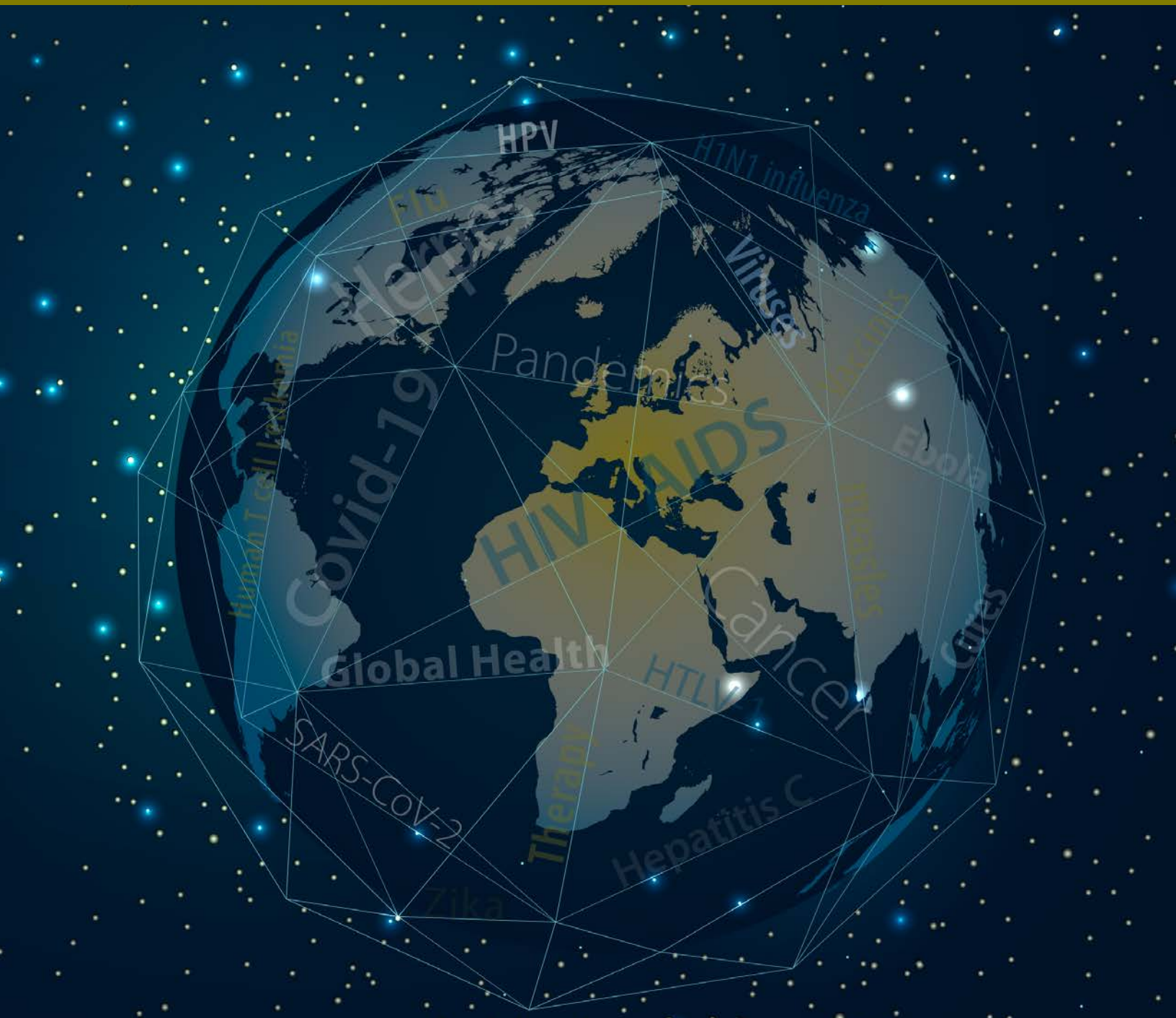
INSTITUTE OF HUMAN VIROLOGY

2020 ANNUAL REPORT



UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

About IHV

The Institute of Human Virology (IHV) is the first center in the United States—perhaps the world—to combine the disciplines of basic science, epidemiology and clinical research in a concerted effort to speed the discovery of diagnostics and therapeutics for a wide variety of chronic and deadly viral and immune disorders—most notably HIV, the cause of AIDS.

Formed in 1996 as a partnership between the State of Maryland, the City of Baltimore, the University System of Maryland and the University of Maryland Medical System, IHV is an institute of the University of Maryland School of Medicine and is home to some of the most globally-recognized and world-renowned experts in the field of human virology. IHV was co-founded by Robert Gallo, MD, director of the of the IHV, William Blattner, MD, retired since 2016 and formerly associate director of the IHV and director of IHV's Division of Epidemiology and Prevention and Robert Redfield, MD, resigned in March 2018 to become director of the U.S. Centers for Disease Control and Prevention (CDC) and formerly associate director of the IHV and director of IHV's Division of Clinical Care and Research.

In addition to the two Divisions mentioned, IHV is also comprised of the Infectious Agents and Cancer 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 SARS-CoV-2, hepatitis C virus, human T cell leukemia viruses 1 and 2, human papillomavirus, herpes viruses and cancer research. IHV's patient base has grown from just 200 patients to approximately 5,000 in Baltimore and Washington, D.C., and more than 2 million in African and Caribbean nations. In particular, IHV is internationally renowned for its basic science and vaccine research, which includes a preventive HIV vaccine candidate in human clinical trials and funded largely by the Bill & Melinda Gates Foundation.

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

Our Mission

The Institute of Human Virology (IHV) was established to create and develop a world-class center of excellence focusing on chronic viral diseases, especially HIV/AIDS, and virally-linked cancers.

The IHV is dedicated to the discovery, research, treatment, and prevention of these diseases.

Its unique structure seeks to connect cohesive, multi-disciplinary research and clinical programs so that new treatments are streamlined from discovery to patient.

The IHV serves patients locally and the scientific community globally.

Director's Message
A Look at the year

Robert C. Gallo, MD

The Institute of Human Virology at the University of Maryland School of Medicine flourished this past fiscal year.

In October 2019, IHV hosted its 21st Annual International Meeting (IHV2019) 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 mainly by **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division of Clinical Care and Research and Head of the Clinical Care Research Unit, Institute of Human Virology, University of Maryland School of Medicine with help from **Man Charurat, PhD**, Professor of Medicine, Director of the Division of Epidemiology and Prevention and Director, CIHEB, Institute of Human Virology, University of Maryland School of Medicine and **Anthony Amoroso, MD**, Associate Professor of Medicine, Associate Director of the Division of Clinical Care and Research and Head of Clinical Care Programs, Institute of Human Virology, University of Maryland School of Medicine. This year, the Institute's faculty voted to focus on one theme, "Progress in HIV/AIDS: Challenges in 2020" which opened with highlights about the recent plan for "Ending the HIV Epidemic by 2030" with expert opinions by Anthony Fauci, MD, Director, National Institute of Allergy and Infectious Diseases (NIAID), Nora Volkow, MD, Director, National Institute of Drug Abuse (NIDA) and ADM Brett P. Giroir, MD, Assistant Secretary for Health at the U.S. Department of Health and Human Services (HHS), among other notable speakers throughout the two day meeting. Welcome remarks were also provided by Maryland Senate President Bill Ferguson and Maryland Delegate Brooke Lierman.

Anthony Fauci, MD

The Meeting, which attracts hundreds of elite scientists who descend upon Baltimore to share ideas and inspire medical virus research collaborations, focused on two critical issues including leveraging scientific advances in the field of HIV to end the HIV epidemic in America and integrating resources to address the ongoing opioid epidemic and prevent its impact on the lives of HIV infected patients.

L to R: Robert Gallo, MD and Dean E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean at the University of Maryland School of Medicine

The first day of the meeting focused on a February 2019 initiative announced between multiple agencies within the federal government to address the HIV epidemic, setting the goal of a 90 percent reduction in HIV incident by 2029. The "Ending the HIV Epidemic" pathway is based in four pillars: (1) Diagnose, with an emphasis on early detection; (2) Treat, initiating ART rapidly; (3) Protect, utilizing prevention strategies such as PrEP; and (4) Respond, detecting new HIV clusters. The initial phase of the initiative targeted 48 counties that serve as hotspots of new infection across the U.S.

Despite progress in reducing incident HIV in the U.S., there remains a disproportionate rise among marginalized populations including black and Latino male-to-male sex (MSM), persons who inject drugs (PWID), black female heterosexuals, and transgender individuals, and a concentration of these new cases in the South. As such, there is a renewed interest in evidence-based prevention strategies to target these populations, many of whom remain out of medical care. Prevention strategies including sexual education, condoms, syringe exchange, and pre-exposure prophylaxis were reviewed, along with challenges and possibilities in wide-spread implementation.

HIV Epidemiology is utilized to not only understand the current state of infection, but to target intervention and prevention efforts. Through molecular sequencing, the field has undergone a transition, enabling transmission mapping and analysis of risk on a scale broader than ever before. At the same time, the epidemiology of HIV/AIDS remains highly connected to individual behavioral patterns, underscoring the role of public health departments in testing and education. During the meeting, various agencies described the utilization of broad epidemiologic approaches to solidify our understanding of HIV in America.

The second day focused on the rising U.S. opioid epidemic marked by staggering rates of opioid overdose death. While rates of HIV acquisition attributable to drug use have declined over the past decade, this rise of opioid misuse, and in particular, injecting drug use, has resulted in localized HIV outbreaks. The meeting analyzed the epidemiology of the overlapping epidemics of HIV and opioid use disorder (OUD).

L to R: The Honorable Brooke Lierman; IHV Board of Advisors Co-Chairs John Evans and Terry Lierman; Middle, L to R: Former UMB President, and current University System of Maryland (USM) Chancellor Jay Perman, MD; NIDA Director Nora Volkow, MD; Bottom, L to R: Assistant Secretary for Health at HHS ADM Brett Giroir, MD; The Honorable William Ferguson

The Honorable Parris Glendening, The Honorable Kathleen Kennedy Townsend, and Warner Greene, MD, PhD

2019 IHV Lifetime Achievement Awards

Following a vote by senior IHV faculty, IHV awarded annual Lifetime Achievement Awards during IHV2019's Gala to three distinguished individuals. They included:

2019 IHV Lifetime Achievement Award for Scientific Contributions—Warner Greene, MD, PhD, Director, Gladstone Center for HIV Cure Research, Nick and Sue Hellmann Distinguished Professor of Translational Medicine, Founding and Emeritus Director, Gladstone Institute of Virology and Immunology (GIVI). Warner was a leader in the new field of the molecular biology of all human retroviruses, beginning with HTLV-1, the first discovered human retrovirus back in 1980, as well as HIV by the mid 1980's. His research focused on many aspects of the understanding of the biology of the virus, including its molecular biology, its genes and their products—how it replicated, how it induced, and other aspects of resistance to infection and the pathogenic mechanisms of how HIV causes disease. In recent years, he has turned his attention towards finding new ways to advance science so that a patient could live a normal life without any drug therapy whatsoever. Warner has also expanded his work to include global health activities in sub-Saharan Africa, and he has mentored more than 130 students and fellows during his career. Warner Greene is a national treasure in the molecular biology of very important viruses and genes.

2019 IHV Lifetime Achievement Award for Public Service—The Honorable Kathleen Kennedy Townsend, former Director of Retirement Security, Economic Policy Institute, Lt. Governor of Maryland (1995-2003). As Maryland's first woman Lt Governor, along with Gov. Glendening, she recruited me and my colleagues to the State. We have great respect for Kathleen beginning with her name, but, far extending beyond her name is her activities for helping people in need, and advancing human health in multiple areas, where she has worked very hard and lent her time. She became one of our early board chairs, is a current IHV Board member and has been a tremendous force in paving the way for the Institute's success here in Maryland. Kathleen previously served as Deputy Assistant Attorney General of the United States, led the fight to make Maryland the first—and only—state to make service a high school graduation requirement, and has served in numerous other public service roles.

2019 IHV Lifetime Achievement Award for Public Service—The Honorable Parris Glendening, President, Smart Growth America's Leadership Institute, President, Governors' Institute on Community Design, Governor of Maryland (1995-2003). When my colleagues and I were being recruited to form our Institute, among other important benefits from Governor Glendening, it was, in particular, his personal commitment to our mission, having shared publicly with us about the death of his brother from AIDS, which brought us closer. In addition to recruiting us and helping to establish our Institute, the Governor has a long history of public service, including his current national and international advocacy on smart growth, sustainability, global climate change, land conservation, transit-oriented development and equity. He was previously elected in local positions in the State and served as a professor at the University of Maryland, College Park for 27 years.

For both the Governor and Lt. Governor, we not only honor them with this Lifetime Achievement Award in Public Service because of their vital roles in the formation of the Institute, which never would have happened without them, but also as a public "thank you," for their local, national, and international service and leadership.

Former Mayor of Baltimore Kurt Schmoke enjoying the IHV 2019 Award Gala

Further, the ongoing transmission of viral infections in people who inject drugs is, in large part, a result of gaps in access to treatment and evidence-based harm reduction strategies. In order to meaningfully interrupt HIV transmission in PWID, strides need to be made to close gaps in care for this marginalized population, including addressing OUD as part of infectious disease care. Speakers during IHV2019 discussed strategies specific to addressing HIV in PWID, incorporating treatment of OUD into infectious disease practice, and the value of harm reduction strategies, such as supervised injection facilities, in improving outcomes in PWID.

Maeve McKean speaking at the IHV2019 Award Gala

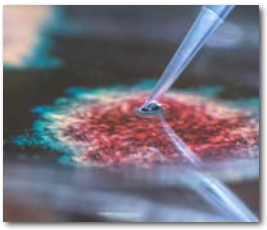
This year, IHV announced the

Maeve Kennedy McKean
Global Public Health Fellowship

Named in honor of the public health activist, Maeve Kennedy McKean who honored her mother, The Honorable Kathleen Kennedy Townsend, during the IHV 2019 Award Gala. Maeve's inspiring life ended tragically alongside her oldest son in April 2020. The Institute worked closely with Maeve over the years, particularly through her mother. Maeve shared her mother's values, sprightly energetic force, devotion to public health and to the needy. The first fellow arrived on July 1 and works on the Institute's efforts in ending the HIV epidemic in Africa within its Center for International Health, Education, and Biosecurity (CIHEB) and Division of Clinical Care and Research.

Division of Infectious Agents and Cancer

In the Division of Infectious Agents and Cancer, 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: Microbial Pathogenesis, Cancer Biology, Immunity & Inflammation, Structural Biology & Molecular Biophysics, and Drug Discovery & Development. The Division was directed by **Wuyuan Lu, PhD**, Professor of Biochemistry and Molecular Biology, Head of the Laboratory of Chemical Biology and Assistant Director of IHV, who stepped down from the directorship this past summer to take a faculty position at Fudan University, Shanghai, China. The incoming Director is **Lishan Su, PhD**, Professor of Microbiology and Immunology of UNC-Chapel Hill, who joins the Institute October 1, 2020. Dr. Su is a world-leading expert on using humanized mouse models to study the infection by and pathogenesis of HIV-1, HBV and HCV; his laboratory has been at the forefront of developing various novel therapies for these chronic viral infections. The Division, under its new leadership, will be renamed the Division of Virology, Pathogenesis and Cancer (VPC) in the coming year. In this year's Annual Report, we highlight research from a few members of our faculty, some of who have been working tirelessly on SARS-CoV-2, the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic.



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 its pursuit of a vaccine against HIV-1 bolstered by a strong multidisciplinary approach based on expertise in molecular and cell biology, virology, immunology, optical physics, structural biology, and translational medicine. The Division collaborates closely with investigators of the IHV Division of Clinical Care and Research on development of the "in house" HIV-1 vaccine, IHV-001, as well as on basic studies of protective antibody responses to HIV-1. The Division focuses on four key problems confronting the development of an HIV-1 vaccine: 1) identification of an immunogen that elicits broadly protective immunity; 2) identification of the correlates and mechanisms of broad protection elicited by IHV001; 3) ensuring that the broad, vaccine-elicited protection persists over long periods without repeated vaccination; and 4) understanding host factors such as innate immunity and vaccine elicited CD4+ T cell responses that augment or attenuate broad, vaccine-elicited protection.

Division of Clinical Care and Research

Over the last year, the Division of Clinical Care and Research continued its pursuits to provide the highest quality clinical care, clinical research and medical education in the Baltimore and Washington, DC metropolitan area as well as lead our institutional response to the COVID-19 pandemic. The Division's team is comprised 40 faculty members and 75 support personnel who over the last year have secured over 75 active grants and contracts and the added four new faculty members. Under the Division's leadership, **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division and Head of the Clinical Care Research Unit, and **Anthony Amoroso, MD**, Associate Professor of Medicine, Associate Director of the Division, Head of Clinical Care Programs, IHV's dynamic and highly productive clinical care and research program flourishes.

In March of this year, with the arrival of the novel coronavirus, our community faced one of its greatest health and infectious disease challenges of our times. Our Division led the University and state efforts in dealing with this novel COVID-19 pandemic by providing leadership and clinical and administrative support during this period. The Division quickly pivoted to provide 24-hour on-call COVID-19 coverage for the multiple hospital departments at the Medical Center and staffing COVID-19 ambulatory clinics in addition to providing on-going ambulatory care via tele-medicine.

The Division continues to support 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. Dr. Kottilil continues to work with this clinical research team on new studies focused on therapeutics and cure for hepatitis B, HIV cure related research, other infectious diseases and the intersection of opioid-use disorder and infectious diseases.

Division of Epidemiology and Prevention

This year, the Division of Epidemiology and Prevention, led by **Man Charurat, PhD**, Professor of Medicine and Global Director, Center for International Health, Education, and Biosecurity, continued to advance their translational and implementation research and training programs locally in Baltimore and globally with emphasis on population science in HIV, HPV, and non-communicable diseases associated with viral infections. The Division consists of 11 faculty responsible for leading 18 federal research awards. The Division published 63 manuscripts in peer reviewed journals in FY20.

Division of Immunotherapy

The Division of Immunotherapy, led by **Yang Liu, PhD**, Professor of Surgery, and established in February 2018, continues its mission in fundamental research and clinical translation on inflammatory diseases and cancer. In the current year, it has made major strikes in revealing novel mechanisms of immunotherapy targeting CTLA-4, providing a new theory on how to develop safer and more effective immunotherapy targeting CTLA-4 for human cancer. The new concept is being tested in clinic as antibodies developed by our commercialization partner, OncoImmune, Inc. has received Food and Drug Administration (FDA) approval for first-in-human clinical trial. Another major achievement includes applying the concept of CD24-Siglec innate immune checkpoint, pioneered by members of the Division, Dr. Yang Liu and **Pan Zheng, MD, PhD**, Professor of Surgery, for the treatment of COVID-19 through a Phase III clinical trial in severe and critical COVID-19 patients.

Center for International Health, Education, and Biosecurity

Under the leadership of Global Director **Man Charurat, PhD, MHS**, Professor of Medicine and Director of the IHV Division of Epidemiology and Prevention, and Associate Director **Kristen Stafford, PhD, MPH**, Associate Professor of Epidemiology and Public Health, Division of Epidemiology and Prevention, Ciheb is helping to build technical capacity from the ground up in low- and middle-income regions. Ciheb's approach in achieving sustainable impact includes developing robust information management systems, employing data for action, enhancing professional education, introducing continuous quality improvement processes, conducting rigorous disease surveillance, and deploying essential infrastructure.

Scientific Core Facilities

IHV's four Core Facilities help advance the Institute's research by providing a broad range of services to faculty and staff at IHV, and across the University campus. Services include cutting-edge technologies and laboratory technical support. Each Core Facility, including the **Animal Core, Flow Cytometry and Cell Core, Imaging Core** and the **µQUANT Core**, is led by an experienced researcher at IHV. More information about each of the Cores, can be found on pages 70-75.

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

The concept of a Global Virus Network (GVN) began back in the 1980's when a small group of virologists realized that virtually no working virologists had a global directive for researching the cause of AIDS during the earliest years of the epidemic. Conversely, important groups such as the World Health Organization which did have a global mandate for combatting the new disease had virtually no resident expertise in the kind of virus that was subsequently shown to be the cause of AIDS, namely, a retrovirus. Examining the history of other great epidemics of the 20th century, Influenza and Polio, reveals similar disconnects between available expertise and the urgent public need to identify causation and prevention modes, particularly during this novel viral pandemic crisis. The GVN is working to close this gap in the current SARS-CoV-2 pandemic crisis.

Led by GVN President, **Christian Bréchot, MD, PhD**, GVN Centers, with strong working relationships among them, are poised to engage in any outbreak situation by providing the world's only network of top basic virologists from around the globe covering all classes of human, and many animal, viral threats. The GVN is a thought leader providing expertise to public and private entities around the world, including launching initiatives to help combat the current pandemic crisis. The IHV is a Center of Excellence of the GVN with a major role in the GVN's formation and the subsequent continued success it experiences today.

Financial Overview

IHV had a strong financial year in FY2020, generating $138,000,000 of total revenue. This was due to relative stability in all 5 Divisions and 1 Center, including Infectious Agents and Cancer, Immunotherapy, Vaccine Research, Clinical Care and Research, Epidemiology and Prevention, and the Center for International Health, Education, and Biosecurity (CIHEB). In FY2019, IHV received funding in the amount of $72,000,000 for a onetime HIV survey in Nigeria. While funding could be expected to reduce by that amount in FY2020, in fact, IHV replaced it with a new 5-year grant for similar surveys in other countries, with year 1 funding at $40,000,000. IHV did realize a small drop in overall CIHEB funding due to changes in the way in which the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) funds will be awarded to indigenous organizations, as predicted in our FY2019 report. We expect these reductions to occur significantly over the next two years, and IHV is working with foresight to prepare for reduced funding while maximizing efforts to replace it.

IHV Leadership

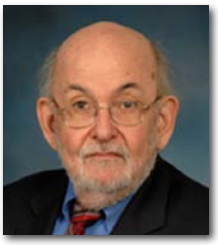
Robert C. Gallo, MD

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

Wuyuan Lu, PhD

Assistant Director
Director, Division of Infectious Agents and Cancer
Institute of Human Virology
Professor, Biochemistry and Molecular Biology
University of Maryland School of Medicine

(In FY2021, Dr. Lu steps down from IHV leadership and becomes part-time to accept a faculty position at Fudan University, Shanghai, China)



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 Kottilil, MBBS, PhD

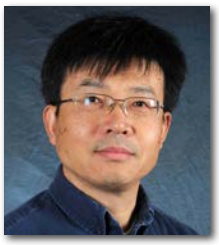
Director, Division of Clinical Care and Research
Head, Clinical Research Unit
Institute of Human Virology
Professor, Medicine
University of Maryland School of Medicine

Man E. Charurat, PhD

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

Yang Liu, PhD

Director, Division of Immunotherapy
Institute of Human Virology
Professor, Surgery
University of Maryland School of Medicine



Lishan Su, PhD

Assistant Director
Director, Division of Virology, Pathogenesis and Cancer, Institute of Human Virology
Professor of Pharmacology
University of Maryland School of Medicine

(In FY2021, Dr. Su becomes head of the Division of Virology, Pathogenesis and Cancer, formerly the Division of Infectious Agents and Cancer)

Anthony Amoroso, MD

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

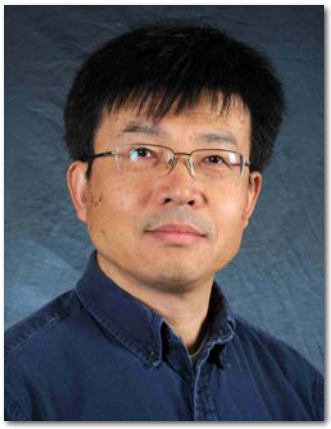
Dave Wilkins

Chief Operating Officer
Institute of Human Virology
University of Maryland School of Medicine

Infectious Agents and Cancer

Wuyuan Lu, PhD

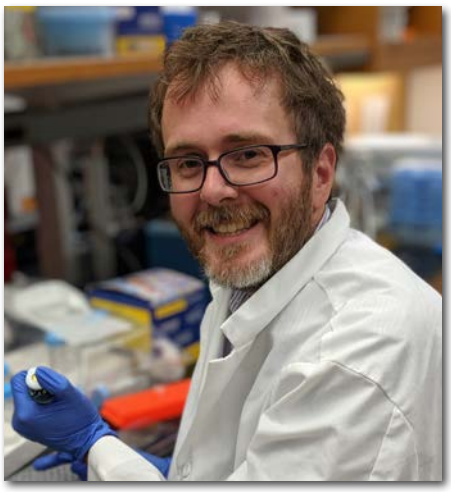
In the Division of Infectious Agents and Cancer, formerly known as Division of Basic Science, nearly two dozen faculty members lead research programs defining the molecular basis of infection and immunity and developing novel therapies and treatments of infectious disease, immune dysregulation, inflammatory 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: Microbial Pathogenesis, Cancer Biology, Immunity & Inflammation, Structural Biology & Molecular Biophysics, and Drug Discovery & Development. The Division had been directed by **Wuyuan Lu, PhD,** Professor of Biochemistry and Molecular Biology, who has recently stepped down from the directorship to take a faculty position at Fudan University, Shanghai, China. The new incoming Director is **Lishan Su, PhD,** Professor of Microbiology and Immunology of UNC-Chapel Hill, joined the Institute on October 1, 2020, and the Division will be renamed, Virology, Pathogenesis and Cancer (VPC). Dr. Su is a world-leading expert on using humanized mouse models to study the infection by and pathogenesis of HIV-1, HBV and HCV; his laboratory has been at the forefront of developing various novel therapies for these chronic viral infections. In this year's Annual Report, we highlight research from a few members of our faculty, some of who have been working tirelessly on SARS-CoV-2, the causative agent of the ongoing coronavirus disease (COVID-19) pandemic.



Lishan Su, PhD

Bonsor Laboratory

Daniel Bonsor, PhD, MChem, Research Associate of Medicine, works on the molecular interactions of carcinoembryonic antigen-related cell adhesion molecules (CEACAMs), a family of twelve human cell surface receptors. The most well-known member is CEACAM5 (CEA), as it forms the basis of the CEA blood test; it aids in the diagnosis, management, monitoring and relapse of certain types of cancer (e.g. colon cancer). These proteins are displayed on the surface of several different cell types where they typically interact with themselves (homodimerization). Certain CEACAMs can interaction with other CEACAMs through heterodimerization. These interactions allow cells to adhere to one another.



Daniel Bonsor, PhD, MChem

Many pathogenic bacteria have evolved proteins which target and bind CEACAMs. These proteins allow the bacteria to selectively target specific cells in order to adhere, colonize and infect. Dr. Bonsor currently works on two sets of bacterial adhesins; i) HopQ from *Helicobacter pylori*, which allows colonization and adhesion of the stomach lining through interactions with CEACAMs, where it causes gastritis and peptic ulcers. Further adhesins tighten the interaction between bacteria and host cells (Bonsor & Sundberg, 2019). The chronic infection of *H. pylori* leads to constant delivery of the oncogenic protein CagA inside human gastric epithelial cells. This causes the disruption of host cell signaling pathways which aids in further colonization and in certain people cause stomach cancer; ii) His collaborator, Alex J. McCarthy, PhD, Lecturer, Imperial College London, identified a protein, Beta, from *Streptococcus agalactiae*. *S. agalactiae* is the major cause of neonatal sepsis in babies. *S. agalactiae* uses Beta to bind to mucosal membranes through interactions with CEACAMs. He and his colleagues have determined that Beta contains an Immunoglobulin domain and that this domain binds CEACAMs. The structure of this immunoglobulin domain is a novel Ig-fold subtype and uses these unique features to bind CEACAMs.

Due to the Coronavirus Pandemic of 2020, Dr. Bonsor has begun research concerning the main protease, MPro, of COVID-19. COVID-19 is an RNA virus, which encodes ten open reading frames (ORF) of transcription. Two of these, ORF1a and ORF1b, encodes for the Polyprotein 1ab of ~7000 amino acids. This large polypeptide is actually several proteins fused together. MPro cleaves Polypeptide 1ab at specific cleavage sites to produce 13 unique proteins
(Figure 1a). Alignment of these cleavage sites show only two amino acids are conserved. Inhibition of MPro prevents cleavage of the polypeptides and inactivation of virial assembly and replication. Therefore, MPro is an important drug target. He has produced protein crystals **(Figure 1b)** and determined the crystal structure of MPro **(Figure 1c)**. Dr. Bonsor is currently trying to resolve the structures of MPro bound to some of these cleavage sites. This would allow us to explain how MPro can accept vastly different cleavage sites, but still be specific. Furthermore, these structures would allow the design of potential inhibitors. **Erik de Leeuw, PhD**, Assistant Professor of Biochemistry and Molecular Biology, and his lab have been synthesizing potential MPro inhibitors based upon the apo form of MPro. They are currently determining structures of
MPro bound to these inhibitors.

Bonsor DA, Sundberg EJ (2019) Roles of Adhesion to Epithelial Cells in Gastric Colonization by Helicobacter pylori. Adv Exp Med Biol

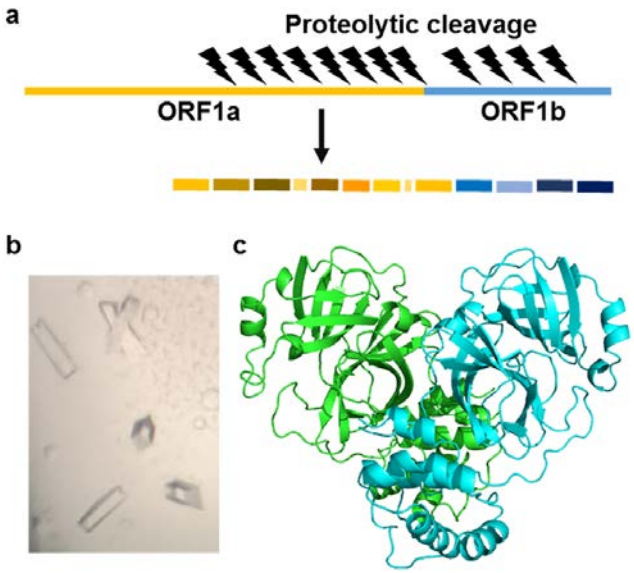


Figure 1. (a) Polyprotein 1ab is encoded by COVID-19 ORF1a and ORF1b. MPro cleaves this polypeptide into 13 unique proteins. **(b)** Crystals of MPro. **(c)** X-ray crystal structure of dimeric MPro determined to a resolution of 1.7 Å.

