



INSTITUTE OF
HUMAN VIROLOGY

2018 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. 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 6,000 in Baltimore and Washington, D.C., and more than 1.3 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.

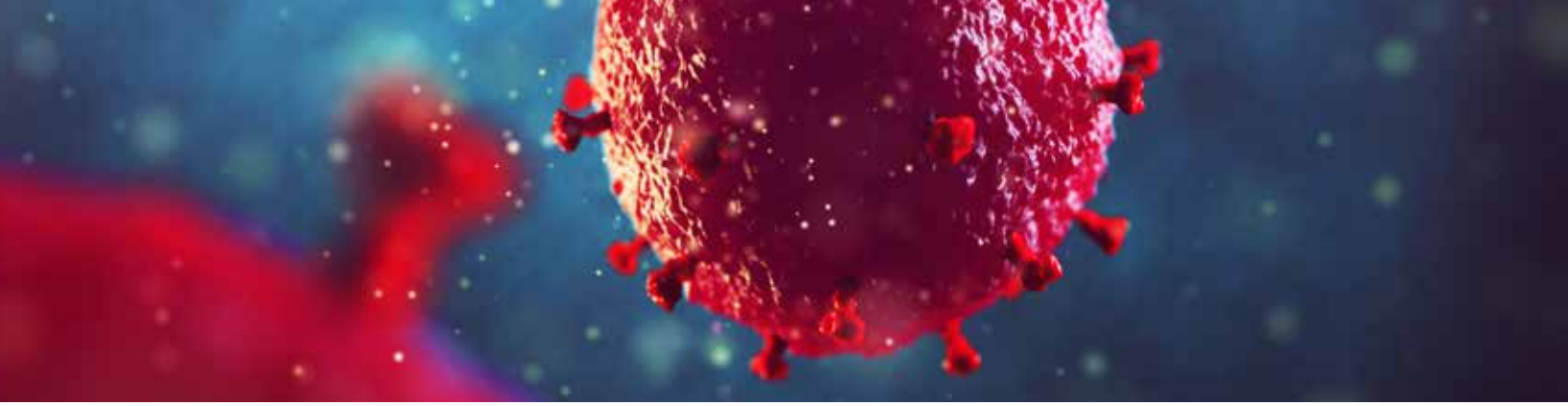


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The Institute of Human Virology is the first institute at the University of Maryland School of Medicine and is affiliated with the University of Maryland Medical Center.

For more information call Nora Samaranayake at 410.706.8614 or visit www.ihv.org



Our Mission

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



Director's Message

A Look at the year

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

In October 2017, IHV hosted its 19th 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. In addition to emerging concepts in cancer therapy, cancer and stem cells, infectious agents and cancer, and viral diagnostics, the meeting included intense discussions on HIV "cure" research, preventative and therapeutic vaccines, immunology and viral pathogenesis, public health science and responses on a global and local level, and clinical virology.

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.

Global health representatives from around the world including, among others, Isaac Adewole, FAS, The Honorable Minister of Health from Nigeria, Anthony Fauci, MD, Director, U.S. National Institute of Allergy and Infectious Diseases (NIAID), and, John Martin, PhD, Executive Chairman, Gilead Sciences, focused on translating laboratory discoveries into public health practice.



Robert C. Gallo, MD



2017 IHV Lifetime Achievement Awards



L to R: Dr. Salim Abdool Karim, Dr. Quarraisha Abdool Karim, Dr. Robert Gallo, and Dr. Peter Palese

Additionally, following a vote by senior IHV faculty, IHV awarded annual Lifetime Achievement Awards in 2017 to three distinguished individuals who have exceptional influence on the field of translational medical research and fundamental research on viruses, and contributed tremendously to HIV/AIDS in public health and epidemiology relevant to prevention and care of infected people. They included:

2017 IHV Lifetime Achievement Award for Scientific Contributions—Peter Palese, PhD, Professor & Chair of Microbiology, Professor of Medicine, Infectious Diseases, Icahn School of Medicine at Mount Sinai, Director, Center of Excellence, Global Virus Network (GVN), Member, IHV Board of Advisors. Dr. Peter Palese's research includes RNA-containing viruses with a special emphasis on influenza viruses. He established the first genetic map for influenza A, B, and C viruses, identified the function of several viral genes, and defined the mechanism of neuraminidase inhibitors (which are now FDA-approved antivirals). He was also a pioneer in the field of reverse genetics for negative strand RNA viruses. His laboratory's research is currently

focused on the development of a universal influenza virus vaccine and oncolytic viruses.

2017 IHV Lifetime Achievement Award for Public Service—Quarraisha Abdool Karim, PhD, Associate Scientific Director, Centre for the AIDS Programme of Research in South Africa (CAPRISA), Adjunct Professor in Public Health, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa. Dr. Quarraisha Abdool Karim is an infectious diseases epidemiologist whose main research interests are in understanding the evolving HIV epidemic in South Africa; factors influencing acquisition of HIV infection in adolescent girls; and sustainable strategies to introduce antiretroviral therapy in resource-constrained settings. She was the Principal Investigator of the landmark CAPRISA 004 tenofovir gel trial which provided proof of concept for Microbicides, highlighted by Science as one of the Top 10 scientific breakthroughs in 2010. Dr. Karim was honored by Sten Vermund, MD, PhD, Dean and Anna M.R. Lauder Professor of Public Health, Professor of Pediatrics, Yale School of Medicine, Yale University School of Public Health.

2017 IHV Lifetime Achievement Award for Public Service—

Salim Abdool Karim, MBChB, PhD, DSc, Director & Professor for Global Health Department of Epidemiology, Centre for the AIDS Programme of Research in South Africa (CAPRISA), Pro Vice-Chancellor (Research), University of KwaZulu-Natal, South Africa. Dr. Salim S. Abdool Karim is a clinical infectious diseases epidemiologist widely recognized for his groundbreaking scientific contributions in HIV prevention and treatment. His contributions to microbicides for HIV prevention spans two decades and culminated in the CAPRISA 004 tenofovir gel trial which provided proof-of-concept that antiretroviral drugs can prevent sexually transmitted HIV infection and herpes simplex virus type 2 in women. He is co-inventor on patents which have been used in several HIV vaccine candidates and his clinical research on TB-HIV treatment has shaped international guidelines on the clinical management of co-infected patients. Dr. Karim was honored by John Martin, PhD, Executive Chairman, Gilead Sciences.

During the meeting, Bernard Roizman, ScD, Joseph Regenstein Distinguished Service Professor of Virology at Viral Oncology Laboratories, The University of Chicago and Mary Klotman, MD, R.J. Reynolds Professor of Medicine, Professor of Pathology, Professor in Molecular Genetics and Microbiology, Member, Duke Human Vaccine Institute, Dean, School of Medicine, Duke University, lectured in Dr. Palese's honor. Dr. Palese also presented the fourth annual Reinhard Kurth Memorial Lecture on "Towards a Universal Influenza Virus Vaccine."

Those honoring Drs. Quarraisha Abdool Karim and Salim Abdool Karim with special presentations included, Thomas Quinn, MD, MS, Associate

Director of International Research, NIAID, Director, Johns Hopkins Center for Global Health, Professor of Medicine and International Research, Johns Hopkins University; John Martin, PhD, Executive Chairman, Gilead Sciences; and, Anthony Fauci, MD, Director, U.S. National Institute of Allergy and Infectious Diseases (NIAID).

During the gala, five IHV faculty members were presented with an IHV Special Director's Award. They included the following: **Alfredo Garzino-Demo, PhD**, Associate Professor of Microbiology and Immunology, Head of the Laboratory of Virus Host Interaction, Division of Basic Science, for his dedication and persistence to HIV pathogenesis with therapeutic implications; **Marzena Pazgier, PhD**, formerly Associate Professor of Biochemistry and Molecular Biology, Head of the Laboratory of Biomolecular Recognition, Division of Vaccine Research, for her dedication, persistence and outstanding productivity to the field of HIV vaccine basic science; **Fabio Romerio, PhD** Assistant Professor of Medicine, Head

of the Laboratory of IHV-1 Persistence & Immunopathogenesis, Division of Basic Science, for his dedication and persistence in unraveling functions of a new gene of HIV; **Nicholas Stamatos, MD**, Assistant Professor of Medicine, Division of Clinical Care and Research, for his dedication and persistence to the science of human glycobiology as it relates to human infectious diseases and cancer; and, **Davide Zella, PhD**, Assistant Professor of Biochemistry and Molecular Biology, Co-Head of the Laboratory of Tumor Cell Biology, Division of Basic Science, for his dedication and persistence in finding new infectious agents associated with cancers of humans.

Restructuring IHV

This past March, IHV Co-founder, Associate Director and Head of the Division of Clinical Care and Research, **Robert Redfield, MD**, was appointed as the next Director of the U.S. Centers for Disease Control and Prevention (CDC). Dr. Redfield is a renowned infectious disease expert, beginning his career in the late 1970's at the Walter Reed Army Medical Center,



L to R: Dr. Alfredo Garzino-Demo, Dr. Robert Gallo, Dr. Marzena Pazgier, Dr. Davide Zella, and Dr. Fabio Romerio



L to R: Terry Lierman, Co-Chair of the IHV Board of Advisors, The Honorable Catherine Pugh, Mayor of Baltimore City, Ambassador James Woolsey of Lux Capital Management, Dr. Leonid Margolis of the National Institutes of Health, Dr. Jay Perman of the University of Maryland, Baltimore, Dr. Robert Gallo of the IHV and The Honorable Kathleen Kennedy Townsend of the Economic Policy Institute

where he made several important scientific contributions to the early understanding of HIV/AIDS. Under his leadership, the Institute's patient base grew from just 200 patients to approximately 6,000 in Baltimore and Washington, D.C., and more than 1.3 million in African and Caribbean nations. At IHV, his research focused on novel strategies to innovatively target host cell pathways to treat and prevent HIV infection and other viral diseases. He was also The Robert C. Gallo, MD Endowed Professor in Translational Medicine, Chief of Infectious Diseases and Vice Chair of Medicine for Clinical Affairs in the UMSOM Department of Medicine. Dr. Redfield is a dedicated and compassionate physician who truly cares about his patients and is deeply committed to ensuring patients receive the highest quality of care possible. Dr. Redfield has served his country well, and consistently demonstrates strong public health instincts that are grounded in science and clinical medicine. In my view, despite the loss to the Institute, I believe this makes him the ideal candidate to direct the CDC.

Since Dr. Redfield's departure, I have named an outstanding clinician and researcher, **Shyam Kottlilil, MBBS, PhD**, Professor of Medicine and Head of IHV's Clinical Research Unit, to take

over as Director of IHV's Division of Clinical Care and Research. He has also become Chief of the Division of Infectious Diseases in the UMSOM Department of Medicine. **Anthony Amoroso, MD**, Associate Professor of Medicine and Associate Director of IHV's Division of Clinical and Care and Research, now serves as Head of the Division's Clinical Care Programs. He has also been appointed as Associate Chief of the Division of Infectious Diseases in the Department of Medicine.

Further, I decided to separate the Center for International Health, Education, and Biosecurity (CIHEB) from the Division of Clinical Care and Research. The Center, formed in 2017 and led by **Deus Bazira, DrPH, MBA, MPH**, Assistant Professor of Medicine, is the culmination of nearly 15 years, under Dr. Redfield's leadership, of designing and implementing successful global health programs through unparalleled leadership. Many IHV faculty and staff over the years dedicated their lives to ending the HIV/AIDS pandemic through this work.

I have also named **Wuyuan Lu, PhD**, Professor of Biochemistry and Molecular Biology and Co-Director of the Division of Basic Science, as Assistant Director of the Institute of Human Virology.



Division of Basic Science

In the Division of Basic Science, nearly two dozen faculty members lead research programs defining the molecular basis of infection and immunity and developing novel therapies and treatments of infectious disease, immune dysregulation, inflammatory disorders and cancer. Approximately 100 scientists, inclusive of faculty, fellows, students and technicians belong to the Division, whose research is supported by a diverse portfolio of federal, state, philanthropic and industrial funds. The Division is organized into five inter-related and inter-disciplinary Research Programs that cover numerous aspects of infection, immunity and inflammation research, including: Structural Biology & Molecular Biophysics; Drug Discovery & Development; Microbial Pathogenesis; Cancer Biology; and Immunity & Inflammation. The Division is directed by **Eric Sundberg, PhD**, Professor of Medicine and **Wuyuan Lu, PhD**.



Division of Vaccine Research

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, continues pursuit of a multidisciplinary approach to developing an HIV-1 vaccine. This approach is broadly based on expertise in molecular and cell biology, virology, immunology, structural biology, and translational medicine. 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 attenuating vaccine-elicited CD4+ T cell responses that provide increased targets for HIV-1 replication.



Division of Clinical Care and Research

As mentioned, in the wake of Dr. Redfield's departure, **Shyam Kottlil, MBBS, PhD** was appointed as the Director of the Division of Clinical Care and Research and **Anthony Amoroso, MD** was appointed as the Division's Chief of Clinical Care. The Division continues to strengthen all three of its key missions including, clinical care, clinical research, and medical education, in both the Baltimore and Washington, DC metropolitan areas. To accomplish this mission, in the past year the Division assembled a team of 44 faculty and 77 support personnel, and secured 78 active grants and contracts. The Division continues to enhance 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 Dr. Amoroso at the new clinical space on the Midtown Campus. Dr. Kottlil and his 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. Between Baltimore and the District of Columbia, the Division treats close to 6,000 individuals.



Division of Epidemiology and Prevention

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, had another successful year conducting research and population-based surveys to guide and develop effective intervention programs to reduce HIV and cancer disease burden. The Division also trained local scientists in implementation and dissemination research and research ethics and maintained robust public health implementation and research programs with IHV-Nigeria. After 15 years of concentrated effort building sustainable research, training and public health programs in Nigeria, the 11 Division faculty have 23 active federal awards totaling \$121M annually. Likewise, the Division continues to pave the way scientifically with 46 peer reviewed publications in FY18.



Division of Immunotherapy

The Division of Immunotherapy, led by **Yang Liu, PhD**, Professor of Surgery, was established in February 2018. Nineteen scientists were recruited from the Children's National Medical Center with generous support from the Department of Surgery, the Cancer Center and the School of Medicine. The overall mission of the Division is two-fold. First, they perform 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 continued to grow since its formal launch in June 2017. Under the direction of **Deus Bazira, DrPH, MBA, MPH**, Assistant Professor of Medicine and Director of CIHEB, the current program portfolio spans 7 countries, more than 15 various projects, and employs a team of over 540 faculty and staff around the world. CIHEB's mission is to improve health outcomes and promote health equity worldwide. From education to care and treatment and from surveillance to testing and linkage to care, CIHEB's achievements and impact rise each year through funded projects in Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania, and Zambia.



Scientific Core Facilities

IHV's four Core Facilities help advance the Institute's research by providing a broad range of services to faculty and staff at IHV, and across the University campus. Services include cutting-edge technologies and laboratory technical support. Each Core Facility, including the Animal Core, Flow Cytometry and Cell Core, Imaging Studies of Pathogens & Cell Interactions Core, and the μ 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.



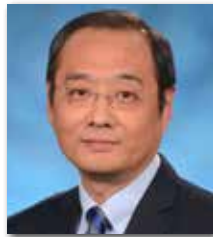
Financial Overview

In Fiscal Year 2018, IHV experienced another year of incredible growth. While the financial growth was primarily a result of significant increases in international funding as is normally the case, each area of IHV grew this year, including Basic Science, Vaccine Research, and Clinical Care and Research. IHV's new Division of Immunotherapy already contributed 5 new grants to IHV's research success. Increases in IHV's CIHEB grants in 7 countries and new significant awards to IHV's Division of Epidemiology and Prevention to conduct a comprehensive HIV survey in Nigeria have driven IHV's funding success to unprecedented heights.

IHV Leadership



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



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



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



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



Deus Bazira, DrPH, MBA, MPH
Director, Center for International Health,
Education, and Biosecurity (CIHEB)
Institute of Human Virology
Assistant 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, 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 **Eric Sundberg, PhD**, Professor of Medicine, and **Wuyuan Lu, PhD**, Professor of Biochemistry and Molecular Biology and Assistant Director of IHV. In this year's Annual Report, the Division highlights research from a few members of their faculty.

de Leeuw Laboratory

During his time at IHV, Erik de Leeuw, PhD, Assistant Professor of Biochemistry and Molecular Biology, has focused on the functional, structural and biological aspects of human α -defensins, effector peptides of innate immunity. Defensins are multi-functional peptides that have antibacterial and antiviral properties. In addition, defending peptides also function in immunity of the human host. Dr. de Leeuw's main research interest is the molecular characterization of the biological activities of these peptides in humans to evaluate their potential as novel therapeutics. His general approach starts with the identification of clinically relevant targets for these peptides, such as bacterial, viral and host factors. Interactions are validated using biochemical, structural, in vitro and computer-




Erik de Leeuw, PhD

based approaches. Together, these approaches are then used to identify small molecule drugs in collaboration with researchers of the University of Maryland School of Pharmacy. Lead molecules are validated by combining structural, biophysical and in vivo animal models and subsequently optimized using medicinal chemistry. The long-term goal of this approach is to evaluate lead candidates in a drug development program as novel anti-infectives or chemotherapeutics leading to human clinical trials. Dr. de Leeuw's laboratory has three research projects currently ongoing:

1. Targeting the Tumor Necrosis Factor Receptor PLAD domain

Receptors of the TNF superfamily such as TNFR1 and TNFR2, CD95 and TRAIL activate distinct intracellular signaling pathways and gene transcription. Signaling through these receptors controls life or death of target cells and plays a critical role in many acute and chronic inflammatory diseases and cancer. The extracellular regions of death receptors contain so-called Pre-Ligand-binding Assembly Domains



or PLADs. PLADs do not bind the TNF α ligand but mediate receptor-chain trimerization, which is essential for subsequent ligand binding and death signaling. Dr. de Leeuw's lab has identified an interaction between human α -defensins, a class of anti-infective peptides, and the PLAD domain of Tumor Necrosis Factor Receptor 1 or TNFR1. The lab has shown that cell killing by Human α -Defensin 5 depends on functional expression of TNF receptors and caspase-8. They showed that signaling events, but not cell death, induced by Human α -Defensin 5 depends on functional expression of the kinase RIPK1. Further, Human α -defensin 5 has in vivo anti-tumor activity. Finally, the lab has identified an interaction between Human α -defensin 5 and the cysteine-rich domain 1 (CRD1) of the Tumor Necrosis Factor Receptor 1 which will allow for the design of small molecule agonists as chemotherapeutic leads.

2. Novel Antivirals: Small molecule inhibitors of Cytomegalovirus

Defensins also act as potent agents against a variety of viruses. Dr. de Leeuw's lab has screened their small molecule library of antimicrobial compounds and identified leads that act against Human cytomegalovirus (HCMV) viral infections in humans. HCMV infection is a major cause of morbidity and mortality in immunosuppressed patients, especially recipients of solid organ or bone marrow transplants. HCMV infection of neonates is associated with deafness, mental retardation, and mortality. Currently used treatment options for CMV infection are associated with adverse events such as myelosuppression and renal toxicity. Safety is a major concern in both the prophylactic and therapeutic

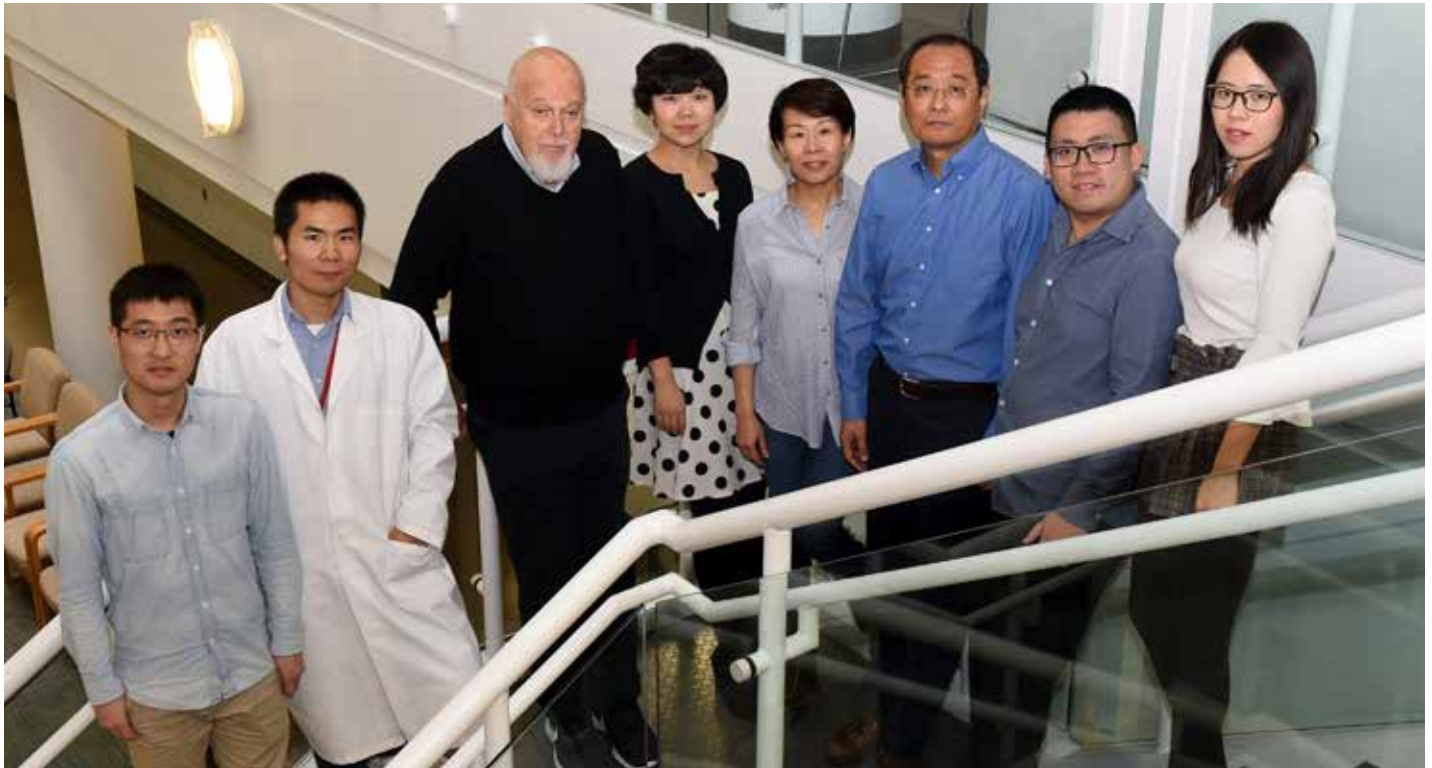
use of currently available approved compounds. Efficacy is an unmet need, primarily in the prophylactic market, and viral resistance to the current drugs is a limitation for the therapeutic use. Thus, there remains a critical unmet medical need for new molecules with novel mechanisms of action targeting patient populations at a high risk of developing CMV.

3. Development of small molecule Lipid II binders as Novel Antibiotics

The ever-increasing emergence of pathogenic strains of bacteria resistant to commonly used antibiotics is a rapidly growing concern in public health. Patients with weakened immunity because of chemotherapy, AIDS or organ transplantation or patients undergoing acute care in hospitals are significantly and increasingly at risk for acquiring opportunistic bacterial infections. In the USA alone, the Centers for Disease Control estimates that ~1.7 million infections per annum occur following hospitalization, with an estimated 99,000 associated deaths.

The discovery and development of novel antibiotic compounds has been slow, and their arsenal of effective antibiotics is dwindling. At the same time, resistance against commonly used classical antibiotics has emerged in all major classes of both Gram-negative and Gram-positive pathogens, including *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and *Staphylococcus aureus*, *Enterococcus faecium*, streptococci and coagulase-negative staphylococci. Thus, there is an urgent need for novel antibiotic agents that inhibit underexploited bacterial targets, for which there are no existing resistance mechanisms. Lipid II is an essential precursor in cell wall biosynthesis and is a validated antibacterial drug target. Dr. de Leeuw's lab was among the first to report on the functional interaction between Lipid II and defensins. Based on this finding, they have identified and characterized low molecular weight synthetic compounds that target Lipid II with high specificity and affinity. This is the first time that synthetic compounds that interfere with Lipid II have been developed.





L to R: Chongbing Liao, Zhenghua Liu, MS, Isaac Witz, PhD, Dan Xu, PhD, Weirong Yuan, MS, Wuyuan Lu, PhD, Wangxiao He and Jin Yan

Lu Laboratory

The Lu laboratory, headed by Dr. Wuyuan Lu, aims to cure a bacterial infection without killing bacteria. As mentioned, increasingly prevalent antibiotic resistance has become a serious threat to global public health, underscoring an urgent need to develop new classes of antibiotics refractory to existing resistance mechanisms including, but not limited to, altering bacterial membrane permeability to control the uptake or efflux of molecules, enzymatically inactivating antibiotics, and modifying the intended target of drug intervention. One of the most attractive strategies to combat antibiotic resistance entails the discovery and development of therapeutics targeting bacterial virulence factors without directly killing bacteria. This anti-virulence strategy induces less selective pressure on bacteria, ensuing a low likelihood for them to develop resistance. One important therapeutic target for this strategy is the Type 3 Secretion System (T3SS) found as cell-surface appendages of many pathogenic Gram-negative bacteria including *E. coli*, *Salmonella*, *Shigella*, *Yersinia*, *Vibrio*, *Burkholderia*, *Chlamydia*, and *Pseudomonas aeruginosa*. The T3SS is composed of ~30 different bacterial proteins, including structural proteins that polymerize into a membrane-anchored, needle-like assembly—“the needle complex,”

effector proteins that are injected through the needle from the bacterial cytoplasm into host cells to promote infection and pathogenesis, and chaperone proteins that bind and protect structural and effector proteins in the bacterial cytosol from premature polymerization and degradation. The “needle” comprises many copies of a single protein, which, prior to its secretion for needle assembly, is protected in a complex formed with chaperone proteins. Small molecule antagonists that specifically inhibit the interaction between the “needle” protein and its chaperones will debilitate the biogenesis of the T3SS needle, promising a novel class of antibiotics for the treatment of bacterial infections.

