



**INSTITUTE OF  
HUMAN VIROLOGY**

# 2019 ANNUAL REPORT



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, William Blattner, MD, retired since 2016 and formerly associate director of the IHV and director of IHV's Division of Epidemiology and Prevention and Robert Redfield, MD, resigned in March 2018 to become director of the U.S. Centers for Disease Control and Prevention (CDC) and formerly associate director of the IHV and director of IHV's Division of Clinical Care and Research.

In addition to the two Divisions mentioned, IHV is also comprised of a Basic Science Division, Vaccine Research Division, Immunotherapy Division, a Center for International Health, Education & Biosecurity, 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 more than 80 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 5,000 in Baltimore and Washington, D.C., and more than 2 million in African and Caribbean nations. In particular, IHV is internationally renowned for its basic science and vaccine research, which includes a preventive HIV vaccine candidate in human clinical trials and funded largely by the Bill & Melinda Gates Foundation.

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The Institute of Human Virology is the first institute 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](http://www.ihv.org)



# Our Mission

The Institute of Human Virology (IHV) 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.



# Director's Message

## *A Look at the year*

The Institute of Human Virology at the University of Maryland School of Medicine experienced yet another milestone year.

In October 2018, IHV hosted its 20th Annual International Meeting at the Four Seasons Hotel in Baltimore. IHV's Annual International Meeting attracts hundreds of elite scientists who descend upon Baltimore to share ideas and inspire medical virus research collaborations. The meeting program's organization was led by **Man Charurat, PhD**, Professor of Medicine, Director of the Division of Epidemiology and Prevention, Institute of Human Virology, University of Maryland School of Medicine. This year, among other viral and cancer related topics, the meeting is holding special sessions on the 40th anniversary of the first human retrovirus, Human T cell Leukemia Virus (HTLV), and the 15th anniversary of the President's Emergency Plan for AIDS Relief (PEPFAR). IHV's Annual International Meeting attracts hundreds of elite scientists who descend upon Baltimore to share ideas and inspire medical virus research collaborations.

Approximately 95 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.

The opening session of this year's meeting highlighted that it has been 40 years since 1978, the discovery of HTLV, the first human retrovirus and the first virus shown to directly cause a human cancer, as reported at a scientific conference and published in 1980 by me and my colleagues. This session was devoted in a retrospective of HTLV-1 research, the current global state of the virus and new frontiers in HTLV-1 studies.



Robert C. Gallo, MD

Participants included, me and Yutaka Tagaya, PhD from the Institute of Human Virology, University of Maryland School of Medicine; Charles Bangham, PhD of the Imperial College London; Genoveffa Franchini, MD of the National Cancer Institute; Antoin Gessain, MD, PhD of the Institut Pasteur; Roberto Accolla, MD, PhD of the University of Insubria; Luigi Chieco-Bianchi, MD of the University of Padova; Masao Matsuoka, MD PhD of the Kyoto University; Eduardo Gotuzzo, MD of the Universidad Peruana Cayetano Heredia; and, Anne Van den Broeke, DVM, PhD of the Institute of Jules Bordet, Universite Libre de Bruxelles.

The U.S. Presidents Emergency Plan for AIDS Relief (PEPFAR) marked its 15th Anniversary during our Annual Meeting. PEPFAR is the world's leader in responding to the global HIV/AIDS crisis since 2003, when President George W. Bush initiated the program. PEPFAR has enhanced health security worldwide by delivering antiretroviral therapy to more than 13.3 million men, women and children; voluntary medical male circumcision to more than 15.2 million men to reduce the risk of HIV; prenatal care that led to

the prevention of 2.2 million perinatal HIV infections; and, support for more than 6.4 million orphans and other vulnerable children impacted by HIV. Despite strides in controlling this worldwide epidemic, there is still a need for programs designed to advance the strengthening of global capacity to prevent, detect and respond to HIV and other infectious disease threats.

This special session on PEPFAR included both Manhattan Charurat, PhD and Anthony Amoroso, MD of the Institute of Human Virology, University of Maryland School of Medicine; The Honorable Mark Dybul, MD of Georgetown University; Lloyd Mulenga, MD, PhD from the Ministry of Health, Zambia; Laura Guay, MD of George Washington University and the Elizabeth Glazer Pediatric AIDS Foundation; and, Scott Geibel, PhD, MPH of the Population Council.

Additionally, following a vote by senior IHV faculty, IHV awarded annual Lifetime Achievement Awards in 2018 to two distinguished individuals who exceptionally influenced the field of translational medical research and fundamental research on viruses, and contributed



Lloyd Mulenga, BScHB, MBChB, MScD, MMED, University of Zambia School of Medicine



William Blattner, MD, Co-Founder, Institute of Human Virology at the University of Maryland School of Medicine



John Martin, PhD, Former Executive Chairman, Gilead Sciences

tremendously to HIV/AIDS in public health and epidemiology relevant to prevention and care of infected people.

The Lifetime Achievement Award Mini-Symposiums, honoring Drs. Henry Masur and Kiyoshi Takatsuki (see next page), were chaired by John Martin, PhD, Gilead Sciences, Inc. and William Blattner, MD, Co-Founder of our Institute and now retired. Honoring Award recipient Dr. Henry Masur was Richard Whitley, MD of the University of Alabama at Birmingham and H. Clifford Lane, MD of the National Institute of Allergy and Infectious Diseases. Honoring Award recipient Dr. Kiyoshi Takatsuki was Masao Matsuoka, MD, PhD and Junji Yodoi, MD, PhD both of Kyoto University.

## 2018 IHV Lifetime Achievement Awards



*Dr. Henry Masur, Dr. Robert Gallo and Dr. Kiyoshi Takatsuki*

### **2018 IHV Lifetime Achievement Award for Excellence in Medical Education, Clinical Care and Clinical Research—**

**Henry Masur, MD**, Chief of Critical Care Medicine Department at the National Institutes of Health (NIH) Clinical Center. Dr. Henry Masur was already a leader in the early 1980s and helped the medical field confront the then new epidemic called AIDS. Currently, Dr. Masur is tackling the ongoing AIDS epidemic disproportionately affecting marginalized people with health disparities in Washington D.C., which has been highly successful in controlling HIV transmission, and for the early, rapid development of hepatitis C therapeutics. Dr. Masur is also a terrific role model and mentor for several HIV and infectious disease physicians, qualities not seen enough these days.

### **2018 IHV Lifetime Achievement Award for Excellence in Clinical Research—**

**Kiyoshi Takatsuki, MD, PhD**, Professor Emeritus at Kumamoto University in Japan. Dr. Kiyoshi Takatsuki was the first to recognize an epidemiological disease occurrence of a specific kind of human leukemia, called Adult T cell Leukemia (ATL). He and his colleagues also discovered very specific features of the leukemic cells that are a virtual diagnostic marker of this leukemia. They defined particular presence of ATL in epidemic form in the south-western part of Japan. Later, my colleagues and I discovered the cause of this disease, Human T cell Leukemia Virus-1 (HTLV-1). Dr. Takatsuki's milestone observation contributed to our ability to open a whole new field of human retroviruses.



### Division of Basic Science (Infectious Agents and Cancer)

In the Division of Basic Science, which will be named the Division of Infectious Agents and Cancer in FY2020, 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, Head of the Laboratory of Chemical Biology and Assistant Director of IHV, and **Eric Sundberg, PhD**, Professor of Medicine, who became Chair of the Department of Biochemistry at Emory University School of Medicine on September 1, 2019. In this year's Annual Report, we highlight research from a few members of our faculty.



### Division of Vaccine Research

The Division of Vaccine Research faculty, led by **George Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Professor of Microbiology and Immunology, employs a multidisciplinary approach to develop an HIV-1 vaccine. This approach is based on divisional expertise in molecular and cell biology, virology, immunology, structural biology, and translational medicine. In addition, the Division of Vaccine Research collaborates intramurally with the Division of Clinical Care and Research on "in house" clinical trials of our vaccine products. The ongoing 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 selective targeting of CD4+ helper T cells that do not increase susceptibility to HIV-1 infection.



### Division of Clinical Care and Research

The Division of Clinical Care and Research, directed by **Shyam Kottlil, MBBS, PhD**, Professor of Medicine and Head of the Clinical Care Research Unit, continues to strengthen all three of its key missions: clinical care, and clinical research and medical education, both in the Baltimore and Washington metropolitan areas. To accomplish these missions this year, the Division assembled a team of 44 faculty and 77 support personnel and secured 90 active grants and contracts. The Division has enhanced its Baltimore-based ambulatory clinical programs in the management and prevention of HIV infection, hepatitis comorbidities and treatment of patients with other infectious diseases under the clinical leadership of **Anthony Amoroso, MD**, Associate Professor of Medicine, Associate Director of the Division, Head of Clinical Care Programs and at the new clinical space on the Midtown Campus where he is Associate Chief of Medicine. Dr. Kottlil and his clinical research team have focused on a series of new initiatives that target expansion of treatment of marginalized patients with chronic hepatitis infection in Baltimore and the District of Columbia. Also, of note this year, was the continued development of the Phase 2 Preventive HIV vaccine trial developed by me and my colleagues, Dr. George Lewis and Anthony DeVico, PhD, Professor of Medicine and Head of the Laboratory of Viral Envelope Studies in the Division of Vaccine Research. Lastly, IHV's clinical team has expanded its research in enhancing our knowledge and improving the lives of people who live with HIV by targeting the opioid epidemic rampant in the Baltimore and DC metropolitan areas. These include development of novel colocation models of care for HIV and hepatitis C, development of novel first-in-class anti-craving molecule, and expansion of patient care in harm reduction centers.





### Division of Epidemiology and Prevention

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine and Director of the Center for International Health, Education & Biosecurity (CIHEB), continues to advance its research endeavors through public health surveillance, evaluation projects, field investigation and analytical studies, in addition to health systems strengthening efforts. After sixteen years of concentrated effort building sustainable research, training and public health programs in Nigeria, the Division is expanding to other sub-Saharan countries. In FY19, the Division's 10 faculty members have 16 active federal awards totaling \$147M. Moreover, the Division published 52 manuscripts in peer reviewed journals in FY19, including 5 first authors and 11 senior authors.



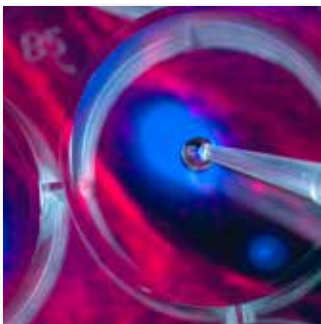
### Division of Immunotherapy

The Division of Immunotherapy, led by **Yang Liu, PhD**, Professor of Surgery, was established in February 2018. The overall mission of the Division is two-fold. First, the Division performs fundamental research on cancer immunology and immunological diseases. Second, in partnership with industry, they perform a full range of translational research ranging from target identification, mechanism of drug action, drug development and novel clinical trials.



### Center for International Health, Education, and Biosecurity

The Center for International Health, Education, and Biosecurity (CIHEB) has made key advances in addressing critical needs in health system capacity that improve the prevention, care, and treatment of HIV and other diseases. CIHEB's mission is to improve the human condition globally, safeguard communities against health-related threats, and promote health equity worldwide. The Center supports the development and sustainability of evidence-based and data-driven, quality health service for HIV, hepatitis, tuberculosis, malaria, emerging infectious diseases, and non-communicable diseases. In 2018-2019, CIHEB's portfolio spanned six countries and employed more than 850 program staff. **Man E. Charurat, PhD, MHS**, Professor of Medicine and Director of the Division of Epidemiology and Prevention, was appointed CIHEB's new Global Director. Under Dr. Charurat's leadership, together with his team of country directors, CIHEB is continuing to expand its global impact.



### 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 Core** and the  $\mu$ QUANT Core, is led by an experienced researcher at IHV. More information about each of the Cores, can be found in this year's annual report.



## IHV is a Global Virus Network (GVN) Center of Excellence

The concept of a Global Virus Network (GVN) began back in the 1980's when a small group of virologists realized that virtually no working virologists had a global directive for researching the cause of AIDS during the earliest years of the epidemic. Conversely, important groups such as the World Health Organization which did have a global mandate for combatting the new disease had virtually no resident expertise in the kind of virus that was subsequently shown to be the cause of AIDS, namely, a retrovirus. Examining the history of other great epidemics of the 20th century, Influenza and Polio, reveals similar disconnects between available expertise and the urgent public need to identify causation and prevention modes.

Led by GVN President, **Christian Bréchet, MD, PhD**, GVN Centers, with strong working relationships among them, are poised to engage in any outbreak situation by providing the world's only network of top basic virologists from around the globe covering all classes of human, and many animal, viral threats. The IHV is a Center of Excellence of the GVN with a major role in its formation and the subsequent continued success it experiences today. GVN is also committed to training the next generation of virologists in order to meet the critical need posed by the graying of members of our own discipline, and to inform and educate policymakers and members of the public about the role of virologists in mitigating viral illness and preventing infections from taking hold in populations. This is especially important as my colleagues and I have noticed a significant decline in students entering the field of virology.



## Financial Overview

IHV had its strongest financial year on record in FY2019, generating \$167,000,000 of total revenue. This was due to steady increases in all 5 Divisions and 1 Center, including Basic Science, Immunotherapy, Vaccine Research, Clinical Care and Research, Epidemiology and Prevention and the Center for International Health, Education, and Biosecurity (CIHEB). The largest increase, a one-time influx of \$72M for a nine-month HIV survey in Nigeria, came from the Division of Epidemiology and Prevention and was the result of a second five-year survey grant that commences in FY2020. Additionally, our international work through CIHEB increased significantly in FY2019 despite changes in the way in which the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) funds will be awarded to indigenous organizations, pointing to a large drop in related funding in FY2020 and beyond.

# IHV Leadership



**Robert C. Gallo, MD**  
Co-Founder & Director  
Institute of Human Virology  
The Homer & Martha Gudelsky Distinguished Professor in Medicine  
University of Maryland School of Medicine



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



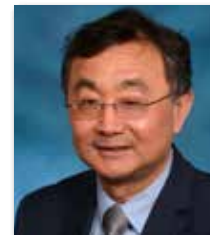
**George K. Lewis, PhD**  
Director, Division of Vaccine Research  
Institute of Human Virology  
The Robert C. Gallo, MD Endowed  
Professorship in Translational Medicine  
University of Maryland School of Medicine



**Shyam Kottlil, MBBS, PhD**  
Director, Division of Clinical Care  
and Research  
Head, Clinical Research Unit  
Institute of Human Virology  
Professor, Medicine  
University of Maryland School of Medicine



**Man E. Charurat, PhD**  
Man E. Charurat, PhD, MHS, Director,  
Division of Epidemiology & Prevention  
Director, Center for International Health,  
Education & Biosecurity (CIHEB)  
Institute of Human Virology  
Professor, Medicine  
University of Maryland School of Medicine



**Yang Liu, PhD**  
Director, Division of Immunotherapy  
Institute of Human Virology  
Professor, Surgery  
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

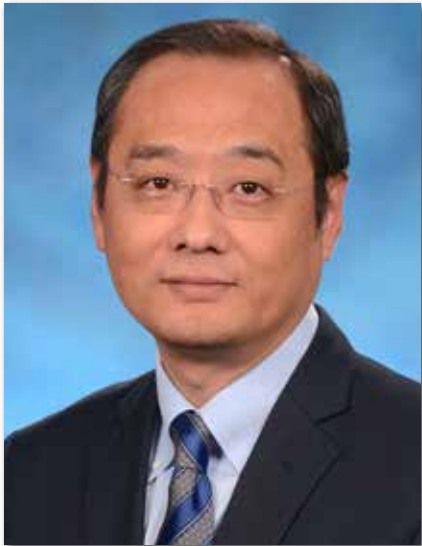


**Anthony Amoroso, MD**  
Associate Director, Division of Clinical Care  
and Research  
Head, Clinical Care Programs  
Institute of Human Virology  
Associate Professor, Medicine  
University of Maryland School of Medicine



**Dave Wilkins**  
Chief Operating Officer  
Institute of Human Virology  
University of Maryland School of Medicine

# Basic Science



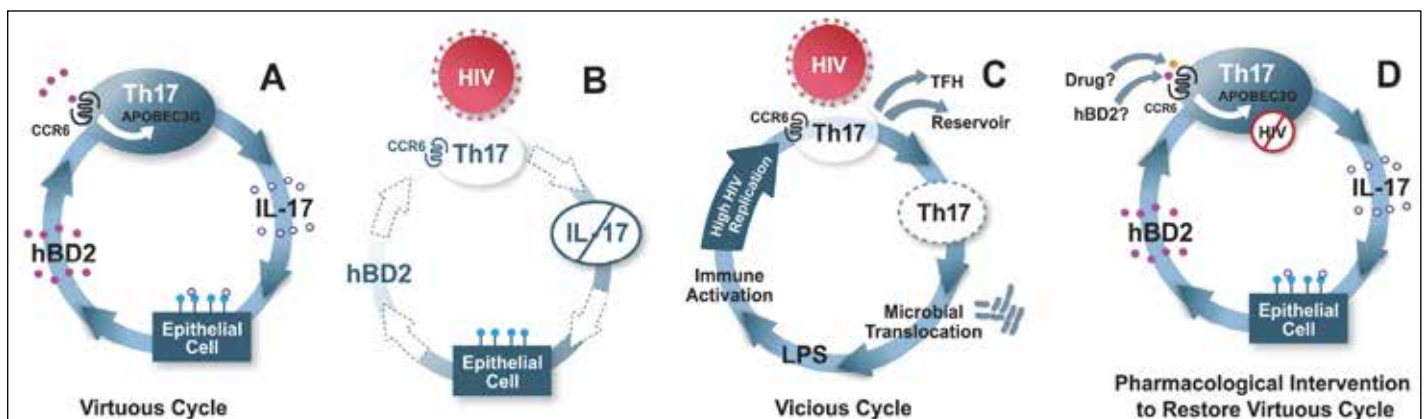
Wuyuan Lu, PhD



Eric Sundberg, PhD

In the Division of Basic Science, which will be named the Division of Infectious Agents and Cancer in FY2020, 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 co-directed by **Wuyuan Lu, PhD**, Professor of Biochemistry and Molecular Biology, Head of the Laboratory of Chemical Biology and Assistant Director of IHV, and **Eric Sundberg, PhD**, Professor of Medicine, who became Chair of the Department of Biochemistry at Emory University School of Medicine on September 1, 2019. In this year's Annual Report, we highlight research from a few members of our faculty.



**Figure 1. Model of the interplay between Th<sub>17</sub> cells, AMPs, and HIV infection in mucosa.** In normal homeostasis (A), Th<sub>17</sub> cells produce IL-17 induces production of hBD2 from epithelial cells. In addition to its antimicrobial activity, hBD2 binds to CCR6 and induces expression of the HIV inhibitor APOBEC3G, protecting Th<sub>17</sub> cells from HIV infection. In gut and vaginal mucosae, where hBD2 is not retained efficiently, the protective effect of hBD2 is less efficient. When HIV infects and kills Th<sub>17</sub> cells (B), IL-17 levels decrease, with parallel decrease in hBD2 production. The loss of Th<sub>17</sub> cells and of AMPs levels result in breakdown of mucosal integrity (C), associated with microbial translocation, with pro-inflammatory conditions driving immune activation and, consequently, HIV replication, in a self-perpetuating vicious cycle of infection. Drugs (or defensins) targeting CCR6 (D) could induce APOBEC3G in CCR6<sup>+</sup>Th<sub>17</sub> cells, protecting them from infection, restoring the virtuous circle. Figure reproduced from *Viruses* **2017**, 9(5), 111; <https://doi.org/10.3390/v9050111>

## Garzino-Demo Laboratory

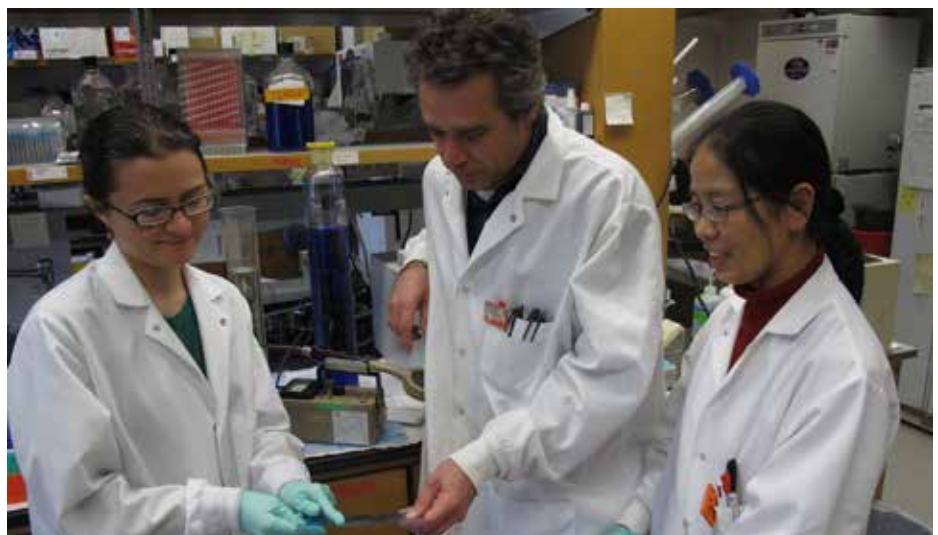
The Laboratory of virus-host interactions, headed by **Alfredo Garzino-Demo, PhD**, Associate Professor of Microbiology and Immunology and Head of the Laboratory of Virus Host Interaction, studies the etiopathogenesis of viral infections, with the aim of developing new therapeutic approaches. The laboratory has been focused on HIV infection for many years but has recently started studies on flaviviruses: Dengue and Zika viruses (DENV and ZIKV, respectively).

**Pathogenesis of HIV infection:** In the last decade, studies performed in the laboratory have characterized that HIV preferentially infects cells that express the CCR6 chemokine receptor. CCR6 is expressed on memory T cells, Th17 cells (i.e., helper T lymphocytes that produce Interleukin (IL) -17, macrophages, and  $\alpha 4\beta 7$  lymphocytes. Interestingly, CCR6 is expressed also on cells that are not infected by HIV, but that have been proven to be depleted in the course of HIV infection, i.e.,  $\gamma\delta$  T cells, and mucosal associated invariant T (MAIT) cells. Some MAIT and  $\gamma\delta$  T cells produce IL17, similarly to Th17 cells. Consequently, HIV infection directly or indirectly targets IL17-producing cells, as shown among others by **Aaron Christensen-Quick, PhD**, a former graduate student in the lab. When IL-17 is produced and released extracellularly, it binds receptors on immune and non-immune cells. In mucosal epithelial cells IL17 causes production of antimicrobial peptides, including defensins (**Figure 1**, opposite page). The laboratory has shown that some human defensins, i.e., human beta defensin (hBD) 2 and 3 protect cells from HIV infection (shown by **Lingling Sun, MD**, Research Specialist, in collaboration with Dr. Wuyuan Lu). Part of that protection is due to a virucidal mechanism, but another component of the activity of hBD2 and hBD3 is mediated by CCR6, which

can bind hBDs besides the chemokine MIP-3 $\alpha$ . The CCR6-mediated inhibition of HIV is due to increased expression of APOBEC3G, an intracellular antiviral factor, as shown in several publications by **Mark K. Lafferty, PhD**, previously a postdoctoral fellow in the lab. Based on these findings, the laboratory has proposed that HIV infection disrupts a homeostatic, "virtuous" cycle, in which cells that produce IL-17 induce production of hBD that contribute to mucosal integrity and protect cells from HIV infection, and initiates a "vicious" cycle where IL-17 is no longer produced by cells eliminated directly or indirectly by HIV, resulting in loss of protection of cells, and of mucosal integrity. The latter causes bacterial products to cross the epithelial barrier, causing activation of the immune system, which is observed in HIV-positive patients even when they are taking antiretroviral therapy. These findings have therapeutic applications, restoring protective levels of APOBEC3G with a CCR6 agonists (like defensins or small molecule agonists). Another target is the aberrant immune activation observed in HIV-positive subjects (see above), which could be reduced by targeting T cell activation pathways. The laboratory is vigorously

pursuing the latter approach. Finally, many cells that express CCR6 that are affected by HIV infection are also highly relevant to tuberculosis (TB). Therefore, the lab is collaborating with **Cristiana Cairo, PhD**, Assistant Professor of Medicine, Division of Epidemiology and Prevention, to study HIV-TB co-infected individuals, hypothesizing that CCR6+ cells play a critical role in both pathologies, exacerbating each other in co-infections.

