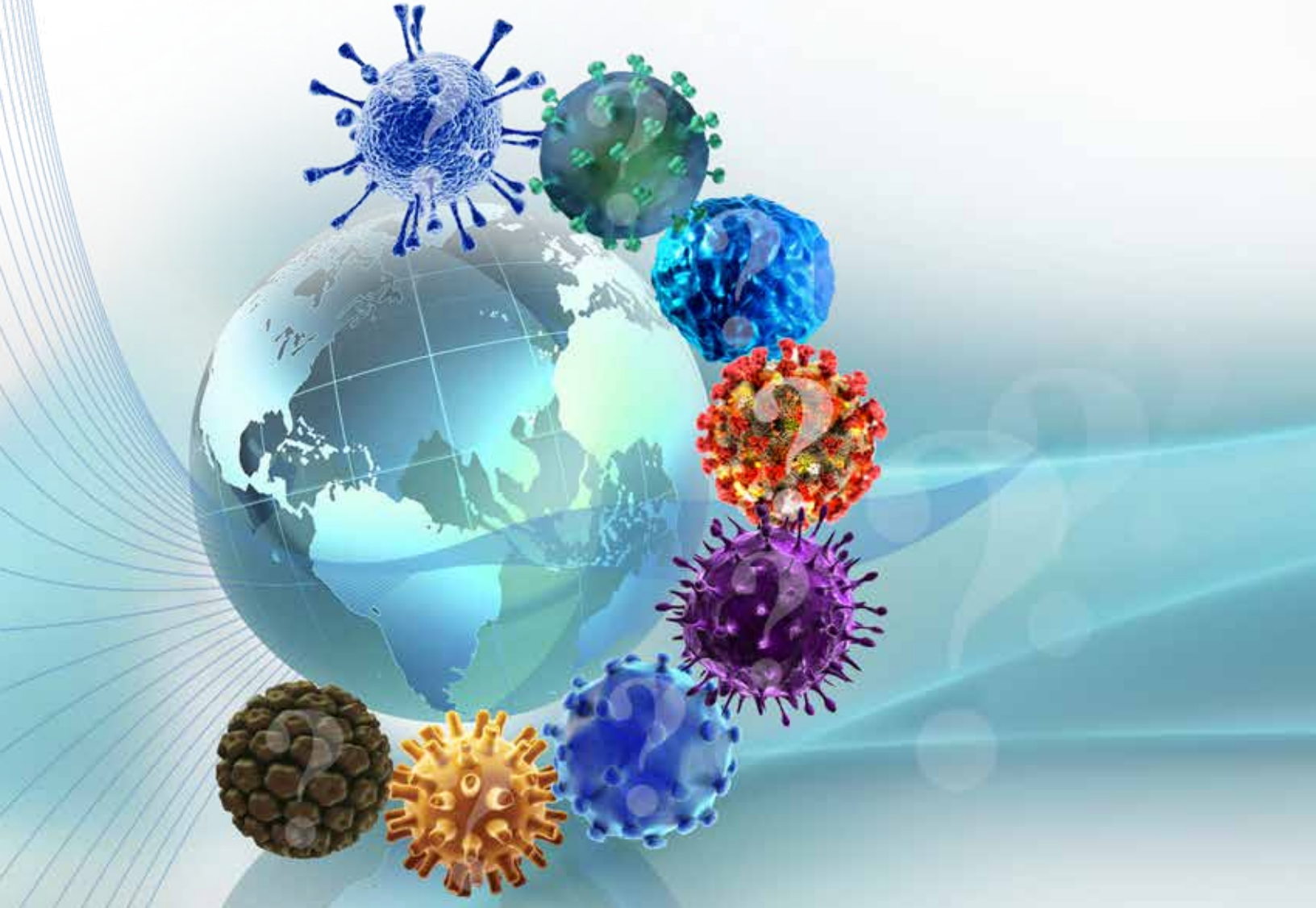
INSTITUTE OF HUMAN VIROLOGY

ANNUAL REPORT 2022



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 Divisions of Virology, Pathogenesis, and Cancer, Vaccine Research, Immunotherapy, a Center for International Health, Education, and 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.

