, and advances in clinical virology.

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 African, American, Asian, and European research institutions.

Additionally, following a vote by senior IHV faculty, IHV awarded annual Lifetime Achievement Awards in 2016 to two distinguished individuals who have had exceptional influence on the field of anti-viral drug and the study of the genetics, replication cycle and mechanisms of cancer induction by animal retroviruses. They included:

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Director's Message (continued)

2016 IHV Lifetime Achievement Awards

Robert Gallo, MD, is joined by IHV Lifetime Achievement Awardees, John Bartlett, MD (2012), Isaac Witz, PhD (2008), Raymond Schinazi, PhD, Hon DSc (2016), Peter Vogt, PhD (2016), and Harald zur Hausen, MD (2015)

Raymond Schinazi, PhD, Hon DSc

2016 IHV Lifetime Achievement Award for Public Service—

Raymond Schinazi, PhD, Hon DSc, Professor of Pediatrics and Director, Laboratory of Biochemical Pharmacology, Emory University and Member, Board of Directors, Global Virus Network (GVN). Dr. Schinazi has authored over 500 peer-reviewed papers and 7 books and holds over 100 issued U.S. patents, which have resulted in 15 New Drug Applications (NDA). He is a world leader in nucleoside chemistry and is best known for his pioneering work on HIV, HBV and HCV drugs. More than 94% of HIV-infected individuals in the US on combination therapy take at least one of the drugs he invented. Dr. Schinazi served on the Presidential Commission on AIDS and is the recipient of numerous awards including the 2015 William S. Middleton Award from the Department of Veterans Affairs. He is internationally recognized as one of the most influential persons in the life science sector.

Peter Vogt, PhD

2016 IHV Lifetime Achievement Award for Scientific Contributions—

Peter Vogt, PhD, Professor, Department of Molecular and Experimental Medicine, The Scripps Research Institute, California. Dr. Vogt's work includes retroviral replication and genetics, with viral and cellular oncogenes and with the identification of novel inhibitors of oncoproteins. He has made groundbreaking contributions to our knowledge of the cellular and molecular biology and to the genetics of retroviral infections, including the interaction between viral and cellular receptors, genetic recombination between retroviruses, and endogenous retroviral genomes. His discovery of the first temperature-sensitive mutant of Rous sarcoma virus provided definitive proof for the existence of oncogenes. His work on the structure of retroviral RNA identified a specific sequence responsible for oncogenic transformation, now known as the src oncogene.

This work led directly to the discovery of the cellular origin of viral oncogenes. Peter's studies of diverse retroviruses resulted in the discovery of several novel oncogenes that have become household words in cellular signaling and are of key importance in human cancer: myc, jun and PI 3-kinase. His recent work involves collaborations with chemists at the Scripps Research Institute in a quest for small molecule regulators of cancer targets, notably protein-protein interactions involving the MYC protein.During the meeting, Harvey Alter, MD, Distinguished National Institutes of Health (NIH) Investigator, Chief, Infectious Diseases Section, Associate Director of Research, Department of Transfusion Medicine, NIH; Mario Stevenson, PhD, Chief, Division of Infectious Diseases, Miller School of Medicine, University of Miami, Member, Scientific Advisory Board, IHV; and, Samuel Broder, MD, former Director of the National Cancer Institute, lectured in Dr. Schinazi's honor.

Those honoring Dr. Vogt, who also presented The Third Annual Reinhard Kurth Memorial Lecture, with special presentations included, Carl Croce, MD, Professor and Chair, Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University College of Medicine; Robin Weiss, MD, PhD, Professor of Viral Oncology, University of College London; and, Joseph Pagano, PhD, Distinguished Professor, Department of Medicine, University of North Carolina, Chair, Scientific Advisory Board, IHV.

Terry Lierman, Chairman, Board of Advisors, IHV and The Honorable Kathleen Kennedy Townsend, Lt. Governor, State of Maryland (1995-2003), Managing Director, The Rock Creek Group, during the Roast & Toast honoring Dr. Gallo's 80th Birthday

L to R: The Honorable Nancy Kopp, Treasurer of the State of Maryland, Dr. Jay Perman of the University of Maryland, Baltimore, The Honorable Brooke Lierman of the Maryland House of Delegates, and Michael Cryor of the Cryor Group

In May, IHV friends and colleagues honored my 80th birthday with a celebratory Roast & Toast. In honor of my commitment to mentor junior scientists in their pursuit of innovative biomedical research and discovery, funds raised for the event went towards a newly formed "Against the Tide Research Fund" for IHV's next generation of risk-taking young scientists. I was pleased to have IHV's Board Chair Terry Lierman emcee the event, as well as "roasters and toasters" including, E. Albert Reece, MD, PhD, MBA, Vice President for Medical Affairs, University of Maryland, John Z. and Akiko K. Bowers Distinguished Professor, Dean, University of Maryland School of Medicine; The Honorable Parris N. Glendening, Governor, State of Maryland (1995-2003), President, Smart Growth America's Leadership Institute; The Honorable Martin O'Malley, Governor, State of Maryland (2007-2015); Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases; Robert Anthony, MD, my cousin, and Chief of Cardiology Emeritus, Saint Mary's Hospital; The Honorable Nancy Kopp, Treasurer, State of Maryland, IHV Board Member; Jeffrey Schlom, PhD, Chief, Laboratory of Tumor Immunology and Biology, National Cancer Institute; John D. Evans, Chairman and CEO, Evans Telecommunications Co. & The John D. Evans Foundation, IHV Board Member; William A. Blattner, MD, Retired, IHV Co-Founder and Board Member; and, The Honorable Kathleen Kennedy Townsend, Lt. Governor, State of Maryland (1995-2003), Managing Director, The Rock Creek Group, IHV Board Member.

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Basic Science Division

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.

Vaccine Research Division

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, pursues a multidisciplinary approach to developing an HIV-1 vaccine based on expertise in molecular and cell biology, virology, immunology, structural biology, and translational medicine. 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.

Clinical Care and Research Division

The Division of Clinical Care and Research, led by **Robert R. Redfield, MD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and IHV Associate Director, continues to strengthen all three of its key missions: clinical care, clinical research, and medical education, both in the Baltimore and Washington metropolitan areas, and globally in Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania and Zambia. To accomplish these missions, the Division has assembled a team of 39 faculty and 95 support personnel, and has secured 71 active grants and contracts. The Division has significantly increased its clinical trial activity under the leadership of Shyam Kottilil, MBBS, PhD, Professor of Medicine and its international public health capacity under the leadership of Deus Bazira, DrPH, MPH, MBA, Assistant Professor of Medicine and the head of IHV's Center for International Health, Education, and Biosecurity. Since 1996, the Institute's patient base has grown from just 200 patients to currently nearly 20,000 in Baltimore and Washington, DC, and more than 1,000,000 in 10 African and 2 Caribbean nations since 2004.

Epidemiology and Prevention Division

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, supports the identification, reduction and eradication efforts for HIV/AIDS, other infectious diseases, and cancer in populations in Baltimore and around the world by deploying innovative research and evaluation studies. This year the Division launched a focused initiative to strengthen and support IHV's mentorship program for early and mid-career faculty. The Division has 8 faculty and the senior faculty have undertaken a multi-pronged approach for the development of early and mid-stage investigators, and the most telling sign of their progress is 39 publications, 13 NIH grants, three large the Centers for Disease Control and Prevention (CDC) President's Emergency Plan for AIDS Relief (PEPFAR) grants, one large Global Fund grant and multiple subcontracts awarded or ongoing in FY17.

Scientific Core Facilities

IHV's four Core Facilities help advance the Institute's research by providing a broad range of services to faculty and staff at IHV, and across the University campus. Services include cutting-edge technologies and laboratory technical support. Each Core Facility, including the Animal Core, Flow Cytometry and Cell Core, Imaging Studies of Pathogens & Cell Interactions Core, and µQUANT Core, is led by an experienced researcher at IHV. In this year's annual report, we will include information about each of the Cores and their research highlights.

Financial Overview

The IHV continues to grow at an extraordinary pace. Several years ago, our funding decreased dramatically when our largest grant ceased to be awarded to US based entities. However, we have steadily grown across all areas since then. This year's increase in grant funding across Divisions ratifies the success of the Institute's original cross-disciplinary vision. The coming years will see even more grant submissions along with our continued focus on philanthropic support. As base funding is in place for each Division for the next three to four years through recent large grant wins, we expect the growth pattern to continue.

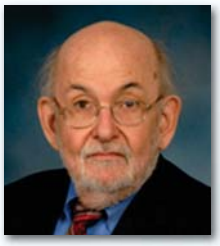
IHV Leadership

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

Wuyuan Lu, PhD

Co-Director, Division of Basic Science
Institute of Human Virology
Professor, Biochemistry and Molecular Biology
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

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

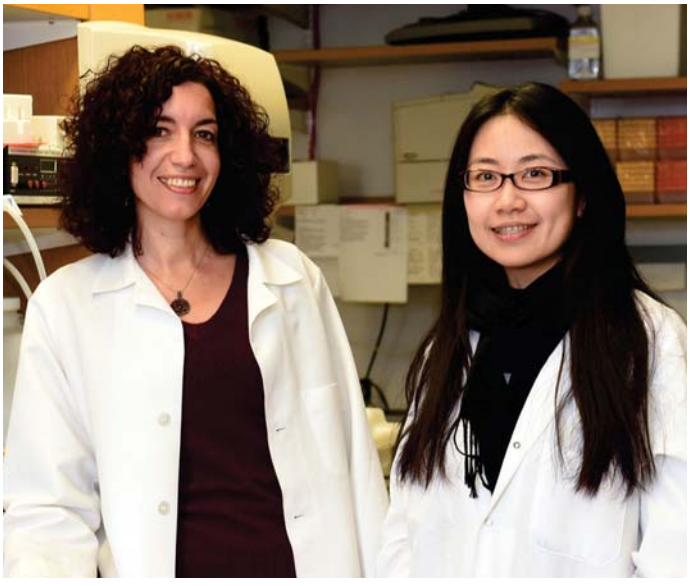
In the Division of Basic Science, nearly two dozen faculty members lead research programs defining the molecular basis of infection and immunity and developing novel therapies and treatments of infectious disease, immune dysregulation, inflammatory disorders and cancer. Approximately 100 scientists, 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 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.

Cairo Laboratory

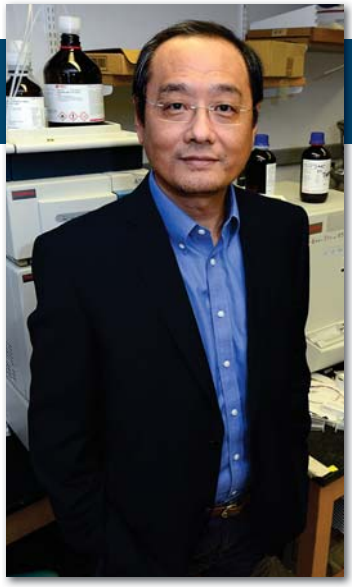
Cristiana Cairo, PhD, Assistant Professor of Medicine, studies immune responses to pathogens of global health relevance in human neonates and adults. The laboratory's model population are human γδ lymphocytes, a subset of CD3+ cells that exert rapid innate-like effector functions and contribute to regulating adaptive immune responses. In particular, in the last few years Dr. Cairo and her mentee, Dr. Hsu, have been focusing on immune responses in early life in the context of two main studies:

A) the functional program of neonatal lymphocytes, including immune-regulatory mechanisms at the fetal maternal interface; B) the impact of prenatal exposure to pathogens on the development of the infant immune system.

For the first study, the lab focused on PD1, an inhibitory receptor that regulates αβ T cell responses and is important for maintaining tolerance at the fetal-maternal interface. Haoting Hsu, PhD, postdoctoral fellow at the HIV since 2014, showed that this molecule is expressed for at least 28 days after activation by neonatal Vδ2 cells, while it is rapidly down-modulated by their adult counterparts. DNA methylation of the PD1 promoter contributes to the prolonged expression of this receptor in neonatal cells. PD1 engagement effectively inhibits TCR-mediated responses by cord blood Vδ2 lymphocytes and the extent of the inhibition correlates with the proportion of PD1+ cells. The current working hypothesis is that prolonged PD1 expression is critical for controlling Vδ2 cell responses during fetal life. Learning how this molecule is regulated in neonatal Vδ2 cells may enable manipulation of their effector functions to improve immune responses in infants.



Christiana Cairo, PhD and Haoting Hsu, PhD



Wuyuan Lu, PhD

Eric Sundberg, PhD

The second project (supported by grant # R01AI104702, NIH) uses placental malaria as a model of maternal infection that exposes the offspring to microbial antigens before birth. Prenatal exposure to microbial antigens, instead of eliciting protective immunity, can paradoxically decrease infant responses to pathogens and childhood vaccination, and increase susceptibility to infections. In a recent study in Malawi, Dr. Cairo confirmed that neonates born to women with placental infection (PM-exposed) display an altered differentiation state compared to neonates born to women without malaria during pregnancy (Unexposed), with signs of previous antigen exposure and recent activation. Interestingly, the proportion of PD1+ Vδ2 cells in the PM-exposed group is significantly lower than in the control group, although PD1 is normally upregulated after activation. This informs the hypothesis that homeostatic proportions of PD1+ Vδ2 cells at birth are maintained by low-potency endogenous antigens, but in the context of an inflammatory response with strong/prolonged antigen stimulation (e.g. during placental infection), substantial PD1 engagement contributes to cell cycle arrest or apoptosis of the most activated clones. Deletion of PD1+ Vδ2 cells would result in a measurable repertoire perturbation and attenuation of effector responses (in agreement with Dr. Cairo's previous results in Cameroon and Nigeria). Loss of innate-like broad antimicrobial function would leave neonates with lowered defenses against early life infections and decreased responses to BCG vaccination.

Finally, Dr. Cairo (in collaboration with Miriam Laufer, MD, MPH, Kirsten Lyke, MD, Franklin Toapanta Yanchapaxi, MD, PhD, and Marcelo Sztein, MD at the Institute for Global Health, University of Maryland School of Medicine), received funding to monitor longitudinally immune responses in HIV-exposed, uninfected (HEU) infants in Malawi (U011HD092308). HEU infants are more susceptible to common infections than their unexposed counterparts, and have higher mortality rate.

However, after widespread availability of antiretroviral therapy (ART) differences in morbidity and mortality between HEU and unexposed infants seem less pronounced, and it's likely that immune perturbations associated with in utero HIV exposure are mitigated by effective ART. This study will allow detailed characterization of T and B cell responses to routine immunization antigens at birth, 4 and 9 months of age in infants born to women with undetectable viral load before conception, women diagnosed late in pregnancy and women with no IHV infection. The goal is to determine whether the mere presence of HIV, even at undetectable levels, is sufficient to drive immune perturbations in HEU infants or sustained viral replication causes these changes.