**Retrocyclin defensins: impact on viral infection and the immune system.** Retrocyclin are defensins "resurrected" from pseudogenes in the human genome that are part of the family of theta-defensins. Theta defensins are 18-mer peptides produced by head-to tail cyclization of two precursor peptides, expressed in non-human primates. They result from gene duplication of defensin genes, with an early stop codon that determines their shorter size relatively to other defensins. In humans, an additional stop codon prevents their expression, so they can be produced only in the lab, by synthesis. Theta defensins, including retrocyclins, display potent antimicrobial activity against a vast range of bacteria, viruses, and fungi. In a collaboration with Dr. Wuyuan



*Alfredo Garzino Demo, PhD, discusses protein expression data with Virginia Carroll, PhD, a former post-doctoral fellow, and Lingling Sun, MD, Research Specialist*

Lu and the lab of Stefanie Vogel, PhD, Professor, Department of Microbiology and Immunology, University of Maryland School of Medicine, the lab has shown that the retrocyclin RC101 can act not just as an antimicrobial agent, but also as an immunomodulator, decreasing production of pro-inflammatory cytokines (IL-1 $\beta$ , TNF $\alpha$ ) and of interferon  $\beta$  from human and murine macrophages activated with LPS or infected by the Influenza A virus. This effect translated *in vivo*, as mice infected with a lethal dose of Influenza A Virus, and then treated with retrocyclin RC101 were protected from inflammation, weight loss, and death. Thus, retrocyclins could be useful to treat infections that cause pathogenic levels of inflammation. The pathogenicity of Flavivirus such as DENV and ZIKV is mediated by inflammation, and the laboratory is currently studying whether and how retrocyclin RC101 can inhibit their replication. The study is led by a visiting scientist, Wei Wang, PhD, Associate Professor, the Wuhan Institute of Virology, Wuhan, China. The success of these studies will warrant further studies of retrocyclin defensins as potential therapeutic or preventive approaches against a broad spectrum of pathogens associated with inflammation.



Olga Latinovic, PhD, MSc

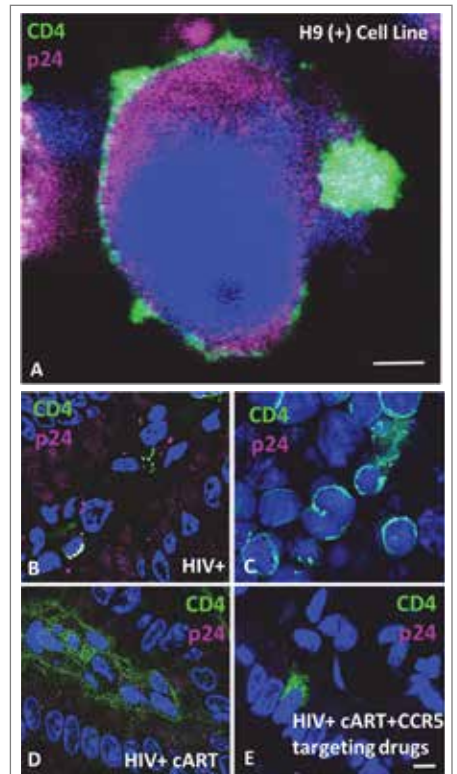
## Latinovic Laboratory

**Olga S. Latinovic, PhD, MSc**, Assistant Professor of Microbiology and Immunology, Head of the Laboratory of Host-Pathogen Interaction and Head of the Imaging Core Facility, works on developing different combinatorial therapeutic approaches to enhance potency and decrease side effects of HIV-1 entry inhibitors. This long-time research interest resulted in the recent review “CCR5 Inhibitors and HIV-1 Infection” (*J of AIDS and HIV Treatment*, December 2018) published in collaborative efforts with **Marvin S. Reitz, PhD**, Adjunct Professor of Medicine and **Alonso Heredia, PhD**, Assistant Professor of Medicine in the Division of Clinical Care and Research.

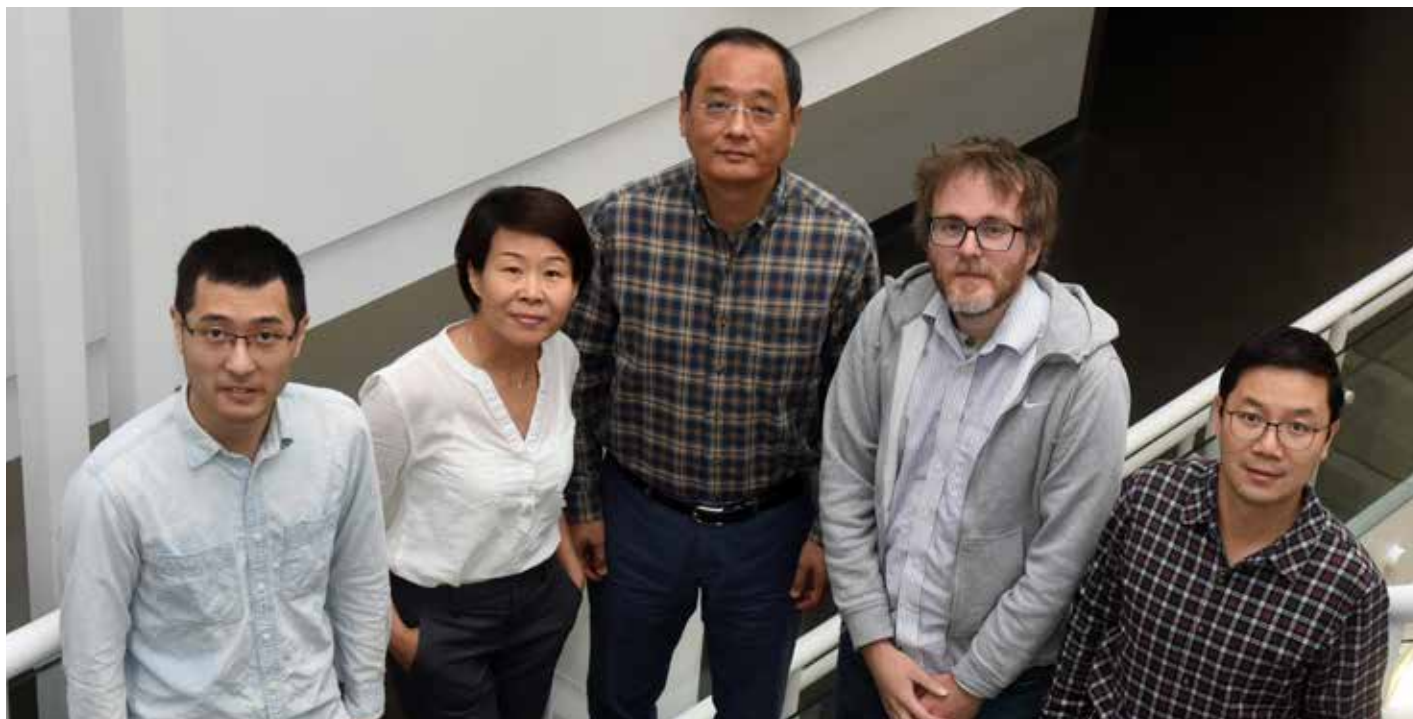
Dr. Latinovic uses a human CD34+ hematopoietic stem cell-engrafted NOD (non-obese diabetic)-SCID (severe combined immunodeficiency)-*il2rg*<sup>-/-</sup> (NSG) mouse model to monitor improved suppression of productive HIV-1 infection and maintenance of human CD4+ T-cells by inclusion of CCR5 targeting drugs with standard, oral cART. This work has validated the hu-mouse model for combined anti-viral therapy studies and was recently published in *AIDS Research and Human Retroviruses* (June, 2019). Current research topics are based on determining whether this improved control of viremia and maintenance of CD4/CD8 T-cell ratios in blood leads to reduction of viral integrated DNA in solid tissue organs and of infected human cells. The study further includes quantitative visualization of HIV-1 infection sites (p24 protein) and human T-cell markers using confocal microscopy (**Figure 2**). Collaborators on this project include IHV colleagues **Fabio Romerio, PhD**, Assistant Professor of Medicine and Head of the Laboratory of IHV-1 Persistence & Immunopathogenesis, Dr. Alonso Heredia and **Yutaka Tagaya, PhD**, Assistant Professor of Medicine, Head of the Laboratory of Cell Biology and Head of the Flow Cytometry & Cell

Sorting Core Facility. The grant has been sent out 2 weeks ago under NIH No 4341883.

Characterizing viral entry into different cell populations expressing CCR5 may lead to a better understanding of relative permissivity to fit HIV-1



**Figure 2. Confocal microscopy visualization of HIV-1 infection sites:** **Panel A** shows a representative image of H9(+) cells expressing HIV-1 structural protein p24 (red) and a human CD4 + T marker (green,) used as a model for this imaging study. The blue signal is from DAPI dye staining of the cell nucleus. **Panel B.** Visualized site of infection—HIV-1 p24 (red) in Lamina Propria intestinal tissue of HIV-1 infected hu-mouse. **Panel C.** CD4+T cells in HIV-1 (-) mouse tissue. **Panel D.** Engrafted human CD4+T cell labeled with anti-CD4+ Ab (green circles) in GALT of an HIV-1 infected mouse under cART treatment. **Panel E.** Human CD4+T cells labeled with anti-CD4 Ab (green circles) within GALT of hu-mouse under combined treatment with cART and CCR5 targeting drugs. Bar size is 10  $\mu$ m. Experiments were performed by Matthew Weichselder, MSc.



L to R: Chongbing Liao, BS; Weirong Yuan, MS; Wuyuan Lu, PhD; Daniel Bonsor, PhD; and, Mengxiang Su, PhD

virions. By creating novel antiviral therapy strategies using various HIV-1 entry inhibitors, Dr. Latinovic is developing super-resolution microscopy methods to quantify CCR5 conformational variations that may relate to susceptibility to productive HIV-1 entry. CCR5's conformational states, can be discriminated by sets of different CCR5 mAbs and fusion proteins. Visualizing and quantifying those states via super-resolution (STORM/TIRF) microscopy will allow us to identify CCR5 conformations most efficiently used by HIV-1. Correlation of conformational populations of CCR5 molecules with rates of viral entry will allow more specific targeting and could lead to the development of more effective entry inhibitors. The significance of this study is that it may identify CCR5 sub-populations not specifically considered in previous anti-viral therapies. Further significance will come from understanding which populations of surface and total CCR5 molecules (internalized and intracellular) are critical for HIV-1 entry based on

the use of STORM/TIRF novel imaging methodologies.

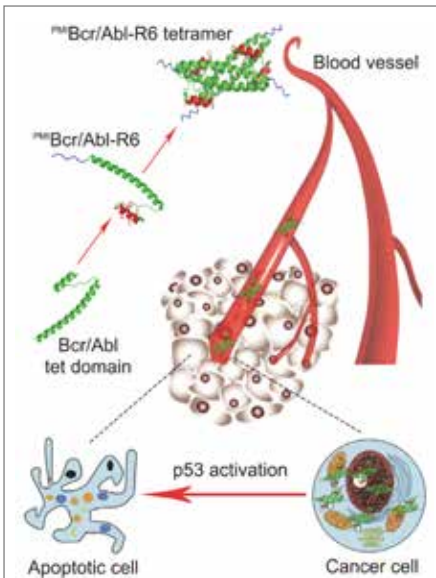
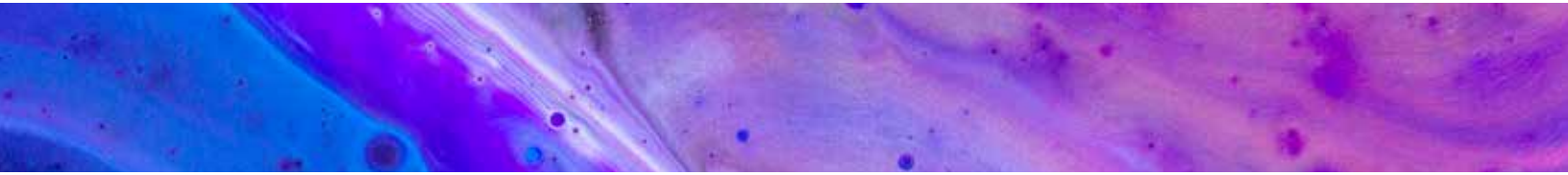
### Lu Laboratory

Led by Division Director, **Dr. Wuyuan Lu**, a research focus of the Lu lab includes an antitumor protein for cancer therapy. The tumor suppressor protein p53 is functionally inhibited and degraded in many tumors by the action of its negative regulators MDM2 and MDMX, contributing to tumor development and progression. Antagonizing MDM2 and MDMX to activate the p53 pathway has been validated as an attractive therapeutic strategy for cancer treatment. Using chemically synthesized MDM2 and MDMX for phage display, the Lu laboratory previously discovered a high-affinity dodecameric peptide antagonist of MDM2 and MDMX, termed PMI (Pazgier et al., PNAS 2009 & Li et al., JMB 2010). However, PMI itself is inactive against tumor cells harboring wild-type p53 and elevated levels of MDM2 and MDMX due to its susceptibility to proteolytic degradation and inability to traverse the cell membrane – two major

pharmacological barriers to peptide therapeutics in general.

To mitigate these problems and endow PMI with the ability to inhibit tumor growth *in vitro* and *in vivo* by activating the p53 pathway, the Lu laboratory identified, as a scaffold protein for peptide epitope grafting, the 72-residue tetramerization domain of the chimeric oncogenic protein Bcr/Abl of chronic myeloid leukemia, which comprises a short N-terminal  $\alpha$ -helix linked via a flexible loop to an elongated C-terminal  $\alpha$ -helix that mediates tetramer formation. PMI was grafted to the N-terminal  $\alpha$ -helix of Bcr/Abl tetramerization domain in place of residues 5-16, and the protein was C-terminally extended by an Arg-repeating hexapeptide (R6) to facilitate its membrane permeabilization (**Figure 3**, next page). The resultant protein <sup>PMI</sup>Bcr/Abl-R6 was chemically synthesized in large quantity and high purity using native chemical ligation.

<sup>PMI</sup>Bcr/Abl-R6 readily folded into an  $\alpha$ -helical protein, as expected, formed



**Figure 3.** Strategy for the design of a protein-based nano-carrier of PMI for cancer therapy. The tetramerization domain of 72 amino acid residues of Bcr/Abl (green) comprises an N-terminal  $\alpha$ -helix linked via a flexible loop to an elongated C-terminal  $\alpha$ -helix that mediates tetramer formation. PMI in red is grafted to the short  $\alpha$ -helical region in place of residues 5-16 of Bcr/Abl, resulting in <sup>PMI</sup>Bcr/Abl. To facilitate membrane permeabilization, <sup>PMI</sup>Bcr/Abl is C-terminally extended by an Arg-repeating hexapeptide (R6) in blue, yielding <sup>PMI</sup>Bcr/Abl-R6. <sup>PMI</sup>Bcr/Abl-R6 forms a stable tetramer, circulates in the blood, accumulates in the tumor, traverse the cell membrane, and activates p53 by antagonizing MDM2/MDMX, leading to inhibition of tumor growth in experimental animals.

a highly stable tetramer in solution, and bound to MDM2 at an affinity of 32 nM. <sup>PMI</sup>Bcr/Abl-R6 was significantly resistant to proteolytic degradation compared with PMI, efficiently permeabilized HCT116 tumor cells, and induced apoptotic cell death by activating the p53 pathway *in vitro*. Importantly, <sup>PMI</sup>Bcr/Abl-R6 passively accumulated and retained extendedly in solid tumors, presumably via the enhanced permeability and retention effect, and potently inhibited tumor

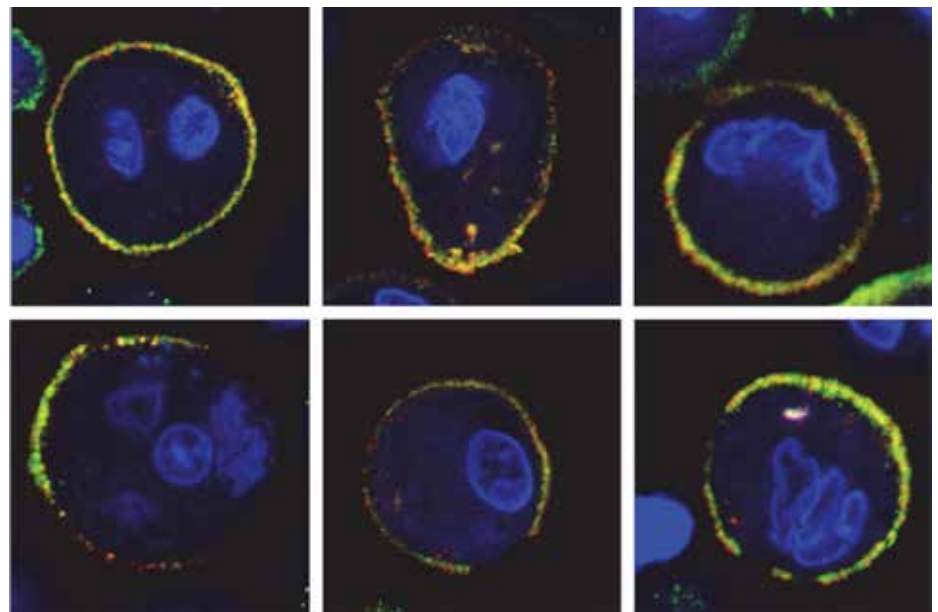
growth in xenograft mice by inducing p53-dependent apoptotic responses *in vivo* with minimal immunogenicity and little toxicity to normal cells, tissues and organs. <sup>PMI</sup>Bcr/Abl-R6 as a dual-specificity antagonist of MDM2 and MDMX and a powerful p53 activator *in vitro* and *in vivo* promises a novel antitumor agent with significant therapeutic potential. These findings have recently been published in *Biomaterials* (Ma et al., *Biomaterials* 2019, 204:1-12).

### Romerio Laboratory.

Over the last 12 months, the laboratory of **Dr. Fabio Romerio** has intensified its efforts to investigate the HIV-1 antisense gene. The existence of this HIV-1 gene was predicted in the late 1980's. It is encoded in the negative strand of the provirus, and it overlap the gene encoding for the envelope glycoproteins, gp120 and gp41. Over the last three decades, a few publications have confirmed its existence and its expression in HIV-1 infected patients, but the study of this

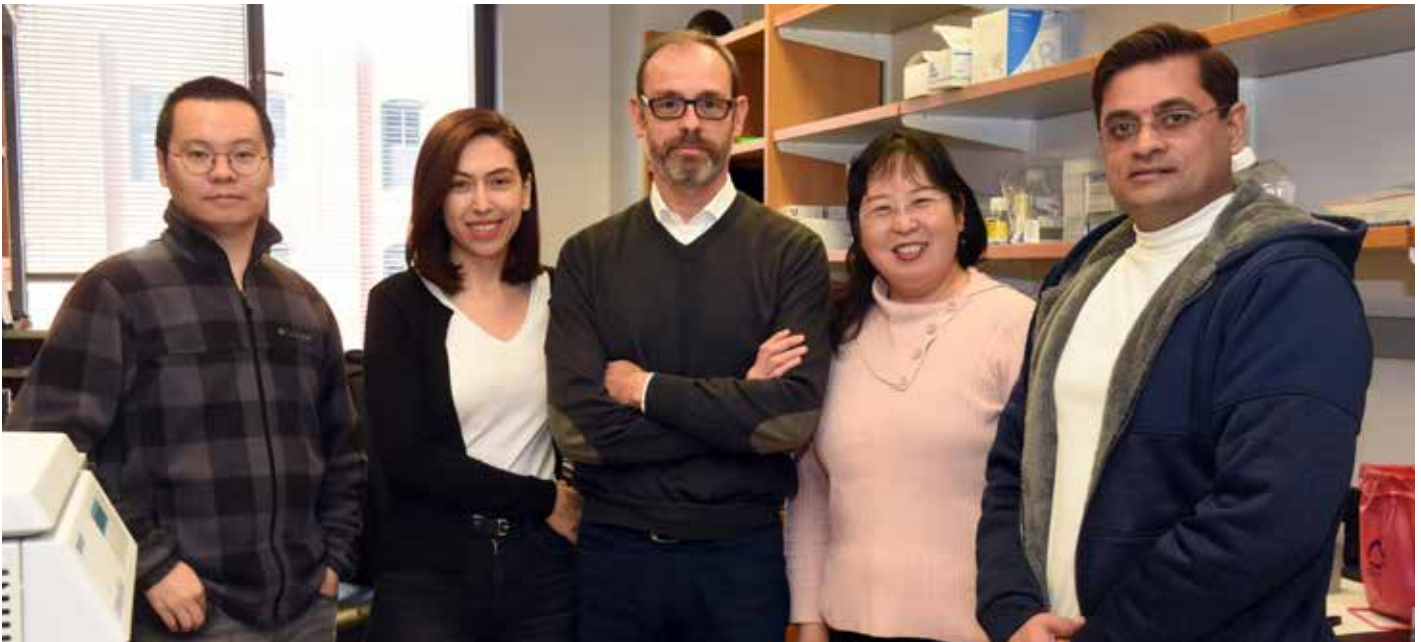
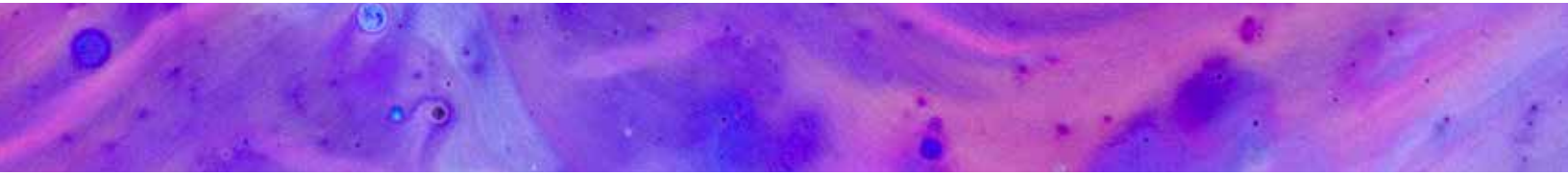
gene has remained largely neglected, and its role in viral replication remains to be determined and demonstrated.

The research in Dr. Romerio's lab focuses on the role of both the transcript (Ast) and the protein (ASP) that are the products of the HIV-1 antisense gene. In recent years, Dr. Romerio has shown Ast suppresses viral replication by recruiting a cellular multi-protein complex (termed PRC2) at the HIV-1 5'LTR. PRC2 introduces epigenetic marks that suppress gene expression, thus promoting viral silencing and latency. During the last year, Dr. Romerio's lab has utilized funding from the American Foundation for AIDS Research (amfAR) to expand these studies toward the investigation of the secondary structure of Ast, and how it relates to its function. A series of mutagenesis experiments have identified five domains along the Ast molecule. The first domain mediates the interaction between Ast and the proviral 5'LTR. The third domain contains the structural elements that are critical for the interaction between



**Figure 4.** Expression of the HIV-1 proteins ASP (red) and gp120 (green) on the cell surface of primary human monocyte-derived macrophages during productive HIV-1 infection. Yellow stain shows co-localization of the two proteins. Nuclei are stained with DAPI (blue). Experiments performed and imaged by Dr. Zahra Gholizadeh (Romerio Lab).



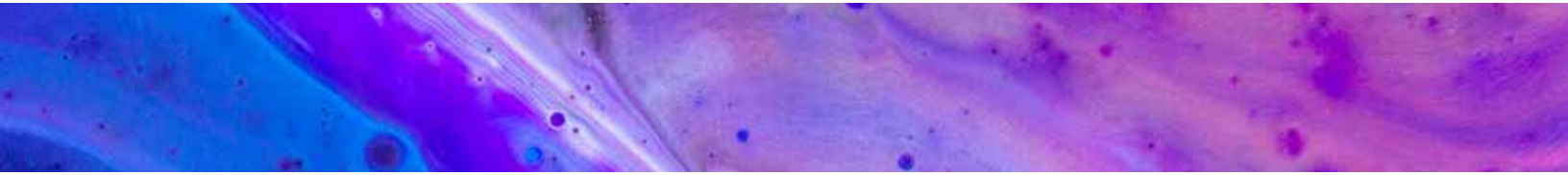


L to R: Rui Li, PhD; Zahra Gholizadeh, PhD; Fabio Romero, PhD; Wei Zhou, MS; and, Shameel Iqbal, PhD

Ast and PRC2. Mutagenesis studies in the remaining three domains showed that they also contain important features that contribute to the full activity of Ast, suggesting that Ast may interact with epigenetic and transcriptional silencers other than PRC2. Studies conducted in collaboration with Dr. Alan Mullen at Harvard Medical School confirmed this hypothesis, and showed that Ast is associated with several repressors. While the functional relevance of these interactions is currently being investigated, the picture emerging from these studies suggests that Ast may function as a scaffold molecule that binds several transcriptional repressors, recruits them to the 5'LTR, and orchestrates their activity. These results also point to Ast as a potential new tool in the design of new curative approaches for HIV-1. The ability to deliver Ast to both infected cells could permanently put HIV-1 to sleep, preventing its ability to produce new copies of itself. Dr. Romero's lab will investigate the possibility to leverage Ast as an HIV-1 in the context of a new 5-year, \$4-million grant from the National Institutes of Health that began in the early Spring 2019.