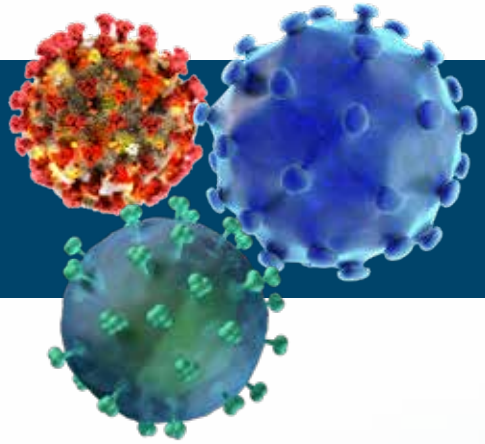
IHV creates an environment where multidisciplinary research, education, and clinical programs work closely together to expedite the scientific understanding of HIV/AIDS pathogenesis and to develop therapeutic interventions to make AIDS and virally-caused cancers manageable, if not curable, diseases.

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% of the Institute's clinical and research effort is targeted at HIV infection, but also includes SARS-CoV-2, hepatitis B and C viruses, 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, funded largely by the Bill & Melinda Gates Foundation.

Contents

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



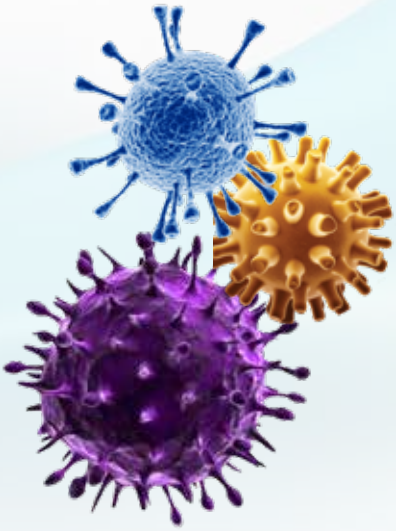
Our Mission

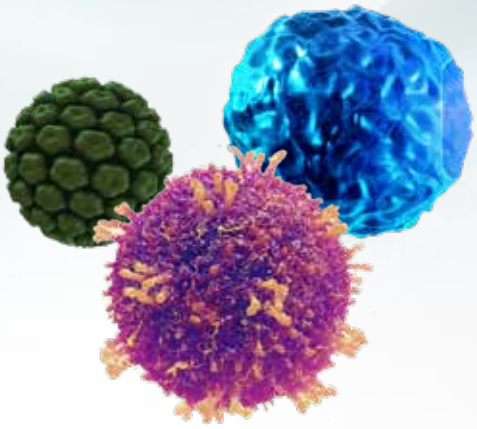
The Institute of Human Virology (IHV) was established to create and develop a world-class center of excellence focusing on chronic viral diseases, especially HIV/AIDS, and virally-linked cancers.

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

This past fiscal year, the Institute of Human Virology (IHV) at the University of Maryland School of Medicine continued to focus research on SARS-CoV-2, and the disease it causes, COVID-19, while concurrently addressing challenges presented by viruses causing chronic infectious diseases. IHV postponed its international annual meeting, when we plan to formally celebrate the 25th anniversary of the founding of the Institute, for September 28-29, 2023, in Baltimore, Maryland.

World Leaders in Science, Healthcare, Academia, Business, and Government Discuss Issues and Ramifications of Long COVID

While my colleagues and I fielded questions about vaccine boosting, variants, drug therapy, and public health safety, we also tackled the issue of long COVID. Led by the Global Virus Network (GVN), and co-hosted by IHV at the University of Maryland, Baltimore (UMB), a first-of-its-kind conference this past summer on the 'Science of Long COVID' reviewed the wealth of cohort (study group) data on long COVID, constructed a framework to characterize and define the conditions, and identified the most critical and urgent areas of research needed to better understand, diagnose, and treat this developing public health crisis.

Across the globe, nearly half of COVID-19 survivors struggle with persistent symptoms four months or more after diagnosis. They are colloquially referred to as having long COVID or known as long haulers. Conference speakers from around the world focused on the vast public health implications of this highly prevalent condition. During the proceedings, we outlined approaches to research this complex phenomenon that has already cost Americans alone an estimated $50 billion annually in lost income, a data point that could translate to $200 billion or more of lost income around the globe.

The prevalence of long COVID is staggering. More than two years into the pandemic, we have concrete and irrefutable proof from cohort studies following individuals as they experience a litany of symptoms—memory problems, relentless fatigue, difficulty breathing, cardiac concerns, insomnia, and more. What we lacked, and what the conference achieved, is a data-driven, scientific baseline that helps scientific, policymaking, and healthcare stakeholders to understand and approach the underlying aspects of long COVID and consequently arrive at a global research framework.