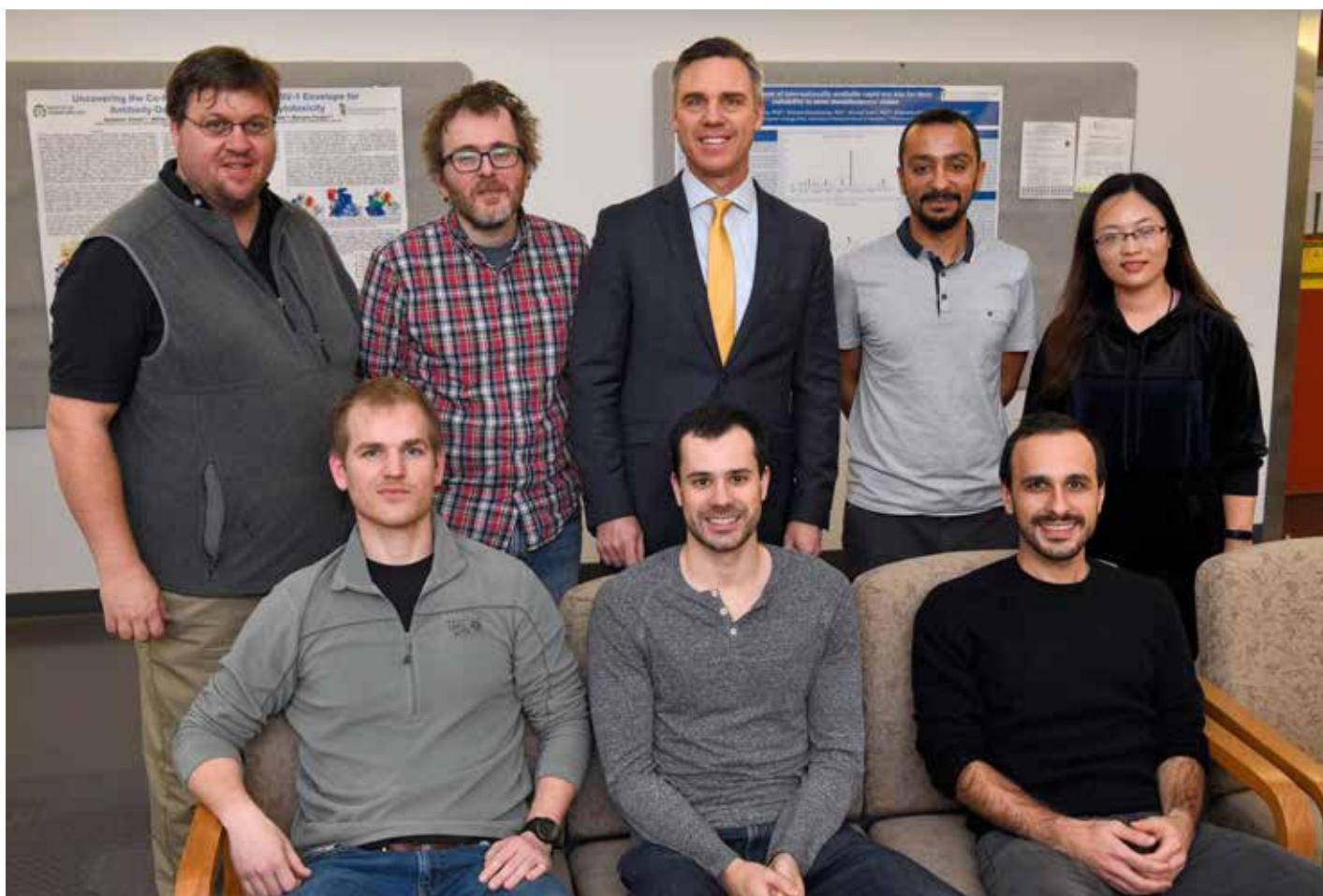
The Lu laboratory recently developed a mechanistically defined sensitive fluorescence polarization assay that can be automated for high throughput screening for potent small molecule inhibitors of the biogenesis of the *Pseudomonas aeruginosa* T3SS needle. *Pseudomonas aeruginosa* is a resistance-prone, opportunistic pathogen that causes fatal acute lung infections in immune-compromised patients and is a major risk factor for pulmonary deterioration associated with chronic cystic fibrosis. Secretion of virulence factors via the T3SS is correlated not only with increased pathogenicity of *Pseudomonas aeruginosa* in cellular and animal models,

but also with poor clinical outcomes in patients with *Pseudomonas*-associated respiratory infections. A low throughput proof-of-concept study performed by Lu and colleagues has led to the serendipitous discovery as well as functional and mechanistic validation of a class of natural herbal compounds in traditional Chinese medicine with known anti-infective activity but unknown mechanisms. These compounds effectively inhibited the biogenesis of the T3SS needle of multidrug-resistant *Pseudomonas aeruginosa*, reduced the secretion of bacterial virulence factors toxic to host cells in vitro, and rescued experimental animals challenged with lethal doses of *Pseudomonas aeruginosa* in a murine model of acute pneumonia. This experimentally proven anti-virulence strategy can be readily applied to targeting many antibiotic-resistant Gram-negative bacteria where the pathogenic T3SS is highly conserved, thus broadly impacting antibiotic drug discovery and development efforts aimed at combating antibacterial resistance.

Sundberg Laboratory

The Sundberg Laboratory, headed by Dr. Eric Sundberg, seeks to understand biological systems at atomic resolution. To do so, the lab uses several methods in structural biology—X-ray crystallography and cryo-electron microscopy (cryo-EM)—to pinpoint precisely where each atom in these molecules that they study is placed in three-dimensional space, painting an incredibly high-resolution picture. With the ability to visualize these microscopic molecules, the lab is able to vastly expand the understanding of how they function. This, in turn, guides the lab in rationalizing the process of developing new drugs.

Of the many projects ongoing in the laboratory to which they apply this general scientific approach, here the lab highlights one in which they are investigating how bacterial construct flagella, the molecular propellers that they use to swim through liquids, such as blood or mucus. Such movement is critical for many pathogenic microbes to access their preferred



Sitting L to R: James Fields, Erik Klontz and Marko Nedeljkovic, PhD; Standing L to R: Greg Snyder, PhD, Daniel Bonsor, PhD, Eric Sundberg, PhD, Daniel Deredge, PhD, and Yajing Wang, PhD

sites of infection in humans where they can cause disease. Understanding how flagella are formed and function could lead to novel strategies for developing new antibiotics or anti-infective drugs.

Flagella are long, filamentous protein appendages extending from the bacterial cell surface that are connected to a motor assembly that spins at speeds of up to 100,000 rpm, propelling the bacterium through liquids. The majority of the flagellar filament is composed of thousands of copies of a single protein called flagellin, or FliC. When flagella are built, the FliC proteins are placed in their proper positions by another protein called FliD, several copies of which form a cap on the end of flagella. Without FliD, bacteria cannot properly assemble flagella and, thus, can no longer swim; this also hinders their ability to cause disease.

When the Sundberg started this project, no high-resolution structures of any FliD protein from any bacterium had been determined. Using X-ray crystallography, they solved the first such structure of FliD, in this case from the pathogenic

bacterium *Pseudomonas aeruginosa*, infection by which is the leading cause of death in cystic fibrosis patients. This first glimpse of how FliD proteins are structurally organized brought many new insights into how FliD functions to fold and sort FliC subunits into the growing flagellar filament, as well as overturned certain dogmatic beliefs concerning these proteins.

To further understand the function of FliD, they needed to visualize the protein on which it acts, FliC. Because FliC forms filaments, which are not amenable to crystallization and, therefore, structure determination by X-ray crystallography, the lab used cryo-EM to determine its structure. Cryo-EM is an old structure determination method that has recently undergone a “resolution revolution,” making it an excellent choice for determining near-atomic resolution structures of many proteins and molecular assemblies. Working with collaborators at the University of Virginia, they determined the structure of the flagellar filament from the same bacterium, *P. aeruginosa*, for which the lab had determined the FliD structure. While the lab was able to visualize the inner core of this FliC filament at high resolution, the parts of the protein that form the exterior regions were only resolvable at moderate resolution, prohibiting them from precisely locating where each atom exists in the structure. Thus, they turned back to X-ray crystallography and crystallized just this part of FliC (and doesn't on its own form filaments) and determined its high-resolution structure. Now, with high-resolution structures of both the inner core and exterior parts of FliC, they built a full model of the *P. aeruginosa* FliC filament.

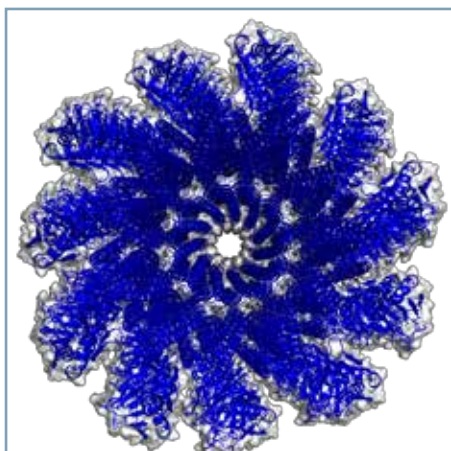
While obtaining structures of both FliD from FliC from the same bacterium has greatly advanced their understanding of how bacterial flagella are formed and function, many questions about these



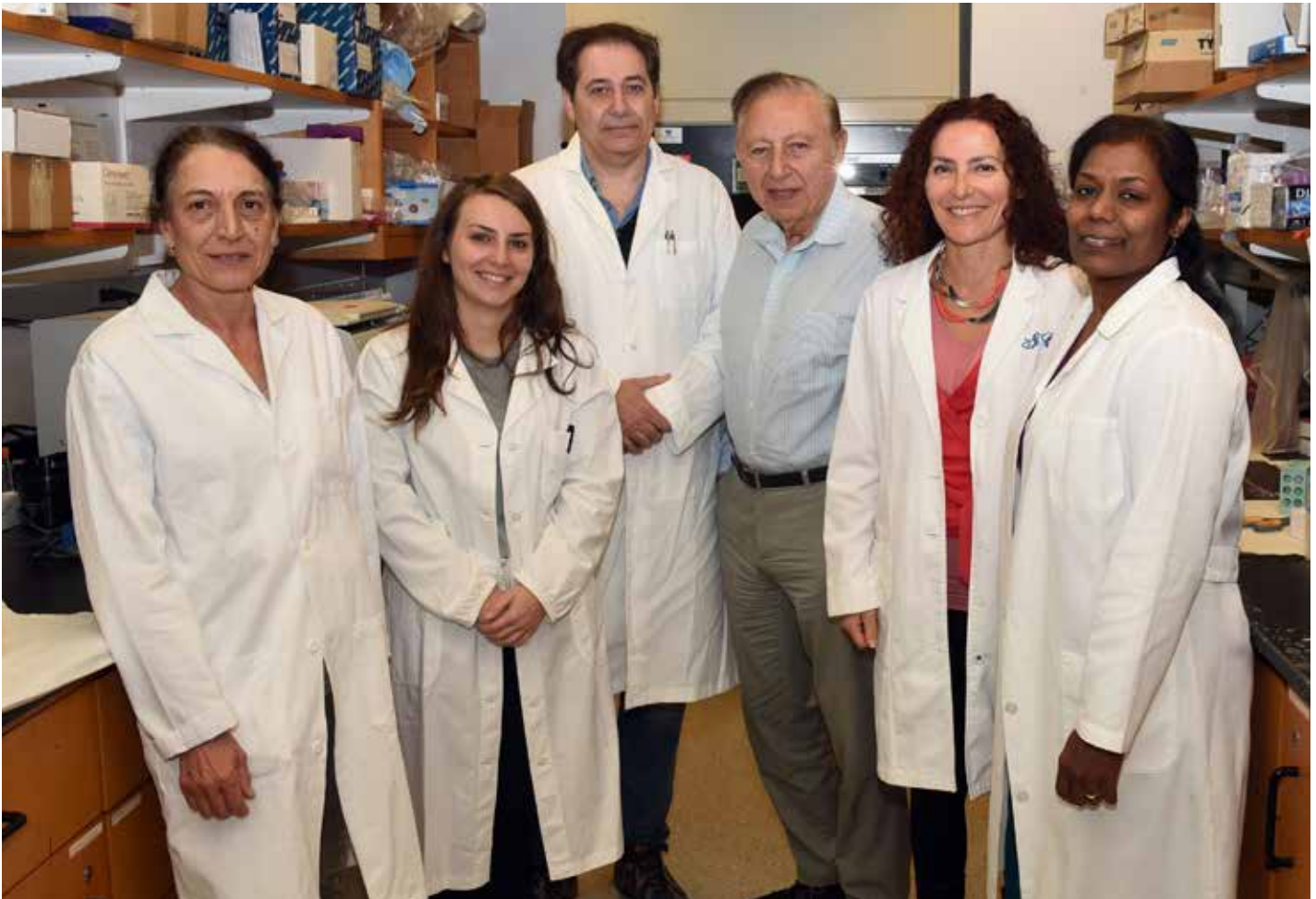
molecular machines remain unanswered. Thus, the lab continues to study these fascinating molecules, pursuing additional structural biology approaches, while expanding their repertoire of techniques to include bacterial genetics, peptide arrays and molecular modeling, in the hopes of determining exactly how each FliC subunit is engaged by the FliD protein in order to fold it and place it in its proper position in the growing flagellum. These future insights will drive the development of drugs that inhibit the movement of *P. aeruginosa* and impair its ability to cause disease.

Gallo-Zella Laboratory

As Co-Heads of the Laboratory of the Tumor Cell Biology, Davide Zella, PhD, Assistant Professor of Biochemistry and Molecular Biology, and Robert C. Gallo, MD The Homer & Martha Gudelsky Distinguished Professor in Medicine and Director, Institute of Human Virology, are continuing the studies on the association between a strain of *Mycoplasma* isolated in the Laboratory and certain human cancers. Lab members include Sabrina Curreli, PhD, Research Associate of Medicine; Francesca Benedetti, PhD, Research Associate of Biochemistry and Molecular Biology; Fiorenza Cocchi, MD, Assistant Professor of Medicine; Joseph Bryant, DVM, former Associate Professor of Pathology; and Selvi Krishnan, PhD, Research Specialist.



Top view of the high-resolution structure of the flagellar filament from *Pseudomonas aeruginosa* bacteria created by combining data obtained using cryo-electron microscopy and X-ray crystallography techniques. Each of the dozens of FliC subunits shown here are depicted in cartoon form in blue, surrounded by their molecular surfaces in grey.



L to R: Fiorenza Cocchi, MD, Francesca Benedetti, PhD, Davide Zella, PhD, Robert Gallo, MD, Sabrina Curreli, PhD, and Selvi Krishnan, PhD

After developing an animal model to study mycoplasma-induced lymphomas, the studies are now focused on the broad oncogenic potential of a Mycoplasma protein that i) reduces activities of human proteins involved in critical cellular pathways required for efficient DNA repair, and ii) impairs p53-dependent anti-cancer functions, resulting in reduced efficacy of anti-cancer drugs that depend on p53 activation to exert their effect. Mycoplasma was detected early in the infected mice, but only low copy numbers of Mycoplasma DnaK DNA sequences were found in some primary and secondary tumors, pointing toward a “hit and run/hide” mechanism of transformation. Phylogenetic amino acid analysis shows that other bacteria associated with human cancers have similar DnaKs, consistent with a common mechanism of cellular transformation mediated through disruption of DNA-repair mechanisms, as well as p53 dysregulation that also results in cancer-drug resistance.

Taken together, these data indicate that some Mycoplasmas (and perhaps certain other bacteria) have cell transforming properties mediated through disruption of DNA-repair mechanisms, as well as p53 dysregulation that also results in cancer-drug resistance. These data may also be clinically relevant because they suggest that the origin of cancers may involve infectious agents more frequently than currently appreciated. Since several human cancers are due at least in part to events leading to DNA repair failures and reduced p53 functions, these could be heightened following certain bacterial infections. It is, thus, obviously of biological interest and potential therapeutic relevance to verify these finding in broader studies in human patients and to understand the physical basis and the mechanism(s) responsible for reduced activities and levels of critical cellular pathways. These results provide a rationale for closer studies on the general relationship between the human microbiota and cancers and identify a potential target for therapeutic intervention.

Basic Science Publications

- Bonsor DA, Zhao Q, Schmidinger B, Weiss E, Wang J, Deredge D, Beadenkopf R, Dow B, Fischer W, Beckett D, Wintrode PL, Haas R, **Sundberg EJ**. The Helicobacter pylori adhesin protein HopQ exploits the dimer interface of human CEACAMs to facilitate translocation of the oncoprotein CagA. *EMBO J*. 2018 Jul 2;37(13). pii: e98664. doi: 10.15252/embj.201798664. Epub 2018 May 3. PubMed PMID: 29724755; PubMed Central PMCID: PMC6028028.
- Badugu R, Jeng BH, Reece EA, **Lakowicz JR**. Contact lens to measure individual ion concentrations in tears and applications to dry eye disease. *Anal Biochem*. 2018 Feb 1;542:84-94. doi: 10.1016/j.ab.2017.11.014. Epub 2017 Nov 26. PubMed PMID: 29183834; PubMed Central PMCID: PMC5817005.
- Badugu R, Reece EA, **Lakowicz JR**. Glucose-sensitive silicone hydrogel contact lens toward tear glucose monitoring. *J Biomed Opt*. 2018 May;23(5):1-9. doi: 10.1117/1.JBO.23.5.057005. PubMed PMID: 29774672; PubMed Central PMCID: PMC5956140.
- Carmona-Gutierrez D, Bauer MA, Zimmermann A, Aguilera A, Austriaco N, Ayscough K, Balzan R, Bar-Nun S, Barrientos A, Belenky P, Blondel M, Braun RJ, Breitenbach M, Burhans WC, Büttner S, Cavalieri D, Chang M, Cooper KF, Côte-Real M, Costa V, Cullin C, Dawes I, Dengjel J, Dickman MB, Eisenberg T, Fahrenkrog B, Fasel N, Fröhlich KU, Gargouri A, Giannattasio S, Goffrini P, Gourlay CW, Grant CM, Greenwood MT, Guaragnella N, Heger T, Heinisch J, Herker E, Herrmann JM, Hofer S, Jiménez-Ruiz A, Jungwirth H, Kainz K, Kontoyiannis DP, Ludovico P, Manon S, Martegani E, Mazzoni C, Megeny LA, Meisinger C, Nielsen J, Nyström T, Osiewicz HD, Outeiro TF, Park HO, Pendl T, Petranovic D, Picot S, Polčić P, Powers T, Ramsdale M, Rinnerthaler M, Rockenfeller P, Ruckenstein C, Schaffrath R, Segovia M, Severin FF, Sharon A, Sigrist SJ, Sommer-Ruck C, Sousa MJ, Thevelein JM, Thivissen K, Titorenko V, Toledano MB, Tuite M, Vögtle FN, Westermann B, Winderickx J, Wissing S, Wölfl S, Zhang ZJ, **Zhao RY**, Zhou B, Galluzzi L, Kroemer G, Madeo F. Guidelines and recommendations on yeast cell death nomenclature. *Microb Cell*. 2018 Jan 1;5(1):4-31. doi: 10.15698/mic2018.01.607. Review. PubMed PMID: 29354647; PubMed Central PMCID: PMC5772036
- Cavallari LH, Lee CR, Beitelshes AL, Cooper-DeHoff RM, Duarte JD, Voora D, Kimmel SE, McDonough CW, Gong Y, Dave CV, Pratt VM, Alestock TD, Anderson RD, Alsip J, Ardati AK, Brott BC, Brown L, Chumnumwat S, Clare-Salzler MJ, Coons JC, Denny JC, Dillon C, Eley AR, Hamadeh IS, Harada S, Hillegass WB, Hines L, Horenstein RB, Howell LA, Jeng LJ, Kelemen MD, Lee YM, Magvanjav O, Montasser M, Nelson DR, Nutescu EA, Nwaba DC, Pakyz RE, Palmer K, Peterson JF, Pollin TI, Quinn AH, Robinson SW, Schub J, Skaar TC, Smith DM, Sriramoju VB, Starostik P, Stys TP, Stevenson JM, Varunok N, Vesely MR, Wake DT, Weck KE, Weitzel KW, Wilke RA, Willig J, **Zhao RY**, Kreutz RP, Stouffer GA, Empey PE, Limdi NA, Shuldiner AR, Winterstein AG, Johnson JA; IGNITE Network. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2018 Jan 22;11(2):181-191. doi: 10.1016/j.jcin.2017.07.022. Epub 2017 Nov 1. PubMed PMID: 29102571; PubMed Central PMCID: PMC5775044.
- DeMarino C, Pleet ML, Cowen M, Barclay RA, Akpamagbo Y, Erickson J, Ndembe N, Charurat M, Jumare J, Bwala S, Alabi P, Hogan M, Gupta A, Hooten NN, Evans MK, Lepene B, Zhou W, Caputi M, **Romerio F**, Royal W 3rd, El-Hage N, Liotta LA, Kashanchi F. Antiretroviral Drugs Alter the Content of Extracellular Vesicles from HIV-1-Infected Cells. *Sci Rep*. 2018 May 16;8(1):7653. doi: 10.1038/s41598-018-25943-2. PubMed PMID: 29769566; PubMed Central PMCID: PMC5955991.
- Gallo RC**, Willems L, **Tagaya Y**. Time to Go Back to the Original Name. *Front Microbiol*. 2017 Sep 22;8:1800. doi: 10.3389/fmicb.2017.01800. eCollection 2017. PubMed PMID: 29018415; PubMed Central PMCID: PMC5615204.
- Giagulli C, D'Ursi P, He W, Zorzan S, Caccuri F, Varney K, Orro A, Marsico S, Otjacques B, Laudanna C, Milanese L, Dolcetti R, Fiorentini S, **Lu W**, Caruso A. A single amino acid substitution confers B-cell clonogenic activity to the HIV-1 matrix protein p17. *Sci Rep*. 2017 Jul 26;7(1):6555. doi: 10.1038/s41598-017-06848-y. PubMed PMID: 28747658; PubMed Central PMCID: PMC5529431
- Günther S, Deredge D, Bowers AL, Luchini A, Bonsor DA, Beadenkopf R, Liotta L, Wintrode PL, **Sundberg EJ**. IL-1 Family Cytokines Use Distinct Molecular Mechanisms to Signal through Their Shared Co-receptor. *Immunity*. 2017 Sep 19;47(3):510-523.e4. doi: 10.1016/j.immuni.2017.08.004. PubMed PMID: 28930661; PubMed Central PMCID: PMC5849085.
- Heredia A, Hassounah S, Medina-Moreno S, **Zapata JC**, Le NM, Han Y, Foulke JS Jr, Davis C, Bryant J, Redfield RR, Wainberg MA. Monotherapy with either dolutegravir or raltegravir fails to durably suppress HIV viraemia in humanized mice. *J Antimicrob Chemother*. 2017 Sep 1;72(9):2570-2573. doi: 10.1093/jac/dkx195. PubMed PMID: 28637235; PubMed Central PMCID: PMC5890682.
- Hildenbrand C, Wedekind L, Li G, vonRenzell JE, Shah K, Rooney P, Harrington AT, **Zhao RY**. Clinical evaluation of Roche COBAS(®) AmpliPrep/COBAS(®) TaqMan(®) CMV test using nonplasma samples. *J Med Virol*. 2018 May 24. doi: 10.1002/jmv.25226. [Epub ahead of print] PubMed PMID: 29797374.
- Howell K, **de Leeuw E**. Cell adhesion properties of human defensins. *Biochem Biophys Res Commun*. 2018 Jul 12;502(2):238-242. doi: 10.1016/j.bbrc.2018.05.150. Epub 2018 May 24. PubMed PMID: 29800568.
- Jaymen A, Szmackinski H, **Lakowicz JR**, Toshchakov VY. Blocking TIR Domain Interactions in TLR9 Signaling. *J Immunol*. 2018 Jun 18. pii: j1800194. doi: 10.4049/jimmunol.1800194. [Epub ahead of print] PubMed PMID: 29914886.
- Klontz EH, Tomich AD, Günther S, Lemkul JA, Deredge D, Silverstein Z, Shaw JF, McElheny C, Doi Y, Wintrode PL, MacKerell AD Jr, Sluis-Cremer N, **Sundberg EJ**. Structure and Dynamics of FcγA-Mediated Fcγ2b-Dependent Resistance in Klebsiella pneumoniae and Escherichia coli. *Antimicrob Agents Chemother*. 2017 Oct 24;61(11). pii: e01572-17. doi: 10.1128/AAC.01572-17. Print 2017 Nov. PubMed PMID: 28874374; PubMed Central PMCID: PMC5655077.
- Kryshchakovych A, Albrecht R, Baslé A, Bule P, Caputo AT, Carvalho AL, Chao KL, Diskin R, Fidelis K, Fontes CMGA, Fredslund F, Gilbert HJ, Goulding CW, Hartmann MD, Hayes CS, Herzberg O, Hill JC, Joachimiak A, Kohring GW, Koning RI, Lo Leggio L, Mangiagalli M, Michalska K, Moul J, Najmudin S, Nardini M, Nardone V, Ndeh D, Nguyen TH, Pintacuda G, Postel S, van Raaij MJ, Roversi P, Shimon A, Singh AK, **Sundberg EJ**, Tars K, Zitzmann N, Schwede T. Target highlights from the first post-PSI CASP experiment (CASP12, May-August 2016). *Proteins*. 2018 Mar;86 Suppl 1:27-50. doi: 10.1002/prot.25392. Epub 2017 Oct 16. PubMed PMID: 28960539; PubMed Central PMCID: PMC5820184.
- Lee I, Bos S, Li G, Wang S, Gadea G, Després P, **Zhao RY**. Probing Molecular Insights into Zika Virus-Host Interactions. *Viruses*. 2018 May 2;10(5). pii: E233. doi: 10.3390/v10050233. Review. PubMed PMID: 29724036; PubMed Central PMCID: PMC5977226.
- Lei R, Hou J, Chen Q, Yuan W, Cheng B, Sun Y, Jin Y, Ge L, Ben-Sasson SA, Chen J, Wang H, **Lu W**, Fang X. Self-Assembling Myristoylated Human α-Defensin 5 as a Next-Generation Nanobiotics Potentiates Therapeutic Efficacy in Bacterial Infection. *ACS Nano*. 2018 Jun 1. doi: 10.1021/acsnano.7b09109. [Epub ahead of print] PubMed PMID: 29856606.
- Li G, **Zhao RY**. Molecular Cloning and Characterization of Small Viral Genome in Fission Yeast. *Methods Mol Biol*. 2018;1721:47-61. doi: 10.1007/978-1-4939-7546-4_5. PubMed PMID: 29423846
- Lu W**. Antimicrobial peptides. *Semin Cell Dev Biol*. 2018 May 31. pii: S1084-9521(18)30132-0. doi: 10.1016/j.semcdb.2018.05.026. [Epub ahead of print] PubMed PMID: 29859256.
- Maes P, Alkhovsky SV, Bào Y, Beer M, Birkhead M, Briese T, Buchmeier MJ, Calisher CH, Charrel RN, Choi IR, Clegg CS, de la Torre JC, Delwart E, DeRisi JL, Di Bello PL, Di Serio F, Digiario M, Dolja VV, Drosten C, Drucierek TZ, Du J, Ebihara H, Elbeaino T, Gergerich RC, Gillis AN, Gonzalez JJ, Haenni AL, Hepojoki J, Hetzel U, Hô T, Hông N, Jain RK, Jansen van Vuren P, Jin Q, Jonson MG, Junglen S, Keller KE, Kemp A, Kipar A, Kondov NO, Koonin EV, Kormelink R, Korzyukov Y, Krupovic M, Lambert AJ, Laney AG, LeBreton M, Lukasevich IS, Marklewitz M, Markotter W, Martelli GP, Martin RR, Mielke-Ehret N, Mühlbach HP, Navarro B, Ng TFF, Nunes MRT, Palacios G, Pawęska JT, Peters CJ, Plyusnin A, Radoshitzky SR, Romanowski V, Salmenperä P, **Salvato MS**, Sanfaçon H, Sasaya T, Schmaljohn C, Schneider BS, Shirako Y, Siddell S, Sironen TA, Stenglein MD, Storm N, Sudini H, Tesh RB,

Tzanetakis IE, Uppala M, Vapalahti O, Vasilakis N, Walker PJ, Wáng G, Wáng L, Wáng Y, Wèi T, Wiley MR, Wolf YI, Wolfe ND, Wú Z, Xú W, Yang L, Yáng Z, Yeh SD, Zhāng YZ, Zhèng Y, Zhou X, Zhū C, Zirkel F, Kuhn JH. Taxonomy of the family Arenaviridae and the order Bunyavirales: update 2018. *Arch Virol.* 2018 Apr 21. doi: 10.1007/s00705-018-3843-5. [Epub ahead of print] PubMed PMID: 29680923.