The investigation of the HIV-1 antisense protein ASP and its potential role in viral replication are more recent endeavors in Dr. Romero's lab. The open reading frame encoding ASP is found exclusively in pandemic HIV-1 strains that belong to groups M, and it is absent in endemic strains that belongs to groups N, O and P. This suggests that ASP may play a role in virus spread or pathogenicity. To begin unraveling the

possible role of ASP in the virus lifecycle, Dr. Romero's lab sought to investigate its expression pattern within infected cells. For these studies, Dr. Romero and his collaborators produced a unique monoclonal antibody that they have utilized in flow cytometry and confocal microscopy analyses. The results emerging from these studies show that ASP resides within the nucleus of infected cells in which HIV-1 is either latent or expressed at very low levels. Following induction of maximal levels of viral expression, ASP translocates to the cytoplasm and to the cell membrane, where it is found in very close proximity of the HIV-1 envelope glycoproteins, gp41 and gp120 (**Figure 4**, opposite page). Moreover, after viral budding and release, ASP can be detected on the surface of HIV-1 particles embedded in the viral envelope. The results of these studies – which have been recently accepted for publication in the *Journal of Virology* – suggest that ASP may represent a new target for the development of preventative and therapeutic vaccine for HIV-1. More recent and still very preliminary studies from Dr. Romero's lab show that the introduction in the HIV-1 genome of mutations that prevent the expression of ASP significantly decrease the viral fitness. To pursue further these studies, Dr. Romero has recently established collaborations with Dr. Hongshuo Song (US Military HIV Research Program, Bethesda, Maryland), Dr. Mary Kearney (National Cancer Institute, Frederick, Maryland), and Drs. Mathias Lichterfeld and Xu Yu (Brigham and Women's Hospital, Boston, Massachusetts).



L to R: Xiaorong Wu; Yutaka Tagaya, PhD; and, Felisa Diaz-Mendez, PhD

## Tagaya Laboratory

The lab of **Dr. Yutaka Tagaya** has two major research focuses: Development of a new multi-cytokine therapy for treating T-cell malignancy (including HTLV-1 diseases) and the role of  $\gamma$ c-cytokine cooperation in normal and pathologic T-cell immune responses. This year the Tagaya laboratory summary will overview the cytokine-related project.


### A. Cytokine co-inhibition therapy to T-cell malignancy patients.

Several years ago, we noticed the need for a new type of multi-cytokine inhibitor that blocks select members of family cytokines for treating certain types of human diseases. We then developed a new technology by which we can synthesize new types of cytokine inhibitors that can target multiple cytokines belonging to a

family and reported it in previous annual reports. We are particularly interested in the interplay of cytokines of the  $\gamma$ c (common-gamma) family (IL-2, -4, -7, -15, and -21). Each of these cytokines has a distinct role in lymphocyte development (IL-7 for T-cells, IL-15 for NK,  $\gamma\delta$ T, NKT, IELs and memory CD8 T-cells, IL-2 for regulatory T-cells etc.) and the overproduction of these cytokines creates necrotizing conditions such as malignancy, autoimmunity and inflammatory diseases. Importantly, there are many human diseases in which these cytokines cooperate, thus the blockade of one single member by using monoclonal antibodies would not have therapeutic effects. That is where our inhibitors come in as we can rationally design inhibitors that are specific for only the relevant cytokines to the disease. In short, our approach allows

us to inhibit only desired members of the  $\gamma$ c-cytokines and we are capable of design distinct inhibitors based on given combinations of target cytokines.

Our lead inhibitor peptide (BNZ-1) blocks the action of IL-2, IL-15, IL-9 (all are members of the  $\gamma$ c-family), but not other cytokines (Nata et al. 2015). This peptide effectively blocked the ex vivo pathogenic activation of T-cells from HTLV-1 (Human T-cell leukemia virus-1) associated myelopathy (HAM/TSP) patients (Massoud et al. 2015). More recently, we showed that the peptide blocks the ex vivo activation and viability of patient-derived T-cells from Large Granular Lymphocyte leukemia (LGL-L) (Wang et al. 2019). Currently we are conducting a phase I/II clinical trial targeting two T-cell malignancies (LGL-L, and cutaneous T-cell lymphoma (CTCL)) (Frohna et al. 2019). We saw 50% of the treated patients who did



not respond well to previous treatments showed response to BNZ-1. In the meantime, we have demonstrated that BNZ-1 is effective in blocking the graft-versus-host disease (GvHD, see below).

***B. A novel T-cell subset that is responsible for the development of the graft-versus-host disease.***

This finding was derived from the multi-cytokine inhibitor project described above. There are publications reporting the involvement of the  $\gamma$ c-family cytokines in the development of the graft-versus-host disease (GvHD). However, the question of which of the 6  $\gamma$ c-family member cytokines are responsible has not been clarified. While we were establishing humanized mouse models for the study of HTLV-1 related T-cell leukemia, we encountered with GvHD development after human CD34+ progenitor cells or peripheral blood mononuclear cells (PBMCs) were engrafted into immunodeficient NSG (non-obese diabetes/severe combined immunodeficiency /  $\gamma$ c<sup>-/-</sup>). This is a well-known fact. To circumvent it, a few systems such as the transplantation of liver and thymus from the same donor of the bone marrow cells has been invented. However, we inversely thought that the simple human PBMC engraft model might help us to study the mechanisms underlying human GvHD. More importantly, treatments for human GvHD after allogeneic hematopoietic stem cell transplant (HSCT) have limitations and new treatment is urgently needed. Available treatments for GvHD include the depletion of host T-cells and the use of immunosuppressive drugs. The T-cell depletion treatment, while depleting the relevant cells to the tissue and organ damages in GvHD, renders the transplant ineffective because the graft-versus-tumor effect will not persist after the treatment. The use of immunosuppressant not only dampens the graft-versus-tumor effect, but also makes the recipients immune-compromised so they become vulnerable to microbial infections. Based on our preliminary finding, we hypothesized that the mouse model of GvHD faithfully reflect the pathologic mechanisms in human GvHD and thus the model can be used to study human GvHD to develop a new type of treatment. We also hypothesized that GvHD is not caused by all CD8 T-cells as literature suggests, but a specific subset might be responsible for driving GvHD forward and therefore the depletion of functional suppression of the "subset" would not cause the T-cell immunity to lose its capacity to engage tumor cells (graft-versus-tumor effect) or invading pathogens. The reason for this hypothesis is the finding that the kinetics of the engraftment of CD8 T-cells

which is allegedly responsible for tissue/organ damages and those of the development of GvHD symptoms (such as skin inflammation and hair-loss, loss of body weight) were not overlapping. We thus postulated that only a subset of CD8 T-cells, but not the entire CD8 T-cells are responsible for the development of GvHD. In fact, after screening over 30 known surface markers expressed on CD8 T-cells, we identified that the initial engraftment and expansion of human CD8 T-cells in NSG mice is followed by the selective expansion of a CD8 subset with an NK-marker expression (the detail of this marker will be disclosed upon acceptance of our manuscript), which coincides with the development of GvHD markers. In addition, we depleted this subset from mice undergoing GvHD and saw the GvHD symptoms have been reverted. Thus, we believe we have identified a new subset of CD8 T-cells that drive the GvHD in the experimental model. We have observed that these subset of CD8 T-cells are under constitutive activation through the TCR and  $\gamma$ c-receptor subunit (CD132). However, the activation of the STAT molecules excluded IL-7, IL-4 and IL-21 as responsible cytokines, leaving IL-2, IL-15 and IL-9 as the suspect of activation. In agreement with this assessment, we could reverse the GvHD progress without depleting the candidate CD8 subset, but by administering our multi-cytokine inhibitor BNZ-1 which inhibits IL-2, IL-15 and IL-9 into mice undergoing GvHD. We also analyzed the TCR repertoire of the suspect CD8 T-cell subset and confirmed that they use much more limited  $\alpha\beta$  TCR repertoire than do conventional CD8 T-cells. The relevance of this finding are as follows; 1) this new subset of CD8 T-cells might play similar roles in human GvHD after HSCT. 2) The depletion of this subset might ameliorate human GvHD while keeping the rest of CD8 T-cells intact, thus maintaining the immune system of the recipient still capable of engaging invading pathogens. 3) Alternatively, the functional suppression of these cells by the IL-2/IL-15 co-inhibition may provide a therapeutic option to human GvHD by specifically suppressing a subset of CD8 T-cells which are responsible for exacerbating GvHD in human patients. In support our working hypothesis, we observed the expansion of similar CD8 subset in a patient who manifested after HSCT.



## Basic Science Publications

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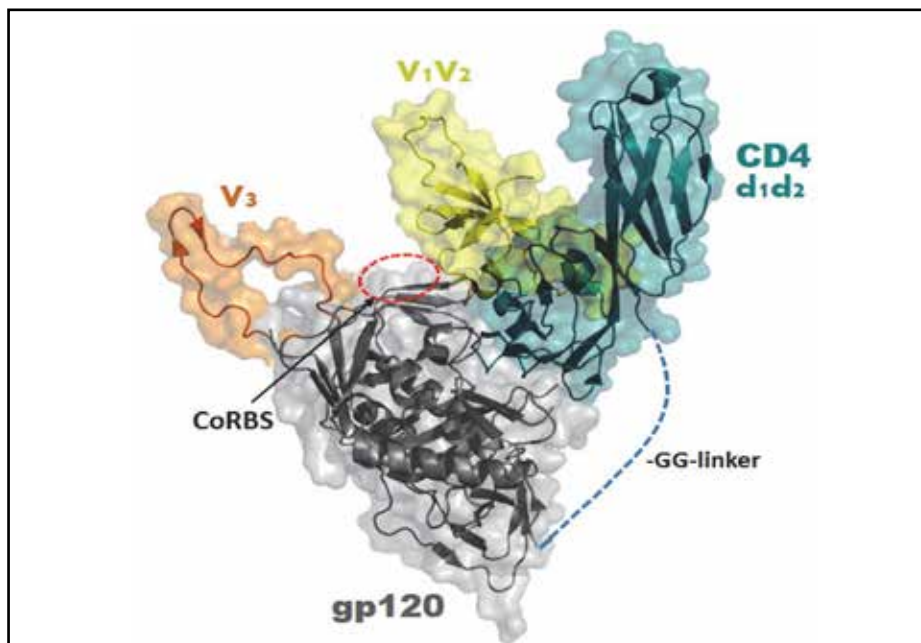
# Vaccine Research



George K. Lewis, PhD

The Division of Vaccine Research faculty, led by **George K. Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Professor of Microbiology and Immunology, employs a multidisciplinary approach to develop an HIV-1 vaccine. This approach is based on divisional expertise in molecular and cell biology, virology, immunology, structural biology, and translational medicine. In addition, the Division of Vaccine Research collaborates intramurally with the Division of Clinical Care and Research on “in house” clinical trials of our vaccine products. The ongoing 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 selective targeting of CD4+ helper T cells that do not increase susceptibility to HIV-1 infection.

Consequent to a large number of preclinical studies, the division has developed an immunogen that elicits cross-reactive protection in animal models. This vaccine is a conformationally constrained protein comprised of HIV-1 gp120 linked to the first two domains of human CD4 by a flexible peptide spacer. This immunogen is denoted as the full-length single chain (FLSC) protein. **Anthony DeVico, PhD**, Professor of Medicine and Head of the Laboratory of Viral Envelope Studies, and his laboratory developed the FLSC vaccine concept in the early years of the IHV with the first publication of its immunochemical and physical chemical profile in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research, led by Dr. George Lewis, in collaboration with colleagues in the IHV Division of Clinical Care and Research, The Military HIV Research Program, and the NIAID, NIH HIV Vaccine Trials Network. The early years of FLSC development were supported by National Institutes of Health (NIH) grants to Division of Vaccine Research members including Dr. Anthony DeVico, Dr. Tim Fouts (now at ABL, Inc.), **Robert Gallo, MD**, The Homer &



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Martha Gudelsky Distinguished Professor in Medicine and IHV Director, and Dr. George K. Lewis. The FLSC vaccine concept was licensed to Wyeth Laboratories in 2002 and transferred to Profectus Biosciences in 2004. In 2007, The Bill and Melinda Gates Foundation awarded a large grant to Dr. Gallo (Principal Investigator) and his collaborators Drs. DeVico, Lewis and Fouts to support the advanced preclinical development of FLSC. In April 2011, a consortium of funders led by the Bill and Melinda Gates Foundation and including the Military HIV Research Program (MHRP) 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. Pursuant to this funding, the IHV recently completed a "first in human" Phase I clinical trial of FLSC where the drug product is designated as IHV-001. This trial was carried out in the IHV Division of Clinical Care and research, led by **Shyam Kottitil, MBBS, PhD**, Professor of Medicine and Director of the IHV Division of Clinical Care and Research, and included **Joel Chua, MD**, Assistant Professor of Medicine, and **Mohammad Sajadi, MD**, Associate Professor of Medicine, also both of that Division. The vaccine proved safe and immunogenic opening the door to subsequent clinical trials. Accordingly, several Phase 1b studies are under development with our partners at the HVTN, Duke, The Swiss Vaccine Institute, GeoVax and the MHRP. 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 UMB 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 collaboration includes Drs. Anthony DeVico, George Lewis, Mohammad Sajadi and **Roberta Kamin-Lewis, PhD**, formerly Associate Professor of Microbiology and Immunology and **Krishanu Ray, PhD**, Associate Professor of Biochemistry and Molecular Biology. 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 and Ray are



L to R: Robin Flinko, BS; Chiara Orlandi, PhD; Meng Li, MD; George Lewis, PhD; Robert Gallo, MD; Bhavna Chawla, PhD; James Foulke, BS; and, Krishanu Ray, PhD



focusing on physicochemical and cell biology of Fc-mediated effector function for this program. These efforts are also supported by a R01 grant awarded to Dr. Krishanu Ray as well as by a R01 and VA Merit Award to Dr. Mohammad Sajadi.

This work has led to the identification of the two most highly conserved epitope regions of gp120, the outer HIV-1 envelope glycoprotein, that are targets of potentially protective antibody responses. First, our FLSC studies led to the identification of Epitope Cluster A, which is a highly conserved target of non-neutralizing antibodies that exert Fc-mediated effector functions against CD4+ cells that have bound HIV-1 or infected CD4+ cells that are budding virus prior to CD4 down regulation by the viral proteins Nef and Vpu. Second, Dr. Sajadi's group in collaboration with Division members has identified a new highly conserved neutralization epitope in the CD4 binding site of gp120. Monoclonal (mAbs) specific for this epitope exhibit the broadest neutralization of HIV-1 reported to date and studies are underway to exploit this property to develop a vaccine based on this structure. Further, these mAbs offer significant possibilities for enhanced prophylaxis and therapy against HIV-1, the latter of which is particularly important for HIV-1 "Cure" initiatives.

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



*Anthony DeVico, PhD*

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. 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 and Dr. Lewis as well as Guido Silvestri, MD and Sudhir Kastri, PhD at Emory along with Warner Greene, MD, PhD at University of California, San Francisco. The program is investigating the cellular and molecular mechanisms underlying poor antibody persistence using the FLSC immunogen in animal models. It will also identify the vaccine elicited CD4+ T cell subsets that compromise antibody-mediated protection against model AIDS viruses in animal models. Both studies will build upon recent studies suggesting that the innate immune environment is altered by HIV-1 exposure and favors infection, which can possibly compromise vaccine efficacy.



## Vaccine Research Publications

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# Clinical Care and Research



Shyam Kottlil, MBBS, PhD

Campus where he is Associate Chief of Medicine. **Shyam Kottlil, MBBS, PhD**, Professor of Medicine, Director of the Division and Head of the Clinical Care Research Unit, and his clinical research team have focused on a series of new initiatives that target expansion of treatment of marginalized patients with chronic hepatitis infection in Baltimore and the District of Columbia.

Dr. Kottlil's areas of focus include hepatitis C and hepatitis B therapeutics, HIV cure related research and evaluation of new products for the treatment of hospitalized influenza. Also, of note this year, was the continued development of the Phase 2 Preventive HIV vaccine trial developed by **Robert Gallo, MD**, the Homer & Martha Gudelsky Distinguished Professor in Medicine and IHV Director, **George Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Director of the Division of Vaccine Research and **Anthony DeVico, PhD**, Professor of Medicine and Head of the Laboratory of Viral Envelope Studies in the Division of Vaccine Research.

IHV's clinical team has expanded its research in enhancing our knowledge and improving the lives of people who

The Division of Clinical Care and Research continues to strengthen all three of its key missions: clinical care, and clinical research and medical education, both in the Baltimore and Washington metropolitan areas. To accomplish these missions this year, the Division assembled a team of 44 faculty and 77 support personnel and secured 90 active grants and contracts.

The Division has enhanced its Baltimore-based ambulatory clinical programs in the management and prevention of HIV infection, hepatitis comorbidities and treatment of patients with other infectious diseases under the clinical leadership of **Anthony Amoroso, MD**, Associate Professor of Medicine, Associate Director of the Division, Head of Clinical Care Programs and at the new clinical space on the Midtown



Anthony Amoroso, MD

live with HIV by targeting the opioid epidemic rampant in the Baltimore and DC metropolitan areas. These include development of novel colocation models of care for HIV and hepatitis C, development of novel first-in-class anti-craving molecule, and expansion of patient care in harm reduction centers.

## CLINICAL PROGRAM

Since its inception, the IHV has provided state of the art, high quality care to the citizens of Maryland, and beyond. With more than 3,500 patients in our Baltimore clinics, the IHV continues to identify unmet patient needs and expand services to address them.

The IHV also continues to provide leadership for the Department of Medicine's Division of Infectious Disease. Combining the two divisions' clinical practices allows

for significant synergies in clinical care and education. The Infectious Disease Fellowship (14 fellows) and 34 dedicated clinical Infectious Disease faculty allows the clinical program to support and sustain IHV's programs in immunocompromised host now including care in the Greenebaum Comprehensive Cancer Center and Solid Organ Transplant Program at University of Maryland Medical Center. Our initiatives in associated research and advanced educational components are further developing and growing the research cohorts within the solid organ transplant program around HIV, solid organ transplantation, and HCV therapy in these patients. Although no longer managing the IHV's international President's Emergency Plan for AIDS Relief (PEPFAR) programs, the clinical program actively supports these



international programs through dedicated clinical faculty, educational programs and strategic planning.

**Growing Ambulatory Programs**—With diminishing Ryan White HIV/AIDS funding, a partnership with the University of Maryland Medical System in ambulatory care was an important strategy for sustaining and growing our HIV care and treatment programs. This is within an overall strategy between the School of Medicine and University of Maryland Medical System (UMMS) to create an ambulatory program targeted at complex chronic medical conditions that disproportionately affect the West Baltimore community. We are still awaiting the much anticipated \$70 million new Mid-Town Campus Ambulatory Tower to house our HIV and Infectious Disease ambulatory practices, however, the first steps in construction of the Ambulatory Tower have visibly begun in May of 2019. The IHV will play a major role in this strategy and has UMMS commitment for new modern outpatient clinic space and significant investment into clinic personnel.

In 2016, the IHV moved its outpatient practices including the JACQUES Initiative, the Evelyn Jordan Center, the general infectious disease clinic, and the IHV Clinic within the Family Health Center at Midtown, to form the University of Maryland Center for Infectious Diseases located on UMMC's Midtown Campus. On World AIDS Day 2018, the HIV arm of the Center was renamed The THRIVE Program of the Institute of Human Virology, to highlight the mission of patient wellness and empowerment. **THRIVE** stands for **T**ogether **H**ealing, **R**eaching, **I**nspiring, to achieve **V**ictory over illness, and **E**mbrace life. A new memorial honoring Evelyn Jordan, Joseph Jacques, and other deceased patients of the former and current clinics was revealed on June 5, 2019, Long Term HIV Survivors Day. The memorial also includes a plaque dedicated in honor and memory of all current and former IHV faculty, staff, and patients locally and globally, for their contributions in the fight against HIV.

**The THRIVE Program**—led by Medical Director **Sarah Schmalzle, MD**, Assistant Professor of Medicine in the Division of Clinical Care and Research, is at the forefront of ending Baltimore's fight against HIV. The mission includes providing holistic patient-centered medical care, integrated psychosocial support services, and innovative clinical research in the treatment and prevention of infectious diseases, including HIV/AIDS and hepatitis C. It is committed to addressing public health epidemics by engaging the community and partnering with programs that serve those communities most impacted by these diseases. Strong collaborations with the city and state health departments and with other major HIV clinics in Baltimore through shared grants has strengthened the services that each clinic offers to their patients. Recent focus areas and initiatives include expanding the primary



*L to R: The THRIVE Program's Robin Palmeiro, LCSW-C; Sarah Schmalzle, MD; and, Tiffany Moritz*

care model to include geriatric assessments for the large proportion of people living with HIV over 50, beginning a new nationally-recognized model of mental health care, increasing the number of medical providers offering specialty services such as fibroscans and buprenorphine for medication-assisted-treatment, developing a streamlined program to transition patients from the University of Maryland, Baltimore's (UMB) adolescent HIV clinic to THRIVE, and increasing use of high-resolution anoscopy to detect and treat anal cancers in same-gender loving men and at-risk women. The THRIVE Program is also strengthening its long term collaboration with the JACQUES Initiative, partnering on initiatives to link sexual assault victims to follow up care for HIV post-exposure prophylaxis, provide in home nursing and social work care to our most socially and medically frail patients, increase linkage to THRIVE for high-risk HIV negative people needing HIV pre-exposure prophylaxis, and integrate our JACQUES treatment coaches into THRIVE's multi-disciplinary care teams to improve patient retention. THRIVE exceeded 10,000 patient encounters for the year, remaining one of the largest ambulatory programs at the University of Maryland School of Medicine.

**The JACQUES Initiative**—2019 has proven to be a significant year for change in IHV's community care program. A new leadership team was created in the wake of the resignation of the program's executive director. The leadership team has refocused its programs around community outreach and community-based HIV testing, active linkage for patients into

care, and retention into care. Since the JACQUES Initiative no longer provides primary HIV care, a significant effort is ongoing to fully integrate JACQUES into The THRIVE Program. Through Centers for Disease Control and Prevention (CDC) grants, The JACQUES Initiative partnership with the Baltimore City Health Department to implement a comprehensive pre-exposure treatment program for men who have sex with men (MSM) continues to develop and expand. The establishment of The Journey Center, which hosted a grand opening in October 2018 and is located at 880 Park Avenue, provides a home for JACQUES and allows for expanding community health and supportive services, highlighted by its new “Exchange” program centered on engaging at risk young men in the West Baltimore Community. The program offers education, support groups, job and housing services, on-site screening tests, counseling and linkage to health services. The JACQUES Initiative truly makes the IHV a recognized innovator and committed partner in community health for Baltimore City.



*Nikki Akparewa, MSN, MPH, RN, educates the late The Honorable Elijah Cummings on JACQUES Initiative programs during the Journey Center Grand Opening*

**Expansion beyond Baltimore City**—To accommodate growing patient populations beyond the city, a suburban practice was established in fall of 2017 in Columbia, Maryland. The practice focus is on complicated post-surgical infections. However, a unique care and research focused Lyme Disease clinic has been an exciting new development. The Lyme clinic partners with the National Institutes of Health (NIH) and has developed an educational and integrative medicine component. **Kalpana Shere-Wolfe, MD**, Assistant Professor of Medicine, Director of the Lyme Wellness Program, developed and runs monthly Lyme Wellness Workshops provided free to the community, and it focuses on techniques to help people live better with their new or chronic Lyme symptoms. Demand for services at this site exceeded capacity at the Columbia site. In addition,

HIV services are now also provided. Strategic partnerships with other UMMS hospitals within the state resulted with our first partnership with Charles Country Regional Medical Center using an innovative “E consultation” method to reach this rural hospital in a physician scarce location. Other partnerships are in the initial planning phases.

**Financial Health Clinical Program**—FY2019 is on target to match FY2017 but slightly under FY2018, showing a plateauing of growth in a difficult health insurance environment. The combined clinical practices (IHV and ID) charged just over \$8,000,000 and collected \$4,591,000 in FY 2019. After physician salary costs, administrative costs, billing costs, malpractice insurance costs and operational cost, the clinical practice realized a revenue that exceeded costs.

**IHV Washington, DC-Based Clinical and Research Programs**

—The IHV’s clinical and research activities reach beyond Baltimore through its DC Partnership for HIV/AIDS Progress Viral Hepatitis Program (DC PFAP) based in Washington, DC. Since 2015, this unique and robust clinical research program has embedded IHV providers and research staff in federally qualified community health centers and non-traditional health care settings to provide both clinical care and clinical research to those often not able to access research. Co-directors, **Sarah Kattakuzhy, MD**, Assistant Professor of Medicine and **Elana Rosenthal, MD**, Assistant Professor of Medicine, provide the day-to-day leadership and clinical management with clinical and research support from **Poonam Mathur, DO, MPH**, Assistant Professor of Medicine, and scientific guidance from Dr. Shyam Kottlilil. To date, over 2,200 unique patients have been linked to care and 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 1,300 patients and has provided treatment for opioid-use disorder in conjunction with HCV treatment for over 75 patients to date.