De Leeuw Laboratory

Erik de Leeuw, PhD, Assistant Professor of Biochemistry and Molecular Biology focuses on the discovery and development of small molecule drugs that act against infectious agents and cancer. He and his colleagues combine *in silico* approaches with structural and functional *in vitro* and *in vivo* assays to obtain the goals of their three major projects listed below:

1. **Development of COVID-19 Mpro inhibitors—**The coronavirus genome contains two overlapping open reading frames (ORF1a and ORF1b) at the 5′ end terminal, which encode polyproteins pp1a and pp1ab. The polyproteins are processed by a 3C-like protease (3CLpro or Main protease, MPro) (11 cleavage sites) and a papain-like protease (PLpro) (3 cleavage sites), resulting in sixteen mature nonstructural proteins, including an RNA-dependent RNA polymerase (RdRp). Both 3CLpro and PLpro are essential for viral replication. The absence of a human ortholog of the enzyme makes it an attractive target for drug design and development against this virus. Drugs that inhibit conserved proteases are capable of preventing replication and proliferation of the virus by interfering with the posttranslational processing of essential viral polypeptides. They can also reduce the risk of mutation mediated drug resistance. The **goal** of this project is to develop drugs that inhibit COVID-19 viral replication by inhibiting Mpro activity. The lab currently generates small molecule inhibitors using medicinal chemistry and computer-aided drug design. These inhibitors will be examined biologically and for binding the protease using co-crystallization efforts, in collaboration with **Daniel Bonsor, PhD**, Research Associate of Medicine, who has solved the structure of the apo-enzyme (**Figure 2** see page 14).

Erik de Leeuw, PhD

2. **Development of TNF receptor agonists—**Antimicrobial peptides called defensins act in adaptive immunity by serving as chemoattractants and activators of immune cells. For certain defensins, receptor-mediated processes have been defined. For most defensins, however, their cognate receptors in adaptive immune responses have yet to be identified. In addition, a deregulated expression and secretion of α- and β-defensins has been described in a number of tumor types, such as renal

cell carcinomas, adenocarcinomas, squamous cell carcinomas of the tongue, bladder carcinomas, T cell lymphomas, lung cancer and head-and-neck carcinomas. For α-defensins, expression is up-regulated and can be detected in tumor cells, in cells surrounding tumors and in biological fluids. The precise role of α-defensins in cancer growth remains elusive. At low concentrations, they can stimulate the proliferation, adhesion and invasiveness of cancer cells; whereas at elevated levels, they exert cytotoxic effects. The lab initially identified a functional synergism between the human α-defensin 5 or HD-5 and TNFα. More recently, they described a functional interaction between human α-defensin 5 and the TNFα signaling pathway. This interaction depended on interactions between HD-5 and the extracellular domain of TNF receptor 1. Detailed study of this interaction has led to the design of small molecule agonists as novel potential chemotherapeutics (**Figure 3**).

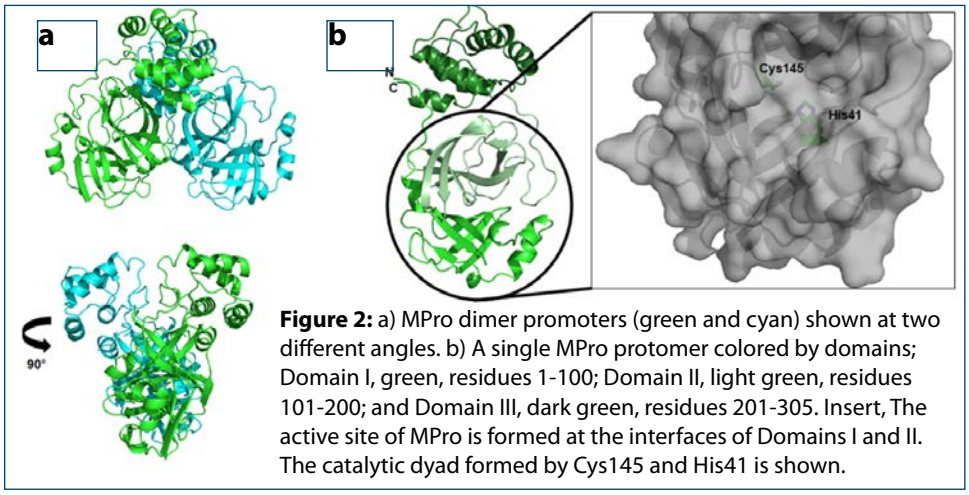


Figure 2: a) MPro dimer promoters (green and cyan) shown at two different angles. b) A single MPro protomer colored by domains; Domain I, green, residues 1-100; Domain II, light green, residues 101-200; and Domain III, dark green, residues 201-305. Insert, The active site of MPro is formed at the interfaces of Domains I and II. The catalytic dyad formed by Cys145 and His41 is shown.

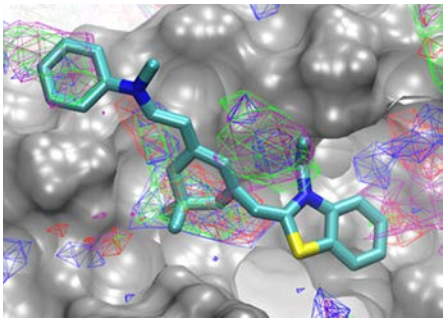


Figure 3: Lead compound 4090-1978 (Stick atom-color representation) overlaid on the SILCS FragMaps and the solvent accessible surface of TNFR1 (silver). FragMaps are shown in wireframe in the respective colors and contours levels for aromatic (purple, -0.9 kcal/mol), aliphatic (green, -0.9 kcal/mol), Hbond acceptor (red, -0.6 kcal/mol) and Hbond donor (blue, -0.6 kcal/mol) functional groups. The spatial distributions of the FragMaps indicate where the respective functional groups will make favorable contributions to binding.

3. **Development of Small Molecule Lipid II Inhibitors—**The relentless rise in antibiotic resistance combined with underinvestment in discovery and development of antibacterial agents will severely affect their ability to treat infections in hospitals and the community. There is an urgent need to develop novel, broad-spectrum antibacterial therapeutics to treat infections caused by antibacterial-resistant pathogens. Development of synthetic Lipid II inhibitors as a novel class of antibiotics with a unique mechanism-of-action represents an important approach to meet the critical clinical need for orally active, novel broad-spectrum antibacterial agents. The lab has identified and characterized chemically diverse compounds that bind Lipid II. Preliminary structure-to-activity relationship studies on one of their lead compounds indicates that the small molecule Lipid II inhibitors they identified can be developed into a novel class of broad-spectrum therapeutics (**Figure 4**).

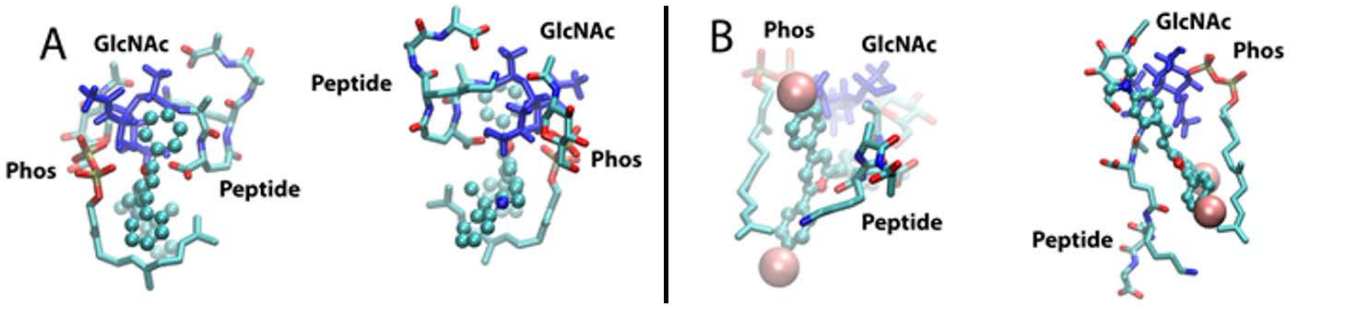


Figure 4: Models of A) BAS00127538 and B) 6jc48-1 in complex with a Lipid II analog. The compounds are shown in CPK, atom colored format and the Lipid II is in VDW representation with atom type coloring with the murinic acids sugars shown in blue. The upper and lower panels are approximately 180˚ rotations of the two complexes.

Garzino-Demo Laboratory

Laboratory of virus-host interactions— The Laboratory of virus-host interactions, headed by **Alfredo Garzino-Demo, PhD,** Associate Professor of Microbiology and Immunology, studies the etiopathogenesis of viral infections, with the aim of developing new therapeutic approaches. The laboratory has been focused on HIV infection for many years, but it has recently started studies on COVID-19.

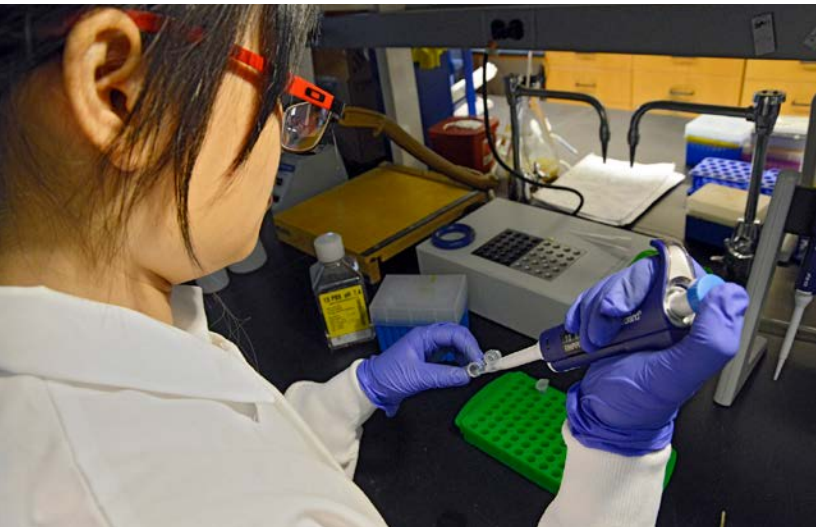
Alfredo Garzino Demo, PhD, discusses protein expression data with Virginia Carroll, PhD, a former post-doctoral fellow, and Lingling Sun, MD, Research Specialist (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

A. The emergence of SARS-CoV-2 in the human population has resulted in a pandemic disease, COVID-19, that has brought most of the developed world to a virtual standstill due to lockdowns to prevent further spreading of the infection. More than 20M reported cases and more than 740,000 deaths have occurred worldwide as of August 12, 2020. Currently diagnosed US COVID-19 cases stand at about 5M, with more than 160,000 reported deaths. These figures do not take into account asymptomatic and non-diagnosed cases, which would significantly increase the toll of the disease on humanity. COVID-19 research is progressing rapidly, starting with the identification of its causative agent, SARS-CoV-2, and its receptor within about a month from the initial description of the illness. However, at present there are very few therapeutic options. Besides treatments to abate inflammation, or convalescent serum/plasma therapy, the only FDA-approved drug available to treat COVID-19 patients is the broad-spectrum antiviral Remdesivir. The identification of antibodies that can neutralize infection, or that can induce antibody-dependent cellular cytotoxicity (ADCC) are research priorities, and so are assays that can detect them, or verify their potency. Currently, most assays are based either on infections with replication competent virus (necessitating highly trained personnel and BSL3 facilities) or single-cycle pseudotype viruses (which are cumbersome to prepare and have variable batch-to-batch titers).In summary, no standardized assay has been developed to properly characterize anti-SARS-CoV-2 antibodies. Their Objective is to develop an advanced assay toolbox of robust, highly reproducible assays to detect neutralizing antibodies, ADCC-inducing antibodies, and produce high-titer pseudovirions. The toolbox will be composed of permutations of well-characterized reagents, adjusted to the needs of each assay. The lab is developing:

1. A non-infectious, high-throughput-ready assay detecting anti-SARS-CoV-2 neutralizing antibodies. They will use well-established cell lines engineered to express the viral Spike protein, or the cellular ACE2 receptor, and monitor fusion using GFP fluorescence as reporter. The lab will use this assay to identify neutralizing antibodies from sera of convalescent patients;
2. An assay to detect anti-SARS-CoV-2 antibodies that can induce antibody-dependent cellular cytotoxicity (ADCC). They will use established cell lines resistant to NK cytotoxicity, to express viral Spike protein, to identify antibodies that induce ADCC;
3. A highly reproducible system to produce pseudotype viruses bearing SARS-CoV-2 Spike protein. Besides developing new assays, the reagents that they will prepare in the course of the studies described above will be useful to improve and optimize pseudotype virus production, which is normally affected by variability due to the efficiency of co-transfecting different constructs.

They will use cell lines permanently expressing viral Spike protein to produce pseudotype SARS-CoV-2 spike viruses at reproducibly high titer. The pseudotypes will be useful for infectivity and neutralization assays.

The toolbox will be of great utility to clinical and basic sciences. Clinicians will be able to quickly determine the presence and potency of neutralizing antibody responses, informing the strategy for the care of the patients. Researcher will benefit tremendously from fast and accurate tools to identify and characterize neutralizing and ADCC-inducing antibodies. As added benefits, the assays that will compose the toolbox can be used also to screen drugs, peptides, and aptamers for their activity



against SARS-CoV-2. Part of these studies will be pursued in collaboration with Joseph P.Y. Kao, PhD, Professor of Physiology, and Eric Legenzov, PhD, Postoctoral Fellow, Department of Physiology.

B. Pathogenesis of HIV infection. In the last decade, studies performed in the laboratory have characterized that HIV preferentially infects cells that express the CCR6 chemokine receptor. CCR6 is expressed on memory T cells, Th17 cells (i.e., helper T lymphocytes that produce Interleukin (IL) -17, macrophages, and α4ß7 lymphocytes. Interestingly, CCR6 is expressed also on cells that are not infected by HIV, but that have been proven to be depleted in the course of HIV infection, *i.e.*, gammadelta T cells, and mucosal associated invariant T (MAIT) cells. Some MAIT and gammadelta T cells produce IL17, similarly to Th17 cells. Consequently, HIV infection directly or indirectly targets IL17-producing cells, as shown among others by Aaron Christensen-Quick, PhD, a former graduate student in the lab. When IL-17 is produced and released extracellularly, it binds receptors on immune and non-immune cells. In mucosal epithelial cells IL17 causes production of antimicrobial peptides, including defensins. The laboratory has shown that some human defensins, i.e., human beta defensin (hBD) 2 and 3 protect cells from HIV infection (shown by Lingling Sun, MD, research specialist, in collaboration with Wuyuan Lu, PhD, Professor, Assistant Director, and Director of the Basic Science Division, IHV, and Department of Biochemistry). Part of that protection is due to a virucidal mechanism, but another component of the activity of hBD2 and hBD3 is mediated by CCR6, which can bind hBDs besides the chemokine MIP-3α. The CCR6-mediated inhibition of HIV is due to increased expression of APOBEC3G, an intracellular antiviral factor, as shown in several publications by Mark K. Lafferty, PhD, previously a postdoctoral fellow in the lab. Based on these findings, the laboratory has proposed that HIV infection disrupts a homeostatic, "virtuous" cycle, in which cells that produce IL-17 induce production of hBD that contribute to mucosal integrity and protect cells from HIV infection, and initiates a "vicious" cycle where IL-17 is no longer produced by cells eliminated directly or indirectly by HIV, resulting in loss of protection of cells, and of mucosal integrity. The latter causes bacterial products to cross the epithelial barrier, causing activation of the immune system, which is observed in HIV-positive patients even when they are taking antiretroviral therapy. These findings have therapeutic applications, restoring protective levels of APOBEC3G with a CCR6 agonists (like defensins or small molecule agonists). Another target is the aberrant immune activation observed in HIV-positive subjects (see above), which could be reduced by targeting T cell activation pathways. The laboratory is vigorously pursuing the latter approach. Finally, many cells that express CCR6 that are affected by HIV infection are also highly relevant to tuberculosis (TB). Therefore, the lab is collaborating with Cristiana Cairo, PhD, Assistant Professor IHV division of Epidemiology, and Department of Medicine, to study HIV-TB co-infected individuals, hypothesizing that $CCR6^{+}$ cells play a critical role in both pathologies, exacerbating each other in co-infections.

Song Laboratory

Hongshuo Song, PhD, Assistant Professor of Medicine, joined IHV in December 2019. In the past 10 years, Dr. Song has made significant contributions to the HIV field. During her postdoc training at Duke University, she discovered the rapid recombination dynamics in early HIV infection and developed a novel software called RAPR in collaboration with scientists at the Los Alamos National Laboratory. The RAPR tool identifies recombination events between highly similar sequences and recently helped scientists discovered potential recombination events in the COVID19 pandemic. When she worked at China CDC as a visiting fellow, Dr. Song found disparate pathogenicity of two HIV-1 phylogenetic clusters, therefore proving that the genetic signatures carried by the transmitting viruses can translate into phenotypic traits that influence disease outcomes.

Hongshuo Song, PhD

Fascinated by the extraordinary diversity of HIV in the pandemic, Dr. Song's group aims at address fundamental questions highly relevant to HIV treatment and

prevention in the context of HIV global phenotypic diversity. The research in her lab focuses on the interface of HIV genetic evolution (both intra-host and population level), phenotype property and pathogenesis, with the long-term goal to translate knowledge into optimizing future HIV prevention and therapeutic approaches in different regions of the world towards the goals of an effective vaccine and long-term ART free remission. Currently, there are two specific directions in the lab.

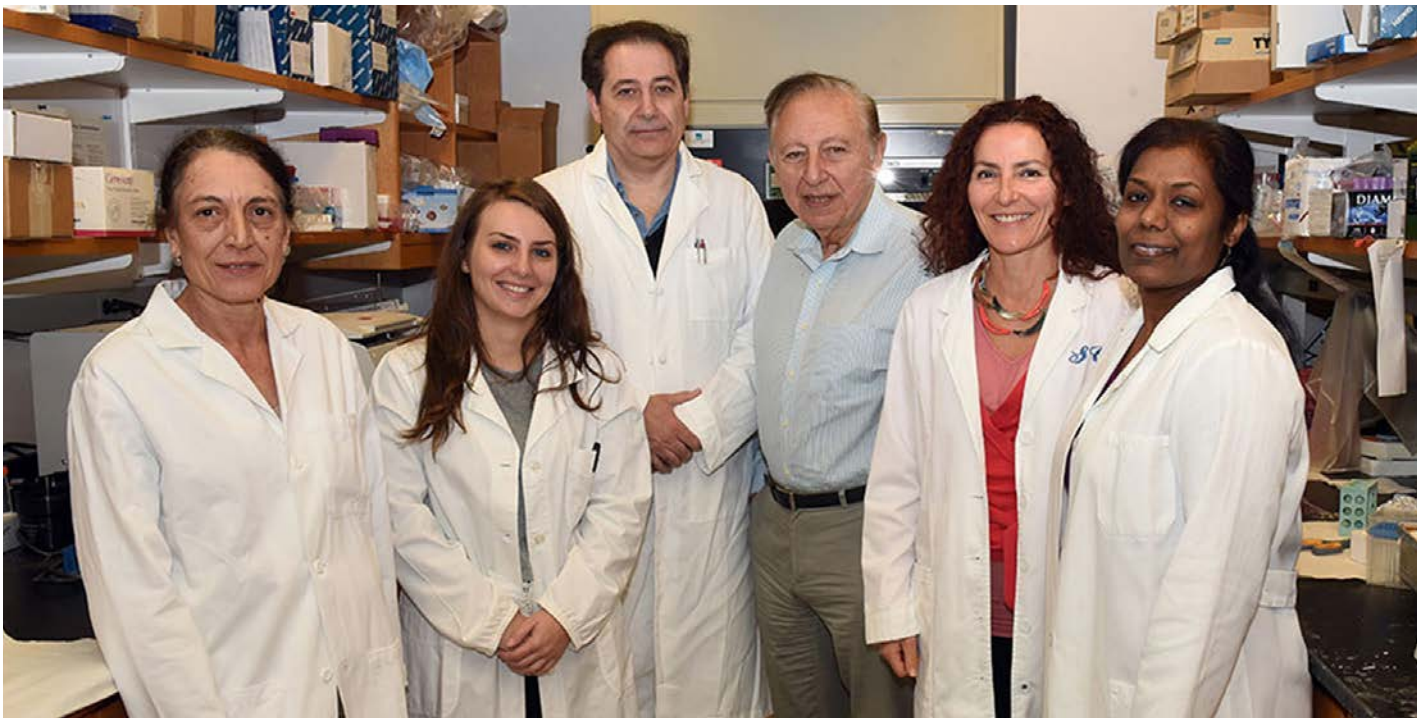
Saini Setua, PhD and Manukumar Honnayakanahalli, PhD are both Postdoctoral Fellows in the Song Laboratory

HIV genetic and phenotypic correlates in therapeutic HIV vaccine trials. As the PI of an active R21 grant "Genetic imprints of therapeutic Ad26/MVA mosaic vaccine in rebound HIV-1 genome from acutely treated individuals", Dr. Song is currently leading an HIV genetic study of a randomized, placebo controlled therapeutic vaccine trial (RV405 trial). The trial is the first time the Ad26/MVA mosaic vaccine strategy was used as a therapeutic approach in HIV infected individuals. Preliminary data showed that the vaccine was safe, induced robust immune responses, and delayed time to viral load rebound by around a week compared to the placebo arm. Although the vaccine did not lead to viremic control after treatment interruption, investigating the virological and immunological correlates of the vaccine outcomes will provide important insight into optimizing future vaccine approaches. The central hypothesis is that both the genetic background of the transmitted/found virus and its evolutionary trajectory in response to vaccine-induced immune responses will correlate with the time to viral load rebound among the vaccine recipients. In addition to the genetic-level research, Dr. Song's lab will further investigate whether the replication fitness of the transmitted viruses correlate with the time to viral rebound and whether any escape mutations selected by the vaccine incur fitness cost.

Deciphering the process of HIV coreceptor switch. Although the phenomenon of HIV coreceptor switch has been discovered for many years and is considered to associate with faster disease progression, the reason why coreceptor switch occurs during natural HIV infection is still a mystery. Currently, several knowledge gaps remain: 1) What is the driving force(s) of HIV coreceptor switch? 2) Why different HIV subtypes tend to have different dynamics and distinct evolutionary pathways of coreceptor switch? 3) What is the causal relation between coreceptor switch and disease progression? For many years, it has been considered that HIV coreceptor switch only occurs at later infection stage. Dr. Song's work at China CDC has identified high prevalence of X4 viruses among relatively early infections, contradicting this traditional opinion. Currently, the group is performing in-depth genetic and phenotypic studies with the goal to decipher the process of HIV coreceptor switch. In addition, Dr. Song recently discovered the first naturally transmitted, X4-tropic HIV-1 strain which does not use CCR5 as the coreceptor in a Thai cohort. The infectious molecular clone of this transmitted/founder virus is being constructed, which will provide a valuable model to investigate the mechanisms of viral pathogenesis induced by X4-tropic virus without laboratory adaptation.

Gallo-Zella Laboratory

The Laboratory of Tumor Cell Biology, co-headed by **Davide Zella**, **PhD,** Assistant Professor of Biochemistry and Molecular Biology and **Robert C. Gallo**, **MD,** The Homer and Martha Gudelsky Distinguished Professor of Medicine, also composed by **Francesca Benedetti**, **PhD**, Research Associate of Biochemistry and Molecular Biology, **Fiorenza Cocchi**, **MD**, Assistant Professor of Medicine, **Sabrina Curreli**, **PhD**, Research Associate of Medicine, and **Arshi Munnawar**, **PhD**, Postdoctoral Fellow, is currently mainly involved in identifying the mechanisms of cellular transformation induced by a bacterial protein, DnaK. In seminal studies, they isolated and characterized a strain of human *Mycoplasma fermentans* able to induce lymphoma in a Severe Combined Immuno-Deficient (SCID) mouse model, similar to a previously described lymphomagenesis dependent upon reduced p53 activity. Mycoplasma was abundantly detected early in infected mice, but only low copy numbers of Mycoplasma DnaK DNA sequences were found in primary and secondary tumors, suggesting a "hit and run/hide" mechanism of transformation, in which the critical events have occurred previous to cancer detection. The lab demonstrated that this Mycoplasma's DnaK binds to human USP10 (ubiquitin carboxyl-terminal hydrolase 10, a regulator of p53 stability), reducing p53 stability and anti-cancer functions, potentially increasing the likelihood of DNA mutations and consequent malignant transformation. By removing conjugated ubiquitin from target proteins, including p53, USP10 increases p53 stability in unstressed cells. This process is very important during DNA-damage response, in which USP10 translocates to the nucleus and deubiquitinates p53, stabilizing it and thus regulating its response to DNA



L to R: Fiorenza Cocchi, MD, Francesca Benedetti, PhD, Davide Zella, PhD, Robert Gallo, MD, Sabrina Curreli, PhD, and Selvi Krishnan, PhD (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

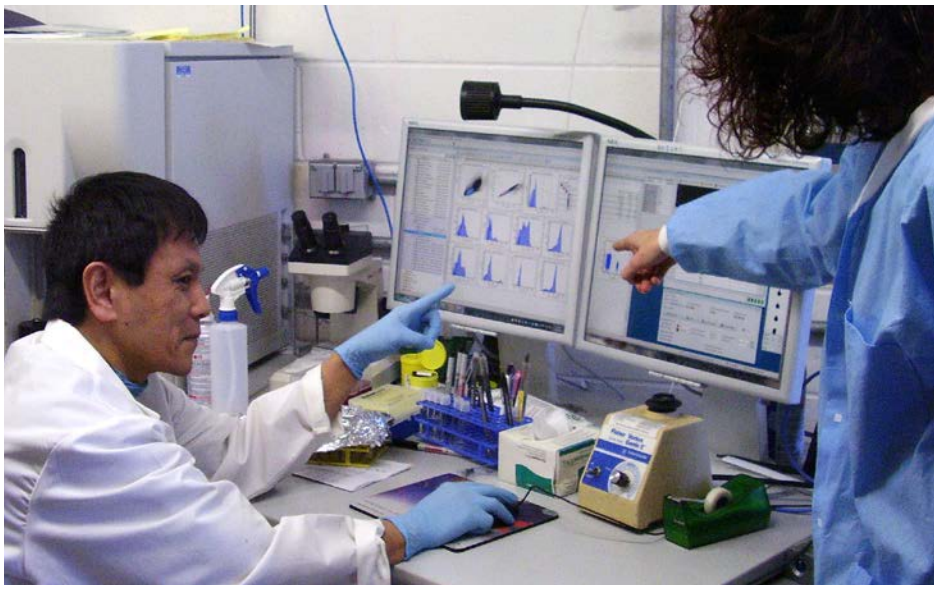
damage. It is thus clear that the reduction in USP10 activity caused by Mycoplasma DnaK can have profound negative effects on the anti-cancer functions of p53 (Zella D. *et al.*, PNAS, Dec 18,115, E12005, 2018). They also showed that Mycoplasma DnaK reduced PARylation activity of PARP1 following DNA damage. PARP 1 is one of the most studied members of the family of PARP proteins, involved in the recognition and subsequent repair of single and double-strand breaks in DNA. Following interaction with forms of damaged DNA, PARP1 activity is increased dramatically, resulting in PARylation of several proteins, including itself, histones, topoisomerase 1 (TOP1), DNA-dependent protein kinase (DNA-PK) and others, and in recruitment of single-strand break repair (SSBR)/base-excision repair (BER) factors to the damaged site. Failure to properly repair DNA damage usually results in apoptosis, thus avoiding accumulation of DNA damage that could ultimately lead to cellular transformation. (Zella D. *et al.*, PNAS, Dec 18, (115), E12005, 2018; Benedetti F. *et al.*., Int. J. Mol. Sci., Feb. 15, (21), 1311, 2020). Additional studies are ongoing in the Lab to identify other proteins that, upon binding to DnaK, may lose or alter their activity and become potentially involved in transforming events, such as regulators of cell cycle, effectors of apoptosis and controllers of cellular development. Phylogenetic amino acid analysis shows that other bacteria associated with human cancers (including certain mycoplasmas, H. *pylori*, F. *nucleatum* and C. *trachomatis*) have closely related DnaKs, indicating a potential common mechanism leading to cellular transformation (Zella D. *et al.*, PNAS, Dec 18,(115), E12005, 2018). The lab is evaluating the effect of these DnaKs on p53 activities in vitro. Finally, in collaboration with **Saman Saadat**, **PhD**, Postdoctoral fellow, they are developing an ELISA test to assess the presence of circulating DnaK in sera from normal individuals and cancer patients.

Given its ability to bind USP10 and reduce p53 stability and activities, it is conceivable that Mycoplasma DnaK can counteract the efficacy of other compounds that depend upon increased p53 activity for their anti-cancer effect. To test this hypothesis, they treated HCT116 adenocarcinoma and AGS (a stomach cancer cell line) with platinum-based compounds (Cisplatin and Carboplatin), that exert their anti-cancer effect through p53 activation. As expected, treatment with the anti-cancer drugs caused a marker reduction in the number of viable cells. When the cells were treated with exogenous DnaK they observed increased resistance to both drugs. To further validate that DnaK was responsible for this effect, they used a peptide (ARV-1502, optimized from A3-APO) which has been previously demonstrated to bind to E. coli DnaK substrate-binding domain and to reduce its ATPase activity. In the presence of ARV-1502, there was a

statistically significant reversal of the effect of Mycoplasma DnaK on anti-cancer drugs. They confirmed binding of the peptide to Mycoplasma DnaK and entry of Mycoplasma DnaK into the cancer cell lines. These data demonstrate that DnaK is responsible for reducing the effect of p53-dependent drugs in select cancer cell lines, and this effect is reversed by a peptide able to bind Mycoplasma DnaK to its substrate binding domain and able to block its ATPase activity. Additional studies are ongoing to correlate levels of DnaK expression with response to anti-cancer drugs

In collaboration with Chozha V. Rathinam, Dr rer nat., Associate Professor of Medicine, and Giovannino Silvestri, PhD, Research Associate of Medicine, they are currently extending these results and validating the underlying mechanisms in an in vivo model of DnaK knock-in mouse designed in their laboratory. DnaK was inserted at the locus of ROSA26 in C57BL/6 mice by CRISPR/Cas-mediated genome editing. The DnaK gene is under the control of the CMV promoter for constitutive expression and carries a V5 Tag for convenient detection. It is important to note that their previous results in vitro show that the V5 tag does not affect the ability of DnaK to reduce protein binding or p53-dependent anti-cancer activities. These animals are currently housed in IHV's animal facility and are currently used to: i) test for higher spontaneous tumor incidence in mice expressing DnaK; ii) assess for increased susceptibility to non-hematopoietic cancers and development, function and response to DNA-damaging agents of peripheral B- and T cells ex vivo. H. Davis, MS, head of the Animal Core Facility and S. Williams, BS, MS, PhD Student, Animal Facility Supervisor, are also participating in these studies.