As part of the process to establish a global research framework, the conference presented key scientific and clinical evidence on long COVID's far-ranging global impact:

- 243 million long COVID cases worldwide with a disproportionate burden affecting women (49% versus 37% for men); continental differences (Asia with 51% of COVID cases becoming long COVID, Europe 44%, U.S. 31%); and lasting elevated risk levels among long COVID survivors for cardiovascular disease and diabetes.
- Striking clinical parallels exist between "COVID-fog" and "chemo-fog," with whole-body inflammation in both causing changes to brain circuitry and cognitive impairment. Different cytokines—immune hormones that affect immune and other cells—may be promising biomarkers, and even therapeutic targets, to measure long COVID's effects in the body and ameliorate long COVID disease.
- Thirty-to-fifty percent of long haulers report breathlessness and 10-20% report cough. More severe lingering effects of long COVID on the respiratory system include damage and scarring of lung tissue. These changes

are not necessarily predicted by the severity of the disease or whether a patient was hospitalized. Vaccination has reduced the numbers of individuals with long COVID respiratory disease, while new COVID variants show milder effects.

- Risk factors for long COVID include type 2 diabetes, SARS-CoV-2 RNAemia (viral RNA in the blood), Epstein-Barr virus viremia (active virus circulating in the blood), microclots, protein misfolding, and both pre-existing and disease-specific autoimmunity. These associations are most detectable at the time of diagnosis, emphasizing the need for early disease measurements to advance understanding.

The IHV supports true collaboration among virologists, medical specialists, governments, and non-governmental organizations alike to combat long COVID's critical threat to international health. The conference wrapped up with a call to action for governments and funding agencies to allocate resources to strengthen scientific training and response mechanisms across priority focus areas.

Could a "broad spectrum" booster increase our immunity to many pathogens simultaneously?

My colleagues and I continued to push for more research in using live attenuated vaccines (LAVs) to stimulate innate immunity and slow the spread of COVID-19, or potential future viruses causing a pandemic. In February 2022, *The New Yorker* explored this theory in an extensive article. While we have an effective four-month vaccine for COVID-19, learning more about how some vaccines can provide substantive broad protection could prepare us for the next viral pandemic threat to mankind.

This year, we published two new studies from the GVN and IHV, in partnership with the Petroleum Industry Health Organization of Iran, providing evidence that getting the oral polio vaccine made from live, weakened poliovirus may protect people from COVID-19 infection by stimulating the immune system. One of these studies demonstrated a lower incidence of COVID infections in countries in which people received the 'live' polio vaccine compared to countries that only received the polio vaccine that does not contain a live virus. These findings were published on March 17, 2022, in *PLOS One*. Another report from the research team showed that when young children received the 'live' polio vaccine their mothers, who were indirectly exposed to the poliovirus vaccine, did not get infected with COVID. This study was published late last year in *JAMA Network Open*.

Although countries like the U.S. and those in Europe are dropping pandemic restrictions, many people in lower income countries remain unvaccinated due to lack of supply. Individuals in these countries are still at high risk for COVID infection and potential complications, particularly since these regions still lack the latest treatments and enough ventilators for those who need them. These live vaccines may provide a stop gap to reduce hospitalizations and deaths until we can get these people COVID vaccines.

Now we have some of the first evidence that LAVs do offer protection against COVID-19. I hope funders take notice and increase support for these types of trials that study the innate immune response and provide significant hope in mitigating future pandemics. Such vaccines could become the badly needed universal countermeasure against emerging infections.

Knowing the Origins of COVID-19 Won't Change Much

In February 2022, I published an opinion-editorial in *TIME* with my colleague, Dr. Dean Jamison, a public health economist at University of California, San Francisco, stating that knowledge of SARS-CoV-2 origins would doubtfully change anything about how we should respond to the challenges of SARS-CoV-2, or how we would prepare for a future pandemic. While it would be nice to know the origin, at least for now, we can act on the assumption that either hypothesis (nature or laboratory leak) could be correct and focus efforts on long-term international collaborative endeavors on SARS-CoV-2 and in preparation for future epidemics and pandemics.