**Clinical Programs in Chronic HBV Infection**—IHV’s Hepatitis B and C treatment programs continue to expand under **Lydia Tang, MB ChB**, Assistant Professor of Medicine, **Eleanor Wilson, MD**, Associate Professor of Medicine, and **Angie Price, DNP**, with locations at the Downtown and Midtown University of Maryland campuses, and the Maryland Veterans Affairs Health Care System. The IHV continues to partner with the Hepatitis B Initiative of Washington, D.C. (HBI-DC), and the Torture Abolition Survivors Support Coalition (TASSC) to increase awareness and provide screening for patients at risk for chronic hepatitis B in the Baltimore/District of Columbia metropolitan area who are not yet engaged in clinical care due to socioeconomic background. Since 2005, over 12,000 people in the DC-metropolitan area have been screened by



*Front Row, L to R: Emade Ebah, MPH; Ashley Davis MSN, APRN, FNP-c; Sarah Kattakuzhy, MD; Elana Rosenthal, MD; Rachel Silk, RN BSN MPH; Julia Mount, BS; Onyinyechi Ogbumbadiugha, MPH; and, Amelia Cover, MSN, AGPCNP-BC Back Row, L to R: Britt Gayle, MD MPH and Christopher Brokus, BA*

HBI-DC, with prevalence rates of 6% 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), and the group is pursuing other collaborations to expand access to research for this underserved population.

## CLINICAL RESEARCH

**Clinical Research Unit (CRU)**—The IHV CRU continues to grow under the direction of **Jennifer Husson, MD**, Assistant Professor of Medicine. The multidisciplinary CRU team is comprised

of two nurse practitioners, three nurse coordinators, a pharmacist, a phlebotomist, one regulatory specialist, two study/research coordinators, one recruitment specialist and three laboratory technicians. During the past year, the CRU has continued to expand its portfolio of clinical trials (27 clinical trials, of which 14 are investigator-initiated and 12 are industry-sponsored). The clinical trials range from phase II to phase IV studies encompassing a variety of topics including viral hepatitis, HIV, NASH and CMV. This year the CRU also began a collaboration with researchers from the Division of Gastroenterology and Hepatology who will investigate NASH and hepatocellular carcinoma. The CRU continues to support the IHV's mission of advancing the understanding and treatment of chronic viral infections in a variety of hosts.

**FLSC Vaccine Program**—The full-length single chain (FLSC) vaccine, as mentioned, was developed by IHV scientists under the leadership of Drs.

Robert Gallo, George Lewis and Anthony DeVico. The clinical component of the FLSC vaccine program is currently headed by **Mohammad Sajadi, MD**, Associate Professor of Medicine. The 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 was carried



*Shyam Kottilil, MBBS, PhD and Jennifer Husson, MD*



*Front Row, L to R: Salma Sharaf, BS; Eleanor Wilson, MD, MHS; Sarah Mitchell, MS, MBA; Kiran Mian, BS; Shyam Kottlil, MBBS, PhD; Jennifer Husson, MD, MPH; Gabrielle Cudjoe, BS; Ilise Marrazzo, RN, BSN, MPH; and, Angie Price, DNP, MSN, CRNP Back Row, L to R: Lydia Mutumbi, AND, BSN, MPH; Joel Chua, MD; Lydia Tang, MBChB; Mikhail Shlyak, BS; Amy Nelson, RN, MS; Richard Chiu; and, Jennifer Hoffmann, MSN, MPH, CRNP*

out at the IHV. This trial, now completed, 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 never previously participated in an HIV vaccine trial, were immunized with the FLSC vaccine. Immunogenicity data analysis is ongoing. Preliminary safety and immunologic results available were selected for oral presentation in this year's ID Week in Washington D.C. FLSC will also be tested in several upcoming vaccine trials at the HVTN (HVTN132 and HVTN 134) and MHRP (RV509 and RV546).

***Collaboration with National Institutes of Allergy and Infectious Disease (NIAID) Intramural Program—***

Collaborations continue between the IHV and the National Institute of Allergy and Infectious Diseases (NIAID) intramural program of the NIH. In this regard, NIAID clinical trials are being recruited at the IHV Clinical Research Unit with Anthony Fauci, MD, Director of NIAID and Tae-Wook Chun, PhD, Chief, HIV Immunovirology Unit of NIAID. In addition, we received a NIH intramural bench to bedside grant to evaluate changes in immune activation using novel imaging techniques among patients undergoing therapy for hepatitis C with or without HIV coinfection with Henry Masur, MD, Chief, Critical Care Medicine Department, NIH. Adriana Marques, MD, Chief, Clinical Studies Unit, Laboratory of Clinical immunology and Microbiology, from NIAID has

established a collaborative Lyme disease program at the Waterloo infectious diseases practice. These endeavors are both unique and expand IHV research capabilities.

**CLINICAL TRIALS 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)

***RESOLVE Trial—***Dr. Eleanor Wilson completed and published results on this study 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 was funded by Gilead Sciences as an investigator-initiated clinical trial.

***STOP-CO Clinical Trial—***Dr. Jennifer Husson, 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 (UCSF) 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.

**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. Elana Rosenthal and Sarah 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. This study is funded both by NIH and by an investigator-initiated clinical trial from Gilead Sciences led by Dr. Kattakuzhy.

**ANCHOR** [A Novel model of Hepatitis C Treatment to Prevent HIV, Initiate Opioid Substitution Therapy, and Reduce Risky Behavior]—ANCHOR is designed to 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. Dr. Elana Rosenthal leads this study funded by Gilead research grant for 100 courses of HCV therapy (sofosbuvir/velapavir) and 100 courses of PrEP, and a Merck investigator-initiated grant that supports treatment (elbasvir/grazoprevir) for an additional 100 patients. Enrollment has completed for the Gilead supported study portion and participants are now in long-term follow-up. Additionally, for the second 100 participants, the study team also collaborated with National Institute of Drug Abuse to use their ecological momentary assessment (EMA) technology to assess cravings and adherence.

**CHROME** [Cardiovascular Disease in HIV and Hepatitis C—Risk Outcomes after Hepatitis C Eradication] CHROME, led by Dr. Poonam Mathur, is a study to treat HCV in mono-infected and HIV co-infected individuals and compare inflammatory markers and radiological changes (MRI) in

HCV mono-infected and HIV/HCV coinfecting patients pre and post treatment, compared to HIV mono-infected patients. This study is funded through a Merck investigator-initiated grant and the National Institutes of Health Bench-to-Bedside Award.

**CoCrystal**—Joel Chua, MD, Assistant Professor of Medicine, is conducting a phase 2a study evaluating the safety and efficacy of combination treatment with two weeks of the non-nucleoside inhibitor CDI-31244 plus six weeks of

sofosbuvir/velpatasvir in patients with HCV genotype 1. The primary goal is to find a regimen with potential for shorter duration therapy for chronic hepatitis C.

**CALIBER** [CD24Fc Administration to Decrease LDL and Inflammation in HIV Patients, Both as Markers of Efficacy and Cardiovascular Risk Reduction]—Dr. Poonam Mathur is the PI for the CALIBER study that uses a novel fusion protein of CD24Fc in a phase 2, randomized, placebo-controlled, double-blinded trial of 64 patients with HIV who are randomized 1:1 to receive doses of CD24Fc 240mg IV or placebo. Aim #1 of the proposal involves the safety and tolerability of the drug in HIV patients, and Aim #2 will evaluate biological effects of CD24Fc on LDL reduction, markers of immune activation, inflammatory markers and cardiac biomarkers, which will be assessed during the dosing window and a 24-week follow-up. This study is funded by an NHLBI SBIR grant (1 R44 HL145964-01A1) partnering with Oncolmmune, Inc.; Dr. Nehal Mehta, Section of Inflammation and Cardiometabolic Diseases, NHLBI.

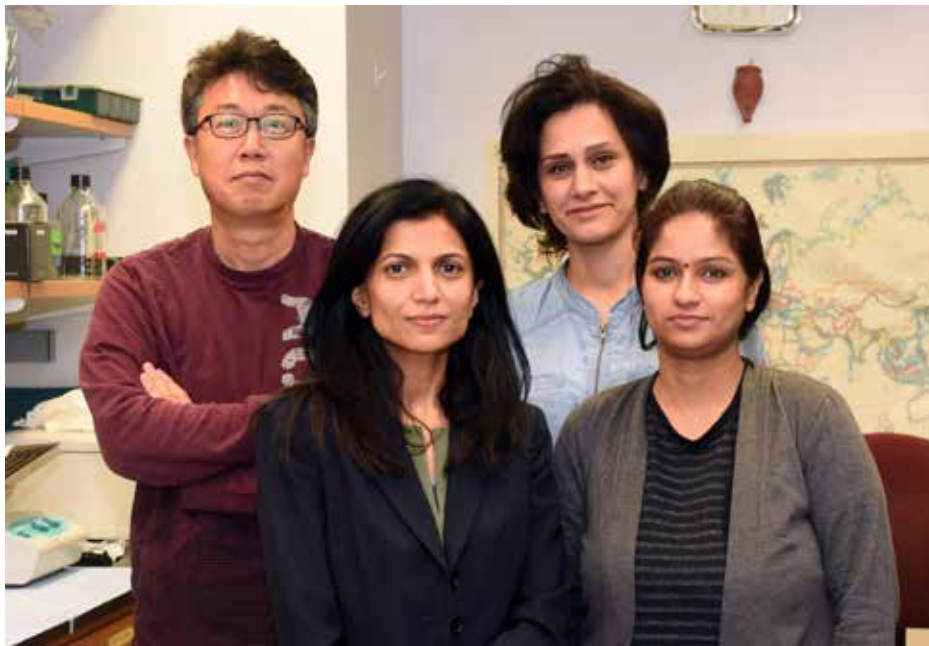
**Hepatotoxicity of ART**— In 2015, Dr. Shyam Kottlil, in collaboration with Kenneth E. Sherman, MD, PhD from the University of Cincinnati, was awarded a R01 grant from NIAID for evaluating the mechanisms of antiretroviral therapy mediated hepatotoxicity.

**HOPE in Action**—Drs. Anthony Amoroso and Jennifer Husson, 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. Dr. Husson has been guiding the infectious disease management of UMB's program in HIV transplantation and is the site principal investigator for this multi-center study. Through this study, the first HIV+ to HIV+ kidney transplant at the University of Maryland was successfully completed earlier this year.

**HIVTR CCR5 Clinical Trial**—Dr. Shyam Kottlil, in collaboration with other investigators from UCSF received a UO-1 award from NIAID to evaluate the use of CCR5 blockade in HIV-infected kidney transplant recipients to increase kidney graft survival.

**TLR-8**—The IHV/CRU is the only site in the United States conducting this study. It is phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and antiviral activity of GS-9688 in virally-suppressed patients with chronic hepatitis B with Dr. Lydia Tang as the PI.

**Clinical Care and Research Division Laboratory Based Programs**—The Kottlil Laboratory actively pursues two targeted research programs: "A Functional Cure Approach



*L to R: KiSeok Lee, PhD; Bhawna Poonia, PhD; Sara Romani, PhD; and, Arshi Khanam, PhD*

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 led by **Bhawna Poonia, PhD**, Associate Professor of Medicine, and Dr. Shyam Kottlil, 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 from Arbutus Pharmaceuticals, and from Gilead Sciences. The Arbutus project focuses on determining the role HBs antigen plays in massive immune dysfunction observed in CHB; this provides a scientific rationale to develop strategies that attempt to reduce HBs antigen levels for inducing immune recovery and potential functional cure. They identified correlation of HBs antigen levels with inhibitory checkpoint molecule expression on T cells and consequently used HBs levels as stratifying variable to determine successful response to anti-PD-1 blocking for recovering anti-HBs immunity. Further research will determine HBs antigen role in intrahepatic immunity and response to PD-1 blocking. Under the projects funded by Gilead Sciences, the laboratory continues to determine immune modulation by TLR8 pathway as a viable strategy to recover anti-HBs B cell response. Using clinical samples from Phase 1 and 2 clinical

trials, where a small molecule selective TLR8 agonist GS-9688 was tested in CHB patients, they identified immune pathways modulated by this agonist. Induction of cytokines IL-12 and IL-18 led to activation of innate and adaptive lymphoid cells and in a subset of patients improved HBs specific B cell response was observed in B cell ELISPOT assays. This has real potential to impact HBV functional cure, which is defined as anti-HBs seroconversion. The mechanism of humoral immune enhancement by TLR8 agonism is currently under investigation in the laboratory.

Alongside an active Hepatitis C clinical trial program, Dr. Kottlil has a highly productive translational/ bench research portfolio focused on unraveling biological correlates of protective immunity to hepatitis C virus in patients undergoing direct-acting antiviral (DAA) therapy. His group 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. Poonia and Kottlil continue their investigations into determinants of SVR with short duration DAA therapy. They recently identified the immune phenotypes that can predict SVR using ultra-short duration DAA therapy of 4 weeks. Higher levels of CD8 T cell frequencies expressing multiple inhibitory receptors including PD-1, LAG-3, Tim-3 and containing HCV specific cells were observed in responders to short duration





regimen, indicating role of activated antigen specific cells in antiviral response. Another area of focus in HCV immunology examines immune defects that continue to persist despite successful DAA mediated SVR, with ramifications for further complications including hepatocellular carcinoma. Continuing their previous studies which show CD8 T cell dysfunctions, they now identified functional defects in gamma delta T cells, an important effector cell population relevant for anti-cancer function in successfully cured patients. Further research will determine persistent hepatic immune dysfunctions as well as correlations of these immune defects with complications like HCC.

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.

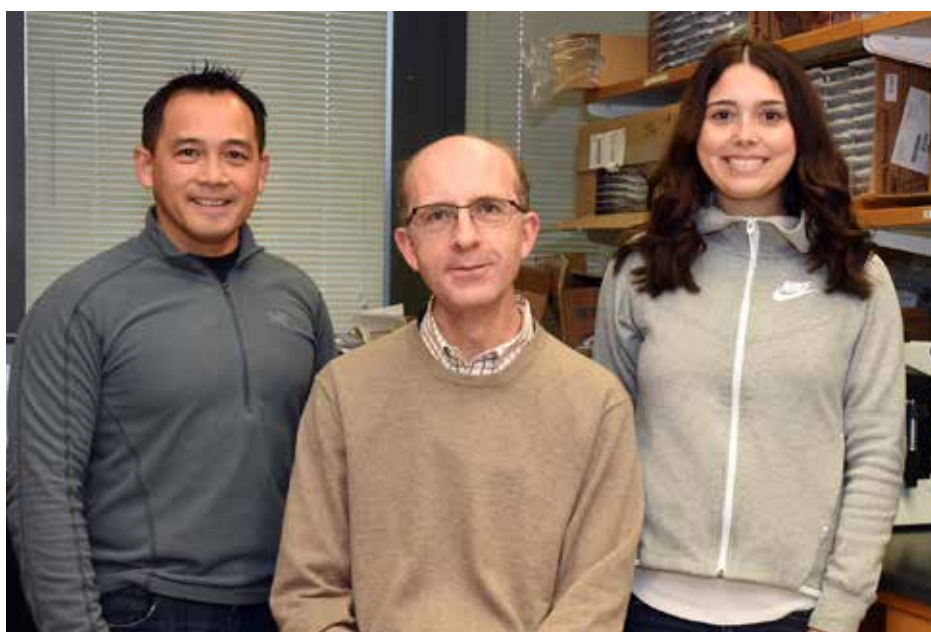
Dr. Poonia is in her third year of an NIH R01 grant from National Institute of Drug Abuse to study the immune correlates of protection from reinfection among people who are marginalized at the highest risk of acquisition of HCV namely, those with HIV infection and people who inject drugs. Using samples from these people who inject drugs (PWID) patients, the laboratory focuses on determining whether anti-HCV immune responses recover after successful SVR. At the same time this cohort provides a unique opportunity to investigate whether failed recovery of immunity after HCV cure is correlated with re-infection.

Thanks to combination antiretroviral therapy (cART) 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. In the project entitled, "*Impact of concomitant chemotherapy on HIV resistance to cART and reservoir size*", funded by

NCI, **Alonso Heredia, PhD**, Assistant Professor of Medicine, the laboratory is investigating drug interactions between chemotherapeutic drugs and antiretrovirals with the goal of improving treatments in the growing population of HIV-infected patients with cancer.

Another area of active investigation in Dr. Heredia's lab is HIV latency. In collaboration with **Fabio Romerio, PhD**, Assistant Professor of Medicine and Head of the Laboratory of IHV-1 Persistence & Immunopathogenesis in the Division of Basic Science, Dr. Heredia is a Co-Investigator in the NIAID funded project "*Sustained HIV remission via sequence-specific epigenetic silencing of latent proviruses.*" In this project, Dr. Heredia is assessing the impact of HIV antisense transcript expression on silencing of HIV proviruses both in tissue culture and in humanized mice. In a related project, Dr. Heredia, in collaboration with Dr. Tae-Wook Chun, from NIAID, is investigating suppression of HIV reactivation in cells from cART-treated patients using various combinations of antibodies.

Yet, another area of research in Dr. Heredia's laboratory is the development of effective antibodies against HIV. In collaboration with Dr. Mohammad Sajadi, he is a Co-Investigator in the project "*Development of a new family of potent and broad neutralizing antibodies*", funded by the Bill and Melinda Gates Foundation. Dr. Heredia's role in the project is to evaluate the anti-HIV activity of anti-HIV Clade C/Pan-neutralizing monoclonal antibodies in humanized mice. In another similar project, "*Bridging Antibody Fc-mediated Antiviral Functions Across Humans and Non-human Primates*," funded by NIAID, he is collaborating with Drs. Anthony DeVico and George Lewis.



L to R: Nhut M Le, BS; Alonso Heredia, PhD; and, Triana Rivera-Megias



His role in this project is to evaluate novel anti-HIV antibodies in humanized mouse models to identify potential protective antibodies for a vaccine in humans. Also, in collaboration with **Olga Latinovic, PhD, MSc**, Assistant Professor of Microbiology and Immunology, Head of the Laboratory of Host-Pathogen Interaction and Head of the Imaging Core Facility in the Division of Basic Science, he is investigating approaches to enhance the anti-HIV activity of entry inhibitors.

Dr. Mohammad Sajadi and his lab are currently focused on humoral immunity in HIV-infected individuals with broadly neutralizing antibodies, working closely with Drs. George Lewis and Anthony DeVico in the Division of Vaccine Research. Dr. Sajadi 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 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. His lab isolated several broad neutralizing antibodies that are among the most potent and broad described to date. Dr. Sajadi also oversees the Natural Viral Suppressors (NVS) cohort, HIV-1 infected individuals who control infection without antiretrovirals.

**Shashwatee Bagchi, MD**, Assistant Professor of Medicine, 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 Kottlil, as well as Drs. Robert Weiss and Todd Brown at Johns Hopkins University. She has multiple projects she is engaged in to address this

clinical problem and consequent research questions, ranging from retrospective cohort studies of our outpatient HIV-infected patients and inpatient HCV-infected patients to a prospective cohort study among HIV and HCV mono-infected and HIV/HCV co-infected. Dr. Bagchi has a NIH K23 grant "Elucidating Chronic Hepatitis C Infection as a Risk Factor for Coronary Heart Disease in HIV-Infected Patients," an Accelerated Translator Incubator Pilot award from the University of Maryland Institute of Clinical and Translational Research "Systemic and Epicardial Fat Inflammation and Local Coronary Atherosclerosis in HCV and HIV Patients," and recently completed activity through Dr. Robert Weiss' NIH R01 "Inflammation and Coronary Endothelial Dysfunction in HIV."

The laboratory of **Nicholas Stamatos, MD, PhD**, Associate 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. In particular, this 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. 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. We expect to demonstrate that controlling the extent of polysialylation of specific glycoconjugates has therapeutic value in various disease states of inflammation and infection. The laboratory was awarded an R01 from the NIAID in the amount of \$2,562,639

over 5 years to continue these studies. The grant entitled "Influence of polysialic acid on leukocyte migration" was awarded under the High Priority Immunology Grants program of NIAID.

Although much is known about the glycosylation of HIV envelope proteins, relatively little is known about how glycosylation of proteins on the surface of permissive lymphocytes affects infection. The Stamatos laboratory 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. We expect 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 our studies are expected to identify a novel target for treatment of HIV infection and provide a blueprint for down-regulating the expression of polySia or modified protein(s) in cells susceptible to infection with HIV-1.

Polysialic acid has provided a useful handle for the Stamatos laboratory identifying proteins whose functions were not previously appreciated on immune cells. Our discovery of polySia modification of neuropilin-2 led to our finding that dendritic cells express semaphorins that cause F-actin reorganization and promote chemotaxis. Thus, the lab's studies identified an additional signaling axis in human dendritic cells mediated by soluble factors. It is likely that these semaphorins promote additional activities of human dendritic cells during innate and adaptive immune responses. The lab expects that the additional polysialylated proteins that they identify on immune cells will have equally significant roles in cell function.

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# Epidemiology and Prevention



Man Charurat, PhD, MHS

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine and Director of the Center for International Health, Education & Biosecurity (CIHEB), continues to advance its research endeavors through public health surveillance, evaluation projects, field investigation and analytical studies, in addition to health systems strengthening efforts. After sixteen years of concentrated effort building sustainable research, training and public health programs in Nigeria, the Division is expanding to other sub-Saharan countries. In FY19, the Division's 10 faculty members have 16 active federal awards totaling \$147M. Moreover, the Division published 52 manuscripts in peer reviewed journals in FY19, including 5 first authors and 11 senior authors.

## PUBLIC HEALTH SURVEILLANCE

The Division of Epidemiology continues to monitor the pulse of the HIV epidemic in sub-Saharan Africa this year through Population-based HIV-focused household surveys in countries supported by the President's Emergency Program for HIV/AIDS Relief. Currently, the Division is conducting surveys in Nigeria, Zambia, and Botswana.

The Division's Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS), led by Dr. Man Charurat, was one of the largest population-based HIV/AIDS household surveys ever conducted. NAIIS directly measured HIV prevalence and viral load suppression across Nigeria and found that the HIV prevalence in Nigeria is lower than previously thought, allowing the country to focus on providing services to the areas of greatest need to control the HIV epidemic. For the first time ever in Nigeria, the US and Nigerian governments have robust data that identifies where HIV is concentrated;

the viral suppression among people living with HIV; the gaps in the HIV response by geography, gender, and age; and what HIV policies and resources are needed to achieve the UN 95-95-95 goals. The NAIIS found that in Nigeria the HIV prevalence – the percentage of people living with HIV – among adults age 15-64

years was 1.5% and among children (age 0-14) was 0.2%. HIV prevalence was the highest among females age 35-39 years at 3.3%. The disparity in HIV prevalence between females and males was greatest among younger adults, with females having more than three times the prevalence of males in this group. NAIIS also found



NAIIS Field team journeying to conduct household surveys



that the prevalence of viral load suppression, a measure of effective HIV treatment in a population, among Nigerian adults living with HIV was 44.5%. Dr. Charurat's Senior Laboratory Advisor, **Alash'le Abimiku, PhD**, Professor of Medicine, and his project director, **Gambo Aliyu, MBBS, PhD**, Assistant Professor of Epidemiology and Public Health, helped lead this effort. Dr. Aliyu recently joined the Nigeria National Agency for the Control of AIDS as the Director General shortly after the completing of the survey. He will help guide NACA to provide an enabling policy environment and stable ongoing facilitation of proactive multi-sectoral planning, coordinated implementation, monitoring and evaluation of all HIV/AIDS prevention and impact mitigation activities in Nigeria.



*NAIIS Field team journeying to conduct household surveys*

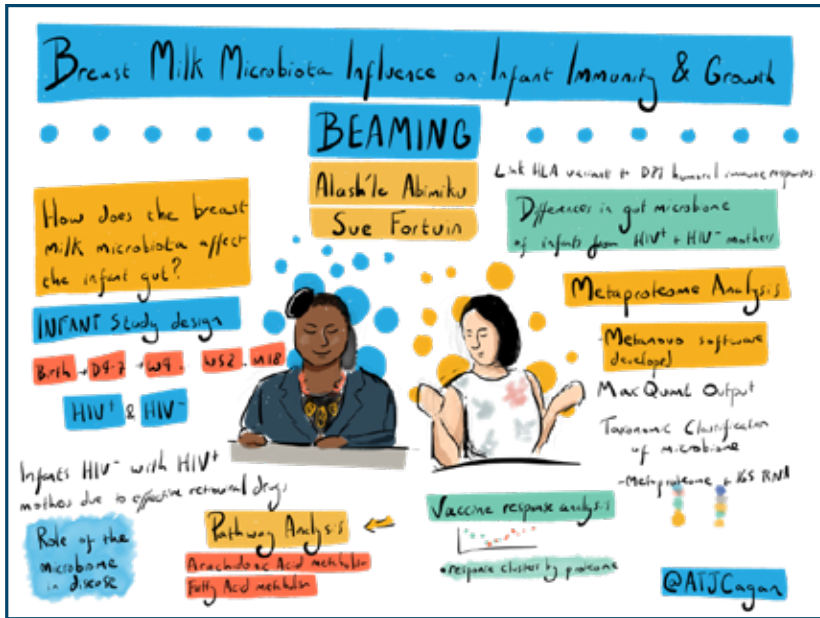
To help guide HIV epidemic control in Nigeria, the Division implemented a formative assessment, hotspot mapping and validation exercise, and multiple-source capture recapture (3S-CRC) exercise as part of a key population size estimation (KPSE) activity. Directed by Dr. Charurat, and managed by **Kristen Stafford, PhD**, Assistant Professor of Medicine and Associate Director of CIHEB, the primary objective of the activity was to obtain population size estimates for female sex workers, men who have sex with men, and people who inject drugs in the US President's Emergency Plan for AIDS Relief (PEPFAR) priority states of Akwa Ibom, Benue, Cross

Rivers, Lagos, Nasarawa, Rivers, and the FCT. Thanks to close involvement of community-based organizations and key informants, our enumerators identified approximately 14,000 "hotspots" that were frequented by key population members across the 6 states plus the federal territory, many of which had been previously unidentified or inaccessible. During 3S-CRC, enumerators conducted over 300,000 interviews with key population members, and the resulting data allowed us to generate reliable, empirical KPSE that will provide critical information for planning and implementing targeted HIV prevention, care and treatment programs, all while accounting for the mixed nature of Nigeria's epidemic. The results of this activity are intended to support efforts to respond to the HIV epidemic outlined in Nigeria's National Strategic Framework, particularly in moving towards location-population strategy and facilitating access to HIV prevention and treatment among members of key and vulnerable populations.