Another project where the Lab has been recently involved is the analysis of SARS-CoV-2 genome and its mutations, with the aim of identifying potential targets of diagnostic/therapeutic intervention. For this line of research, they collaborated with several Italian colleagues (Rudy Ippodrino, PhD and Bruna Marini, PhD, from Ulisse Biomed, Trieste; Maria Pachetti, PhD, from the University of Trieste; and Silvia Angeletti, MD, PhD and Massimo Ciccozzi, PhD Unicampus Biomedico, Rome). By analyzing a subset of complete SARS-CoV-2 genomic sequences from COVID-19 patients deposited in the GISAID database, their group was among the first to identify a mutation in the viral RNA-dependent RNA polymerase (RdRp) catalytic subunit, also called nsp12 protein. Coronaviruses use an RNA-dependent RNA polymerase (RdRp) complex composed of a catalytic subunit, nsp12 and two accessory proteins, nsp7 and nsp8, to replicate their genomes. SARS-CoV-2 RdRp shares a high homology with the RdRp of SARS-CoV, suggesting that function and mechanism of action are conserved between the two complexes. Their data clearly identified the appearance in COVID-19 patients of a viral variant with mutations in the RNA polymerase gene (nsp12) and Spike protein (D614G) clustered together, which eventually became the dominant viral strain both in Europe and in the USA (Pachetti M. et al., J. Transl. Med., Apr. 22, (18); 179, 2020). Since mutations in the polymerase complex can lead to drug resistance, it is important to characterize SARS-CoV-2 RNA polymerase mutations to identify possible drug resistant viral phenotypes. Additionally, understanding how mutations alter structure and binding of nsp12 to its partner proteins may help in designing new anti-viral drugs. In addition, they demonstrated a correlation between high temperatures and reduced mortality rates of COVID-19 patients. Their data indicate that social distancing measure are more successful in the presence of higher average monthly temperatures in reducing COVID-19-related death rate, and a high level of population density seems to negatively impact the effect of lockdown measures (Benedetti F. et al., J. Transl. Med, Jun 23, (18), 251, 2020). They also recently identified a deletion in the non-structural protein-1 (nsp1) of SARS-CoV-2. Nsp1 is arguably the most important pathogenic determinant, and previous studies on SARS-CoV indicate that it is both involved in viral replication and hampering the innate immune system response. This deletion was found widespread through different geographical areas. Structural prediction modelling, done in collaboration with Greg Snyder, PhD, Assistant Professor of Medicine, suggests an effect on the C-terminal tail structure and indicates that the virus is undergoing profound genomic changes, most likely becoming less pathogenic (Benedetti F. et. al., J. Transl. Med., Aug. 31, 18, 329, 2020).



Yutaka Tagaya, MD, PhD discussing data analysis with an investigator (Photo taken before the SARS-CoV-2/ COVID-19 pandemic)

Tagaya Laboratory

The lab is headed by **Yutaka Tagaya, MD, PhD**, Assistant Professor of Médecine, and includes **Felisa Diaz-Mendez, PhD** and **Xiaoron Wu**. Their research focuses on understanding the mechanism of lymphocyte activation in connection with Cancer Biology and a translational application of cytokine biology for treating human T-cell malignancies.

The major project started from a novel idea on cytokine intervention that I conceptualized shortly before Dr. Tagaya joined the IHV and since developed the idea into a few peptide compounds one of which is currently being tested in a clinical trial (in cooperation with a company that Dr. Tagaya co-founded) for treating two human T-cell malignancies (Large-Granular-Lymphocyte Leukemia, LGLL and cutaneous T-cell lymphoma, CTCL) which are without established curative treatments.

IL-2/IL-15 co-inhibition therapy for treating immunologic and hematologic human disorders including human T-cell malignancies

Before joining the IHV, Dr. Tagaya was involved in the research on two T-cell growth factors, interleukin (IL)-2 and IL-15. Both are cytokines that primarily function as growth factors for Natural Killer (NK) and subsets of T-cells (e.g., regulatory T-cells (T-regs) and CD8 memory T-cells) as they and others have identified. They share structural homology and receptor subunits thus are functionally redundant as T- and NK-growth factor. Later study demonstrated that they are sibling cytokines that belong to the gc(common-g) family (including IL-2, -4, -7, -9, -15 and -21) which share the gc (CD132) molecule in their receptors. They have shown some time ago that the overproduction of IL-15 by transgenesis in mice led to the development of T-cell malignancies that resemble human LGLL and CTCL. The lab also demonstrated that malignant cells from these human T-cell malignancies show dependency on these sibling cytokines (IL-2/15). Anti-Cytokine strategy as a therapy is a long-approved application, but they noticed that the currently available modalities do not provide useful options to treat human diseases that are caused by the cooperation of more than two sibling cytokines (and they also demonstrated in a publication that there exist many human disease which are caused by such cooperation of cytokines from a family). A neutralizing antibody to one cytokine would not block the action of other functionally redundant cytokines in the mixture thus therapeutically would not be efficacious (and the clinical use of combined antibodies is financially challenging though scientifically sound). Small molecule signal inhibitors such as the ones for the Jak-STAT pathway which is used by a wide variety of cytokines would block too many cytokines without specificity of targets and side effects arising from this reason has been documented in publications. This way, they identified a critical gap in the existing treatment strategy and aimed at developing an inhibitor that specifically blocks IL-2 and IL-15 simultaneously, but no other cytokines. They rationally designed peptide inhibitors that mimic the shared structure of IL-2/IL-15, a portion (D-helices) of IL-2/IL-15 binding to the shared gc-molecule, ran *in silico* screening of potential candidate compounds, synthesized the chosen peptides (~120) and tested each of them using specific cytokine bioassay to screen for a novel IL-2/IL-15 inhibitor. This represents a novel attempt that has not been tried in the past. They also used bioassays detecting inhibitors for other gc-cytokines (i.e., IL-4, 9, and 21) and identified a few others that show unique target specificities which are being studies for additional therapeutic applications. Of note is that these inhibitors represent a novel class of anti-cytokine drugs that block more than two cytokines form a family simultaneously and specifically. Among them, the IL-2/IL-15 co-inhibitor, named BNZ-1, was proven not to block the function of other cytokines, including those of the gc-family that share the gc-subunit in their receptors with IL-2 and IL-15components. BNZ-1 showed potent blocking capacity to IL-2 and IL-15 *in vivo* in pre-clinical mouse and non-human

primate models. Remarkably, BNZ-1 protected mice from IL-15-induced T-cell malignancy that resembles human LGLL in their IL-15-transgenic model. With these data, they obtained an IND for BNZ-1 to be used in treating LGLL and CTCL. They then collaborated with 6 clinical centers in the US that are specialized for treating LGLL and CTCL patients (Ohio State University James Cancer Center, University of Virginia, Moffitt Cancer, Center, City of Hope Medical Center in Los Angeles, University of Pittsburgh Medical Center, Rochester Skin Lymphoma Medical Group for the recruitment of patients and initiated a multi-center phase I/II clinical trial of treating CTCL and LGLL with BNZ-1 (NCT03239392). The trial began in June 2018 and was completed in July of 2020, in which 20 LGLL patients and 30 CTCL patients that were refractory to other conventional and investigational therapies were treated with weekly injections of BNZ-1 for 3 months and the clinical conditions, pharmacokinetics, pharmacodynamics data were examined.

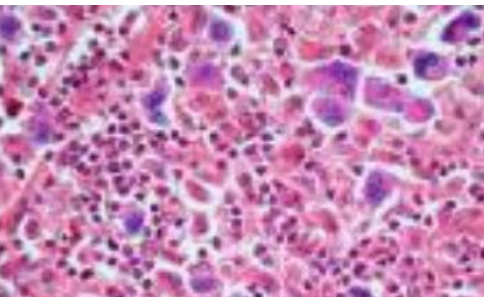
LGLL Treatment

LGLL is a chronic leukemia affecting CD8 T-cells and NK-cells with a frequency of 2~5% of chronic lymphoproliferative disease. The median age at diagnosis is 60 years. Though LGLL is a slow-progressive malignancy, majority of patients eventually require treatment and once the leukemia enters the aggressive phase the prognosis is poor. Yet, there is no approved curative treatment for LGLL. Thus, the development of new and effective treatment for this disease represents an unmet medical need. They chose to treat CD8-type LGLL following experts' suggestions. 20 patients were grouped into 4 cohorts each of which receive monthly intravenous (i.v.) administration of 0.5, 1.0, 2.0, and 4.0 mg/kg of PEGylated BNZ-1, respectively, for 3 months. Blood samples were collected weekly for the first month then monthly for pharmacokinetics and pharmacodynamics analyses. The lab investigated the percentages and surface markers expressed on major subsets of blood cells to analyze the response, activation status and functional property of them. Their working hypothesis dictates that they should see specific apoptotic response of leukemic cells (but not that of normal CD4 and CD8 T-cells) in patients to the IL-2/IL-15 co-inhibition treatment mediated by BNZ-1 because the treatment abrogates the growth signal that is required for the propagation of leukemic cells *in vivo* (Wang et al. Leukemia, 2019). Indeed, they observed this by a flow-cytometric analysis in 13 of the total 20 enrolled patients as early as at 24 hr after the initiation of the BNZ-1 treatment even at the lowest dose (0.5 mg/kg, which maintains BNZ-1 concentration in the circulation barely around the minimum effective dose). This stands as a proof-of-concept *in vivo*. It is the first demonstration that anti-IL-15/anti-IL-2 co-inhibition would be efficacious in treating LGLL patients. Out of the 13, 4 cases showed partial ~ complete remission based upon clinical findings such as the increase of neutrophils and improvements in anemia that normally associate with LGLL. Flow analysis of blood cells also demonstrated that LGLL leukemic cells (as defined by CD3+CD8+CD5dimCD16+) showed significant decrease in number, allowing the expansion of other lineages of normal blood cells in the periphery, which explains why these patients experienced increased number of neutrophils and red blood cells, a restoration of normal hematopoiesis. It is also of note that regardless of the changes in clinical findings, normal NK and regulatory T-cells (T-regs) showed expected decrease in their percentages similar to what they have observed in the phase I trial involving normal healthy individuals (NCT 03046459 and 03239379, Frohna et al. J Clin Pharmacol. 2020), because IL-2 and IL-15 are the *in vivo* nurturing cytokines for T-regs and NK cells, respectively. This, however, did not cause vulnerability of the patient to opportunistic infections by viruses such as CMV or autoimmunity. The diminished percentages of NK and T-regs represent a surrogate marker for the action of BNZ-1 in a patient and those cells show a quick recovery once the treatment is terminated. It was also demonstrated that BNZ-1 is a safe drug in humans as there were minimum adverse effects (slight nausea etc.).

CTCL Treatment

CTCL is the second most common extranodal non-Hodgkin's lymphoma. It presents a malignancy of CD4 T-cells origin. Among the 13 identified subtypes, mycosis fungoides (MF) is the most common (~90% of the cases) indolent mature T-cell lymphoma whereas the second frequent subtype is Sezary syndrome (SS) with aggressive nature characterized by erythroderma and blood involvement of clonally expanded T-cells. Advanced CTCL has a poor prognosis with a 5-year survival of 42~63%. Like LGLL, there is no established curative treatment for CTCL. They have enrolled in total 30 CTCL

Yutaka Tagaya, MD, PhD working in IHV's Flow Cytometry and Sorting Core Facility, which he heads



patients that showed poor response to other conventional and investigational therapies. Two were Sezary and the other 28 were diagnosed MF. Like LGLL, they were grouped into 4 cohorts each of which received 0.5, 1.0. 2.0, 4.0 mg/kg of PEGylated BNZ-1 as weekly i.v. injections for the duration of 3 months. In select cases upon the consent of the patient and clinician's opinion, the treatment was extended over 3 months (the longest was 510 days).

Unlike LGLL, they did not see direct response of malignant cells in the circulation (including SS), but clinicians report the shrinkage of tumor mass in responding patients. The assessment of the efficacy of the IL-2/IL-15 co-inhibition therapy by BNZ-1 depended on the mSWAT (modified Severity Weighted Assessment Tool) determined at patient visits to clinical sites and the flow cytometry finding of various subsets of blood cells conducted in my lab. Based upon mSWAT scores, about 40% (Overall response rate, ORR) of the cases showed partial to complete remission. Flow analysis demonstrated that while CD7loCD4 T-cells (suspects for circulating malignant CD4 T-cells) showed little changes in response to the treatment, CD8 T-cells compartment underwent dynamic changes in ~20 cases out of the total 30. First, in majority of the cases the CD8 T-cells compartment showed signs of chronic activation because the percentages of terminal effector cells are much higher than normal. Effector CD8 T-cells are the major source of Granzyme B and Perforin, the two representative lytic enzymes defining cytotoxic T-cells (CTLs). Therefore, the percentages of Perforin / Granzyme B positive cells among CD8 T-cells are higher than those in normal individuals, suggesting the highly inflammatory nature of CD8 T-cells in CTCL patients. The IL-2/IL-15 co-inhibition blocks the differentiation of naïve CD8 T-cells into effector cells and their expression of lytic enzymes because IL-15 and/or IL-2 are the drivers of these processes. Curiously, the mSWAT scores and the CD8 biomarkers (percentages of Perforin/Granzyme B among CD8 T-cells) showed parallel kinetics, suggesting that the mSWAT score is describing CTL-mediated destruction of skin legions in response to the growth of malignant CD4 T-cells. Alternatively, the IL-2/IL-15 co-inhibition may target the common element that is located at the root of skin damages and inflammatory activation of CD8 T-cells.

Summary and future perspectives:

- **Large-Granular Lymphocyte Leukemia**
  a. This is the first demonstration that LGL leukemic cells are dependent on IL-15 and/or IL-2 *in vivo* and that intervention to their growth-promoting mechanism shows clinical efficacy. Unlike the "total kill" anti-cancer strategy, the current strategy aims at a specific mechanism that support the leukemic propagation of malignant cells and therefore is expected to be efficacious and safe.
  b. Thirty ~ Forty % (ORR) of the enrolled cases that were refractory to other conventional and investigational therapies showed partial ~ complete response.
  c. The cases with objective response showed sustained apoptotic death of leukemic cells whereas those with poor response showed only transient apoptotic response of leukemic cells from day 2 to day 15, after which the response subsided. Preliminary single cell RNA-Seq (scRNA-Seq) analysis of one poor-responding case demonstrated a disappearance of major leukemic cells (a proof that the IL-2/IL-15 co-inhibition directly obliterated the leukemic cells) as early as day 2, but the recurrence of a similar cell population around day 29. The detailed molecular comparison of the original and recurred leukemic cells is under investigation. Expansion of the sc-RNA Seq to include responding and additional non-responding cases is underway.
- **Cutaneous T-cell Lymphoma.**
  a. ORR was around 40% of the enrolled cases which were refractory to other conventional and investigational therapies. Thus, the IL-2/IL-15 co-inhibition may provide a novel therapeutic option to those who did not respond well to other types of treatments.
  b. In a few patients, the treatment was extended over one year with weekly injections of the drug. The patients responded stably and steadily to the treatment and showed minimum adverse effects thus also demonstrating the safe nature of their BNZ-1 inhibitor upon long use.
  c. Though ORR in CTCL was similar to that in LGLL treatment, the mechanism of action (MOA) in CTCL seems different from that in the treatment of LGLL. First, unlike LGLL, malignant CD4 T-cells do not seem to be the direct target. Instead, effector and effector-memory CD8 T-cells with high expression of Perforin and Granzyme B were dramatically reduced in number during the treatment in responding patients.
  d. Curiously, the mSWAT score showed parallel kinetics to those of CD8 biomarkers (i.e., the percentage of Perforin/Granzyme B-positive cells in the entire CD8 T-cell pool), suggesting that the improvement of patient's skin conditions may be corelated with the decrease of inflammatory nature in cytotoxic CD8 T-cells.

e. It is therefore likely that the IL-2/IL-15 co-inhibition therapy reduces disease burden in CTCL by targeting inflammatory CD8 T-cells that are activated in the patient as a part of anti-lymphoma and lymphoma-induced activation of CD8 T-cells. As a corollary, the IL-2/IL-15 co-inhibition therapy may be combined with other therapies that directly target malignant CD4 T-cells to improve the ORR.

f. The delineation if these two parameters (mSWAT score and CD8 biomarkers) are linked as a cause-consequence relationship is underway.

g. Additionally, they have gathered plethora of surface marker information on the blood cells from patients before and during treatment and detailed investigation to find conditions which dictate if a CTCL patient would respond to their novel therapy is being undertaken.

Control of fatal airway viral infections by suppressing the early phase T-cell activation through the co-inhibition of IL-2 and IL-15.

The idea described above, the co-inhibition of IL-2 and IL-15 for subsiding pathogenic T-cell activations can be expandable to treat infectious diseases including viral infections that cause severe and fatal airway infections. One current target we are aiming at is the recent COVID-19 by SARS-CoV2.

As described above, IL-2 and IL-15 are two T-/NK-cell stimulatory cytokines that belong to the gc (common gamma) family. These two cytokines share two signaling components in their receptors (b/CD122 and gc/CD132 and show functional redundancies. However, under normal lymphocyte development and homeostasis of the resting immune system, IL-2 and IL-15 seem to have distinct functions with minimum overlap as knockout mice lacking each cytokine have non-overlapping phenotypes (IL-15 KO mice show profound decrease of NK cells, memory CD8 T-cells, gd T-cells, and IELs but manifest no apparent disorders whereas IL-2 KO mice have severely reduced activity of the T-regs and manifest autoimmunity). This is partly because IL-2 and IL-15 are produced by different types of cells. IL-2 is exclusively produced by activated T-cells whereas IL-15 is a product of activated monocytes/dendritic cells. During the normal immune activation, the early activation of the innate cells leads to the production of IL-15 whereas the subsequent antigen presentation by innate cells to T-cells induce the production of IL-2. Thus, there is little spatial and temporal overlap between the production of IL-2 and IL-15.

However, this is not true under pathologic activation of the immune system. For example, chronic microbial infection (or the chronic presence of antigens that activate T-cells) would keep both innate and adapted immune cells constantly activated and the production of IL-15 and that of IL-2 overlap. Under these circumstances, attempts blocking the hyperactivation of T-cells which give rise to negative consequences through cytokine-release syndrome or graft-versus-host disease (GvHD) will be unsuccessful until both IL-2 and IL-15 are inhibited. In fact, we have seen the need to inhibit both of these cytokines simultaneously to completely subside the pathogenic activation of T-cells in a number of disease models including that for the Myelopathy associated with HTLV-1 (HAM/TSP, HTLV-1 associated myelopathy/tropical spastic paraparesis) and more recently under fatal airway infection of LCMV in humanized mice. Curiously, LCMV does not cause fatality in humans or in mice under normal infectious conditions. However, the same infection of humanized mice in which graft-versus-host response caused by the activation of grafted human T-cells against mouse tissue cells is aggravated by the LCMV infection to cause a fatal airway inflammation. In this model, anti-IL-2 treatment or anti-IL-15 treatment was not effective to prevent host mice manifesting morbidity and mortality whereas the IL-2/IL-15 co-inhibition by their novel BNZ-1 inhibitor completely protected host mice. Moreover, IL-2/IL-15 co-inhibition significantly lowered the production levels of proinflammatory cytokines (e.g., interferon-g, TNF-a, and IL-6) in humanized mice whereas anti-IL-2 or anti-IL-15 therapy only had partial inhibitory effects on the production of proinflammatory cytokines, suggesting that the co-inhibition of IL-2 and IL-15 is the only way to control the cytokine-release syndrome (CRS) which leads to the fatal airway-inflammation. Similar observation that the inhibition of IL-2 and/or IL-15 leads to the abrogation of a fatal airway inflammation was made with the influenza virus. These observations made us to propose the IL-2/IL-15 co-inhibition in treating severe airway inflammation in COVID-19 patients. Since treatment options are desperately sought after under the current pandemic, and a number of publications suggest the overproduction of IL-2 and IL-15 in COVID-19 patients, and the elevated production of proinflammatory cytokines indicative of the occurrence of CRS in SARS-CoV2 infection, the IL-2/IL-15 co-inhibition might be an effective treatment strategy to prevent the severe and fatal pneumonia. Work is underway to develop a mouse model using mouse-adapted SARS-CoV2 (MA strain) to test the efficacy of the IL-2/IL-15 co-inhibition therapy which we have developed into clinical trials for treating human T-cell malignancies.

The lab also studies a T-cell oncogenesis caused by a retrovirus human T-cell leukemia virus-1 (HTLV-1) and the role of a special type of CD8 T-cells expressing the NKG2A antigen in the pathogenesis of the graft-versus-host disease. Research on these topics will be described in the future issues of the annual report.

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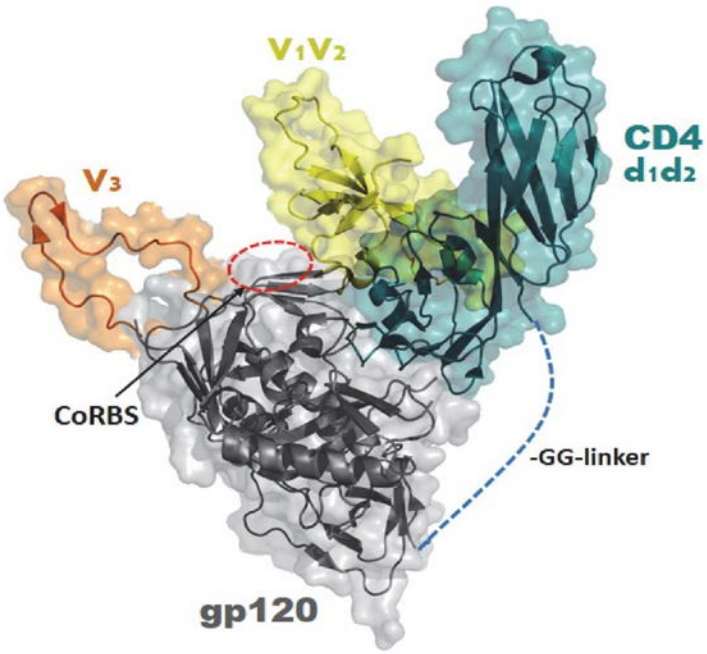
Vaccine Research

George K. Lewis, PhD

The Division of Vaccine Research faculty, led by **George K. Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Professor of Microbiology and Immunology, continues its pursuit of a vaccine against HIV-1 bolstered by a strong multidisciplinary approach based on expertise in molecular and cell biology, virology, immunology, optical physics, structural biology, and translational medicine. The Division collaborates closely with investigators of the IHV Division of Clinical Care and Research on development of the "in house" HIV-1 vaccine, IHV-001, as well as on basic studies of protective antibody responses to HIV-1. The Division focuses on four key problems confronting the development of an HIV-1 vaccine: 1) identification of an immunogen that elicits broadly protective immunity; 2) identification of the correlates and mechanisms of broad protection elicited by IHV001; 3) ensuring that the broad, vaccine-elicited protection persists over long periods without repeated vaccination; and 4) understanding host factors such as innate immunity and vaccine elicited CD4+ T cell responses that augment or attenuate broad, vaccine-elicited protection.

The lion's share of Divisional research centers around IHV-001, the conformationally constrained gp120 immunogen developed in the Division and advanced to clinical trials via extensive preclinical studies over the last twenty years. IHV001 is a conformationally constrained protein comprised of HIV-1 gp120 linked to the first two domains of human CD4 by a flexible peptide spacer. This immunogen is denoted as the full-length single chain (FLSC) protein. **Anthony DeVico, PhD**, Professor of Medicine and Head of the Laboratory of Viral Envelope Studies, and his laboratory developed the FLSC vaccine concept in the early years of the IHV with the first publication of its immunochemical and physical chemical profile in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research, led by Dr. George Lewis, in collaboration with colleagues in the IHV Division of Clinical Care and Research, The Military HIV Research Program, and the National Institutes of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH) HIV Vaccine Trials Network. The early years of FLSC development

Molecular Model of the FLSC Immunogen



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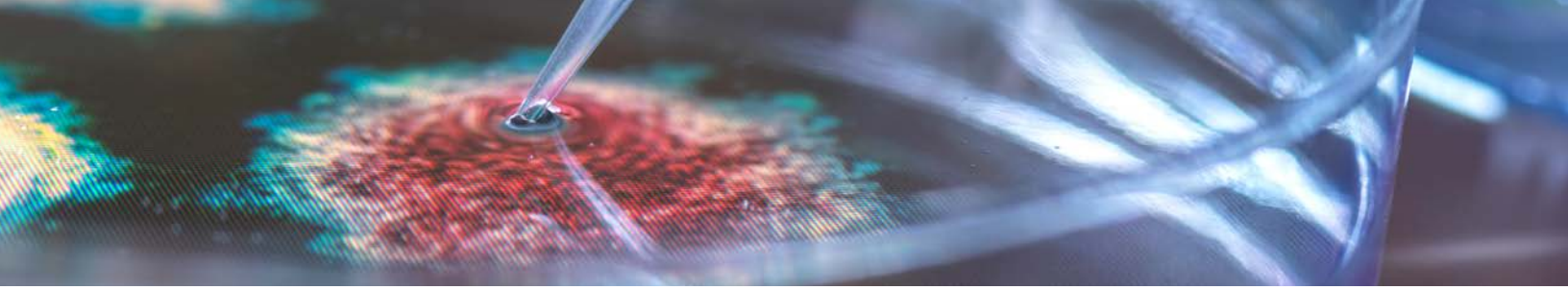

were supported by NIH grants to Division of Vaccine Research Members including Dr. Tony DeVico, Dr. Tim Fouts (now at ABL, Inc.), **Robert C. Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine and IHV Director, and Dr. George Lewis. The FLSC vaccine concept was licensed to Wyeth Laboratories in 2002 and transferred to Profectus Biosciences in 2004. In 2007, The Bill and Melinda Gates Foundation awarded a large grant to Dr. Gallo (Principal Investigator) and his collaborators Drs. DeVico, Lewis, and Fouts to support the advanced preclinical development of FLSC. In April 2011, a consortium of funders led by the Bill and Melinda Gates Foundation and including the Military HIV Research Program (MHRP) as well as the National Institutes of Allergy and Infectious Disease, NIH, funded an additional grant to the IHV under Dr. Gallo's leadership for continuing support of the clinical development of FLSC for Phase I and Phase 2 clinical trials.

Based on these long-term efforts and extensive research funding, the IHV recently completed a "first in human" Phase I clinical trial of FLSC where the drug product is designated as IHV-001. This trial was a collaboration between the IHV Division of Clinical Care and Research, led by **Dr. Shyam Kottilil, MBBS, PhD**, Professor of Medicine and Head of the Clinical Research Unit, and included **Joel Chua, MD**, Assistant Professor of Medicine, and **Mohammad Sajadi, MD**, Associate Professor of Medicine, also both of that Division. The vaccine proved safe and immunogenic and it is now the basis for several Phase 1b studies that are scheduled to begin in early 2021 in collaboration with our partners at the Military HIV Research Program, The HIV Vaccine Trials Network, and the NIAID, NIH. This program continues to represent the efforts of investigators from diverse scientific backgrounds that exemplifies the IHV's bench-to-bedside research model that was the vision of Dr. Gallo in establishing the IHV almost twenty-five years ago.

Both pre-clinical studies and our first Phase I clinical trial of IHV-001 have shed new light on the correlates and mechanisms of protective immunity to HIV-1. In our pre-clinical studies, we unexpectedly found that protection correlates largely with Fc-mediated effector function and not virus neutralization. This collaboration includes Drs. DeVico, Lewis and Sajadi, **Roberta Kamin-Lewis, PhD**, formerly Associate Professor of Microbiology and Immunology, and **Krishanu Ray, PhD**, Associate Professor of Biochemistry and Molecular Biology. This work was supported initially by a grant from The Bill and Melinda Gates Foundation as well as two R01 grants to Dr. Lewis. More recently, the work is supported by a collaborative P01 grant with investigators at Duke University, Harvard University, Dartmouth University, Northwestern University, and the University of Pennsylvania. Drs. DeVico, Lewis, and Ray are focusing on physicochemical and cell biology of Fc-mediated effector function for this program. These efforts are also supported by funding from the US Military Defense Threat Reduction Agency to Dr. Lewis, a R01 grant awarded to Drs. Krishanu Ray as well as by a R01, and VA Merit Award to Dr. Mohammad Sajadi.

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

Dr. DeVico's group has developed new tools to characterize target epitopes on free virions, virions entering target cells, and virions budding from infected cells

Anthony DeVico, PhD

L to R: Robin Flinko, BS; Chiara Orlandi, PhD; Meng Li, MD; George Lewis, PhD; Robert Gallo, MD; Bhavna Chawla, PhD; James Foulke, BS; and, Krishanu Ray, PhD (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

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

Dr. Sajadi's group has developed new methods for the isolation of human mAbs based on a combination of proteomics and deep sequencing and is applying it to isolate new bnAbs from HIV-1 infected volunteers. Serum antibodies are fractionated by affinity chromatography and isoelectric focusing to identify fractions enriched for specific biological activities, including neutralization breadth, Fc-mediated effector function, or both. The enriched protein fractions are sequenced and the variable region sequences matched against DNA sequences obtained

by deep sequencing from the same individual. His group has developed an algorithm to rapidly pair VH and VL sequences to reconstitute the specificity and biological activities found in the serum antibodies from HIV-1 infected volunteers. This novel approach has led to the identification of a number of new bnAbs that are under characterization. He will continue this work under the aegis of his VA merit award and R01 grants.

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

Vaccine Research Publications

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Clinical Care and Research

Shyam Kottilil, MBBS, PhD

Over the last year, the Division of Clinical Care and Research continued its pursuits to provide the highest quality clinical care, clinical research and medical education in the Baltimore and Washington, DC metropolitan area as well as lead our institutional response to the COVID-19 pandemic. The Division's team is comprised 40 faculty members and 75 support personnel who over the last year have secured over 75 active grants and contracts and added four new faculty members. Under the Division's leadership, **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division and Head of the Clinical Care Research Unit, and **Anthony Amoroso, MD**, Associate Professor of Medicine, Associate Director of the Division, Head of Clinical Care Programs, IHV's dynamic and highly productive clinical care and research program flourishes.

Anthony Amoroso, MD

In March of this year, with the arrival of the novel coronavirus, our community faced one of its greatest health and infectious disease challenges of our times. Our Division led the University and state efforts in dealing with this novel COVID-19 pandemic by providing leadership and clinical and administrative support during this period. The Division quickly pivoted to provide 24-hour on-call COVID-19 coverage for the multiple hospital departments at the Medical Center and staffing COVID-19 ambulatory clinics in addition to providing on-going ambulatory care via tele-medicine.

The Division continues to support 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. Dr. Kottilil continues to work with this clinical research team on new studies focused on therapeutics and cure for hepatitis B, HIV cure related research, other infectious diseases and the intersection of opioid-use disorder and infectious diseases.