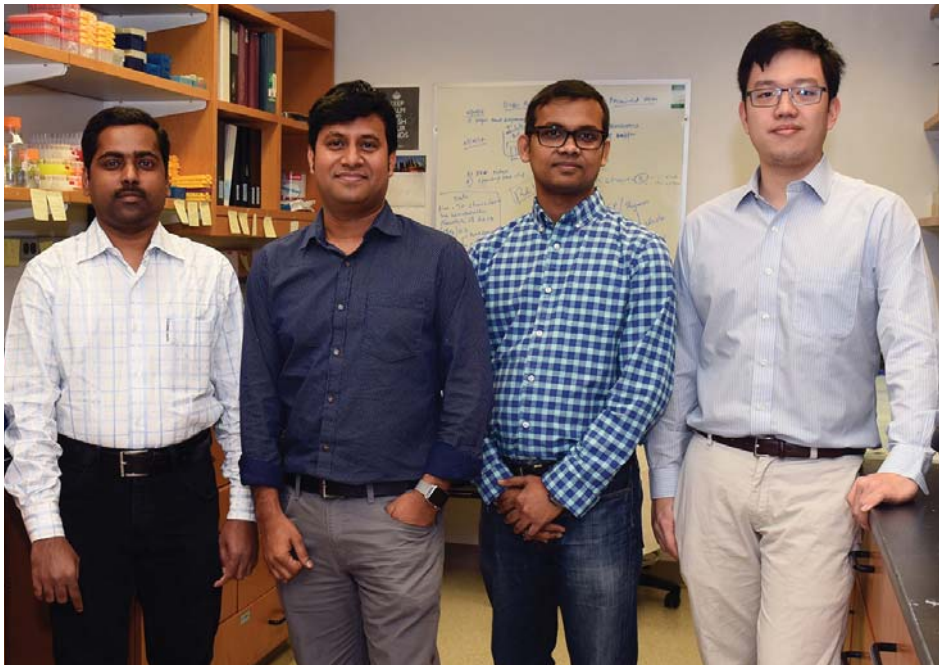
Rathinam Laboratory

In Fall-2016, **Chozha Rathinam, PhD**, Assistant Professor of Medicine, joined the IHV. In the past few years at Columbia University, the Rathinam laboratory has made seminal contributions to the field of stem cell biology. In particular, studies emerged from the Rathinam lab have unequivocally proven the importance of ubiquitylation events and E3 ligases in the control of Hematopoietic Stem Cell (HSC) development and functions. More recently, the Rathinam lab has started exploring the functions of NF-kB pathway in the biology of HSCs.

NF-kB signaling pathway is one of the most extensively studied and understood pathways, however, the physiological consequences of augmented NF-kB signaling in Stem Cells have not been understood. Despite many recent studies documenting constitutive activation of NF-kB in patients with hematological disorders, including Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS), it is remains unclear if constitutive NF-kB signaling is sufficient and/or necessary for the onset of these diseases. Research in our lab will specify the role of NF-kB in the pathophysiology mediated by Stem Cells and identify novel NF-kB mediated signal transduction pathways. In addition, these studies will provide key insights into the molecular pathways by which deregulated NF-kB signals affect the biology of human Hematopoietic Stem Cells. This work would utilize various transgenic and knockout mouse models and a novel line of humanized mouse model. Knowledge obtained through the proposed research would aid the development of newer and more successful therapies for human hematologic diseases that arise due to constitutive NF-kB activation.

In addition to the focus on HSCs, our lab has been interested in unraveling the genetic events that give rise to the origin of Leukemic Stem Cells (LSCs). One of the major challenges in cancer biology is to define aberrant molecular pathways that cause transformation of normal stem cells to cancer stem cells. Pioneering studies over a decade have highlighted the phenotypic and functional similarities between normal stem cells and cancer stem cells. Growing evidence suggests that pathways that regulate the self-renewal of normal stem cells are deregulated in cancer stem cells resulting in the continuous expansion of self-renewing cancer cells and tumor formation. Our lab has recently documented that a deficiency in c-Cbl mediated ubiquitylation events results in the transformation of normal HSCs into LSCs. Strikingly, when we blocked signal transduction pathways mediated through the cytokine-Flt3L in HSCs, the onset of leukemia in c-Cbl mutant animals is prevented. In line with our observations, recent studies from several groups have reported that human cancers including MPD, AML and JMML are associated with frequent mutations in c-CBL. Overall, these observations highlight the importance of ubiquitylation events and underline the key functions of E3 ubiquitin ligases in the prevention of hematologic cancer. Currently, we are actively engaged in the identification of signal transduction pathways that contribute to the transformation of normal HSCs into LSCs. In addition, we focus on the importance of post-translational modifications of signal transducers in the phenomenon of Leukemic transformation.

Another line of investigation in our lab is focused on unraveling the molecular identities of Mesenchymal Stem Cells. Mesenchymal Stem Cells (MSCs) are multipotent stem cells that

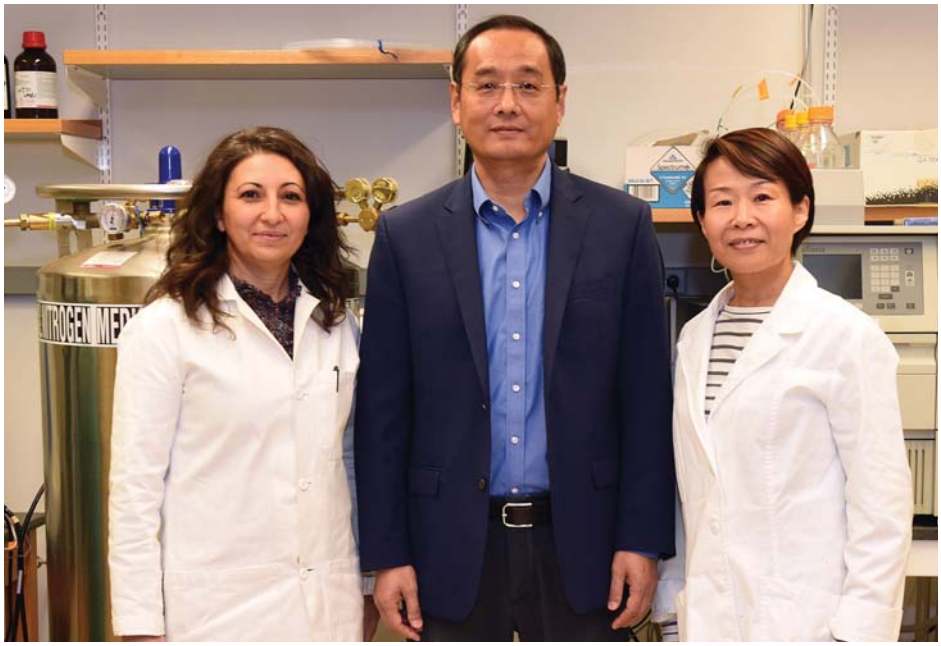


L to R: Panjamurthy Kuppuswamy, MSc, PhD, Chozha Rathinam MSc, PhD, Ram Lakhan MSc, PhD, Huanwen (Alvin) Chen, MD Candidate (Class of 2020)

can differentiate into many lineages, including Osteoblasts, Chondrocytes, Myocytes and Adipocytes. MSCs also play a very important role in immune modulation through secretion of a variety of cytokines, growth factors and chemokines. Recently, MSCs and its progenies are shown to form and control the hematopoietic "niche" of the bone marrow. These properties make these specialized cells potentially ideal candidates for tissue engineering and cell based therapies. While MSCs hold a great promise as therapeutic agents in regenerative medicine, the cellular and molecular identities of MSCs are not well elucidated. In fact, only in the past few years the exact immunophenotype of murine MSCs has been described. In an effort to contribute to a better understanding of MSC biology, we are interested in uncovering both extrinsic and intrinsic factors that control MSC self-renewal and functions.

Lu Laboratory

When a host defense peptide goes rogue… **Dr. Wuyuan Lu's** laboratory studies the structure and function relationships for and mechanisms of action of human defensins – a family of antimicrobial peptides found primarily in phagocytes and epithelial cells that play important protective roles in host defense against infectious microbes such as bacteria and viruses. The human enteric defensins 5 and 6 (HD5 and HD6), highly expressed by Paneth cells of the small intestine, are two members of the alpha-defensin family. Many studies demonstrate that HD5 and HD6 protect against enteropathogens in the gut and help maintain intestinal homeostasis by forming an antimicrobial barrier that segregates the gut microbiota from host epithelium to limit tissue inflammation and microbial translocation. A team of scientists from the IHV (Marzena Pazgier, PhD, Assistant Professor of Biochemistry and Molecular Biology in the Division of Vaccine Research, William D. Tolbert, PhD, Research Associate of Biochemistry and Molecular Biology, Division of Vaccine



L to R: Anna Lucia Tornesello, PhD, Wuyuan Lu, PhD, and Weirong Yuan, MS

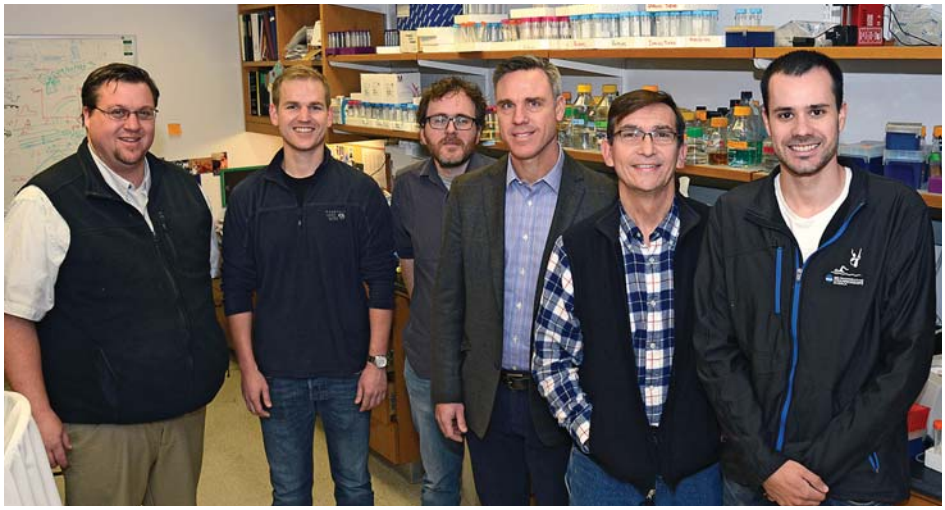
Research, and Weirong Yuan, MS of the Lu laboratory), Xi'an Jiaotong University, University of Strathclyde, Institut Pasteur and University of California Davis, led by Dr. Lu, have recently made a surprising discovery that Shigella, the etiological agent of over 160 million annual cases of bacillary dysentery worldwide, exploits HD5 to attain its extraordinary ability to colonize and destruct the intestinal epithelium.

A long-standing enigma concerning the pathogenesis of Shigella is how the pathogen can be so extremely infectious and contagious, despite lacking fimbriae or other clear mechanisms for mucosal adhesion. Moreover, while Shigella is highly infectious in humans, it does not readily infect other animals. Their study, a collaborative effort from five institutions, unveiled an unprecedented molecular mechanism that addresses both of these striking observations. They discovered that (1) HD5 promotes Shigella infection in vitro and in vivo and exacerbates Shigella-elicited tissue damage ex vivo in a sequence and structure-dependent fashion; (2) fimbria deficiency in Shigella confers its sensitivity to HD5-mediated enhancement in bacterial infection; (3) HD5 targets multiple bacterial membrane proteins to promote Shigella adhesion to and invasion of host cells. This work, which includes extensive blending of biochemical, biophysical and structural data, mechanistic and functional findings at the molecular and cellular levels, and in vivo and ex vivo results, strongly indicates that Shigella subverts innate host defense to colonize and invade the intestinal epithelium by turning HD5 into a molecular accomplice that imparts its extraordinary infectivity and pathogenicity.

Sundberg Laboratory

Dr. Eric Sundberg's research program uses the tools of structural biology to investigate molecular recognition in infectious diseases in order to define the molecular bases for pathogenesis and immunity. Of the many projects currently underway in the laboratory, here we highlight two projects in which we are investigating the activities of certain bacterial enzymes involved in immune evasion and antibiotic resistance, in order to rationalize future drug development.

In order to evade host immunity, many bacteria produce immunomodulatory enzymes. *Streptococcus pyogenes*, one of the most common human pathogens, secretes unique endoglycosidases, EndoS and EndoS2, which remove



L to R: Greg Snyder, PhD, James Fields, Daniel Bonsor, PhD, Eric Sundberg, PhD, Robert Beadenkopf, MS, and Erik Klontz

biantennary complex- and high mannose-type carbohydrates in a highly specific manner from human IgG antibodies. This renders antibodies incapable of eliciting host effector functions through either complement or Fc γ receptors (FcγRs), providing the bacteria with a survival advantage. Because antibodies are central players in many human immune responses and bridge the innate and adaptive arms of immunity, the analysis and manipulation of the enzymatic activity of EndoS/EndoS2 impacts diverse fields in biomedicine. In particular, modifying antibody glycan structures can have significant impacts on their abilities to bind to FcγRs and the subsequent immune system reactions that they induce. The next generation of therapeutic antibodies is already being constructed with modified glycan chemistries to tailor the immune reactions to increase their clinical potency. EndoS and EndoS2, and glycosynthases derived thereof, are key enzymes in the future of antibody engineering. We recently determined the X-ray crystal structures of EndoS and EndoS2, alone and in complex with various glycans, which now provide a roadmap with which to overcome many of the current antibody engineering limitations of such enzymes.

Antimicrobial resistance in Gram-negative bacteria has reached critical levels. Systemic infections from these organisms are associated with high mortality rates. Importantly, antimicrobial resistance has implications beyond the immediate issues of morbidity and mortality; none of the advances of modern medicine – including complex surgery, transplantation, cancer chemotherapy, and intensive care – are possible without effective antibiotics. Inhibition of resistance mechanisms that potentiate the activity of existing agents may be a viable approach to combat resistant pathogens. To this end, we have recently characterized a novel small molecule inhibitor of FosA, a bacterial enzyme that degrades the antibiotic fosfomycin. We have determined high-resolution X-ray crystal structures of FosA alone and in complex with both fosfomycin and ANY1, the inhibitor molecule. These structural data provide the foundation from which to develop improved versions of ANY1 that could increase the effectiveness of fosfomycin such that it could be used clinically against a more numerous and diverse group of bacterial pathogens.