In May 2019, Dr. Charurat was awarded another HIV surveillance Population-based HIV Impact Assessment award from Centers for Disease Control and Prevention (CDC) (UGGH0002171) to conduct surveys in multiple sub-Saharan African countries. Dr. Charurat and team have commenced work in Zambia and Botswana.

## **FIELD EPIDEMIOLOGY AND ANALYTICAL STUDIES**

Through our partnership with IHV-Nigeria, the Division conducted field epidemiology and analytical studies. Led by Dr. Abimiku, The Breast Milk Microbiota Influence on Infant Immunity Growth (BEAMING) nested study, funded by the NIH under H3Africa, investigates how breast milk affects infants' gut bacteria and how this in turn affects infants' growth and their ability to respond to childhood vaccination from birth cohorts of HIV exposed uninfected infants in Nigeria and South Africa. Preliminary results illustrate that the taxonomic classification show that the major classes such as Actinobacteria, Bacilli, and Gammaproteobacteria are shown on both 16S rRNA and metaproteome analysis although the proteomics analysis can identify additional bacterial organism that are not identified by 16S rRNA analysis. There was also a dynamic shift in the metaproteomes from birth to 4-7 days after birth from 2784 proteins to 4659 proteins after the initiation of breastfeeding indicating that the possible major shift in the metaproteome could be attributed to the introduction of the mothers' breastmilk microbiome. We are currently analysing milk products to identify the bacterial major classes found in breast milk that may be contributing to the infant microbiome.



Advertisement for BEAMING study for recruitment of mothers and infant

**Nadia Sam-Agudu, MD**, Associate Professor of Epidemiology and Prevention, continues to work on optimal care models to transition HIV + adolescents to adult care. Recently she conducted a cluster randomized trial to compare the effectiveness of an intervention to achieve Viral Suppression through Intensive Support for Transitioning Adolescents Living with HIV in Nigeria (VITAL) through an NIH R-01 and she is awaiting the results. Her goal is to recruit 360 adolescents living with HIV at 18 cluster-randomized healthcare facilities from all six geo-political zones. The study sites will be randomly assigned (1:1) to the intervention group (IG) or control group (CG). VITAL is a combination intervention consisting of a graduated transition program, a transition case management team, plus a pre-and post-transition peer-led Organized Support Group. The primary outcome is post-transition retention in care among adults living with HIV. Secondary outcomes are viral suppression rates and psychosocial wellbeing measured by four psychometric tests that will assess for improvements in perceived mental

health and shifts from external to more internalized health locus of control.

**Rebecca Nowak, PhD**, Assistant Professor of Epidemiology and Public Health, found that screening with high resolution anoscopy (HRA) improved with experience and time (Nowak et al *Journal of Global Oncology* 2019). This suggested that using HRA as a first-line screening tool was feasible. However, detection of high-grade disease was low, highlighting the need for ongoing evaluation and mentoring. For the men screened, Dr. Nowak also conducted an evaluation of patient satisfaction and knowledge of the symptoms of anal cancer after their first experience with HRA screening. In summary, despite a high level of anxiety before the procedure, there was a high-level of satisfaction that did not differ by HIV infection status or number of anal biopsies experienced during screening. Pain/discomfort and knowledge of clinical symptoms were two areas needing improvement during the implementation of screening.

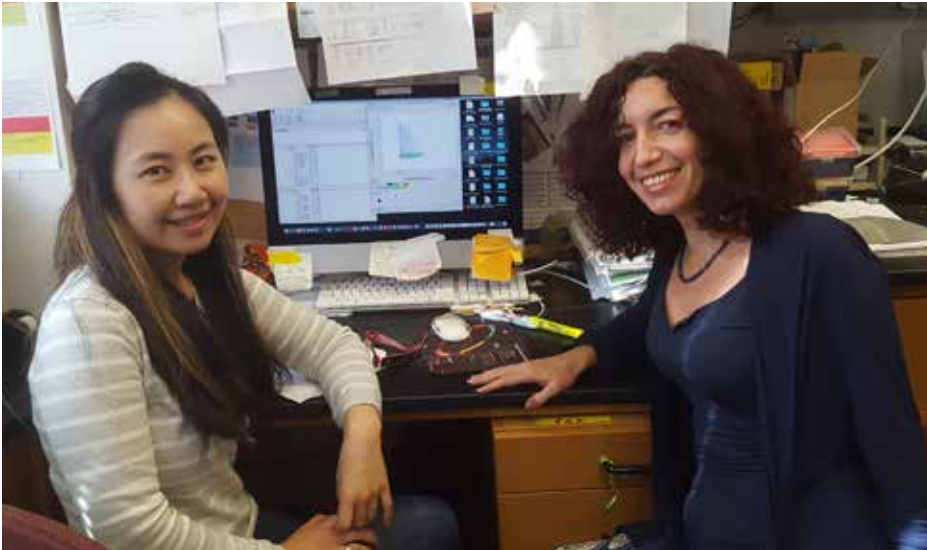
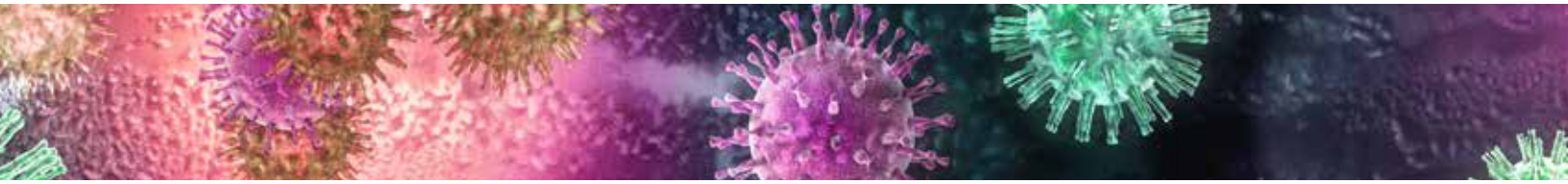
Dr. Nowak also conducted one of the first studies to cluster anal microbiota in men (Nowak et al. *AIDS Research*

and *Human Retroviruses* 2019). Her research found that one of the resulting clusters of anal microbiota was overrepresented with a bacteria genera, *Sneathia*, and associated with oncogenic human papillomavirus (HPV), HPV-16. Although sample sizes were small, the same association has been observed in women and suggests it may not be spurious.

Additionally, this year in *JAIDS*, Dr. Nowak reported one of the highest HIV incidence rates, 15.4/100 person years [PY], among men who have sex with men (MSM) in sub-Saharan Africa in Nowak et al. *JAIDS* 2019. The rates were particularly high among those under 19 years of age as compared to those 25 years or older (30.9/100 PY vs 6.9/100 PY, respectively). Independent risk factors included larger sexual networks, networks with an older sexual partner, receptive anal sex, condomless sex, no history of testing for HIV and rectal gonorrhea.

The Impact of in Utero HIV Exposure on Infant T and B cell responses in Malawi was led by **Cristiana Cairo, PhD**, Assistant Professor of Medicine. This U01 study, led by Drs. Cristiana Cairo and Miriam Laufer, Professor of Pediatrics, University of Maryland School of Medicine, is a longitudinal analysis of T and B cell responses in HIV exposed uninfected (HEU) infants in Malawi. HEU infants are more susceptible to common enteric and respiratory infections than their unexposed counterparts and have higher mortality rate. However, studies conducted after widespread availability of antiretroviral therapy (ART) have shown less pronounced differences in morbidity and mortality between HIV exposed and unexposed infants. It is very likely that the immune perturbations associated with in utero HIV exposure are mitigated by effective ART and the longer the control of the HIV infection is during gestation, the less immune alterations and





L to R: Haoting Hsu, PhD and Cristiana Cairo, PhD

clinical risk of disease the infant will experience. To test this hypothesis, the study, now at the beginning of its third year, has been enrolling three well-characterized mother-infant cohorts from two health centers in Malawi. The three groups to be compared are: (1) infants born to women diagnosed with HIV infection (and  $>10^4$  copies/ml viral load) at the first antenatal visit at or after 20 weeks of gestation, (2) infants born to women on ART with undetectable viral load before conception throughout pregnancy, and (3) HIV unexposed infants born to HIV uninfected mothers. All HIV-infected women receive the same ART regimen and breastfeed their infants during the 9-month follow up period. The study will assess infant adaptive immune response by probing the immune system at birth, 4 and 9 months of age with both polyclonal stimuli and routine immunization antigens, to which all infants are exposed in the first three months of life. The results will provide important evidence for public health policy, to help determine the optimal timing of ART treatment and maximize infant health and survival. In the first two years of clinical activities, the study team screened more than

600 women, out of whom more than 350 were enrolled. More than 200 mothers already delivered and about 200 infants have been enrolled in the 9-month follow up. The infant follow is anticipated to end by August-September 2020.

**Clement Adebamowo, BM, ChB, ScD, FWACS, FACS**, Professor of Epidemiology and Public Health, led the African Collaborative Center for Microbiome and Genomics Research (ACCME), a multi-institutional collaborative research that has created a prospective cohort of 17,600 women who are followed up every 6 months. ACCME's current study is focused on understanding the mechanism of cervical cancer and identifying new biomarkers that can be used in cervical cancer prevention. ACCME studies the interaction between the vaginal microbiome, host genetic factors and molecular variants of Human Papilloma Virus (HPV) to determine correlates of viral persistence in the causal pathway of cervical cancer, a major cause of preventable cancer morbidity and mortality in low- and middle-income countries like Nigeria. To date, the ACCME Project has completed epidemiological risk

factors and Genome Wide Association studies of persistent high-risk HPV infection, vaginal microbiome and cervical cytokines. This research project offers several opportunities to advance understanding of cervical carcinogenesis, viral oncogenesis, new biomarker discovery and risk stratification by genotype in a cohort of African women.

Dr. Adebamowo also led the African Female Breast Cancer Epidemiology Study in Nigeria (AFBRECANE), focused on breast cancer, which is the commonest cancer in women globally and in Nigeria. The AFBRECANE study seeks to resolve controversies about the epidemiology and molecular subtypes of breast cancer in African women, particularly, the incidence of breast cancer overall and of molecular subtypes of breast cancer, the contributions of indigenous African diets to breast cancer incidence and the role of Vitamin D. In the absence of prospective cohort studies, we engage innovative research design and analytic techniques to use data from population-based cancer registries (PBCR) to study the epidemiological factors associated with incident breast cancer and molecular subtypes. We are also conducting the first genome wide association study (GWAS) of breast cancer in indigenous African women. The AFBRECANE Study supports other global breast cancer research projects including the National Cancer Institute's (NCI) Confluence Study of 300,000 breast cancer cases and controls, and the Breast Cancer Genetic Study in African-Ancestry Populations that includes 20,000 cases and 20,000 controls.

The Indigenous Linguistic and Cultural Concepts of Heritability and Comprehension of Genomics Research in Nigeria (INDIGENE) Study (Adebamowo, PI) is a NHGRI funded research that is exploring linguistic and cultural concepts that are used



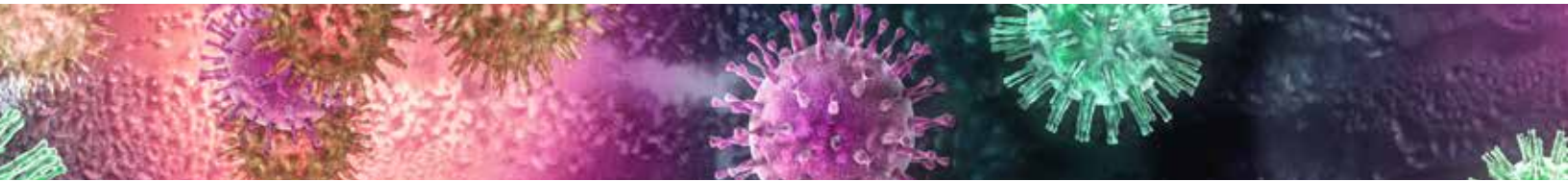
*Clement Adebamowo, BM, ChB, ScD, FWACS, FACS, leading a collaborative meeting for ACCME study*

to describe heritability of traits and diseases by indigenous Yoruba in Nigeria. In the study, we identify and use words, idioms, proverbs and sayings from Yoruba language to improve comprehension of genomics research. This will enhance the quality and adequacy of informed consent. We have already identified words, concepts, proverbs and other expressions which are used to express knowledge and understanding of transmissibility or inheritability of characters, traits and diseases among the Yoruba. These words show that the Yoruba understand genomics concepts such as traits, dominance, heritability, recessivity sex-linkage and their relationship to physical traits and diseases. We have created an online database of these words (<https://indigenestudy.bioethicscenter.net/home>) and have invited interested individuals in different parts of Africa to contribute to the database. We will constantly update the record and invite everyone to contribute to it. The next step in this ongoing research project is a clinical trial of two types of consent forms, one that is the standard consent form used for genomics of breast cancer research in Nigeria, and intervention is an enhanced consent form developed from the outcome of Phase 1 of the INDIGENE research project which incorporates concepts that are used by members of the community to communicate heritability of traits and diseases. We will evaluate significant differences in comprehension of informed consent between the two

groups of participants.

**Niel Constantine, PhD, MT(ASCP)**, Professor of Pathology, Head of the Laboratory of Viral Diagnostics, is the principal investigator on a number of projects in the diagnostic arena. His laboratory provides serologic and molecular testing capabilities to the IHV staff, performs research activities for the development of new test technologies, has several US government contracts for evaluating internationally available test technologies, provides training for international students, and continues to conduct Food and Drug Administration (FDA) clinical trials for diagnostic devices. His laboratory also provides support for laboratory infrastructure improvement and quality assurance, as evidenced by his many years of contributing to the Division's PEPFAR program in Nigeria for laboratory improvement.

His current activities include a 7-year on-going contract through the US government (USAID, FHI360, PFSCM, and PSCM) to assess the test indices of more than 11 different types of rapid tests from 16 manufacturers that are currently used in 26 countries. Collectively, these contracts total over \$2,000,000. The performance of test kits for HIV, hepatitis, HBV, syphilis, Cryptococcus and pregnancy was assessed using appropriate panels of sera. Results indicated that, of the 1,502 rapid test kit lots evaluated, 1,491 (99.3%) successfully passed the evaluation. Of the 11 lots from five manufacturers that did not pass, 3 lots were found to produce high



Niel Constantine, PhD, MT (ASCP)

background that interfered with reading, 2 lots performed inadequately with high-temperature testing, 4 lots gave two false-positive results and 2 lots gave two false-negative results. In one case, the failure resulted in cessation of bulk purchase of test kits by the US Government and removal from the World Health Organization's (WHO) e-catalogue. In another case, the manufacturer acknowledged that their internal lot release results indicated a less than usual level; that was subsequently addressed by the manufacturer. Another current activity is a \$91,000 funded FDA clinical trial for assessment of a rapid syphilis test that offers the detection of specific antibodies to *T. pallidum*. A total of 330 subjects are being enrolled at the IHV and the IHV's JACQUES Journey Center where several sample media are collected and tested by the investigational test and compared to the results of a reference test. The trial will continue into 2020.

Dr. Constantine's current efforts are also directed toward the development of a variety of novel technologies aimed at increasing sensitivity, simplifying procedures, and developing test technologies for resource-limited

facilities in developing countries. More specifically, his staff is pursuing a test technology that incorporates signal-boosting strategies to address early detection of HIV acute infection, using a simple Point of Care methodology.

The Microbiome Affects Risk of Development and Growth in HIV-exposed but Uninfected Infants (MARGIN) study led by Dr. Man Charurat, is in the final year. The MARGIN is looking at the growing population of HIV-exposed but uninfected infants (HEU) at risk for early life development abnormalities including growth faltering, higher morbidities and increased risk for infant diarrhea. The study is investigating that the infants' altered gut microbiota contributes to the reported growth abnormalities and adverse clinical outcomes. A cohort of 300 HIV-positive and HIV-negative mothers and their infants were enrolled and we have sequenced close to 1500 infant samples to date, which provides us with gut microbiome information along a timeline from birth

to 18 months postpartum. Preliminary analyses show the gut microbiome diversity to be greater in HEU infants compared to control infants (HIV-unexposed uninfected infants; HUU), and a significant larger number of HEU infants were underweight compared to HUU infants. Our preliminary study results suggest that the effect of perinatal factors, including the mode of delivery, breastfeeding, and antibiotics use, shape the microbiome composition, which in turn may influence the host immune responses. Sample analysis and manuscript development are currently ongoing.

In its fourth year of funding, Dr. Charurat has developed one of the largest cohorts of men who have sex with men (MSM) in Africa with 2,591 individuals enrolled through Building Trust. Of these, 2,174 have been tested for HIV and 1,071 tested HIV positive. Our data highlights the fact that MSM lag behind other HIV-infected groups in Nigeria with respect to ART initiation, and continuing HIV Care. The study is investigating stigma against sexual



Building Trust Clinic staff along with Rebecca Nowak, PhD

orientation and how that negatively impacts patient outcomes; the impact of pre-exposure prophylaxis (PrEP); and, applying phylo-dynamic analysis to link bio-behavioral and ego-network data. PrEP for HIV prevention was introduced along with a questionnaire designed to measure awareness and willingness. The questionnaire was administered to 789 enrolled HIV negative participants. Of 789 participants, 719 (91.2%) showed interest in taking PrEP every day and/or after a sexual act, 545 (69.1%) were successfully contacted and 433 (54.9%) scheduled an appointment, 409 (51.8%) attended scheduled appointment and 400 (50.7%) initiated PrEP. PrEP follow up and sample analysis for PrEP adherence is ongoing.

## EVALUATION PROJECTS

The Division, in partnership with IHV-Nigeria, plays an important role in evaluation of HIV and tuberculosis (TB) services in Nigeria. Our evaluation projects help the US and Nigerian governments evaluate the operations, impact and outcomes of their HIV and TB public health services.

As Project Principal Investigator of the Action to Control HIV Epidemic through Evidence (ACHIEVE), **Patrick Dakum, MBBS**, Assistant Professor of Epidemiology and Public Health, is offering ART services in 450 facilities, prevention of mother-to-child transmission services in 469 facilities, TB services in 78 facilities and HIV counseling and testing services in 576 facilities in Nigeria. Since 2004 to June 2019, IHV-Nigeria has cumulatively provided HIV testing to over 8.7 million individuals, care and support to 422,441 individuals, treatment to over 304,000 patients including 18,751 children and 86,164 pregnant women in Nigeria.



*Patrick Dakum, MBBS*

Through a data driven response in Rivers State in Nigeria, Dr. Dakum in collaboration with Dr. Stafford, are applying the SURGE intervention to ensure that 199,577 persons infected with HIV know their status, place at least 170,166 people living with HIV (PLHIV) on treatment by bridging the treatment gap from the present 21% to 81% and attain viral suppression for at least 161,657 PLHIV on treatment by September 2020.

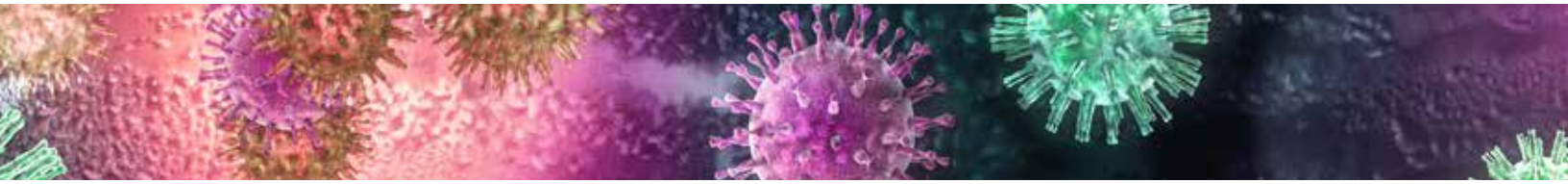
With the Global Fund Public Private Mix (PPM) TB award, Dr. Dakum is ensuring the scale up TB prevention, diagnostic and treatment services through private sector engagement. The target is to notify 17,749 TB cases (all forms) from non-national TB program providers—private/non-governmental facilities; attain a 90% treatment success rate; notify 581 TB cases (RR-TB and/or MDR-TB); and, enroll 552 MDR-TB patients for treatment. The aim of the grant is to increase TB PPM coverage from 2.5% in 2017 to 34% in 2020 and the PPM contribution to the National TB case notification from 11% in 2017 to 35% in 2020.

## HEALTH SYSTEMS STRENGTHENING

The NIH funded West African H3Africa biorepository at the Institute of Human Virology H3Africa Biorepository (I-HAB) led by principal investigator Dr. Abimiku, has provided biobanking services to several NIH funded research sites located in Nigeria, Ghana, Benin Republic and Mali. The hallmark of biobanking is a collection of well-annotated biospecimens and associated data collected, processed and maintained according to well-established standards and protocols. I-HAB employs a multifaceted, comprehensive approach to maintain best practices according to International Society for Biological and Environmental Repositories (ISBER), applicable areas of International Organization for Standardization (ISO) 15189 and biobank industry standards. Generally, ISO guidance pertains specifically to Quality Management Systems and therefore overlaps with some areas of ISBER best practices but offers more details in some areas such as document



*Alash'le Abimiku, PhD*



*ASCO SOCRON Conference in Lagos, Nigeria*

development. Industry standards generally pertain to publications, international meetings and other forums which are useful to remain abreast of trends and new technologies/practices pertaining to biobanking. A significant mandate of the I-HAB focuses on building capacity of clinical sites such that the biological samples collected and processed at the clinical sites are of high quality before they reach the biorepository for long-term storage. I-HAB has trained several individuals at several clinical sites from Nigeria, Accra, Kumasi, Tanzania, Mali, Republic of Benin, and more recently supported the University of Maryland Nigerian AIDS Indicator Impact Survey (NAIS) by developing a high-quality biorepository at the National Reference Laboratory at the Nigerian Centers for Disease Control.

The Entrenching Research Ethics Training in Nigeria (ENTRENCH) grant (Adebamowo PI) continues to build an integrated research ethics regulatory environment for Nigeria through provision of short-, medium- and long-term training, and support of the National Health Research Ethics Committee and institutional health research ethics committees. To date, the Entrench program and its predecessor, the West African Bioethics Training Program has provided full scholarship Master's degree in Bioethics training at the University of Ibadan to 51 West African biomedical researchers; members and administrators of institutional health research ethics committees and individuals who are believed by their institutions to be current or future leaders in research ethics. In view of the fact that many members of ethics committees who require training in research ethics have other primary assignments and cannot take sufficient time off to complete a Master's degree program, we introduced a three-month-long

blended diploma in research ethics that is based on six credits graduate course. To date 75 individuals have completed this blended diploma in research ethics. The ENTRENCH program partners with the Biomedical Research Alliance of New York (BRANY) to provide a range of research and ethics courses in the Collaborative Institutional Training Initiative (CITI Program) to researchers in Nigeria. This ensures that Nigerian researchers and research staff are receiving the same types of research ethics training and certifications that their colleagues in the US receive. This enhances collaboration and mutual understanding. To date, over 14,000 CITI trainings have been completed through the ENTRENCH Program website.

In 2019, the ENTRENCH Program received a supplement from the National Institutes of Aging to research and develop ethical guidelines for research in Alzheimer's Disease and Alzheimer's Disease Related Dementia – the Research Ethics of Alzheimer's Disease and Alzheimer's disease-related dementias (AD/ADRD) in Nigeria (READING Project). The research engages Alzheimer's Disease and Alzheimer's Disease Related Dementia patients, researchers and research associates on their experience of participating in AD/ADRD research. The outcome of this study is combined with current research literature and guidelines of AD/ADRD from other parts of the world to develop ethics guidelines for AD/ADRD research in Nigeria.