SARS-CoV-2 PANDEMIC RESPONSE

The Division of Clinical Care and Research has been on the frontline tackling the COVID-19 pandemic that affected the University of Maryland Baltimore (UMB) community in an unprecedented manner. IHV's clinical faculty provided critical roles in preparation planning, systems coordination, and direct patient care throughout the University of Maryland Medical System and the Veteran Administration (VA) Maryland Heath Care System during the pandemic. Dr. Amoroso served an instrumental role on University of Maryland Medical Center (UMMC) incident command, advising facility design for airborne biocontainment units and other infection prevention measures, admission triage, surveillance, treatment protocols, and testing protocols. The Division faculty were on call 24 hours a day, seven days a week to support multiple system emergency departments under the IHV leadership of **Eleanor Wilson, MD** Associate Professor of Medicine. New IHV faculty, **John Baddley, MD**, Professor of Medicine, led a newly formed COVID-19 inpatient consult team which supported critical and acute care units. **Lydia Tang, MD**, Assistant Professor of Medicine led essential efforts to obtain personal protective equipment for the faculty and for the hospital. **Rohit Talwani, MD**, Associate Professor of Medicine, was the first faculty to obtain remdesivir for emergency use for University of Maryland Medical System (UMMS), and along with **Patrick Ryscavage, MD**, Assistant Professor of Medicine, developed system wide treatment guidelines. Clinical faculty took on critical roles in patient care at several UMMS hospitals as a crisis in shortages in infectious disease consultants arose. With an increasing number of health care worker infections and deaths reported in New York City, stress related to personal safety and how to safely return home to one's family after clinical shifts arose. The Division played a critical role in advising and supporting providers, and distributing information throughout the Medical Center, and ultimately played a key role in establishing employee testing centers. Much needed outpatient care for infected employees was provided by **Britt Gayle, MD**, Assistant Professor of Medicine.

Finally, IHV investigators initiated several clinical trials on COVID-19 in collaboration with the National Institutes of Health (NIH) and major industry partners. Dr. Kottilil and **Bahwna Poonia, PhD,** Associate Professor of Medicine, received a supplement to their

NIDA grant to investigate COVID-19 progression and immunity in subjects with HIV infection and opioid use disorder. **Mohammad Sajadi, MD**, Associate Professor of Medicine, has a study to research humoral response in COVID-19 infection in addition to a collaboration with the NIH on COVID-19 infected lung tissue. **Joel Chua, MD**, Assistant Professor of Medicine, led two industry sponsored treatment studies for COVID-19. Dr. Kottilil and his team are conducting a clinical trial with the experimental drug CD24Fc to see if it may help to prevent the damage caused by an over reactive immune system infected with COVID-19. The team is pursuing several other COVID-19 studies.

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 2,500 patients in our Baltimore clinics, the IHV continues to identify unmet patient needs and expand services to address them. The IHV also continues to provide leadership for the Department of Medicine's Division of Infectious Disease. Combining the two divisions' clinical practices allows for significant synergies in clinical care and education. The Infectious Disease Fellowship (14 fellows) and 43 Infectious Disease faculty providing clinical care allows for growth in the IHV's programs in the immunocompromised host to include care and research in the Greenabaum Comprehensive Cancer Center and Solid Organ Transplant Program at University of Maryland Medical Center.

Ambulatory Programs:

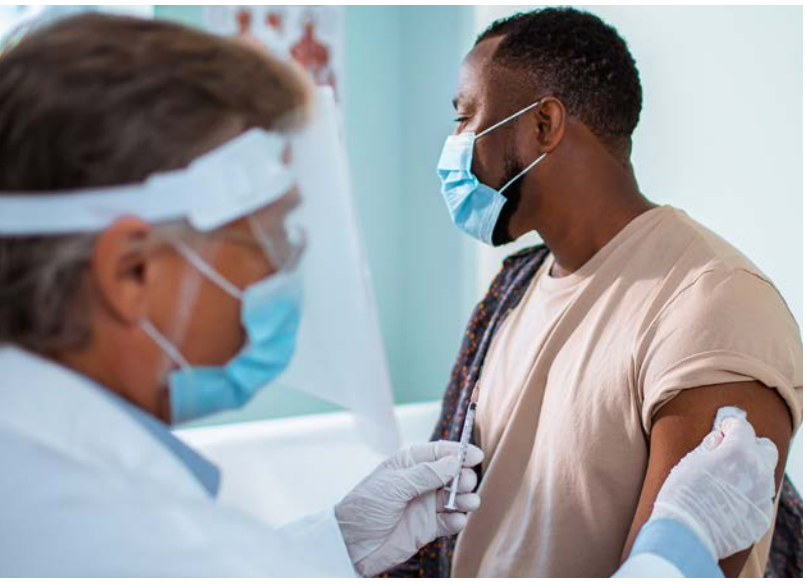
HIV Care: The THRIVE program (Together Healing, Reaching, Inspiring, to achieve Victory over illness, and Embrace life), formerly known as the Center for Infectious Disease, was renamed on World AIDS Day in December 2018 and has evolved and re-defined itself since. The mission of THRIVE is "to deliver high quality comprehensive health care that inspires individuals to thrive." This mission is realized through four core values: deliver quality primary and specialty care that focuses on prevention and treatment of acute and chronic infections; meet patients' medical and psychosocial needs by providing comprehensive, patient-centered, compassionate, interprofessional team-based care that incorporates a wide range of integrated services; elevate the medical, emotional, social, and sexual health and well-being of diverse individuals and communities; and collaborate with academic, governmental, community, and research partners that further these values. The program, led by Medical Director **Sarah Schmalzle, MD**, Assistant Professor of Medicine, is at the forefront of ending Baltimore's fight against HIV. THRIVE provides care to approximately one quarter of the people living with HIV in Baltimore City, receiving private and federal funding to both provide care otherwise not available to under-insured patients, and to expand available services to meet the needs of our patients. Strong collaborations with the city and state health departments and with other major HIV clinics in Baltimore through shared grants has strengthened the services that each clinic offers to their patients. Recent focus areas and initiatives include expanding the primary care model to include geriatric assessments for the large proportion of people living with HIV over 50, offering immediate appointments and same day antiretroviral therapy to newly diagnosed patients, and expanding our medication assisted treatment (MAT) program for patients with opioid use disorder. Initiatives for general infectious disease at THRIVE include rolling out penicillin allergy skin testing, and providing follow up appointments to patients seen in the Emergency Department for skin and soft tissue infections. The THRIVE program is also strengthening its long term collaboration with the JACQUES Initiative, partnering on initiatives to link sexual assault victims to follow up care for HIV post-exposure prophylaxis, provide in home nursing and social work care to our most socially and medically frail patients, increase linkage to THRIVE for high-risk HIV negative people needing HIV pre-exposure prophylaxis, and utilizing our JACQUES treatment coaches to outreach to a larger proportion of patients to improve patient retention.

The COVID-19 pandemic drastically affected THRIVE's ability to provide these comprehensive multi-disciplinary services in person. The THRIVE clinic space was repurposed as a

L to R: The THRIVE Program's Robin Palmeiro, LCSW-C; Sarah Schmalze, MD; and Tiffany Moritz (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

COVID-19 assessment center, which was run and staffed by THRIVE physicians from March through July and THRIVE temporarily was housed within another clinic. Nevertheless, the program was able to successfully pivot to telemedicine platforms, provide medical equipment for home monitoring so that patients would not have to leave their homes (e.g. blood pressure cuffs), and adjust staff roles and available funding and resources to meet new demands. Through tremendous efforts by all THRIVE staff and providers, the volume of visits lost in the early part of the pandemic was recovered through aggressive telemedicine work and patient retention efforts.

Faculty Practices: IHV clinicians initiated three new programs in 2020. **James Doub, MD**, Assistant Professor of Medicine, formed a musculoskeletal infectious disease program (MSK ID). The MSK ID program is borne out of the desire and necessity to reduce morbidity and mortality of musculoskeletal and biofilm infections. To meet these aims, Dr. Doub formed collaborations with surgical colleagues and with University of Maryland, Baltimore laboratories to conduct translational research in the use of bacteriophage therapy in prosthetic joint infections to cure these infections without removal of prosthetic materials. He devised a clinical protocol for using bacteriophage therapy in prosthetic joint infections and is moving toward applying this protocol to a phase 1 clinical trial. **Kalpana Shere-Wolfe, MD**, Assistant Professor of Medicine and Director of the Lyme Program at the Waterloo location, launched a monthly Lyme Wellness Workshop in June 2019 that was offered free to the public presenting on such topics as Lyme prevention, nutrition and Lyme, and sleep wellness and Lyme. These workshops were then held virtually during the COVID-19 pandemic. Returning from international posting (IHV's PEPFAR funded work) **Paul Saleeb, MD,** Assistant Professor of Medicine, has been expanding our clinical management services for inpatients and outpatients with multidrug resistant tuberculosis and nontuberculous mycobacterial diseases. Dr. Saleeb now serves as one of the state's physician consultants in the Department of Health Center for TB Control and Prevention.



The JACQUES Initiative: Under a new leadership team, JACQUES has strategically refocused its programs around community outreach, engagement, HIV prevention, rapid testing, and linkage and retention into care. Additionally, the JACQUES Initiative and the THRIVE clinic are actively working on consolidating their partnership while identifying and strengthening areas of programmatic collaboration and integration, mainly through the TRAC (Treatment, Retention & Adherence Center). Through CDC grants, the JACQUES Initiative partnered with the Baltimore City Health Department and other health organizations to implement a comprehensive HIV pre-exposure prophylaxis program (PrEP) focusing on men who have sex with men (MSM) and transgender clients that will continue to develop and expand in 2020-2021 through the Ending the Epidemic initiative. The establishment of The JACQUES Journey Center located at 880 Park Avenue has provided a home for the Initiative and allowed for expanding community health and supportive services, highlighted by The EXCHANGE Program centered on engaging at-risk young MSM and LGBTQ-identified youth in the Baltimore community. The Center offers health education, support groups, job and emergency housing referrals, on-site HIV/HCV rapid screenings, health-related peer counseling and linkage to health services. The JACQUES Initiative's Testing and Linkage to Care team is also responsible for responding to all HIV routine testing at UMMC/MTC, ensuring prompt engagement in care for newly diagnosed and out-of-care patients. Furthermore, The JACQUES Initiative, in collaboration with the forensic team at Mercy Hospital and THRIVE, ensures linkage to care for patients referred for nPEP (non-occupational Post- Exposure Prophylaxis), most of whom are victims of sexual violence. Lastly, the JACQUES Initiative works in collaboration with Maryland's Department of Corrections to ensure that patients released from its system have a smooth transition to access HIV care.

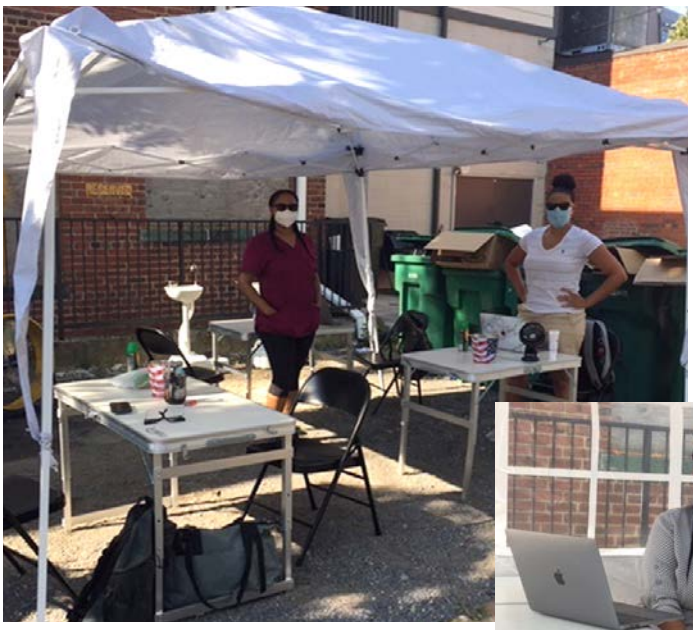
Financial Health Clinical Program: FY2020 was on target to match or exceed FY2019 but significant losses were experienced in both the inpatient and outpatient programs over the last 4 months of the year related to the COVID-19 pandemic. The combined clinical practices (IHV and ID) charged just under $7,250,000 and collected $3,763,546 in FY 2020. After physician salary costs, administrative costs, billing

costs, malpractice insurance costs, and operational cost, the clinical practice will not realize a revenue that exceeds costs for this past year. Support has come from the Medical School and the Department of Medicine.

IHV's Community Based Clinical and Research Programs to Address Infectious Diseases and Opioid Use Disorder

The IHV's clinical and research activities reach beyond the University campus, through its DC Partnership for HIV/AIDS Progress Comorbidities Program (DC PFAP). Since 2015, this unique clinical research program has embedded IHV providers and research staff in community-based settings such a syringe service program, opioid treatment program, and federally qualified community health centers in Washington, DC and Baltimore. In these settings, IHV staff and collaborators are able to engage populations generally excluded from research, such as minorities and people who use drugs, and enact studies across the spectrum of translational research, including the ANCHOR, GRAVITY, LOOP, and SEARCH protocols. These investigations seek to better understand the continuum of care of individuals with infectious complications of opioid use disorder, and implement treatment models to improve both infectious and drug-use associated outcomes. This program is led by co-directors, **Sarah Kattakuzhy, MD**, Assistant Professor of Medicine, and **Elana Rosenthal, MD**, Assistant Professor of Medicine, with program management by **Rachel Silk, RN**, clinical and research support by **Dr. Britt Gayle**, **Ashley Davis, NP** and **Amelia Cover, NP**, and study coordination by **Rahwa Eyasu NP, Emade Ebah, MPH**, and **Onyinyechi Ogbumbadiugha**.

Additionally this year, Dr. Kattakuzhy received funding from the UMB



The modified clinic at HIPS was moved into the parking lot to more safely serve our patients during COVID. Rahwa Eyasu, MSN, FNP and Ashley Davis, CRNP (left) and Rahwa Eyasu, MSN, FNP (right)

CARE's grant to develop and implement an opioid-use disorder (OUD) resident education training program in buprenorphine (called AIROH) at University of Maryland Medical System. ARIOH is designed to improve the knowledge and skills of medical residents on the front lines of the opioid epidemic. She is working in close collaboration with UMB's Department of Psychiatry and Division of Addiction Treatment. Dr. Rosenthal received funding from the NIH as one of three institutions in the United States to evaluate OUD, HIV, and HCV-related outcomes among adults who are hospitalized with infections associated with injection of opioids (called CHOICE).

Clinical Programs in Chronic Viral Hepatitis

IHV's hepatitis B (HBV) and C (HCV) treatment programs continue to expand under Drs. Tang and Wilson, and **Angie Price, DNP**, with locations at the Downtown and Midtown University of Maryland campuses, and the Veterans Affairs Maryland Health Care System (VAMHCS). The IHV has established a comprehensive clinical program to screen, link, and treat patients with chronic hepatitis B infection, while simultaneously conducting translational research on the immunopathogenesis of HBV persistence, with the aim of developing therapeutics targeting the cure of HBV chronic infection. The IHV continues to partner with the Hepatitis B Initiative of Washington, D.C. (HBI-DC) to increase awareness and provide screening for patients at risk for chronic hepatitis B in the Baltimore/District of Columbia metropolitan area, where a majority of patients have not been engaged in clinical care due to socioeconomic background. Since 2005, over 18,000 people in the DC-metropolitan area have been screened by HBI-DC, with prevalence rates of 6% for hepatitis B. Those who tested positive are linked to care for further evaluation and treatment. Since 2016, Dr. Tang has received multiple grants to support the hepatitis B clinical research program and recently successfully completed a single-site phase 2

Front Row, L to R: Salma Sharaf, BS; Eleanor Wilson, MD, MHS; Sarah Mitchell, MS, MBA; Kiran Mian, BS; Shyam Kottilil, MBBS, PhD; Jennifer Husson, MD, MPH; Gabrielle Cudjoe, BS; Ilise Marrazzo, RN, BSN, MPH; and, Angie Price, DNP, MSN, CRNP Back Row, L to R: Lydiah Mutumbi, AND, BSN, MPH; Joel Chua, MD; Lydia Tang, MBChB; Mikhail Shlyak, BS; Amy Nelson, RN, MS; Richard Chiu; and, Jennifer Hoffmann, MSN, MPH, CRNP (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

clinical trial evaluating a new experimental drug for chronic hepatitis B treatment. She also collaborates with public health investigators at the George Washington University School of Nursing and the Maryland Department of Health, assisting with the development and delivery of outreach and educational materials. The group is pursuing other collaborations to expand access to research, including investigational new therapeutic agents, for this underserved population.

In her role as Director of the Hepatitis Clinic at the VAMHCS, Dr. Wilson has participated in one of the largest HCV treatment initiatives in Maryland, with more than 2,000 patients treated in just over four years. As part of a variety of collaborative projects, she has investigated post-HCV treatment outcomes, including HBV reactivation, fibrosis progression, diagnosis of malignancies, and cardiovascular events in her VA cohort. At the IHV, Dr. Wilson also completed the largest single-site phase 2b clinical trial of an investigational combination DAA for the treatment of relapsed HCV, with more than 75 patients recruited from the Baltimore/DC area. Ongoing projects include investigating outcomes in vaccination against viral hepatitis and initiatives to expand screening initiatives and treatment access for at risk patients.

CLINICAL RESEARCH

Clinical Research Unit (CRU): The IHV Clinical Research Unit continues to grow under the direction of **Jennifer Husson, MD**, Assistant Professor of Medicine. The multidisciplinary CRU team is comprised of two nurse practitioners, two nurse coordinators, a pharmacist, a phlebotomist, one regulatory specialist, four study/research coordinators, and three laboratory technicians. During the past year, the CRU continued to expand its portfolio to 42 clinical trials. The clinical trials range from phase 2 to phase 4 studies encompassing a variety of topics including viral hepatitis, HIV, nonalcoholic steatohepatitis (NASH) and cytomegalovirus (CMV) both investigator initiated and industry sponsored studies. The CRU has continued to expand upon its collaboration with researchers from the Division of Gastroenterology and Hepatology who investigate NASH and hepatocellular carcinoma. Additionally, with the coronavirus pandemic, the CRU has played an active role in bringing clinical therapeutic trials to patients hospitalized with COVID-19. The CRU continues to support the IHV's mission of advancing the understanding and treatment of chronic viral infections in a variety of hosts.

FLSC Vaccine Program: The full-length single chain (FLSC) vaccine was developed by IHV scientists under the leadership of Dr. Robert Gallo, George Lewis, PhD, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Director of the IHV Division of Vaccine Research and Anthony DeVico, PhD, Professor of Medicine in the IHV Division of Vaccine Research. The clinical component of the FLSC vaccine program is currently headed by **Mohammad Sajadi, MD**, Associate Professor of Medicine. The Phase 1a (dose escalation), randomized, placebo-controlled, double-blinded clinical trial designed to evaluate the safety and immunogenicity of a HIV vaccine called FLSC (full length single chain) in healthy volunteers without HIV infection was carried out at the IHV. This trial represents true translational impact of IHV on meeting the needs of HIV-infected individuals. Healthy volunteers of 18-45 years of age, and those who have never previously participated in an HIV vaccine trial were immunized with the FLSC vaccine, and this study is now completed. Immunogenicity data analysis is ongoing. Preliminary safety and immunologic results available have been selected for oral presentation in this year's ID Week in Washington D.C. FLSC will also be tested in several upcoming vaccine trials at the HVTN (HVTN132 and HVTN 134) and MHRP (RV509 and RV546).

Collaboration with National Institutes of Allergy and Infectious Disease (NIAID) Intramural Program: The collaborations between the IHV and with the NIAID intramural program of the National Institutes of Health (NIH) continue expanding. NIAID clinical trials are still being recruited at the IHV CRU (Anthony Fauci, MD, Director of NIAID and Tae-Wook Chun, PhD, Chief, HIV Immunovirology Unit). In addition, the Division has two NIH intramural bench to bedside grants; one to evaluate changes in immune activation using novel imaging techniques among patients undergoing therapy for hepatitis C with or without HIV coinfection and the other compare radiological changes (MRI) in HCV mono-infected and HIV/HCV coinfected patients pre and post treatment, compared to HIV mono-infected patients (Henry Masur, MD, Chief, Critical Care Medicine Department, NIH). Finally, the research collaboration continues between Adriana Marques, MD (Chief, Clinical Studies Unit, Laboratory of Clinical immunology and Microbiology) from NIAID and the Lyme disease program at the Waterloo infectious diseases practice. These opportunities continue to provide the IHV the opportunity to augment its research capabilities.

CLINICAL TRIALS PROGRAM

The Division continues its rapid growth of clinical research initiatives that focus on novel, investigator initiated clinical trials and continues to be one of the most dynamic clinical research programs. Major investigator-initiated clinical trials are highlighted below.

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/velapasvir) and 100 courses of PrEP, and a Merck investigator initiated grant that supports treatment (elbasvir/grazoprevir) for an additional 100 patients. Enrollment has completed for the Gilead supported study portion and participants are now in long-term follow-up. Additionally, for the second 100 participants, the study team also collaborated with National Institute of Drug Abuse to use their ecological momentary assessment (EMA) technology to assess cravings and adherence.

APOSTLE: **Joel Chua, MD,** Assistant Professor of Medicine finished conducting a single center, phase 2 study evaluating the antiviral activity of Ledipasvir (LDV) and Sofosbuvir (SOF) either in fixed dose combination or as monotherapy in subjects infected with HBV. The primary objective is to evaluate the change of serum hepatitis B surface antigen as an indicator of antiviral activity of LDV and/or SOF in subjects with chronic hepatitis B from baseline to end of 12 weeks of treatment. This study was funded by Gilead Sciences as an investigator-initiated clinical trial.

Best HBV: Dr. Chua is conducting a single center, open-label phase 4 study to evaluate the efficacy, safety, and tolerability of treatment with fixed dosed combination bictegravir/emtricitabine/tenofovir alafenamide in adults with HIV-1 and HBV coinfection who are currently on antiretroviral therapy, with HIV RNA <50 copies/mL for at least six months. This study was funded by Gilead Sciences as an investigator-initiated clinical trial.

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

CHROME (Cardiovascular Disease in HIV and Hepatitis C; Risk Outcomes after Hepatitis C Eradication)**:** CHROME, led by Dr. Mathur, to treat HCV in mono-infected and HIV co-infected individuals and compare inflammatory markers and radiological changes (MRI) in HCV mono-infected and HIV/HCV coinfected patients pre and post treatment, compared to HIV mono-infected patients. This study is funded through a Merck investigator-initiated grant and the National Institutes of Health Bench-to Bedside Award.

CoCrystal: Dr. Chua is also conducting a phase 2a study evaluating the safety and efficacy of combination treatment with two weeks of the non-nucleoside inhibitor CDI-31244 plus six weeks of sofosbuvir/velpatasvir in patients with HCV genotype 1. The primary goal is to find a regimen with potential for shorter duration therapy for chronic hepatitis C.

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.

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

HOPE in Action: Dr. Husson, along with our transplant surgery team and investigators from Johns Hopkins University, won an U01 award from NIAID to evaluate the use of HIV-infected donor kidneys for transplantation into HIV-infected kidney transplant recipients. Dr. Husson has been guiding the infectious disease management of UMB's program in HIV transplantation and is the site principal investigator for this multi-center study. Through this study, the first HIV+ to HIV+ kidney transplant at the University of Maryland was successfully completed and preliminary data has been accepted for publication.

HIVTR CCR5 Clinical Trial: Dr. Kottilil 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.

SEARCH: These are a series of investigator-initiated studies funded by the The Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative, led by Dr. Kattakuhzy to investigate the therapeutic potential of an investigational agent in the treatment of opioid use disorder.

LOOP: This investigator-initiated study funded by the JC Martin Foundation and led by Dr. Rosenthal is designed to research the long-term outcomes of persons with opioid-use disorder.

STOP-CO Clinical Trial: Drs. Husson, and Rolf Barth, MD, Associate Professor of Surgery, University of Maryland School of Medicine, along with collaboratUCSF 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. With enrollment completed, the IHV in collaboration with UCSF is currently analyzing data.

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

COVID-19 Clinical Trails

CAN-COVID: Dr. Chua is the site investigator for a phase 3 randomized, double-blind, placebo- controlled study to assess the efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia.

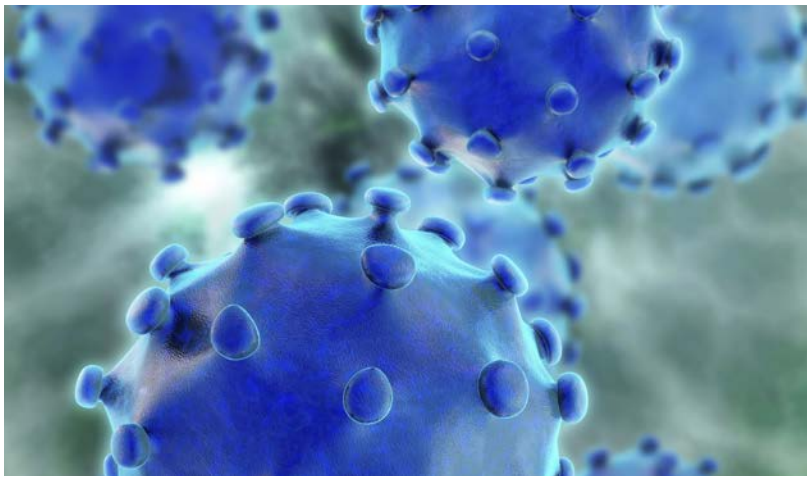
HAT-COVID: Dr. Chua was also the site investigator for this multi-center, randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of hydroxychloroquine monotherapy and in combination with azithromycin in patients with moderate and severe COVID-19 disease. This study was closed by the sponsor.

SAC-COVID: This study led by Dr. Kottilil is using the novel drug CD24Fc to examine if it may help to reduce multiple inflammatory cytokines and protect lung tissue from the injuries and damage caused by an over reactive immune system.

CLINICAL CARE AND RESEARCH DIVISION LABORATORY BASED PROGRAMS

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

Currently available nucleus/tide analog antiviral treatments are successful in achieving HBV suppression in a vast majority of patients. However, these treatments are required life long and do not result in viral clearance. Discontinuation

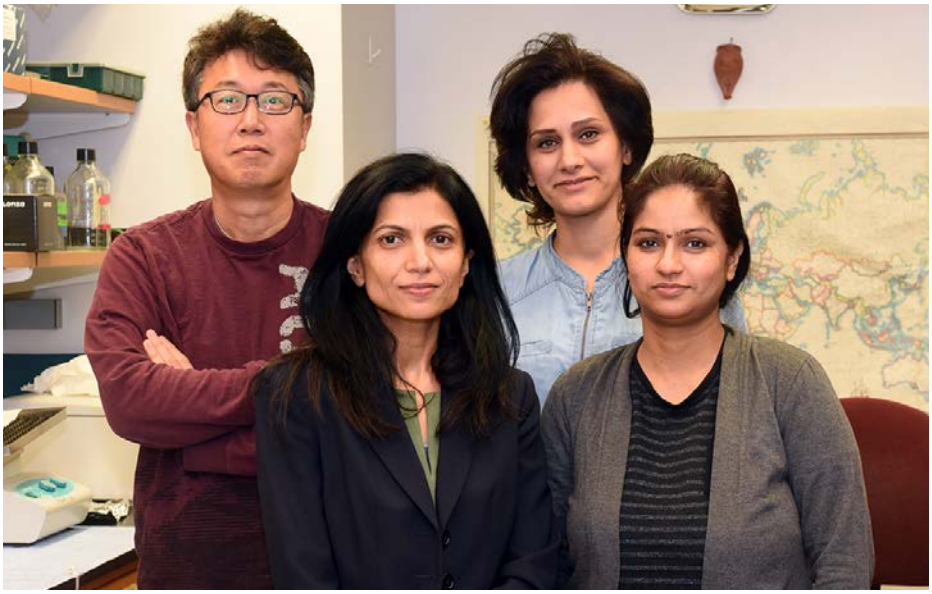


of therapy prior to hepatitis B surface antigen (HBsAg) loss, or seroconversion, is associated with relapse of HBV, in the majority of cases. Achieving HBsAg loss or seroconversion defines chronic hepatitis B (CHB) functional cure and is the goal of Dr. Kottilil's translational research program. Their ongoing efforts in this direction focus on multiple approaches that include targeting the viral, and or host, factors required for viral persistence, and novel immune-based therapies, including immunomodulation and therapeutic vaccines.

These research efforts led by Drs. Poonia and Kottilil primarily delineate intrahepatic and peripheral immune responses to HBV that correlates with development of protective immunity. Three separate projects are presently funded by research grants from Arbutus Pharmaceuticals, and from Gilead Sciences. The central goal of the Arbutus project is determining the role HBsAg plays in massive immune dysfunction observed in CHB. HBsAg levels stay persistently high in chronically infected patients even with long term effective antiviral treatment and this has led to the hypothesis that the antigen is immunomodulatory. Defining role of HBsAg in immunosuppression will provide a scientific rationale to develop strategies that attempt to reduce HBsAg levels for inducing immune recovery and potential functional cure. In published results from this project, they identified correlation of HBsAg levels with inhibitory checkpoint molecule expression on helper CD4+ T cells, indicating immune dysregulating role of this antigen. Importantly, use of serum HBsAg levels as stratifying variable determined successful response to anti-PD-1 blocking for recovering anti-HBs immunity. As a result of successful project collaboration, further funding was received from Arbutus and continued efforts aim to identify additional targets to pursue for improving immune response in CHB. For this, a comprehensive evaluation of multiple checkpoint/inhibitory molecules that associate with HBsAg levels and immune dysfunction

will be performed. Further, role of soluble inhibitory molecules and their mechanism of inhibiting HBV specific immunity will be determined. Under the projects funded by Gilead Sciences, the central question remains exploring the TLR8 pathway as a viable strategy to recover HBV specific immune response with the goal of achieving functional cure. Using clinical samples from Phase 1 and 2 clinical trials, where a small molecule selective TLR8 agonist GS-9688 was tested in CHB patients, they previously identified immune pathways modulated by this agonist. Induction of cytokines IL-12 and IL-18 led to activation of innate and adaptive lymphoid cells and in a subset of patients improved HBs specific B cell response was observed in B cell ELISPOT assays. Further studies have identified the mechanism behind this improvement in B cell response. TLR8 signaling led to induction of follicular helper T cell differentiating cytokines in monocytes of treated patients. These TLR8 differentiated Tfh when co-cultured with autologous B cells led to generation of plasma cells and improvement in HBsAg specific B cell response. This function of TLR8 has real potential to impact HBV functional cure, which is defined as anti-HBsAg seroconversion.