IHV Supports Statement from GVN on 2022 Russian Invasion of Ukraine

This year, the world witnessed Putin's horrific atrocities towards the Ukraine. The following is a shortened version of the statement issued by the GVN, of which IHV is a founding member:

While GVN is an apolitical organization, its members are motivated by the fundamental tenet of medicine; 'to do no harm' and are dedicated to honoring the sanctity of life irrespective of culture, ethnicity, nationality, or race. We are scientists, not politicians, but we are compelled to raise our voices in unison to protest the invasion and wanton destruction of Ukrainian cities and the savage killing of innocent civilians and members of the military who are defending their Homeland in the name of freedom and autonomy. They seek only peace. Mr. Putin, grant them peace. Mr. Putin, cease the armed hostilities immediately and enter into negotiations conducted in accord with respect for human life and dignity. We are committed to universal moral principles that govern the humane treatment of human beings and dictate the norms of civilized relations between nations. The current invaders of Ukraine are not exempted from the unequivocal adherence to these principles, for all members of humanity, 'are not islands separate and apart, but part of the main.' Mr. Putin, stop the aggression now!

In the spirit of interconnectedness, we urge the combatants to cease hostilities and engage in negotiations to peacefully resolve their armed conflict. May this war in which the bitterest enmities have been invoked, be terminated with 'malice toward none and justice for all.' May the sacrifices and suffering already endured be an impetus for peace, and may our common humanity provide the moral imperative by which the sanctity of life and human dignity take precedence over the bristling antagonisms which provided an incitement to force.

Let peace not be cast as a victory or defeat for either side, but as a triumph of morality arrived at by ethical individuals acting on behalf of their respective nations. When morality emerges as victorious, we can rest assured that mankind endures and prevails as the ultimate beneficiary.

Distinguished Alumni Award by the University of Chicago Medical and Biological Sciences Alumni Association (UChicago MBSAA)

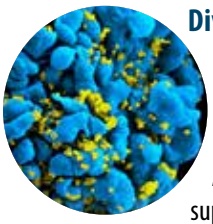
This past year, I received a personally fulfilling honor for my lifetime achievements by the University of Chicago Medical and Biological Sciences Alumni Association. Being at the University of Chicago was a great inspiration for me by being so surrounded by excellence and by mentors who delighted in helping the beginning physician-scientist. I will never forget those days which deeply impacted my entire career.

Dr. Steven Rosenberg Keynotes IHV's Greenebaum Annual Lecture

This past June, IHV's Sixteenth Marlene and Stewart Greenebaum Lecture was presented by Steven A. Rosenberg, MD, PhD, Chief of the Surgery Branch at the National Institute of Health's National Cancer Institute (NCI), in Westminster Hall, a beautiful historic building in downtown Baltimore. The Greenebaum family sponsors IHV's series of prominent annual (aside from the pandemic) Greenebaum lectures insisting that the keynote speaker be someone who has made substantial scientific contributions, while caring for the betterment of the human condition. Dr. Rosenberg spoke on "Lymphocytes as a 'Living Drug' for the Immunotherapy of Cancer." The lecture was attended by over 150 participants.

(L to R Back Row) Dave Wilkins, Lishan Su, PhD, Man Charurat, PhD, MHS, President Bruce Jarrell, MD, FACS, Shyam Kottilil, MBBS, PhD, and Former Dean Albert Reece, MD, PhD, MBA, (L to R Front Row) Michael Greenebaum, Steven Rosenberg, MD, PhD, Robert Gallo, MD, Isaac Witz, PhD, and Kevin Cullen, MD

IHV Divisions



Division of Virology, Pathogenesis, and Cancer (VPC)

In the Division of Virology, Pathogenesis, 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 interrelated and interdisciplinary Research Programs that cover numerous aspects of infection, immunity. and inflammation research including Microbial Pathogenesis, Cancer Biology, Immunity and Inflammation, Structural Biology and Molecular Biophysics, and Drug Discovery and Development.

The Division is directed by **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology, Microbiology and Immunology, who is also Interim Director of the Division of Immunotherapy.

Division of Vaccine Research

The Division of Vaccine Research is led by **George K. Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, Professor of Microbiology and Immunology, and IHV's Deputy Director.

The Division of Vaccine Research is pursuing the development of an AIDS vaccine under the IHV "bench-to-clinic" model of translational research. In this vein, The Division of Vaccine Research continues its 26-year search for a broadly protective AIDS vaccine. This search employs a robust multidisciplinary approach based on virology, immunology, cell biology, structural biology, molecular biology, optical physics, and translational medicine. The Division collaborates closely with investigators of the IHV Division of Clinical Care and Research on developing the "in-house" HIV vaccine, full-length single chain (FLSC), and on fundamental studies of protective antibody responses to HIV. These combined efforts resulted in a successful "first in humans" phase I clinical trial of the IHV-001 AIDS vaccine that was developed and evaluated completely within the walls of the IHV.