Tagaya Laboratory

Yutaka Tagaya, PhD, Assistant Professor of Medicine and Head of the Flow Cytometry Core, has a laboratory with three research foci: 1. Virology (HTLV-1's oncogenesis and novel T-cell therapy); 2. Cytokine Biology (Development of multi-cytokine inhibitors and their clinical applications); 3. Immunology (unique subset of CD8 T cells with NKG2C expression). The second part has seen a major advancement since last year. One unique and general characteristic of cytokines is that they form families based on the structural similarities and usage of shared receptor components. Cytokines belonging to a family often have redundant functions because they share intracellular signaling cascades. It has become clear that many human diseases pathogenically involve more than two cytokines from a single family (to name a few, IL-15 and IL-7 for Rheumatoid arthritis, IL-21 and IL-15 for Celiac Disease, IL-2, IL-15 and IL-9 for HTLV-1 associated myelopathy, HAM), which are called "multi-cytokine diseases (MCDs)". In MCDs, each cytokine often drives the target cells to near-saturated response. The combination does not increase the strength of the cellular response, but makes the disease more difficult to diagnose and treat, because neutralizing only one (out of the many) factor is not expected to cause any visible inhibition on the pathogenic cells ex vivo and no efficacy would be expected in vivo. Dr. Tagaya's lab noted that "no effect of targeting one cytokine" should not be hastily interpreted as "the target cytokine is irrelevant to the disease." It is possible that there have been examples of this in previous clinical trials without satisfactory outcomes. In addition to the technical limitation, monoclonal antibody which is the most common anti-cytokine modality, cannot be combined to treat MCDs because of the high cost. Some years ago, Dr. Tagaya saw this technical and practical limitation of the current anti-cytokine strategy and started designing multi-cytokine inhibitors (MCIs). In other words, Dr. Tagaya wanted to develop a special stone that can shoot many birds of a feather. To this end, he co-founded a company BIONIZ Inc. (now BIONIZ Therapeutics, Irvine, CA) with Nazli Azimi, PharmD, PhD, a former colleague of his at the National Cancer Institute (NCI),

and established its scientific division before joining the IHV. We aimed at targeting the γc-family cytokines (IL-2, -4, -7, -9, -15, -21) because of their profound impacts on immune responses and on the lymphocyte development. They chose to develop antagonistic peptides based on the D-helix of these cytokines because their D-helices interact with the shared γc-molecule, thus a logical target to design MCI. They designed peptides by conserving critical residues that participate in the physical interaction with the γc, but rationally altered amino acids at non-critical positions and screened them using specific in vitro cytokine assay and generated 3 peptides (BNZ 132-1, -2, and -3) for therapeutic application. BNZ 132-1 inhibits IL-2, IL-15 and IL-9, but not other γc-or non-γc cytokines, whereas BNZ 132-2 selectively inhibits IL-21 and IL-15, and BNZ 132-3 targets IL-4 and IL-9. Importantly, their strategy not only allowed them to design MCIs, but ones with distinct target specificities. On the one hand, the design team continues to expand the repertoire of such MCIs with different target specificities to cover diverse target diseases. On the other hand, the research team studies each peptide using in vitro and in vivo systems. The mode of action (MOA) and the in vitro proof-of-concept of the lead peptide BNZ132-1 have been demonstrated in their recent publication. From the defined target cytokine spectrum, BNZ 132-1 suited to treat HAM, a progressive and incurable myelopathy caused by HTLV-1 infection and in fact we demonstrated that BNZ 132-1, but not anti-IL-2 or anti-IL-15Ab alone, efficiently blocks the ex vivo activation phenotypes of T-lymphocytes from HAM patients. In this disease, the HTLV-1 infection causes the upregulation of IL-2 and IL-15 proteins in infected CD4 T cells, and these cytokines in turn cause the hyperactivation CD8 T cells which cross the brain-blood barrier and damage the spinal cord by producing inflammatory factors. Therefore, BNZ 132-1 is expected to intercept this process by blocking IL-2 and IL-15 simultaneously. They have completed mandated toxicology, pharmacodynamics and pharmakokinetics studies using mice and non-human primates and received an IND approval from the FDA of BNZ 132-1 for treating HAM (July 2016) and started the Phase I-a (Nov 2016), in which we administered PEGylated form of BNZ 132-1 to healthy volunteers with varying doses (0.2, 0.4, 0.8, 1.6, 3.2, 6.4mg/kg, single IV injection). The team has recently completed this phase and saw temporal reduction of NK cells and regulatory T cells as expected from the known in vivo action of IL-2 and IL-15, the target cytokines, on the homeostasis of these two subsets of lymphocytes. They also delayed and temporal decrease of central memory CD8 T cells which are also controlled in vivo by these two cytokines. They saw minimum toxicity. With these results, FDA has now approved us to proceed to the Phase I-b, multiple-administration studies to further test the safety of BNZ 132-1 (starting in Sept 2017). In the meantime, the Tagaya lab research has shown additional potential clinical applications for this peptide. Previously, Dr. Tagaya's group at the NCI demonstrated that the over-expression of IL-15 in mice can cause a CD8 T-cell leukemia which resembles human LGL (Large-granular lymphocyte) leukemia and established a mouse model to study this disease. In their recent study, Dr. Tagaya's group saw that BNZ 132-1 effectively cure the LGL-like CD8 T-cell leukemia caused by IL-15 in our model mice. They are collaborating with the Loughran group (University of Virginia, the original discoverer of the LGL-leukemia) and Caligiuri group (Ohio State University, international leading expert on T-cell leukemia) and set up an LGL-leukemia consortium to conduct a clinical trial treating LGL-leukemia (and cutaneous T-cell lymphoma, CTCL) with BNZ 132-1. FDA has recently approved our IND petition of BNZ 132-1 for LGL-leukemia and we will soon commence treating LGL-leukemia with BNZ 132-1 (Oct~Nov, 2017). Furthermore, additional lab studies suggested that BNZ 132-1 can strongly control graft-versus host disease by subsiding inflammatory responses of CD8 T cells by inhibiting IL-2 and IL-15 (manuscript in preparation). They also saw its efficacy in reversing autoimmune hair-loss in mice which is a model for human Alopecia areata (manuscript in preparation). Finally, they saw potential application of BNZ 132-1 to controlling cytokine release syndrome (a.k.a. cytokine storm) which is associated with fatalities seen in viral infections including those by Influenza and Ebola (manuscript in preparation) viruses. The Tagaya lab also has on-going research and clinical application on other BNZ peptides but will describe the progress at another occasion.

L to R: Juan Zapata, PhD, Xiaorong Wu, MS, Terry-Elinor Reid, PhD, collaborating from the IHV Animal Core Facility, Yutaka Tagaya, PhD, Ngeh Toyang, PhD, collaborating from the IHV Animal Core Facility, and Josephine Geh, MS

Basic Science Publications

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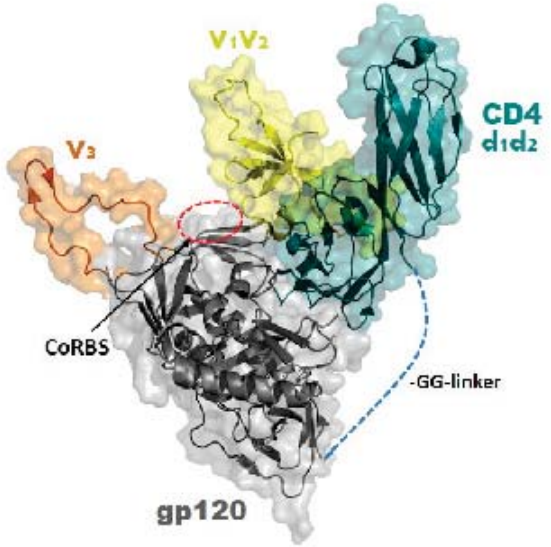
Vaccine Research Division

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, pursues a multidisciplinary approach to developing an HIV-1 vaccine based on expertise in molecular and cell biology, virology, immunology, structural biology, and translational medicine. 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 laboratory developed the FLSC vaccine concept in the early years of the Institute of Human Virology (IHV) with the first publication of its physical chemical profile in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research in collaboration with colleagues in the IHV Division of Clinical Care and Research, The Military HIV Research Program, and Profectus Biosciences. The early years of FLSC development were supported by National Institutes of Health (NIH) grants to Division of Vaccine Research Members including Dr. DeVico, Tim Fouts, PhD (now at ABL, Inc.), **Robert Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine and IHV Director, and Dr. George 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, including the Military HIV Research Program as well as the National Institutes of Allergy and Infectious Disease (NIAID), 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 R. Redfield, MD, The

Molecular Model of the FLSC Immunogen



George K. Lewis, PhD

Robert C. Gallo, MD Endowed Professorship in Translational Medicine and IHV Associate Director. The Phase I clinical trial also involves Drs. DeVico, Gallo, and Lewis of the Division of Vaccine Research, Charlie Davis, MD, Associate Professor of Medicine in the Division of Clinical Care and Research, and Jennifer Schwartz, PhD at Profectus Biosciences. Dr. Davis is the protocol chair of the Phase I clinical trial. In addition to the Phase I study, several Phase 1b studies are under development with our partners at The HIV Vaccine Trials Network, Duke Human Vaccine Research Institute, The Military HIV Research Program, Geovax, Inc., and Profectus Biosciences. This program represents the cumulative efforts of a large group of investigators who were brought together by Dr. Gallo to work on an HIV-1 vaccine when the IHV was established twenty years ago. It exemplifies the IHV's bench-to-bedside research model and represents the only HIV vaccine candidate to be clinically tested by University of Maryland, Baltimore in over 20 years.

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 Division of Vaccine Research collaboration includes Drs. DeVico and Lewis, **Roberta Kamin-Lewis, PhD**, Associate Professor of Microbiology and Immunology, **Marzena Pazgier, PhD**, Professor of Biochemistry and Molecular Biology, **Krishanu Ray, PhD**, Associate Professor of Biochemistry and Molecular Biology, and Mohammad Sajadi, MD, Associate Professor of Medicine in the Division of Clinical Care and Research. 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

L to R Back Row: Marzena Pazgier, PhD, Krishanu Ray, PhD, William D. Tolbert, PhD, Meng Li, MD, George Lewis PhD, and Chiara Orlando, PhD; L to R Center Row: Maria Luisa Visciano, PhD and Bhavna Chawla, PhD; L to R Front Row: Paula Dean and Robin Flinko; Pictured Right Anthony Devico, PhD

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. 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 simian/human immunodeficiency virus (SHIV) challenges. A bnAb that protects completely, a nAb that protects partially, and an nnAb that does not protect. However, the bnAb and nnAb mediated strong post-infection control of viremia. These three patterns define overlapping windows of protection that remain mechanistically undefined in vivo, raising the possibility that these windows might be broadened once their mechanisms are understood at the physical chemical level. Accordingly, we have developed new tools to define the mechanism of each pattern of antibody-mediated protection

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

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

Dr. Pazgier's group has produced the first atomic level epitope maps for the highly conserved Epitope Cluster A on gp120 that is a hotspot for antibody-cellular cytotoxicity (ADCC). This epitope cluster was implicated as a target of potentially protective antibodies in the RV144 vaccine trial and it is also a similar target for FLSC elicited antibodies in animal models. Dr. Pazgier's group has also developed a novel "inner-domain" protein that is stabilized in the CD4-bound conformation that expresses Cluster A epitopes with and without the

co-expression of V1/V2 epitopes also implicated as protective sites in RV144. This construct has proven useful for additional crystallographic trials, epitope mapping of immune responses, and eliciting antibodies to epitopes of Cluster A in animal models. Dr. Pazgier's group recently identified a new gp120 structure, the 8-stranded β-sandwich, that is recognized by the C11-like monoclonal antibody N12-i2. This structure appears to be a new intermediate that is formed during HIV-1 entry into CD4+ cells. Dr. Pazgier recently received a second R01 grant in collaboration with institute investigators and Andrés Finzi, PhD in Montreal to develop antibody-drug conjugates for the HIV-1 cure initiative. She will continue these studies under the aegis of her R01 grants 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 Dr. DeVico, Dr. Lewis, Wuyuan Lu, PhD, Professor of Biochemistry and Molecular Biology and Co-Director of the Division of Basic Science, and Dr. Pazgier as well as Guido Silvestri, MD at Emory 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.

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Clinical Care and Research Division

The Division of Clinical Care and Research, led by **Robert R. Redfield, MD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and IHV Associate Director, continues to strengthen all three of its key missions: clinical care, clinical research, and medical education, both in the Baltimore and Washington metropolitan areas, and globally in Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania and Zambia. To accomplish these missions, the Division has assembled a team of 39 faculty and 95 support personnel, and has secured 71 active grants and contracts.

This year, the Division continues to expand its Baltimore based ambulatory clinical programs in the management and prevention of HIV infection, HCV, and treatment of patients with other infectious diseases under the clinical leadership of Anthony Amoroso, MD, Associate Professor of Medicine, at the new clinical space on the Midtown Campus. Shyam Kottilil, MBBS, PhD, Professor of Medicine, Co-Director of IHV's Clinical Research Unit, and Associate Director for IHV's Clinical Care and Research Division, and his team have also recently initiated a targeted program to expand treatment of patients with chronic HBV infection in our nation's capital.

Dr. Kottilil's areas of focus include Hepatitis C and HBV therapeutics, HIV cure related research, and evaluation of new products for the treatment of hospitalized influenza. Also, of note this year was the full enrollment of the Phase 1 Preventive HIV vaccine trial developed by Robert Gallo, MD, The Homer & Martha Gudelsky Distinguished Professor in Medicine and IHV Director, and colleagues. The trial is scheduled to be completed by July 2018.

IHV's JACQUES Initiative (JI) has expanded its outreach to also include HCV with significant success. The JI program leadership has also developed an innovative care model, known as the Journey Center, to enhance our ability to fully engage men and women at risk for HIV infection into preventive care and enhance the clinical use of pre-exposure prophylaxis (PrEP) in Baltimore.

The IHV Division's Center for International Health, Education, and Biosecurity (CIHEB), led by Deus Bazira, DrPH, MBA, MPH, Assistant Professor of Medicine, continues to secure significant new funding with more than 20 individual grants exceeding $50,000,000 in annual funding and grant funding secured through 2022.

CLINICAL PROGRAM

The clinical program experienced significant changes in leadership this year. Dr. Amoroso was appointed Associate Director of Infectious Diseases to lead the expanding ambulatory and inpatient practices. After margining the Institute's HIV ambulatory practices into one practice in 2016, this year continues to be one of forging new identity, re-defining goals, and re-thinking quality of care delivery for the Baltimore HIV-affected population.

The leadership of this new clinical practice of over 3,500 patients is now provided by Sarah Schmalzle, MD, Assistant Professor of Medicine, with outpatient "encounter" goals anticipated to reach over 15,000 visits. There are several exciting and impactful care initiatives and grants to support innovation in care including the implementation of the care delivery model developed through the JACQUES Initiative to serve as best practice for caring for individuals with chronic medical illnesses in Baltimore and beyond.

Robert Redfield, MD

The IHV Clinical Practice continues to provide HIV primary medical care, Hepatitis C treatment programs targeting HPV infections in patients living with HIV, HIV prevention services, and general infectious diseases consultation and care. It also provides integrated 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 IHV Clinical Practice remains closely linked with the JACQUES Community Outreach Program and the JACQUES Treatment Adherence Center (TAC) to provide supportive, caring services to those most in need and these programs are becoming more interwoven. The IHV Clinical Practice fully provides expert inpatient consultation and care at the University of Maryland Medical Center (UMMC) and the University of Maryland Midtown Campus (UMMT) hospitals.

Center for Infectious Disease (CID)

Over the past year, practices of the Institute including the JACQUES Initiative, the Evelyn Jordan Center, the General Infectious Disease Clinic, and the Family Health Center at Midtown have successfully combined their ambulatory practices at Armory Place at the Midtown Campus of the University of Maryland Medical Center. Bruce Gilliam, MD, Associate Professor of Medicine and then Medical Director of the Center, oversaw the merger, and has since turned over this role to Dr. Sarah Schmalzle, who works closely with Drs. Redfield, Amoroso, and Patrick Ryscavage, MD, Assistant Professor of Medicine, to focus the mission and vision of the new Center, and ensure a strong collaborative atmosphere. Drawing from the strengths of the combined clinics, the Center offers comprehensive, integrated, and innovative care, to lead advances in the care of people living with, or at risk for, HIV while concomitantly treating patients with viral hepatitis

Members of IHV's Center for Infectious Diseases led by Sarah Schmalzle, MD (far left)

and other infections. Throughout the merger, relationships between medical and mental health providers, social workers, and their patients have been preserved, allowing for continuity of medical and psychosocial care coordination.

Persons living with HIV have access to HIV specialty care, primary care, women's health and cancer screening, anal cancer screening, medical nutrition therapy evaluation and counseling, mental health counseling, psychiatric care, substance abuse counseling, and buprenorphine maintenance therapy. Through close collaboration and partnerships with both on-site Doctors of Pharmacy and the JACQUES Initiative's Treatment Adherence Center (TAC), patients have assistance in managing and understanding complex medication regimens, can have pillboxes filled by a PharmD, and can access the TAC for directly administered antiretroviral therapy and close peer support, all tailored to each patient's needs. Laboratory services are available on site as well. All patients have an assigned social worker who assesses and assists with complex psychosocial needs, medical insurance, treatment adherence, housing, and any additional needs. Further, a partnership with the University of Maryland School of Law allows for free legal counsel for patients living with HIV also.