The goal of the Hepatitis C Immunology Program is twofold. This highly productive translational/bench research portfolio focuses on unraveling biological correlates of protective immunity to hepatitis C virus (HCV) for informing vaccine approaches as well as continues to examine immune perturbations in successfully cured patients. Using samples collected from various clinical trials, Drs. Poonia and Kottilil continue their investigations into determinants of sustained virologic response (SVR) with directly acting anti-viral (DAA) therapy. Early work from their group demonstrated HCV specific T cell responses are augmented by DAA therapy in patients with SVR, suggesting a role for immune responses in HCV clearance with non-immune based DAA therapy. To identify immune correlates of success to DAA therapy, they studied cohorts of patients that were treated for a very short duration of 4 to 6 weeks. This resulted in successful viral clearance in a subset of patients allowing investigation of differentiating immune responses in successful versus failed cases. Immune phenotypes that predicted SVR included CD8 and CD4 T cells expressing multiple inhibitory receptors including PD-1, LAG-3, Tim-3 and containing HCV specific cells, indicating role of activated antigen specific cells in antiviral response. An important area of focus in HCV immunology examines immune defects that continue to persist despite successful DAA mediated SVR, with ramifications for further complications including hepatocellular carcinoma. They have shown both adaptive and innate immune defects that persist in cured individuals, including CD8+ T cell gamma delta T cells, MAIT cells and NK cell defects, important effector cells relevant for antiviral and anti-cancer function in successfully cured patients. Ongoing research will determine long-term persistence of these and other immune alterations as well as correlations of these immune defects with complications like fibrosis and HCC. An unanswered question in HCV research since the availability of highly effective curing treatment regimens is the need for a prophylactic vaccine. It is not known whether patients that are cured develop protective immunity and if that is effective in preventing re-infections, especially in patients with continued high-risk behavior. These questions are being answered in projects funded by investigator initiated clinical research studies by Gilead Sciences. Dr. Poonia is in her fourth year of an NIH R01 grant from National Institute of Drug Abuse to study the immune correlates of protection from reinfection among people at the highest risk of acquisition of HCV namely, those with HIV infection and people who inject drugs. Using samples from these PWID patients, the laboratory is

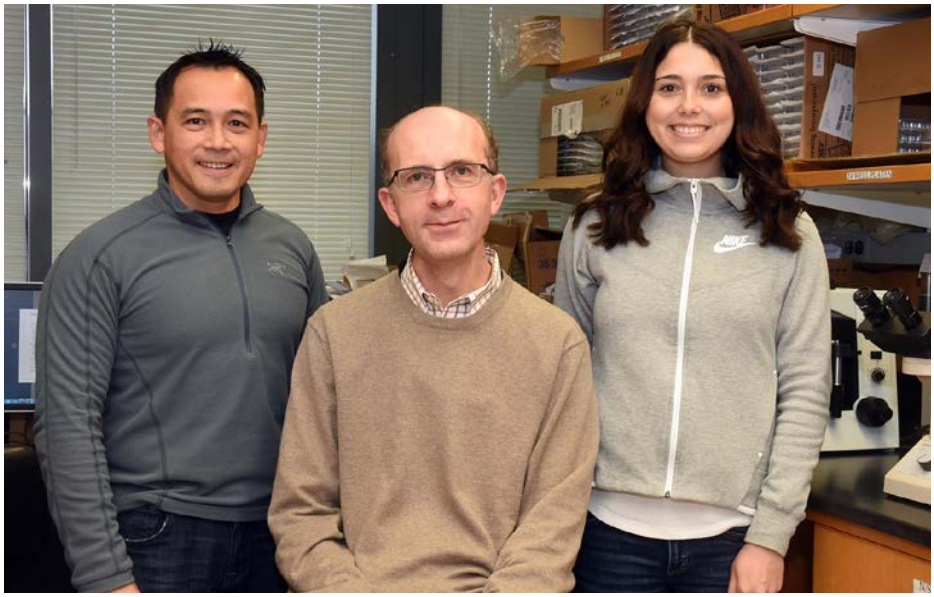


Poonia Lab: L to R: KiSeok Lee, PhD; Bhawna Poonia, PhD; Sara Romani, PhD; and, Arshi Khanam, PhD (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

investigating the immune defects that distinguish PWID from non-PWID as well as whether anti-HCV immune responses recover after successful SVR in these patients. This cohort with continued risk behavior provides a unique opportunity to investigate whether failed recovery of immunity after HCV cure is correlated with re-infection. Recently, she also received a supplement to this grant for investigating COVID-19 progression and immunity in subjects with HIV infection and opioid use disorder. There is a potential to identify immune deficiencies in this subset of patients that contribute to more severe disease progression. This will be critical for optimizing treatment strategies and designing vaccine candidates that generate protective immunity for this and future coronavirus infections in people with underlying opioid-use disorder.

Due to combination antiretroviral therapy (cART), patients with HIV are living longer, but increasingly often they necessitate treatment for comorbidities such as cancer. Currently, lung cancer is the leading cause of cancer death in patients with HIV. In the project entitled, "*Impact of concomitant chemotherapy on HIV resistance to cART and reservoir size*", funded by NCI, **Alonso Heredia, PhD**, Associate Professor of Medicine, laboratory is investigating drug interactions between chemotherapeutic drugs and antiretrovirals with the goal of improving treatments in the growing population of HIV-infected patients with cancer.

Another area of active investigation in Dr. Heredia's lab is HIV latency. In collaboration with Fabio Romerio, of IHV's Infections Agents and Cancer Division, Dr Heredia is a co-Investigator in the NIAID funded project "*Sustained HIV remission via sequence-specific epigenetic silencing of latent proviruses.*" In this project, Dr. Heredia is assessing



Heredia Lab: L to R: Nhut M Le, BS; Alonso Heredia, PhD; and, Triana Rivera-Megias (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

the impact of HIV antisense transcript expression on silencing of HIV proviruses both in tissue culture and in humanized mice. In a related project, Dr. Heredia, in collaboration with Dr. Tae-Wook Chun, from NIAID, is investigating suppression of HIV reactivation in cells from cART-treated patients using various combinations of antibodies.

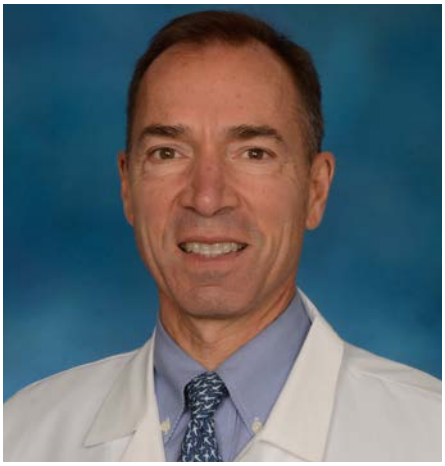
Yet another area of research in Dr. Heredia's laboratory is the development of effective antibodies against HIV. In collaboration with Dr. Sajadi, he is a Co-Investigator in the project "*Development of a new family of potent and broad neutralizing antibodies,*" funded by the Bill and Melinda Gates Foundation. Dr. Heredia's role in the project is to evaluate the anti-HIV activity of anti-HIV Clade C/ Pan-neutralizing monoclonal antibodies in humanized mice. In another similar project, "*Bridging Antibody Fc-mediated Antiviral Functions Across Humans and Non-human Primates*", funded by NIAID, he is collaborating with Drs. DeVico and Lewis, from IHV's Vaccine Division. His role in this project is to evaluate novel anti-HIV antibodies in humanized mouse models to identify potential protective antibodies for a vaccine in humans. Also, in collaboration with Dr. Olga Latinovic, from IHV's Infectious Agents and Cancer Division, he is investigating approaches to enhance the anti-HIV activity of entry inhibitors.

Dr. Sajadi and his lab currently focus 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 three active grants, and is funded by the NIH, the Bill and Melinda Gates Foundation, and the VA. Dr. Sajadi has isolated several anti-HIV broad neutralizing antibodies that are among the most potent and broad described to date, which are currently undergoing pre-clinical development. He is also working on a project to understand the humoral response in COVID-19 infection.

Shashwatee Bagchi, MD, Assistant Professor of Medicine, is currently focused on investigating the cardiovascular complications of patients who have chronic hepatitis C infection, HIV infection, or both, and works closely with Dr. Robert Weiss and Dr. Todd

Brown at Johns Hopkins University and Dr. Shana Burrowes at Boston University. She has multiple projects she is engaged in to address this clinical problem and consequent research questions, ranging from retrospective cohort studies of our outpatient HIV-infected patients and those in the MACS/WIHS cohort to a prospective cohort study among HIV and HCV mono-infected and HIV/HCV co-infected. Dr. Bagchi has a NIH K23 grant "Elucidating Chronic Hepatitis C Infection as a Risk Factor for Coronary Heart Disease in HIV-Infected Patients," and recently completed an Accelerated Translator Incubator Pilot award from the University of Maryland Institute of Clinical and Translational Research "Systemic and Epicardial Fat Inflammation and Local Coronary Atherosclerosis in HCV and HIV Patients."

The laboratory of **Nicholas Stamatos, MD, PhD**, Associate Professor of Medicine, conducts 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, his laboratory is studying how changes in the polysialic acid (polySia) content of specific cell surface glycoproteins on monocytes and monocyte-derived dendritic cells and macrophages influence the immune capacity of these cells. Experiments are being conducted using a murine model of pneumonia to test the hypothesis that regulated expression of polysialylated proteins on leukocytes helps direct cell homing and a well-orchestrated immune response during infection with *pneumococcus* and influenza virus. These experiments demonstrated impaired leukocyte migration in cells devoid of polySia, but paradoxically, improved survival of polySia-deficient mice after infection. Current experiments are designed to help explain the protective advantage of polySia deficiency. The overriding

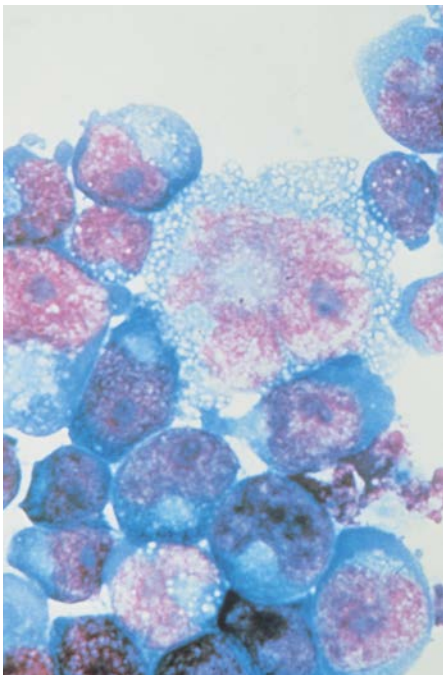


Nicholas Stamatos, MD, PhD

goal of this work is to demonstrate that controlling the extent of polysialylation of specific glycoconjugates has therapeutic value in various disease states of inflammation and infection. The laboratory is funded by an R01 from the National Institute of Allergy and Infectious Diseases in the amount of $2,562,639 over 5 years. 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. Work from this laboratory previously demonstrated that removal of sialic acid from the surface of peripheral blood mononuclear cells using an exogenous bacterial neuraminidase promoted infection with HIV-1. Recently, this laboratory demonstrated that activated human lymphocytes express not only monomeric sialic acid, but also polySia, and that removing this glycan enzymatically diminishes infection by HIV-1. Experiments are underway 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 these 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. The Stamatos group's discovery of polySia modification of neuropilin-2 led to the finding that dendritic cells express semaphorins that cause F-actin reorganization and promote chemotaxis. Thus, these studies identified an additional signaling axis in human dendritic cells mediated by soluble factors. These semaphorins likely promote additional activities of human dendritic cells during innate and adaptive immune responses. It is expected that the additional polysialylated proteins that are identified on immune cells will have equally significant roles in cell function.



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Epidemiology and Prevention

Man Charurat, PhD, MHS

This year, the Division of Epidemiology and Prevention, led by **Man Charurat**, **PhD,** Professor of Medicine and Global Director, Center for International Health, Education, and Biosecurity, continued to advance their translational and implementation research and training programs locally in Baltimore and globally with emphasis on population science in HIV, HPV, and non-communicable diseases associated with viral infections. The Division consists of 11 faculty responsible for leading 18 federal research awards. The Division published 63 manuscripts in peer reviewed journals in FY20.

Translational and Implementation Research Program

Alash'le Abimiku, PhD

Alash'le Abimiku, PhD, Professor of Medicine, and Executive Director of the International Research of Excellence at the Institute of Human Virology, Nigeria (Abimiku Picture) has established a laboratory network and infrastructure including a BSL-3 for TB diagnostics activity, a robust lab QA/QC component, a comprehensive laboratory training program, and a biorepository network under the Institute of Human Virology-Nigeria PEPFAR program. Her research focuses on understanding microbial shifts and how they affect vaccine response. She is PI of the NIH funded BEAMING study and H3Africa Biorepository (I-HAB).

The preliminary data from the **BEAMING** (Breast Milk Microbiota Influence on Infant Immunity Growth) study continues to show a dynamic shift in the microbiome of HIV exposed uninfected infants (HEU) compared to their HIV uninfected (HU) counterparts. An increase in proteins were also seen following initiation of breastfeeding indicating the possible introduction of the mothers' breastmilk microbiome in the Nigerian and South African birth cohort. She is currently analyzing milk products to identify the bacterial major classes found in breast milk that may be contributing to the infant microbiome. In addition, the immune response to pediatric vaccination exemplified by the anti-tetanus IgG response to the pediatric combo Diphtheria/ Pertussis/Tetanus (DPT) vaccine show high baseline titres in Nigerian infants compared to their South African counterparts and a decrease in titres following vaccination only among Nigerian HEU infants which is interesting. There was also clear difference in the diversity and frequency of HLA-DRB1 and HLA-DQB1class II region associated with vaccine-induced antibody response in infants from the two African countries, and between HEU and HU infants. By bringing all these data together, Dr. Abimiku hopes to advance the understanding of the differences seen in HEU compared to their HU counterparts.

COVID protection

I-HAB (IHVN H3Africa Biorepository), Dr. Abimiku and her team in Nigeria continue to provide high quality biobanking services to several NIH funded research sites located in Nigeria, Ghana, Gambia, Benin Republic and Mali; the IHV Epi Division's population based seroprevalence survey, as well as several NIH funded research grants that belong to IHV faculty and other US based institutions. I-HAB continues to

New IHVN building

employ a multifaceted, comprehensive approach to maintain best practices according to International Society for Biological and Environmental Repositories (ISBER), applicable areas of ISO 15189 and biobank industry standards. I-HAB has also continue to train and mentor staff from Pan African institutions; and support the Nigerian National Biorepository at the Nigerian Centers for Disease Control. During COVID, the biorepository has supported processing and storage of samples from volunteers and patients suspected to be infected with SARS COV-2 (see picture 1 covid) and is poised to support vaccine clinical trials for COVID and other infectious agents. With the completion of the new IHVN campus, the expanded space at the basement for the biorepository and the installation of a liquid nitrogen plant; the initial investment by NIH will be sustained through the provision of high-quality biorepository services to all investigators including IHV-UMB investigators. (Pictured on page 45, the new IHVN building) IHAB serve as the biorepository core for the **SickleGenAfrica U54** center grant to conduct translational research in Sickle cell anemia across five African countries using well processed, preserved and quality controlled and redundantly protected human biological samples accessible to the H3Africa and larger research community. Intravascular hemolysis is associated with release of potentially toxic molecules such as free heme into the circulation that act as danger associated molecular pattern (DAMP) molecules and promotes early death in Sickle Cell Disease (SCD). Africans may harbor hitherto unknown genetic variants as an adaption to hemolytic stress associated sequelae with intravascular hemolysis and subsequent failure of multiple organs that may be exacerbated with bacterial infections and severe sepsis. Given these facts, the study aims to research the role that cytoprotective proteins namely haptoglobin, hemopexin, alpha-1-microglobulin, heme oxygenase-1 and ferritin, which collectively neutralize the major hemolysis DAMP molecules, *cell-free hemoglobin and free heme,* which are genetic modifiers of SCD that may have potentially more powerful impact on the phenotype of SCD in the African setting.

Clement Adebamowo, BM, ChB, ScD, FWACS, FACS

Clement Adebamowo, BM, ChB, ScD, FWACS, FACS, Professor of Epidemiology and Public Health, Director for Global Health Cancer Research and Associate Director Population Science Program, Marlene and Stewart Greenebaum Comprehensive Cancer Center (picture Clement) conducts research on the epidemiology of cancer. He is PI of two NIH/ Wellcome Trust funded Human Heredity and Health in Africa (H3Africa) initiatives on genomics research and education in Africa (ACCME and AFBRECANE). The African Collaborative Center for Microbiome and Genomics Research (**ACCME**) is a U54 Collaborative Center funded by the NIH Office of the Director that is completing the first systematic Genome-wide Association Study of persistent high-risk HPV infection and cervical cancer in 11,700 women in Nigeria. The project also studies the vaginal microenvironment's cytokines and microbiota for associations with risk of prevalent and persistent high-risk HPV infection. The outcome of the project laid the foundation for our pending U54 grant to the NCI for study of HPV infection, immune checkpoint inhibitors, CRISPR-Cas 9 and cervical cancer in HIV positive women in Nigeria and Tanzania. The components of the application were rated excellent to outstanding, so he is optimistic for funding. Dr. Adebamowo is also collaborating with the National Cancer Institute to comprehensively sequence all the HPV identified in the study as part of an Intergovernmental Personnel Act (IPA) Mobility Program within the Cancer Moonshot program.

The African Female Breast Cancer Epidemiology (**AFBRECANE**) study is the first systematic study of the genomics and epidemiology of molecular subtypes of breast cancer in indigenous African populations. Linkage with cancer registries established under our NCI funded D43 grant enables the team to be one of the few studies to compute incidence of molecular subtypes of breast cancer. Dr. Adebamowo is

HIV Prevention, Care, and Treatment Programs (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

using multiple approaches to measure vitamin D levels—Food Frequency Questionnaires, serum measurements and Mendelian Randomization – and evaluate its association with breast cancer risk in African women who have fairly similar sun exposure, but in another first, the analyses will be adjusted for skin tone and color. The molecular subtyping in this study is enabling an industry partnership with Cepheid to evaluate Strat4 – their rapid test for molecular subtypes of breast cancer. AFBRECANE study also informed the Point of Care Tool for Breast Cancer (PoCBreCa) study (pending R21 grant; score 2 percentile) where he will validate a cell phone-based application for molecular subtyping of breast cancer that Dr. Adebamowo developed.

Dr. Adebamowo is also responding to the COVID-19 pandemic locally in Baltimore. In Baltimore, in collaboration with colleagues at University of Maryland College Park, he is funded by the UMB-UMCP Empower program for a study titled ***"Predicting and Improving COVID-19 Vaccine Acceptance among African Americans during the Coronavirus Pandemic."***

Nadia Sam Agudu, MD

Nadia Sam Agudu, MD, Associate Professor of Pediatrics, (picture Nadia) conducts research in the areas of prevention of mother-to-child transmission of HIV (PMTCT) and differentiated service delivery for pediatric and adolescents including access to HIV testing, transition of care, PrEP, and other sexual and reproductive health services. As multi-PI (Tepper/Charurat/Sam-Agudu) of the NIH-funded Adolescent to Adult Patient-centered HIV Transition (**ADAPT**, R01HD089866) study she is leading the investigation in Nigeria and testing the impact of peer support in the form of an adolescent patient transition advocate on successful transition to adult HIV care. Dr. Sam-Agudu and a team of 12 clinician-scientists, six nurse coordinators, six laboratory scientists and other key study staff are in Phase II of ADAPT. ADAPT Phase I collected data to inform transition strategies in resource-limited settings to gain insight on implementation barriers for successful transition. Phase II focuses on the prospective trial where the patient transition advocate peer support is tested. The COVID-19 pandemic prompted a halt in study activities in March 2020, implementation resumed in October 2020 with Phase II being continued. Enrollment is currently at 88% (n=264) of the targeted 300 adolescents living with HIV; the study expects to complete this delayed enrollment before the end of 2020.

Dr. Sam-Agudu became a new member of the *Fogarty's Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA)*, which has funded Dr. Sam-Agudu to lead a collaborative mentorship program in Implementation Science for talented early investigators in West and Central Africa. UMB's inaugural Presidents' Global Impact Fund has also awarded Dr. Sam-Agudu a grant (in partnership with Prof. Alash'le Abimiku) to support the Implementation Science mentorship program.

Cristiana Cairo, PhD

Cristiana Cairo, PhD, Assistant Professor Medicine, studies human immune responses to pathogens of global health relevance, with a focus on responses elicited by microbial exposure before birth or in early life. The fetal immune system, compared to its adult counterpart, follows an alternate functional program that promotes fetal-maternal tolerance, but results in increased susceptibility to infections in infancy. Dr. Cairo has been studying: A) the functional program of neonatal innate-like lymphocytes; B) the impact of in utero exposure to pathogens, specifically P. falciparum or HIV, on the development of the infant immune system.

Functional program of neonatal Vδ2 T cells and impact of placental malaria. Dr. Cairo investigated the role of PD1 as regulator of Vδ2 cell function. The results were recently finalized

after performing multiple functional assays (proliferation, cytokine production, cytotoxic mediator production, degranulation) with neonate and infant specimens. PD1 appears to act as a previously underappreciated regulator of Vδ2 cell cytotoxic potential at birth (and probably during fetal life); however, within the first year of age other inhibitory receptors may become more important. Thus, PD1 represents a potential target to modulate Vδ2 cell function in early life, with implications for immune-protection against diverse pathogens during infancy. Interestingly, detailed functional analysis of approximately 80 cord blood specimens, obtained from neonates with 4 types of prenatal malaria exposure, suggested that perturbed PD1 expression at birth mediates the impact of placental malaria on neonatal Vδ2 cell function. This study indicated that in utero exposure to P. falciparum (specifically placental malaria) primes fetal Vδ2 cells, altering their differentiation, responses to in vitro stimulation, and, most likely, their antimicrobial function in infants.

HIV-exposed, uninfected (HEU) infants are more susceptible to common infections than their unexposed counterparts, and immune-perturbation is thought to contribute to this clinical outcome. Dr. Cairo MPI (Cairo/Laufer) for the **Impact of in-Utero HIV exposure on infant T and B cell responses in Malawi** (U01HD092308) in collaboration is assessing immune responses in HEU infants in Malawi from birth to 9 months of age. This study entails characterization of T and B cell responses to routine immunization antigens in infants born to: a) women with undetectable HIV viral load before conception and through pregnancy; b) women with HIV high viremia, diagnosed late in pregnancy and c): women with no HIV infection. The goal is to determine whether the extent of immune perturbations in HEU infants correlates with the degree of exposure to HIV viral replication during gestation. So far, more than 400 infants have been enrolled in the study, and approximately 120 completed follow up. The COVID-19 pandemic forced a suspension of in person clinical activities for a few months but follow up and recruitment have recently resumed. Experimental system optimization is currently ongoing at the IHV and experiments will begin within the next month.

Dr. Cairo is also involved in a new study led by Dr. M. Laufer to assess neurocognitive development in the same cohort of Malawian HEU infants (R01HD100235). In this context, Dr. Cairo will help investigate a potential link between monocyte activation at birth and neurocognitive outcomes in infants and young children.

Man Charurat, PhD, Professor of Medicine and Global Director, Center for International Health, Education, and Biosecurity, is Principal Investigator (picture-Man) of four NIH grants focused in Nigeria.

Man Charurat, PhD, MHS meets with Nigerian officials (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

The Microbiome Affects Risk of Growth in HIV-exposed but Uninfected Infants—Nigeria (**MARGIN,** R01DE025174) study focuses on HIV-exposed uninfected infants and HIV unexposed infants and has demonstrated significant differences in the gut and oral microbiota which could further explain the higher frequency of early childhood co-morbidities among HIV exposed uninfected infants. The study team just completed the characterization of the mid-vaginal sample, maternal stool samples, oral samples, and skin samples to investigate the relationship of infants' early gut microbiota to maternal pattern in HIV-infected and uninfected women. He is also measuring the risk of persistent diarrhea, malaria, and pneumonia in association with change in infant gut microbiota and has found that greater gut permeability associated with lower weight-for-length Z-score, in the HIV-exposed group (P=0.02). Further, he is also completing a longitudinal analyses to characterize the functional differences in the infant gut microbiota between HIV-EU and HIV-UU infants. In a substudy led by **Dr. Cairo**, longitudinal mononuclear cell specimens of HIV-exposed and HIV-unexposed infants are also being analyzed to test whether gut dysbiosis is associated with perturbation of innate-like cell subsets, specifically Vδ2 T cells and MAIT cells. A preliminary analysis suggests that Vδ2 T cells in HEU neonates display altered differentiation, with increased expression of the cytotoxic mediator perforin and other receptors associated with cytotoxic function. Analysis of MAIT cells is still ongoing, but a developmental pattern in cytokine production and expression of receptors associated with specific function has emerged regardless of HIV exposure status.

In the **Building Trust** study (R01AI120913), Dr. Charurat made seminal contributions to key population research. With over 40 publication, Dr. Charurat's Trust and Building Trust research established one of the largest longitudinal cohort of HIV+ and HIV- MSM ins sub-Saharan Africa. Recently, Building Trust worked in collaboration with the Imperial College, United Kingdom and used phylogenetic sequences of HIV-1 collected from multiple cohorts to show links between HIV-infections among women in the general population and HIV infections among MSM. **Rebecca Nowak, PhD,** Assistant Professor of Epidemiology and Public Health, together with Dr. Charurat and Sarah Robbins, a doctoral student, found the prevalence of oral sex practices was nearly 70% and factors associated with oral sex practices included living with HIV, self-identifying as a woman, mobile phone ownership, receptive anal sex practices, and having multiple male sexual partners. Oropharyngeal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were nearly 3 times more likely to be detected in those engaging in oral sex practices (Robbins et al. *PLoS One* 2020). **Dr. Nowak** also evaluated the retention of members of the TRUST cohort and found that it was suboptimal with loss to follow-up (LTFU) occurring in 56% of the men followed. Although, participants at risk and living with HIV had a median follow-up time of 12 months and 21 months, respectively. Factors associated with retention included living with HIV and other STIs, but loss was higher for those who did not own a cell phone, sold sex, and had never previously been tested for HIV before enrolling in Building Trust (Kayode et al. *JIAS* 2020). The findings are leading to new programmatic policy to capture a more accurate size estimation of MSM and an increased funding support to provide treatment and care for MSM.

Rebecca Nowak, PhD

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

Niel Constantine, PhD, MT (ASCP)

(Photo taken before the SARS-CoV-2/COVID-19 pandemic)

His current activities include an 8-year on-going contract through the US government (USAID, FHI360, PFSCM, and PSCM) to assess the test indices of more than 11 different types of rapid tests from 16 manufacturers that are currently used in 26 countries. The FHI360 contract was renewed in January 2020 for an additional 2 years. The performance of test kits for HIV, hepatitis, HBV, syphilis, Cryptococcus, and pregnancy was assessed using appropriate panels of sera. In FY 20, all but one test kit successfully passed the evaluation. Another activity included an FDA 510K clinical trial for assessment of a rapid syphilis test that offers the detection of specific antibodies to *T. pallidum*. A total of 300 subjects were consented and enrolled at the IHV and the IHV's Jacques Journey Center under the Division of Clinical Care and Research, where several sample media were collected and tested by the investigational test and compared to the results of a reference test. The trial was aborted in March 2020 due to COVID restrictions.

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

technology that incorporates signal-boosting strategies to address early detection of HIV acute infection, using a simple Point of Care methodology.

Patrick Dakum, MBBS, MPH, Assistant Professor of Epidemiology and Public Health and Chief Executive Officer at the IHV-Nigeria, is leading the implementation of the CDC funded PEPFAR public health program for IHV in Nigeria (ACHIEVE, U2GGH002099) in a complex, mixed epidemic environment. This is a five-year grant that is currently being implemented in 4 states of Nigeria (Rivers, Nasarawa, Katsina and the Federal Capital Territory). The ACHIEVE program is aimed at reducing HIV burden and mortality by increasing access to ART for HIV-infected person towards achieving epidemic control. His vast experience in public health and achievements in managing the first 2 HIV PEPFAR grants (ACTION and ACTION PLUS-UP) contributed to the CDC Funding of the ACHIEVE grant. Dr. Dakum has managed and supervised the total sum of $92,081,098 in the first three years of the ACHIEVE program implementation. A total of 4,435,866 received HIV counseling and testing with 138,077 positive identified and 119,419 on ART. The organization has 208,263 patients currently being managed and followed up with quality HIV care. The suppression rate for the entire program is over 93% with excellent HIV programing and mentorship ongoing in all supported states to achieve 95- 95- 95 target. Dr Dakum also chairs the Community Advisory Board for the Dolutegravir and Darunavir Evaluation in Adults Failing Therapy (D2EFT) an NIH Multicountry Study that is a follow on to the Strategic Timing of ART Initiation (START) and in tis position provides overall guidance for this important study. As part of developing a robust Implementation Science Research Dr. Dakum has led the analysis and manuscript writing/ Publication on a cohort of Elderly Patients living with HIV/AIDS in Nigeria and continues to design studies to understand the needs of these group of patients.

Patrick Dakum, MBBS, MPH (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

Dr. Dakum also leads UMB-IHV Division of Epidemiology's effort to establish a long-term research cohort of persons living with HIV in Nigeria. The goal of this project is to characterize the burden, risk profile, pathogenesis, trends, and clinical outcomes of chronic non-communicable diseases (NCDs) among PLHIV. Such a cohort will also enable exploration of important implementation issues, including optimal screening strategies, treatment and prevention approaches, models of care, as well as barriers to their implementation, sustainability and scalability. Understanding these mechanistic and implementation factors will be invaluable towards identifying interventions for meaningful reduction in morbidity and mortality. Preparations for this research cohort are underway and enrollment of participants will commence soon.