The Epidemiology Research Training for Public Health Impact in Nigeria (Epi-Nigeria) project, led by Dr. Alash'le Abimiku and Dr. Man Charurat, provides HIV research training to develop the capacity of the Institute of Human Virology Nigeria (IHV-Nigeria) as a research leader in achieving global health goals for preventing a resurgence of the epidemic by increasing efficiency of treatment and prevention services. Eight Nigerian



physicians and pharmacists from Bayero University in Kano, University of Benin, University of Nigeria in Nsukka and the Institute of Human Virology-Nigeria are enrolled in the University of Maryland graduate school's online MSHS degree in Implementation Science. The degree is designed to build research and public health capacity in Nigeria by teaching students to apply research and evaluation approaches to identify and address barriers in scale-up of HIV related evidence-based interventions in local settings and to translate such interventions into practice. The eight Fogarty trainees will be graduating in December 2019. Drs. Abimiku and Charurat, supported by **Jibreel Jumare, MBBS, PhD**, Research Associate of Epidemiology and Public Health, have teamed up with the UMB Graduate School to add three additional courses to the MSHS degree. Additionally, two other Fogarty trainees from the Institute of Human Virology-Nigeria are enrolled in the UMB

Graduate School PhD program in Epidemiology and Human Genetics. The UMB program in Epidemiology has a strong quantitative focus, providing the two Nigerian PhD trainees with the tools necessary to conduct world-class research to address important clinical and public health questions. They will be initiating their dissertation research work in Nigeria in 2020. All of our trainees will apply their research training to engage in relevant research for HIV/AIDS epidemic control in Nigeria.



*Kristen A. Stafford, PhD, MPH*

Under the SHIELD (U2GGH001976) project, Drs. Man Charurat with Kristen Stafford work to improve the quality of HIV service delivery across all PEPFAR implementing partners in Nigeria to rapidly increase progress towards epidemic control. Drs. Charurat and Stafford are developing and implementing a robust national data repository and visualization system to guide program planning for epidemic control and other disease surveillance integration. They are enhancing the national data repository (NDR) user experience; laying the framework for the integration of data from the Global Fund and Government of Nigeria (GON) sites into the NDR; developing robust systems to support data demand and information use by stakeholders at all levels; supporting and sustaining health information exchange and integration across the NDR and other relevant health information systems; establishing a customer portal for NDR data requests for non-reporting related studies; providing technical support to comprehensive partners to implement Nigeria MRS; establishing and sustaining HIV case-based surveillance systems to support data for care; extending case-based surveillance capabilities to include Integrated Disease Surveillance Response (IDSR) of priority diseases; establishing Electronic Granular Site Management systems within NDR; maintaining robust data quality assurance and improvement systems; generating platforms for HIV sentinel surveillance and mortality surveillance within the NDR; and, creating systems to generate near real-time visualization of standard and custom outcome indicator.



*Man Charurat, PhD, MHS*

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## Epidemiology and Prevention Publications *(continued)*

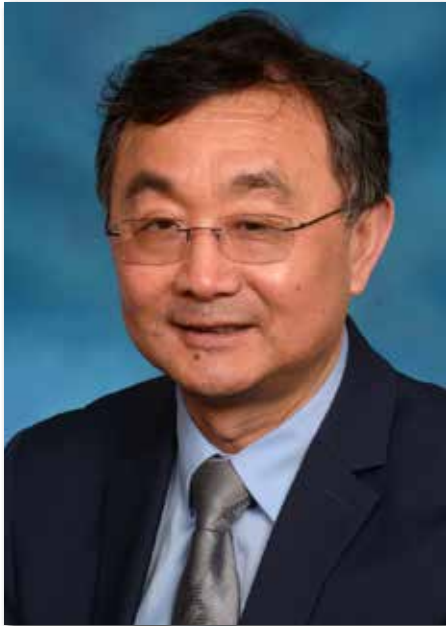
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- Anal Microbial Patterns and Oncogenic Human Papillomavirus in a Pilot Study of Nigerian Men Who Have Sex with Men at Risk for or Living with HIV. **Nowak RG**, Bentzen SM, Ravel J, Crowell TA, Dauda W, Ma B, Liu H, Blattner WA, Baral SD, **Charurat ME**; TRUST/RV368 Study Group. *AIDS Res Hum Retroviruses.* 2019 Mar;35(3):267-275. doi: 10.1089/AID.2018.0158. Epub 2018 Oct 17.
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# Immunotherapy



Yang Liu, PhD

The Division has identified a pathway that selectively suppresses innate immune responses to danger-associated molecular patterns (DAMPs) but not pathogen-associated molecular patterns (PAMPs). Since this pathway is mediated by sialic acid on CD24 and Siglec receptors on innate immune effector cells, the Division calls this pathway sialoside-based pattern recognition. Over the years, they have extended the significance of this pathway into a number of pathological conditions, including chronic inflammation, autoimmune diseases, cancer immunotherapy-related adverse effect and metabolic syndrome. More recently, **Pan Zheng, MD, PhD**, Professor of Surgery, collaborated with **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division of Clinical Care and Research and Head of the Clinical Care Research Unit, to initiate a clinical trial to test how fortifying this pathway with a novel biological drug can reduce chronic inflammation and metabolic disorder

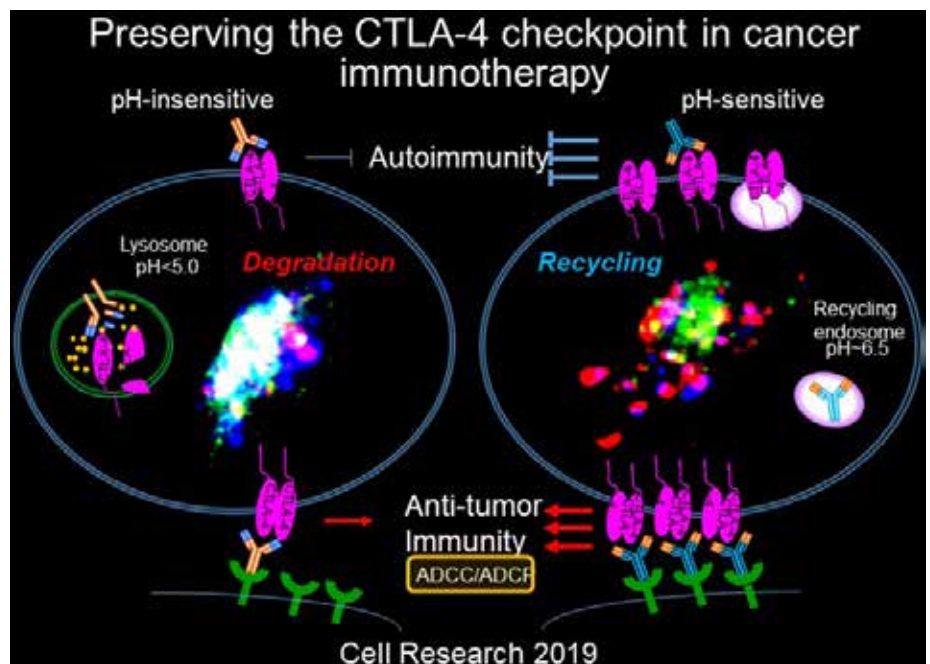
The Division of Immunotherapy, led by **Yang Liu, PhD**, Professor of Surgery, was established in February 2018. The overall mission of the Division is two-fold. First, the Division performs fundamental research on cancer immunology and immunological diseases. Second, in partnership with industry, they perform a full range of translational research ranging from target identification, mechanism of drug action, drug development and novel clinical trials.

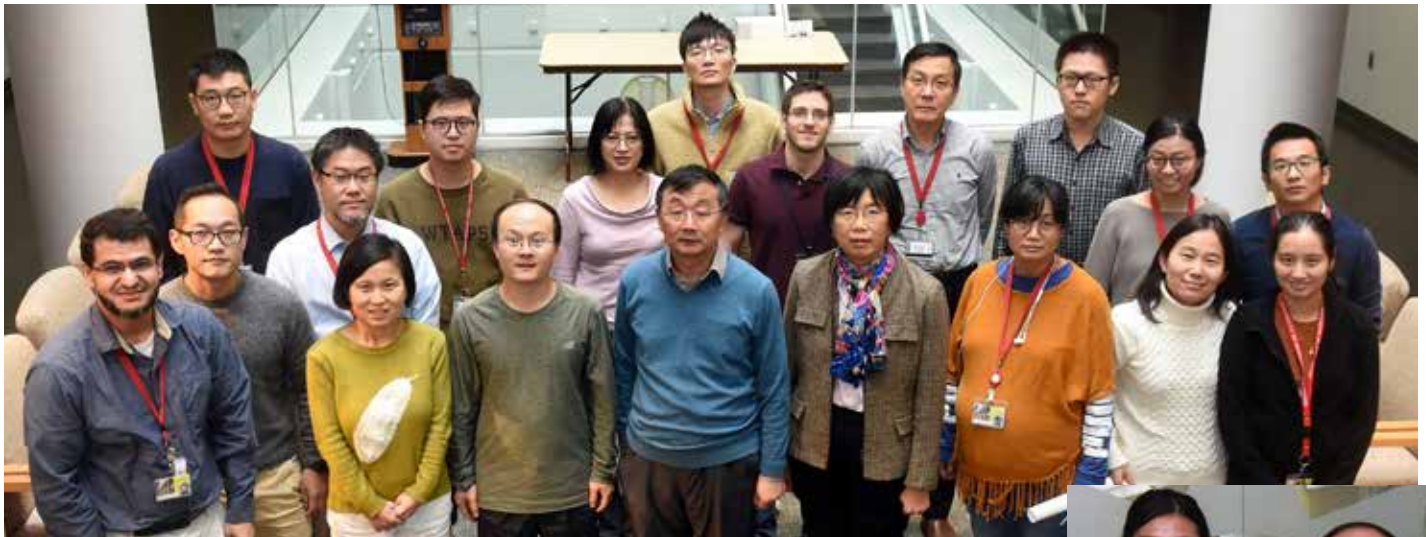
and therefore the risk of heart disease in patients with HIV infection. This trial is supported by a National Institutes of Health (NIH) grant and has received approval from the U.S. Food and Drug Administration. It is expected that patients will be dosed within this year.

The study on the role of CD24 in immune regulation suggests that one may be able to selectively reduce immune attacks of host tissue without negatively affect immunity against infection and cancer. To test this notion, the Division has engaged in a decade-long effort with Oncolmmune, Inc. to develop a fusion protein that activates the pathway for the treatment of immunological diseases. Recently, they have unblinded a phase IIA clinical

trial that not only supports their phase I safety data, but also reveals promising effect of CD24Fc in improving clinical outcome among leukemia patients undergoing hematopoietic transplantation. The phase II trial has been successfully completed and a phase III trial is being planned.

Another major research direction in the Division of Immunotherapy is to understand the mechanism by which CTLA-4 can be targeted for cancer immunotherapy. CTLA-4 is a major target for cancer immunotherapy. The traditional view is that antibodies against CTLA-4 block negative signaling by CTLA-4 ligand that prevents priming of naive T cells in the lymphoid organ. However, their work

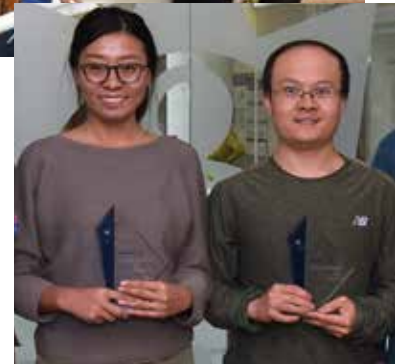




**Front Row, L to R:** Musleh Muthana, PhD; Wei Wu, BS; Chunxia, Ai, MM, MB; Xuexiang, Du, PhD; Yang Liu, PhD; Pan, Zheng, MD, PhD; Juanjuan, Su, PhD; Zhihong, Xue, PhD; and, Yan Zhang, PhD **Back Row, L to R:** Zexu Ma, PhD; Toshihiko Tanno, DVM, PhD; Hung-Yen (Peter) Chou, PhD candidate; Yan Liu, PhD; Peng Zhang, PhD; Chris Bailey, PhD candidate; Yin Wang, PhD; Yunyi Wang, PhD candidate; Mingyue Liu, PhD; and, Xu Wang, PhD

demonstrated that CTLA-4 is not a cell-intrinsic negative regulator for cancer-reactive T cells, and suggested that CTLA-4 blockade is unlikely responsible for clinical benefit of anti-CTLA-4 antibodies. The Division has recently systemically tested the concept of checkpoint blockade by anti-CTLA-4 antibodies and reported that such blockade is neither necessary nor contributory to tumor rejection. Two of the papers that elucidated the new concept were well received in the scientific community and have received the Sanofi-Cell Research outstanding papers award.

Based on this new concept, they developed a new generation of non-blocking antibodies that show strong activity in tumor rejection but much reduced adverse effect when compared to drugs used in clinic. Drs. Liu and Zheng are collaborating with Dr. Christian Rolfo and Dr. Soren Bentzen at the comprehensive cancer center to initiate first-in-human clinical trial of the new drug. The investigator initiated trial will be sponsored by Oncolmmune, Inc.



Mingyue Liu, PhD and Xuexiang Du, PhD win the 2018 Sanofi-Cell Research Outstanding Research Article Award for their articles "A reappraisal of CTLA-4 checkpoint blockade in cancer immunotherapy" and "Uncoupling therapeutic from immunotherapy-related adverse effects for safer and effective anti-CTLA-4 antibodies in CTLA4 humanized mice" published in the April 2018 issue of *Cell Research*

## Immunotherapy Publications

**Liu Y, Zheng P** How Do Anti-CTLA-4 Antibodies Promote Cancer Immunity? *Trends Immunol* 2018 (Dec). 39:953-956.

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**Peng Zhang, Hung-Yen Chou**, Lei Young, **Pan Zheng and Yang Liu** En Masse Discovery of Anti-Cancer Monoclonal Antibodies by De novo Assembly of Immunoglobulin Sequences from Cancer Tissue Transcriptomes and Genome Sequences. *Cell Mol Immunol* (In Press).

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

The Center for International Health, Education, and Biosecurity (CIHEB) has made key advances in addressing critical needs in health system capacity that improve the prevention, care, and treatment of HIV and other diseases. CIHEB's mission is to improve the human condition globally, safeguard communities against health-related threats, and promote health equity worldwide. The Center supports the development and sustainability of evidence-based and data-driven, quality health service for HIV, hepatitis, tuberculosis, malaria, emerging infectious diseases, and non-communicable diseases.

In 2018-2019, CIHEB's portfolio spanned six countries and employed more than 850 program staff. **Man E. Charurat, PhD, MHS**, Professor of Medicine and Director of the Division of Epidemiology and Prevention, was appointed CIHEB's new Global Director. Under Dr. Charurat's leadership, together with his team of country directors, CIHEB is continuing to expand its global impact. Below, we introduce each of the country directors and highlight some of the program achievements in their respective nations.



Man Charurat, PhD, MHS



Ndwapu Ndwapu, MD

## CIHEB Botswana

CIHEB Botswana is helping support the Government of Botswana in expanding HIV service capacity and surveillance through a joint initiative called the Botswana-University of Maryland School of Medicine Health Initiative (BUMMHI).

Botswana Country Director **Ndwapu Ndwapu, MD** is leading the CIHEB team in Botswana and is

strengthening CIHEB's impact in securing epidemic control. A physician and pioneer in establishing publicly funded antiretroviral treatment, with extensive experience in Tuberculosis (TB) treatment and programming, Dr. Ndwapu is the former Director of Clinical Services at the Botswana Ministry of Health.

### Projects

In 2018-2019, CIHEB Botswana continued implementation of a host of initiatives, including the Botswana Partnership for Advanced Clinical Education (BPACE) Project. This initiative supported 105 Botswana Ministry of Health facilities in 13 districts in providing care and treatment services. It also provided preventative interventions in three districts to adolescent girls and young women under the United States Agency for International Development's (USAID) DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored and Safe) partnership.

BPACE's accomplishments in the past year included improved linkage, and initiation of, antiretroviral treatment. The project

established extended clinic hours and expanded services in 42 clinics by enabling them to offer 14-day starter packs at all times (even when the pharmacy is closed). Prior to the implementation of starter packs only 29.63% of males had initiated treatment on the same day of diagnosis. By mid 2019, 46.34% of males initiated the same day (a two-fold increase). In addition, male clients tested during after-hours or on the weekend were twice as likely to initiate antiretroviral treatment within a few days after testing (fast-track pathway). Further, female same-day initiation increased from 32.87% to 54.62% in the same period.

BPACE also introduced new specialized personnel to make testing and treatment a smooth process. Facility Community Tracking Officers (FCTOs) and Expert Clients assisted in providing services at all 105-supported facilities. FCTOs helped track patients across the care continuum and Expert Clients assessed client readiness for antiretroviral care and guided them from testing points to antiretroviral enrollment. With the addition of these personnel, the percentage of clients linked into care increased from 65% to 90% and the average percentage of clients retained in care rose to 96.5%. FCTOs also spearheaded an active viral load appointment system (a care system of monitoring viral load with documentation and tracking of clients who miss appointments) and ensured that documentation of registers, appointments, and filing of results are kept up to date. As a result of their work, viral load monitoring at supported sites increased from 73% to 96%. Viral load suppression among people living with HIV at supported sites also increased from 94% to 98%.

Fundamental to reducing the spread of HIV is the prevention of mother to child transmission of HIV. To achieve this objective, BPACE supported facilities in identifying women without documented or invalid HIV status to obtain HIV



The BUMMHI team in Botswana

testing. It also conducted peer reviews of registers to close documentation gaps. These interventions resulted in improved testing of women at antenatal clinics from 83% to 99.7%. The uptake of antiretroviral treatment among pregnant women increased from 80.2% to 99.8%. In addition, early infant diagnosis of HIV in exposed infants at supported sites rose from 60% to 90%. The BUMMHI team in Botswana.

### Projects

The five-year project, Boresha Maabara (Swahili for “improve laboratory services”), and entitled “Implementation of Sustainable Laboratory Quality Systems in the Republic of Kenya” has been supporting the Ministry of Health (MoH), the National Public Health Laboratory Services (NPHLS), and the Kenya National Blood Transfusion Services to strengthen laboratory systems and provide national leadership for and coordination of the provision of sustainable high-quality TB/ HIV diagnostic services. Having just completed its fourth year, Boresha Maabara has contributed to the development of national laboratory-related policy documents and national tools including: the National Laboratory Strategic Plan, Kenya Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA) Guideline and the Kenya Biorisk Management Curriculum, to name a few. Other achievements include spearheading the integration of quality management systems in the lab, including external quality assessments and lab accreditation, as an integral component of its work. Thanks to Boresha Maabara, eight laboratories have been recently accredited including the national TB reference laboratory and seven are awaiting the finalization of this process.



Emily Koech, MD

### CIHEB Kenya

CIHEB’s work in Kenya continues to make progress in building health service capacity and in expanding prevention efforts for HIV and TB under the leadership of Kenya Country Director, **Emily Koech, MD**. A physician and public health specialist, Dr. Koech’s 14 years of experience and knowledge of HIV programs at the national, regional and facility level has helped to expand

and strengthen CIHEB’s impact in Kenya. She was formerly the Director of Programs for ICAP at Columbia University, and was an Antiretroviral Officer and Program Manager for the Kenyan National AIDS and STI Control Program (NAS COP) during the successful rollout of antiretroviral therapy in the country’s public sector. As the CIHEB Country Director in Kenya, Dr. Koech provides leadership in the design, implementation and evaluation of high-quality projects funded by the National Institute of Health and the Centers for Disease Control and Prevention (CDC) under the President’s Emergency Plan for AIDS Relief (PEPFAR).

CIHEB Kenya has also been implementing Partnership for Advanced Care and Treatment (PACT) projects funded by the CDC under PEPFAR. PACT Timiza (*timiza* is Swahili for “fulfill” or “accomplish”) is being implemented in partnership with Kisii and Migori County Health Departments. The project is supporting health management teams and designated facilities to deliver an enhanced and integrated high-impact package of sustainable HIV prevention and treatment



services towards achieving epidemic control. In the past year, the project provided HIV testing services (HTS) to 662,887 individuals, of whom 8,264 (1.2%) were diagnosed with HIV; it also initiated 6,972 new patients on antiretroviral treatment (ART). Furthermore, the program provided HTS to 48,152 pregnant women in antenatal care of whom 3,946 (8%) were identified to be HIV-infected and 3,912 (99%) of these were provided with ART for prevention of mother-to-child transmission of HIV. In addition, 18,136 males received voluntary male circumcision services—an intervention proven to be effective in HIV prevention—while 879 female sex workers and 204 men who have sex with men were reached with HIV prevention services.

Similarly, PACT Endeleva has been working in Nairobi City County and has made considerable progress in scaling up HIV services. In the past year, the program provided HTS to 350,791 individuals of whom 5,665 (1.6%) were diagnosed with HIV and 4,872 (86%) were initiated on ART. Furthermore, the program provided HTS to 36,984 pregnant women in antenatal care, 1,865 (5%) of whom were identified to be HIV-infected and 1,835 (98%) of these were provided with ART for prevention of mother-to-child transmission of HIV. During this

period, 35,820 female sex workers, 3,573 men who had sex with men, and 4,123 people who inject drugs (PWID) were reached with HIV prevention services, while 2,070 PWIDs had been initiated on methadone as an opioid substitution therapy.

Two additional ongoing PEPFAR projects currently implemented by CIHEB Kenya are the Technical Assistance for Public Health Impact in Kenya (TAPHIK) and the Partnership for Advanced Clinical Education (PACE) Kamilisha (*kamilisha* is Swahili for “to complete”). TAPHIK, in partnership with the Kenya Medical Research Institute, is providing support for HIV and TB program implementation, including, a) building capacity and infrastructure for program evaluations and surveillance projects for HIV/AIDS and TB, b) building HIV and TB laboratory capacity for the provision of high-quality specialized tests for the region, c) supporting non-communicable disease surveillance, d) supporting the management of the HIV Research Laboratory and its work in the community, and e) supporting the Health and Demographic Surveillance System (HDSS) platform.

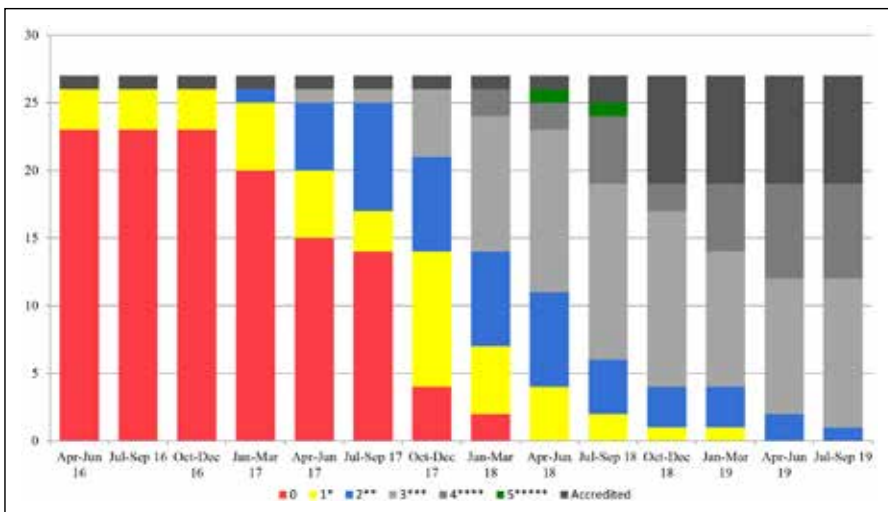
The PACE Kamilisha project is a five-year grant awarded in 2017 that is building upon the successes of the initial PACE program implemented by

the University of Maryland, Baltimore (UMB) from September 30, 2009 through September 29, 2015. This project is focused on strengthening in-service and pre-service HIV training. The PACE Kamilisha program is led by CIHEB as the prime recipient and included the University of Nairobi (UoN) as a sub-recipient, with the main role of continuing to develop and institutionalize advanced infectious disease training in Kenya through the sustainable operationalization of the Unit of Clinical Infectious Diseases (UCID) within the UoN’s School of Medicine. Among its accomplishments, the program recently supported the revision process for the National HIV Integrated Training Curriculum (NHITC) to reflect changes and updates in national HIV guidelines.

CIHEB Kenya is also implementing a five-year smoking cessation study funded by the National Institute of Health (NIH). This randomized control trial is evaluating the most promising and accessible behavioral and pharmacologic treatments aimed at achieving maximal efficacy for smoking cessation among HIV-infected people who smoke. Having completed its second year, the study has enrolled 300 participants from those receiving care in a methadone maintenance program at CIHEB supported clinics in Nairobi. The participants are randomized to one of four cessation treatments. The results of the study will provide policymakers, community leaders, and clinicians with critical evidence of the most effective smoking cessation treatments for HIV smokers in the methadone maintenance setting.