Martin F, **Tagaya Y**, **Gallo R**. Time to eradicate HTLV-1: an open letter to WHO. *Lancet.* 2018 May 12;391(10133):1893-1894. doi: 10.1016/S0140-6736(18)30974-7. Epub 2018 May 10. Erratum in: *Lancet.* 2018 May 18;.. PubMed PMID: 29781438.

Medina-Moreno S, Dowling TC, **Zapata JC**, Le NM, Sausville E, Bryant J, Redfield RR, Heredia A. Targeting of CDK9 with indirubin 3'-monoxime safely and durably reduces HIV viremia in chronically infected humanized mice. *PLoS One.* 2017 Aug 17;12(8):e0183425. doi: 10.1371/journal.pone.0183425. eCollection 2017. PubMed PMID: 28817720; PubMed Central PMCID: PMC5560554.

Mengistu M, Tang AH, Foulke JS Jr, Blanpied TA, Gonzalez MW, Spouge JL, **Gallo RC**, Lewis GK, DeVico AL. Patterns of conserved gp120 epitope presentation on attached HIV-1 virions. *Proc Natl Acad Sci U S A.* 2017 Nov 14;114(46):E9893-E9902. doi: 10.1073/pnas.1705074114. Epub 2017 Oct 30. PubMed PMID: 29087304; PubMed Central PMCID: PMC5699032.

Niu F, Yan J, Ma B, Li S, Shao Y, He P, Zhang W, He W, Ma PX, **Lu W**. Lanthanide-doped nanoparticles conjugated with an anti-CD33 antibody and a p53-activating peptide for acute myeloid leukemia therapy. *Biomaterials.* 2018 Jun;167:132-142. doi: 10.1016/j.biomaterials.2018.03.025. Epub 2018 Mar 14. PubMed PMID: 29571049; PubMed Central PMCID: PMC5889738.

Pauza CD, Liou ML, Lahusen T, Xiao L, Lapidus RG, **Cairo C**, Li H. Gamma Delta T Cell Therapy for Cancer: It Is Good to be Local. *Front Immunol.* 2018 Jun 8;9:1305. doi: 10.3389/fimmu.2018.01305. eCollection 2018. Review. PubMed PMID: 29937769; PubMed Central PMCID: PMC6003257.

Pierce BG, Boucher EN, Piepenbrink KH, Ejemel M, Rapp CA, Thomas WD Jr, **Sundberg EJ**, Weng Z, Wang Y. Structure-Based Design of Hepatitis C Virus Vaccines That Elicit Neutralizing Antibody Responses to a Conserved Epitope. *J Virol.* 2017 Sep 27;91(20). pii: e01032-17. doi: 10.1128/JVI.01032-17. Print 2017 Oct 15. PubMed PMID: 28794021; PubMed Central PMCID: PMC5625506.

Prantner D, Shirey KA, Lai W, **Lu W**, Cole AM, Vogel SN, **Garzino-Demo A**. The θ -defensin retrocyclin 101 inhibits TLR4- and TLR2-dependent signaling and protects mice against influenza infection. *J Leukoc Biol.* 2017 Oct;102(4):1103-1113. doi: 10.1189/jlb.2A1215-567RR. Epub 2017 Jul 20. PubMed PMID: 28729359; PubMed Central PMCID: PMC5597516.

Richman DD, **Gallo RC**. Mark Wainberg. *Curr Opin HIV AIDS.* 2017 Sep;12(5):423-424. doi: 10.1097/COH.0000000000000394. PubMed PMID: 28771448.

Salvato MS, Lukashovich IS, Medina-Moreno S, **Zapata JC**. Diagnostics for Lassa Fever: Detecting Host Antibody Responses. *Methods Mol Biol.* 2018;1604:79-88. doi: 10.1007/978-1-4939-6981-4_5. PubMed PMID: 28986826.

Salvato MS, Lukashovich IS, Yang Y, Medina-Moreno S, Djavani M, Bryant J, Rodas JD, **Zapata JC**. A Primate Model for Viral Hemorrhagic Fever. *Methods Mol Biol.* 2018;1604:279-290. doi: 10.1007/978-1-4939-6981-4_22. Review. PubMed PMID: 28986843.

Shubin Z, **Tagaya Y**, Poonia B. Functional polymorphisms in rhesus macaque FCGRT and β 2-m. *Immunogenetics.* 2018 Mar;70(3):179-183. doi: 10.1007/s00251-017-1022-6. Epub 2017 Aug 7. PubMed PMID: 28785825; PubMed Central PMCID: PMC5823023.

Tagaya Y, **Gallo RC**. The Exceptional Oncogenicity of HTLV-1. *Front Microbiol.* 2017 Aug 2;8:1425. doi: 10.3389/fmicb.2017.01425. eCollection 2017. Review. PubMed PMID: 28824561; PubMed Central PMCID: PMC5539117.

Trastoy B, Klontz E, Orwenyo J, Marina A, Wang LX, **Sundberg EJ**, Guerin ME. Structural basis for the recognition of complex-type N-glycans by Endoglycosidase S. *Nat Commun.* 2018 May 14;9(1):1874. doi: 10.1038/s41467-018-04300-x. PubMed PMID: 29760474; PubMed Central PMCID: PMC5951799.

Valere K, **Lu W**, Chang TL. Key Determinants of Human α -Defensin 5 and 6 for Enhancement of HIV Infectivity. *Viruses.* 2017 Aug 29;9(9). pii: E244. doi: 10.3390/v9090244. PubMed PMID: 28850095; PubMed Central PMCID: PMC5618010.

Wang F, Burrage AM, Postel S, Clark RE, Orlova A, **Sundberg EJ**, Kearns DB, Egelman EH. A structural model of flagellar filament switching across multiple bacterial species. *Nat Commun.* 2017 Oct 16;8(1):960. doi: 10.1038/s41467-017-01075-5. PubMed PMID: 29038601; PubMed Central PMCID: PMC5643327.

Wen Y, Ouyang Z, Devreese B, He W, Shao Y, **Lu W**, Zheng F. Crystal structure of master biofilm regulator CsgD regulatory domain reveals an atypical receiver domain. *Protein Sci.* 2017 Oct;26(10):2073-2082. doi: 10.1002/pro.3245. Epub 2017 Aug 22. PubMed PMID: 28758290; PubMed Central PMCID: PMC5606546.

Wu L, Zhang H, Jiang Y, **Gallo RC**, **Cheng H**. Induction of antitumor cytotoxic lymphocytes using engineered human primary blood dendritic cells. *Proc Natl Acad Sci U S A.* 2018 May 8;115(19):E4453-E4462. doi: 10.1073/pnas.1800550115. Epub 2018 Apr 19. PubMed PMID: 29674449; PubMed Central PMCID: PMC5948994.

Xu D, Liao C, Zhang B, Tolbert WD, He W, Dai Z, Zhang W, Yuan W, Pazgier M, Liu J, Yu J, Sansonetti PJ, Bevins CL, Shao Y, **Lu W**. Human Enteric α -Defensin 5 Promotes Shigella Infection by Enhancing Bacterial Adhesion and Invasion. *Immunity.* 2018 Jun 19;48(6):1233-1244.e7. doi: 10.1016/j.immuni.2018.04.014. Epub 2018 May 29. PubMed PMID: 29858013; PubMed Central PMCID: PMC6051418.

Yan J, He W, Yan S, Niu F, Liu T, Ma B, Shao Y, Yan Y, Yang G, **Lu W**, Du Y, Lei B, Ma PX. Self-Assembled Peptide-Lanthanide Nanoclusters for Safe Tumor Therapy: Overcoming and Utilizing Biological Barriers to Peptide Drug Delivery. *ACS Nano.* 2018 Feb 27;12(2):2017-2026. doi: 10.1021/acsnano.8b00081. Epub 2018 Feb 2. PubMed PMID: 29376322.

Zhang D, Wang R, Xiang Y, Kuai Y, Kuang C, Badugu R, Xu Y, Wang P, Ming H, Liu X, **Lakowicz JR**. Silver Nanowires for Reconfigurable Bloch Surface Waves. *ACS Nano.* 2017 Oct 24;11(10):10446-10451. doi: 10.1021/acsnano.7b05638. Epub 2017 Sep 20. PubMed PMID: 28921957; PubMed Central PMCID: PMC5656513.

Zhang D, Xiang Y, Chen J, Cheng J, Zhu L, Wang R, Zou G, Wang P, Ming H, Rosenfeld M, Badugu R, **Lakowicz JR**. Extending the Propagation Distance of a Silver Nanowire Plasmonic Waveguide with a Dielectric Multilayer Substrate. *Nano Lett.* 2018 Feb 14;18(2):1152-1158. doi: 10.1021/acs.nanolett.7b04693. Epub 2018 Jan 12. PubMed PMID: 29320635; PubMed Central PMCID: PMC5814343.

Zhang J, **Lakowicz JR**. A superior bright NIR luminescent nanoparticle preparation and indicating calcium signaling detection in cells and small animals. *Cell Biosci.* 2018 Jun 5;8:37. doi: 10.1186/s13578-018-0235-1. eCollection 2018. PubMed PMID: 29928497; PubMed Central PMCID: PMC5987641

Zhao RY. Yeast for virus research. *Microb Cell.* 2017 Sep 18;4(10):311-330. doi: 10.15698/mic2017.10.592. Review. PubMed PMID: 29082230; PubMed Central PMCID: PMC5657823.

Zhu L, Badugu R, Zhang D, Wang R, Descrovi E, **Lakowicz JR**. Radiative decay engineering 8: Coupled emission microscopy for lens-free high-throughput fluorescence detection. *Anal Biochem.* 2017 Aug 15;531:20-36. doi: 10.1016/j.ab.2017.05.020. Epub 2017 May 17. PubMed PMID: 28527910; PubMed Central PMCID: PMC5530754.

Zhu L, Zhang D, Wang R, Wen X, Wang P, Ming H, Badugu R, **Lakowicz JR**. Out-of-Focal Plane Imaging by Leakage Radiation Microscopy. *J Opt.* 2017;19. pii: 095004. doi: 10.1088/2040-8986/aa79cc. Epub 2017 Aug 9. PubMed PMID: 29545944; PubMed Central PMCID: PMC5846715

Zou G, **de Leeuw E**. Neutralization of *Pseudomonas aeruginosa* Exotoxin A by human neutrophil peptide 1. *Biochem Biophys Res Commun.* 2018 Jun 22;501(2):454-457. doi: 10.1016/j.bbrc.2018.05.011. Epub 2018 May 10. PubMed PMID: 29738776.

Vaccine Research

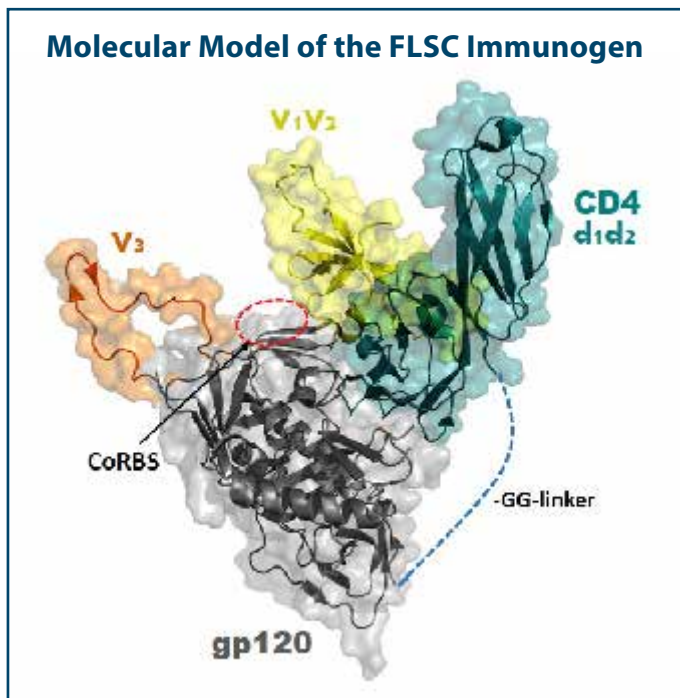


George K. Lewis, PhD

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, continues pursuit of a multidisciplinary approach to developing an HIV-1 vaccine. This approach is broadly based on expertise in molecular and cell biology, virology, immunology, structural biology, and translational medicine. 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 attenuating vaccine-elicited CD4+ T cell responses that provide increased targets for HIV-1 replication.

The first major problem, development of an immunogen that elicits cross-reactive protection is being pursued via a conformationally constrained vaccine comprised of gp120 linked to the first two domains of CD4 by a flexible peptide spacer that elicits cross-protective immunity against model AIDS viruses in animal models. This immunogen is denoted as the full-length single chain (FLSC) protein. **Anthony DeVico, PhD**, Professor of Medicine, and his laboratory developed the FLSC vaccine concept in the early years of the

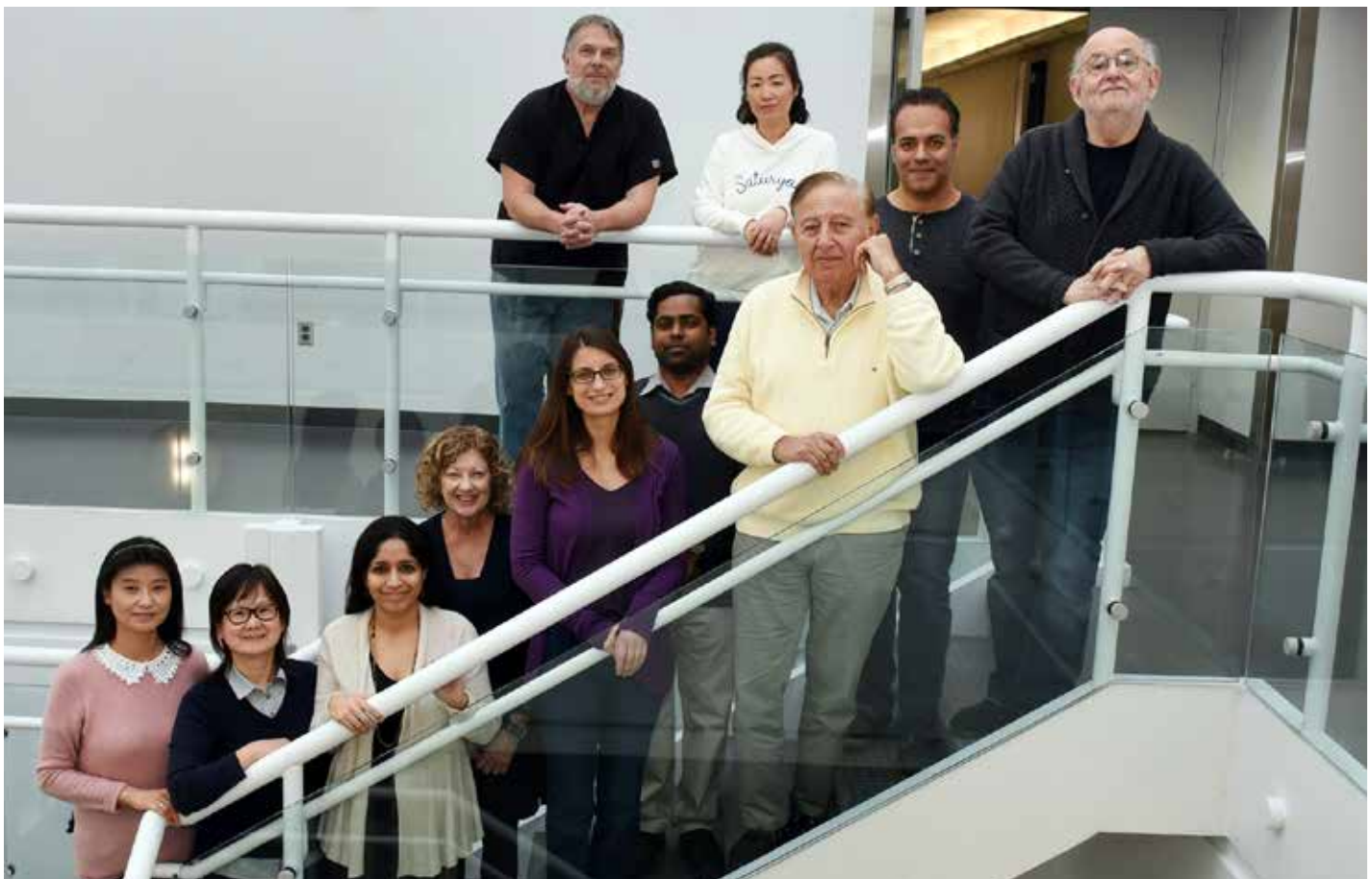
Institute of Human Virology (IHV) with the first publication of its immunochemical and physical chemical profile in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research, led by Dr. George Lewis, in collaboration with colleagues in the IHV Division of Clinical Care and Research, The Military HIV Research Program, and Profectus Biosciences. The early years of FLSC development were supported by National Institutes of Health (NIH) grants to Division of Vaccine Research Members including Dr. DeVico, Dr. Tim Fouts (now at ABL, Inc.), **Robert Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine and IHV Director, and Dr. Lewis. The FLSC vaccine concept was licensed to Wyeth Laboratories in 2002 and transferred to Profectus Biosciences in 2004. In 2007, The Bill and Melinda Gates Foundation awarded a large grant to Dr. Gallo (Principal Investigator) and his collaborators Drs. DeVico, Lewis, and Fouts to support the advanced preclinical development of FLSC. In April 2011, a consortium of funders led by The Bill and Melinda Gates Foundation and including the Military HIV Research Program as well as the National Institutes of Allergy and Infectious Disease (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 and collaborators 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 previously by Dr. Robert R. Redfield, who now the Center for Disease Control and Prevention (CDC) Director, and is currently led by **Shyam Kottilil, MBBS**,





PhD, Professor of Medicine and Director of the IHV Division of Clinical Care and Research. The Phase I clinical trial also involves Drs. DeVico, Gallo, and Lewis of the Division of Vaccine Research and **Joel Chua, MD**, Assistant Professor of Medicine, **Mohammad Sajadi, MD**, Associate Professor of Medicine, and **Charles Davis, MD**, Associate Professor of Medicine of the Division of Clinical Care and Research, as well as **Jennifer Schwartz, PhD** at Profectus Biosciences. Dr. Davis is the protocol chair of the Phase I clinical trial. In addition to the Phase I study, several Phase 1b studies are under development with our partners at The HIV Vaccine Trials Network, Duke Human Vaccine Research Institute, The Military HIV Research Program, Geovax, Inc., and Profectus Biosciences. This program represents the cumulative efforts of a large group of investigators who were brought together by Dr. Gallo to work on an HIV-1 vaccine when the IHV was established twenty years ago. It exemplifies the IHV's bench-to-bedside research model and represents the only HIV vaccine candidate to be clinically tested by 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. DeVico, **Roberta Kamin-Lewis, PhD**, Associate Professor of Microbiology and Immunology, **Marzena Pazgier, PhD**, Professor of Biochemistry and Molecular Biology, **Krishanu Ray, PhD**, Associate Professor of Biochemistry and Molecular Biology, and Dr. Sajadi. 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.



Members of the Division of Vaccine Research



Drs. DeVico, Lewis, Pazgier, and Ray are focusing on physicochemical and cell biology of Fc-mediated effector function for this program. These efforts are also new R01 grants awarded to Drs. Marzena Pazgier and Krishanu Ray as well as by a R01 and VA Merit Award to Dr. 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, IHV's 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. Anthony DeVico's group has developed new tools



Anthony DeVico, PhD

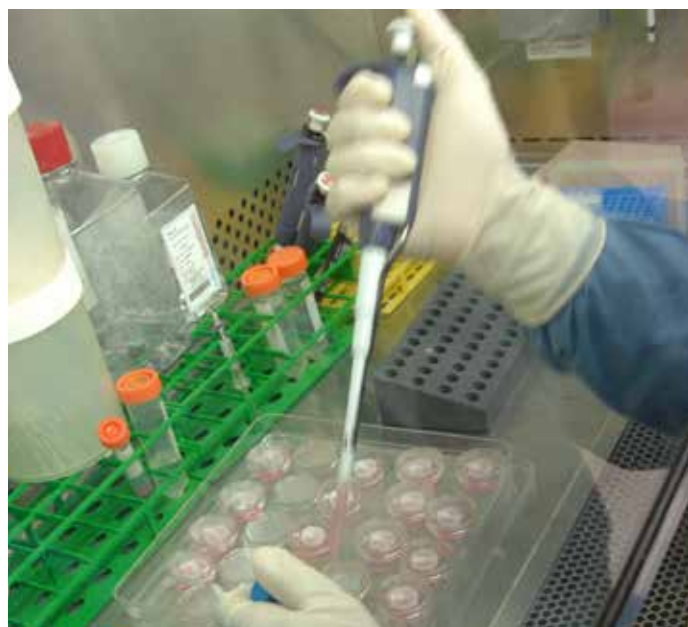
to characterize target epitopes on free virions, virions entering target cells, and virions budding from infected cells for each type of mAb. This work is leading to an increasingly clear picture of temporal epitope exposure during different phases of the viral replicative cycle that defines windows of opportunity for antibodies to interfere with infection by neutralization, Fc-


mediated effector function, or both. This work provides a virological and immunological explanation for the correlates of protection we have linked with the FLSC vaccine strategy. This research involves broad application of several cutting edge technologies, including Fluorescence Correlation Spectroscopy, Fluorescence Resonance Energy Transfer, confocal microscopy and super-resolution microscopy.

Dr. Lewis's group has developed passive immunization models to evaluate the mechanisms of antibody-mediated protection in vivo. His group is also developing quantitative in vitro models to determine the relative potencies of mAb candidates

to be evaluated in passive immunization studies in vivo. This work has led to the identification of "prozones" both in vitro and in vivo for Env specific Fc-mediated effector function. His group is also exploring the mechanism of a novel pattern of mAb synergy in ADCC involving an allosteric effect through which the binding of antigen to the Fab region of a mAb causes a distal conformational change in the Fc-region that leads to increased Fc-receptor binding.

Dr. Pazgier's group has produced the first atomic level epitope maps for the highly conserved Epitope Cluster A on gp120 that is a hotspot for antibody-cellular cytotoxicity (ADCC). This epitope cluster was implicated as a target of potentially protective antibodies in the RV144 vaccine trial and it is also a similar target for FLSC elicited antibodies in animal models. Dr. Pazgier's group has also developed a novel "inner-domain" protein that is stabilized in the CD4-bound conformation that expresses Cluster A epitopes with and without the co-expression of V1/V2 epitopes also implicated as protective sites in RV144. This construct has proven useful for additional crystallographic trials, epitope mapping of immune responses, and eliciting antibodies to epitopes of Cluster A in animal models. Dr. Pazgier's group recently identified a new gp120 structure, the 8-stranded β -sandwich, that is recognized by the C11-like monoclonal antibody N12-i2. This structure appears to be a new intermediate that is formed during HIV-1 entry into CD4+ cells. Dr. Pazgier recently received a second R01 grant in collaboration with institute investigators and **Andrés Finzi, PhD** in Montreal to develop antibody-drug conjugates for the HIV-1 cure initiative. She will continue these studies under the aegis of her R01 grants and the collaborative P01 grant.





Dr. Ray's group has adapted Fluorescence Correlation Spectroscopy and Fluorescence Resonance Energy Transfer to study the interaction of antibodies with Env on virions and in solution. These methods permit the solution-phase characterization of conformational effects that occur after antigen binding leading to increased binding to Fc-receptors. These methods permit co-localization of epitopes to single Env molecules on virions and in solution. He will continue these studies under the aegis R01 and the collaborative P01 grant.

Dr. Sajadi's group has developed new methods for the isolation of human mAbs based on a combination of proteomics and deep sequencing and is applying it to isolate new bnAbs from HIV-1 infected volunteers. Serum antibodies are fractionated by affinity chromatography and isoelectric focusing to identify fractions enriched for specific biological activities, including neutralization breadth, Fc-mediated effector function, or both. The enriched protein fractions are sequenced and the variable region sequences matched against DNA sequences obtained by deep sequencing from the same individual. His group has developed an algorithm to rapidly pair VH and VL sequences to reconstitute the specificity and biological activities found in the serum antibodies from HIV-1 infected volunteers. This novel approach has led to the identification of a number of new bnAbs that are under characterization. He will continue this work under the aegis of his VA merit award and R01 grants.