Shenghan Lai, MD, Professor of Epidemiology and Public Health, joined the IHV in April 2020. In the last few month with IHV, Lai's group continued to work on U01 (U01DA040325) study entitled, **"Effects or HIV, Cocaine, and Prolonged ART use on Subclinical Cardiovascular Disease,"** to explore whether, and how, cocaine use exacerbates HIV-associated cardiovascular and cognitive comorbidities. Lai, **Hong Lai, PhD** Associate Professor of Epidemiology and Public Health, and the research team randomly selected 300 individuals with subclinical coronary artery disease (210 male; age: 48.0±7.2 years; 226 HIV-infected, 174 cocaine-users) from 1429 cardiovascular asymptomatic participants of a prospective epidemiological study between May 2004 and August 2015. Drs. Shenghan Lai, Hong Lai, and the research team analyzed the effects of cocaine use, human immunodeficiency virus (HIV)-infection and atherosclerotic cardiovascular disease-risk (ASCVD) on the temporal changes (4.0±2.3 years between CTAs) using their radiomic

Shenghan Lai, MD

signatures. (R21DA048780: **The Impact of Cocaine Abstinence or reduced use on Radiomic Features of non-Calcified Coronary Plaques in HIV-infected Cocaine Users with Silent Coronary Artery Disease.)** The changes of 1276 radiomic features were analyzed using linear mixed models correcting for factors that may change plaque structure: high-sensitivity C-reactive protein, statin use, positive family history and total plaque volume to account for any potential intrinsic correlation between volume and morphology. Clusters among significant radiomic features were identified using hierarchical clustering. Bonferroni corrected p-values <0.00004 (0.05/1276) were considered significant. The study showed that cocaine use was associated with 23.7% (303/1276), HIV-infection with 1.3% (17/1276) and elevated ASCVD with 8.2% (104/1276) of the radiomic features. There was no overlap among radiomic parameters significantly associated with elevated ASCVD-risk and cocaine use or HIV-infection, indicating that conventional cardiovascular risk factors change different structural features than cocaine use or HIV-infection. Lai and team found 13 unique clusters among the 409 significant parameters, eight of which were only affected by cocaine use and three only by ASCVD-risk. This study demonstrates that radiomics-based precision phenotyping indicated that conventional risk factors, cocaine use, and HIV-infection each had different effects on morphologic changes in coronary atherosclerosis over 4 years. These results suggest that different cardiovascular risk factors may uniquely determine the characteristics of coronary atherosclerosis (the revised manuscript for this study is under review).

Additionally, in the few months, Lai's group submitted 3 NIH grant applications, two R01 and one U01 supplement. The first R01 is entitled **"Cocaine abstinence in Relation to HIV-associated Comorbidities among Underserved African American Cocaine Users."** The goals of this study are: (1) to examine whether cocaine abstinence will significantly retard NCP progression, (2) to examine whether cocaine abstinence will (a) retard cognitive decline as assessed by the NIH Toolbox, (b) reduce endothelial damage as assessed by ET-1, and (c) lessen high risk plaque features in HIV-infected cocaine users with CCTA-confirmed SCA. If successful, this study will for the first time demonstrate that a well-implemented behavioral intervention will lead to cocaine abstinence, and cocaine abstinence will achieve noticeably cardiovascular and cognitive health benefits among cocaine users with HIV-related comorbidities. The second R01 is entitled "Vitamin D deficiency and multiple chronic conditions among African Americans." Dr. Lai proposes a 2-year randomized, double-blind, placebo-controlled clinical trial to examine whether supplementation with vitamin D prevents, delays or improves multiple chronic conditions (MCCs) in middle-aged and older AAs with vitamin D deficiency, defined as 25(OH)D<20 ng/mL. A total of 240 AA men and women aged ≥55 years with vitamin deficiency will be recruited and randomized to one of the following two groups: 200 IU of vitamin D daily (the control group) or 4,000 IU of vitamin D daily for 24 months (the supplementation group) with a total period of 5 years. The primary endpoint of this trial is a composite endpoint of time to the first occurrence of any one of the following MCCs: 1) development or progression of subclinical coronary atherosclerosis, 2) significant decline of telomere length, 3) development of cognitive impairment, or death. The secondary endpoints are time to any occurrence of the individual aforementioned MCCs, and time to co-occurring MCCs. The proposed specific aim is to investigate the efficacy and safety of 2-years of vitamin D supplementation to prevent, delay or improve MCCs in AA adults aged ≥ 55 years with vitamin D deficiency. The third application Lai's group submitted is a supplemental application to his U01. Responding to NOT-OD-20-120, this supplemental application proposes to conduct a large sero-epidemiological study of COVID among underserved African Americans in Baltimore. Lai proposes a 2-year longitudinal study to increasing reach, access, uptake, and impact for COVID-19 testing, and to create strategies to widely disseminate up-to-date FDA-authorized/approved testing technology based on detection of viral nucleic acids and antibody tests among underserved vulnerable AA population in Baltimore. To accomplish our

(Photo taken before the SARS-CoV-2/COVID-19 pandemic)

goals, Dr. Lai has strategically established a community partnership with the New Psalmist Baptist Church (NPBC) in Baltimore City. The late US Congressman Elijah Cummings, who was an IHV Board of Advisors member, was a member of this church for nearly 40 years, and he was one of the strongest supporters of our Heart study and helped to recruit a significant number of study participants from this church since 2003. Lai proposes to recruit 6,000 AAs, including our ongoing Heart Study participants into this investigation for COVID-19 antibody testing. In year 1, all study participants will undergo two COVID-19 antibody tests and interviews (since 75% of the funds must be allocated to expenses in the first year). In year 2, one interview will be conducted. Since the study will recruit participants who have received/will receive free RT-PCR testing at NPBC, this study has the potential to characterize COVID-19 infection, and identify factors that are associated with COVID-19 associated morbidity and mortality in this population


Peter Memiah, DrPH

Peter Memiah, DrPH, Associate Professor of Medicine and NIH fellow in the HIV Intervention Science Training Program (HISTP), is an international expert in gender-based violence, continuous quality improvement and adolescent health. He developed a mobile phone app called REACH (Reaching and Engaging Adolescents and young adults for Care continuum in Health) a comprehensive multi-dimensional survey for assessing behavioral, psycho-social and lifestyle constructs among adolescents aged 10–24 years. Funded through the Council for the Development of Social Science Research in Africa (**CODESRIA**) a fellowship program supporting African Scholars who collaborate with Tertiary Institutions in Africa. Dr Memiah partnered with the University of Nairobi (Institute of Development Studies) to address adolescent health, a key issue of interest for Kenya and globally. The REACH app helps illuminate adolescent vulnerability—and leverages on mobile phone proliferation to collect multi-faceted, real-time information from young people—who are also considered a risky-yet hard to reach population. The REACH app downloadable from google play and IOS app store was built using a "design thinking" systematic approach to enhance the user experience. All processes, including consenting procedures, referrals and reimbursement of the participants, were accomplished through a dynamic e-system with an inbuilt real-time dashboard. The pilot study conducted in Nairobi, Kenya used a respondent-driven recruitment method yielding a total of 887 adolescents. Preliminary findings include the successful use of design thinking for app development in adolescent populations and examining determinants of friendship patterns, HIV risk perception, gender-based violence, and mental health distress- including suicide ideation, these findings have been disseminated through journal publications and scientific presentations. Importantly, there has been no unambiguous, standard survey assessment approach for adolescents, from Africa that understand patterns of risks, protective factors and outcomes among this highly vulnerable group. The REACH app therefore provides a promising direction for the next generation of effort in reducing adolescent risk behavior and there is a concerted effort for longitudinal follow up and scale up of the its use. Dr. Memiah and his collaborators are also piloting the use of gamifications to increase self-knowledge and efficacy of safety decisions for this age group. The experience from REACH indicates that use of m-health approaches offers sustainable gains for prevention and interventions in the future.

Rebecca Nowak, PhD, Assistant Professor of Epidemiology and Public Health (picture Becca), working with the Building TRUST Study in Nigeria, evaluated patient satisfaction and knowledge of anal cancer symptoms after men who have sex with men (MSM) experienced high-resolution anoscopy as a first line screening tool for anal cancer. Despite a high level of pre-procedure anxiety, there was a high level of satisfaction irrespective of HIV infection status or the number of anal biopsies experienced during screening. Pain/discomfort and knowledge of clinical symptoms were two areas needing improvement (Nowak et al. *BMC Cancer* 2020). Because there was a low detection of high-grade disease during screening, Dr. Nowak confirmed that the men had a sufficient burden

Rebecca Nowak, PhD, with Nigerian physician, Wuese Dauda, MBBS (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

of human papillomavirus (HPV) to be at risk of developing precancer. Dr. Nowak found 92% and 74% of the MSM screened had any or high-risk HPV infection and HPV16, the most carcinogenic, was the second most abundant type detected (23%) (Nowak et al. *Papillomavirus Research* 2020). This work was presented orally at the International anal Neoplasia Society Scientific Meeting (IANS), in Amsterdam, Netherlands in fall 2019.

As part of Dr. Nowak's NIH funded K grant (K07CA225403), **"Role of anal microbiota, local cytokines and HIV in persistence of high-risk human papillomavirus,"** her preliminary data suggests that anal HPV16 has the highest annual persistence and is associated with an anal microbiota comprised of a diverse set of anaerobic bacteria. This abstract was accepted as a poster presentation at the 8th Annual Symposium on Global Cancer Research Meeting in Washington DC during the spring of 2020 (Nowak et. al. *JCO Global Oncology* 2020).

Kristen Stafford, MPH, PhD, Associate Professor of Epidemiology and Public Health, Deputy Director, Center for International Health, Education, and Biosecurity and Director of the Master of Science in Epidemiology and Clinical Research, was awarded funding in FY20 to perform a population-based household seroprevalence survey for SARS-CoV-2 in three states in Nigeria (**COVID-19 Nigeria**). This survey is part of the national public health emergency response and is being conducted in collaboration with the Nigeria Centre for Disease Control (NCDC) and the US CDC. The survey is collecting nasal, oropharyngeal, and blood samples from 10,200 individuals across 2,040 households in 102 enumeration areas and inform the State and National level SARS-CoV-2 mitigation strategies and public health response. In addition to the cross-sectional survey to estimate prevalence of active infection and previous exposure, the survey includes longitudinal follow up among households with at least one PCR positive and at least one PCR negative member to estimate household transmission and the secondary attack rate. Data collection will be completed by the end of November and results available shortly after. Left over blood following processing and aliquoting of the blood samples are also being sent to PLASVIREC and I-HAB to promote further research on host and pathogen genomics, and host response with **Dr. Abimiku**.

Kristen A. Stafford, PhD, MPH

In the **SHIELD** (NUGGH001976), significant progress has been made on the National Data Repository (NDR) which now receives patient level data from all PEPFAR support antiretroviral therapy sites and has also begun accepting data from Government of Nigeria operated facilities. The NDR currently contains longitudinal data for 1,195,329 unique patients actively on treatment and almost 2,000,000 ever initiated on treatment. The NDR is now the primary source for reporting PEPFAR target achievement to the US Government

Testing for TB and Malaria (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

EPI-NIgeria (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

for the Nigeria PEPFAR program. We have successfully added functionality for case-based surveillance to monitor individual patients based on sentinel surveillance events such as a new AIDS diagnosis, new opportunistic infection diagnosis, and mortality. The NDR is also being used to monitor recency testing in near real time and we have been asked to add additional diseases to the NDR including malaria and TB. In the next year, quarterly data freezes will be implemented and a request system for access to the deidentified data for research purposes will be implemented.

Training Program

In addition to the translational and implementation science research executed by the Division of Epidemiology and Prevention at IHV, the Division is also involved in research training at the Graduate School, the School of Medicine's Master of Science in Epidemiology and Clinical Research, and internationally through NIH support.

Dr. Clement Adebamowo's Entrenching Research Ethics in Nigeria (**ENTRENCH**) project, funded through the Fogarty International Center at NIH, is the primary resource for development of bioethics education and research infrastructure in Nigeria. To date, this grant has trained 52 Masters degrees candidates, 1 PhD, 120 medium term hybrid diplomas, and 25,000 participants in short in-person or online research ethics training. The program currently operates in 2 universities—the University of Ibadan, Nigeria where it implements an MSc Bioethics program and has just ensured the establishment of the first Department of Bioethics and Medical Humanities in Africa at the university. In 2019, the Entrench Project commenced an MSc Bioethics training and an MPH training with Bioethics concentration at the University of Nigeria Nsukka. Planning for implementation of training programs are at advanced stages in 3 other universities in different geopolitical zones in Nigeria. The ENTRENCH program is also introducing novel training programs that are responsive to new NIH guidance, the COVID-19 situation and changing global research environment.

Epi-Nigeria, also funded by Fogarty International Center at NIH is led by **Drs. Man Charurat and Alash'le Abimiku.** Epi-Nigeria has matriculated eight Master of Science in Health Sciences with a concentration in Implementation and Dissemination Science Research through the University of Maryland, Baltimore Graduate School. All eight graduated engaged in capstone research projects linked to analyzing data towards achieving the UNAIDS's Fast Track targets of 90% of people living with HIV know their status; of whom 90% are on treatment; of whom 90% are virally suppressed (90-90-90). Additionally, three PhD candidates in the UMB Graduate School inched closer to their degree in Epidemiology. Two candidates commenced dissertation work in Hepatitis B and HIV exposed infants and adherence and behavioral risk to HIV pre-exposure prophylaxis in Nigerian MSM and transgender women.

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Immunotherapy

Yang Liu, PhD

The Division of Immunotherapy, led by **Yang Liu, PhD**, Professor of Surgery, and established in February 2018, continues its mission in fundamental research and clinical translation on inflammatory diseases and cancer. In the current year, it has made major strikes in revealing novel mechanisms of immunotherapy targeting CTLA-4, providing a new theory on how to develop safer and more effective immunotherapy targeting CTLA-4 for human cancer. The new concept is being tested in clinic as antibodies developed by our commercialization partner, OncoImmune, Inc. has received Food and Drug Administration (FDA) approval for first-in-human clinical trial. Another major achievement includes applying the concept of CD24-Siglec innate immune checkpoint, pioneered by members of the Division, Dr. Yang Liu and **Pan Zheng, MD, PhD,** Professor of Surgery, for the treatment of COVID-19 through a Phase III clinical trial in severe and critical COVID-19 patients.

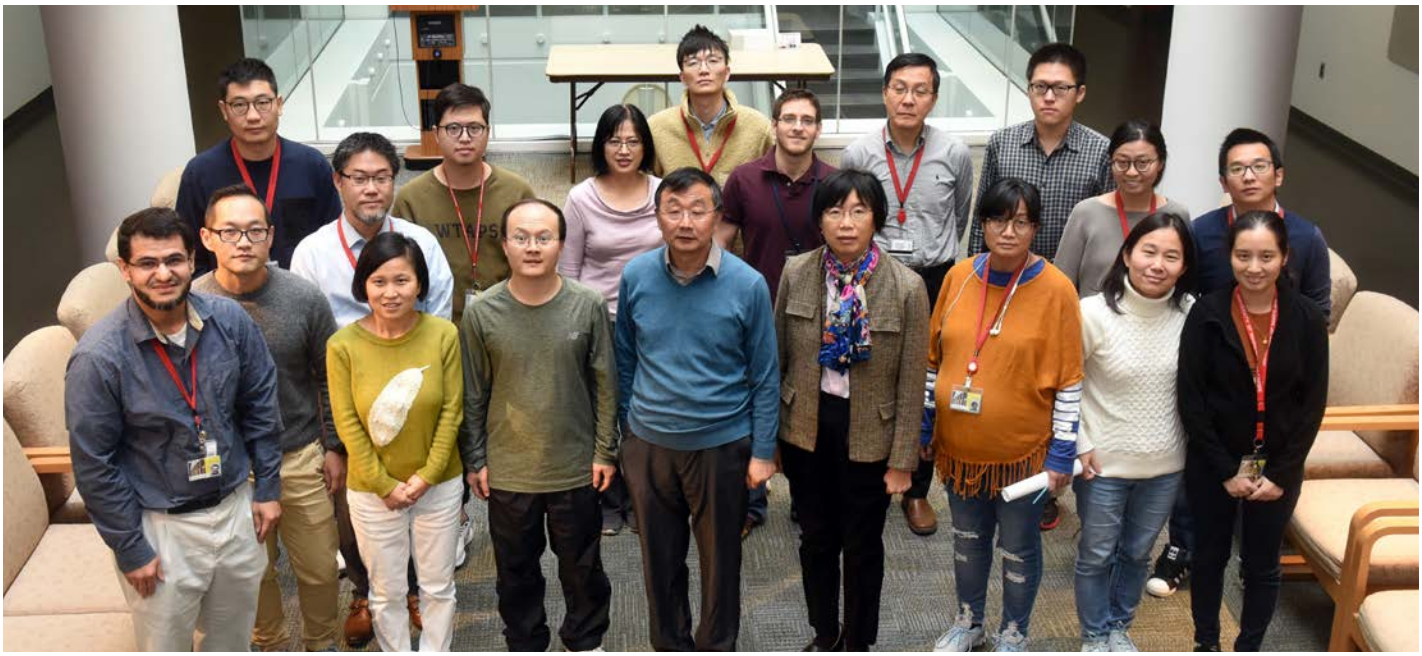
Pan Zheng, PhD

Currently several checkpoint inhibitors have been approved by the Food and Drug Administration for treatment of cancer, including a CTLA-4 targeting drug. Toxicity has greatly limited the clinical efficacy of the CTLA-4-targeting drug. In the area of cancer research, it is generally thought that there is a trade-off between efficacy and toxicity of drugs. Our new work revealed a new method that improves safety and, at the same time, leads to better efficacy. Fundamentally, we discovered that the drugs that cause severe adverse effect in the animal models do so by driving cell surface CTLA-4 molecules into one cell's waste basket shredder called lysosomes, where mutual destruction of the drug and drug targets occurred. This caused a "double whammy:" reducing the amounts of both drug and drug targets. Since CTLA-4 molecule is known to protect us against autoimmune diseases, such as lupus, rheumatoid arthritis and diabetes, antibody-induced CTLA-4 destruction directly leads to an autoimmune adverse effect of drugs targeting the CTLA-4 molecules.

To avoid this problem, we compared the antibodies with different toxicity and found that while the toxic antibodies drive CTLA-4 antibodies to waste station lysosomes, the safer antibodies separated from its target before the cargo containing the drug and its target reached the waste station. As a result, the safer antibodies and its target both recycled back. Recycling of CTLA-4 have two distinct effects: outside of cancer, it protects host against autoimmune diseases; inside cancer, it serves as a drug target for elimination of the cell that causes immune suppression and allows cancer progression.

This finding prompted the team to design antibodies that spontaneously separate from its target within the cell. To achieve this goal, they designed drugs whose binding to CTLA-4 is strictly pH sensitive: with tight binding to CTLA-4 at neutral pH, but disassociating from CTLA-4 when the antibody-drug cargo undergo acidification inside the cells. The authors showed in animal models that this engineering largely abrogated toxicity while preserving and even enhancing anti-cancer efficacy.

In our efforts to combat COVID-19, we have analyzed the pathogenesis of SARS-CoV-2 infection in COVID-19 patients and identified four critical aspects that are linked to the CD24-Siglec innate immune checkpoint. First, in collaboration with Yong-Tang Zheng, PhD, Professor from Chinese Academy of Science, we observed in Chinese Rhesus monkeys that the CD24Fc, a



Front Row, L to R: Musleh Muthana, PhD; Wei Wu, BS; Chunxia, Ai, MM, MB; Xuexiang, Du, PhD; Yang Liu, PhD; Pan, Zheng, MD, PhD; Juanjuan, Su, PhD; Zhihong, Xue, PhD; and, Yan Zhang, PhD Back Row, L to R: Zexu Ma, PhD; Toshihiko Tanno, DVM, PhD; Hung-Yen (Peter) Chou, PhD candidate; Yan Liu, PhD; Peng Zhang, PhD; Chris Bailey, PhD candidate; Yin Wang, PhD; Yunyi Wang, PhD candidate; Mingyue Liu, PhD; and, Xu Wang, PhD (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

fusion protein consists of extracellular domain of CD24 and IgG1 Fc fragment, suppressed pneumonia induced by Simian Immunodeficiency Virus (SIV), including pathological feature of acute respiratory stress. Second, in collaboration with Lishan Su, PhD, Professor of Immunology and Virology Lineberger Comprehensive Cancer Center, Department of Microbiology and Immunology, School of Medicine, The University of North Carolina at Chapel Hill and Member, Global Virus Network, we showed that CD24Fc reduces T cell lymphopenia and exhaustion in HIV-infected humanized mice. Third, clinical trial data from OncoImmune revealed that CD24Fc suppresses expression of multiple inflammatory cytokines. Fourth, the same clinical data set also revealed CD24Fc actively repressed multiple genes responsible for clotting, which has recently found to be critical for COVID-19 pathogenesis. These findings support clinical testing of CD24Fc for the treatment of severe and critical COVID-19 patients. This Phase III clinical trial is sponsored by OncoImmune, Inc. and approved by FDA, and open at 12 major medical centers, including University of Maryland, Baltimore.

Immunotherapy Publications

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Center for International Health, Education and Biosecurity (CIHEB)

Man Charurat, PhD, MHS

Ciheb's team of experts in medicine, public health, infectious diseases, laboratory science, health information technology, communications, and epidemiology are engaging communities and regional and national governments to effectively respond to exigent health challenges. They are supporting evidence-based and data-driven health service development for HIV, hepatitis, tuberculosis, malaria, emerging infectious diseases, and non-communicable diseases.

Under the leadership of Global Director **Man E. Charurat, PhD, MHS**, Professor of Medicine and Director of the IHV Division of Epidemiology and Prevention, and Associate Director **Kristen Stafford, PhD, MPH,** Associate Professor of Epidemiology and Public Health, Division of Epidemiology and Prevention, Ciheb is helping to build technical capacity from the ground up in low- and middle-income regions. Ciheb's approach in achieving sustainable impact includes developing robust information management systems, employing data for action, enhancing professional education, introducing continuous quality improvement processes, conducting rigorous disease surveillance, and deploying essential infrastructure.

Kristen A. Stafford, PhD, MPH

In 2019-2020, Ciheb expanded its project portfolio from six to eight countries. In addition to ongoing initiatives in Botswana, Kenya, Nigeria, Rwanda, Tanzania, and Zambia, Ciheb launched new laboratory capacity building projects in Malawi and Mozambique. Together, these efforts are fulfilling the Center's mission to improve the human condition globally, safeguard communities against health-related threats, and promote health equity worldwide.

Coordinated global effort is essential to address the COVID-19 pandemic, and countries on the African continent are particularly vulnerable. Ciheb has been leveraging its resources and expertise to address the challenges of COVID-19, developing effective response strategies while also ensuring the continued success of HIV/AIDS prevention, treatment, and care.

Looking ahead, Ciheb seeks to strengthen and expand its response efforts, while continuing to build its relationships with healthcare providers and empowering them to establish local independent organizations that further their respective nation's public health goals.

Ciheb is funded by the US Centers for Disease Control and Prevention under the President's Emergency Plan for AIDS Relief (PEPFAR), the National Institutes of Health, and UNICEF. Below, the Center presents updates and select achievements from its programs across eight countries.

BOTSWANA

Ciheb in Botswana is helping support the Government of Botswana in expanding HIV service capacity and surveillance through a joint initiative called the Botswana-University of Maryland School of Medicine Health Initiative (Bummhi). Bummhi is contributing towards the attainment of epidemic control of HIV in Botswana. It is the largest HIV treatment partner with the Botswana Ministry of Health and Wellness and has been helping care for approximately 118,000 HIV patients on antiretroviral treatment.

Country Director **Ndwapi Ndwapi, MD** is leading the team in Botswana. A physician and pioneer in establishing publicly funded antiretroviral treatment with extensive experience in TB treatment and programming, Dr. Ndwapi is the former Director of Clinical Services at the Botswana Ministry of Health. Together with a senior management team, including **Dr. Reson Marima**, the Director of Technical Services; **Dr. Milton Montebatsi**, the Deputy Director, Care and Treatment; and **Mr. Peter Kironyo** the Director of Finance and Administration; along with over 300 staff.

Projects

Botswana Partnership for Advanced Clinical Education (BPACE). The BPACE Project has been supporting 52 high-volume facilities of the *Botswana Ministry of Health and Wellness* in 12 districts in providing care and treatment services. The grant is supporting more than 120,000 clients on treatment across the current 52 healthcare facilities. More than 30,000 HIV positive individuals have been newly enrolled on antiretroviral treatment since the beginning of the program.

BPACE has supported the implementation of key strategies to attain the UNAIDS 95-95-95 targets. These include supporting health facilities to improve processes that strengthen the care continuum from HIV testing to linkage to care. In the past year, 92% of all newly diagnosed HIV infected people have been initiated on antiretroviral therapy (ART), with nearly 60% starting ART on the same day of diagnosis. Of the 118,000 people supported on treatment, 98% are virally suppressed. Through the BPACE program, Ciheb has partnered with three district health management teams to expand HIV services access through facility-led outreach mobile services to underserved communities in hard-to-reach areas and to target HIV service outreach for men within the community.

BPACE has continued to support personnel at health facilities to strengthen the delivery of client-centered services, including facility case tracking officers and expert clients, the latter are persons who are HIV positive and have openly declared their status. These personnel have assisted in providing services at all 52-supported facilities. Expert clients have provided peer navigation, health talks, and psychosocial support to newly diagnosed HIV infected individuals to support linkage to treatment. In addition, they have followed patients who have missed appointments or defaulted from care and treatment and returned them into treatment. They have maintained appointment systems for viral load blood draws to contribute to high viral load testing coverage. Throughout the implementation, the indicators for retention, viral load coverage, and viral suppression have remained above 97%.

The prevention of mother-to-child transmission continues to have high testing and treatment coverage for over 99% of clients, with mother-to-child transmission holding at 0.6% throughout the year. The BPACE program has also supported the national program towards pre-validation for elimination of mother-to-child-transmission of HIV.

COVID-19 Response. The first case of COVID-19 was detected in Botswana in late March and the Botswana Government imposed a country-wide lockdown on April 2, which required extreme social distancing. Bummhi focused on implementing two immediate measures at the clinics it supports to ensure continued treatment of HIV patients: 1) decongesting waiting areas and 2) expediting clinic visits so that patient exposure would be limited. Bummhi also deployed mobile testing clinics, assisted with contact tracing, and supported the development of COVID-19 surveillance measures.

Fifth Botswana AIDS Impact Survey (BAIS V). Preparation for the BAIS V began in 2019. This Centers for Disease Control and Prevention survey is among the ongoing Population Based HIV Impact Assessments (PHIAs) being conducted in select nations. BAIS V is a cross-sectional, household-based nationally representative survey that is assessing the prevalence of HIV as well as key HIV-related health indicators, such as incidence, , viral load suppression, and risk behaviors and will describe uptake of key HIV prevention, care, and treatment services.

Members of the Botswana Presidential COVID-19 Task Force inspect the data dashboard being built for the 2020 BAIS V population-based HIV impact survey. Present in the photo: National Coordinator of the Presidential COVID-19 Taskforce Dr. Kereng Masuku, Bummhi Country Director Dr. Ndwapi Ndwapi, and Deputy National Coordinator of the Presidential COVID-19 Taskforce Dr. Mogomotsi Matshaba.

This two-stage cluster survey of approximately 13,500 randomly selected households in Botswana will include nearly 29,000 eligible participants aged 15-64 years, of whom more than 24,000 are expected to participate in an interview. From this group, about 21,000 are expected to participate in a blood draw and HIV testing. In addition, the survey expects nearly 3,800 children aged 6 weeks to 14 years born from HIV positive mothers and mothers of unknown HIV status to participate in the blood draw and HIV testing. The total number of expected participants in the blood draw and HIV testing will near 25,000.

From September 2, 2019 to March 17 2020, the BAIS V team was preparing for survey implementation. Following the onset of the COVID-19 pandemic, the BAIS V Steering Committee paused the survey.

The Botswana Presidential COVID-19 Task Force has developed guidelines for return to work policies as has CDC for survey resumption. These guidelines have been reviewed by the BAIS V principal investigators and representatives from the Ministry of Health and Wellness. Preparations for restarting the survey in a COVID-compliant manner are underway, with a view to resuming once a date is agreed upon by the Government of Botswana, Ciheb, and CDC.

KENYA

Ciheb's work in Kenya continues to make progress in building health systems capacity and in expanding prevention efforts for HIV and tuberculosis (TB) under the leadership of Kenya Country Director **Emily Koech, MD** supported by a senior management team comprising of the Finance and Administration Director **Mr. Mathew Kimani** and program directors **Dr. Caroline Ngeno** and **Dr. Rebecca Wangusi** along with program managers from each of the grants implemented by the country. With its country office headquarters in Nairobi and 3 regional offices in Western Kenya, Ciheb employs more than 150 staff working in 4 locations. The country office provides funding to county governments and to Kenya Medical Research Institute for hiring of a multidisciplinary team of approximately 990 frontline healthcare workers providing healthcare services in public national and county health facilities. Ciheb's Kenya projects projects are funded by the National Institute of Health and the Centers for Disease Control and Prevention under PEPFAR.

A lab technician inputs sample data at Meru Teaching and Referral Hospital in Meru, Kenya.

Projects

Boresha Maabara. Swahili for "improve laboratory services," the Boresha Maabara Project has been supporting the Kenya Ministry of Health, the National Public Health Laboratory Services, and the Kenya National Blood Transfusion Services to strengthen laboratory systems and provide national leadership for and coordination of the provision of sustainable high-quality TB/HIV diagnostic services.

The program has provided significant support to the National Public Health Laboratory for its oversight role of other laboratories in the country. It has also contributed to the development of national laboratory-related policy documents and national tools, enhanced inter-laboratory networking, reduced turnaround time for results, and improved the quality of tests. It has also contributed to the accreditation of national HIV and TB reference laboratories and regional laboratories.

Other laboratory-related achievements include strengthening technical working groups in 10 counties, improving reporting, forecasting and management of lab commodities, entrenching use of continuous quality improvement principles in lab services, and ensuring quality of rapid HIV testing services.

Partnership for Advanced Care and Treatment (PACT) Timiza and Endeleza. The PACT Timiza (*timiza* is Swahili for "fulfill" or "accomplish") and PACT Endeleza (*endeleza* is Swahili

for "sustain" or "continue") projects collaborate with health management teams from the governments of Kisii, Migori, and Nairobi counties to provide universal, high-quality, comprehensive, and integrated HIV prevention, care, and treatment services across 289 health facilities.

Hundreds of thousands of individuals have received HIV testing services in both programs, with more than 105,000 identified as HIV positive and linked to treatment services. PACT Timiza was supporting over 87,000 clients on antiretroviral therapy (ART) (approximately 3,000 children <10 years and 5,700 adolescents 10-19 years) across 241 healthcare facilities within Migori and Kisii counties. Similarly, PACT Endeleza supported nearly 29,000 clients on ART (468 children <10 years, 844 adolescents 10-19 years) in 48 facilities in Nairobi, including 8 in community-based drop-in-clinics that serve key populations (i.e., female sex workers, men who have sex with men, and people who inject drugs).