## CIHEB Nigeria

**Kristen A. Stafford, PhD, MPH**, Assistant Professor of Medicine, was appointed CIHEB Nigeria Country Director in 2019. Dr. Stafford is an infectious disease epidemiologist and CIHEB’s Associate Director. She has over 25 years of experience working in domestic and international HIV treatment programs and began her career as an HIV case manager in



Summary of ISO Accreditation and Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA) Scores for Regional Labs, N=27



CIHEB Kenya Team during the Launch of the Revised NHITC During the Kenya HIV Prevention, Care and Treatment Conference

Baltimore. Her experience includes serving as the Director of the Outcomes and Evaluation Program at the Institute of Human Virology for an 8 country, 240 clinic, 700,000 patient HIV care and treatment program funded through PEPFAR.



Kristen A. Stafford, PhD, MPH

### Projects

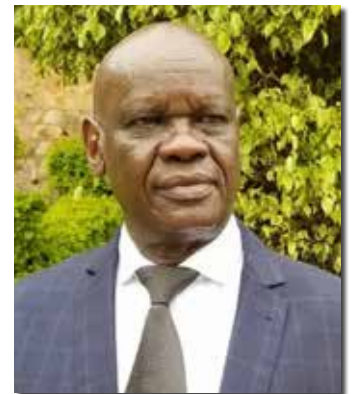
Among CIHEB Nigeria's ongoing initiatives for 2018-2019 is the Strengthening Epidemic Response and Surveillance (SERS) project. This five-year CDC-supported initiative is improving the epidemiology, surveillance, reporting and information management of diseases of public health concern in Nigeria. Launched in late 2015, SERS is providing support to the Nigeria Center for Disease Control (NCDC) in strengthening the surveillance reporting system and implementation of the Integrated Disease Surveillance Response (IDSR) strategy along with other implementing agencies. SERS' purpose is to strengthen information systems in Nigeria to improve the country's ability to achieve international health regulation compliance and global health security targets.

In 2018-2019, SERS' accomplishments included established surveillance reporting using a mobile app and SMS-based communication in 270 local government areas across 29 states; enhanced the development of Nigeria's Disease Surveillance Database reporting and Repository; launched a bio-surveillance information system to improve early threat identification; and, enhanced the laboratory information systems of 11 laboratories to strengthen workflow management and quality assurance.

In the coming year, SERS will launch a Surveillance Outbreak Response Management and Analysis System (SORMAS) to integrate epidemiology and laboratory data during outbreaks, deploy and institutionalize continuous surveillance training using ECHO model, strengthen the functionality of the NCDC Event Based Surveillance (EBS) and Connect Center (CC) and improve the user experience of all the suite of applications to strengthen data use for health action.

### CIHEB Rwanda

CIHEB's Rwanda team is led by **Cyprien Baribwira, MD**, Adjunct Assistant Professor of Medicine. A pediatrician by training, Dr. Baribwira spent the last 30 years in the field of pediatrics in sub-Saharan Africa as a lecturer, clinician and researcher. He is the former head of pediatrics at the University of Rwanda and joined UMB in 2009 as Medical Director for the AIDSRelief project. He has been the CIHEB Country Director since 2011.



Cyprien Baribwira, MD

### Projects

In 2017, CIHEB Rwanda launched the PEPFAR-funded Imakaza Project (*i'makaza* in the local language of Kinyarwanda means "to sustain"). Formally entitled Enhancing Sustainable and Integrated Health, Strategic Information and Laboratory Systems for Quality Comprehensive HIV Services through Technical Assistance, Imakaza is institutionalizing national, provincial and district HIV oversight and delivery systems to provide high quality HIV service delivery. The initiative is focused on meeting the goals of universal access to

treatment and long-term epidemic control in the context of dynamic evidence-driven programming.

In the past year, the Imakaza project has supported the Rwanda Ministry of Health, Rwanda Biomedical Center, HIV Division across several initiatives, including: 1) updating its HIV, Sexually Transmitted and Other Blood-Borne Infections Prevention, Care and Treatment guidelines, 2) developing HIV e-learning training materials to be used for healthcare providers in antiretroviral clinics across the country, 3) developing Integrated Clinical Mentorship Guidelines, and 4) building a laboratory information management system to strengthen the capacity and quality of the country's laboratory network to support HIV diagnosis, prevention, care and treatment, disease monitoring and surveillance.

In the next year, Imakaza will be focusing on supporting the National Reference Lab to improve capacities in systems to aid healthcare providers in utilizing e-lab systems to improve patient outcomes. It will also support the development of a continuous quality improvement framework and an integrated clinical mentorship model based on an index-testing initiative.



*Abubakar Maghimbi, MD*

### CIHEB Tanzania

CIHEB Tanzania is led by Country Director **Abubakar Maghimbi, MD**, Assistant Clinical Professor of Medicine and Adjunct Assistant Professor of Medicine. Dr. Maghimbi has 17 years of experience in infectious diseases and more than eight years working on PEPFAR funded projects. Before assuming the post of Country Director in 2017, Dr. Maghimbi was the

CIHEB Tanzania Technical Director and the interim Country Director. Dr. Maghimbi joined UMB as part of the AIDSRelief program (a PEPFAR funded track 1 project) in Tanzania, where he served as a Clinical Advisor and Technical Assistance Team Leader.

Dr Maghimbi has helped to greatly expand CIHEB Tanzania's work and impact, and he is leading the ongoing implementation of the Reaching, Engaging and Acting for Health (REACH) Project. This five-year PEPFAR-funded project completed its third year and is working in ten regions of Tanzania. This national level technical assistance program is focused on improving uptake of data and evidence for faster HIV epidemic control achievement. REACH supports the Government of Tanzania and CDC-funded local clinical implementing partners in minimizing systemic and structural barriers that impede the development of quality HIV/AIDS services.

In the past year, REACH supported 121 health facilities and trained and mentored 791 health providers on continuous quality improvement (CQI) methodologies, with the aim of improving PEPFAR clinical cascade indicators. The monthly reporting platform for routine monitoring of program performance developed and maintained by REACH continues to be used by all PEPFAR Tanzania implementing partners. REACH has also developed and is widely recognized for platforms that support real-time data quality checks, SMS weekly reporting, CQI reporting, and the Data Analytics Companion (DAC), a powerful tool that performs in-depth patient-level data analytics.



*Robb Sheneberger, MD*

### CIHEB Zambia

CIHEB Zambia is led by Country Director **Robb Sheneberger, MD**, Assistant Professor of Family Medicine. Dr. Sheneberger has been leading UMB initiatives in Zambia since 2004 and assisting the Government of the Republic of Zambia by serving on multiple partnership working groups and developing differentiated care systems to support 90-90-90 goals.

Dr. Sheneberger was a significant contributor to the Zambian National ART Guidelines that were the first in Africa to adopt tenofovir as first line therapy, and the incorporation of discordant couples into antiretroviral eligibility, and has continued to provide guidance to Zambia as they have expanded to a test and start approach. He has also directed the creation of a Masters in HIV Medicine and a Masters in Medicine-Infectious Diseases with the University of Zambia School of Medicine at the University Teaching Hospital in Lusaka to train medical providers in HIV expertise.

In 2013 he began working on a differentiated service delivery approach to scale-up 90-90-90 and close gaps in the cascade. The Community HIV Epidemic Control (CHEC) differentiated service delivery is now widely utilized in Zambia for targeted community and index HIV testing of adolescents, key populations, and others. The CHEC model also was used as the basis for subsequent CIHEB Zambia programs.

### Projects

The Stop Mother And Child HIV Transmission (SMACHT) project completed its fourth year. It began as a prevention of mother- to-child transmission grant, but after its first year was expanded to a comprehensive HIV care and treatment grant, and peaked last year with support to over 300 facilities in the Southern Province. The community approach to improving outcomes for patients with HIV that is utilized in our other two community grants was designed





The Community Impact to Reach Key and Underserved Individuals for Treatment and Support (CIRKUIITS) team at the launch of the Western Province Surge for HIV Epidemic Control in Mongu, Zambia

and implemented through SMACHT. In the final year, it is providing technical assistance to the Southern Provincial Health Office in four districts.

Other ongoing projects include the Community Impact to Reach Key and Underserved Individuals for Treatment and Support (CIRKUIITS). Having completed its first year of implementation, CIRKUIITS utilizes a targeted community approach to improve prevention, care and treatment outcomes in Lusaka, Eastern, and Western Provinces to achieve UNAIDS 90-90-90 goals. It focuses on adolescents; key populations, including men who have sex with men, female sex workers, and prison populations; men under 30 and transient populations; pregnant and breastfeeding women and their families; as well as, the general population. Based on significant success in year one, the grant was expanded in geographic scope in year two with a 40% increase in budget.

The Zambia Community HIV Epidemic Control for Key Populations (ZCHECK) is a five-year project that has completed its third year. The grant focuses on providing community linkage to the health facilities to improve the targets for UNAID 90-90-90 goals in the Southern and Lusaka Provinces. ZCHECK has focused primarily on target populations, including adolescents, pregnant women and their children, young men, men who have sex with men, female sex workers, transgenders, injection drug users, and prisoners. ZCHECK has also been the leader in pre-exposure prophylaxis (PrEP) in Zambia. In year four, it is focused on moving targets closer to 95-95-95 goals set by CDC.

## CIHEB Publications

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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 Imaging Core**, and  $\mu$ QUANT Core, is led by an experienced researcher at IHV. Below is an overview of the Core Facilities.



*L to R: Alfred Dye; Sumiko Williams, MS; Juan Zapata, PhD; Albert Hunter; Cheryl Bass; Harry Davis, MS; Glenda Jackson; Chris Adams; and, Catherine Crews*

## ANIMAL CORE FACILITY

The Animal Core Facility is directed by **Harry Davis, MS** who follows in the footsteps of its former head, **Joseph Bryant, MS, DVM**, who was Associate Professor of Pathology and Director of the Division of Animal Models and retired in July 2017 after twenty-two years of leadership and service with IHV. Dr. Bryant now serves as a consultant to the IHV. Mr. Davis had previously served as the facility manager for twenty-two years prior to becoming the head. Mr. Davis is associated with fifty percent of the Animal Study Proposals (ASPs) for the IHV. He also serves as a major contributor for several National Institutes of Health (NIH) funded RO1 grants and has been a co-author on over 10 research publications in the Institute. Mr. Davis will continue to direct

the Animal Core and 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 and HIV-associated neurocognitive disorders (HAND).

Mr. Davis has a staff of ten animal research care personnel and two Research Associates 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. 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 Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accredited facility and is a part of the overall animal care and use program here at the medical school. We have over 20,000 square feet of space for housing rodents, primates, and other species if requested.

## DEVELOPMENT OF SPECIAL PROGRAMS IN THE ANIMAL CORE FACILITY

### A. NSG humanized mouse program

The Animal Core facility is currently developing a research program for Humanizing mice for investigators in the IHV. We have designed a program to provide several NSG animal models.

The models are listed below:

- NSG ATL human cells: 2 models for HTLV-1-induced leukemia
- NSG PBMC humanized mice: Model for GVHD.
- NSG CD133+ humanized mice: Model for human liver studies
- NSG PBMC and CD34+ humanized mice: Acute and chronic models for HIV infection

**Juan Zapata, PhD**, Research Associate of Medicine, is instrumental in the development of the program

### B. HIV-1 Transgenic Rat Distribution Program

The Animal Core maintains the only source of the HIV-1 transgenic rat animal model in the United States. We are currently working with the University to distribute the model to other researchers. We have provided a plethora of letters of support for NIH funded research submissions.

*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**

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

*Collaborators in the Division of Basic Science include:*

**Robert Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine, Director of IHV and Co-Head of the Laboratory of Tumor Cell Biology

**Davide Zella, PhD**, Assistant Professor of Biochemistry and Molecular Biology and Co-Head of the Laboratory of Tumor Cell Biology

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

**Mika Popovich**, Adjunct Professor of Medicine

**Olga Latinovic, PhD**, Assistant Professor of Microbiology and Immunology, Head of the Laboratory of Host-Pathogen Interaction and Head of the Imaging Core Facility

**Sabrina Currelli, PhD**, Research Associate of Medicine

**Fiorenza Cocchi, MD**, Assistant Professor of Medicine

**Francesca Benedetti, PhD**, Research Associate of Biochemistry and Molecular Biology

**Chozha Rathinam Dr. rer. nat.**, Associate Professor of Medicine and Head of the Laboratory of Stem Cell & Cancer Biology

### **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, **Daive Zella, PhD**, and **Robert Gallo, MD**, together with **Sabrina Currelli, PhD**, **Fiorenza Cocchi, MD**, **Joseph Bryant, DVM**, and **Francesca Benedetti, PhD**, have found an association between Mycoplasma sequences and certain human cancers. Together with their previous studies showing that certain strains of mycoplasma induce lymphomas in immune-deficient mice, these data further strengthen the possibility that Mycoplasma could play a role in the first steps of cellular transformation.

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

**Alonso Heredia, PhD**, Assistant Professor of Medicine

**Olga Latinovic, PhD, MSc**, Assistant Professor of Microbiology and Immunology, Head of the Laboratory of Host-Pathogen Interaction and Head of the Imaging Core Facility

**Nichols Stamatatos, MD, PhD**, Associate Professor of Medicine

**Function of Polysialic Acid in Immune Cell Activity**—**Nichols Stamatatos, 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 is collaborating from Jamaica with the Animal Core on a flavonoid from *Tillandsia recurvate* showing potent anticancer activity against AIDS-defining and non-AIDS defining cancers.

**The use of the HIV-1 Transgenic Rat Model Neurological Studies**—Walter Royal, MD 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 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**—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.

**Stem Cell and Cancer Biology**—**Chozha V. Rathinam, Dr. rer. nat.** 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.

#### **Animal Core Publication**

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## FLOW CYTOMETRY AND CELL CORE FACILITY

The IHV Flow Core serves the IHV community with varying needs associated with flow cytometry.

Flow Cytometry is a fundamental tool for the modern virology/immunology/cell biology research. The IHV Flow Core is headed by

**Yutaka Tagaya, MD, PhD**, Assistant Professor of Medicine and Head of the Laboratory of Cell Biology, IHV Basic Science Division, who has over 30 years of experience with flow cytometry technology. The Flow Core's operation is primarily maintained by **Felisa Diaz-Mendez, PhD** who joined the IHV Flow Core in March of 2019.

The IHV has two major instruments.

1. BD's FACS Aria (3 lasers—405 nm violet, 488 nm blue and 633 nm red—up to 12 independent color analysis and fluorescence-based cell sorting including a single cell/indexing option), located in the north BSL3 facility (Room N664) of IHV.
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), located in N568.

While the Aria is operated only by the Flow Core staff, each trained user can use the 10-color GUAVA machine for flow analysis (for the initial training, please contact Dr. Felisa Diaz-Mendez at [FDiazMendez@ihv.umaryland.edu](mailto:FDiazMendez@ihv.umaryland.edu)). The IHV Flow Core is the only facility in the University of Maryland

*Yutaka Tagaya, PhD and Felisa Diaz-Mendez, PhD working on infectious sorting inside the BSL3 Lab*



Baltimore (UMB) campus that can sort infectious cells. We offer services to labs at the IHV, University of Maryland School of Medicine, and other University of Maryland Schools and outside groups. For setting up the service, please contact Dr. Diaz-Mendez at [FDiazMendez@ihv.umaryland.edu](mailto:FDiazMendez@ihv.umaryland.edu).

The IHV Flow Core not only operates the machine, but also works with each investigator by consulting on the experimental design and by training individual researchers on instruments and software (if necessary). The Flow Core will also offer help with advanced data analysis using the FlowJo software. Through the IHV IT department, we help each investigator obtain a copy of FlowJo at a cost. For detail, please contact Dr. Yutaka Tagaya at [ytagaya@ihv.umaryland.edu](mailto:ytagaya@ihv.umaryland.edu).

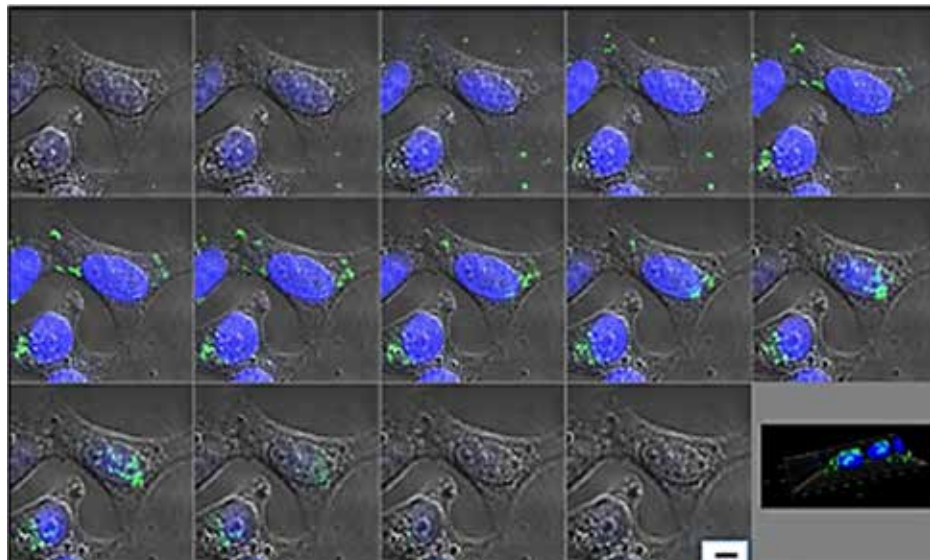
Multi-color analysis or cell sorting is complex, and requires proper guidance based on the appropriate understanding on the fluorochromes and the machine. We have been successfully working with many IHV investigators to conduct multi-color flow cytometry/sorting which helped them in their publications and in receiving NIH funding supports.

## IMAGING CORE FACILITY

The Imaging Core Facility was established in 2012 as the first IHV Imaging Core Facility. **Olga S. Latinovic, PhD, MSc**, Assistant Professor of Microbiology and Immunology and Head of the Laboratory of Host-Pathogen Interaction, Division of Basic Science, established the lab and has led the facility since its beginning. The laboratory was equipped with newly launched Confocal LSM 800 Airy scan Microscope by Zeiss, in 2017, which is utilized daily.

The Facility is primarily focused on quantitative image analyses of pathogens and host cell interactions. The demand for the imaging studies significantly increased in the year of 2019, introducing the possibility of adding additional fluorescence microscopes. The facility operates with online scheduling as of June 2019. Some projects of the Facility are listed below:

**Mycoplasma project**—Dr. Latinovic was involved in the Mycoplasma project since the beginning of her post-doctoral years at IHV, working



**Figure 1.** Intracellular uptake of exogenous DnaK-V5 by mycoplasma-free HCT116 cells. Confocal images of exogenous DnaK-V5 protein of *M. fermentans* in HCT116 cells treated with DnaK-V5 protein (Nuclear localization). The figures show the collected Z-stacks of the corresponding gallery of images, each presenting a 0.5- $\mu\text{m}$ -thick slice. Zella et al, PNAS 2018.

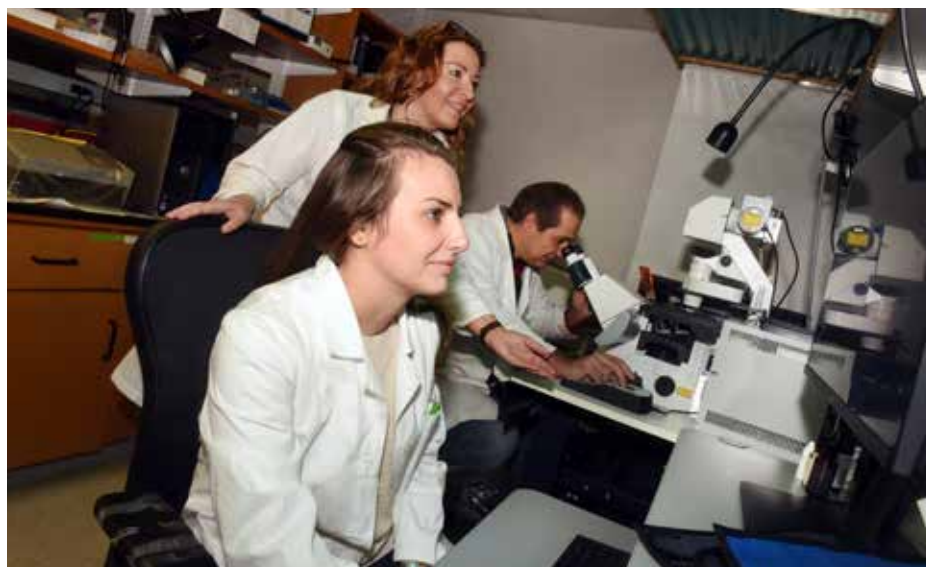
originally with **Fabio Romerio, PhD**, Assistant Professor of Medicine and Head of the Laboratory of HIV-1 Persistence & Immunopathogenesis, Division of Basic Science, and **Davide Zella, PhD**, Assistant Professor of Biochemistry and Molecular Biology and Co-Head of the Laboratory of Tumor Cell

Biology, Division of Basic Science in 2009. Their initial observations demonstrated the rosetting patterns of mycoplasma interactions with human lymphocytes.

The small, imaging part of the mycoplasma project is related to the direct visualization and quantitative studies of mycoplasma DnaK protein, focusing on its cytoplasmic and perinuclear intracellular location and its interactions with p53. The project is directed by Dr. Davide Zella and **Robert Gallo, MD**, The Homer and Martha Gudelsky Distinguished Professor in Medicine and Director of IHV, and has resulted in a PNAS publication in December 2018, "Mycoplasma promotes malignant transformation in vivo and its DnaK has broad oncogenic properties" (Figure 1).

### **HIV-1 Latency Research**—

Dr. Latinovic is using a variety of super resolution, confocal microscopy methodologies and image analysis in collaboration with Dr. Fabio Romerio and his associates, **Yvonne Affram, PhD**, a former post-doc and **Zahra Gholizadeh, PhD**, a current post-



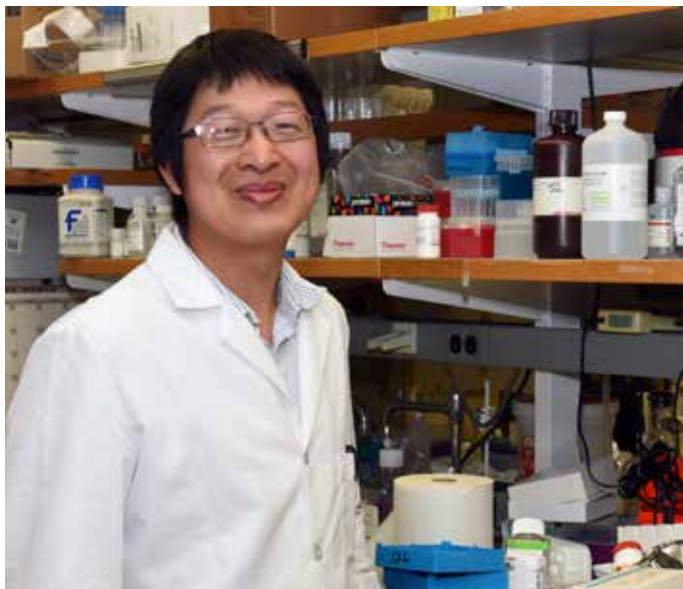
Francesca Benedetti, PhD, Research Associate of Biochemistry and Molecular Biology, Division of Basic Science, Olga Latinovic, PhD, MSc and Davide Zella, PhD, Assistant Professor of Biochemistry and Molecular Biology and Co-Head of the Laboratory of Tumor Cell Biology



doc. They are investigating the subcellular localization of the HIV-1 antisense protein, ASP, as well as its interactions with proteins of the nuclear and cellular membranes. Their findings have led to the conclusion that ASP may be a previously unrecognized structural protein of the HIV envelope. This could have implications for better understanding HIV-1 infection and for the development of new vaccine and therapeutic strategies. A manuscript describing these studies has been accepted for publishing at *Journal of Virology*.

### **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 in the 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 Luminex L200 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 22 research groups at IHV, and 2 UMB groups outside IHV.



Christian Bréchet, MD, PhD

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

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a Center of Excellence of the Global Virus Network with a major role in its formation and the 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 C. 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 International Scientific Advisor, 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. The GVN offices are headquartered at the IHV, and led by GVN's President **Christian Bréchet, MD, PhD**, former President of France's internationally renowned Institut Pasteur.