The Center works closely with the JACQUES Initiative through their IMPACT (described below) grant for HIV prevention among young same gender loving men and transwomen (PIs: Drs. Schmalzle and Ryscavage). The prevention program continues to expand, with 9 medical providers now specializing in pre-(PrEP) and post-exposure prophylaxis (PEP), and partnerships in place with the UMMC Emergency Department, and with Mercy's Emergency Department program for victims of sexual assault for PEP provision and follow up.

For patients with chronic Hepatitis C infection, the CID offers a comprehensive program to take a patient through diagnosis, staging of liver disease using FibroScan technology, prior authorization through their insurance companies for direct acting antivirals, and finally through initiation of treatment, monitoring response to treatment, and for the clear majority, cure of Hepatitis C.

The CID sees patients with a variety of other infections, and provides follow up for patients leaving the hospital requiring outpatient intravenous antibiotics. The Center also provides antibiotic infusions on-site and skin testing for penicillin allergy.

The Center has seen a recent increase in interest from students of medicine, pharmacy, and nursing, as well as internal medicine residents from the UMMC Main and Midtown campuses.

The CID recognizes the benefits to patients, the scientific community, and public health which can be gained by having an active and collaborative research program in place, and is working to make our patients aware of research opportunities through the IHV.

JACQUES Initiative

In FY2017, the JACQUES Initiative (JI) updated its mission, vision, and strategy to meet the needs of evolving public health epidemics and to support the directives of the Clinical Division of the IHV: to change lives, engage communities, and support health systems affected by HIV and Hepatitis C (HCV). JI's core services include institutional capacity building, community engagement, HIV and Hepatitis C testing, outreach services, treatment support, support groups, education, prevention, and volunteer opportunities. JI's strategy is to facilitate greater access to HIV and Hepatitis C care by implementing the transformation of individual, institutional, and community-based education and supportive services in alignment with the goals of the National HIV/AIDS Strategy, and the Action Plan for the Prevention, Care, & Treatment of Viral Hepatitis.

Through routine clinical visits and community screening programs, JI has reached 20,000 individuals for HIV testing and linkage to care services, as well as 11,000 for HCV testing and linkage to care services. JI also provided support for daily, weekly and monthly observed therapy for HIV and other diseases to 408 clients through 14,670 visits to our Treatment Adherence Center.

Major gains were made in institutional capacity-building, especially development of infrastructure for routine HCV testing and linkage to care, with the following achievements:

1. Implementation of a reflex to HCV RNA for positive HCV antibody tests run at UMMC's downtown and Midtown campuses.
2. Expansion of routine testing for HIV and HCV through an automated process to the ambulatory setting at UM-affiliated primary care sites through use of a Best Practice Advisory (BPA).
3. Expansion of routine testing for HCV to the UMMC Midtown Emergency Department through an automated prompt in Epic.
4. Epic in-basket notifications for the JACQUES Initiative linkage to care team for individuals who screen positive for HCV, or have a history of HCV. This infrastructure allows for timely identification and linkage to care for persons with HCV using our medical center.
5. Creation of HCV "smart order sets", which use eligibility criteria to pre-select patients who are eligible for testing in the UMMC Midtown inpatient setting. We plan to expand this infrastructure to the downtown campus in the upcoming year.

The JI community outreach program continues to engage with the most vulnerable populations. Recent emphasis is placed on reaching same gender loving men and transwomen through the CDC-funded/Baltimore City Health Department Project IMPACT, a high impact prevention program implemented in concert with the IHV Clinical Practice. In FY2017, over $300,000 of funding was used for staff to reach the community through outreach, social networking, and awareness-raising, and to link individuals at high risk for HIV prevention to biomedical prevention services.

JACQUES Initiative staff work to address Baltimore's HIV epidemic by expanding access to comprehensive prevention

This year, JI's Treatment Adherence Center (TAC) relocated to the Midtown campus. This provides an opportunity for treatment adherence services to be co-located with the clinical services offered by the IHV Clinical Practice. In addition to easing access to both TAC and clinical services, the re-location provides an opportunity for a more collaborative approach for patient care.

In this upcoming year, JI will work toward achieving its goal of providing supportive services in a community based location so citizens can access services which include education, support groups, testing, linkage to care, and peer support in one location.

IHV Washington, DC-Based Clinical Programs

Since Dr. Kottilil's recruitment to the IHV, our clinical program has expanded to involve Washington, DC. To date, over 1,600 unique patients have been linked to care and have been seen in one of the IHV supported DC clinics. Approximately 25% of those patients have HIV co-infection with HCV, and the remaining primarily have HCV-mono-infection. The Washington program has provided HCV treatment for well over 1,000 patients. Dr. 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 under Lydia Tang, MB ChB, Associate Professor of Medicine and Eleanor Wilson, MD, Assistant Professor of Medicine, located at the Downtown and Midtown campuses, and Angie Price, NP, at the Baltimore Veterans Hospital. 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 IHV 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 has established 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. Dr. Tang has received three grants to support the HBV clinical research program (TEMUL from Gilead Sciences, Roche Laboratories, TRUCULTURE and FOCUS grant from Gilead Sciences).

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

CLINICAL RESEARCH

Clinical Research Unit (CRU): The IHV 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 three nurse practitioners, three nurse coordinators, a pharmacist, a phlebotomist, a regulatory specialist, four study/research coordinators, and three laboratory technicians. During the past year, the CRU has seen significant expansion in novel clinical trials (28 clinical trials, of which 13 are investigator initiated, and 15 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: This ongoing Phase 1a (dose escalation), randomized, placebo-controlled, 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, which was initially led by Dr. Gilliam, is now led by Charles Davis, MD, Associate Professor of Medicine and Dr. Chua. This preventive FLSC vaccine was developed by IHV scientists under the leadership of Dr. Robert Gallo Gallo, George Lewis, PhD, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Director of the IHV Division of Vaccine Research and Anthony DeVico, PhD, Professor of Medicine in the IHV Division of Vaccine Research, and this trial represents 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, and this study is now fully enrolled.

Hepatitis C Clinical Trial Program

There has been a rapid expansion of the clinical research program focused on novel, investigator initiated clinical trials. This program is one of the most productive clinical research programs in the country with key publications evaluating shortened durations of therapy of 6 weeks, success of retreatment of hepatitis C patients with high cure rates (Kohli et al. LANCET 2015 PMID: 25591505, Kattakuzhy S. et al. Annals of Intern Med PMID: 26595450, Wilson E et al. Clin Infect Dis PMID: 26503379, PMID: 26521268, Bourlieire M et al. NEJM PMID 28564589, Wyles et al, Clin Infect Dis PMID 28369210)

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 manuscript was recently published as a major article in the Annals of Intern Med (PMID: 28785771). This research has the potential to be a genuine game-changer for global hepatitis C therapy (funded by NIAID, Gilead Sciences, Inc.). After the successful completion of this trial, the ASCEND model is being investigated in international settings in Rwanda (David Riedel, MD, MPH, Assistant Professor of

Medicine; Gilead Grants) and in two sites, Mumbai and Imphal in India (Gilead Investigator-initiated grants).

RESOLVE Trial: A major clinical dilemma confronting clinicians today is how to treat patients who fail direct-acting antiviral (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: Drs. Jennifer Husson and Anthony Amoroso 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 to evaluate clinical and immunologic outcomes of treating HCV using Zepatier, before or after renal transplantation.

STOP-CO Clinical Trial: Drs. Redfield, Kottilil, and Rolf Barth, MD, Associate Professor of Surgery, University of Maryland School of Medicine, along with collaborators from NIH and University of California at San Francisco were awarded a novel U01 grant from the NIAID/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.

MAVERIC: Dr. Lydia Tang is developing a cohort of HIV and HCV co-infected subjects who are being followed for progression of liver fibrosis 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, Drs. Elana Rosenthal and 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, transgender 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 100 courses of HCV therapy (Epculsa) and 100 courses of PrEP, and a Merck Investigator initiated proposal to support treatment for an additional 100 patients.

TIGER (The Initiative for immiGrant Engagement for Recognition of hepatitis B): is an innovative project representing an academic & community collaboration between the 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.

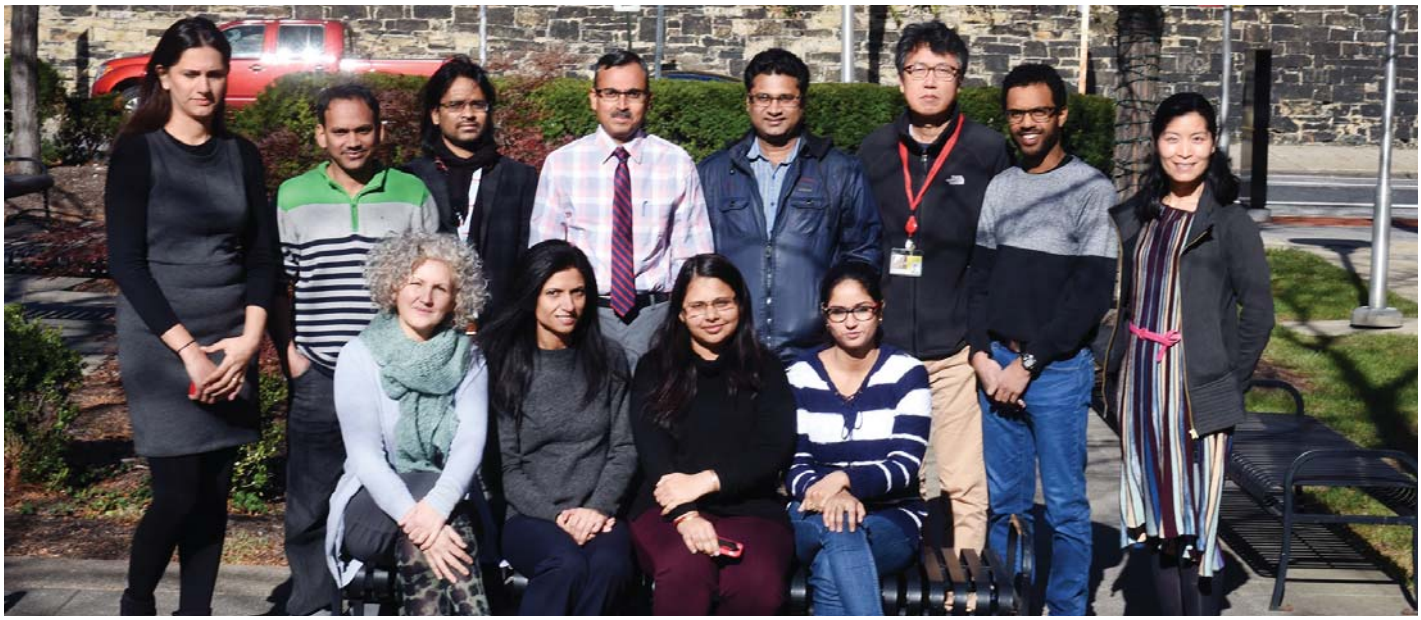
TEMUL (Tenofovir AlafenaMide for HBV—a LongitUdinaL study) Tenofovir Alafenamide (TAF): a pro drug of tenofovir was developed which has shown similar safety and efficacy to TDF in chronic hepatitis B patients. TEMUL is a study aimed at establishing a real-life cohort of urban patients with chronic hepatitis B who will be initiated on TAF.

Hepatotoxicity of ART: In 2015, Dr. Kottilil, in collaboration with Kenneth E. Sherman, MD, PhD from the University of Cincinnati, was awarded a R01 grant from NIAID for evaluating the mechanisms of antiretroviral therapy mediated hepatotoxicity.

HOPE in Action: Dr. Anthony Amoroso, along with our transplant surgery team and investigators from Johns Hopkins University, won an U01 award from NIAID to evaluate the use of HIV-infected donor kidneys for transplantation into HIV-infected kidney transplant recipients.

HIVTR CCR5 Clinical Trial: Dr. Redfield recently won an U01 award from NIAID to evaluate the use of CCR5 blockade in HIV-infected kidney transplant recipients to increase kidney graft survival.

HIV and Comorbidities: Shashwatee Bagchi, MD, Assistant Professor of Medicine, studies the cardiovascular outcomes associated with chronic viral infections, including HIV and HCV. She conducts clinical trials to stratify cardiovascular risk associated with HIV and HCV and utilize laboratory based assays to evaluate underlying immune activation. She was recently awarded a K23 grant from the National Heart Blood and Lung Institute to pursue atherosclerotic changes associated with HCV cure in patients with or without HIV infection, using CT angiography.



Members of the Clinical Care and Research laboratory-based programs led by Shyam Kottilil, MBBS, PhD (pictured back row, center)

Clinical Care and Research Division Laboratory Based Programs

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 most 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 Bhawna Poonia, PhD, Assistant Professor of Medicine, 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 research grants form Arbutus Pharmaceuticals, and from Gilead Sciences.

Alongside an 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 sustained virologic response (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, Drs. Kottilil and Poonia continue their investigations into determinants of SVR with short duration DAA therapy. With ongoing follow up of a large cohort of patients, they continue to evaluate the persistence of adaptive immune responses to HCV in patients who achieve SVR to determine long term protection for reinfection in patients with continued high risk behavior. These projects are funded by three investigator initiated clinical research studies by Gilead Sciences.

Recently, Dr. Poonia was awarded an NIH R01 grant from National Institute of Drug Abuse to study the immune correlates of protection of reinfection among people who are marginalized at the highest risk of acquisition of HCV namely, those with HIV infection and people who inject drugs.

Thanks to antiretroviral therapy (ART) patients with HIV are living longer, but increasingly often they necessitate treatment for comorbidities such as cancer. Currently, lung cancer is the leading cause of cancer death in patients with HIV. The Redfield laboratory is investigating cellular targets that may help control both HIV and malignancy in patients.

One cellular target we are actively investigating is mammalian target of rapamycin (mTOR), a conserved cellular serine/threonine kinase that forms two complexes in cells, mTORC1 and mTORC2. mTORC1 promotes translation initiation and synthesis of cellular proteins, whereas mTORC2 regulates full activation of the AKT pathway, and also regulates PKC signaling pathways. Previous work by our group has shown that pharmacological targeting of mTORC-1 with allosteric inhibitor Rapamycin reduces cell expression of CCR5, a main co-receptor of HIV, and inhibits virus entry. The potential of targeting mTOR to impact the HIV reservoir in under active investigation in both the humanized mouse model, and a proof of concept trial in HIV infected solid organ transplant recipients.

We have also showed that dual targeting of mTORC-1 and -2 with catalytic inhibitor INK-128 reduces CCR5 (and thereby virus entry), and also provirus transcription. We showed that INK-128 reduces HIV replication in humanized mice in the absence of toxicity. 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 pharmacological inhibition of CDK9 with Indirubin 3'-monoxime (IM) inhibits HIV transcription both in vitro and in vivo in humanized mice. More recently, we have demonstrated that targeting of CDK9 with IM inhibits HIV during the chronic phase of the disease in the absence of toxicity. 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 suggest that targeting of 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 malignancy.