These counties in rural and urban Kenya serve mobile populations at risk of poor treatment outcomes. The programs have supported the transition of adult populations to more effective antiretroviral regimens and established functional viremia clinics. They have also scaled-up differentiated care models for various populations, including multi-month dispensing, institution of robust patient support systems, structured counseling, and patient tracking systems. The programs further provided voluntary male circumcision services—an intervention proven to be effective in HIV prevention—and HIV prevention services to female sex workers and men who have sex with men. In two clinics supported by the program in Nairobi, more than 1,100 people who inject drugs are receiving comprehensive harm reduction services, including medically assisted therapy with methadone.

PACT Endeleza staff with Nairobi County health staff reviewing COVID-19 protocols at the Ngara health facility.

Technical Assistance for Public Health Impact in Kenya (TAPHIK). The CDC-funded TAPHIK Project has collaborated with the Kenya Medical Research Institute (KEMRI) to pilot an HIV case-based surveillance system (CBS) in a region in Western Kenya where CDC has been partnering with KEMRI to support a health and demographic surveillance system (HDSS). The project developed an interactive point-of-registration and linkage system to link the HDSS database to the medical records of HIV-infected individuals seeking care services at 14 pilot health facilities through an interoperability layer running on a Mirth platform.

Select sentinel events along the HIV continuum of care were extracted into the CBS database and used to monitor implementation and outcomes of HIV treatment. Furthermore, the program is at an advanced level of planning for piloting the use of the CBS system to collect information from facilities with paper-based records using scan forms and an open source software, Open Data Kit, to capture patient information from source records and transmit this to the CBS database for processing.

Tobacco Cessation Study. Ciheb's first NIH-funded randomized control trial is examining tobacco cessation pharmacotherapy and behavioral interventions among HIV-infected individuals. HIV has been shown to be associated with a greater likelihood of tobacco use, which further aggravates the risk of non-communicable diseases that are now seen to be causing increasing morbidity and mortality in HIV populations. Unfortunately, smoking cessation interventions are not included as part of the comprehensive package of services currently provided in HIV treatment clinics. In this second year of implementation, the study conducted formative research, completing 50 participant interviews and three focus

PACT Endeleza team with Nairobi County staff at the launch of the algorithm for TB screening in schools during World TB Day (Photo taken before the SARS-CoV-2/ COVID-19 pandemic)

group discussions that provided useful information on the study populations and guided the finalization of the study instruments.

MALAWI AND MOZAMBIQUE

In 2019, Ciheb launched two five-year comprehensive programs in Malawi and Mozambique to strengthen and advance laboratory systems. The initiatives are focused on improving HIV and tuberculosis (TB)-related laboratory infrastructure, including accreditation, data utilization to monitor HIV care and treatment, training, and adherence to quality management systems in each country as part of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). The Malawi and Mozambique programs build upon existing Ciheb laboratory initiatives in Nigeria and Kenya, which were also funded through PEPFAR.

Leading the Malawi and Mozambique programs is **Alash'le Abimiku, PhD,** Professor of Medicine, Division of Epidemiology and Prevention, Executive Director of the International Research Centre of Excellence at the Institute of Human Virology Nigeria, which she co-founded; and a Principal Investigator and Senior Technical Advisor for Laboratory Services at Ciheb.

Ciheb's work in Malawi is registering significant impact in building health systems capacity and in expanding prevention efforts for HIV, TB, and COVID-19 under the direction of acting Country Director **Visopo Harawa, PhD**, supported by a senior management team comprised of the Finance and Administration Director **Mrs. Winnie Musunga** and four technical leads. The country program employs 40 staff based at its country office in Lilongwe, some of whom are seconded to the Ministry of Health headquarters and in four referral hospital laboratories in the northern, central, eastern, and southern regions. In addition to supporting HIV and TB PEPFAR programming, the program supported the activation of 11 molecular labs to conduct COVID-19 polymerase chain reaction platform (PCR) tests for the country and facilitated the training of 66 laboratory technologists to perform the tests.

Mozambique is the newest addition to UMB Ciheb program, supporting the Mozambique Ministry of Health in strengthening the laboratory systems for diagnosis of HIV and TB, and expanding COVID-19 testing to the sub-national level using the GeneXpert platform. The country operations based in Maputo will have a team of three technical advisors and one administrative assistant, under the direction of the Country Lead **Mr. Dinis Jaintilal**.

The CDC has provided supplemental funding to develop related testing capacity in both Malawi and Mozambique to support governments' efforts of both countries. Fortunately, the real-time PCR platforms to test for HIV are the same for COVID-19, thereby expanding the already developed molecular laboratories and HIV proficient staff to also test for COVID-19. The automated machines are capable of completing about 400 COVID-19 tests per day. Both countries

have benefited from training materials and protective gear for COVID-19 from Ciheb supported programs.

Ciheb's work with the respective ministries of health in each country is ensuring country-level support for capacity development and policies for the management of high-quality lab services, thereby building strong country ownership which is further strengthen by south-to-south mentorship and collaboration among regional African laboratory networks for sustainability.

NIGERIA

With 100 staff in the capital city Abuja, Ciheb is guided under the new leadership of Country Director **Sylvia Adebajo, MBBS, MPH, MSc, PhD**, who is supported by a senior management team comprised of **Dr. Sanmi Adedokun** as the deputy country Director and Director of Strategic Information, **Keno Eghota, Alhassan Abdulkadir, Dr. Baffa Ibrahim**, and **Dr. Ibrahim El-Imam** as heads of the departments of finance/accounting, health informatics, operations/program management and epidemiology/ surveillance/monitoring and evaluation, respectively.

Projects

Strengthening HIV Field Epidemiology, Infectious Disease Surveillance and Lab Diagnostics (SHIELD). The five-year SHIELD project is a CDC-funded initiative under PEPFAR focused on improving the quality of HIV service delivery across PEPFAR- and Nigerian Federal Ministry of Health–supported projects in Nigeria. Ciheb works with the national health system (above site) to conduct evaluations, improve data management, develop and manage health information systems, and implement continuous quality improvement.

SHIELD's recent activities included the launch of a more robust, faster and user-friendly National Data Repository (NDR) (dubbed NDR 3.0). The NDR is a repository of de-identified patient-level data from facilities across the country. HIV client data is collected that allows tracking of the 95-95-95 cascade at the national level.
Improvements to the NDR platform focused on data ingestion performance, an increase in analytics processing speed, the elimination of duplicate patients, and improved data concurrence between facility electronic medical records (EMRs) and the NDR. Ciheb also led the development effort around NigeriaMRS (NMRS), which is a fork of the open source EMR platform OpenMRS, and championed the transition from facilities using legacy EMRs to NMRS 2.0, thus allowing

Ciheb Nigeria technical staff offers a stepdown demonstration to a health facility clinician of the different modules within the Nigeria-MRS, an Electronic Medical Record (EMR) which is being deployed for use in facilities. The project is part of the SHIELD project

for better EMR standardization across facilities and the centralization of EMR development efforts.

Ciheb also spearheaded the development of portable biometric systems for the collection of patient biometric data, thus paving the way for client de-duplication at both the facility and national levels.

To accelerate the impact of the public health response to the HIV epidemic, the SHIELD project also supported the implementation of the HIV recent infection testing in 19 states and case-based surveillance with upgrades built into the NMRS and the NDR to support these surveillance activities. Commodity management modules have also been developed and incorporated into the NMRS and the NDR to track supply versus utilization of antiretrovirals and rapid test kits at the facility level for PEPFAR-supported facilities.

Turnaround time for return of results for viral load testing has been a lingering problem with Nigeria's treatment program. It often takes one to six months for results from sample collection. To improve this turnaround time as well as foster interoperability between PEPFAR- and Ministry-supported HIS platforms, Ciheb worked with a partner organization developing the laboratory information management system (LIMS) to implement an LIMS-EMR direct data handshake system, whereby patient laboratory requests captured on EMRs are synchronized directly to the LIMS platform and results returned directly to the various EMRs.

Strengthening Epidemic Response and System (SERS). Funded by the CDC through PEPFAR, SERS is a multiyear initiative focused on improving the epidemiology, surveillance, reporting, and information management of diseases of public health concern in Nigeria. It is a vehicle through which Ciheb provides support to the Nigeria Center for Disease Control in strengthening the surveillance reporting system and implementing the Integrated Disease Surveillance and Response (IDSR) strategy along with other implementing agencies. SERS' overall goal is to strengthen information systems in Nigeria to improve the country's ability to achieve international health regulation compliance and global health security targets.

SERS has prioritized the accomplishment of some strategic initiatives targeted towards achieving its set goal. Some of these achievements included the establishment of surveillance reporting using a mobile app (mSERS) for SMS-based weekly reporting across eight states in Nigeria through 144 local government area disease surveillance and notification officers and 40 state surveillance frontline officers.

Other achievements included update and enhancement of the mSERS reporting system to support the reporting of newly assigned diseases for weekly reporting; refresher training for disease surveillance frontline officers in two states (Niger and Akwa Ibom States) and support the expanded use of the Surveillance Outbreak Response Management and Analysis System (SORMAS) – an application adapted to Nigeria for case-based surveillance and disease outbreak management.

Participants at the "Dashboard for Self-assessment" training on COVID-19 held in collaboration with the Nigeria Centre for Disease Control

The Ciheb SERS team also worked in collaboration with the NCDC team to build the capacity of 262 disease surveillance frontline officers on the use of SORMAS; provided the frontline officers with tablets and internet data for SORMAS implementation; enhanced the functionalities of the NCDC Connect Centre applications and processes to strengthen the country's response to COVID-19; and built the capacity of over 250 Connect Centre Agents (1st and 2nd Line Responders) to support NCDC's response to COVID-19.

In addition, Ciheb also established a follow-up team to support NCDC in monitoring arriving airline passengers for COVID-19 for a period of three months. More than 3,500 persons were monitored over a period of 14 days.

Project ECHO. Ciheb piloted the first "telementoring" healthcare project in Nigeria in 2018 called Project ECHO™, an initiative developed and promoted by the Project ECHO Institute at the University of New Mexico School of Medicine. ECHO, which stands for Extension for Community Health Outcomes, uses teleconferencing to link specialists with practitioners and create "communities of practice" in underserved areas.

Through Project ECHO, Ciheb has been able to provide technical support to implementing partners with site assessments and deployment of conferencing infrastructure. Ciheb recently coordinated a central immersion training of 140 participants from 25 organizations in Nigeria, with a step-down training of 416 participants across six HIV "surge states." The ECHO sessions have been an avenue to share relevant information, guidance, and strategies to sustain the gains of the PEPFAR antiretroviral treatment program in the midst of the COVID-19 pandemic and travel restrictions, allowing for greater protection of healthcare workers while maintaining patient treatment.

The ECHO platform has also supported PEPFAR regional meetings to discuss the HIV program in the context of COVID-19, thereby creating avenues to share experiences, challenges, successes and best practices that can be adopted across regions.

Nigeria AIDS Indicator and Impact Survey (NAIIS). Another of Ciheb Nigeria's initiatives is the NAIIS, which is funded by the CDC under PEPFAR. The NAIIS is part of PEPFAR's Population-Based HIV Impact Assessment (PHIA) projects, which determine the prevalence of key HIV-related health indicators, including HIV incidence, prevalence, viral load suppression, CD4 distribution, and risk behaviors.

The NAIIS findings, announced In 2019, indicate that Nigeria has made progress in its fight against HIV epidemic, but is still not on track towards the UNAIDS's 95-95-95 goals. Though the NAIS found a lower national HIV prevalence among Nigerians, only one in every three persons living with HIV reported knowing their status. In 2020, the data was further examined to obtain deeper insights into both HIV epidemiology and other disease entities, in order to inform future studies as well as provide insight into behavioral and biological contexts of HIV across all states in Nigeria. NAIIS data is now hosted on the National Bureau of Statistics's National Data Archive portal.

RWANDA

Ciheb's Rwanda team is being led by **Cyprien Baribwira, MD,** Adjunct Assistant Professor of Medicine. A pediatrician by training and former senior lecturer at the University of Rwanda, Dr. Baribwira joined the University of Maryland, Baltimore programs in Rwanda in 2009, and he has been leading the programs as country director since 2011. Together with a small high qualified senior management team including **Dr. Jackson Sebeza**, the program manager /CQI specialist and **Dr. Kiromera Athanase**, an experienced senior technical assistant, the Rwanda team is providing high-level technical assistance to the Rwanda Ministry of Health, which currently has one most successful HIV programs in Africa.

Projects

COVID-19 Response. In 2020, Ciheb's Rwanda team was tasked by the Rwanda Ministry of Health and CDC Rwanda to provide support to help adapt HIV services in context of COVID-19. The goal was to ensure those infected with HIV continued to get antiretroviral treatment and to develop to protective measures to keep people safe at health facilities. In response, Ciheb developed guidelines and standard operating procedures (SOPs) to be followed at healthcare facilities treating HIV patients. The SOPs provide step-by-step guidance to providers, including screening procedures for nurses to prioritize symptomatic patients and to quickly isolate them.

Project staff counseling a client (Photo taken before the SARS-CoV-2/COVID-19 pandemic).

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

In the past year, the Imakaza project has supported the Rwanda Ministry of Health, Rwanda Biomedical Center, HIV Division across several initiatives, including:

1. Updating the National Guidelines for Prevention and Management of HIV.
2. Developing HIV e-learning training materials to be used for healthcare providers in antiretroviral clinics across the country.
3. Developing clinical mentorship guidelines incorporating continuous quality improvement (CQI).
4. Building a laboratory information management system to strengthen the capacity and quality of the country's laboratory network to support HIV diagnosis, prevention, care, and treatment; disease monitoring; and surveillance; piloting an HIV integrated care model in an outpatient department.

In the next year, Imakaza shall be phasing out and transition project activities to the Ministry of Health. Imakaza will be focusing on supporting the National Reference Lab to improve capacities in systems to aid healthcare providers in utilizing e-lab systems to improve patient outcomes. It will also support the scale up of a CQI strategy to improve patient outcomes.

Addressing HIV in Young Women and Children. The Rwanda team, with funding from UNICEF, is working to lower maternal-to-child transmission of HIV; eliminate new pediatric HIV infections; and improve maternal, newborn, and child health and survival in the context of HIV. The interventions are focusing on pregnant and breastfeeding mothers, including adolescent and young and single mothers and their babies and partners and children aged 2-18 who were born to HIV positive women enrolled in an HIV treatment program.

Ciheb Rwanda will scale-up a CQI strategy to improve index testing, partner notification services, and family testing within antenatal care. Ciheb Rwanda will also utilize a web-based CQI app for tracking CQI progress and gaps to ensure course correction that had been developed by its sister team in Tanzania. The use of the CQI app is in line with UNICEF's data-driven programming.

The initiative will support the Rwanda Strategic Plan for HIV, whose goals include lowering maternal to child transmission of HIV and ending the AIDS epidemic by 2030. The project is similarly in line with the global agenda to eliminate new pediatric HIV infections and improve maternal, newborn, and child health and survival in the context of HIV.

TANZANIA

Ciheb's Tanzania team is comprised of 53 clinical and supporting staff led by Country Director **Abubakar Maghimbi, MD**. Dr. Maghimbi has *17 years of experience in infectious diseases and more than 8 years working on PEPFAR funded projects. He is also an assistant clinical professor of medicine and adjunct faculty of the UMB School of Medicine.* Dr Maghimbi has helped to expand Ciheb Tanzania's work and impact, and he is leading the ongoing implementation of its projects.

Projects

Reaching, Engaging and Acting for Health (REACH). The REACH Project is a five-year PEPFAR-funded project working in 10 regions of Tanzania. This national-level technical assistance program is focused on improving uptake of data and evidence for faster HIV epidemic control achievement. REACH supports the Government of Tanzania and CDC-funded local clinical implementing partners in minimizing systemic and structural barriers that impede the development of quality HIV/AIDS services.

A nurse seeing a client (Photo taken before the SARS-CoV-2/COVID-19 pandemic).

REACH is supporting approximately 120 health facilities and has trained and mentored more than 400 healthcare providers on continuous quality improvement (CQI) methodologies, with the aim of improving PEPFAR clinical cascade indicators. A digital CQI platform developed under the REACH project for reporting and supporting routine monitoring of program performance was scaled up to more PEPFAR implementing partners. Currently the platform is being used in 200 facilities and has more than 650 quality improvement projects targeting different areas of HIV/AIDS service delivery.

Through the REACH project, Ciheb Tanzania developed the platforms for which it is widely known, that support real-time data quality checks, SMS weekly reporting, CQI reporting, and granular data analysis through the Data Analytics Companion (DAC), a powerful tool developed by Ciheb Tanzania that performs in-depth patient-level data analytics.

Given the efficiency and the user-friendliness of Ciheb Tanzania's tools, the Government of Tanzania, through its National AIDS Control Program, has adopted the digital CQI platform tool to support its Quality Improvement Collaborative initiative. The CQI digital platform has also been adopted by other Ciheb country offices in Zambia, Kenya, Botswana, and Rwanda.

REACH also has a national ECHO coordination role and supports HIV clinics using ECHO.

Ciheb Tanzania has also developed the following technologies to support implementation:

- An Android application (IQSMS) for daily and weekly monitoring of HIV and viral load testing indicators.
- Real-time data quality assurance to inform data gaps in government data reporting tools such as DHIS2.
- Quality management of laboratory proficient testing for reporting laboratory proficiency testing data.
- An index contacts tracking tool for the electronic tracking of sexual contacts of newly identified HIV positive clients.
- A monthly reporting tool (Monthly Portal) that aggregates data reported by all health facilities and supports data visualization at the regional, district, and facility levels, providing opportunities for performance comparison across facilities and regions and enabling better planning and health resources rationalization for the program and by facilities and regional health management teams.

Afya Kamilifu. Afya Kamilifu (which means "complete health" in Swahili) is a comprehensive HIV care-and-treatment program that is being implemented in partnership with Amref Health Africa. As a subgrantee, Ciheb Tanzania supports tuberculosis-HIV and tuberculosis clinics and pediatric and adolescent HIV care. It also leads the project's overall CQI, cutting across all departments and thematic areas in the project.

Through district-based mentorships, data-driven site visits by project staff, and by building the technical capacity of facility healthcare workers, Ciheb has improved performance across numerous key indicators. For example, isoniazid preventative therapy completion rates improved from 32% to above 90%, viral load suppression in children and adolescents improved from 54% to 82%, and the proportion of children in an optimized antiretroviral regimen has remarkably improved. Also, Ciheb has initiated CQI projects across all key indicators at CDC tier I and II facilities.

COVID-19 Response. In 2020, and in efforts to minimize the spread of COVID-19, CDC Tanzania and the implementing partners scaled down physical site visits substantially. To ensure HIV service delivery was not interrupted, Ciheb Tanzania demonstrated an effective way of remote support for health facilities using various online platforms, such as Zoom and ECHO. Ciheb was able to continue supporting facilities in data analysis, identification of performance gaps, and initiating quality improvement activities.

The DAC tool was effective in supporting remote data analysis. Quality improvement projects were initiated for areas that were not performing well and documented in the digital CQI platform. The use of the digital CQI platform increased from approximately 300 projects in March 2020 to more than 650 projects by July 2020. The Ciheb team held multiple Zoom calls with QI teams from all the supported regions where they would present their ongoing QI activities directly from the platform. These calls were attended by implementing partners and members of the regional and council health management teams.

ZAMBIA

Ciheb in Zambia is led by Country Director **Robb Sheneberger, MD**, Assistant Professor of Family Medicine. Dr. Sheneberger has been leading IHV/UMB initiatives in Zambia since 2004, and assisting the Government of the Republic of Zambia by serving on multiple partnership working groups and developing differentiated care systems to support 95-95-95 goals. Dr. Sheneberger was a significant contributor to the Zambian National ART Guidelines that were the first in Africa to adopt tenofovir-based first-line antiretroviral therapy, and the incorporation of discordant couples into antiretroviral eligibility, and has continued to provide guidance to Zambia as the country expanded to a test and start approach. **Cassidy Claassen, MD, MPH**, Assistant Professor of Medicine, has been a major contributor to the development and implementation of PrEP in Zambia, and **Lottie Hachaambwa, MB, ChB**, Assistant Professor of Medicine, has been instrumental in supporting advanced clinical education for HIV and Infectious Diseases through a Master of Medicine & Infection Diseases at the University of Zambia School of Medicine. Both Drs. Claassen and Hachaambwa have been leaders in supporting the MOH response to COVID-19.

Projects

Stop Mother and Child HIV Transmission (SMACHT). The SMACHT project began as a prevention of mother-to-child transmission grant, but after its first year was expanded to a comprehensive HIV care and treatment grant, and peaked in its fourth year with support to over 300 facilities in the Southern Province. The community approach to improving outcomes for patients with HIV that is utilized in our other two community grants was designed and first implemented through SMACHT. It has also been providing technical assistance to the Southern Provincial Health Office in four districts.

Community Impact to Reach Key and Underserved Individuals for Treatment and Support (CIRKUITS). CIRKUITS utilizes a targeted community approach to improve HIV prevention, care, and treatment outcomes in Lusaka, Eastern, and Western Provinces to achieve UNAIDS 95-95-95 epidemic control. It focuses on adolescents; key populations, including men who have sex with men, female sex workers, and prison populations; men under 30 and transient populations; pregnant and breastfeeding women and their families; as well as the general population. Based on significant success in year one, the grant was expanded in geographic scope in year two with a 40% increase in budget.

Zambia Community HIV Epidemic Control for Key Populations (Z-CHECK). This five-year project focuses on providing community interventions to interrupt HIV transmission by identifying and linking each HIV-infected individual along a supported pathway to achieve viral suppression. Using effective interventions, Z-CHECK aims to improve the targets for UNAID 95-95-95 goals in the Southern and Lusaka Provinces. Z-CHECK has focused primarily on target populations, including adolescents, pregnant women and their children, young men, men who have sex with men, female sex workers, transgenders, injection drug users, and prisoners. Z-CHECK has also been the leader in pre-exposure prophylaxis (PrEP) in Zambia. In year 4 it is focused on moving targets closer to 95-95-95 goals set by CDC.

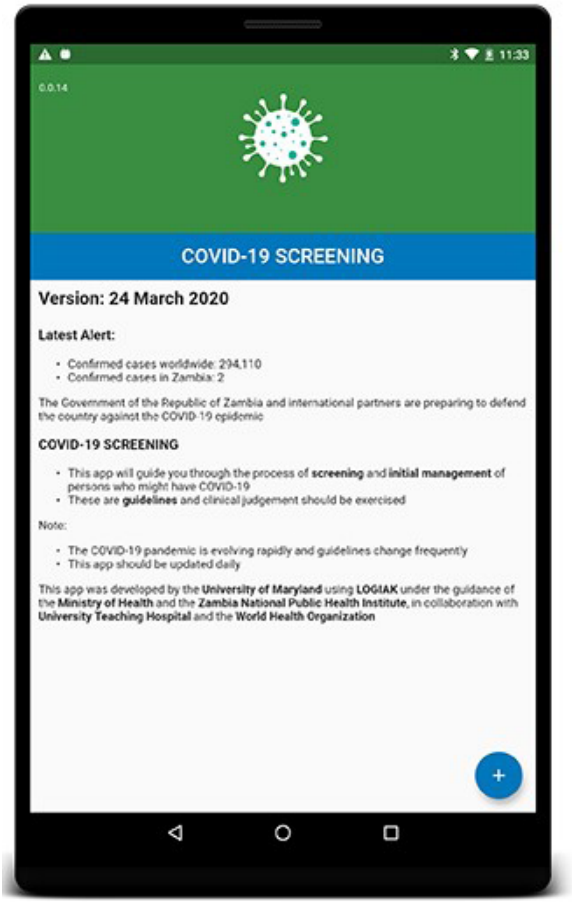
The first shipment of facemasks are delivered to staff at the University Teaching Hospital in Lusaka, Zambia

Both CIRKUITS and ZCHECK will be receiving additional funding in the next fiscal year to implement the DREAMS initiative. DREAMS is a global, public-private partnership between the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), Bill & Melinda Gates Foundation, Girl Effect, Johnson & Johnson, ViiV Healthcare, and Gilead. The program seeks to reduce new HIV infections in adolescent girls and young women, between 10 and 24 years old, across 10 sub-Saharan African countries. DREAMS is designed to meet the complex needs of AGYW by helping them become more Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe.

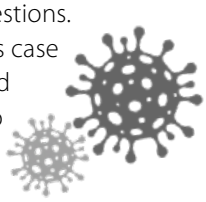
In response to the COVID-19 pandemic, Ciheb in Zambia has participated in the development of national case-management guidelines for the Zambian Ministry of Health and provided clinical guidance for COVID-19 cases—particularly severe cases. Ciheb is also ensuring that health facilities in remote areas beyond the capital city of Lusaka have access to the latest clinical guidance with respect to COVID-19 and HIV via tele-mentoring sessions. In addition, Ciheb Zambia led a community response to develop and create locally made personal protective equipment for hospital health care workers in Lusaka.

COVID-19 Screening App

To assist Zambian physicians in screening respiratory patients for COVID-19, Ciheb Zambia has developed this smartphone app. The app leads clinicians through a set of evaluative steps to determine whether a patient's clinical symptoms require that they be tested for COVID-19. Data collected by the app is also helping to monitor the extent of the outbreak in Zambia.



To further assist Zambian physicians in screening respiratory patients for COVID-19, Ciheb in Zambia developed a smartphone app to help clinicians determine whether a patient's clinical symptoms require testing for COVID-19 by guiding them through a series of screening questions. The app is continually updated as case definitions change. Data collected by the app, in turn, are helping to monitor the outbreak in Zambia.



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Scientific Core Facilities

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 Core Facility**, and µQUANT Core, is led by an experienced researcher at IHV. Below is an overview of the Core Facilities.

L to R: Alfred Dye; Sumiko Williams, MS; Juan Zapata, PhD; Albert Hunter; Cheryl Bass; Harry Davis, MS; Glenda Jackson; Chris Adams; and, Catherine Crews (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

Animal Core Facility

The Animal Core Facility is directed by **Harry Davis**, **BS, MS,** who previously served as the facility manager for 22 years prior to becoming the Director. He is associated with sixty percent of the Animal Study Proposals (ASPs) for the IHV, serves as a major contributor for several NIH funded RO1 grants and has been a co-author on over 15 research publications in the Institute. He continues to direct the Animal Core and further its mission to support developing animal models as it relates to HIV/AIDS, pathogenesis studies, HIV-1 matrix protein P-17 implicated in virally associated lymphomas, stem cell biology, mycoplasma and cancer, and HIV-associated neurocognitive disorders (HAND).

Joseph Bryant, MS, DVM, who was Associate Professor of Pathology and Director of the Division of Animal Models, retired in July 2017 after twenty-two years of leadership and service with IHV and has since served as a consultant to the Animal Core Facility.

Mr. Davis has a staff of nine animal research care personnel who are responsible for the care of animals at IHV as well as assisting investigators on various scientific endeavors. The Animal Core provides a rich environment for Investigators to conduct HIV and HIV-associated research, and is a state-of-the-art, facility that strives to provide a safe, efficient, and cost-effective environment for animal experimentation.

Research at the Animal Core Facility

The Animal Core Facility currently manages twenty animal use protocols for the Institute. These protocols include vaccine studies using non-human primates, therapeutic studies using immuno-deficient mice and working with investigators using transgenic and knockout mice. The Core provides for translation of basic biomedical knowledge for prevention or new treatments, which often requires the use of animals as models or as a means of testing therapeutics and/or vaccines.

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

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

Development of Special Programs in the Animal Core Facility

A. NSG humanized mouse program

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

The models are listed below:

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

For HIV infection

Lishan Su, PhD, The Charles Gordon Smith Endowed Professor for HIV Research and Professor of Pharmacology, joins IHV this fall and will be instrumental in the continued development and growth of the program.

B. HIV-1 Transgenic Rat Distribution Program

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

Collaborative efforts between the Division of Infectious Agents and Cancer and the Animal Core Facility include the development of Animal Models. Projects include:

HIV/AIDS Non-Hodgkin Lymphomas

A. Pathogenesis Studies

B. Development of Animal Models for AIDS/NHL

C. HIV-1 matrix protein p17 implicated in virally associated lymphomas

D. Mycoplasma and Cancer

Collaborators in the Division of Infectious Agents and Cancer include:

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

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

Mika Popovic, MD, PhD, Adjunct Professor of Medicine

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

Fiorenza Cocchi, MD, Assistant Professor of Medicine

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

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

Giovannino Silvestri, PhD, Research Associate of Medicine

HIV-1 matrix protein p17 implicated in virally associated lymphomas

Recent studies by most of the **aforementioned members** of the Division of Infectious Agents and Cancer, 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 Infectious Agents and Cancer, 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.

DnaK and Mycoplasma Project

Continuing the studies on the relationship between Mycoplasma and cancer, **Davide Zella, PhD,** and **Robert Gallo, MD**, together with **Joseph Bryant, DVM, Francesca Benedetti, PhD, Giovannino Silvestri**, **PhD**, and **Saman Saadat**, **PhD,** Postdoctoral Fellow.

Human *Mycoplasma fermenta* was isolated and characterized this strain of *ns* able to induce lymphoma in a Severe Combined Immuno-Deficient (SCID) mouse model, similar to a previously described lymphomagenesis dependent upon reduced p53 activity. Mycoplasma was abundantly detected early in infected mice, but only low copy numbers of Mycoplasma DnaK DNA sequences were found in primary and secondary tumors, suggesting a "hit and run/hide" mechanism of transformation, in which the critical events have occurred previous to cancer detection. We demonstrated that this Mycoplasma's DnaK binds to human USP10 (ubiquitin carboxyl-terminal hydrolase 10, a regulator of p53 stability), reducing p53 stability and anti-cancer functions, potentially increasing the likelihood of DNA mutations and consequent malignant transformation. We also showed that Mycoplasma DnaK reduced PARylation activity of PARP1 following DNA

damage. PARP 1 is one of the most studied members of the family of PARP proteins, involved in the recognition and subsequent repair of single and double-strand breaks in DNA. We are currently extending these results and validating the underlying mechanisms in an *in vivo* model of DnaK knock-in mouse designed in our laboratory. DnaK was inserted at the locus of ROSA26 in C57BL/6 mice by CRISPR/Cas-mediated genome editing. The DnaK gene is under the control of the CMV promoter for constitutive expression and carries a V5 Tag for convenient detection. It is important to note that our previous results *in vitro* show that the V5 tag does not affect the ability of DnaK to reduce protein binding or p53-dependent anti-cancer activities. These animals are currently housed in our animal facility and are currently used to: i) test for higher spontaneous tumor incidence in mice expressing DnaK; ii) assess for increased susceptibility to non-hematopoietic cancers and development, function and response to DNA-damaging agents of peripheral B- and T cells ex vivo.