This past year, the GVN added twelve new members including ten new Centers of Excellence, the University of Nebraska Medical Center (UNMC), West African Centre for Cell Biology of Infectious Pathogens (WACCBIP) at the University of Ghana, Colombia-Wisconsin One-Health Consortium (CWOHC) the University of Wisconsin-Madison Global Health Institute, U.S. Food and Drug Administration's Office of Vaccine Research and Review, Smorodintsev Research Institute of Influenza of the Ministry of Health of the Russian Federation, Manipal Institute of Virology, The Tropical Medicine Institute "Alexander von Humboldt" of the Universidad Peruana Cayetano Heredia, Korea National Institute of Health's Center for Infectious Diseases Research, the Wyss Institute for Biologically Inspired Engineering at Harvard University and two Affiliates, the Research Institute of Virology Ministry of Health of the Republic of Uzbekistan and Antiviral Pharmacology Laboratory and Clinical Trials Research Center Virology Program at the University of Zimbabwe. GVN Members represent expertise covering every class of human virus, and currently comprise virologists from 52 Centers of Excellence

and 9 Affiliates in 32 countries, and its numbers continue to grow. GVN has held international meetings in Ireland, Italy, USA, Germany, Russia, Sweden, Grenada, Estonia, China, Japan, Australia, France and Spain.

Further, the GVN launched the Anticipation & Preparedness Taskforce (A&P Taskforce). The A&P Taskforce is led by Dr. Christian Bréchet and Co-Chaired by **Elodie Ghedin, PhD**, Director of the Center for Genomics and Systems Biology, and Professor of Biology and Global Public Health at New York University, and Giuseppe Ippolito, MD, the Scientific Director of the National Institute for Infectious Diseases (INMI) "Lazzaro Spallanzani" in Rome and Director of the World Health Organization (WHO) Collaborating Center for clinical care, diagnosis, response and training on Highly Infectious Diseases at INMI. The Taskforce's biodefense and biosecurity initiative is led by **James LeDuc, PhD**, the director of the Galveston National Laboratory and a professor in the Department of Microbiology and Immunology at the University of Texas Medical Branch in Galveston. The Taskforce is comprised of more than a dozen experts from GVN Centers of Excellence and Affiliates and its mission is to develop and employ innovative and pioneering approaches to identify and elucidate the impact and magnitude of future viral epidemics by coalescing mathematic modelling with epidemiology, genomics, medicine and public health. The Taskforce works closely



GVN Africa Meeting in Entebbe



## Participants of the GVN Short Course



with public health authorities, existing networks and institutions as well as disseminates vital clinical and scientific information on best practices for the diagnosis and management virus related pathogens.

The 11<sup>th</sup> International GVN meeting was held in partnership with the Spanish Society of Virology in Barcelona, Spain June 9-12, 2019. The meeting focused on pressing topics covering immunology and vaccines, anti-viral drug therapy, virus-host interaction, diagnostic virology and epidemiology, morphogenesis and structural biology, emerging and re-emerging viruses, viruses as biotechnological tools and trending topics in virology. Further, top virologists from varying fields emphasized the need to take collective awareness of the link between animal and human health and ecosystems, and to work cohesively to safeguard the health of the planet. "Now, more than ever, we must be reactive to give quick responses to epidemic outbreaks," said **Marion Koopmans, DVM, PhD**, head of the department of virosciences of Erasmus MC in Rotterdam, who is director of its GVN Center of Excellence, and a worldwide reference in zoonotic viral diseases and emerging viruses.

The recent Ebola outbreak in West Africa emphasizes the need for a more forward-looking research agenda. During a meeting held in May 2019 in Entebbe, Uganda, the GVN launched the Africa GVN, a regional GVN chapter dedicated to leveraging the network's broad resources and to combat viral diseases together despite English and French speaking language challenges on the continent. The announcement came as the Democratic Republic of Congo faces a growing Ebola outbreak, which jumped the

border to Uganda. Meeting participants were comprised of top virologists from around the world with a focus on African scientists; countries included those from Cameroon, Central African Republic, Germany, Ghana, Guinea, Ivory Coast, Madagascar, Netherlands, Nigeria, Senegal, South Africa, Uganda and USA. The meeting focused on joint training and education initiatives, collaborative research in viral epidemics and creating partnerships with international organizations, industries, academia and governments.

This summer, GVN launched its Sixth Annual Short Course in Basic and Translational Virology held July 28-August 3 for 18 early career human and animal virologists from Argentina, Bolivia, Germany, Hong Kong, Jamaica, Japan, Kenya, Nigeria, South Korea and United States of America. The preeminent one-week course on basic, translational, and clinical aspects of viruses features world-renowned researchers drawn from GVN Centers of Excellence, comprising foremost experts in every class of virus causing disease in humans and some animals. The Short Course is designed to counter a declining number of researchers entering the field of basic and translational 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; Shyam Kottilil, MBBS, PhD; Yutaka Tagaya, PhD; Clement Adebamowo, BM, ChB, ScD, FWACS, FACS; Jose Esparza, MD, PhD; Jibreel Jumare, MBBS, Ph.D., MRCP; Niel Constantine, PhD, MT(ASCP); and, Marv Reitz, PhD**. 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.

In addition to Dr. Bréchet, GVN's staff headquartered at IHV includes **Natalia Mercer, PhD**, Program Director, **Marcus Gallo, MS**, Research Associate, Virus Watch Group & Centers Coordinator and **Kevin Kishpaugh**, Operations 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 International Scientific Advisor of the GVN, **Dave Wilkins**, who oversees GVN's finances, and **Nora Samaranayake**, who serves as GVN's Senior Advisor on Public Relations. Other contributors include **Shyam Kottilil, MBBS, PhD; Wuyuan Lu, PhD; Man Charurat, PhD; Yutaka Tagaya, PhD; Alash'le Abimiku, MD, PhD; Clement Adebamowo, BM, ChB, ScD, FWACS, FACS; Marv Reitz, PhD; Niel Constantine, PhD, MT(ASCP); George Lewis, PhD; and, Anthony DeVico, PhD**. IHV also appreciates its own Board of Advisors for donating time and energy towards the advancement of the GVN mission.



*Insectary Core Facility Tour at Johns Hopkins Bloomberg School of Public Health during the GVN Short Course*

# IHV Faculty

## DIVISION OF BASIC SCIENCE

*(Name Change in FY2020 to Infectious Agents and Cancer)*

**Wuyuan Lu, PhD, Director,  
Division Basic Science, Assistant Director**

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Professor, Biochemistry and Molecular Biology,  
Institute of Human Virology  
University of Maryland School of Medicine

**Eric J. Sundberg, PhD, Co-Director,  
Division of Basic Science**

Head of the Laboratory of Structural Immunology &  
Oncology, Professor, Medicine,  
Institute of Human Virology  
University of Maryland School of Medicine

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**Francesca Benedetti, PhD—HV, Laboratory of  
Tumor Cell Biology, Research Associate, Biochemistry and  
Molecular Biology**

**Daniel Bonsor, MChem, PhD: IHV, Laboratory of Chemical  
Biology, Research Associate, Medicine**

**Fiorenza Cocchi, MD—IHV, Laboratory of Tumor Cell Biology,  
Assistant Professor, Medicine**

**Sabrina Curreli, PhD—IHV, Laboratory of Tumor Cell Biology,  
Research Associate, Medicine**

**Erik de Leeuw, PhD—IHV, Assistant Professor, Biochemistry  
and Molecular Biology**

**Robert C. Gallo, MD—IHV Director, Co-Head of the  
Laboratory of Tumor Cell Biology, Homer & Martha Gudelsky  
Distinguished Professor in Medicine and Professor of  
Microbiology and Immunology**

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

**Selvi Krishnan, PhD: IHV, Laboratory of Tumor Cell Biology,  
Research Assistant**

**Joseph R. Lakowicz, PhD—IHV, Associate Member and  
Professor, Biochemistry and Molecular Biology**

**Olga Latinovic, PhD, MSc—IHV, Head of the Laboratory of  
Host-Pathogen Interaction and IHV Imaging Core Facility,  
Assistant Professor, Microbiology and Immunology**

**Chozha V. Rathinam, Dr. rer. nat.—IHV, Head of the  
Laboratory of Stem Cell & Cancer Biology, Associate Professor,  
Medicine**

**Fabio Romero, PhD—IHV, Head of the Laboratory of IHV-1  
Persistence & Immunopathogenesis, Assistant Professor,  
Medicine**

**Maria Salvato, PhD—IHV, Head of the Laboratory of  
Arenavirus Disease & Vaccines, Professor, Medicine**

**Greg Snyder, PhD—IHV, Assistant Professor, Medicine**

**Yutaka Tagaya, PhD—IHV, Head of the Laboratory of Cell  
Biology, Head of the Flow Cytometry & Cell Sorting Core  
Facility, Assistant Professor, Medicine**

**Isaac Witz, PhD—IHV, Professor (P/T), Microbiology and  
Immunology**

**Juan Zapata, PhD—IHV, Research Associate, Medicine**

**Davide Zella, PhD—IHV, Co-Head of the Laboratory of  
Tumor Cell Biology, Assistant Professor, Biochemistry and  
Molecular Biology**

**Richard Zhao, PhD—IHV, Associate Member and Professor,  
Pathology**

## DIVISION OF VACCINE RESEARCH

**George Lewis, PhD, Director,  
Division of Vaccine Research**

The Robert C. Gallo, MD Endowed Professorship in  
Translational Medicine, Professor of Microbiology and  
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University of Maryland School of Medicine

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**Anthony DeVico, PhD—IHV, Head of the Laboratory of Viral  
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**Robert C. Gallo, MD—IHV, Director, Co-Head of the  
Laboratory of Tumor Cell Biology, Homer & Martha Gudelsky  
Distinguished Professor in Medicine and Professor of  
Microbiology and Immunology**

**Chiara Orlandi, PhD—IHV, Research Associate, Biochemistry  
and Molecular Biology**

**Krishanu Ray, PhD—IHV, Associate Professor, Biochemistry  
and Molecular Biology**

**William D. Tolbert, PhD—IHV, Research Associate,  
Biochemistry and Molecular Biology**

## DIVISION OF CLINICAL CARE AND RESEARCH

**Shyamasundaran Kottlil, MBBS, PhD, Director,  
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**Anthony Amoroso, MD, Associate Director,  
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**Carla Alexander, MD—IHV, Assistant Professor, Medicine**

**Shashwatee Bagchi, MD—IHV, Assistant Professor, Medicine**

**Joel Chua, MD—IHV Assistant Professor, Medicine**

**Cassidy Claassen, MD, MPH—IHV, Assistant Professor,  
Medicine**

**James Doub, MD—IHV, Assistant Professor, Medicine**

**Anthony Edozien, MD—IHV, Assistant Professor, Medicine**

**Lottie Hachaambwa, MB ChB—IHV, Assistant Professor,  
Medicine**

## DIVISION OF CLINICAL CARE AND RESEARCH

*Continued*

**Alonso Heredia**, PhD—IHV, Assistant Professor, Medicine  
**Jennifer Husson**, MD—IHV, Assistant Professor, Medicine  
**Wisna Jean**, MD—IHV, Assistant Professor, Medicine  
**Sarah Kattakuzhy**, MD—IHV, Assistant Professor, Medicine  
**Mariam Khambaty**, MD—IHV, Clinical Assistant Professor, Medicine  
**Poonam Mathur**, DO—IHV, Assistant Professor, Medicine  
**Megan Morales**, MD—Assistant Professor, Medicine  
**Heather Nace**, MD—IHV, Clinical Assistant Professor (PT), Medicine  
**Anthea Nwandu**, MD—IHV, Assistant Professor, Medicine  
**Michael Obiefune**, MBBS—IHV, Assistant Professor, Family Medicine  
**Devang Patel**, MD—IHV, Assistant Professor, Medicine  
**Bhawna Poonia**, PhD—IHV, Associate Professor, Medicine  
**David Riedel**, MD, MPH—IHV, Associate Professor, Medicine  
**Elana Rosenthal**, MD—IHV, Assistant Professor of Medicine  
**Brenna Roth**, MD—IHV, Visiting Instructor, Medicine  
**Patrick Ryscavage**, MD—IHV, Assistant Professor, Medicine  
**Kapil Saharia**, MD, MPH—IHV, Assistant Professor of Medicine  
**Mohammad Sajadi**, MD—IHV, Associate Professor, Medicine  
**Paul Saleeb**, MD—IHV, Assistant Professor of Medicine  
**Sarah Schmalzle**, MD—IHV, Assistant Professor, Medicine  
**Robb Sheneberger**, MD—IHV, Assistant Professor, Family Medicine  
**Nicholas Stamatou**, MD—IHV, Associate Professor, Medicine  
**Kristen Stafford**, MPH, PhD—IHV, Assistant Professor, Medicine  
**Rohit Talwani**, MD—IHV, Associate Professor, Medicine  
**Lydia Tang**, MB ChB—IHV, Assistant Professor, Medicine  
**Greg Taylor**, MD—IHV, Associate Professor, Family and Community Medicine  
**Eleanor Wilson**, MD—IHV, Associate Professor, Medicine  
**Daniel Wolde-Rufael**, MD—IHV, Assistant Professor, Medicine

## DIVISION OF IMMUNOTHERAPY

**Yang Liu, PhD, Director,**  
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**Yan Liu**, PhD—IHV, Assistant Professor, Surgery  
**Fei Tang**, PhD—IHV, Research Associate, Surgery  
**Toshihiko Tanno**, DVM, PhD—IHV, Research Associate, Surgery  
**Yin Wang**, PhD—IHV, Assistant Professor, Surgery  
**Peng Zhang**, PhD—IHV, Research Associate, Surgery  
**Yan Zhang**, PhD—IHV, Research Associate, Surgery  
**Pan Zheng**, MD, PhD—IHV, Professor, Surgery

## DIVISION OF EPIDEMIOLOGY AND PREVENTION

**Man E. Charurat, PhD, MHS, Director,**  
**Division of Epidemiology and Prevention**

Professor, Medicine,  
Institute of Human Virology  
University of Maryland School of Medicine

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**Alash'le Abimiku**, MSc, PhD—IHV, Professor, Medicine  
**Clement Adebamowo**, MD—IHV, Professor, Epidemiology and Public Health  
**Gambo G. Aliyu**, MBBS, MS, PhD—IHV, Assistant Professor, Epidemiology and Public Health  
**Niel T. Constantine**, Ph.D., MT(ASCP)—IHV, Head of the Laboratory of Viral Diagnostics, Professor, Pathology  
**Cristiana Cairo**, PhD—IHV, Assistant Professor, Medicine  
**Patrick Dakum**, MBBS, MPH—IHV, Assistant Professor, Epidemiology and Public Health  
**Jibreel Jumare**, MS, PhD—IHV, Research Associate, Epidemiology and Public Health  
**Rebecca Nowak**, PhD—IHV, Assistant Professor, Epidemiology and Public Health  
**Habib R. Omari**, MPH, PhD—IHV, Research Associate, Epidemiology and Public Health  
**Nadia Sam-Agudu**, MD—IHV, Assistant Professor, Epidemiology and Prevention

## CENTER FOR INTERNATIONAL HEALTH, EDUCATION & BIOSECURITY (CIHEB)

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University of Maryland School of Medicine

**Kristen A. Stafford, PhD, MPH, Associate Director, CIHEB**  
Nigeria Country Director, Assistant Professor, Medicine,  
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**Alash'le Abimiku**, MON, PhD—IHV, Professor, Medicine  
**Cyprien Baribwira**, MD—IHV, Country Director, Rwanda, Adjunct Assistant Professor, Medicine  
**Cassidy Claassen**, MD, MPH—IHV, Assistant Professor, Medicine  
**Lottie Hachaambwa**, MB ChB—IHV, Assistant Professor, Medicine  
**Emily Koech**, MD—IHV, Country Director, Kenya  
**Abubakar Maghimbi**, MD—IHV, Country Director, Tanzania, Adjunct Assistant Professor, Medicine  
**Peter Memiah**, DrPH, MSc—IHV, Director Quality and Outcomes, Associate Professor, Medicine  
**Ndwapi Ndwapi**, MD—IHV, Country Director, Botswana  
**Brenna Roth**, MD—IHV, Visiting Instructor, Medicine  
**Robb Sheneberger**, MD—IHV, Country Director, Zambia, Assistant Professor, Family Medicine

# IHV Faculty *(continued)*

## SCIENTIFIC CORE FACILITIES

### Animal Core Facility

**Harry Davis, MS**—Head of the Animal Core Facility (non-faculty member)

**Louis DeTolla, VMD, MS, PhD, DACLAM**—IHV Associate Member, Director, IHV Veterinary Resources, and Professor, Pathology, Medicine (Infectious Diseases), and Epidemiology and Public Health

### Flow Cytometry & Cell Sorting Core Facility

**Yutaka Tagaya, PhD**—IHV, Head of the Laboratory of Cell Biology, Head of the Flow Cytometry & Cell Sorting Core Facility, Assistant Professor, Medicine

### Imaging Core Facility

**Olga Latinovic, PhD**—IHV, Head of the Laboratory of Host-Pathogen Interaction and IHV Imaging Core Facility, Assistant Professor, Microbiology and Immunology

### μQuant Core Facility

**Ping-Hsin (Rex) Lin, MS**—Head of the μQuant Core Facility (non-faculty member)

## FORMER IHV FACULTY NOW ADJUNCT

**Jason Bailey, DO**—IHV, Clinical Assistant Professor, Clinical, Division of Clinical Care and Research

**Ulrike Buchwald, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Farley Cleghorn, MD, MPH**—IHV, Adjunct Assistant Professor, Medicine, Division of Clinical Care and Research

**Joanna Cole, MD**—IHV, Visiting Clinical Instructor, Medicine, Division of Clinical Care and Research

**Guesly Delva, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**John Farley, MD, MPH**—IHV, Adjunct Associate Professor, Medicine, Division of Epidemiology and Prevention

**Suzanne Gartner, PhD**—IHV, Adjunct Associate Professor, Medicine, Division of Basic Science

**Bruce Gilliam, MD**—IHV, Clinical Professor, Medicine, Division of Clinical Care and Research

**Luciano Kapelusznik, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Michael Levin, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Otha Myles, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Nicaise Ndembi, PhD**—IHV, Adjunct Associate Professor, Medicine, Division of Epidemiology and Prevention

**Marvin Reitz, PhD**—IHV, Adjunct Professor, Medicine, Division of Basic Science

**Chidi Nwizu, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Joseph O'Neill, MD, MPH**—IHV, Clinical Professor, Medicine, Division of Clinical Care and Research

**Anuoluwapo Osinusi, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Mikulas Popovic, MD, PhD**—IHV, Adjunct Professor, Medicine, Division of Basic Science

**Alan Schmaljohn, PhD**—IHV, Adjunct Professor, Microbiology and Immunology

**Nathaniel Smith, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Leonard Sowah, MD**—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Rohit Talwani, MD**—IHV, Clinical Associate Professor, Medicine, Division of Clinical Care and Research

## ADJUNCT FACULTY

**William Anthony**, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Cyprien Baribwira**, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Luigi Buonaguro**, MD—IHV, Adjunct Associate Professor, Medicine, Division of Basic Science

**Arnaldo Caruso**, MD, PhD—IHV, Adjunct Professor, Medicine, Division of Basic Science

**Prakash Chandra**, Dphil—IHV, Adjunct Professor, Medicine, Division of Basic Science

**José G. Esparza**, MD, PhD—IHV, Adjunct Professor, Medicine, Division of Vaccine Research

**Jon Fielder**, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Henry Francis**, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Joseph Fraumeni**, MD—IHV, Adjunct Professor, Medicine, Division of Epidemiology and Prevention

**Jessie Githanga**, MB ChB, MMed—IHV, Clinical Assistant Professor, Medicine (Nairobi, Kenya), Center for International, Health, Education & Biosecurity

**Athanase Kiromera**, MBBS—IHV, Clinical Assistant Professor, Medicine, Center for International, Health, Education & Biosecurity

**Alain Lafeuillade**, MD, MPH—IHV, Adjunct Assistant Professor, Medicine, Division of Clinical Care and Research

**Louiselle LeBlanc**, MD—IHV, Clinical Assistant Professor, Medicine, Center for International, Health, Education & Biosecurity

**Sanjiv Lewin**, MD—IHV, Clinical Professor, Medicine, Center for International, Health, Education & Biosecurity

**Henry I.C. Lowe**, PhD—IHV, Adjunct Professor, Medicine, Division of Basic Science

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**Abubakar Maghimbi**, MD—IHV, Clinical Assistant Professor, Medicine, Center for International, Health, Education & Biosecurity

**Marybeth Maritim**, MB, ChB—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

**Peter Maro**, MBBS—IHV, Clinical Assistant Professor, Medicine, Center for International, Health, Education & Biosecurity

**Sekela Mwakyusa**, MD—IHV, Clinical Assistant Professor, Medicine, Center for International, Health, Education & Biosecurity

**Walter Mwanda**, MB ChB—IHV, Clinical Associate Professor, Medicine, Center for International, Health, Education & Biosecurity

**Erling Norrby**, MD, PhD—IHV, Adjunct Professor, Medicine, Division of Basic Science

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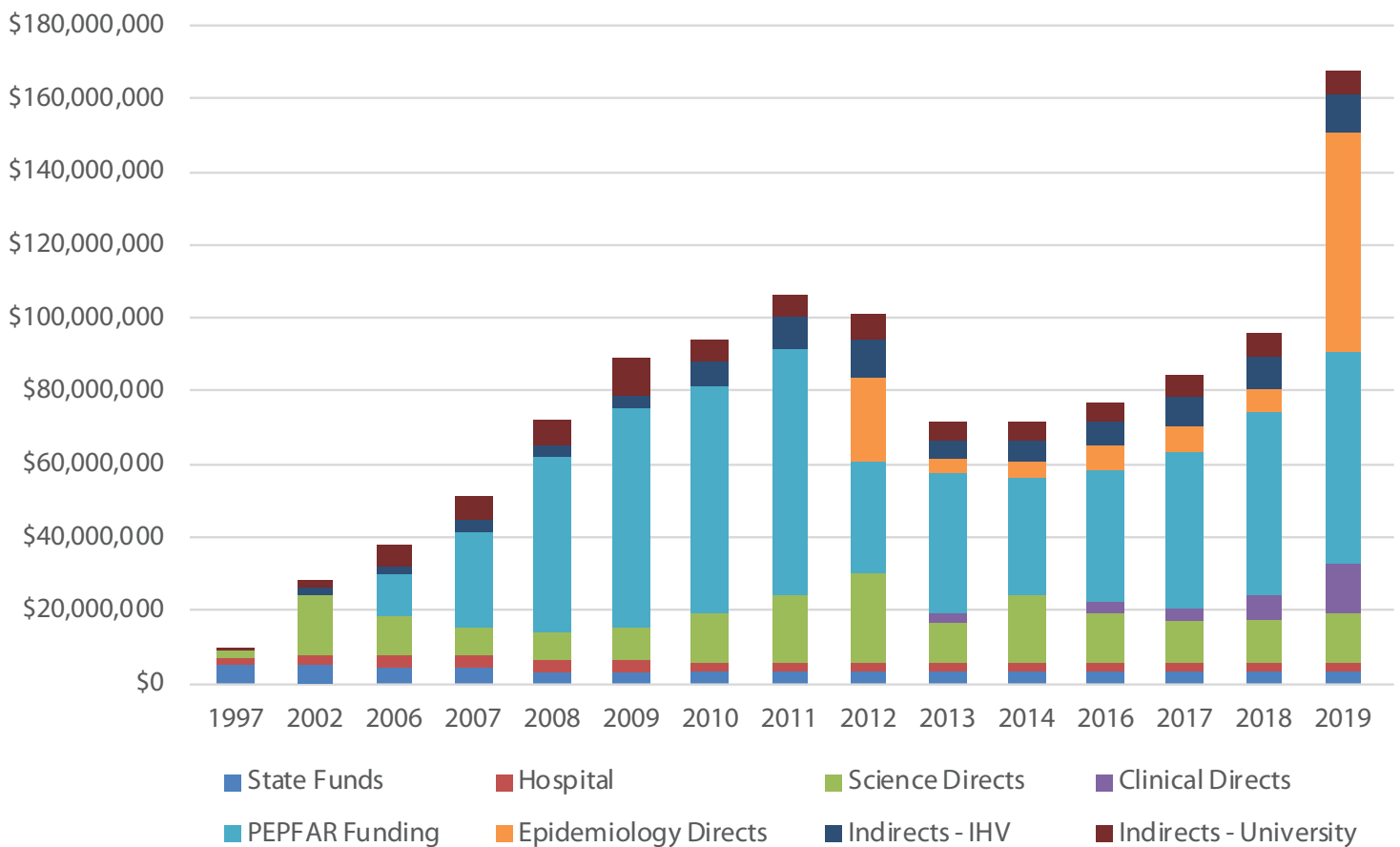
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# Financial Overview

IHV had its strongest financial year on record in FY2019, generating \$167,000,000 of total revenue. This was due to steady increases in all 5 Divisions and 1 Center, including Basic Science, Immunotherapy, Vaccine Research, Clinical Care and Research, Epidemiology and Prevention and the Center for International Health, Education, and Biosecurity (CIHEB). The largest increase, a one-time influx of \$72M for a nine-month HIV survey in Nigeria, came from the Division of Epidemiology and Prevention and was the result of a second five-year survey grant that commences in FY2020. Additionally, our international work through CIHEB increased significantly in FY2019 despite changes in the way in which the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) funds will be awarded to indigenous organizations, pointing to a large drop in related funding in FY2020 and beyond.



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