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

Vaccine Research Publications

- Xu D, Liao C, Zhang B, **Tolbert WD**, He W, Dai Z, Zhang W, Yuan W, **Pazgier M**, Liu J, Yu J, Sansonetti PJ, Bevins CL, Shao Y, Lu W. 2018. Human Enteric alpha-Defensin 5 Promotes Shigella Infection by Enhancing Bacterial Adhesion and Invasion. *Immunity* 48:1233-1244.e1237.
- Sajadi MM, Dashti A, Rikhtegaran Tehrani Z, **Tolbert WD**, Seaman MS, Ouyang X, Gohain N, **Pazgier M**, Kim D, Cavet G, Yared J, Redfield RR, **Lewis GK**, **DeVico AL**. 2018. Identification of Near-Pan-neutralizing Antibodies against HIV-1 by Deconvolution of Plasma Humoral Responses. *Cell* **173**:1783-1795.e1714.
- Pollara J, Orlandi C, Beck C, Edwards RW, Hu Y, Liu S, Wang S, Koup RA, Denny TN, Lu S, Tomaras GD, **DeVico A**, **Lewis GK**, Ferrari G. 2018. Application of area scaling analysis to identify natural killer cell and monocyte involvement in the GranToxiLux antibody dependent cell-mediated cytotoxicity assay. *Cytometry A* 93:436-447.
- Lewis GK**. 2018. High-Dimensional Immunology for Schizophrenia Research: A Short Perspective. *Schizophr Bull* 44:1005-1009.
- Gilchuk P, Kuzmina N, Ilinykh PA, Huang K, Gunn BM, Bryan A, Davidson E, Doranz BJ, Turner HL, Fusco ML, Bramble MS, Hoff NA, Binshtein E, Kose N, Flyak AI, **Flinko R**, **Orlandi C**, Carnahan R, Parrish EH, Sevy AM, Bombardi RG, Singh PK, Mukadi P, Muyembe-Tamfum JJ, Ohi MD, Saphire EO, **Lewis GK**, Alter G, Ward AB, Rimoin AW, Bukreyev A, Crowe JE, Jr. 2018. Multifunctional Pan-ebolavirus Antibody Recognizes a Site of Broad Vulnerability on the Ebolavirus Glycoprotein. *Immunity* 49:363-374.e310.
- Domi A, Feldmann F, Basu R, McCurley N, Shifflett K, Emanuel J, Hellerstein MS, Guirakhoo F, **Orlandi C**, **Flinko R**, **Lewis GK**, Hanley PW, Feldmann H, Robinson HL, Marzi A. 2018. A Single Dose of Modified Vaccinia Ankara expressing Ebola Virus Like Particles Protects Nonhuman Primates from Lethal Ebola Virus Challenge. *Sci Rep* 8:864.
- Tolbert WD**, Gohain N, Alsaifani N, Van V, **Orlandi C**, Ding S, Martin L, Finzi A, **Lewis GK**, **Ray K**, **Pazgier M**. 2017. Targeting the Late Stage of HIV-1 Entry for Antibody-Dependent Cellular Cytotoxicity: Structural Basis for Env Epitopes in the C11 Region. *Structure* **25**:1719-1731.e1714.
- Mengistu M, Tang AH, Foulke JS, Jr., Blanpied TA, Gonzalez MW, Spouge JL, **Gallo RC**, **Lewis GK**, **DeVico AL**. 2017. Patterns of conserved gp120 epitope presentation on attached HIV-1 virions. *Proc Natl Acad Sci U S A* **114**:E9893-e9902.
- Lewis GK**, **Pazgier M**, Evans DT, Ferrari G, Boumazos S, Parsons MS, Bernard NF, Finzi A. 2017. Beyond Viral Neutralization. *AIDS Res Hum Retroviruses* **33**:760-764.
- Lewis GK**, **Pazgier M**, **DeVico AL**. 2017. Survivors Remorse: antibody-mediated protection against HIV-1. *Immunol Rev* **275**:271-284.
- Gonzalez M, **DeVico AL**, Spouge JL. 2017. Conserved signatures indicate HIV-1 transmission is under strong selection and thus is not a "stochastic" process. *Retrovirology* **14**:13.
- Abdel-Moneim AS, Varma A, Pujol FH, **Lewis GK**, Paweska JT, Romalde JL, Soderlund-Venermo M, Moore MD, Nevels MM, Vakharia VN, Joshi V, Malik YS, Shi Z, Memish ZA. 2017. Launching a Global Network of Virologists: The World Society for Virology (WSV). *Intervirology* 60:276-277.

Clinical Care and Research



Shyam Kottilil, MBBS, PhD

Robert Redfield, MD, The Robert C. Gallo, MD Endowed Professor in Translational Medicine, Co-Founder and Associate Director of the Institute of Human Virology (IHV) and Director of the Division of Clinical Care and Research, was appointed by President Donald J. Trump as the Director of the Center for Disease Control and Prevention (CDC) in Atlanta on March 21, 2018. Following Dr. Redfield's departure, **Shyam Kottilil, MBBS, PhD**, Professor of Medicine and Head of the Clinical Care Unit in the IHV Division of Clinical Care and Research was appointed as Director of the IHV Division and Chief of the Division of Infectious Diseases in the University of Maryland School of Medicine (UMSOM) Department of Medicine.

Anthony Amoroso, MD, Associate Professor of Medicine and Associate Director of IHV's Division of Clinical Care and Research, was appointed as Head of Clinical Care within the IHV Division and Associate Chief of the Division of Infectious Diseases in the UMSOM



Anthony Amoroso, MD

Department of Medicine. The Division continues to strengthen all three of its key missions: clinical care, clinical research, and medical education, both in the Baltimore and Washington, DC metropolitan areas. To accomplish this mission, in the past year the Division assembled a team of 44 faculty and 77 support personnel, and secured 78 active grants and contracts.

The Division continues to enhance 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 Dr. Amoroso at the new clinical space on the Midtown Campus. Dr. Kottilil and his 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. Kottilil's areas of focus include hepatitis C and HBV therapeutics, HIV cure related research, and evaluation of new products for the treatment of hospitalized influenza. Also, of note this year was the completion of the Phase 1 Preventive HIV vaccine trial developed by IHV colleagues, Robert Gallo, MD, The Homer & Martha Gudelsky Distinguished

Professor in Medicine and Co-Founder and Director of the IHV, George Lewis, PhD, The Robert C. Gallo, MD Endowed Professor in Translational Medicine and Director of the IHV's Division of Vaccine Research, and Anthony DeVico, PhD, Professor of Medicine in the Division of Vaccine Research.

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

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 approximately 6,000 patients in IHV's Baltimore and DC clinics, the IHV continues to identify unmet patient needs and expand services to address them.

Over the past decade the IHV has assumed leadership for the Department of Medicine's Division of Infectious Disease. Combining the two divisions' clinical practices has allowed significant growth in clinical care and education. Importantly, its robust Infectious Disease fellowship (18 fellows) and 25 dedicated clinical Infectious Disease faculty allows the clinical program to support and sustain IHV's enormous international President's Emergence Plan For AIDS Relief (PEPFAR) programs and ambulatory HIV care programs, as well as grow 10 infectious disease services across two hospitals and seven ambulatory practices. The University of Maryland



Members of the Center for Infectious Diseases including from left Robyn Palmeiro, LCSW-C, Michael Obiefune, MBBS, a patient, and Neha Sheth-Pandit, PharmD, BCPS, AAHIVP

Medical Center is investing in two major programs, including a comprehensive cancer center and a solid organ transplant program. As the number of immunocompromised patients grows, IHV has developed and expanded three additional integrated consult services and three ambulatory clinics. One is integrated in the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center and the others are integrated into the Solid Organ Transplant Program. There are now eight faculty assigned to these programs with an associated research (HIV and HCV in solid organ transplantation) and an advanced educational component. Research cohorts have been developed within the solid organ transplant program around HIV and solid organ transplantation, and HCV therapy in these patients.

Growing Ambulatory Programs:

With diminishing Ryan White HIV/AIDS Program funding, a new partnership with the University of Maryland Medical System (UMMS) in ambulatory care has become important for sustaining and growing the Institute's HIV care and treatment programs. This IHV-UMMS partnership has been central

to the development of the Center for Infectious Diseases (CID) which was opened in late 2017, and located at the University of Maryland Midtown Campus. The overall strategy between the School of Medicine and UMMS is to create an ambulatory program targeted at complex chronic medical conditions that disproportionately affect the West Baltimore community. To this end, the state of Maryland is investing \$50 million in a new Midtown Campus Ambulatory Tower to house these new "Centers." The first steps in construction of the Ambulatory Tower began in February 2018. 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.

The CID, comprised of IHV faculty, combines three formerly separate IHV clinics (Evelyn Jordan Center, Family Health Center and the JACQUES Clinic) into one comprehensive ambulatory care program. In addition, post hospitalization infectious disease transitional care programs for patients with complicated infectious and IHV's HCV treatment clinic was added. The CID has already exceeded its planned

15,000 patient encounters for the year. **Sarah Schmalzle, MD**, Assistant Professor of Medicine, was promoted as Medical Director of the CID. Her major interests include HIV clinical outcomes and HIV prevention strategies. Under her leadership, multiple improvement projects have been initiated. Dr. Schmalzle's major ambulatory care initiative is providing services to patients through four "teams." Each patient is assigned to a specific provider, however, the patients are supported through a team comprised of a mid-level provider, a nurse case manager, social workers, and medical assistants. Team-based care increases access for patients while simultaneously shifts some burden from providers. The IHV's CID is piloting this strategy as the model for care of complex medical conditions for the other planned "Centers".

The JACQUES Initiative: With the creation of the CID, The JACQUES Initiative no longer provides primary HIV care, and is now focusing on its four major programs: Testing, Linkage to Care, Prevention, and Adherence Support. Formerly located in the IHV, the Adherence Support Program has moved to the Midtown Campus. The program, now called the Treatment Adherence Center (TAC) is integrated to support the CID's HIV patients. A collaboration with School of Pharmacy faculty advances TAC's services and integration. Through a CDC grant, The JACQUES Initiative recently began a partnership with the Baltimore City Health Department to implement a comprehensive pre-exposure treatment program for men who have sex with men (MSM) under the leadership of **Patrick Ryscavage, MD**, Assistant Professor of Medicine and the JACQUES Initiative Medical Director. A new initiative led by **Jamie Mignano, PhD(c), MSN, MPH, RN**, Executive Director of The JACQUES Initiative, is the establishment of The Journey Center



JACQUES Initiative staff collaborate with the UMMC Midtown Community Health Education Center to deliver health screenings through the UMMC outreach van

located at 880 Park Avenue. It is the hub for expanding community health and supportive services. The overall goal of the Center is to be an internationally recognized, community-based health program. The Center will offer education, support groups, job and housing services, on-site screening tests, counseling and linkage to health services.

Expansion beyond Baltimore City: The University of Maryland Medical Center (UMMC) has become a regional referral center where many patients receive complex surgical procedures in Baltimore City though they reside in Southern and Eastern Maryland. To accommodate growing patient populations beyond the city, a suburban practice was established in fall of 2017 in Columbia, Maryland. The initial practice focus is on complicated post-surgical infections, and a Lyme disease clinic was added as a service to the community. Partnering with other UMMS hospitals within the state are in an initial planning phase. The first partnership includes Charles Country Regional Medical Center to utilize an innovative “E consultation” method to reach this rural hospital in a physician scarce location.

Financial Health Clinical Program: FY2018 is on target to exceed FY2017 combined charges for the inpatient and ambulatory programs by an additional \$900,000. The combined clinical practices charged just over \$5,000,000 and collected \$2,439,000 in FY 2017. After salary costs, administrative costs, billing costs, and operational cost the clinical practice realized a revenue that exceeded costs and is on target for the same in FY2018.

IHV Washington, DC-Based Clinical and Research Programs:

Since 2015, IHV’s clinical program continues its work in Washington, DC. To date, over 1,800 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. **Sarah Kattakuzhy, MD**, Assistant Professor of Medicine, **Elana Rosenthal, MD**, Assistant Professor of Medicine, and **Poonam Mathur DO**, Assistant Professor of Medicine, continue to provide the day-to-day leadership and clinical management, guided by Dr. Kottlilil. During this year, the team established a hepatitis C standard of care clinic in a harm-reduction drop-in center in northeast Washington, DC whose clients do not typically access health care in traditional health care settings. The team also began providing treatment for opioid-use disorder in conjunction with HCV treatment.

Clinical Programs in Chronic HBV Infection: The Division’s Hepatitis B and C treatment programs continue to expand under **Lydia Tang, MB ChB**, Assistant Professor of Medicine and **Eleanor Wilson, MD**, Assistant Professor of Medicine, located at the Downtown and Midtown campuses, and **Angie Price, NP**, at the Baltimore Veterans Hospital.

Chronic hepatitis B infection in the Baltimore/District of Columbia metropolitan area is mainly defined by a patient population that is not yet engaged in clinical care due to socioeconomic background. The IHV has partnered with the Hepatitis B Initiative of Washington, D.C. (HBI-DC), and the Torture Abolition Survivors Support Coalition (TASSC). Over 5,700 people in the DC-metropolitan area have been screened by HBI-DC, with prevalence rates of 6.4% for hepatitis B. Those who tested positive are linked to care and subsequently referred for further evaluation and treatment. In collaboration, the IHV has established a clinical program to screen, link, and treat patients with chronic hepatitis B infection, and conduct research on immunopathogenesis of HBV persistence aimed to develop therapeutics targeting the cure of HBV chronic infection. Dr. Tang has received three grants to support the HBV clinical research program (TEMUL from Gilead Sciences, Roche Laboratories, TRUCULTURE and FOCUS grant from Gilead Sciences).

CLINICAL RESEARCH

Clinical Research Unit (CRU): The IHV CRU has recently expanded with **Jennifer Husson, MD**, Assistant Professor of Medicine, and **Joel Chua, MD**, Assistant Professor of Medicine, joining the team. The multidisciplinary CRU team is comprised of two nurse practitioners, three nurse coordinators, a pharmacist, a phlebotomist, two regulatory specialists, four study/research coordinators, and three



Members of the Clinical Research Unit

laboratory technicians. During the past year, the CRU has continued its significant expansion in novel clinical trials (27 clinical trials, of which 18 are investigator-initiated, and 9 are industry-sponsored) in the management of viral hepatitis and HIV infections. The CRU aims to support the IHV's goal of advancing research in the field of chronic viral diseases.

FLSC Vaccine Trial: This 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, led by **Charles Davis, MD**, Associate Professor of Medicine and Dr. Chua. This preventive FLSC vaccine was developed, as mentioned, by IHV scientists under the leadership of Dr. Robert Gallo, Dr. George Lewis and Dr. Anthony DeVico in the IHV Division of Vaccine Research. This trial represents true translational impact of IHV on meeting the needs of HIV-infected individuals. Healthy volunteers of 18-45 years of age, and those who have never previously participated in an HIV vaccine trial were immunized with the FLSC vaccine, and this initial study is now completed.

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

Over the past year, Dr. Kottilil established collaborations with the National Institute of Allergy and Infectious Diseases

(NIAID) intramural program of the National Institutes of Health (NIH) through Anthony Fauci, MD, Director of NIAID and Tae-Wook Chun, PhD, Chief, HIV Immunovirology Unit. Thus, NIAID clinical trials are being recruited at the IHV CRU. IHV 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 (Henry Masur, MD, Chief, Critical Care Medicine Department, NIH). More recently, Adriana Marques, MD (Chief, Clinical Studies Unit, Laboratory of Clinical Immunology and Microbiology) from NIAID has established a collaborative Lyme disease program at the University of Maryland's Waterloo infectious diseases practice. These endeavors are both unique and expand IHV research capabilities.

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



ASCEND Study: Despite the rapid development of highly effective therapy for hepatitis C, a major restriction of treatment expansion remains the lack of skilled community-based providers available to treat HCV infections. Dr. Kattakuzhy conducted the ASCEND trial in community clinics in DC. 92.1% of patients receiving care from specialists, 96.7% of patients receiving care from primary care physicians, and 94.9% of patients receiving care from nurse practitioners were cured. This manuscript was recently published as a major article in the *Annals of Intern Med* (PMID: 28785771). This research has the potential to be a genuine game-changer for global hepatitis C therapy (funded by NIAID, Gilead Sciences, Inc.). After the successful completion of this trial, the ASCEND model is being investigated in international settings in Rwanda (**David Riedel, MD, MPH**, Assistant Professor of Medicine; Gilead Grants) and in two sites, Mumbai and Imphal in India (Gilead Investigator-initiated grants).

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

Renal Transplant Merck Trial: Drs. Jennifer Husson and Anthony Amoroso instituted a practice to manage hepatitis C and HIV in patients undergoing renal transplant. Subsequently, Dr. Husson was awarded an investigator-initiated grant from Merck to evaluate clinical and immunologic outcomes of treating HCV using Zepatier, before or after renal transplantation.

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

MAVERIC: Dr. Tang conducted an interventional clinical trial using Maraviroc, a CCR5 antagonist in HIV and HCV co-infected subjects who are being followed for progression of liver fibrosis to build upon their existing understanding of CCR5 antagonism in-vivo on the hepatitis C virus, and liver fibrosis in this recently approved unique study, supported by ViiV Pharmaceuticals

GRAVITY [Geomapping Resistance and Viral Transmission in Risky Populations]: The goal of GRAVITY is to identify newly acquired cases of HIV and HCV in high risk populations, and to better understand characteristics associated with viral transmission in Washington, DC. Drs. Rosenthal and Kattakuzhy have obtained NIH and Gilead Sciences funding to implement HIV and HCV screening programs in those who inject drugs, men who have sex with men, transgender individuals, and sex workers. 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. Rosenthal leads this study funded by Gilead research grant for 100 courses of HCV therapy (sofosbuvir/velapatasvir) 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 the National Institute of Drug Abuse to use their ecological momentary assessment (EMA) technology to assess cravings and adherence.

CHROME [Cardiac MRI Study]: A collaborative study to evaluate cardiac MRI changes in HIV and HIV/HCV infected patients. This study is funded through a Merck investigator initiated grant and the National Institutes of Health Bench-to-Bedside Award.

CoCrystal: Dr. Chua 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/velapatasvir in patients with HCV genotype 1. The primary goal is to find a regimen with potential for shorter duration therapy for chronic hepatitis C.

HEPATITIS B CLINICAL TRIAL PROGRAM

TEMUL (Tenofovir Alafenamide for HBV—a Longitudinal study): Tenofovir Alafenamide (TAF), a pro drug of tenofovir was developed which has shown similar safety and efficacy to TDF in chronic hepatitis B patients. TEMUL is a study being led by Dr. Lydia Tang aimed at establishing a real-life cohort of urban patients with chronic hepatitis B who initiated on TAF.

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



HOPE in Action: Drs. Anthony Amoroso and Jennifer Husson, along with their 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. The study team successfully completed its first transplant in June 2018.

HIVTR CCR5 Clinical Trial: Dr. 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.

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

APOSTLE: Dr. Chua is principal investigator for this investigator-initiated study with Gilead, a phase 2 open-label study of ledipasvir/sofosbuvir for 12 weeks in patients with hepatitis B infection aimed at evaluating whether ledipasvir/sofosbuvir has an effect on hepatitis B.

TLR-8: Dr. Tang and her team are conducting a 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.

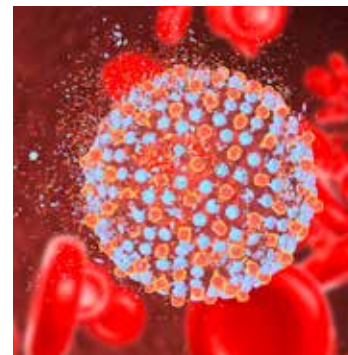
CLINICAL CARE AND RESEARCH DIVISION LABORATORY BASED PROGRAMS

The Kottlil Laboratory actively pursues two targeted research programs: "A Functional Cure Approach to Chronic Hepatitis B infection" and "Hepatitis C Immunology Program." Although



Shyam Kottlil, MBBS, PhD and Angie Price, MSN, CRNP

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. Their ongoing efforts focus on developing novel strategies to achieve sustained cure, or elimination of HBV. These novel approaches include targeting the viral, and or host, factors required for viral persistence, and novel immune-based therapies, including therapeutic vaccines. These efforts are led by **Bhawna Poonia, PhD**, Assistant Professor of Medicine, and Dr. Kottlil, and are focused on delineating intrahepatic and peripheral immune responses to HBV antigens that correlates with development of protective immunity. Three separate projects are presently funded by research grants from Arbutus Pharmaceuticals, and from Gilead Sciences.

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 DAA therapy. His group recently demonstrated that enhancement of intrahepatic type I interferon expression in patients achieves sustained virologic response (SVR) with DAA therapy. Furthermore, adaptive immune responses, precisely interferon gamma producing T cells to HCV antigens, were augmented by DAA therapy in patients with SVR, suggesting a role for innate and adaptive immune responses in HCV clearance with non-immune based DAA therapy. Using the samples collected from various clinical trials, Drs. Kottlil and Poonia continue their investigations into determinants of SVR with short duration DAA therapy. With ongoing follow up of a large cohort of patients, they continue to evaluate the persistence of adaptive immune responses to HCV in patients who achieve SVR to determine long-term protection for reinfection in patients with continued high-risk behavior. These projects are funded by three investigator initiated clinical research studies by Gilead Sciences.

Dr. Poonia is in her second year of an NIH R01 grant from National Institute of Drug Abuse to study the immune correlates of protection of reinfection among people who are



Members of the Clinical Laboratory Group

marginalized at the highest risk of acquisition of HCV namely, those with HIV infection and people who inject drugs.

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. **Alonso Heredia, PhD**, Assistant Professor of Medicine, and his lab are investigating cellular targets that may help control both HIV and malignancy in patients.

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

They also showed that dual targeting of mTORC-1 and -2 with catalytic inhibitor INK-128 reduces CCR5 (and thereby virus entry), and also provirus transcription. They showed that INK-128 reduces HIV replication in humanized mice in the absence of toxicity. They are currently evaluating the activity of mTORC-1/2 inhibitors against cancer because the mTOR pathway is often upregulated in cancers common in HIV patients, such as cancers of lung and liver. Their preliminary studies demonstrate that targeting of mTORC-1/2 inhibits the growth of lung cancer and hepatocellular carcinoma tumor xenografts in mice, suggesting these agents may help control both HIV and comorbid cancers in the HIV population.

Another area of active investigation is the targeting of cellular Cyclin-dependent kinase (CDK-9), a cofactor of the HIV Tat protein. They have previously demonstrated that pharmacological inhibition of CDK9 with Indirubin 3'-monoxime (IM) inhibits HIV transcription both *in vitro* and *in vivo* in humanized mice. More recently, they have demonstrated that targeting of CDK9 with IM inhibits HIV during the chronic phase of the disease in the absence of toxicity. Because CDK9 can be dysregulated in cancer cells, they are also pursuing targeting of CDK9 as a potential therapy against both HIV and cancer. They suggest that



targeting of host factors important for HIV replication and for rapid growth of tumor cells may provide novel therapies against both diseases in the growing population of HIV patients with malignancy. They are evaluating an CDK9 inhibitor currently in cancer clinical trials for activity against both HIV and cancer in humanized mice.

Because HIV-infected patients with cancer undergo treatments with both chemotherapy and cART, they are also assessing the impact of conventional cytotoxic chemotherapy on the antiviral activity of cART. Currently there are no guidelines for the use of cART in cancer patients treated with chemotherapy. Their data demonstrate that approved cytotoxic drugs have disparate effects on the antiviral activity of antiretrovirals, with some cytotoxic drugs enhancing while other suppressing antiretrovirals. These data suggest that some combinations of cART and chemotherapy have reduced antiviral activity, which could increase the risk of treatment failure and increase the size of the HIV reservoir.

Mohammad Sajadi, MD, Associate Professor of Medicine, and his lab are currently focused on humoral immunity in HIV-infected individuals with broadly neutralizing antibodies. He works closely with Drs. Lewis and DeVico in the Vaccine Research Division. 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 has developed a novel method to sequence antibodies directly from blood, and is using this technique to study the circulating antibodies that constitute the broad neutralization response in rare individuals with HIV. His lab isolated several broad neutralizing antibodies that are among the most potent and broad described to date (recently published in *Cell*). Dr. Sajadi also oversees the NVS cohort, HIV-1 infected individuals who control infection without antiretrovirals.

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

Disease in HIV-Infected Patients", and also receives support through Dr. Robert Weiss' NIH R01 "Inflammation and Coronary Endothelial Dysfunction in HIV".

The laboratory of **Nicholas Stamatos, MD**, Assistant Professor of Medicine, includes research focused on understanding how modulation of the carbohydrate content of cell surface proteins influences the functional capacity of cells of the immune system. 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. They expect to demonstrate that controlling the extent of polysialylation of specific glycoconjugates has therapeutic value in various disease states of inflammation and infection. Their laboratory was recently awarded an R01 from the National Institute of Allergy and Infectious Diseases (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 human immunodeficiency virus (HIV) envelop proteins, relatively little is known about how glycosylation of proteins on the surface of permissive lymphocytes affects infection. They 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. They 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 their 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 identifying proteins whose functions were not previously appreciated on immune cells. They found that dendritic cells express semaphorins cause F-actin reorganization and promote chemotaxis. Thus, their studies have 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. They expect that the additional polysialylated proteins that they identify on immune cells will have equally significant roles in cell function.