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. Lewis and DeVico in the Vaccine Research Division. He has two active grants, an NIH R01 entitled, "Discovery of acidic epitopes for HIV-1 broadly neutralizing seroantibodies," and a VA Merit Award entitled, "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. The lab has isolated several broad neutralizing antibodies that are among the most potent and broad described to date.

The laboratory of Nicholas Stamatos, MD, Assistant Professor of Medicine, includes research 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 is studying 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. Polysialic acid is a unique glycan modification of at least three proteins, neural cell adhesion molecule, neuropilin-2 (NRP-2), and E-selectin ligand-1, that are expressed at different stages of monocyte maturation. Polysialic acid on O-linked glycans on NRP-2 sequesters chemokine CCL21 and promotes chemokine receptor CCR7-mediated migration, a function that may be different from its role on monocytes. He has shown that loss of polySia by peritoneal macrophages enhances phagocytosis of Klebsiella pneumoniae and promotes dendritic cell-induced lymphocyte activation. He has also found that ST8 SiaIV-/- mice, in which leukocytes are devoid of detectable polySia, are highly susceptible to intranasal infection with a sublethal dose of Streptococcus pneumoniae when compared to WT mice. 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. He expects to demonstrate that controlling the extent of polysialylation of specific glycoconjugates (i.e. by regulating the activity of sialidases and/or sialyltransferases) with mAbs or pharmacologic inhibitors will have therapeutic value in various disease states of inflammation and infection.

Although much is known about the glycosylation of human immunodeficiency virus (HIV) envelop proteins, relatively little is known about how glycosylation of proteins on the surface of permissive lymphocytes affects infection. 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 has proposed 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. He has also found that removal of polySia from a specific protein on the surface of lymphocytes or in the extracellular milieu markedly inhibits infection, in contrast to our finding with monomeric sialic acid. He expects to identify a novel polysialylated protein(s) expressed by activated lymphocytes and to define the mechanism by which it promotes binding of HIV-1 to the cell surface. The results from his 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.

Polysialic acid has provided a useful handle for our identifying proteins whose functions were not previously appreciated on immune cells. Class 3 semaphorins are soluble proteins that signal through neuropilin/plexin coreceptors and are well-recognized for their role in guiding axonal migration during neuronal development. The discovery of polysialylated NRP-2 expression in human dendritic cells prompted him to examine a potential role of the semaphorin/neuropilin signaling axis in these cells. He has found that dendritic cells express semaphorins 3A, 3C and 3F and that these semaphorins, likely with coreceptors NRP-1, NRP-2 and plexins-A1 and/or -A3, cause F-actin reorganization and promote chemotaxis. Thus, his

studies have identified an additional signaling axis in human dendritic cells mediated by soluble factors. It is likely that these semaphorins and NRPs promote additional activities of human dendritic cells during innate and adaptive immune responses. Dr. Stamatos expects that the additional polysialylated proteins that he identifies on immune cells will have equally significant roles in cell function.

Dr. Shashwatee Bagchi is currently focused on investigating the cardiovascular complications of patients who have chronic hepatitis C infection, HIV infection, or both, and works closely with Dr. Shyam Kottilil, as well as Sanjay Rajagopalan, MD at Case Western Reserve University and Robert Weiss, MD at Johns Hopkins University. She has multiple projects she is engaged in to address this clinical problem and consequent research questions, ranging from a retrospective cohort study of our HIV-infected clinic patients to developing a prospective cohort study among HIV and HCV mono-infected and HIV/HCV co-infected. Additionally, she is the site PI for a randomized controlled trial evaluating the efficacy of colchicine in reducing endothelial injury among HIV-infected patients. Dr. Bagchi has a NIH K23 grant titled "Elucidating Chronic Hepatitis C Infection as a Risk Factor for Coronary Heart Disease in HIV-Infected Patients", and also receives support through Dr. Robert Weiss' NIH RO1 "Inflammation and Coronary Endothelial Dysfunction in HIV".

Center for International Health, Education, and Biosecurity (CIHEB)

Created in 2016 to lead the IHV's international health programs, the Center for International Health, Education, and Biosecurity (CIHEB)'s mission is to improve individual health outcomes and thereby population health, to safeguard communities against health-related threats, and to promote health equity worldwide. CIHEB currently implements 17 programs in seven countries with an annual funding portfolio of greater than $52 million, predominantly focusing on HIV, TB, and biosecurity.

Expanding international portfolio: CIHEB has experienced tremendous growth under the leadership of Dr. Deus Bazira. Since September 2016, CIHEB has been awarded a projected $212 million in new federal funding over five years from CDC, launching nine new programs across Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania, and Zambia. These programs enable CIHEB to expand our work in those Sub-Saharan African countries bearing the greatest burden of the HIV pandemic.

Botswana: Our work in Botswana began in 2015 with a $24.5 million CDC funded award , and in 2017 launched a second grant FEDISA-HIV ("End HIV/AIDS"), a $16M program supporting the Government of Botswana to scale-up quality Community HIV Testing and Counseling (CHTC), and Linkage to Care (LTC) for people living with HIV (PLHIV) in priority PEPFAR districts.

Haiti: In 2016, CIHEB's Haiti team completed a five-year educational, and technical assistance grant, while simultaneously launching a new project in partnership with Catholic Medical Mission Board (CMMB). Our in-country team has quickly become a preferred partner for technical assistance throughout many clinical sites in Haiti.

Kenya: CIHEB Kenya was awarded more than $117 million over five years through four new programs in HIV service delivery, laboratory systems strengthening, and national medical education, making Kenya our largest country program. Alongside direct implementation of HIV care and treatment, our support of the Kenya Medical Research Institute (KEMRI) and the University of Nairobi is increasing research capacity and building infectious disease expertise in Kenya's strongest academic institutions. CIHEB Kenya's Medically Assisted Therapy (MAT) Methadone clinics continue to be flagship successes.

Nigeria: CIHEB Nigeria's $22 million Strengthening HIV Field Epidemiology, Infectious Disease Surveillance, and Lab Diagnostics (SHIELD) program (2016 to 2021) supports the Government of Nigeria in developing a robust method of collecting and evaluating data to identify gaps in HIV health care. SHIELD expands on the ongoing success of Nigeria's Strengthening Epidemic Response Systems (SERS) program, which has enabled our Nigeria team to emerge as leaders in innovative use of data for biosurveillance and outbreak response.

Rwanda: CIHEB Rwanda's "IMAKAZA" (To Sustain) program was launched in 2017. IMAKAZA strengthens and institutionalizes sustainable national, provincial, and district HIV oversight and delivery systems through training and mentorship to improve healthcare worker competencies, targeting universal access to treatment and long-term epidemic control through dynamic evidence driven programming. CIHEB's Partnership for Advanced Clinical Mentorship (PACME) grant led by Dr. David Riedel, recently completed five and a half years of educating 3,833 health care workers (primarily nurses, medical doctors, and social workers) through didactic and online teaching approaches.

Tanzania: CIHEB Tanzania's REACH program is CDC's high-level strategic partner, providing targeted technical assistance to local clinical/implementing partners, MDH, THPS, and AGPAHI, and 10 regional government health management teams. Over the last year, REACH has driven progress on saturating HIV testing and treatment in Dar es Salaam and implementing "Test and Start", where all individuals who are newly tested as HIV positive are immediately offered the chance to start antiretroviral therapy (ART). In its first year, REACH has become known for its innovative use of data analysis to improve the national HIV care cascade.

Zambia: CIHEB Zambia has three active programs, two of which employ the Community HIV Epidemic Control (CHEC) model. CHEC uses community health workers (CHWs) equipped with electronic tablets running SmartCare Lite to test, diagnose, and link HIV-infected people to care. Zambia's newest approximately $17 million Z-CHEC program expands this successful model in partnership with the Government of Zambia to ensure strong linkage between facilities and communities in HIV testing and treatment.

Kenya

Nigeria

Tanzania

Zambia

Several teams from IHV's Center for International Health, Education and Biosecurity

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Epidemiology and Prevention Division

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, supports the identification, reduction and eradication efforts for HIV/AIDS, other infectious diseases, and cancer in populations in Baltimore and around the world by deploying innovative research and evaluation studies. This year the Division launched a focused initiative to strengthen and support IHV's mentorship program for early and mid-career faculty.

Man Charurat, PhD, MHS

The Divisions' senior faculty have undertaken a multi-pronged approach for the development of early and mid-stage investigators, and the most telling sign of their progress is 39 publications, 13 NIH grants, three large the Centers for Disease Control and Prevention (CDC) President's Emergency Plan for AIDS Relief (PEPFAR) grants, one large Global Fund grant and multiple subcontracts awarded or ongoing in FY17. One of the keys to the Division's success is our outstanding early and mid-stage faculty in international research highlighted below. Within the past year, our early and mid-stage faculty have submitted over $264M in funding. In addition, the Division oversees the Implementation and Dissemination Science Track for University of Maryland Baltimore Graduate School's Master of Science and supports the PhD in Epidemiology with the mission to build HIV/AIDS research capacity in advanced epidemiology approaches in the next generation of Nigerian scientists.

Patrick Dakum, MBBS, MPH, Assistant Professor of Epidemiology and CEO of the Institute of Human Virology, Nigeria (IHV-Nigeria), has supported and nurtured the growth of the IHV-Nigeria since 2004. He has played a central role in developing research capacity and public health implementation at IHV-Nigeria. As a leader in providing quality health services, capacity building and research in West Africa, IHV-Nigeria currently has a substantial research enterprise funded by the National Institutes of Health (NIH), the CDC, the World Health Organization (WHO), Global Fund, and international foundations. IHV-Nigeria's International Research Center of Excellence (IRCE), directed by **Alash'le Abimiku, MON, PhD**, Professor of Medicine, complements IHV-Nigeria's Public Health Implementation Center through which Dr. Dakum, Principal Investigator for the large CDC PEPFAR grant in Nigeria and Principal Recipient for the Global Fund Drug Resistant Tuberculosis Grant (DR-TB), implements

Groundbreaking for IHV-Nigeria's new International Research Center of Excellence building

the public health grants. Dr. Abimiku was recently awarded another NIH award entitled, "Breast Milk Microbiota Influence on Infant Immunity and Growth (BEAMING)." This $1.3M award is funded to study how the breast milk affects the gut bacteria in infants exposed but un-infected by HIV affects their growth and their ability to respond to childhood vaccinations. Dr. Abimiku's leadership in international research and training was recently highlighted along with scientist leaders at the Centre for the Aids Programme of Research in South Africa (CAPRISA) in Lancet 2017.

The Division's ACTION Plus-up project is a 5-year CDC award with a goal to enhance the delivery of comprehensive HIV services for epidemic control in scale-up subnational areas and sustain services in maintenance areas through effective, evidence-based, data-driven and efficient strategies. Through innovative implementation models, Dr. Dakum has been able to achieve an increased uptake and yield of HIV testing among high-risk individuals and populations in facilities and communities in Nigeria. While testing of pregnant women for HIV was expanded, linkage of identified positives significantly improved in general, up to 98% in some locations. Retention of patients also increased with innovative approaches, such as differentiated community care and pharmacy models which decentralized drug pick-ups. The capacity of the laboratories was strengthened through improved networks, logistics and quality management systems with focus on early infant diagnosis and viral load monitoring. A rigorous quality assurance program is being implemented through the WHO Stepwise Laboratory Improvement Process Towards Accreditation (SLIPTA) and ISO 15189 accreditation of clinical laboratories.

To strengthen patient management and monitoring and improve patient outcomes, an electronic medical system

was deployed to all 318 treatment centers and the aggregate data integrated with the National Data Repository for access and use to improve program implementation in Nigeria. Through the NigeriaQual project, an award to the IHV and in collaboration with IHV-Nigeria to support the national quality improvement initiative in Nigeria, the project has successfully participated in 6 rounds of quality improvement performance measurement exercises. From an initial 63 facilities in 18 states in the first round, the number of facilities has steadily increased with each round. To date, capacity has been built in 120 facilities in 21 states to conduct the biannual performance measurement exercise. Dr. Dakum was notified of the successful application of the subsequent PEPFAR 3.0 funding, the ACTION to control HIV epidemic through evidence (ACHIEVE Project, $24.9M annually) runs September 30, 2017-Sept 29, 2022.

Dr. Dakum is also Project Director for IHV-Nigeria's Global Fund Drug-Resistant Tuberculosis Grant (DR-TB). The goal of the Grant is to ensure prompt access to high quality, patient-centered DR-TB diagnosis, treatment and follow-up services, thus contributing to improved treatment outcomes and reduction in DR-TB transmission in Nigeria. Key achievements in the DR-TB Program from 2011 to date include access to diagnosis for 160,222 presumptive DR-TB cases, enrollment of 3,706 DR-TB patients on treatment; capacity building for 1,729 health care workers including Doctors, Nurses, Laboratory professionals and Community Health Workers, 76% of States have DR-TB Treatment Centre's established, 100% of States have constituted State DR-TB expert teams, 40% of Local Governments have capacity to manage DR-TB patients in the community, 100% Zonal coverage of TB Reference Laboratories and 90% of the TB Reference laboratories have adequate performance on External Quality Assurance, 100%. This grant is extended to June 30, 2018.

Nadia A. Sam-Agudu, MD, presents at the 2017 International AIDS Society meeting in Paris, France

Nadia A. Sam-Agudu, MD, Assistant Professor of Epidemiology and Prevention and a pediatric infectious disease specialist, is one of our physician-researchers based full-time in Nigeria. Her research background in resource-limited settings includes Ghana and Nigeria and focuses on maternal and child health. She just completed a study funded by the WHO and Canadian government's INSPIRE initiative entitled, "the MoMent study," (PI Dr. Nadia Sam-Agudu). The study was a prevention of mother-to-child transmission of HIV (PMTCT) implementation research study. After 5 years of implementation in rural North-Central Nigeria, the study ended in September 2017. A total of 497 HIV-positive women were enrolled, along with 408 live-born HIV-exposed infants. The primary outcomes of interest were maternal retention in PMTCT programs, and timely presentation of infants for early infant diagnosis (EID) testing by 2 months of age. MoMent reported that structured maternal peer support increased maternal retention at 6 and 12 months post-delivery by ~ 6 and ~7-fold respectively, and timely infant EID presentation by ~4 fold. Maternal viral load suppression at 6 months postpartum was also improved by ~5 fold. Dr. Sam-Agudu presented these high impact findings as part of a plenary presentation on "Ending Pediatric AIDS" at the 2017 International AIDS Society meeting in Paris, France. MoMent findings were published in the Journal of AIDS, May 2017. This year, Dr. Sam-Agudu became an NIH independent investigator and received a $1.13M NICHD R01 award to test health-system-based innovative approaches to support adolescents living with HIV. In the upcoming year, she will be expanding on her prior work in pediatric malaria through collaborations with other University of Maryland, Baltimore (UMB) faculty and under continued mentorship from Dr. Man Charurat.

Through MPower funding, **Rebecca Nowak, PhD**, Assistant Professor of Epidemiology and Prevention and an infectious disease epidemiologist, in collaboration with Soren Bentzen, PhD, DMSc, Professor of Epidemiology & Public Health, University of Maryland School of Medicine and Jacques Ravel, PhD, Professor of Microbiology and Immunology, Institute for Genome Sciences, University of Maryland School of Medicine, explored the impact of HIV and antiretroviral therapy (ART) on the anal microbiota composition of young men who have sex with men (MSM) from Nigeria (Nowak et al. AIDS 2017). Her cross-sectional study found that those with and without HIV infection did not differ in their microbiota. However, those on ART had a shift in their composition. More specifically, there was a lower diversity in the Bacteroidetes phylum, an increase in three genera of the Firmicutes phylum, and an increase of Campylobacter of the Proteobacteria phylum. These findings were independent of any reported use of co-trimoxazole, an antibiotic recommended by WHO for adults with <350 cells/µl on ART. This important work was highlighted in an editorial comment written by James Goedert, MD of the National Cancer Institute in the same issue of AIDS.