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

Projects include:

Alonso Heredia, PhD, Assistant Professor of Medicine

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

Nichols Stamatos, MD, PhD, Assistant Professor of Medicine

Evaluating Treatment with CCR5

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

Humanized Mice for HIV Studies

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

Function of Polysialic Acid in Immune Cell Activity

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

Other Collaborative efforts with the Animal Core Facility include:

Henry Lowe, PhD, Adjunct Professor of Medicine, IHV

Walter Royal, MD, Professor and Chair, Department of Neurobiology, Morehouse School of Medicine

Tapas Makar, PhD, Adjunct Assistant Professor, University of Maryland School of Medicine

Development of Natural Plants as Anti-Cancer Drugs

Henry Lowe, PhD, IHV Adjunct Professor of Medicine, is collaborating from Jamaica with the Animal Core on a flavonoid from *Tillandsia recurvate* showing potent anticancer activity against AIDS-defining and non-AIDS defining cancers.

The use of the HIV-1 Transgenic Rat Model Neurological Studies

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

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

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

Stem Cell and Cancer Biology

Chozha Rathinam, Dr. rer. nat., 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.

IHV Flow Cytometry and Sorting (IHV FLOW) Core Facility

The IHV Flow Core serves the IHV community with varying needs associated with flow cytometry. Flow Cytometry is a fundamental tool for the modern virology/immunology/cell biology research. The IHV Flow Core is headed by **Yutaka Tagaya, MD, PhD**, Assistant Professor of Medicine and Head of the Laboratory of Cell Biology, IHV Division of Infectious Agents and Cancer, who has over 30 years of experience with Flow cytometry technology. The Flow Core's operation has been maintained by **Felisa Diaz-Mendez, PhD** as the chief operator/trainer. Each user will be charged with fees based upon usage (please ask the Flow Core staff for pricing).

The IHV 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 (Room N664).
2. Millipore's GUAVA. GUAVA can handle up to 10 colors (FITC, PE, PerCPCy5.5, PECy7, APC, APC-Cy7, Violet 421, Violet 510, Violet 605 and Violet 650) which is located in N568.

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 (for the training, please contact Dr. Diaz-Mendez at FDiazMendez@ihv.umaryland.edu). At the moment, the IHV Flow Core is the only facility that can sort infectious cells (cells infected by Hepatitis viruses, Influenza, HIV and HTLV) at the University of Maryland, Baltimore. We are also authorized to run lymphocytes and hematopoietic cells from COVID-19 patients. We offer services to Labs at the IHV, UMB and beyond this campus. For setting up the service, please contact us at ytagaya@ihv.umaryland.edu. For analysis and sorting involving the Aria machine, we created a web-based calendar system (for detail, please contact the IHV IT department to have your outlook linked with the IHV Flow CORE Calendar) so that the users can book the machine time.

The IHV Flow Core not only operates the machine, but also works with each investigator by being consulting on the experiment design and 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. For detail, please contact ytagaya@ihv.umaryland.edu.

Multi-color analysis or cell sorting is complex and requires proper guidance based on the appropriate under-standing on the fluoro-chromes and the machine. We have been successfully working with many IHV investigators to conduct multi-color flow cytometry/sorting which helped them in their publications and in grant submissions.

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

Testimonials by the Core users

"My laboratory evaluates the anti-HIV activity of therapeutics in preclinical animal models, with a focus on humanized mice. My group has a need to isolate cells from these mice and separate human and mouse cells by surface marker identification which requires the use of Flow Cytometer and Cell sorter. The research involves the use of various types of humanized mice for different purposes and the analysis can be quite elaborate and complicated. The IHV Flow Cytometry Core is providing critical assistance in the evaluation and characterization of human cell subsets in these humanized mice."

"My group is involved in studying mechanisms of immune escape in the tumor micro-environment and critically depends on our collaboration with the IHV Flow Core. When we had an unexpected issue with our cells and needed immediate assistance, the IHV Flow Core was accommodating and understanding of our situation. They helped us to sort the cells on a moment's notice and saved our experiment. This is just an example of the work they do. Having the IHV Flow Core as a regular resource greatly facilitates the research done by my team."

Imaging Core Facility

The Imaging Facility was established in 2012 as the first IHV Imaging Facility. **Dr. Olga Latinovic**, Assistant Professor of Microbiology and Immunology and Head of the Laboratory of Host-Pathogen Interaction, Division of Infectious Agents and Cancer, established IHV's Imaging Facility and has led the facility since its conception. The laboratory was equipped with a newly launched Confocal LSM 800 Airyscan Microscope by Zeiss in 2017, and recently, with Nikon's Fluorescence Microscope in 2020, which are both heavily utilized daily. The Facility is primarily focused on quantitative image analyses of pathogens and host cell interactions that contribute to various IHV projects. The demand for imaging studies significantly increased in the year of 2019 which resulted in numerous published works and projects. During the first week of June 2019, Nikon's team hosted a highly informative demo session showing the potential of the new generation of fluorescence microscopes, the Eclipse Ti2. This Eclipse Ti2 Inverted Research Scope system is terrific for the 3D imaging of precious tissue samples and it includes a motorized stage, options for live and fixed cell imaging, a detectable far red 730 nm excitation wavelength (in addition to the existing 4 colors detectable on the confocal system), large diameter observation optics, a microarray imaging option, and additional cameras for large–volume data acquisition with a 4.5x bigger imaging field than the one on the existing confocal system (needed for tissue imaging). The facility also operates with online scheduling as of June 2019. Some of the main projects of the facility are listed below:

Mycoplasma project—Dr. Latinovic was involved in the Mycoplasma project working originally with **Davide Zella, PhD,** Assistant Professor of Biochemistry and Molecular Biology and Molecular Biology and Co-Head of the Laboratory of Tumor Cell Biology, Division of Infectious Agents and Cancer, and the team in 2009. Their initial observations demonstrated the resetting patterns of mycoplasma interactions with human lymphocytes. The imaging part of the mycoplasma project is related to the direct visualization and quantitative studies of mycoplasma DnaK protein, focusing on its cytoplasmic and perinuclear intracellular location and its interactions with p53. The entire project is directed by Dr. Davide Zella and **Robert Gallo, MD**, The Homer and Martha Gudelsky Distinguished Professor in Medicine and Director of IHV, and the imaging parts of the project were included in a *PNAS* publication in 2019, "Mycoplasma promotes malignant transformation *in vivo* and its DnaK has broad oncogenic properties" (**Figure 1**) and in *Intl Journ of Mol Sci,* in 2020, "Role of Mycoplasma Chaperone DnaK in Cellular Transformation."

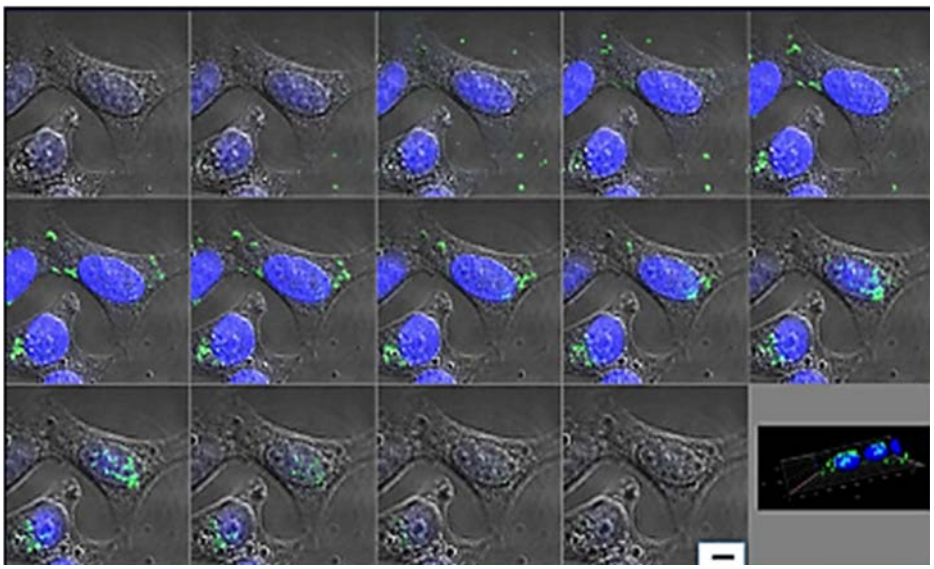


Figure 1. Intracellular uptake of exogenous DnaK-V5 by mycoplasma-free HCT116 cells. Confocal images of exogenous DnaK-V5 protein of M. fermentans in HCT116 cells treated with DnaK-V5 protein (Nuclear localization). The figures show the collected Z-stacks of the corresponding gallery of images, each presenting a 0.5-µm-thick slide. Zella et al, PNAS 2019.

HIV-1 Latency Research—Dr. Latinovic was using a variety of super resolution, confocal microscopy methodologies and quantitative image analysis in collaboration with **Fabio Romerio, PhD**, formerly Assistant Professor of Medicine, **Yvonne Affram, PhD,** a former post-doc and **Zahra Gholizadeh, PhD**, a current post-doc. They were investigating the subcellular localization of the HIV-1 antisense protein, ASP, as well as its interactions with proteins of the nuclear and cellular membranes. Their observations have led to the finding that ASP may be a previously unknown structural protein of the HIV envelope. This finding could have implications for much deeper understanding of HIV-1 infection. It could also have an implication for the development of a new vaccine and therapeutic strategies against HIV/AIDS. Their work resulted in a published work at *Journal of Virology* (Affram *et al,* 2019). The efforts towards HIV-1 latency research have been invested

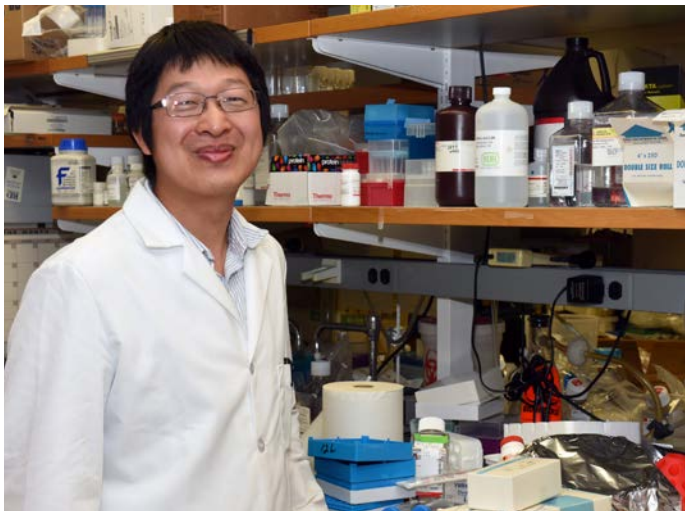
Francesca Benedetti, PhD, Research Associate of Biochemistry and Molecular Biology, Division of Basic Science, Olga Latinovic, PhD, MSC and Davide Zella, PhD, Assistant Professor of Biochemistry and Molecular Biology and Co-Head of the Laboratory of Tumor Cell Biology (Photo taken before the SARS-CoV-2/ COVID-19 pandemic)

into Dr. Latinovic's project. The project aims to investigate the intracellular HIV-1 DNA levels of HIV-1 infected hu-mice upon cART intensification with entry inhibitors. Using confocal imaging, Dr. Latinovic plans to map the sites of HIV-1 infection (p24 protein) in infected and treated hu-mouse tissues.

International collaboration—Cauliflower Mosaic Virus TAV—The lab was involved in an international collaboration with investigators from Italy (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST)). The project revealed that the Cauliflower Mosaic Virus CaMV transactivator/viroplasmin protein (TAV) shares sequence similarity with, and behaves like the human ribonuclease H1 (RNase H1) in reducing DNA/RNA hybrids detected with S9.6 antibody in HEK293T cells. Imaging studies showed that TAV is clearly expressed in the cytosol and in the nuclei of transiently transfected human cells, similar to its distribution in plants. This work (Turri *et al*, 2020) was published at Biomedical Research International.

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

Core services include: routine immunoassays (e.g. ELISA); endotoxin testing; monoclonal antibody and recombinant protein screening, production, purification, and labeling; production and maintenance of virus and cell stocks; and maintenance of common use equipment. The latter includes a BIACORE T200, a SpectraMax M2 ELISA plate reader, an ABI simpliAmp PCR machine, a StepOnePlus qPCR machine, an ABI QuantStudio3 qPCR machine, a Luminex L200 System, and a Miltenyi Biotec autoMACS cell separator. The core serves the UMB campus and Baltimore research community on a fee-for service basis and welcomes the opportunity to work with investigators to establish new immunoassay and protein production protocols. A complete list of µQUANT core services can be found in the IHV website. (http://www.ihv.org/Research/Core-Facilities/Quant-Core/) 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 4 UMB groups outside of IHV.



Ping-Hsin Lin, MS in his lab

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

Christian Bréchot, MD, PhD

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a Center of Excellence of the Global Virus Network with a major role in its formation and the subsequent continued success it experiences today. Since the HIV/AIDS outbreak of the early 1980's, it has been the goal of IHV Co-Founder and Director **Robert Gallo, MD,** also The Homer & Martha Gudelsky Distinguished Professor in Medicine, 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, DC by Dr. Gallo, who also serves as GVN's International Scientific Advisor, and his colleagues William Hall, MD, PhD, and the late Reinhard Kurth, MD. Dr. Hall is Professor of Microbiology at the University College Dublin (UCD) in Dublin, Ireland. Dr. Kurth was the former Director of the Paul Ehrlich Institute and the Robert Koch Institute and Chairman of the Foundation Council at Ernst Schering Foundation in Berlin, Germany in addition to serving as a member of the IHV Board of Advisors. At the inaugural meeting in DC, attendees from more than a dozen countries affirmed and ratified GVN's goals and objectives. Since that three-day meeting, GVN was incorporated by the U.S. government as a non-profit, 501(c)(3) organization. The GVN offices are headquartered at the IHV, and led by GVN's President Christian Bréchot, MD, PhD, former President of France's internationally renowned Institut Pasteur.

In late 2019, a group of infectious disease experts had an idea—to create a coalition among leaders in the public and private sectors that could help prepare for how the global health community responds to emerging pandemics and collaborate to end major viral pandemics. As the initial program formed between Abbott and the GVN, the group quickly realized they would be developing a blueprint for pandemic preparedness, while in the middle of one. The GVN Corporate Centers of Excellence Coalition was first created in late 2019 as a way to bring together the world's foremost virologists and prominent companies to catalyze and facilitate the development, evaluation and testing of diagnostics, therapeutics, treatments and vaccines for viral epidemics and pandemics that pose a threat to public health. As a leader in infectious disease testing and blood screening, Abbott joined as the inaugural member of the coalition. The collaboration with GVN plans to focus on three initial areas: Strengthening preparedness; Sharing research on known pathogens and emerging pathogens; and, Providing insights on the potential impact of this research.

In the early weeks of the pandemic, Abbott brought together a team of its scientists to develop diagnostic and antibody tests to detect the virus and the antibodies that develop after an infection. One of the key elements for developing these tests were virus samples to ensure the accuracy of our test. Through the Corporate Centers of Excellence program, Abbott collaborated with GVN to identify additional virus samples in different patient populations and has worked with GVN to determine new locations to conduct research. The coalition is also developing the framework to collaborate and share research on COVID-19 and SARS-CoV-2. Abbott and GVN are establishing a SARS-CoV-2 biobank—or repository that stores biology samples—to study and validate antibody tests. The GVN Corporate Centers of Excellence Coalition will continue to add new members.

Early in the SARS-CoV-2 global pandemic, the GVN convened internal meetings to bridge gaps in the global emergency response and serve as a "go-to" resource for members needing assistance in obtaining and disseminating cutting-edge scientific research. Among other things, GVN has cultivated scientific ideas to mitigate the spread of SARS-CoV-2 and tested technologies to identify efficacy.

Mohammad Sajadi, MD

Anthony Amoroso, MD

Through GVN's Center of Excellence at the IHV, **Mohammad Sajadi, MD**, Associate Professor of Medicine, Division of Clinical Care and Research and **Anthony Amoroso, MD**, Associate Professor of Medicine and Associate Chief of Infectious Diseases who is also Chief of Clinical Care Programs for IHV, published "Temperature and Latitude Analysis to Predict Potential Spread and Seasonality for COVID-19" on Elsevier's SSRN site and determined that temperature and latitude may have a direct link to the spread and seasonality of COVID-19. In the paper published in March, the researchers found that all cities experiencing significant outbreaks of COVID-19 had very similar winter climates with an average temperature of 41 to 52 degrees Fahrenheit, an average humidity level of 47 to 79 percent with a narrow east-west distribution along the same 30-50 N" latitude.

IHV's **Robert Gallo, MD** and **Davide Zella, PhD**, Assistant Professor of Biochemistry and Molecular Biology, Division of Infectious Agents and Cancer, announced in April that scientists from IHV and Trieste, Italy characterized a novel mutation in the RNA polymerase of certain viral strains of SARS-CoV-2 carried by patients located in Europe and North America. In addition, different patterns of mutations were identified in viral strains corresponding to different geographical areas. The data, published by the *Journal of Translational Medicine*, were obtained by analyzing more than 200 widespread full-length genomic sequences from the National

L to R:
Shyam Kottilil, MBBS, PhD,
Robert Gallo, MD and
Konstantin Chumakov, PhD

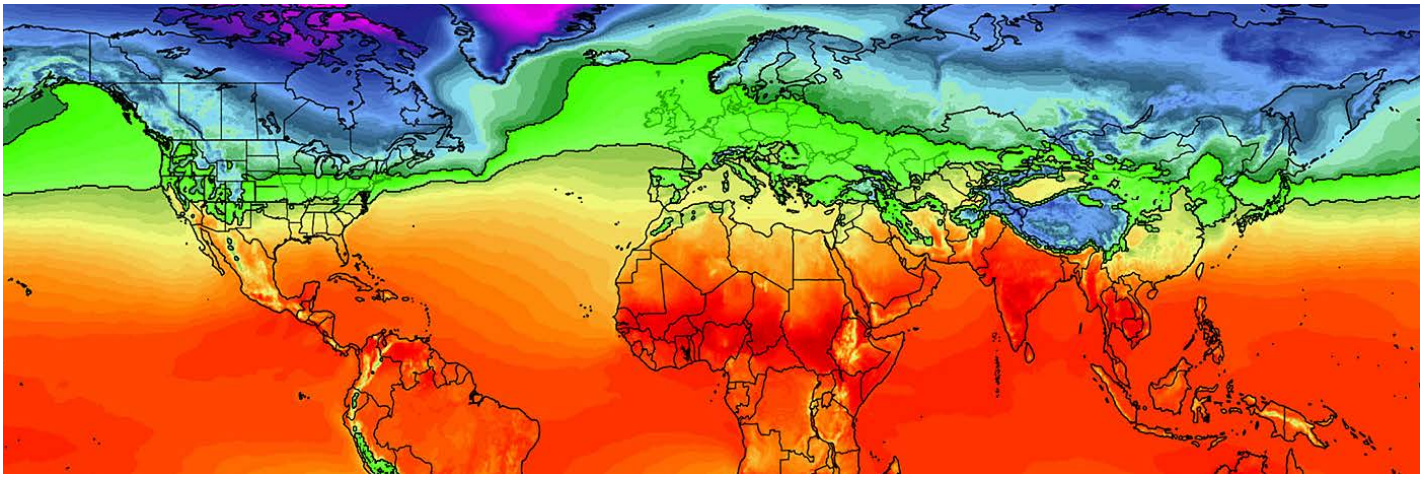
Center for Biotechnology Information (NCBI) and the Global Initiative on Sharing All Influenza Data (GISAID) databases from December 2019 to March 2020.

Further, Dr. Gallo and Dr. Zella, in collaboration with scientists from Campus Biomedico in Rome, Italy announced in August the results of studies showing the emergence of a SARS-CoV-2 viral strain with a deletion in a protein known as nsp1. These data were published by the *Journal of Translational Medicine* and may indicate the emergence of a less pathogenic viral strain. The researchers analyzed SARS-CoV-2 genome sequences from several countries and discovered a previously unknown deletion that is widespread and spans varying geographical areas. Modelling analysis of the newly identified deletion of SARS-CoV-2 nsp1 suggests that this deletion could affect the structure of the C-terminal region of the protein, important for both regulating viral replication and hampering the innate immune system response. The research indicates that the virus may become less pathogenic.

The GVN has also advanced a concept developed by IHV's **Dr. Robert Gallo** and **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division and Head of the Clinical Care Research Unit, and Konstantin Chumakov, PhD, Associate Director for Vaccines at the Food & Drug Administration (FDA) and a GVN Center Director, to use the existing and proven safe Oral Polio Vaccine (OPV) as a preventive measure against SARS-CoV-2. Non-specific protective effects of OPV have been demonstrated several times against a broad set of different virus outbreaks in the 1960's and 70's. More recent studies confirmed these observations and revealed that other live vaccines produce pronounced non-specific protective effects, whereas inactivated vaccines do not. Data from randomized clinical studies showed that OPV immunization campaigns reduced all-cause mortality despite the complete absence of poliovirus circulation. The emerging body of evidence suggests that besides inducing specific humoral and cellular immune responses, OPV may activate multiple branches of the immune system, including training innate immunity and thus increasing resistance to a broad spectrum of pathogens, including SARS-CoV-2. GVN and IHV continue to seek funding for clinical trials to test OPV against SARS-CoV-2.

IHV faculty participated in GVN's virtual 2020 Special Annual Meeting held September 23-24, 2020. Key findings during the meeting regarding SARS-CoV-2 and COVID-19 research included:

- "Super-spreaders" and "super-spreading" events are major drivers of the pandemic, indicating that only a handful of those infected seem be exponentially contagious. Further, short-range aerosol-driven transmission contributes to the dissemination of the virus, particularly in the context of the super spreading events.
- Key pandemic response strategies—the need to take better advantage of the major technology progress in diagnostics, a key driver for the control of infectious diseases; salivary sampling



This map reflects average temperature data from March 2019 to April 2019 to predict the at risk zone for community transmission of COVID-19. The zone at risk for significant community spread in the near-term include land areas within the green bands, outlined in dark black but may change based on actual average temperatures in 2020 during this time period. CREDIT: Image from Climate Reanalyzer, Climate Change Institute, University of Maine, USA. Image manipulation by Cameron Gutierrez and Glenn Jameson.

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

will very much increase our testing capacity, including in school settings; novel rapid and cheap molecular rapid diagnostic tests combined with digital-based transmission of the results, tracing and isolation should be widely emphasized, an understanding of communicability and transmission and, most importantly, the creation of a unified and multidisciplinary response with mechanisms for information sharing among international virologists and independent authorities.

- An evaluation of vaccine development—timing, an analysis of the candidates, side-effects and managing the world's expectation for a satisfactory and timely vaccine. Until a classical, effective vaccine is available, vaccines that stimulate the body's innate immune system, such as the oral polio vaccine and BCG, are integral in protecting against infection.
- A very strong statement against SARS-CoV-2 being the result of human manipulation.
- An update on the available and future therapies, emphasizing the need to combine novel antiviral and immunomodulatory molecules as well as the need to contemplate in the future antivirals with broad spectrum against several viruses.

During the virtual meeting, the GVN presented Doherty Institute Director, University of Melbourne Professor Sharon Lewin, FRACP, PhD, FAAHMS with **GVN's Robert C. Gallo Award for Scientific Excellence and Leadership in Medical Virology** for her outstanding clinical virology research and clinical trials, her leadership in Australian medical science as Director of the Doherty Institute, and her leadership in the GVN.

A video of the GVN press conference including participation by Dr. Robert Gallo following the meeting can be found at **www.gvn.org.** The press conference includes a summary of the meeting's findings with participation from other GVN members, and a panel discussion "From HIV to SARS-CoV-2 and Beyond" moderated by David Scheer, an advisor and entrepreneur in life sciences with a lifelong career in global public health non-profits. Panelists included Dr. Gallo, Dr. Bréchot and Dr. Eric Rubin, *New England Journal of Medicine* Editor.

This past year, the GVN added four new Centers of Excellence including, Cleveland Clinic, the University of Southern Denmark, the Center for Emerging Viruses, Inflammation and Therapeutics of the Menzies Health Institute Queensland (MHIQ) at Griffith University, Australia and the Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products of the Russian Academy of Sciences. GVN Members represent expertise covering every class of human virus, and currently comprise virologists from 57 Centers of Excellence and 10 Affiliates in 33 countries, and its numbers continue to grow. GVN has held international meetings in Ireland, Italy, USA, Germany, Russia, Sweden, Grenada, Estonia, China, Japan, Australia, France and Spain.

In addition to Dr. Bréchot, GVN's staff headquartered at IHV includes Linman Li, MBA, MPH, PMP, CPH, Vice President, Shin-Hee Lee, PhD, Program Director, Marcus Gallo, MS, Research Analyst & Center Outreach Coordinator, Chandrani Raysarkar, Media and Public Relations Senior Specialist 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, as mentioned,serves as Co-Founder and International Scientific Advisor of the GVN, **Dave Wilkins**, who oversees GVN's finances, and **Nora Samaranayake**, who serves as GVN's Senior Advisor on Public Relations. Other contributors include **Mohammad Sajadi, MD; Anthony Amoroso, MD; Davide Zella, PhD; Shyam Kottilil, MBBS, PhD; Wuyuan Lu, PhD; Yang, Liu, PhD; Pan Zheng, MD, PhD; Man Charurat, PhD; Yutaka Tagaya, PhD; Alash'le Abimiku, MON, PhD; Clement Adebamowo, BM, ChB, ScD, FWACS, FACS; Marv Reitz, PhD; Niel Constantine, PhD, MT(ASCP); George Lewis, PhD;** and, **Anthony DeVico, PhD**. IHV also appreciates its own Board of Advisors for donating time and energy towards the advancement of the GVN mission.

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Institute of Human Virology
University of Maryland School of Medicine
(In FY2021, Lu steps down from IHV leadership and becomes part-time to accept a faculty position at Fudan University, Shanghai, China.)

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David Riedel, MD, MPH—IHV, Associate Professor, Medicine
Brenna Roth, MD—IHV, Assistant Professor, Medicine
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Imaging Studies of Pathogens & Cell Interactions Core Facility
Olga Latinovic, PhD—IHV, Head of the Laboratory of Host-Pathogen Interaction and IHV Imaging Core Facility, Assistant Professor, Microbiology and Immunology

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

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

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

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

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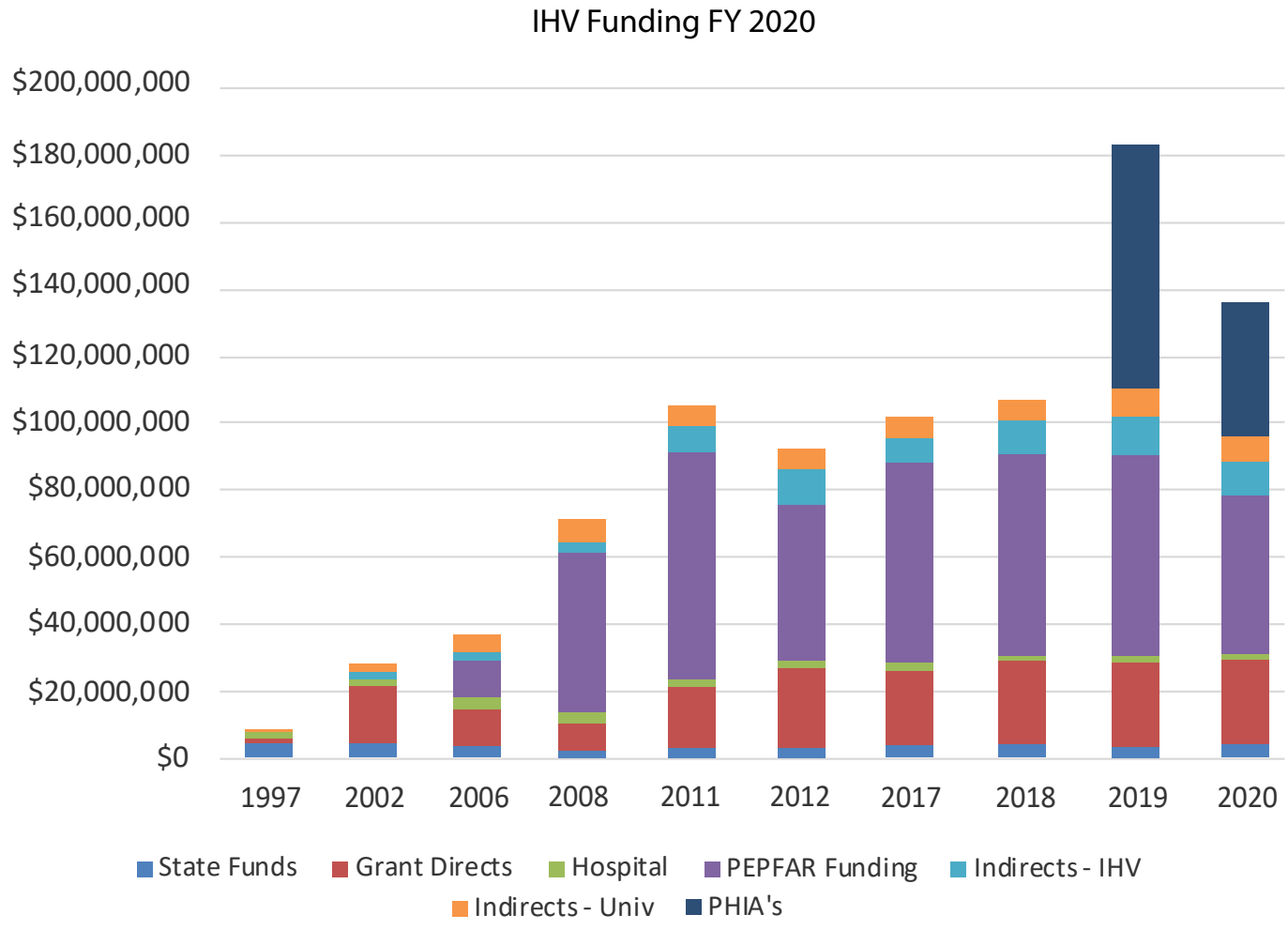
Financial Overview

IHV had a strong financial year in FY2020, generating $138,000,000 of total revenue. This was due to relative stability in all 5 Divisions and 1 Center, including Infectious Agents and Cancer, Immunotherapy, Vaccine Research, Clinical Care and Research, Epidemiology and Prevention, and the Center for International Health, Education, and Biosecurity (CIHEB). In FY2019, IHV received funding in the amount of $72,000,000 for a onetime HIV survey in Nigeria. While funding could be expected to reduce by that amount in FY2020, in fact, IHV replaced it with a new 5-year grant for similar surveys in other countries, with year 1 funding at $40,000,000. IHV did realize a small drop in overall CIHEB funding due to changes in the way in which the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) funds will be awarded to indigenous organizations, as predicted in our FY2019 report. We expect these reductions to occur significantly over the next two years, and IHV is working with foresight to prepare for reduced funding while maximizing efforts to replace it.



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