Clinical Care and Research Publications

- Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, Vierling JM, Tran TT, Pianko S, Bansal MB, de Lédinghen V, Hyland RH, Stamm LM, Dvory-Sobol H, Svarovskaia E, Zhang J, Huang KC, Subramanian GM, Brainard DM, McHutchison JG, Verna EC, Buggisch P, Landis CS, Younes ZH, Curry MP, Strasser SI, Schiff ER, Reddy KR, Manns MP, Kowdley KV, Zeuzem S; POLARIS-1 and POLARIS-4 Investigators (**Kottitil, S**). Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med*. 2017 Jun 1;376(22):2134-2146.
- O'Brien TR, **Kottitil S**, Feld JJ, Pfeiffer RM. Race or Genetic Makeup for HCV Treatment Decisions? *Hepatology*. 2017 Jun;65(6):2124-2125.
- Shubin Z, Li W, **Poonia B**, Ferrari G, LaBranche C, Montefiori D, Zhu X, Pauza CD. An HIV Envelope gp120-Fc Fusion Protein Elicits Effector Antibody Responses in Rhesus Macaques. *Clin Vaccine Immunol*. 2017 Jun 5;24(6).
- Chua JV, Kottitil S**. Are we nearing the end in the fight against hepatitis C? *Expert Rev Gastroenterol Hepatol*. 2017 Jun;11(6):499-500.
- Wyles D, Brau N, **Kottitil S**, Daar E, Ruane P, Workowski K, Luetkemeyer A, Adeyemi O, Doehle B, Huang KC, Osinusi A, McNally J, Brainard D, McHutchison JG, Naggie S, Sulkowski M. for the ASTRAL-5 investigators. Sofosbuvir and Velpatasvir for the Treatment of HCV in Patients Coinfected with HIV-1: an Open-Label, Phase 3 Study. *Clin Infect Dis*. 2017 Jul 1;65(1):6-12.
- Nguyen T, Guedj J, Uprichard S, Kohli A, **Kottitil S** and Perelson A. The paradox of highly effective sofosbuvir-based combination therapy despite slow viral decline: can we still rely on viral kinetics. *Sci Reports*. 2017 Aug 31;7(1):10233.
- Bagchi S, Burrowes S, Fantry LE, Hossain MB, Tollera GH, **Kottitil S**, Pauza D, Miller M, Baumgarten M, Redfield RR. Factors Associated with High Cardiovascular Risk in a Primarily African-American, Urban HIV-Infected Population *SAGE Open Med*. 2017 Aug 10;5:2050312117725644
- Heredia, A.**, S. Hassounah, **S. Medina-Moreno**, J. C. Zapata, N. M. Le, Y. Han, J. S. Foulke, Jr., C. Davis, J. Bryant, R. R. Redfield, and M. A. Wainberg. Monotherapy with either dolutegravir or raltegravir fails to durably suppress HIV viraemia in humanized mice. *The Journal of antimicrobial chemotherapy*. 2017 72:2570-2573.
- Shrivastava S, Wilson, E, Poonia, B, Tang L**, Osinusi A, Kohli A, **Kottitil, S**. Augmentation of HCV specific immunity and SVR. *J. V Hepat*. 2017 Sep;24(9):742-749.
- Meissner EG, Kohli A, Higgins J, Lee Y-J, Prokunina O, Wu D, Orr C, Masur H and **Kottitil S**. Rapid Changes in Peripheral Lymphocyte Concentrations During Interferon-free Treatment of Chronic HCV Infection. *Heptol Comm*. 2017 Sep;1(7):586-594.
- Kattakuzhy S, Gross C, Emmanuel B**, Teferi G, Jenkins V, **Silk R**, Akoth E, Thomas A, Ahmed C, Espinosa M, **Price A, Rosenthal E, Tang L, Wilson E**, Bentzen S, Masur H, **Kottitil S**; and the ASCEND Providers. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. *Ann Intern Med*. 2017 Sep 5;167(5):311-318.
- Mwumvaneza Mutagoma, Helene Balisanga, Samuel S. Malamba, Dieudonné Sebuho, Eric Remera, **David J. Riedel**, Steve Kanters and Sabin Nsanzimana. Hepatitis B virus and HIV co-infection among pregnant women in Rwanda. *BMC Infectious Diseases BMC Series*. 2017 Sep 11; 17:618.
- Mathur P**, Comstock E, McSweeney E, Mercer N, Kumar NS, **Kottitil S**. A pilot study to expand treatment of chronic hepatitis C in resource-limited settings. *Antiviral Research*. 2017 Oct;146:184-190.
- Kimberly L. Levinson, **David J. Riedel**, Lauren S. Ojalvo, Wesley Chan, Ana M. Angarita, Amanda N. Fader, and Anne F. Rositch. Gynecologic cancer in HIV-infected women: treatment and outcomes in a multi-institutional cohort. *AIDS*. 2017 Oct; 32:171-177.
- Emmanuel B, Wilson EM, O'Brien T, Kottitil S**, Lau G. Shortening the duration of therapy for chronic hepatitis C infection. *The Lancet Gastro & Hepatol*. 2017 Nov;2(11):832-836. doi: 10.1016/S2468-1253(17)30053-5.
- Husson JS**, Ravichandran B, Jonche S, **Kottitil S, Wilson E**. Eight Weeks of Ledipasvir/Sofosbuvir in Kidney Transplant Recipients With Hepatitis C Genotype 1 Infection. *Transplant Direct*. 2017 Nov 3;3(12):e229.
- Abutaleb A, and **Kottitil S**. Vedroprevir in the Management of Hepatitis C Infection. *Exp Opin on Invest Drugs*. 2017 Dec;26(12):1399-1402.
- O'Brien TR, **Kottitil S**, Pfeiffer RM. *IFNL4* Genotype is Associated with Relapse for 8-Week Treatment with Sofosbuvir, Velpatasvir and Voxilaprevir. *Gastroenterology*. 2017 Dec;153(6):1694-1695.
- Chaudhury C, Sheehan J, Chairez C, Akoth E, **Gross C, Silk R, Kattakuzhy S, Rosenthal E, Kottitil S**, Masur H, and Hadigan C. No Improvement in Hemoglobin A1c following Hepatitis C Viral Clearance in Patients with and without HIV Co-infection. *J. Infect Dis*. 2017 Dec 27;217(1):47-50.
- Comstock E, Kim C-W, Murphy AA, Emmanuel B, Zhang X, Sneller MC, Poonia B and Kottitil S. Transcriptional profiling of PBMCS unravels B cell mediated immunologic imprints in HCV vasculitis. *PLoS ONE*. 2017 12(12):e0188314.
- Medina-Moreno, S.**, T Dowling, J Zapata, N. M. Le, E. Sausville, J. Bryant, R. Redfield, and **A. Heredia**. Targeting of CDK9 with indirubin 3'-monoxime safely and durably reduces HIV viremia in chronically infected humanized mice. *PloS one*. 2017 12:e0183425.
- Heil EL, Pinales L, Mathur P, Morgan DJ, Harris AD, Srinivasan A, Tham, KA; CDC Prevention Epicen Accuracy of Provider-Selected Indications for Antibiotic Orders. *Infect Control Hosp Epidemiol*. 2018 Jan;39(1):111-113.
- Tang L**, Parker A, Flores Y, Dellario M, Dockson C, **Amoroso A, Kottitil S. and Wilson E**. Treatment of hepatitis C with 8 weeks of ledipasvir/sofosbuvir: highly effective in a predominantly black male patient population. *J. Vir Hep*. 2018 Feb;25(2):205-208.

Rosenthal E, Kattakuzhy S and Kottlilil S. Time to End Treatment Restrictions for People With Hepatitis Who Inject drugs. *Lancet Gastroenterol Hepatol.* 2018 Mar;3(3):142-143.

Younossi Z, Stepanova M, Sulkowski M, Wyles D, **Kottlilil S**, Hunt S. The Sofosbuvir and Velpatasvir Regimen is Associated with High Efficacy and Improvement of Patient-Reported Outcomes in Patients Co-infected with Hepatitis C and Human Immunodeficiency Virus: The Data from ASTRAL-5 Study. *Liver International.* 2018 37(12):1796-1804.

Kottlilil S. Shortening Treatment for Hepatitis C Virus Infection. *Gastroenterol Hepatol (N Y).* 2018 Mar;14(3):186-188.

Mücke MM, Backus LI, Mücke VT, Coppola N, Preda CM, Yeh ML, **Tang LSY**, Belperio PS, **Wilson EM**, Yu ML, Zeuzem S, Herrmann E, Vermehren J. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2018 Mar;3(3):172-180.

Sajadi MM, Chen W, Dilsizian V. Targeted Bacteria-Specific 18F-Fluoro-Maltohexaose but Not FDG PET Distinguishes Infection From Inflammation. *JACC Cardiovasc Imaging.* 2018 Apr 13. pii: S1936-878X(18)30283-3.

Mathur P, Emmanuel B, Sneller MC, Zhang X, and **Poonia B, Kottlilil S.** Recovery of Hepatitis C-Specific T cell response after Rituximab therapy in hepatitis C Mixed Cryoglobulinemic vasculitis. *J Med Virol.* 2018 May;90(5):936-941.

Tang L, Covert E, Wilson E, Kottlilil S. Treatment of Hepatitis B infection: A Systematic Review. *JAMA.* 2018 May 1;319(17):1802-1813.

Abutaleb A, **Kottlilil S, Wilson E.** Glecaprevir/pibrentasvir expands reach while reducing cost and duration of hepatitis C virus therapy. *Hepatol Intl.* 2018 May;12(3):214-222.

Sajadi MM, Dashti A, Rikhtegaran Tehrani Z, Tolbert WD, Seaman MS, Ouyang X, Gohain N, Pazgier M, Kim D, Cavet G, Yared J, Redfield RR, Lewis GK, DeVico AL. Identification of Near-Pan-neutralizing Antibodies against HIV-1 by Deconvolution of Plasma Humoral Responses. *Cell.* 2018 Jun 14;173(7):1783-1795.e14.

Mathur P, Comstock E, Makuza JD, Emmanuel B, Sebeza J, Kiromera A, **Wilson E, Kattakuzhy S, Nelson A, Kottlilil S, Riedel DJ.** Implementation of a Unique Hepatitis C Care Continuum Model in Rwanda. *J Public Health (Oxf).* 2018 Jul 6.

Katherine A. Scilla, Dan P. Zandberg, Søren M. Bentzen, Candace Mainor, Jonathon Heath, Olga B. Ioffe, Ashley L. Cellini, Martin J. Edelman, **David J. Riedel**, Josephine L. Feliciano. Case-control study of PD-1, PD-L1 and B7-H3 expression in lung cancer patients with and without human immunodeficiency virus (HIV) infection. *Lung Cancer.* 123 (2018) 87–90.

David J Riedel, Kristen A Stafford, Peter Memiah, Modupe Coker, Cyprien Baribwira, Jackson Sebez, Eva Karorero, Sabin Nsanzimana, Fernando Morales, and Robert R Redfield. Patient-level outcomes and virologic suppression rates in HIV-infected patients receiving antiretroviral therapy in Rwanda. *International Journal of STD & AIDS.* 2018 Aug;29(9):861-872.

Trehanpati N, Khanam A, Hissar S, Khosla R, David P, Sehgal R, Ashish Kumar¹, Prashar A, Bhardwaj A, **Kottlilil S**, Sarin SK. Sequential Therapy with Tenofovir plus Peg Interferon reduces T cell exhaustion and Improves Dendritic Cell phenotype and function by mir-155 regulation compared to Tenofovir monotherapy in chronic HBV patients. *J Clin & Cell Immunol.* 2018 (in press).

Ridden L, **Kottlilil S. and Chua J.** Treatment of hepatitis C in HIV infected patients. *Internal Medicine reviews.* 2018 (in press).

Shenderov M, **Nelson A, Hoffmann J, Talwani R, Kottlilil S.** A novel LIPS assay to detect HBV serologies. *Future Vir.* 2018 (in press).

Bon D, Kohli A, Osinusi A, **Nelson A, Kottlilil S**, and Herrmann E. A mathematical model of HCV decay kinetics in patients receiving sofosbuvir and ledipasvir *PLoS Comp Biol.* (2018 (in press).

Khanam A and **Kottlilil S.** Defective innate immunity in acute-on chronic liver failure: immunotargets for therapeutics. *Gut.* 2018 (in press).

Wilson E, Kottlilil S and Poonia B. "Can directly acting antiviral regimens against hepatitis C induce host immune responses' *Future Virology.* 2018 (in press).

Mathur P, Kottlilil S. and Wilson E. Voseyi: A Salvage regimen for HCV 2018, *Hep Intern.* 2018 (in press).

Narayan, S, **Kottlilil S, Chua J.** The challenges in the management of HIV/HBV Coinfection. *Medical Research Archives.* 2018 (in press).

Ayithan N, Ghosh A, Lau A, **Kottlilil S**, Gaggar A, **Poonia B.** TLR8 agonism enhances HBV specific antiviral humoral immunity. *Hepatology.* 2018 (in press).

Ghosh A, **Kottlilil S, Poonia B.** Incomplete recovery of GD T cells in HCV patients after SVR. *Hepatology.* 2018 (in press).

Shrivastava S, Ward H, Mondal RK, Bhatta M, Sherman KE, **Kottlilil S, Tang L.** CCR5+ T cells homing to the liver exhibit inflammatory and profibrogenic signatures in chronic HIV/HCV infected subjects. *Hepatology.* 2018 (in press).

Narayan S., Abutalib A, **Kottlilil S.** and Sherman KE. Mechanisms for Chronicity in HEV Infection. *Lancet Gastro & Hep.* 2018 (in press).

Agarwal T, Gaggar A, Subramanian GM, **Kottlilil S**, Chwodhury A, Rao PNM Guo X, Know SJ, Mchutchison JG, Shah S, Sarin SK, and Trehanpati N. PNPLA3 polymorphisms Are Associated With Elevated Serum ALT Levels Among HCV Genotype 3 Infected Patients in India. *Hepatology International.* 2018 (in press).

Mee T, Chaudhury C, Chairez C, McLaughlin M, **Silk R, Gross C, Kattakuzhy S, Rosenthal E, Kottlilil S**, Masur H, Stanley T, Hadigan C Testosterone in Men with Chronic Hepatitis C Infection and After Hepatitis C Viral Clearance. *Hepatology.* 2018 (in press).

Epidemiology and Prevention



Man Charurat, PhD, MHS

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, had another successful year conducting research and population-based surveys to guide and develop effective intervention programs to reduce HIV and cancer disease burden. The Division also trained local scientists in implementation and dissemination research and research ethics and maintained robust public health implementation and research programs with IHV-Nigeria. After 15 years of concentrated effort building sustainable research, training and public health programs in Nigeria, the 11 Division faculty have 23 active federal awards totaling \$121M annually. Likewise, the Division continues to pave the way scientifically with 46 peer reviewed publications in FY18. Below are a few highlights from the year.

RESEARCH AND POPULATION-BASED SURVEYS

Nigeria AIDS Indicator and Impact Survey (NAIIS)

Implemented by Dr. Charurat and **Gambo Aliyu, MBBS, PhD** Assistant Professor of Epidemiology and Public Health, the 2018 Nigeria AIDS Indicator and Impact Survey (NAIIS), is the largest HIV survey ever conducted in a single country. The NAIIS objectives are to characterize HIV incidence, prevalence, viral load suppression, CD4 T-cell distribution, and risk behaviors and to describe uptake of HIV prevention, care, and treatment services at the national and sub-national level. Secondary objectives include prevalence estimates for hepatitis B virus (HBV), hepatitis C virus (HCV) infections, and HBV/HIV and HCV/HIV co-infections. Spanning all regions of Nigeria, the household-based survey employs a two-stage clustering method for sampling that randomly selects a total of 90,675 households from 3,551 enumeration areas. Overall sample size is 172,603 individuals, qualifying NAIIS as the largest household-based survey to

date. Approximately 160,000 adults and adolescents have been reached since the survey's inauguration. To improve efficiency and data quality, the Division is pioneering the use of CSPro in the Population-based HIV Impact Assessment, in which a real-time remote monitoring Dashboard was developed. To identify, assess, and equip 98 satellite laboratories across Nigeria and train

over 1,900 field team members in just four months, the Division relied on pre-existing collaborations with the University of Maryland, Baltimore's (UMB) Maryland Global Initiatives Corporation (MGIC) and Institute of Human Virology-Nigeria (IHV-Nigeria) to provide a core of local personnel and infrastructure that has been integral to the success of NAIIS.



NAIIS Laboratory Data Management System planning meeting with Gamel Aliyu, MBBS, PhD and Alash'le Abimiku, MSc, PhD



President of Nigeria's inauguration of the NAIS project in Nigeria

Key Population Size Estimation in Nigeria

The Key Population Size Estimation is an activity of the SHIELD grant. The \$6.4M Center for Disease Control and Prevention (CDC) grant, "Improving the Quality of HIV Service Delivery and Other Priority Public Health Interventions (SHIELD)" led by Dr. Charurat and **Bola Gobir, MBBS**, Assistant Professor of Medicine in IHV's Center of International Health, Education, and Biosecurity (CIHEB), supports the President's Emergency Plan For AIDS Relief (PEPFAR) Nigeria program. The program improves the quality of HIV service delivery through standardized monitoring and evaluation (M&E) processes data quality assessment and improvement (DQA&I), strengthens the Health Management Information System (HMIS) and conducts key population size estimations and outcome evaluation studies. The Key Population Size Estimation is in six states in Nigeria (Lagos, Benue, Nasarawa, Cross River, Rivers, and Akwa Ibom, and the Federal Capital Territory). These states were purposely selected because of current broad HIV programming experiences, evidence from literature, data from key informants, and their

characterization as cosmopolitan and commercial centers. The states also pulled together people from the three major ethnic groups in Nigeria and different economic, environmental and social strata. Since the six states are part of the PEPFAR programming network in Nigeria, the size estimation will help to determine the denominator base for programming and policy. Multiple-source capture-recapture will be used to estimate the size of Female Sex Workers, Men having Sex with Men (MSM) and People with Injection Drugs. The survey will use combination of both direct (venue-based captures, e.g. brothels) and indirect data sources (non-venue-based captures, e.g. online networks) to estimate the population size of all Key Population sub-groups.

Microbiome Affects Risk of Development and Growth in HIV-exposed but Uninfected Infants

The Microbiome Affects Risk of Development and Growth in HIV-exposed but Uninfected Infants in Nigeria (MARGIN) study, directed by Dr. Charurat and supported by **Jibreel Jumare, MBBS, PhD**, Research Associate of Epidemiology and Public Health, is a longitudinal study looking at the role of microbiome in growth and development of HIV-exposed uninfected children. The study, in the final year, enrolled 150 HIV-infected and 150 uninfected pregnant women at the University of Benin Teaching Hospital (UBTH) in Southern Nigeria. Babies born to these mothers were also recruited at birth and the mother-infant pairs followed over 6 scheduled visits for 18 months, with comprehensive clinical assessments, anthropometric measurements and sample collections for microbiome analysis. Preliminary analysis of accrued data found evidence of significantly greater impairment of linear and ponderal growth among HIV-exposed, uninfected children (HEU) as compared to HIV-unexposed, uninfected (HUU) children. Similarly, analysis of microbiome data, thus far, indicates that higher



Man Charurat, PhD and Bola Gobir, MBBS, MBH with the Minister of Health and NACA Director General planning the ECHO training for Medical Education and HIV/AIDS care delivery



MARGIN health care worker providing home care kit for expectant mother

gastrointestinal microbiome diversity is associated with higher risk for adverse growth and infectious morbidity. Finally, additional analyses are underway to explore the impact of microbial composition, gut permeability, and bacterial translocation on growth and co-morbidity outcomes.

Building TRUST

Despite the challenges faced by MSM in Nigeria because of criminalization of same sex practices, Building TRUST continues to offer HIV and STI screening to this vulnerable population. The one-stop, community-friendly clinic provides support to over 2,100 MSM, making it one of the largest MSM cohorts in sub-Saharan Africa. The Building TRUST study under the direction of Dr. Charurat and supported by **Habib Omari, MD, PhD**, Research Associate of Epidemiology and Public Health, has produced over 17 peer-reviewed research articles and presented 19 abstracts in scientific conferences. Building TRUST found an HIV incidence (new infection rate) of 15.4% in the MSM cohort, which accounts for one of the highest rates among members of key populations. Proven HIV biomedical interventions, such as Pre-exposure Prophylaxis (PrEP), are being introduced to reduce transmission. Furthermore, the study revealed that HIV risk is not attributable to individual factors alone, but rather a combination of factors that may include risks associated with specific characteristics of an individual's sexual partnerships. Using phylogenetic analyses, Building TRUST is exploring HIV phylogenetic linkages to identify putative HIV transmission sources.

TRUST-Anal Cancer Study

Rebecca Nowak, PhD, Assistant Professor of Epidemiology and Public Health, completed her University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center (UMGCC) P30 Anal Cancer Study, a screen and treat investigation nested in the Building Trust MSM cohort. With

the risk for anal cancer being 52-fold higher among MSM living with HIV and screening for anal cancer unavailable in Nigeria and throughout sub-Saharan Africa, this National Cancer Institute (NCI) funded study was the first of its kind. HIV-infected MSM with controlled viremia, more than 8 years since their sexual debut, and eternal warts were at increased odds for anal dysplasia. Dr.



Rebecca Nowak, PhD, with Nigerian physician, Wuese Dauda, MBBS

Nowak presented these findings orally at the International Anal Neoplasia Society's Scientific Meeting in Montreal, Canada and was awarded best abstract for outstanding research in international cohorts.

Role of Anal Microbiota, Local Cytokines and HIV in Persistence of High-risk HPV

Dr. Nowak was recently awarded a 5-year K07 career development grant from NCI and the Office of AIDS Research, titled "Role of anal microbiota, local cytokines and HIV in persistence of high-risk human papillomavirus." She will undertake formal training and mentoring in microbiota, mucosal immunity and molecular biology of carcinogenesis and will learn how to rigorously integrate these components analytically to identify markers associated with persistent high-risk human papillomavirus (HR-HPV) during HIV infection. Dr. Nowak conducted a cross-sectional study to illustrate the feasibility of clustering anal microbiota and examined the distribution of clinical and behavioral characteristics by cluster membership. She will evaluate these characteristic clusters as well as the cytokine milieu longitudinally as risk factors for persistent HR-HPV during her K07.

Laboratory of Viral Diagnostics

The Division's Laboratory of Viral Diagnostics led by **Niel Constantine, PhD, MT(ASCP)**, Professor of Pathology, has the capability to develop sensitive diagnostic methods (serologic and molecular), perform Food and Drug Administration (FDA) clinical trials, evaluate a variety of diagnostic methods, and support other investigators for their testing needs. During the past year, the laboratory has (1) been active in two government funded and international funded efforts to evaluate rapid diagnostic tests for HIV, hepatitis B & C, syphilis, pregnancy, and cryptococcus antigen from 14 countries; (2) performed a multicenter FDA clinical trial to evaluate a multiplex rapid test that detects HIV and syphilis simultaneously; (3) developed a serotype specific



Alash'le Abimiku, MSc, PhD and Man Charurat, PhD host the Graduate School's MSHS hybrid training in Nigeria for Dissemination and Implementation Science Research

ELISA method for *P. gingivalis*; and, (4) assisted with the development of a highly sensitive molecular amplification method to detect HIV p24 antigen.

IMPLEMENTATION AND DISSEMINATION RESEARCH AND RESEARCH ETHICS TRAINING

Epidemiology Research Training for Public Health Impact in Nigeria (Epi-Nigeria)

Epi-Nigeria, a National Institutes of Health (NIH)-Fogarty funded research capacity building grant led by Dr. Charurat and **Alash'le Abimiku, MSc, PhD**, Professor of Medicine, is designed to build capacity in the next generation of Nigerian research scientists in the field of Implementation and Dissemination Science Research. Eight Nigerian students completed their first year in the newly-created, UMB online Master of Science in Health Science (MSHS) with a concentration in Dissemination and Implementation Science, and two Nigerian Physicians are doctoral candidates in the Epidemiology program based in Baltimore. The MSHS Implementation and Dissemination Science Research program was developed in collaboration with the UMB graduate school. Dr. Charurat,

Patrick Dakum, MBBS, MPH, Assistant Professor of Epidemiology and Public Health, **Nadia Sam-Agudu, MD**, Assistant Professor of Epidemiology and Public Health and Dr. Jumare are developing and teaching new courses in Implementation and Dissemination Science Research. **Clement Adebamowo, BM, ChB, ScD, FWACS, FACS**, Professor of Epidemiology and Public Health, is developing and leading a course in Global Non-Communicable Epidemiology, and Dr. Abimiku is overseeing the research capstones. Upon completion of their training, the

Fogarty scholars (PhD and MSHS) will join the group of well-educated faculty at IHV-Nigeria's International Research Center of Excellence (IRCE) to continue research collaborations and support their continued growth as research scientists.

Entrenching Research Ethics Training in Nigeria (ENTRENCH)

Dr. Adebamowo, a leader in Research Ethics in West Africa, has been developing a modern, research ethics training in Nigeria since 2004. His most recent Fogarty-NIH grant titled, "Entrenching Research Ethics Training in Nigeria (Entrench)," provides short-term training in Protection of Human Subjects of Research, Responsible Conduct of Research (RCR), the Nigerian National Code for Health Research Ethics, and more. Recognizing that most individuals who serve on ethics committees require more than introductory training in research ethics, but they are unable to take extended periods away from their primary occupation, Dr. Adebamowo and colleagues from the University of Ibadan, Nigeria, introduced the Blended Diploma in Research Ethics, an online-offline program that is based on two, three-credit courses that are part of the MSc Bioethics program at the University of Ibadan, Nigeria.



Dave Wilkins, MBA and COO of IHV, visits IHV-Nigeria's site for the International Center for Research Excellence with Patrick Dakum, MBBS, and Charles Mensah, MBA

IHV-NIGERIA'S ROBUST RESEARCH AND PUBLIC HEALTH IMPLEMENTATION PROGRAMS

Established in 2004, IHV-Nigeria, led by Dr. Patrick Dakum, CEO, Charles Mensah, COO, and Dr. Alash'le Abimiku, Executive Director, has pressed forward to help fulfill the mission of the Division and become a Center of Excellence for implementing innovative health service programs, training and research studies in Nigeria. IHV-Nigeria currently has \$45M in annual funding and is building a permanent home for the International Center of Research Excellence in Nigeria to house IHV-Nigeria's extensive laboratory, research, and public health programs built over the last decade within the Division.



PEPFAR Community Mobilization Activity in Nigeria

Action to Control HIV Epidemic through Evidence (ACHIEVE) Project

The Division of Epidemiology and Prevention continues to benefit from the ongoing support of IHV-Nigeria in developing cohorts with PEPFAR-funded Action to Control HIV Epidemic through Evidence (ACHIEVE) in 4 states, including Nasarawa, Kano, Katsina and the Federal Capital Territory. Led by Dr. Dakum, ACHIEVE offers antiretroviral therapy services in 316 facilities, prevention of mother-to-child transmission services in 403 facilities, TB services in 78 facilities and HIV counseling and testing services in 405 facilities. Since 2004, IHV-Nigeria has cumulatively provided HIV testing to over 9.7 million, care and support to 497,441 individuals, treatment to over 374,809 patients including 21,793 children and 94,558 pregnant women in Nigeria.

Global Fund Multi-Drug Resistant TB (MDR TB) Project

Dr. Dakum also leads the Global Fund Multi-Drug Resistant TB (MDR TB) grant which seeks to strengthen MDR TB prevention and control in Nigeria through treatment centers and diagnostic laboratories. To date, 46,000 clients suspected



H3 Africa IHAB biorepository at IHV-Nigeria

of drug resistant TB have been tested and 5,056 MDR-TB patients placed on second-line anti-TB drugs.

H3Africa Biorepository Initiative I

The NIH and Wellcome Trust have

invested over \$76 million in Human Hereditary and Health in Africa (H3Africa) since 2011 to support applications from African institutions led by African scientists on genomic research of diseases relevant to the African continent. Dr. Abimiku was funded to develop a West Africa Biorepository, IHAB, for H3Africa. IHAB is both a local and regional resource for biobanking activities, which provides onsite mentorship and training on shipping of biological samples, operationalization of a regional biobank, in collaboration with the Economic Community of West African States (ECOWAS) First Multidisciplinary Technical Committee, and access to storage and use of samples during a public health emergency. Mentees served as panelists at the World Health Organization (WHO) Third Consultation on Biobanking and participated in several conferences on the standardization of biorepositories.