Dr. Nowak is also evaluating the persistence of high-risk human papillomavirus (HR-HPV) in HIV infected and uninfected MSM. In collaboration with Kevin Cullen, MD, Marlene and Stewart Greenebaum Distinguished Professor in Oncology and Director of the University of Maryland's Greenebaum Comprehensive Cancer Center (UMGCCC), Dr.

Rebecca Nowak, PhD (far right) and Joel Palefsky, MD (second from left) of University of California, San Francisco with the TRUST Anal Cancer Screening Team in Abuja, Nigeria

Nowak validated his next generation sequencing assay for detection of multiple genotypes of HR-HPV and found it comparable to the gold standard, Linear Array (Nowak et al. Virology Journal 2017). Longitudinal rectal swab samples that span a year of follow-up are currently undergoing testing for HR-HPV using this next generation sequencing assay.

Through support from NCI, Dr. Nowak, in collaboration with Drs. Joel Palefsky, from University of California, San Francisco and **Clement Adebamowo, BM.CHB.(Hons), DSc**, Professor of Epidemiology and Prevention, completed her implementation of an anal cancer screen and treatment program using high resolution anoscopy. This is the first of its kind in sub-Saharan Africa where the risk of anal cancer is unknown. Within a year, the team completed 530 screenings that comprised both a training and research component. For the 362 men in the research component, the median age was 25 years (interquartile range 23-30), 59% were HIV-positive, and the majority (58%) had 1-10 lifetime number of partners. Preliminary data on anal dysplasia found 48.2% were normal, 46.4% had LSIL, and 5% had HSIL. It is likely the high-grade precancer was underdiagnosed but the team is currently treating all cases of HSIL and future work will re-evaluate those in the screening cohort for more valid prevalence estimates of anal dysplasia.

Under the mentorship of **Drs. Man Charurat**, Cullen, Ravel, Bentzen, Raina Fichorova, MD, PhD at Harvard Catalyst, and Joel Palefsky, MD at University of California, San Francisco, Dr. Nowak submitted a K07 career development grant application titled, "Role of anal microbiota, local cytokines and HIV in persistence of high-risk human papillomavirus" to the NCI and received a fundable impact score. Her goals of this career development are to undertake formal training and mentoring in microbiota, mucosal immunity, and molecular biology of carcinogenesis and to learn how to integrate these components analytically to identify cancer prevention markers.

Clement Adebamowo, BM.CHB.(Hons), DSc, Professor of Epidemiology and Prevention, also works to develop local research capacity. He has successfully mentored 12 early-stage degree and postdoctoral students in non-communicable disease epidemiology. Trainees conducted several nutritional epidemiology studies in Nigeria. This includes the development of a food frequency questionnaire for African foods consumed in Nigeria and a food composition database to convert this into nutrients. Additionally, he directs the West African Bioethics Program which has provided medium-term training certificates in research ethics for 842 biomedical researchers, awarded 34 master's degrees in bioethics, and deliveries of the online West African Bioethics–Collaborative Institutional Training Initiative program to 6,115 participants in West Africa. Currently, he is focusing on sustaining and maintaining the research infrastructure built through three new NIH awards: the ENTRENCH Program which is a collaborative research ethics training program jointly implemented by the UMB and University of Ibadan, Nigeria; MACH 14 Project, a multi-site collaborative international clinical trial, comparing daily moderate alcohol consumption to the risk of CV disease; and the AFBRECANE Study which is conducting breast cancer research in Nigeria to understand the epidemiology and genomic determinants of incidence of breast cancer and its molecular subtypes, and the role of diet in etiology of breast cancer in Nigeria.

Gambo Aliyu, MBBS, MS, PhD, Assistant Professor of Epidemiology and Public Health, is the newest faculty member. Dr. Aliyu received a Bachelor of Medicine, Bachelor of Surgery, from the Ahmadu Bello University, Zaria, Nigeria in 1995. He received a Master of Science in Clinical Research from UMB in 2008 and a PhD in Epidemiology from UMB in 2012 through the University's Fogarty Scholar program: UM-IHV AIDS International Training Research Program. His education epitomizes his drive to be a physician-scientist in global health research. Currently, Dr. Aliyu is working very closely with the CDC to conduct the country-wide Test and Start and Community ART studies under the Strengthen HIV Field Epidemiology, Infectious Disease Surveillance, and Lab Diagnostic (SHIELD Project, PI: Charurat) being implemented jointly with the Division of Clinical Care and Research. The goal of these impact evaluation studies is to evaluate specific interventions among specific populations to provide

SHIELD project's field epidemiology in rural Nigeria

Ernest Ekong, MBBS, PhD (second from left) and Patrick Dakum, MBBS, MPH (center) with ADAPT site teams

evidence of the effectiveness of the intervention. Under the leadership of the Division in Nigeria, the IHV and UMB are recognized as the implementing partner with expertise in research evaluations, clinical quality improvement, and implementation science.

Ernest Ekong, MBBS, PhD, Clinical Researcher full-time in IHV-Nigeria, is one of the three PIs (MPI: Charurat, Tepper, Ekong) in the Adolescent to Adult Patient-centered HIV Transition (ADAPT) Study. The study aims to measure successful transition and viral suppression in 15 to 19-year-old adolescents living with HIV (ALHIV) transitioned to the adult clinic. Three main specific aims of accessing the most important patient-centered outcomes for process of transition, measuring the impact of Peer Transition Advocates vs. Education Interventionist approaches to the process of transition, and Identifying the demographic, social support, psychosocial correlates of successful transition and outcomes are targeted. To date, thirty focus group discussions held at 6 clinical sites in Nigeria were conducted with 267 participants made up of five distinct participant groups including healthcare providers, caregivers, ALHIV with successful transition, ALHIV who have had unsuccessful transition, and ALHIV preparing for transition. Each focus group had approximately 10 participants, and two moderators who were nurses in pediatric ART clinic trained on FGD facilitation. Early findings of this work were recently accepted for presentation at the International conference on AIDS and STIs in Africa 2017. Currently, the study is randomizing sites into two study arms.

Dr. Ekong is also the PI of The Strategic Timing of Antiretroviral Therapy (START) Study, the randomized clinical trial that investigated the optimal time to begin ART in over 200 sites around the globe. The study funded by the NIAID through the INSIGHT group. In May 2015, the Data Safety Monitoring Board unblinded the study team to the results of the trial, notifying the team that the data showed that starting ART while the CD4 is still above 500 cells/mm3 is superior to waiting. The risk of the primary composite endpoint was reduced by more than 50% in people who were randomized to start ART immediately after entering the study. The difference was statistically significant. Subsequent changes followed the publication of these results with all participants on the deferred arm group immediately offered treatment irrespective of CD4 count. The START study is billed to continue to 2021, with focus on the possible effects of prolonged ART use.

Habib Omari, MD, PhD, Research Associate of Epidemiology and Public Health, focuses on key populations such as men who have sex with men (MSM) who are disproportionally affected with HIV infection worldwide. In Nigeria, although the prevalence of HIV infection in general population is about 4%, the prevalence of HIV among MSM is over 50%. Given the high HIV prevalence, exploration of transmission risk factors and implementation of HIV preventive strategies is critical. Building Trust is the prospective cohort study that evaluates network-based recruitment of MSM into HIV counseling and testing (HCT), clinical care, treatment and prevention at trusted community based one-stop clinics in Nigeria. In March 2013, the IHV, in collaboration with the IHV-Nigeria, the Johns Hopkins University, and the International Center for Advocacy on the Right to Health, and the US Military HIV Research Program established trusted community based one-stop clinics for MSM. Study participants attend these clinics every three months for a total of seven visits. HIV infected patients receive HIV treatment under test and treat model irrespective of CD4 cell count. Upon completion of their visits, HIV infected may opt to continue receiving treatment within these clinics. Screening for other sexually transmitted infections such as gonorrhea, chlamydia and syphilis is performed regularly for all MSM at their scheduled visits. As of September 2017, 2,024 MSM have been recruited. Of these, 1,489 (73.5%) tested for HIV and 847 (56.9%) are HIV infected. Among HIV infected, 594 (70.1%) are receiving ART within these trusted community based one-stop clinics. Given the

Habib Omari, MD, PhD

high HIV prevalence and realizing the effectiveness of medical prevention, 222 HIV uninfected participants completed pre-exposure prophylaxis (PrEP) survey questionnaire and 165 (74.3%) are willing to initiate PrEP. Recently, the study received additional award from Gilead Sciences to support PrEP and test system-based intervention to optimize its delivery at scale.

To date, more than 10 peer reviewed manuscripts have been published in journals and several abstracts have been presented at International conferences including CROI and IAS. Among our publications was an exploration into the immediate effect of the law that criminalize MSM in Nigeria (Schwartz et al., Lancet HIV 2016). The TRUST group (PI: **Charurat**) showed a decrease in the number of MSM seeking health care services post the law, suggesting intervention targeting MSM are needed to improve their health seeking behaviors in order to prevent HIV spread. Analysis on the determinants of incident STI showed besides individual characteristics, network factors such age, engaging in sex under the influence of alcohol, network size are also predictive of STI incidence (Omari et al., STI 2017). Current analysis showed social support systems are associated with HIV testing, ART initiation and viral suppression indicating the effectiveness of one stop shop model particularly in high HIV burden settings. Structured coalescent analyses indicate that a substantial proportion of HIV infections in the general female population are linked epidemiologically to the MSM to female bridge. In these analyses we demonstrated that specific treatment approaches for all MSM living with HIV averts approximately half as many infections over 20 years (Volz et al,Virus Evol).

Jibreel Jumare, MBBS, MS, PhD, Research Associate of Epidemiology and Public Health, successfully completed of the PhD program in Epidemiology at the University of Maryland School of Medicine, sponsored through IHV-UMB's NIH Fogarty AIDS International Training and Research Program. A clinician with cognate experience and background training from Nigeria, United Kingdom and Ireland, Dr. Jumare has a

Jibreel Jumare, MBBS, MS, PhD

longstanding affiliation with IHV-UMB, having worked for many years as a Regional Manager and later as Associate Director of Clinical Services for the Institute of Human Virology Nigeria. He contributed immensely towards the achievement of the Institute's training, research, and public health objectives.

Dr. Jumare works with Walter Royal, MD, Professor of Neurology, University of Maryland School of Medicine, and PI for NIMH funded NeuroAIDS R01 grant in Nigeria) to support the implementation, analysis and reporting of this study, which looked at the 'Correlates of Monocyte Associated Virus in HIV Neurocognitive Impairment'. The study found significant correlation between the severity of HIV associated neurocognitive disorders (HAND) and levels of cell free virus (HIV RNA) within plasma and cell associated virus (HIV DNA) within peripheral blood lymphocytes, as well as a correlation with plasma levels of monocyte activation markers (soluble CD14, monocyte chemoattractant protein [MCP-1]). The study also demonstrated that individuals infected with HIV-1 subtype G had significantly worse cognitive function as compared to those infected with CRF02_AG clade in Nigeria, thereby providing additional evidence in support of other reports indicating differences in HIV clades for disease progression. These findings were presented by Dr. Jumare at different international conferences including a platform presentation at the 69th annual meeting of the American Academy of Neurology held in April 2017 in Boston, MA. A manuscript looking at 'HAND and Cell Associated HIV DNA' was recently published in the 'Journal of Neurovirology', while another manuscript looking at 'HAND and HIV-1 Subtypes' has been provisionally accepted for publication in the 'Clinical Infectious Disease Journal'. Furthermore, these results will constitute the bedrock of a grant application underway seeking to further explore the mechanistic basis of the relevant viral and host factors involved in HAND pathogenesis

Dr. Jumare also working on the NIH funded MARGIN study (PI: Charurat) and CIHR funded Infant study (PI: Abimiku) that is looking respectively at the role of microbiome and immune responses in growth and development among HIV exposed but uninfected children. Preliminary analysis for both studies show strong evidence of significant differences in both linear and ponderal growth trajectories between HIV exposed uninfected children (HEU) and HIV unexposed uninfected controls (HUU). Dr. Jumare is working under the mentorship of Dr. Charurat and Dr. Abimiku to expand the scope of these studies to include generating preliminary data on neurodevelopment of the HEU children in preparation for a grant submission that will explore this in depth. Finally, Dr. Jumare serves as the Academic Advisor to the PhD and Master of Science Health Science candidates supported through the NIH Fogarty funded "Epidemiology Research Training for Public Health Project in Nigeria" (MPI: Charurat/ Abimiku). He monitors the academic progress of these students in addition to providing guidance and teaching assistance as needed. Working with the Principal Investigators, alongside the Fogarty Coordinator in Nigeria (Sunny Philips. MD, MBA, MPH, MSc, MWACP), Dr. Jumare organizes quarterly review meetings for the Master of Science students during which key concepts in research methodology and public health themes are discussed. This face to face forum is expected to augment the online classes taken by the students, as well as broaden the scope of their learning experience and skill acquisition opportunities.

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Scientific Core Facilities

The Institute of Human Virology's (IHV) four Scientific Core Facilities help advance the Institute's research by providing a broad range of services to faculty and staff at IHV, and across the University campus. Services include cutting-edge technologies and laboratory technical support. Each Core Facility, including the **Animal Core, Flow Cytometry and Cell Core, Imaging Studies of Pathogens & Cell Interactions Core**, and **µQUANT Core**, is led by an experienced researcher at IHV. Below is an overview of the Core Facilities.

Back Row L to R: John Tripline, Maurice White, Albert Hunter, and Alfred Dye; Front Row L to R: Jabré Ross, Sumiko Williams, Harry Davis, MS, and Eugene Ateh, DVM

Animal Core Facility

The Animal Core Facility, is currently led by **Harry Davis, MS**, who follows in the footsteps of its former head, **Joseph Bryant, DVM**, who was Associate Professor of Pathology and Director of the Division of Animal Model and retired since July 2017 after twenty-two years of leadership and service with IHV. The Animal Core Facility will continue its mission to support developing animal models as it relates to HIV/AIDS, pathogenesis studies, HIV-1 matrix protein P-17 implicated in virally associated lymphomas, stem cell biology, mycoplasma and cancer.

Mr. Davis has a staff of eight animal research care personnel who are responsible for the care of animals at IHV 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, facility that strives to provide a safe, efficient, and cost-effective environment for animal experimentation.

Research at 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 Core 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 Core 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; and 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 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 the Animal Core Facility include the development of Animal Models. Projects include:

HIV/AIDS Non-Hodgkin Lymphomas

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

Collaborators in the Division of Basic Science include:

- **Robert Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine and Director of IHV
- **Davide Zella, PhD**, Assistant Professor of Biochemistry and Molecular Biology
- **Garzino-Demo, PhD**, Associate Professor of Microbiology and Immunology
- **Mika Popovich**, Adjunct Professor of Medicine
- **Olga Latinovic, PhD**, Assistant Professor of Microbiology
- **Virginia Carroll, PhD**, Postdoctoral-fellow
- **Sabrina Currelli, PhD**, Research Associate
- **Fiorenza Cocchi, MD**, Assistant Professor of Medicine
- **Francesca Benedetti, PhD**, Fellow
- **Chozha V. Rathinam MSc, PhD**, Assistant Professor of Medicine

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 the Core provides a unique platform for the study of lymphoma that develops because 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.