Breast Milk Microbiota Influence on Infant Immunity Growth (BEAMING)

The BEAMING study led by Dr. Abimiku leverages stored samples and preliminary observations from her recently completed INFANT study, in which a cohort of 500 HIV+ and 150 HIV- moms and their infants were enrolled with biomedical samples collected from birth to age 2 in Nigeria and South Africa. BEAMING, now in year two, is a nested study funded by NIH to investigate microbial shifts in the infant gut microbiota and how this affects growth and immune response to pediatric vaccines. Preliminary results show that both Proteomic and 16S rRNA gene analysis show differences in the relative abundance of microbiota of the gut of HIV-Exposed Uninfected (HEU) compared to that of HIV-Unexposed (HU). Whether these differences could be



Alash'le Abimiku, MSc, PhD conducting research in IHV-Nigeria's PLASVERIC laboratory and ISO 15189 certified laboratory in Jos, Nigeria

partially explained and/or maintained by breastfeeding is what the BEAMING study will reveal.

African Collaborative Center for Microbiome and Genomics Research (ACCME)

Dr. Adebamowo leads the NIH-Funded African Collaborative Center for Microbiome and Genomics Research (ACCME), a multi-clinical site project in Nigeria involving the comprehensive genomics research laboratory at the IHV-Nigeria. The study involves three projects. The first, enrolled 11,700 women into an investigation of epidemiologic determinants of persistent high risk HPV infection and cervical cancer; the second study is a genome-wide association study into the risk of persistent high-risk HPV infection and cervical cancer; and the third study researches the role of vaginal microbiome and cervical cytokines and host, as well as viral epi-genomics in persistent high risk HPV infection and cervical cancer. This award contributed significantly to the literature including the identification of prevalent and persistent types of HPV in Nigerian women and the identification of novel genomic risk factors for HPV infections, patterns of prevalent and persistent community state types of vaginal microbiome, prevalent and persistent Mycoplasma spp infection and their association with prevalent and persistent high risk HPV infection.

African Female Breast Cancer Epidemiology Study in Nigeria (AFBRECANE)

Dr. Adebamowo leads the NIH-funded African Female Breast Cancer Epidemiology (AFBRECANE) Study, which includes four clinical site investigations in Nigeria at the IHV-Nigeria. The study aims to conduct the first adequately powered genome-wide association study (GWAS) of breast cancer using an entirely indigenous African population. AFBRECANE, in



Clement Adebamowo, BM, ChB, ScD, FWACS, FACS (far left) with Robert Gallo, MD (center) and industrial partners

collaboration with the Pathology Department, UMGCCC, will also implement a detailed study of the molecular subtypes of breast cancer in Nigerian patients. The study will resolve the debate on the prevalence of molecular subtypes of breast cancer in Nigerian patients and generate information about genetic risk of molecular subtypes of breast cancer. As an integrative epidemiology research platform with high quality data, phenotyping, trained personnel and top-class laboratory support, AFBRECANE has already attracted new collaborations from industrial partners, i.e., Cepheid Corporation, CA and researchers from other universities.

Adolescent Coordinated Transition (ACT)

Dr. Sam-Agudu completed her second year leading the Adolescent Coordinated Transition (ACT) study. This NIH-funded study aims to test the impact of structured peer support and time to transition on post-transition outcomes among 216 adolescents living with HIV in Nigeria. ACT is implemented

at 12 sites in 9 states across all 6 geopolitical zones in Nigeria, leveraging the Nigeria Implementation Science Alliance's consortium of local NGOs and international partners. Representing the IHV-Nigeria, Dr. Sam-Agudu expects that findings from ACT will assist in policy-making for quality transition/post-transition service delivery and better outcomes for adolescents living with HIV in Nigeria and in similar settings.



Adolescents enroll in the ACT study

Epidemiology and Prevention Publications

- Rodriguez-Hart C, Musci R, **Nowak RG**, German D, Orazulike I, Ononaku U, Liu H, Crowell TA, Baral S, **Charurat M**; TRUST/RV368 Study Group. Sexual Stigma Patterns among Nigerian Men Who Have Sex with Men and Their Link to HIV and Sexually Transmitted Infection Prevalence. *AIDS Behav*. 2018 May;22(5):1662-1670. doi: 10.1007/s10461-017-1982-4.
- Crowell TA, Hardick J, Lombardi K, Parker Z, Kokogho A, Amusu S, Odeyemi S, Ivo A, Baral SD, **Nowak RG**, Adebajo S, **Charurat ME**, Ake J, Gaydos CA; TRUST/RV368 Study Group. Asymptomatic lymphogranuloma venereum among Nigerian men who have sex with men. *Sex Transm Infect*. 2018 Jan 29. pii: sextrans-2017-053414. doi: 10.1136/sextrans-2017-053414. [Epub ahead of print]
- Mulder N, **Abimiku A**, Adebamowo SN, de Vries J, Matimba A, Olowoyo P, Ramsay M, Skelton M, Stein DJ. H3Africa: current perspectives *Pharmgenomics Pers Med*. 2018 Apr 10;11:59-66. doi: 10.2147/PGPM.S141546. eCollection 2018. Review.
- Jumare J, Ndembu N, El-Kamary SS, Magder L, Hungerford L, Burdo T, Eyzaguirre LM, **Dakum P**, Umlauf A, Cherner M, **Abimiku A**, **Charurat M**, Blattner WA, Royal W 3rd. Cognitive Function Among Antiretroviral Treatment-Naive Individuals Infected With Human Immunodeficiency Virus Type 1 Subtype G Versus CRF02_AG in Nigeria. *Clin Infect Dis*. 2018 Apr 17;66(9):1448-1453. doi: 10.1093/cid/cix1019.
- Avong YK, Aliyu GG, Jatau B, Gurumnaan R, Danat N, Kayode GA, Adekanmbi V, **Dakum P**. Integrating community pharmacy into community based anti-retroviral therapy program: A pilot implementation in Abuja, Nigeria. *PLoS One*. 2018 Jan 10;13(1):e0190286. doi: 10.1371/journal.pone.0190286. eCollection 2018.
- ..Ezeanolue EE, Menson WNA, Patel D, Aarons G, Olutola A, Obiefune M, **Dakum P**, Okonkwo P, Gobir B, Akinnurele T, Nwanda A, Khamofu H, Oyeledun B, Aina M, Eyo A, Oleribe O, Ibanga I, Oko J, Anyaika C, Idoko J, Aliyu MH, Sturke R; Gaps and strategies in developing health research capacity: experience from the Nigeria Implementation Science Alliance. *Nigeria Implementation Science Alliance. Health Res Policy Syst*. 2018 Feb 12;16(1):10. doi: 10.1186/s12961-018-0289-x.
- Cornelius LJ, Ereka SC, Okundaye JN, **Sam-Agudu NA**. A Socio-Ecological Examination of Treatment Access, Uptake and Adherence Issues Encountered By HIV-Positive Women in Rural North-Central Nigeria. *J Evid Inf Soc Work*. 2018 Jan-Feb;15(1):38-51. doi: 10.1080/23761407.2017.1397580. Epub 2017 Dec 13.
- ..Nachega JB, **Sam-Agudu NA**, Mofenson LM, Schechter M, Mellors JW. Reply to Kojima and Klausner. *Clin Infect Dis*. 2018 Apr 27. doi: 10.1093/cid/ciy345. [Epub ahead of print] No abstract available.
- Sam-Agudu NA**, Aliyu MH, Adeyemi OA, Oronsaye F, Oyeledun B, Ogi AG, Ezeanolue EE. Generating evidence for health policy in challenging settings: lessons learned from four prevention of mother-to-child transmission of HIV implementation research studies in Nigeria *Health Res Policy Syst*. 2018 Apr 17;16(1):32. doi: 10.1186/s12961-018-0309-x.
- Odiachi A, Ereka S, Cornelius LJ, Isah C, **Ramadhani HO**, Rapoport L, **Sam-Agudu NA**. HIV status disclosure to male partners among rural Nigerian women along the prevention of mother-to-child transmission of HIV cascade: a mixed methods study. *Reprod. Health*. 2018 Mar 2;15(1):36. doi: 10.1186/s12978-018-0474-y.
- Sam-Agudu NA**, Pharr JR, Bruno T, Cross CL, Cornelius LJ, Okonkwo P, Oyeledun B, Khamofu H, Olutola A, Ereka S, Menson WNA, Ezeanolue EE. Correction to: Adolescent Coordinated Transition (ACT) to improve health outcomes among young people living with HIV in Nigeria: study protocol for a randomized controlled trial. *Trials*. 2018 Feb 13;19(1):104. doi: 10.1186/s13063-018-2463-4.
- Nachega JB, **Sam-Agudu NA**, Mofenson LM, Schechter M, Mellors JW. Achieving Viral Suppression in 90% of People Living With Human Immunodeficiency Virus on Antiretroviral Therapy in Low- and Middle-Income Countries: Progress, Challenges, and Opportunities. *Clin Infect Dis*. 2018 May 2;66(10):1487-1491. doi: 10.1093/cid/ciy008.
- Molina JM, Grund B, Gordin F, Williams I, Schechter M, Losso M, Law M, **Ekong E**, Mwelase N, Skoutelis A, Wiselka MJ, Vandekerckhove L, Benfield T, Munroe D, Lundgren JD, Neaton JD; INSIGHT START study group. Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial. *Lancet HIV*. 2018 Apr;5(4):e172-e180. doi: 10.1016/S2352-3018(18)30003-1. Epub 2018 Jan 16.
- Ramadhani HO**, Muiruri C, Maro VP, Nyombi B, Omondi M, Mushi JB, Lirhunde ES, Bartlett Patient-Initiated Repackaging of Antiretroviral Therapy, Viral Suppression and Drug Resistance. *JAIDS Behav*. 2018 May;22(5):1671-1678. doi: 10.1007/s10461-017-1721-x.
- Avong, Y. K., **Aliyu, G. G.**, Jatau, B., Gurumnaan, R., Danat, N., Kayode, G. A., . . . **Dakum, P.** (2018). Integrating community pharmacy into community based anti-retroviral therapy program: A pilot implementation in Abuja, Nigeria. *PLoS ONE*, 13(1), e0190286. <http://doi.org/10.1371/journal.pone.0190286>
- Adebamowo S., **Adebamowo C.** Neurodevelopmental outcomes of twins compared with singleton children: a systematic review. *Twin Research and Human Genetics* 2018 Feb 8:1-10. doi: 10.1017/thg.2018.3. [Epub ahead of print] PubMed PMID: 29415789.
- Holmes M. D., Dalal S., Sewram V., Diamond M. B., Adebamowo S. N., Ajayi I. O., **Adebamowo C.**, Chiwanga F. S., Njelekela M., Laurence C., Volmink J., Bajunirwe F., Nankya-Mutyoba J., Guwatudde D., Reid T. G., Willett W. C., Adami H. O., Fung T. T. Consumption of processed food dietary patterns in four African populations. *Public Health Nutr*. 2018 Feb 1:1-9. doi: 10.1017/S136889001700386X. PubMed PMID: 29388531.
- Kaye J., Terry S. F., Juengst E., Coy S., Harris J. R., Chalmers D., Dove E. S., Budin-Ljøsne I., **Adebamowo C.**, Ogbe E., Bezuidenhout L., Morrison M., Minion J. T., Murtagh M. J., Minari J., Teare H., Isasi R., Kato K., Rial-Sebbag E., Marshall P., Koenig B., Cambon-Thomsen A. Including all voices in international data-sharing governance. *Hum Genomics*. 2018 Mar 7;12(1):13. doi: 10.1186/s40246-018-0143-9. PubMed PMID: 29514717.
- Schaub FX, Dhankani V, Berger AC, Trivedi M, Richardson AB, Shaw R, Zhao W, Zhang X, Ventura A, Liu Y, Ayer DE, Hurlin PJ, Cherniack AD, Eisenman RN, Bernard B, Grandori C; **Cancer Genome Atlas Network**. Pan-cancer Alterations of the MYC Oncogene and Its Proximal Network across the Cancer Genome Atlas. *Cell Syst*. 2018 Mar 28;6(3):282-300.e2. doi: 10.1016/j.cels.2018.03.003. PubMed PMID: 29596783.
- Ellrott K, Bailey MH, Saksena G, Covington KR, Kandoth C, Stewart C, Hess J, Ma S, Chiotti KE, McLellan M, Sofia HJ, Hutter C, Getz G, Wheeler D, Ding L; MC3 Working Group; **Cancer Genome Atlas Research Network**. Scalable Open Science Approach for Mutation Calling of Tumor Exomes Using Multiple Genomic Pipelines. *Cell Syst*. 2018 Mar 28;6(3):271-281.e7. doi: 10.1016/j.cels.2018.03.002. PubMed PMID: 29596782.
- Berger A. C., A. Korkut, R. S. Kanchi, A. M. Hegde, W. Lenoir, W. Liu, Y. Liu, H. Fan, H. Shen, V. Ravikumar, A. Rao, A. Schultz, X. Li, P. Sumazin, C. Williams, P. Mestdagh, P. H. Gunaratne, C. Yau, R. Bowlby, A. G. Robertson, D. G. Tiezzi, C. Wang, A. D. Cherniack, A. K. Godwin, N. M. Kuderer, J. S. Rader, R. E. Zuna, A. K. Sood, A. J. Lazar, A. I. Ojesina, **C. Adebamowo**, S. N. Adebamowo, K. A. Baggerly, T.-W. Chen, H.-S. Chiu, S. Lefever, L. Liu, K. MacKenzie, S. Orsulic, J. Roszik, C. S. Shelley, Q. Song, C. P. Vellano, N. Wentzensen, The Cancer Genome Atlas Network A Comprehensive Pan-Cancer Molecular Study of Gynecologic and Breast Cancers. *Cancer Cell*. 2018 Apr 9;33(4):690-705.e9. doi: 10.1016/j.ccell.2018.03.014. Epub 2018 Apr 2. PubMed PMID: 29622464.
- Campbell JD, You C, Bowlby R, Liu Y, Brennan K, Fan H, Taylor AM, Wang C, Walter V, Akbani R, Byers LA, Creighton CJ, Coarfa C, Shih J, Cherniack AD, Gevaert O, Prunello M, Shen H, Anur P, Chen J, Cheng H, Hayes DN, Bullman S, Pedamallu CS, Ojesina AI, Sadeghi S, Mungall KL, Robertson AG, Benz C, Schultz A, Kanchi RS, Gay CM, Hegde A, Diao L, Wang J, Ma W, Sumazin P, Chiu HS, Chen TW, Gunaratne P, Donehower L, Rader JS, Zuna R, Al-Ahmadie H, Lazar AJ, Flores ER, Tsai KY, Zhou JH, Rustgi AK, Drill E, Shen R, Wong CK; **Cancer Genome Atlas Research Network**, Stuart JM, Laird PW, Hoadley KA, Weinstein JN, Peto M, Pickering CR, Chen Z, Van Waes C. Genomic, Pathway Network, and Immunologic Features Distinguishing Squamous Carcinomas. *Cell Rep*. 2018 Apr 3;23(1):194-212.e6. doi: 10.1016/j.celrep.2018.03.063. PubMed PMID: 29617660.
- Thorsson V, Gibbs DL, Brown SD, Wolf D, Bortone DS, Ou Yang TH, Porta-Pardo E, Gao GF, Plaisier CL, Eddy JA, Ziv E, Culhane AC, Paull EO, Sivakumar IKA, Gentles AJ, Malhotra R, Farshidfar F, Colaprico A, Parker JS, Mose LE, Vo NS, Liu J, Liu Y, Rader J, Dhankani V, Reynolds SM, Bowlby R, Califano A, Cherniack AD, Anastassiou D, Bedognetti D, Rao A, Chen K, Krasnitz A, Hu H, Malta TM, Noushmehr H, Pedamallu CS, Bullman S, Ojesina AI, Lamb A, Zhou W, Shen H, Choueiri TK, Weinstein JN, Guinney J, Saltz J, Holt RA, Rabkin CE; **Cancer Genome Atlas Research Network**, Lazar AJ, Serody JS, Demicco EG, Disis ML, Vincent BG, Shmulevich L. The Immune Landscape of Cancer. *Immunity*. 2018 Apr 4. pii: S1074-7613(18)30121-3. doi: 10.1016/j.immuni.2018.03.023. [Epub ahead of print] PubMed PMID: 29628290.
- Liu J, Lichtenberg T, Hoadley KA, Poisson LM, Lazar AJ, Cherniack AD, Kovatich AJ, Benz CC, Levine DA, Lee AV, Omberg L, Wolf DM, Shriver CD, Thorsson V; **Cancer Genome Atlas Research Network**, Hu H. An Integrated TCGA Pan-Cancer Clinical Data Resource to Drive High-Quality Survival Outcome Analytics. *Cell*. 2018 Apr 5;173(2):400-416.e11. doi: 10.1016/j.cell.2018.02.052. PubMed PMID: 29625055.

Bailey MH, Tokheim C, Porta-Pardo E, Sengupta S, Bertrand D, Weerasinghe A, Colaprico A, Wendl MC, Kim J, Reardon B, Ng PK, Jeong KJ, Cao S, Wang Z, Gao J, Gao Q, Wang F, Liu EM, Mularoni L, Rubio-Perez C, Nagarajan N, Cortés-Ciriano I, Zhou DC, Liang WW, Hess JM, Yellapantula VD, Tamborero D, Gonzalez-Perez A, Suphavitai C, Ko JY, Khurana E, Park PJ, Van Allen EM, Liang H; MC3 Working Group; **Cancer Genome Atlas Research Network**, Lawrence MS, Godzik A, Lopez-Bigas N, Stuart J, Wheeler D, Getz G, Chen K, Lazar AJ, Mills GB, Karchin R, Ding L. Comprehensive Characterization of Cancer Driver Genes and Mutations. *Cell*. 2018 Apr 5;173(2):371-385.e18. doi: 10.1016/j.cell.2018.02.060. PubMed PMID: 29625053.

Huang KL, Mashl RJ, Wu Y, Ritter DI, Wang J, Oh C, Paczkowska M, Reynolds S, Wyczalkowski MA, Oak N, Scott AD, Krassowski M, Cherniack AD, Houlihan KE, Jayasinghe R, Wang LB, Zhou DC, Liu D, Cao S, Kim YW, Koire A, McMichael JF, Huchtagowder V, Kim TB, Hahn A, Wang C, McLellan MD, Al-Mulla F, Johnson KJ; **Cancer Genome Atlas Research Network**, Lichtarge O, Boutros PC, Raphael B, Lazar AJ, Zhang W, Wendl MC, Govindan R, Jain S, Wheeler D, Kulkarni S, Dipersio JF, Reimand J, Meric-Bernstam F, Chen K, Shmulevich I, Plon SE, Chen F, Ding L. Pathogenic Germline Variants in 10,389 Adult Cancers. *Cell*. 2018 Apr 5;173(2):355-370.e14. doi: 10.1016/j.cell.2018.03.039. PubMed PMID: 29625052.

Malta TM, Sokolov A, Gentles AJ, Burzykowski T, Poisson L, Weinstein JN, Kamińska B, Huelsken J, Omberg L, Gevaert O, Colaprico A, Czerwińska P, Mazurek S, Mishra L, Heyn H, Krasnitz A, Godwin AK, Lazar AJ; **Cancer Genome Atlas Research Network**, Stuart JM, Hoadley KA, Laird PW, Noushmehr H, Wiznerowicz M. Machine Learning Identifies Stemness Features Associated with Oncogenic Dedifferentiation. *Cell*. 2018 Apr 5;173(2):338-354.e15. doi: 10.1016/j.cell.2018.03.034. PubMed PMID: 29625051.

Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, Dimitriadou S, Liu DL, Kantheti HS, Saghafinia S, Chakravarty D, Daian F, Gao Q, Bailey MH, Liang WW, Foltz SM, Shmulevich I, Ding L, Heins Z, Ochoa A, Gross B, Gao J, Zhang H, Kundra R, Kandoth C, Bahceci I, Dervishi L, Dogrusoz U, Zhou W, Shen H, Laird PW, Way GP, Greene CS, Liang H, Xiao Y, Wang C, Iavarone A, Berger AH, Bivona TG, Lazar AJ, Hammer GD, Giordano T, Kwong LN, McArthur G, Huang C, Tward AD, Frederick MJ, McCormick F, Meyerson M; **Cancer Genome Atlas Research Network**, Van Allen EM, Cherniack AD, Ciriello G, Sander C, Schultz N. Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell*. 2018 Apr 5;173(2):321-337.e10. doi: 10.1016/j.cell.2018.03.035. PubMed PMID: 29625050.

Ding L, Bailey MH, Porta-Pardo E, Thorsson V, Colaprico A, Bertrand D, Gibbs DL, Weerasinghe A, Huang KL, Tokheim C, Cortés-Ciriano I, Jayasinghe R, Chen F, Yu L, Sun S, Olsen C, Kim J, Taylor AM, Cherniack AD, Akbani R, Suphavitai C, Nagarajan N, Stuart JM, Mills GB, Wyczalkowski MA, Vincent BG, Hutter CM, Zenklusen JC, Hoadley KA, Wendl MC, Shmulevich L, Lazar AJ, Wheeler DA, Getz G; **Cancer Genome Atlas Research Network**. Perspective on Oncogenic Processes at the End of the Beginning of Cancer Genomics. *Cell*. 2018 Apr 5;173(2):305-320.e10. doi: 10.1016/j.cell.2018.03.033. PubMed PMID: 29625049.

Hoadley KA, Yau C, Hinoue T, Wolf DM, Lazar AJ, Drill E, Shen R, Taylor AM, Cherniack AD, Thorsson V, Akbani R, Bowlby R, Wong CK, Wiznerowicz M, Sanchez-Vega F, Robertson AG, Schneider BG, Lawrence MS, Noushmehr H, Malta TM; **Cancer Genome Atlas Network**, Stuart JM, Benz CC, Laird PW. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. *Cell*. 2018 Apr 5;173(2):291-304.e6. doi: 10.1016/j.cell.2018.03.022. PubMed PMID: 29625048.

Liu Y, Sethi NS, Hinoue T, Schneider BG, Cherniack AD, Sanchez-Vega F, Seoane JA, Farshidfar F, Bowlby R, Islam M, Kim J, Chatila W, Akbani R, Kanchi RS, Rabkin CS, Willis JE, Wang KK, McCall SJ, Mishra L, Ojesina AI, Bullman S, Pedamallu CS, Lazar AJ, Sakai R; **Cancer Genome Atlas Research Network**, Thorsson V, Bass AJ, Laird PW. Comparative Molecular Analysis of Gastrointestinal Adenocarcinomas. *Cancer Cell*. 2018 Apr 9;33(4):721-735.e8. doi: 10.1016/j.ccell.2018.03.010. Epub 2018 Apr 2. PubMed PMID: 29622466.

Wang Z, Yang B, Zhang M, Guo W, Wu Z, Wang Y, Jia L, Li S; **Cancer Genome Atlas Research Network**, Xie W, Yang D. lncRNA Epigenetic Landscape Analysis Identifies EPIC1 as an Oncogenic lncRNA that Interacts with MYC and Promotes Cell-Cycle Progression in Cancer. *Cancer Cell*. 2018 Apr 9;33(4):706-720.e9. doi: 10.1016/j.ccell.2018.03.006. Epub 2018 Apr 2. PubMed PMID: 29622465.

Taylor AM, Shih J, Ha G, Gao GF, Zhang X, Berger AC, Schumacher SE, Wang C, Hu H, Liu J, Lazar AJ; **Cancer Genome Atlas Research Network**, Cherniack AD, Beroukhir M, Meyerson M. Genomic and Functional Approaches to Understanding Cancer Aneuploidy. *Cancer Cell*. 2018 Apr 9;33(4):676-689.e3. doi: 10.1016/j.ccell.2018.03.007. Epub 2018 Apr 2. PubMed PMID: 29622463.

Ricketts CJ, De Cubas AA, Fan H, Smith CC, Lang M, Reznik E, Bowlby R, Gibb EA, Akbani R, Beroukhir M, Bottaro DP, Choueiri TK, Gibbs RA, Godwin AK, Haake S, Hakimi AA, Henske EP, Hsieh JJ, Ho TH, Kanchi RS, Krishnan B, Kwiatkowski DJ, Lui W, Merino MJ, Mills GB, Myers J, Nickerson ML, Reuter VE, Schmidt LS, Shelley CS, Shen H, Shuch B, Signoretti S, Srinivasan R, Tamboli P, Thomas G, Vincent BG, Vocke CD, Wheeler DA, Yang L, Kim WT, Robertson AG; **Cancer Genome Atlas Research Network**, Spellman PT, Rathmell WK, Linehan WM. The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. *Cell Rep*. 2018 Apr 3;23(1):313-326.e5. doi: 10.1016/j.celrep.2018.03.075. PubMed PMID: 29617669.

Chiu HS, Somvanshi S, Patel E, Chen TW, Singh VP, Zorman B, Patil SL, Pan Y, Chatterjee SS; **Cancer Genome Atlas Research Network**, Sood AK, Gunaratne PH, Sumazin P. Pan-Cancer Analysis of lncRNA Regulation Supports Their Targeting of Cancer Genes in Each Tumor Context. *Cell Rep*. 2018 Apr 3;23(1):297-312.e12. doi: 10.1016/j.celrep.2018.03.064. PubMed PMID: 29617668.

Seiler M, Peng S, Agrawal AA, Palacino J, Teng T, Zhu P, Smith PG; **Cancer Genome Atlas Research Network**, Buonamici S, Yu L. Somatic Mutational Landscape of Splicing Factor Genes and Their Functional Consequences across 33 Cancer Types. *Cell Rep*. 2018 Apr 3;23(1):282-296.e4. doi: 10.1016/j.celrep.2018.01.088. PubMed PMID: 29617667.

Jayasinghe RG, Cao S, Gao Q, Wendl MC, Vo NS, Reynolds SM, Zhao Y, Climente-González H, Chai S, Wang F, Varghese R, Huang M, Liang WW, Wyczalkowski MA, Sengupta S, Li Z, Payne SH, Fenyo D, Miner JH, Walter MJ; **Cancer Genome Atlas Research Network**, Vincent B, Eyrae E, Chen K, Shmulevich I, Chen F, Ding L. Systematic Analysis of Splice-Site-Creating Mutations in Cancer. *Cell Rep*. 2018 Apr 3;23(1):270-281.e3. doi: 10.1016/j.celrep.2018.03.052. PubMed PMID: 29617666.

Peng X, Chen Z, Farshidfar F, Xu X, Lorenzi PL, Wang Y, Cheng F, Tan L, Mojmudar K, Du D, Ge Z, Li J, Thomas GV, Birsoy K, Liu L, Zhang H, Zhao Z, Marchand C, Weinstein JN; **Cancer Genome Atlas Research Network**, Bathe OF, Liang H. Molecular Characterization and Clinical Relevance of Metabolic Expression Subtypes in Human Cancers. *Cell Rep*. 2018 Apr 3;23(1):255-269.e4. doi: 10.1016/j.celrep.2018.03.077. PubMed PMID: 29617665.

Knijnenburg TA, Wang L, Zimmermann MT, Chambwe N, Gao GF, Cherniack AD, Fan H, Shen H, Way GP, Greene CS, Liu Y, Akbani R, Feng B, Donehower LA, Miller C, Shen Y, Karimi M, Chen H, Kim P, Jia P, Shinbrot E, Zhang S, Liu J, Hu H, Bailey MH, Yau C, Wolf D, Zhao Z, Weinstein JN, Li L, Ding L, Mills GB, Laird PW, Wheeler DA, Shmulevich I; **Cancer Genome Atlas Research Network**, Monnat RJ Jr, Xiao Y, Wang C. Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas. *Cell Rep*. 2018 Apr 3;23(1):239-254.e6. doi: 10.1016/j.celrep.2018.03.076. PubMed PMID: 29617664.

Gao Q, Liang WW, Foltz SM, Mutharasu G, Jayasinghe RG, Cao S, Liao WW, Reynolds SM, Wyczalkowski MA, Yao L, Yu L, Sun SQ; Fusion Analysis Working Group; **Cancer Genome Atlas Research Network**, Chen K, Lazar AJ, Fields RC, Wendl MC, Van Tine BA, Vij R, Chen F, Nykter M, Shmulevich I, Ding L. Driver Fusions and Their Implications in the Development and Treatment of Human Cancers. *Cell Rep*. 2018 Apr 3;23(1):227-238.e3. doi: 10.1016/j.celrep.2018.03.050. PubMed PMID: 29617662.

Ge Z, Leighton JS, Wang Y, Peng X, Chen Z, Chen H, Sun Y, Yao F, Li J, Zhang H, Liu J, Shriver CD, Hu H; **Cancer Genome Atlas Research Network**, Piwnicka-Worms H, Ma L, Liang H. Integrated Genomic Analysis of the Ubiquitin Pathway across Cancer Types. *Cell Rep*. 2018 Apr 3;23(1):213-226.e3. doi: 10.1016/j.celrep.2018.03.047. PubMed PMID: 29617661.

Saltz J, Gupta R, Hou L, Kurc T, Singh P, Nguyen V, Samaras D, Shroyer KR, Zhao T, Batiste R, Van Arnam J; **Cancer Genome Atlas Research Network**, Shmulevich I, Rao AUK, Lazar AJ, Sharma A, Thorsson V. Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images. *Cell Rep*. 2018 Apr 3;23(1):181-193.e7. doi: 10.1016/j.celrep.2018.03.086. PubMed PMID: 29617659.

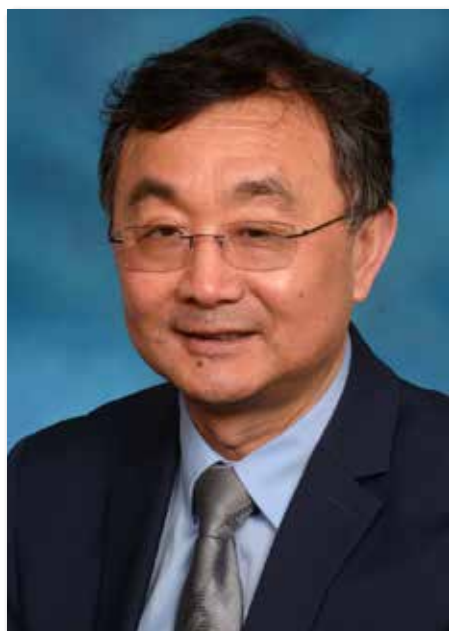
Way GP, Sanchez-Vega F, La K, Armenia J, Chatila WK, Luna A, Sander C, Cherniack AD, Mina M, Ciriello G, Schultz N; **Cancer Genome Atlas Research Network**, Sanchez Y, Greene CS. Machine Learning Detects Pan-cancer Ras Pathway Activation in The Cancer Genome Atlas. *Cell Rep*. 2018 Apr 3;23(1):172-180.e3. doi: 10.1016/j.celrep.2018.03.046. PubMed PMID: 29617658.

Chen H, Li C, Peng X, Zhou Z, Weinstein JN; **Cancer Genome Atlas Research Network**, Liang H. A Pan-Cancer Analysis of Enhancer Expression in Nearly 9000 Patient Samples. *Cell*. 2018 Apr 5;173(2):386-399.e12. doi: 10.1016/j.cell.2018.03.027. PubMed PMID: 29625054; PubMed Central PMCID: PMC5890960.

Dareng E. O., Olanijyan Y., Adebamowo S. N., Eseyin O. R., Odutola M. K., Obiefuna E. M., Offiong R. A., Pharoah P. P., **Adebamowo C. A.** Age, HIV status and research context determined attrition in a longitudinal cohort in Nigeria. *J Clin Epidemiol*. 2018 Apr 18. pii: S0895-4356(18)30111-2. doi: 10.1016/j.jclinepi.2018.04.012. [Epub ahead of print] PubMed PMID: 29679747

Wang S, Ogundiran TO, Ademola A, Oluwasola OA, Adeoye AO, Sofoluwa A, Morhason-Bello I, Odedina SO, Agwai I, **Adebamowo C.**, Obajimi M, Ojengbede O, Olopade OI, Huo D. Development of a Breast Cancer Risk Prediction Model for Women in Nigeria. *Cancer Epidemiol Biomarkers Prev*. 2018 Apr 20. pii: cebp.1128.2017. doi: 10.1158/1055-9965.EPI-17-1128. [Epub ahead of print] PubMed PMID: 29678902.

Immunotherapy



Yang Liu, PhD

The Division of Immunotherapy, led by **Yang Liu, PhD**, Professor of Surgery, was established in February 2018. Nineteen scientists were recruited from the Children's National Medical Center with generous support from the Department of Surgery, the Cancer Center and the School of Medicine. The overall mission of the Division is two-fold. First, they perform 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.

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, they call this pathway sialoside-based pattern recognition. Over the years, they have extended the significance of this pathway into a number of pathological conditions, including autoimmune diseases, cancer immunotherapy-related adverse effect and metabolic syndrome. More recently, the Division collaborated with Pavan Reddy, MD at the University of Michigan to investigate the role of CD24-Siglec G interaction in pathogenesis graft vs host diseases.

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.

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 naïve T cells in the lymphoid organ. However, their work 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. 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. Their work raised the intriguing possibility that for CTLA-4 targeting, autoimmune disease is not a necessary price for cancer immunity.

With the laboratory's relocation to IHV, they will not only continue to work on the two major areas of research, but also extend the potential significance of the above pathway in HIV infection and solid organ transplantation.



Laboratory of Yang Liu, PhD, pictured center in the front row

Immunotherapy Publications

Tang F, Du X, Liu M, Zheng P, Liu Y. Anti-CTLA-4 antibodies in cancer immunotherapy: selective depletion of intratumoral regulatory T cells or checkpoint blockade? *Cell Biosci.* 2018 Apr 18;8:30. doi: 10.1186/s13578-018-0229-z. eCollection 2018.

Zhu J, Liu JQ, Shi M, Cheng X, Ding M, Zhang JC, Davis JP, Varikuti S, Satoskar AR, Lu L, Pan X, **Zheng P, Liu Y, Bai XF.** IL-27 gene therapy induces depletion of Tregs and enhances the efficacy of cancer immunotherapy. *JCI Insight.* 2018 Apr 5;3(7). pii: 98745. doi: 10.1172/jci.insight.98745. [Epub ahead of print]

Flores R, **Zhang P, Wu W, Wang X, Ye P, Zheng P, Liu Y.**

Siglec genes confer resistance to systemic lupus erythematosus in humans and mice. *Cell Mol Immunol.* 2018 Mar 5. doi: 10.1038/cmi.2017.160. [Epub ahead of print]

Du X, **Tang F, Liu M, Su J, Zhang Y, Wu W, Devenport M, Lazarski CA, Zhang P, Wang X, Ye P, Wang C, Hwang E, Zhu T, Xu T, Zheng P, Liu Y.** A reappraisal of CTLA-4 checkpoint blockade in cancer immunotherapy. *Cell Res.* 2018 Apr;28(4):416-432. doi: 10.1038/s41422-018-0011-0. Epub 2018 Feb 22.

Du X, Liu M, Su J, **Zhang P, Tang F, Ye P, Devenport M, Wang X, Zhang Y, Liu Y, Zheng P.** Uncoupling therapeutic from immunotherapy-related adverse effects for safer and effective anti-CTLA-4 antibodies in CTLA4 humanized mice. *Cell Res.* 2018 Apr;28(4):433-447. doi: 10.1038/s41422-018-0012-z. Epub 2018 Feb 20.

Li D, Hu M, **Liu Y, Ye P, Du P, Li CS, Cheng L, Liu P, Jiang J, Su L, Wang S, Zheng P, Liu Y.** CD24-p53 axis suppresses diethylnitrosamine-induced hepatocellular carcinogenesis by sustaining intrahepatic macrophages. *Cell Discov.* 2018 Feb 6;4:6. doi: 10.1038/s41421-017-0007-9. eCollection 2018.

Tang F, Zhang P, Ye P, Lazarski CA, Wu Q, Bergin IL, Bender TP, Hall MN, Cui Y, Zhang L, Jiang T, Liu Y, Zheng P. A population of innate myelolymphoblastoid effector cell expanded by inactivation of mTOR complex 1 in mice. *Elife.* 2017 Dec 5;6. pii: e32497. doi: 10.7554/eLife.32497.

Zhang P, Wu X, Basu M, Dong C, Zheng P, Liu Y, Sandler AD. MYCN Amplification Is Associated with Repressed Cellular Immunity in Neuroblastoma: An *In Silico* Immunological Analysis of TARGET Database. *Front Immunol.* 2017 Nov 3;8:1473. doi: 10.3389/fimmu.2017.01473. eCollection 2017.

Li N, Zheng P, Liu Y. The CD24-Siglec G axis protects mice against cuprizone-induced oligodendrocyte loss: targeting danger signal for neuroprotection. *Cell Mol Immunol.* 2018 Jan;15(1):79-81. doi: 10.1038/cmi.2017.47. Epub 2017 Jul 31.

Toubai T, Rossi C, Oravec-Wilson K, Zajac C, Liu C, Braun T, Fujiwara H, Wu J, Sun Y, Brabbs S, Tamaki H, Magenau J, **Zheng P, Liu Y, Reddy P.** Siglec G represses DAMP-mediated effect on T cells. *JCI Insight.* 2017 Jul 20;2(14). pii: 92293. doi: 10.1172/jci.insight.92293.

Center for International Health, Education and Biosecurity (CIHEB)



Deus Bazira, DrPh, MBA, MPH

The IHV Center for International Health, Education, and Biosecurity (CIHEB) has continued to grow since its formal launch in June 2017. Under the direction of **Deus Bazira, DrPH, MBA, MPH**, Assistant Professor of Medicine and Director of CIHEB, the current program portfolio spans 7 countries, more than 15 various projects, and employs a team of over 540 faculty and staff around the world. CIHEB's mission is to improve health outcomes and promote health equity worldwide.

From education to care and treatment and from surveillance to testing and linkage to care, CIHEB's achievements and impact rise each year through funded projects in Botswana, Haiti, Kenya, Nigeria, Rwanda, Tanzania, and Zambia. Their vast team of experts in medicine, public health, infectious diseases, health systems, laboratory science, health information technology, and epidemiology launched new projects in Botswana, Kenya, and Rwanda in 2017, in addition to continuing to implement ongoing projects in the seven countries. Below, the Center presents select achievements in the last year, and an overview of a few program highlights.

In Zambia, CIHEB manages two Centers for Disease Control and Prevention (CDC) co-operative Agreements (Co-Ags) as the prime recipient, providing comprehensive prevention, care, and treatment support to government facilities in the Southern Province. The Stop Mother And Child HIV Transmission (SMACHT plus) project was expanded from a prevention of mother-to-child transmission (PMTCT) award to a comprehensive HIV response program covering the whole Southern Province, which is home to 12% of the country's population and supports 311 health facilities. The Zambia Community HIV Epidemic Control

for Key Populations (ZCHECK) cooperative agreement is a comprehensive prevention, care, and treatment program focusing on community support to Key and Priority Populations. Both programs implement the CIHEB **CHC© (Community HIV Epidemic Control) Model**—a CIHEB differentiated care innovation that utilizes Community Peer Health Volunteers enhanced with the use of mobile health technology to expand service delivery at a community level. This model has been validated and the International AIDS Society (IAS) recently funded a publication to showcase it as a best practice model for HIV differentiated care delivery that is scalable to benefit large populations.

CIHEB Zambia has been the main technical assistance support partner to the Ministry of Health (MoH) leading the development of PrEP (Pre-Exposure Prophylaxis) guidelines and rolling out of the PrEP program targeting the most at risk persons in Zambia. To date, more than 200 individuals have been enrolled on PrEP. Data from PrEP initiation led to two successful submissions including an oral presentation, *Pre-Exposure Prophylaxis in Zambia: Policy Engagement and Initial Implementation* at the INTEREST Conference in Kigali, Rwanda in June 2018 and a poster presentation at the International Aids Society Conference in Amsterdam in July 2018. CIHEB Zambia also had two abstracts accepted for poster presentations at the upcoming Infectious Diseases Week in San Francisco to be held in October 2018 including *The UNZA/UMB MMed ID Collaboration: Training and Retaining HIV Specialist Physicians in Zambia*, by **Lottie Hachaambwa, MB ChB**, Assistant Professor of Medicine and *High Frequency*



An HIV+ pregnant mother with her HIV-free child attends antenatal clinic at an IHV/CIHEB supported facility in Livingstone, Zambia, to ensure that her second child is also born free of HIV



CIHEB Tanzania team

of Multi-Drug Resistant Organisms (MDRO) at University Teaching Hospital (UTH), Lusaka, Zambia, by **Brenna Roth, MD**, Visiting Instructor of Medicine. CIHEB Zambia currently provides comprehensive care services to 60,659 people living with HIV (PLHIV) as of March 2018.

CIHEB Tanzania currently implements a national level technical assistance program titled, REACH, whose main purpose is to improve uptake of data and evidence for faster HIV epidemic control achievement. The program, a 5-year CDC cooperative agreement runs from September 2016 through September 2021. In this role, CIHEB Tanzania is the main technical partner to CDC and the MoH, and directly strengthens capacity of the government's 10 Regional Health Management Teams and 3 Local Implementing Partners to effectively manage the HIV response, and to adopt and rapidly scale-up key innovations and best practices. This work builds on previous programs for tuberculosis (TB) control funded by the World Health Organization (WHO) TB REACH, HIV Drug Resistance Surveillance, and comprehensive HIV service delivery projects implemented through the President's Emergency Plan For AIDS

Relief (PEPFAR) funding. The current program indirectly benefits over 700,000 PLHIV who are receiving antiretroviral treatment.

CIHEB Tanzania has pioneered the use of Geospatial Mapping to hotspot community areas with high undiagnosed HIV cases. This work has helped to optimize community HIV testing programs and improved HIV positivity yield, which has resulted in higher program fidelity. In some areas, yield has improved from 1% to more than 7%. To date this mapping exercise has been completed in 10 regions of the country that cover more than 40% of the population. The information generated has provided better insight into major drivers of HIV infections,



Geospatial Mapping to hotspot community areas with high undiagnosed HIV cases in Tanzania

HIV service coverage, sub-populations most at risk, and those that remain undiagnosed. Most importantly, the hotspot community mapping has enhanced Index Partner Testing Services through more effective sexual and social network identification.

The program has developed and led implementation of a suite of health technology solutions to improve PEPFAR's programs efficiency, reporting, and use of data, as well as evidence to inform key decisions. These have included:

1. **Electronic Reporting Platform**—(first of its kind) for all quality improvement activities, including a quality improvement (QI) toolkit repository. This solution allows tracking and reporting on all qualitative and quantitative QI related achievements, and helps to guide future capacity enhancement interventions
2. **DHIS2-DQA**—a data quality monitoring tool primarily designed to ensure the quality of HIV/AIDS data reported to the National District Health Information System, the main national health information system.
3. **IQ-SMS**—a weekly mobile data reporting tool designed to collect HIV testing services data from facilities.
4. **Data-X-Change**—a web-based system used to transfer HIV/AIDS data into the main PEPFAR data reporting system, DATIM, on a quarterly basis for increased accountability & transparency.
5. **Monthly Reporting Tool**—that aggregates data reported by all health facilities. This allows data visualization at a national level and provides opportunities for performance comparison across facilities and regions for better planning and health resource rationalization.



Quality improvement collaborative training presentation in Mwanza, Tanzania

Aside from the continuous quality improvement (CQI) and monitoring and evaluation (M & E) systems, CIHEB Tanzania has developed an e-Referral technology solution designed to assist health facilities to issue electronic referrals and track patients within the care system. This has enabled better patient tracking, will improve patient retention, and will allow for actualization of provider collaborative care networks for improved population health outcomes. Further, CIHEB Tanzania has developed The Kijana AFYA Facebook platform, an open forum for adolescents and young adults to access information and answers on sexual reproductive health and HIV/AIDS. This platform is poised to increase access for adolescents and youth to key services, and to promote retention in care and treatment adherence through enhanced peer support.

In Rwanda, CIHEB launched the “IMAKAZA” (To Sustain) program in 2017. IMAKAZA strengthens and institutionalizes sustainable national, provincial, and district HIV oversight and delivery systems through training and mentorship to improve healthcare worker competencies, targeting universal access to treatment, and long-term epidemic control through dynamic evidence driven programming. In addition, the program provides technical assistance to the

MoH and health facilities to adopt, implement, scale up, and replicate best practices and proven health innovations. This program builds on the history of successful partnership with the Government of Rwanda dating back to 2004. To date, CIHEB Rwanda is the main PEPFAR technical assistance partner in the country to assist the MoH with implementing a sustainable comprehensive HIV response. The program benefits all of the 104,000 PLHIV currently receiving treatment and has helped the country achieve more than 91% viral suppression for those receiving treatment. Patient retention in care remains high at 92%, one of the highest in the world.

Further, CIHEB Rwanda provides ongoing technical expertise to develop and update key policies and guidelines. During this year, CIHEB Rwanda supported the Rwanda Biomedical Center (RBC), the technical arm of the MoH, to revise and update the National Guidelines for Prevention and Management of HIV. In addition, the CIHEB Rwanda Team trained health providers as part of guidelines dissemination and faster adoption process. Additionally, the IMAKAZA Program has collaborated with RBC and the Rwanda Office of the U.S. CDC to develop the Differentiated Service Delivery Model (DSDM) aimed at expanding care delivery through more efficient approaches at the community

level. This model of care delivery is being rolled out to 22 health facilities. Alongside the differentiated service delivery model implementation, the IMAKAZA program team will continue to collaborate with MoH’s RBC and CDC to monitor and evaluate the impact of the model of improving efficiency in care delivery and effectiveness of the model measured by patient outcomes. CIHEB Rwanda continues the long-standing activity of training all 42 district and university teaching hospital-based mentors to keep them informed of new knowledge and at the cutting edge of HIV and related infectious diseases medicine. This activity has been credited with making the Rwanda MoH one of the few that leads direct HIV service delivery with no international organizations involvement, except for the technical assistance support provided mainly by the CIHEB Rwanda Team. The IMAKAZA Program provides a template for how to make national HIV response sustainable and lift external financial resources to reach more PLHIV with prevention and treatment services. IMAKAZA Program follows a very efficient model for providing technical assistance to a country.



Review of quality indicators, QI Training in Mwanza, Tanzania



CIHEB Nigeria team

In Nigeria, CIHEB implements a Global Health Security program with several interventions called **SERS (Strengthening Epidemic Response Systems)**. This program is funded by CDC through its Global Health Security Agenda. Central to the implementation of this project is capacity building of frontline healthcare workers, following the agreed WHO AFRO Region Integrated Disease Surveillance and Response (IDSR) guidelines. Through an on-the-job training strategy at the State level, over 9,000 frontline health workers have been trained, and 570 members of State level surveillance teams across 29 states in Nigeria. In addition, CIHEB Nigeria has networked laboratories to support the surveillance systems in the country through the Basic Laboratory Information System (BLIS). As of June 2018, a total of 10 laboratories have been networked across the six geopolitical zones of the country for collection and reporting of key laboratory data used to redefine surveillance activities at the Nigerian Center for Disease Control (NCDC).

Traditional surveillance systems have often been criticized for lagging behind outbreaks within communities, especially in regions where health facilities are not readily accessible. Complementary (event-based) surveillance systems have served to bridge this gap. In Nigeria, CIHEB developed and deployed an event-based surveillance system (Tatafo©) to mine health-related data on social media using local language and terms referring to specific diseases within rural and urban regions. This system has proven to be extremely useful by providing an avenue

for NCDC to quickly dispel and/or confirm rumors about outbreaks across the country.

The Strengthening Epidemic Response Systems (SERS) project team is also working to improve antimicrobial resistance by surveillance of antibiotic use in non-traditional sources, such as patient medicine stores and pharmacies. Antimicrobial resistance remains a big problem in Nigeria, fueled by weak regulations governing sales and access to antimicrobial drugs that are largely available as over the counter medications with no prescription needed to buy them. CIHEB adapted the “WHO methodology for a global program on surveillance of antimicrobial consumption” leveraging existing structures for Integrated Disease surveillance and mSERS© (mobile SERS), and created a platform deployed in various community pharmacies and patient medicine stores for antibiotics consumption monitoring. Consumption data refers to estimates derived from aggregated data where there is no information available on the patients who are receiving the medicines, or why the antimicrobials are being used. These data sources provide a proxy estimate of use of antimicrobials and will be key in providing information to the scope of resistance in Nigeria.

In addition, the SERS program has developed a Mobile Reporting System (mSERS©). The reporting system, “mSERS,” is a SMS-based platform that automates bi-directional data collection, while enabling supervision and oversight of the entire reporting process. It uses mobile telephone technology, because GPRS and data network

may not be cost effective in rural areas. mSERS[©] was designed to improve the existing public health surveillance system, enable the submission of routine and emergency report using SMS, to provide insight into the reporting process at all levels, and to provide a communications framework through which reports can be submitted in a timely manner. mSERS[©] functions as a register of users for reporting, weekly reminders, processing reports, and sending summaries and reports via email.

Further, CIHEB collaborates with IHV's Division of Epidemiology and Prevention to implement two other programs in Nigeria: The Nigeria AIDS Impact Survey (Population-based HIV/AIDS Impact Assessment), and SHIELD: Strengthening HIV Field Epidemiology, Infectious Diseases Surveillance, and Lab Diagnostics. Collectively, IHV's work in Nigeria has positioned the organization to emerge as the key technical partner to the Government of Nigeria and U.S CDC for program evaluation, epidemiological surveillance, and implementation science.

2017 was a landmark year for CIHEB Kenya's HIV/AIDS and TB mitigation efforts. Having surpassed the 1 million mark for patients on antiretroviral drugs (ART), Kenya continued with its march toward epidemic control, immediate ART initiation for all newly diagnosed patients, full access to viral load testing for patients on ART, and an overall community virologic suppression rate of 83%. Additionally, an improved uptake and quality of PMTCT was realized with the rate of newly diagnosed HIV positive infants at six weeks of age falling from 5.2% in 2016 to 3% nationally.

For CIHEB Kenya, 2017-2018 was also an important milestone, as implementation of three of five new federally funded grants, worth over \$27 million annually, to combat the HIV/AIDS epidemic in partnership with the Ministry of Health, the Kenya Medical Research Institute (KEMRI), and the County Health Departments in 12 counties began. The overall goal is to contribute to the Government of Kenya's commitment to HIV epidemic control, by decreasing HIV incidence and reducing HIV-associated morbidity and mortality in Kenya. From July 2017- June 2018, through CIHEB Kenya's prevention, care, and treatment programs, 1,220,780 individuals were tested for HIV, of which 14,215 newly diagnosed patients were identified, and 12,186 were linked to care and treatment services within Nairobi, Kisii, and Migori counties. About 69,812 pregnant women were tested for HIV, and a total of 5,198 HIV positive women were receiving ART for their own health and to protect their infants from acquiring HIV infection. Overall, in 2017, within our Nairobi City County program, the proportion of infants acquiring HIV infection by 18 months was 3.72%. More

than 88,930 patients were on ART, including 8,655 children and adolescents, with an overall viral suppression rate of over 90%.

During the same period, CIHEB Kenya also provided methadone replacement therapy to 1,055 people who inject drugs, 25% of those who are HIV and/or hepatitis B/C co-infected, in a unique community facility linked comprehensive harm reduction service in Nairobi. CIHEB Kenya also supported the accreditation of the National TB and the National HIV Reference Laboratories and is preparing 4 regional laboratories for accreditation. Finally, during this period CIHEB Kenya supported the review, updating, and printing of the national HIV integrated curriculum which supports health care worker training at the point of service. CIHEB Kenya remains the national MoH technical partner for strengthening the HIV health workforce through innovative mentorship and training interventions, and for management of complicated HIV cases including pioneering the establishment of viremia clinics, a model that has been identified by PEPFAR as a best practice which is being promoted for replication in all PEPFAR-supported countries.

The CIHEB Botswana University of Maryland School of Medicine Health Initiative (CIHEB-BUMMHI) is funded to support the Government of Botswana to achieve epidemic control of HIV and is implementing services through the cascade of HIV prevention, care, and treatment within the facility and at community level. CIHEB currently implements two projects including, FEDISA-HIV, a community HIV testing, and linkage to treatment program, and the Botswana Partnership for Advanced Clinical Education (BPACE), a national technical assistance and facility service delivery program. Both programs implement aspects of recently introduced HIV prevention programs targeting Adolescent Girls and Young Women (AGYW), called **DREAMS**, an acronym that embodies the core objectives of the program to ensure that AGYW are **D**etermined, **R**esilient, **E**mpowered, **A**IDS-Free, **M**entored, and **S**afe.