Stem Cell and Cancer Biology

Chozha V. Rathinam MSc, PhD, is researching a way to understand the role of protein modifications in the development and maintenance of Myeloid Leukemia. The use of animal models to gain a better understanding of the role of ubiquitylation pathways is vital to understand the biology of stem cells. The studies using and developing numerous transgenic models is being performed in the Animal Core.

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

- **Alonso Heredia, PhD**, Assistant Professor of Medicine
- **Olga Latinovic, PhD, MSc**, Assistant Professor of Medicine
- **Nichols Stamatos, MD, PhD**, Assistant Professor of Medicine

Evaluating Treatment with CCR5

Alonso Heredia, PhD and Olga Latinovic, PhD are evaluating treatment with a CCR5 antagonist to slow tumor progression in HIV transgenic mice with early states of tobacco-induced NSCLC (small lung cancer). The Animal Core 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.

Function of Polysialic Acid in Immune Cell Activity

Nichols Stamatos, MD, PhD is evaluating the function of Polysialic cell activity through the development and characterization of transgenic mice.

Other Collaborative efforts with the Animal Core Facility include:

- **Henry Lowe, PhD**, Adjunct Professor of Medicine, IHV
- **Walter Royal, MD**, Professor, Department of Neurology, University of Maryland School of Medicine
- **Tapas Makar, PhD**, Adjunct Assistant Professor, University of Maryland School of Medicine
- **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 from Jamaica is collaborating with the Animal Core on a flavonoid from Tillandsia recurvate showing potent anticancer activity against AIDS-defining and non-AIDS defining cancers. The Animal Core's collaborative research has focused on drug discovery from plants from 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 Core 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 Core to study HIV primary central nervous system lymphoma (PCNSL) as a malignant diffuse large B cell lymphoma that occurs in 3-5% HIV patients.

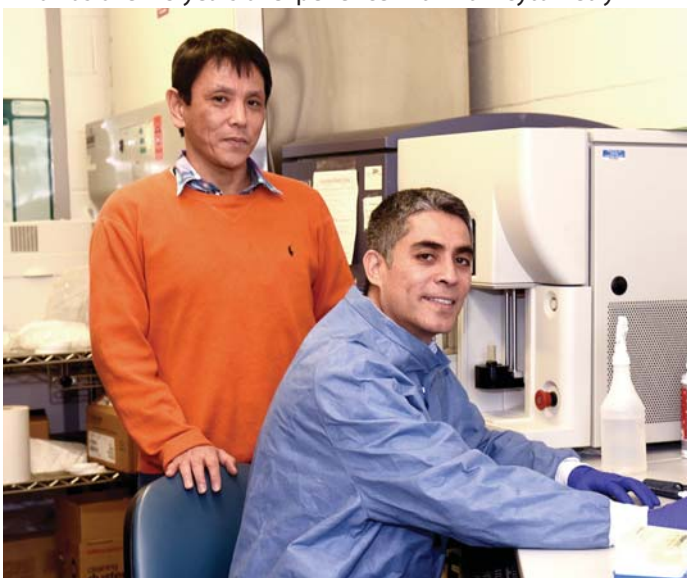
Animal models have been critical in making progress in understanding of HIV PCNSL pathogenesis and investigating potential therapeutic strategies. The HIV-1 Tg26 mouse model develops PCNSL similar to what is seen in HIV PCNSL. The Core has evaluated the HIV1 Tg mouse model at the molecular level.

Purging Latent AHIV Reservoirs through a Combination HIV Therapeutic

Trevor Castor, PhD, President & Chief Executive Officer at Aphois Corporation, is a collaborator. 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.

Flow Cytometry and Cell Core Facility

The mission of the Flow Cytometry and Cell Core Facility is to serve the IHV community with varying needs associated with flow cytometry. Flow Cytometry has been a critical tool for virology/immunology/cell biology research over the past 30 years and has become fundamental. However, the proper design, well-calibrated machine and appropriate interpretation of the collected data are essential for avoiding common pitfalls. The IHV Flow Core is headed by **Yutaka Tagaya, MD, PhD**, Assistant Professor of Medicine, Division of Basic Science, who has over 25 years of experience with Flow cytometry technology. The Flow Core has been in operation since Dr. Tagaya's arrival in 2011. Its daily operation heavily depends on **Juan C. Zapata, PhD**, Research Associate of Medicine, Division of Basic Science, as the chief operator/trainer. Each user will be charged with fees based upon usage (ask the FlowCore for pricing).



Yutaka Tagaya, PhD and Juan Zapata, PhD

The IHV has two major instruments.

1. BD's FACSAria (3 lasers–405 nm violet, 488 nm blue and 633 nm red—which allow 12 independent color analysis and fluorescence-based cell sorting including a single cell/indexing methodology), located in the north BSL3 facility (Room N664)
2. Millipore's GUAVA. GUAVA can handle up to 10 colors (FITC, PE, PerCPCy5.5, PECy7, APC, APC-Cy7, Violet 421, Violet 510, Violet 605 and Violet 650) which is located in N568.

The Core offers help in the two areas, including polychromatic (especially over 8 colors) flow data collection/analysis and cell sorting (including infectious cell sorting and sorting of yeast cells). Now, the IHV Flow Core is the only facility that can sort infectious cells at the University of Maryland, Baltimore campus.

The IHV Flow Core not only operates the machine, but will also work with each investigator by consulting on the experimental design and by training the researcher for instruments and software (if necessary). The Flow Core will also offer help with basic and advanced data analysis using the FlowJo (common flow cytometry software available through the IT department of the IHV) program.

With the Aria, each investigator can analyze up to 12 color samples, operated by the FlowCore personnel. Cell sorting can be done into two ways, four ways, and into various tissue culture plates. The machine is also capable of sorting a single cell into each well of the 96-well plate (single cell sorting) with fluorescence data from each of the cell recorded (Index sorting) which is extremely helpful in applications such as separating each clone of antigen-specific T/B cells for further analysis.

The GUAVA is open for public access but training is needed beforehand, which is provided by the FlowCore staff upon request. This machine can handle up to 10 colors. In addition, this machine can be programed into a high-throughput mode by automatically analyzing samples that have been prepared in 96-wells. Unlike some clinical flow labs, the IHV Flow Core does not provide high-throughput analyses, but each investigator can do this by using the GUAVA machine.

The IHV Flow Core has worked with all Divisions/Labs of IHV, as cell-based biology is the foundation of the research here at the IHV.

We encourage each investigator by stating that neither a multi-color staining or a fluorescence cell-sorting is difficult. However, proper guidance based on the appropriate understanding on the optical and chemical characteristics of each fluorochrome, their potential interference, and hands-on experience with the expression levels of each molecule of interest would greatly reduce the cost and time for obtaining publication-quality data. We have been successfully working with several IHV investigators to conduct a 12-color polychromatic flow

cytometry which helped them in their experimental execution as well as multiple grant submissions.

Currently, the Flow Core extensively works with **Cristiana Cairo, PhD**, Assistant Professor of Medicine, Division of Basic Science, and her group for cell sorting and multi-color flow cytometry; **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Co-Director of IHV's Clinical Research Unit, and Associate Director for Division of Clinical Care and Research, and his group by cell sorting and staining for the analyses of the immunity under HCV-infection; the lab of **Alfredo Garzino-Demo, PhD**, Associate Professor of Microbiology and Immunology, Division of Basic Science, by sorting CCR6 positive cells for their research; the lab of **Fabio Romerio, PhD**, Assistant Professor of Medicine, Division of Basic Science, for the characterization of the various cellular impacts of anti-sense protein and transcripts encoded by HIV-1; Dr. Tagaya's group for the sorting of leukemic and non-leukemic cells from ATL (adult-T cell leukemia) patients to graft into humanized mouse for immunologic characterization and immunization purposes; and, the lab of **Nicolas Stamatos, MD**, Assistant Professor of Medicine, Division of Clinical Care and Research, for investigating the relevance of the polysialation in T-cell activation. We also have a few labs from the University of Maryland School of Medicine which use our service for cell sorting and flow cytometry.

Testimonials

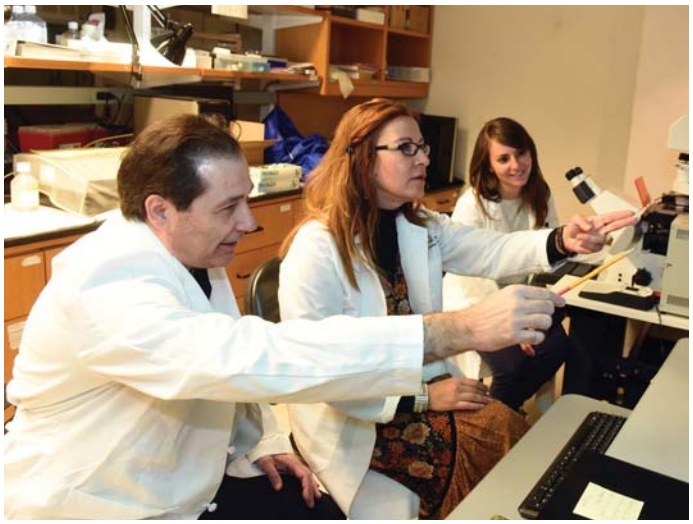
Bhawna Poonia, PhD, Assistant Professor of Medicine, Division of Clinical Care and Research: We are studying immune dysfunctions in association with chronic virus infection, in particular that with HBV and HCV so that we could explore immunomodulatory strategies for viral control and cure. To this end, we need to analyze clinical samples (PBMCs and liver lymphocytes) obtained from HBV/HCV infected patients by multi-parameter immuno-phenotyping and the help from the IHV Flow Core is essential. We also conduct FACS sorting for further molecular characterization of CD8 T cells that are specific for HBV/HCV. In short, my project critically depends on collaborating with the IHV Flow Core.

Cristiana Cairo, PhD, Assistant Professor of Medicine, Division of Basic Science: My lab is interested in T cell development; we study function and regulation of gammadelta T cells in neonates. Due to the low frequency of these cells in cord blood (<0.5% of lymphocytes), multi-parameter flow cytometry is the only viable approach to investigate their phenotypic and functional characteristics. Simultaneous analysis of more than 10 surface or intracellular markers is critical for obtaining detailed single-cell information for a statistically meaningful number of cells. In addition, isolation of high purity target cells (>98%) by fluorescence-activated cell sorting is essential for our studies investigating regulatory mechanisms at the molecular level. Specifically, we are examining epigenetic and transcriptional regulation of the inhibitory receptor PD1. These analyses would not be possible without the support provided by the IHV Flow Core, whose personnel always manage to accommodate our needs regardless of their hectic schedule. Having a dedicated Flow Core here at the IHV is essential for advancing our NIH-funded research, and their services certainly improve our scientific productivity.

The IHV Flow Core will continue serving the IHV with expert knowledge by facilitating the Institute's state-of-the-art research ongoing.

Imaging Studies of Pathogens & Cell Interactions Facility

The Imaging Studies of Pathogens & Cell Interactions Facility launched in 2012 as the first IHV Imaging Facility. Since then, **Olga S. Latinovic, PhD. MSc**, Assistant Professor of Microbiology and Immunology, Division of Basic Science and Clinical Care and Research, has led the facility. The Core Facility is primarily focused on image analysis studies. The Core uses different microscopes located in three rooms on IHV's 2nd and 6th floors: Fluorescent microscope by Olympus (S 288D), newly launched Confocal LSM 800 Airy scan Microscope by Zeiss (S 615) and Super Resolution microscope by Nikon (N 636A). A few projects of the Core Facility are listed below.



Davide Zella, PhD, Olga Latinovic, PhD, MSc, and Francesca Benedetti, PhD

p17 Project

Dr. Latinovic uses 3D images via confocal microscopy methods with Alfredo Garzino-Demo, PhD, Associate Professor of Microbiology and Immunology, Division of Basic Science, Frank Denaro, PhD, Associate Professor of Biology, Morgan State University, Mika Popovic, PhD, Adjunct Professor of Medicine, Division of Basic Science, Robert Gallo, MD, The Homer & Martha Gudelsky Distinguished Professor in Medicine, Director of IHV, Divisions of Basic Science and Vaccine Research, and the p17 group for the visualization and the quantification of angiogenesis caused by the HIV matrix protein p17 in nude mice. This part of the IHV's p17 project is the continuation of their published studies on the p17 related angiogenesis work by Basta, Latinovic et al, 2015.

Mycoplasma project

Dr. Latinovic was originally involved in the parts of the Mycoplasma project since her post-doctoral training at IHV when working closely on the topic with Fabio Romerio, PhD, Assistant Professor of Medicine, Division of Basic Science, and Davide Zella, PhD, Assistant Professor of Biochemistry and Molecular Biology, Division of Basic Science, and the group

back in 2008. Their original observations were related to the rosetting patterns of mycoplasma interaction with human lympohocytes. The current needs of the project are specifically related to the direct visualization studies of the mycoplasma protein DNAK and its interactions with the p53 protein in cell lines, directed by Drs. Zella and Gallo. The group is addressing this task to design proper experimental conditions for this part of the Mycoplasma project utilizing novel imaging methods, such as PALM - Photoactivated localization microscopy and STORM- Stochastic Optical Reconstruction Microscopy (STORM).

HIV Latency Research

Dr. Latinovic is utilizing both, super resolution and confocal microscopy methodologies in collaboration with Dr. Romerio who investigates the sub cellular localization of the HIV-1 antisense protein, ASP, as well as its interactions with proteins of the inner nuclear membrane. This study may have implications for better understanding of HIV latency and manuscript is in preparation.

HIV Vaccine Project

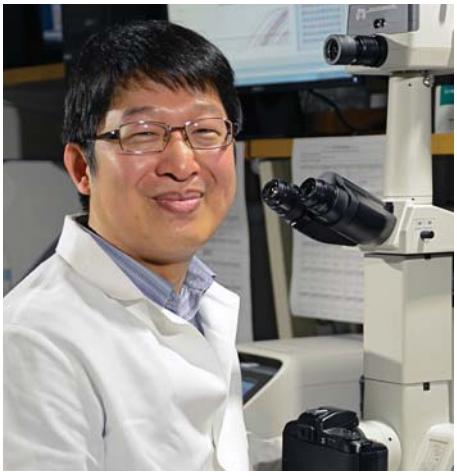
The Division of Vaccine Research investigators have used the Nikon nSTORM superresolution microscope to obtain unprecedented, direct, 3D visual images of HIV attached to its target cell. Using this super resolution microscope, they have been able to determine how and where key antiviral antibody binding sites are presented under these conditions. This valuable information provides a virological basis for vaccine development and for understanding how vaccine candidates, including the IHV's construct, may offer protection against infection via antibody responses. The Division of Vaccine Research has published 3 studies in which superresolution imaging was of critical importance. IHV investigators also use the new Airyscan confocal instrumentation to understand the nature of immune complex formation and its relationships with Fc receptor binding and associated effector functions. The Airyscan instrument is being further used to establish how key antiviral anibody targets are exposed during cell-cell HIV spread in cell cultures and in tissues.