These programs are enacted across 13 districts, six of which are designated by PEPFAR as "scale-up" districts where the estimated treatment coverage for ART is less than 81%, and seven of which are known as "maintenance" districts, where the treatment coverage is more than 81%. FEDISA-HIV is implementing community HIV Testing services in the scale up districts to identify HIV positive individuals whose treatment coverage for ART is low. In Botswana, these include AGYW, young men aged 15-24 years, and men aged 25 years and above. CIHEB is implementing targeted HIV testing strategies including index client partner testing,



Mentoring of lay counselors in the community in Botswana

targeted mobile testing, and targeted community testing to identify “hotspots.” In collaboration with District Health Management Teams (DHMTs), CIHEB provides outreach integrated HIV testing and ARV services at a community level as part of differentiated care, and to improve access to treatment for sub-populations living far away from a health facility.

Within the last year, the program in Botswana has supported 135,907 clients on treatment and 13,812 of these were HIV positive individuals newly enrolled on treatment. CIHEB is supporting health facilities to improve processes that strengthen the care continuum from HIV testing to linkage, which in the last year has improved from the mid-60%’s to 88%. For the individuals enrolled on treatment, retention is at 89% and viral suppression for clients receiving VL at 98%. For the period from April 2017–March 2018, 13,812 HIV positive clients were enrolled on ARV treatment across sites that CIHEB supports. CIHEB also partners with the MoH District Health Management Team to expand HIV services access through facility led outreach mobile services to the underserved community in hard to reach areas. This initiative has been piloted in the Mahalapye district of Botswana, and so far, has enrolled 48 clients on treatment. Further, CIHEB Botswana supports capacity

building of health care workers through various HIV related trainings and clinical mentorship to accelerate task sharing in the delivery of HIV services. In the last two years, CIHEB has collaborated with the MoH to train 1,333 health care workers including more than 200 Nurse Prescribers in different aspects of HIV care management, and has provided coaching to more than 645 health care professionals to institutionalize systematic use of data to improve quality of service delivery.

CIHEB Publications

Claassen C, Hachaambwa L, Phiri D, Watson D, Patel D, Bositis C, Bositis A, Mubangizi D, Redfield R, Mwaba P, Sheneberger R. The Arc of Human Immunodeficiency Virus Capacity Development: Insights from a Decade of Partnership for Medical Education in Zambia. *Am J Trop Med Hyg.* 96(5), 2017, pp. 1011-1013

Riedel DJ, Stafford KA, Memiah P, Coker M, **Baribwira C, Sebeza J,** Karorero E, Nsanzimana S, Morales F, Redfield RR. Patient-level outcomes and virologic suppression rates in HIV-infected patients receiving antiretroviral therapy in Rwanda. *Int J STD AIDS* 2018; 2018 Jan 1:956462418761695

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 and Cell Interactions Core, and μ QUANT Core**, is led by an experienced researcher at IHV. Below is an overview of the Core Facilities.

ANIMAL CORE FACILITY

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

Mr. Davis has a staff of ten animal research care personnel, including two research associates, who are responsible for animal care and assisting investigators with 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 work with investigators using transgenic and knockout mice. The Core informs 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 services. It is an Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accredited facility and is part of the overall animal care and use program at the University of Maryland School of Medicine. The Core has 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

NSG humanized mouse program

The Animal Core is currently developing a research program for humanizing mice, including several NSG animal models:

- 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, and **Sandra Medina-Moreno, BS, MS**, Laboratory Supervisor, are the Core's research team that were instrumental in the development of the program

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. Currently, the Core is working towards distributing the model to other researchers.

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

HIV/AIDS Non-Hodgkin Lymphomas

- a. Pathogenesis Studies
- b. Development of Animal Models for AIDS/NHL



Front row L to R: Harry Davis, MS, Sumiko Williams, MS, Catherine Crews, Tearra Hamilton and Maurice White; Back row L to R: John Tripline, Albert Hunter, Alfred Dye and Chris Adams

- c. HIV-1 matrix protein p17 implicated in virally associated lymphomas
- d. Mycoplasma and Cancer

Collaborators in the Division of Basic Science include:

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

HIV-1 matrix protein p17 implicated in virally associated lymphomas

Recent studies by the aforementioned members of the Division of Basic Science, in collaboration with a team of Italian scientists led by **Arnaldo Caruso, MD, PhD** of

University of Brescia Medical School, who is also an Adjunct Professor of Medicine in the Division of Basic Science, suggested that the HIV-1 matrix protein p17, a structural protein important for viral assembly and maturation, is the culprit closely associated with lymphoma development in HIV/AIDS patients. The TG26 transgenic mouse model developed in the Core provides a unique platform for the study of lymphoma that develops because of HIV-1 gene expression. The connection between HIV-1 p17 and dysregulation of the immune system are intriguing and need to be studied to understand the full consequences of HIV-1 infection. The TG26 mouse model provides unique opportunities for studying the pathogenic effects of HIV-1 gene expression in the absence of active viral replication.

Mycoplasma

Continuing the studies of the relationship between mycoplasma and cancer, Drs. Davide Zella and Robert Gallo, together with Drs. Sabrina Currelli, Fiorenza Cocchi, Joseph Bryant, and Francesca Benedetti, have found an association between mycoplasma sequences and certain human cancers. Together, with their previous studies showing that certain strains of mycoplasma induce lymphomas in 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 Medicine

Nichols Stamatou, MD, PhD, Assistant Professor of Medicine

Evaluating Treatment with CCR5

Alonso Heredia, PhD and Olga Latinovic, PhD are evaluating treatment with a CCR5 antagonist to slow tumor progression in HIV transgenic mice with early states of tobacco-induced NSCLC (small lung cancer). The Animal Core developed a mouse model for the study of lung cancer in the setting of HIV infection. The mouse model may allow the evaluation of novel treatments for patients with HIV and lung cancer.

Humanized Mice for HIV Studies

Since the Division of Vaccine Research developed the Full Length Single Chain Fc protein (FLSC 1IgG1), Drs. Heredia and Latinovic are researching this protein as a potent antiviral therapy candidate by identifying implications for in vivo studies in humanized mice.

Function of Polysialic Acid in Immune Cell Activity

Nichols Stamatou, 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 Apho Corporation

Development of Natural Plants as Anti-Cancer Drugs

Henry Lowe, PhD, IHV Adjunct Professor of Medicine, PhD from Jamaica is collaborating with the Animal Core on a flavonoid from *Tillandsia recurvata* 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, Professor in the Department of Neurology at the University of Maryland School of Medicine, is utilizing the HIV-1 transgenic rat model to study the in vivo effects of nicotinamide adenine dinucleotide (NAD) associated in suppressing nervous system inflammation and other neuropathological abnormalities mediated by HIV-1

infection. For these studies, the Core utilizes two transgenic rat models of HIV-1 infection, including a well-established model developed on a wild-type F334 Fisher rat background (the HIV1TgNu+rat), which provides a model of HIV infection in the presence of severe immunodeficiency.

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

Tapas Makar, PhD, Adjunct Assistant Professor in the Department of Neurology at the University of Maryland School of Medicine, is collaborating with the Core to study HIV primary central nervous system lymphoma (PCNSL) as a malignant diffuse large B cell lymphoma that occurs in 3-5% HIV patients. Animal models are 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

Publications

Royal, W; Can, A; Gould, T; Guo, M; Huse, J; Jackson, M; **Davis, H; Bryant, J.** Cigarette smoke and nicotine effects on brain proinflammatory responses and behavioral and motor function in HIV-1 transgenic rats *J of Neurovirology*. 2018 Apr 24(2):246-253.

Bryant JL, Guda PR, Asemu G, Subedi R, Ray S, Khalid OS, Shukla V, Patel D, **Davis H,** Nimmagadda VKC, Makar TK. Glomerular mitochondrial changes in HIV associated renal injury. *Exp Mol Pathol*. 2018 Jun;104(3):175-189. Mar 31.

Bryant JL, Guda PR, Ray S, Asemu G, Sagi AR, Mubariz F, Arvas MI, Khalid OS, Shukla V, Nimmagadda VKC, Makar TK. Renal aquaporin-4 associated pathology in TG-26 mice. *Exp Mol Pathol*. 2018 Jun;104(3):239-249

Mubariz F, **Bryant JL,** Nimmagadda VKC, Ray J, **Makar TK.** AQP4 and HIVAN. *Exp Mol Pathol*. 2018 Aug;105(1):71-75.

Officer at Aphoix 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 MSc, PhD, Assistant Professor of Medicine, 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.

FLOW CYTOMETRY AND CELL CORE FACILITY

The Flow Cytometry and Cell Core Facility serves the IHV community with varying needs associated with flow cytometry. Flow Cytometry is a fundamental tool for modern virology/immunology/cell biology research. The IHV Flow Core is headed by **Yutaka Tagaya, MD, PhD**, Assistant Professor of Medicine in the Division of Basic Science, who has over 30 years of experience with flow cytometry technology. The Flow Core's operation is maintained by **Juan C. Zapata, PhD**, Research Associate of Medicine in the Division of Basic Science, as the chief operator/trainer. Each user is charged with fees based upon usage (please ask the FlowCore staff for pricing).



Juan Zapata, PhD and Yutaka Tagaya, PhD



Juan Zapata, PhD operates the Flow Cytometry and Cell Core Facility's Aria sorter

The Core has two major instruments:

1. BD's FACSAria (3 lasers—405 nm violet, 488 nm blue and 633 nm red—which allows 12 independent color analysis and fluorescence-based cell sorting including a single cell/indexing methodology), located in the north BSL3 facility
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)

While the Aria is only operated by the Flow Core staff (because it is located inside the BSL3 facility), each trained user can use the 10-color GUAVA machine for flow analysis. At the moment, the IHV Flow Core is the only facility that can sort infectious cells (cells infected by hepatitis viruses, HIV and HTLV) at the University of Maryland, Baltimore (UMB). We offer services to labs at the IHV, UMB, and externally.

The IHV Flow Core not only operates the equipment, but also works with each investigator by consulting on the experimental design and by training the researcher for instruments and software (if necessary). The Flow Core will also offer help with advanced data analysis using the FlowJo. The IT department of the IHV can help each investigator to install a copy of FlowJo at a cost.

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 has contributed to their publications and in grant submissions.

The IHV Flow Core will continue serving the IHV and UMB to accomplish their mission in medical biology. For more information, please contact us at ytagaya@ihv.umaryland.edu.



Olga Latinovic, PhD, MSc

IMAGING STUDIES OF PATHOGENS AND CELL INTERACTIONS FACILITY

The Imaging Studies of Pathogens and Cell Interactions Facility was established in 2012 as the first IHV Imaging Facility and is led by **Olga Latinovic, PhD, MSc**, Assistant Professor of Microbiology and Immunology in the Division of Basic Science. The laboratory was equipped with a Confocal LSM 800 Airyscan Microscope by Zeiss since 2017. The Facility is primarily focused on image analysis, studies of pathogens, and host cell interactions. A few projects of the Facility include:

p17 Project

Dr. Latinovic uses 3D images via confocal microscopy methods with **Alfredo Garzino-Demo, PhD**, Associate Professor of Microbiology and Immunology in the Division of Basic Science, Frank Denaro, PhD, Associate Professor of Biology at Morgan State

University, **Mika Popovic, PhD**, Adjunct Professor of Medicine in the Division of Basic Science, **Robert Gallo**,

MD, The Homer & Martha Gudelsky Distinguished Professor in Medicine and Director of IHV, and the p17 group for the quantification studies of angiogenesis that is caused by the HIV matrix protein p17 in nude mice (Figure 1). The group demonstrated dose-response effect of refp17 angiogenesis expressed as endothelial cell migration in matrigel plugs. This part of the IHV's p17 project is the continuation of their published studies on the p17 related angiogenesis work by Basta, Latinovic

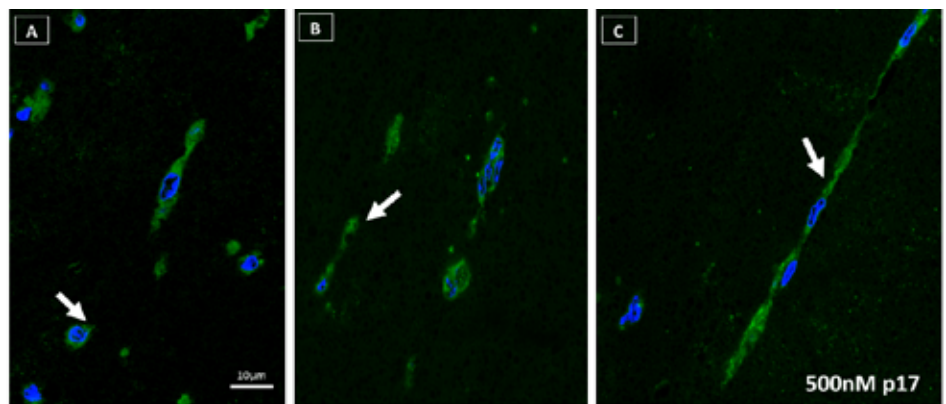


Figure 1. A) Single isolated cell in early stage of differentiation; B) Spindle cell shape, lining up; C) Formation of the early vessel

Note: seen in other conc as well, this 500 nM is just a representative

et al, 2015. Altogether, the work resulted as submitted RO1 proposal, in May 2018.

Mycoplasma Project

Dr. Latinovic was involved in areas of the Mycoplasma project since the beginning of her post-doctoral years at IHV when working closely on the topic originally with **Fabio Romerio, PhD**, Assistant Professor of Medicine in the Division of Basic Science, and

Davide Zella, PhD, Assistant Professor of Biochemistry and Molecular Biology in the Division of Basic Science, and the group back in 2009.

Their original observations were related to the rosetting patterns of mycoplasma interaction with human lymphocytes. The current focus of the mycoplasma imaging related areas of this project are specifically related to the direct visualization studies of the mycoplasma's protein DNAK, its mapping sites inside the cells, and its interactions with the p53 protein in different cell lines. The project is directed by Drs. Gallo and Zella.

HIV-1 Latency Research

Dr. Latinovic utilizes super resolution and confocal microscopy methodologies and image analysis in collaboration with Dr. Romerio to

investigate 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 led to the conclusion that HIV-1 antisense protein ASP may be a new structural protein of the HIV envelope. This study could have implications for better understanding of HIV-1 infection and for the development of new vaccine and therapeutic strategies. A manuscript describing these studies is in preparation.

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.

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 troubleshooting all protocols utilized and has developed laboratory Standard Operating Procedures. Its aim is to provide consistent, cost effective services that allow researchers to compare results generated within a week. The Core has been very successful in meeting these goals, and as such, its existence has optimized the pace and scope of research at IHV.

Core services include: routine immunoassays (e.g. ELISA); endotoxin testing; monoclonal antibody and recombinant protein screening, production, purification, and labeling; production and maintenance of virus and cell stocks; and maintenance of common use equipment. The

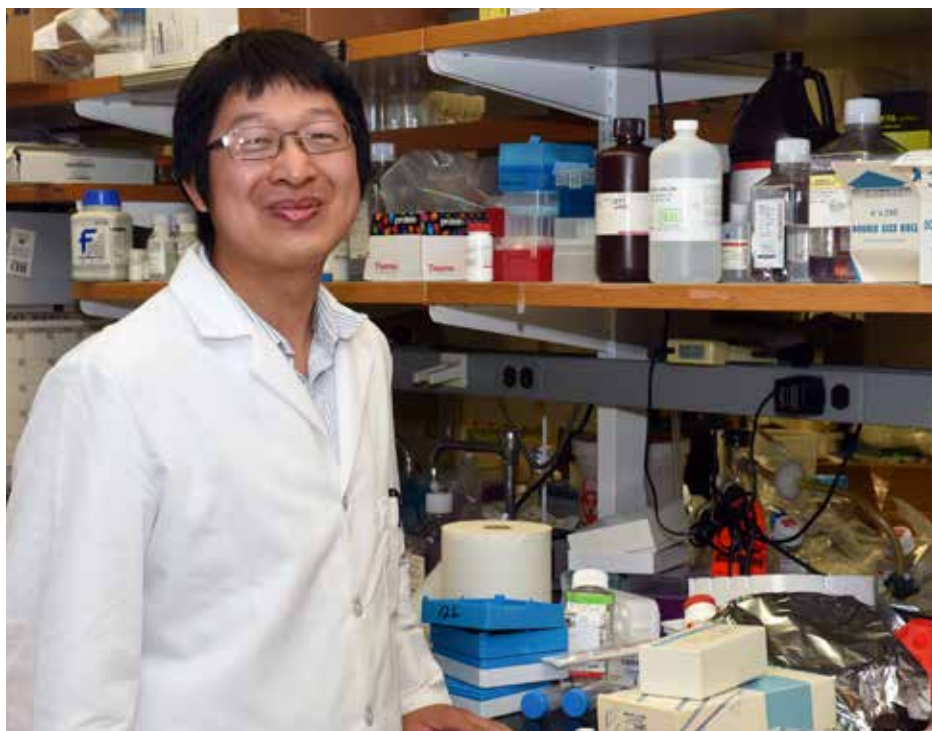


latter includes a BIACORE T200, a SpectraMax M2 ELISA plate reader, an ABI simpliAmp PCR machine, and a StepOnePlus qPCR machine. Several other new and/or refurbished pieces of equipment include an ABI QuantStudio3 qPCR machine, a BioRad BioPlex System, and a Miltenyi Biotec autoMACS cell separator.

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

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

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



Ping-Hsin "Rex" Lin, MS

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



Christian Bréchet, MD, PhD

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a Center of Excellence of the Global Virus Network with a major role in its formation and 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 Scientific Director, and his colleagues **William Hall, MD, PhD**, and the late **Reinhard Kurth, MD**. Dr. Hall is Professor of Microbiology at the University College Dublin (UCD) in Dublin, Ireland. Dr. Kurth was the former Director of the Paul Ehrlich Institute and the Robert Koch Institute and Chairman of the Foundation Council at Ernst Schering Foundation in Berlin, Germany in addition to serving as a member of the IHV Board of Advisors. At the inaugural meeting in DC, attendees from more than a dozen countries affirmed and ratified GVN's goals and objectives. Since that three-day meeting, GVN was incorporated by the U.S. government as a non-profit, 501(c)(3) organization. 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 the Africa Center of Excellence for Infectious Diseases of Humans and Animals

(ACEIDHA) at the University of Zambia in Lusaka as an Affiliate via two GVN Centers of Excellence, Hokkaido University (HU) in Sapporo, Japan and University College Dublin in Dublin (UCD), Ireland. The GVN added new Centers of Excellence with the Uganda Virus Research Institute (UVRI) and a Singaporean consortium of 7 virology research intuitions led by Duke-NUS Medical School.

GVN Members represent expertise covering every class of human virus, and currently comprise virologists from 45 Centers of Excellence and 7 Affiliates in 29 countries, and its numbers continue to grow. GVN has held subsequent meetings in Ireland, Italy, USA, Germany, Russia, Sweden, Grenada, Estonia, China, Japan, and Australia.

The 9th International GVN meeting, in partnership with The Peter Doherty Institute for Infection and Immunity and Institut Pasteur, in Melbourne, Australia September 25-27, 2017 held an impressive session on one of the most potent human carcinogens, human T cell leukemia virus subtype 1 (HTLV-1),

which is also the first human retrovirus discovered by Dr. Gallo and is endemic in regions around the world particularly in the Aboriginal population of Australia. The GVN session inspired a group of renowned scientists and activists to call the World Health Organization (WHO) to support the promotion of proven, effective transmission prevention strategies on this debilitating and deadly virus through an open letter. An abbreviated version of the letter, Time to eradicate HTLV-1: an open letter to WHO, was published in The Lancet May 12 issue. The full letter was published on the GVN website. The initiative was covered internationally in press by organizations such as CNN, Newsweek, ABC News (Australia), and The Guardian, among many others, and has resulted in \$8 million in funding from the Australian government to form a taskforce on HTLV-1.

In addition to serving as a successful advocate for raising awareness about HTLV-1, the GVN contributed expertise to viral outbreaks around the world this past year. The Democratic Republic



Participants of the Fifth Annual GVN Short Course on Medical Virology



Participants of GVN's 9th International Meeting in Melbourne, Australia

of the Congo (DRC) faced a deadly Ebola outbreak in which several of GVN's Centers contributed research and sent scientists to the DRC. The GVN also served as a hub to aggregate and disseminate information on each Center's individual responses to the outbreak to better coalesce and inform a collective approach. In tandem with organizations such as the WHO's Global Outbreak Alert and Response Network (GOARN), and other international institutions, the GVN coordinated research and response efforts and serve as a catalyst for shared information to focus efforts on the areas in greatest need. Further, last year, Kerala, India experienced a deadly outbreak of Nipah virus in which GVN members provided scientific, clinical and epidemiological expertise in addition to reagents to laboratories in the field.

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

This summer, GVN launched its Fifth Annual Short Course on Medical Virology held August 5-11, 2018 for 16 early career medical virologists from Austria, Canada, China, Jamaica, Japan, Kenya, Nigeria, Saudi Arabia, Trinidad, United States, and Zambia. 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. The Short Course is designed to counter a declining number of researchers entering the field of medical virology. IHV hosted many meetings and provided

an array of experts to speak to participants throughout the week. IHV faculty and staff supporting the important event included **Robert Gallo, MD; Shyam Kottilil, MBBS, PhD; Man Charurat, PhD; Yutaka Tagaya, PhD; Clement Adebamowo, BM, ChB, ScD, FWACS, FACS; Jose Esparza, MD, PhD; Alfredo Garzino-Demo, PhD; Niel Constantine, PhD, MT(ASCP); and, Kathleen Neuzil, MD, MPH, FIDSA**, on campus at the University of Maryland School of Medicine. Burgeoning medical virologists were encouraged to participate in deep discussions and interaction with medical virology leaders in addition to meeting with policymakers and leaders at the National Institutes of Health in Bethesda, Maryland and Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland.

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

The GVN, in partnership with the Fondation Mérieux (FM) and the University of Veterinary Medicine Hannover (TiHo), convenes the 10th International Global Virus Network Meeting on Eradication and Control of (Re-)Emerging Viruses in Annecy, France November 28-30, 2018.



Robert Gallo, MD leads a panel discussion on the status of HTLV-1 research during the 9th International GVN Meeting in Melbourne

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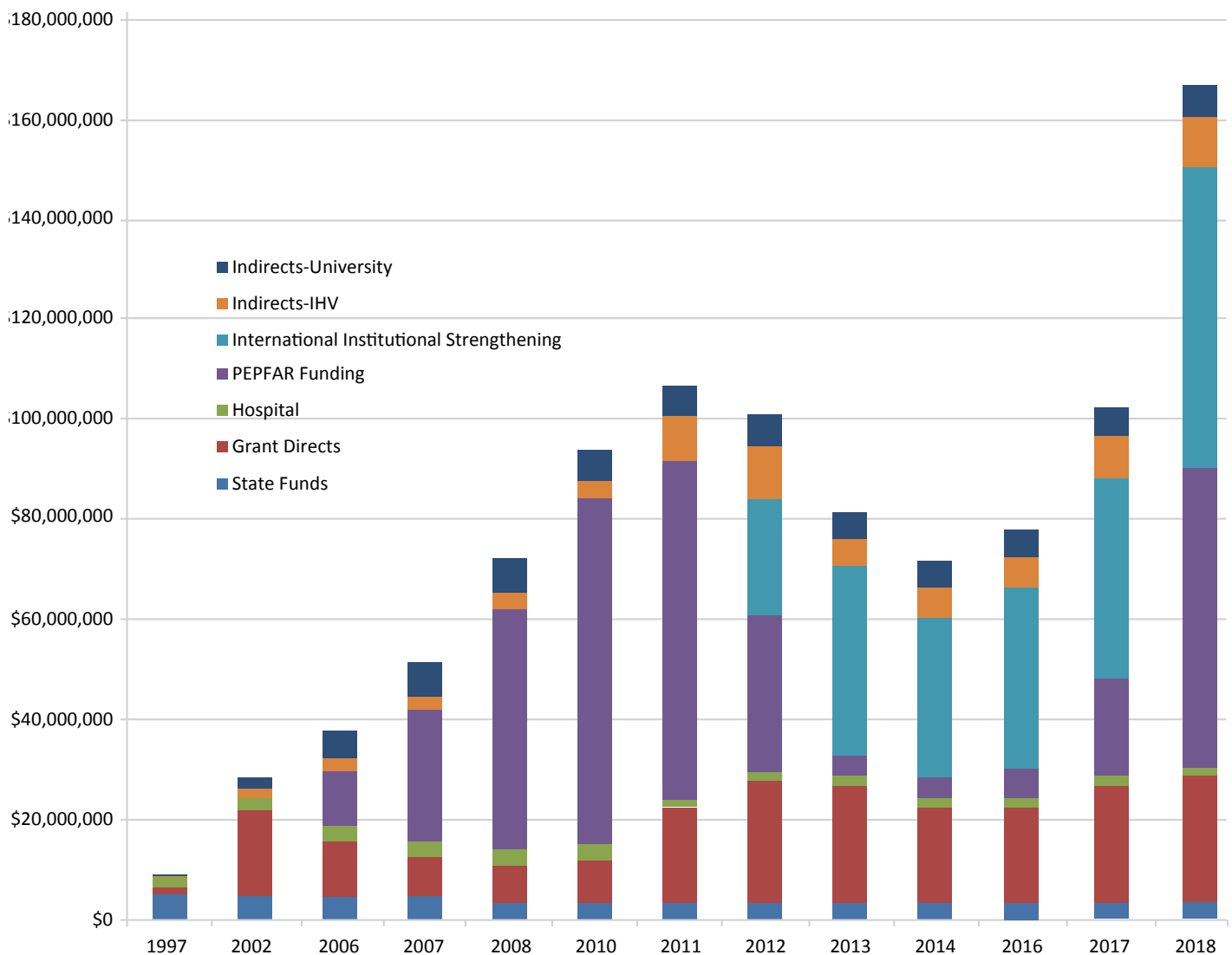
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Financial Overview

In Fiscal Year 2018, the Institute of Human Virology (IHV) experienced another year of incredible growth. While the financial growth was primarily a result of significant increases in international funding as is normally the case, each area of IHV grew this year, including Basic Science, Vaccine Research, and Clinical Care and Research. IHV successfully recruited a laboratory to launch the new Division of Immunotherapy, which already has contributed 5 new grants to IHV's research success. Increases in IHV's Center for International Health, Education, and Biosecurity (CIHEB) grants in 7 countries and new significant awards to IHV's Division of Epidemiology and Prevention to conduct a comprehensive HIV survey in Nigeria have driven IHV's funding success to unprecedented heights.

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



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