HTLV/HBZ Project

Dr. Latinovic is using microscopy methods in the project of the Tagaya Lab on studying the Human T cell Leukemia Virus-1 (HTLV-1), in the purpose of designing novel therapies against a T-cell leukemia caused by this virus. Dr. Latinovic and Yutaka Tagaya, MD, PhD, Assistant Professor of Medicine, Division of Basic Science, are collaborating on determining the subcellular localization and potential endosomal inclusion of an anti-sense protein called HBZ (HTLV-1 basic-zipper factor) because immunity against this protein is crucial for developing curative immunotherapy. The study will facilitate Dr. Tagaya's attempts to create enhanced immunity against HBZ through the understanding of the way HBZ can be presented to T cells in HTLV-1 infected individuals. The Core Facility is equipped with both, confocal and the state-of-the-art high-resolution microscopes, both of which greatly facilitate this project's efforts in accomplishing the research goal. The collaboration will be expanded by involving Professor Roberto Accolla, PhD from the University of Umbria in Italy, who generated an anti-HBZ monoclonal antibody which will be extensively used in this ongoing HTLV-1 research.

µQUANT Core Facility

The µQUANT Core Facility began with the co-founding of the Institute of Human Virology (IHV) in 1996. The Core provides quality immunological and biological services to researchers at IHV, the University of Maryland Baltimore (UMB), and to other collaborators locally and nationally. **Ping-Hsin Lin, MS** runs the daily operations of the core with academic oversight from Anthony DeVico, PhD, Professor of Medicine, Division of Vaccine Research.



Ping-Hsin Lin, MS

IHV founded the µQUANT Core Facility to include a variety of centralized cores to provide both cost savings and standardized methods. The core has devoted significant time to trouble-shooting all protocols utilized and has developed laboratory Standard Operating Procedures. Its aim is to provide consistent, cost effective services that allow researchers to compare results generated within a week. The Core has been very successful in meeting these goals, and as such, its existence has optimized the pace and scope of research at IHV.

Core services include: routine immunoassays (e.g. ELISA); endotoxin testing; monoclonal antibody and recombinant protein screening, production, purification, and labeling; production and maintenance of virus and cell stocks; and maintenance of common use equipment. The latter includes a BIACORE T200, a SpectraMax M2 ELISA plate reader, an ABI simpliAmp PCR machine, and a StepOnePlus qPCR machine. Several other new and/or refurbished pieces of equipment include an ABI QuantStudio3 qPCR machine, a BioRad BioPlex System, and a Miltenyi Biotec autoMACS cell separator.

The core serves the UMB campus and Baltimore research community on a fee-for service basis and welcomes the opportunity to work with investigators to establish new immunoassay and protein production protocols.

A complete list of µQUANT core services can be found in the IHV website. (http://www.ihv.org/research/facility.html)

The µQUANT Core Facility is heavily involved in supporting many IHV programs and projects. This past year, the Core supported scientific projects by providing routine testing and customized experiments to 17 research groups at IHV, and 2 UMB groups outside IHV.

GVN IHV: A Global Virus Network (GVN) Center of Excellence


Christian Bréchot, MD, PhD

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 fiscal year, the International Vaccine Institute (IVI) in Seoul, South Korea, Emory University in Atlanta, GA, USA, and, Tulane University School of Medicine in New Orleans, LA, USA were added to the GVN. Subsequently, the Mérieux Foundation in Lyon, France and Rega Institute for Medical Research, University of Leuven, Belgium were also added. GVN's members represent expertise covering every class of human virus, and currently comprise virologists from 40 Centers of Excellence and 6 Affiliates in 24 countries, and its numbers continue to grow. GVN has held subsequent meetings in Ireland, Italy, USA, Germany, Russia, Sweden, Grenada, Estonia, China, Japan and Australia.

The GVN, in partnership with The Peter Doherty Institute for Infection and Immunity and Institut Pasteur, convened the 9th International Global Virus Network Meeting in Melbourne, Australia September 25-27, 2017 where IHV was well represented. During the meeting, the GVN announced the appointment of Christian Bréchot, MD, PhD as President of the GVN. Dr. Bréchot, who recently stepped down as President of France's internationally renowned Institut Pasteur, assumed his new position with the GVN effective October 1, 2017. Also during the meeting in Melbourne, the GVN presented Diane Griffin, MD, PhD, Professor, Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health (a GVN Center of Excellence) with The GVN Robert C. Gallo Award for Scientific Excellence and Leadership for her work on the pathogenesis of viral infections, particularly related to measles and alphavirus encephalomyelitis, as well as her contributions to advancing the GVN mission.

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. This past fiscal year, 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.

This year, a collaborative project led by Shyam Kottilil, MBBS, PhD, Professor of Medicine, Co-Director of IHV's Clinical Research Unit, and Associate Director for IHV's Clinical Research


Participants of the 9th International Global Virus Network Meeting held in Melbourne, Australia September 25-27, 2017

in Division, launched between India and IHV to develop an HCV training model for medical providers in India that can be duplicated and applied to other areas of South Asia. Generic medications are available and approved to use in India, but only a few providers have any experience in the management of HCV with interferon/ribavirin, and there are no infectious disease specialists in country with experience using new oral agents. Similar to when antiretroviral therapy was rolled out in the mid-2000s, India now has an acute need for providers to be trained in the management of HCV. The collaboration with India utilizes a decentralized mentorship plan to build local capacity through high-level clinical mentoring to 50 physician and nurse mentors who will then be responsible for mentoring an average of 10 health care workers at each health facility, reaching more than 500 health care workers throughout the country. Dr. Kottilil also initiated a pilot study to develop an integrated clinical database to support an ongoing project in Arunachal Pradesh, India. GVN will assist in developing, maintaining and facilitating collection of data, assimilation and provide expertise in evaluating outcomes.

This summer, GVN launched its Fourth Annual Short Course on Medical Virology held August 13-19, 2017 for 15 early career medical virologists from Australia, Brazil, India, Jamaica, Japan, Lithuania, Malaysia, Nigeria, Portugal, Russia, South Africa, and the United States. The preeminent one-week course on basic, translational, and clinical aspects of viruses features world-renowned researchers drawn from GVN Centers of Excellence, comprising 39 Centers of Excellence and six affiliates in 24 countries and comprises foremost experts in every class of virus causing disease in humans. The Short Course is designed to counter a declining number of researchers entering the field of medical virology. 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; Man Charurat, PhD, Yutaka Tagaya, PhD; Clement Adebamowo, BM, ChB, ScD, FWACS, FACS; George Lewis, PhD; Niel Constantine, PhD, MT(ASCP); and, Mathew Frieman MD, on campus at the University of Maryland School of Medicine. 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 and Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland.

Participants of the Global Virus Network Fourth Annual Short Course on Medical Virology held August 13-19, 2017 in Baltimore, Maryland, USA

In addition to newly appointed Dr. Bréchot, GVN's staff headquartered at IHV includes Natalia Mercer, PhD, Program Director, Edward McSweegan, PhD, Program Director, and Marcus Gallo, MS, Research Associate. IHV faculty and staff contributed time generously to the GVN throughout the year, including most notably Robert Gallo, MD, who serves as Co-Founder and Scientific Director of the GVN, Dave Wilkins, who oversees GVN's finances, and Nora Samaranayake, 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, Clement Adebamowo, BM, ChB, ScD, FWACS, FACS, and, Joyce Johnson. IHV also appreciates its own Board of Advisors also donating time and energy towards the advancement of the GVN mission.

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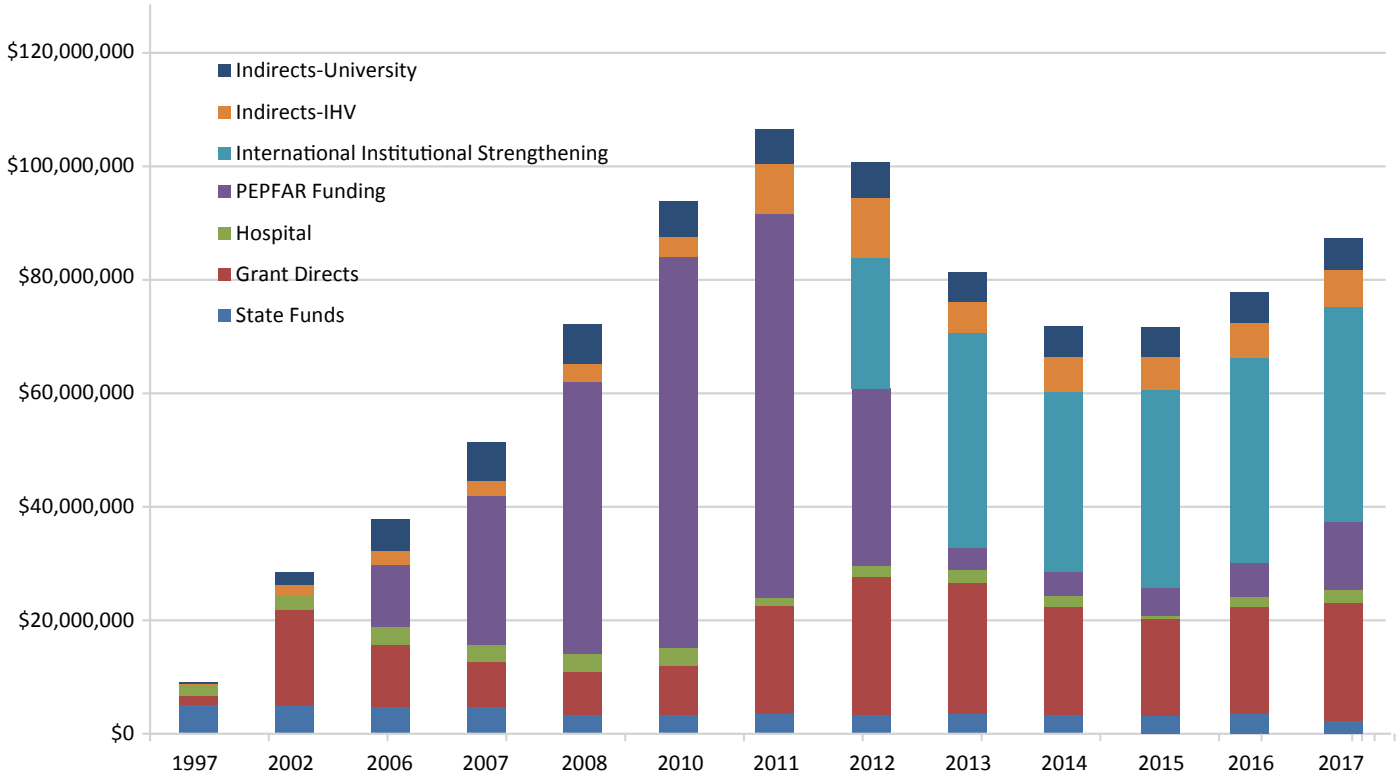
Financial Overview

The Institute of Human Virology continues to grow at an extraordinary pace. Several years ago, our funding decreased dramatically when our largest grant ceased to be awarded to US based entities. However, we have steadily grown across all areas since then. This year's increase in grant funding across Divisions ratifies the success of the Institute's original cross-disciplinary vision.

Despite cutbacks in NIH funding, IHV's **Basic Science Division** research portfolio grew due to RO-1 grant wins by multiple principal investigators. These include a new grant won by new faculty member, Dr. Choz Rathinam. Our **Vaccine Research Division** grew significantly with a new award from NIH to study fundamental aspects of durability and balance in an HIV vaccine response while it launched the Phase 1 Clinical Trial for our Bill and Melinda Gates Foundation funded HIV vaccine candidate. IHV's **Clinical Care and Research Division** continues its rapid growth in each of its areas of focus: Baltimore clinical treatment activities, our Clinical Trials Unit and through our new Center for International Health, Education and BioSecurity. Our **Epidemiology and Prevention Division** continued its important work in Nigeria and has applied for a significant funding award for the upcoming year, which if awarded, would add 20% to IHV's overall funding.

The coming years will see even more grant submissions along with our continued focus on philanthropic support. As base funding is in place for each Division for the next 3-4 years through recent large grant wins, we expect the growth pattern to continue.



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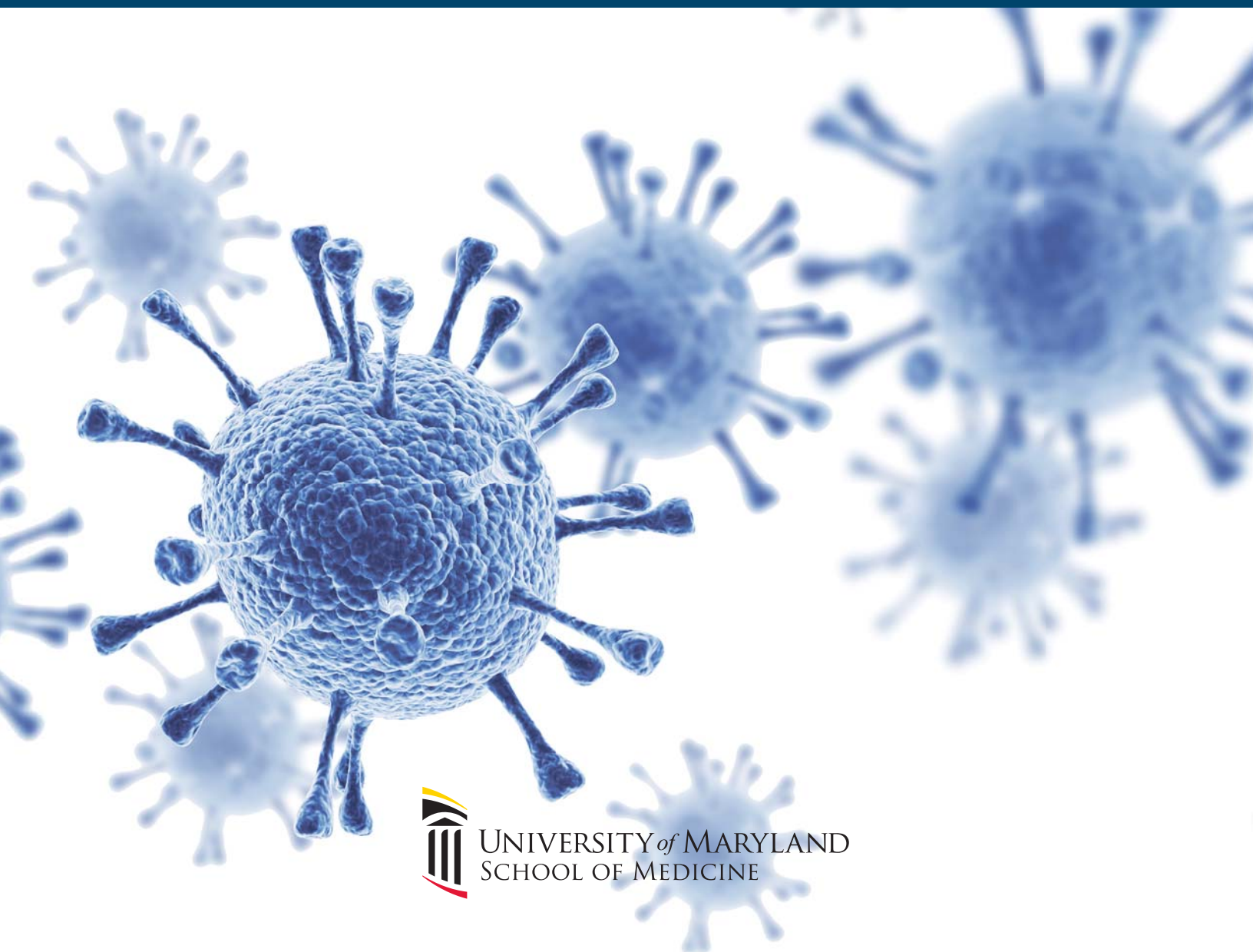

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