Division of Clinical Care and Research

The Division of Clinical Care and Research continues to lead in providing the best clinical care, clinical research, and medical education in the Baltimore and Washington, D.C. metropolitan area. The Division has 38 faculty members and more than 60 support personnel who managed 58 active grants and contracts this year.

The Division is led by **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, with clinical leadership by **Anthony Amoroso, MD**, Professor of Medicine, for most of the year. In April 2022, Dr. Amoroso took on a new role as Director of the Clinical Innovations Program.

Drs. Kottilil and Amoroso developed a clinical care and research program that enables delivery of the most advanced medical care to our patients while pursing the research questions that will most impact their lives. The Division supports a large Baltimore-based outpatient clinical program that provides exceptional care in managing and preventing HIV and hepatitis, the conditions that accompany these viral infections, as well as treating patients with other infectious diseases. The clinical research program under Dr. Kottilil's direction, continues to study therapeutics and cures for hepatitis B and HIV, COVID-19, infectious diseases associated with opioid-use disorder, and other infectious diseases.

Division of Epidemiology and Prevention

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, Epidemiology and Public Health, and Director of the Center for International Health, Education, and Biosecurity (Ciheb), continues a focus on research. The Division published 91 manuscripts in peer-reviewed journals in FY22 and 14 faculty led 20 federal research awards.

Division of Immunotherapy

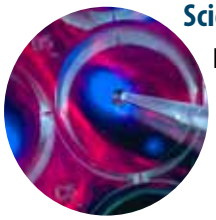
The Division of Immunotherapy is currently led by Interim Director **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology, Microbiology and Immunology, and Director of the Division of Virology, Pathogenesis, and Cancer. The Division continues its fundamental research on cancer immunology and immunotherapy.

Center for International Health, Education, and Biosecurity

The Center for International Health, Education, and Biosecurity (Ciheb) has made key advances in addressing critical needs in health system capacity that improve the prevention, care, and treatment of HIV and other infectious and noncommunicable diseases. In FY22, Ciheb improved and expanded programs in Botswana, Kenya, Malawi, Mozambique, Nigeria, Rwanda, Tanzania, and Zambia.

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 Deputy Director **Kristen Stafford, PhD, MPH**, Associate Professor of Epidemiology and Public Health, Division of Epidemiology and Prevention, Ciheb has conducted rigorous disease surveillance, employed data for action, enhanced professional education, developed robust information management systems, expanded continuous quality improvement processes, and deployed essential infrastructure.

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.



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 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 in this year's annual report.

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

GVN
GLOBAL VIRUS NETWORK

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a Center of Excellence of the Global Virus Network (GVN) 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**, 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 enough medical virologists are trained to meet these challenges.

GVN was officially co-founded in 2011 at the Italian Embassy in Washington, D.C. by Dr. Gallo, who also serves as Chair of GVN's Scientific Leadership Board, with 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, 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 D.C., 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.

Financial Overview

IHV's grants and contracts portfolio was again significant in FY22, generating $100,500,000 of total revenue. All of IHV's five Divisions and one Center, including Virology, Pathogenesis, and Cancer, Immunotherapy, Vaccine Research, Clinical Care and Research, Epidemiology and Prevention, and the Center for International Health, Education, and Biosecurity (Ciheb), performed significant basic research, clinical care, clinical research, and epidemiology programs. In the international arena, the trend for more awards to indigenous organizations will continue, and this is reflected in funding drops in each of these areas—a trend that will likely continue in FY23. IHV has been established and is supporting indigenous organizations in four countries (Kenya, Botswana, Zambia, and Tanzania) to successfully compete to win relevant grants. The Immunotherapy, Vaccine Research, and Virology, Pathogenesis, and Cancer Divisions continue to deliver significant basic science and vaccine development grants.

IHV Leadership

Robert C. Gallo, MD

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

George K. Lewis, PhD

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

Man E. Charurat, PhD, MHS

Director, Division of Epidemiology
and Prevention
Director, Center for International Health,
Education and Biosecurity (Ciheb)
Institute of Human Virology
Professor, Medicine
University of Maryland School of Medicine

Shyam Kottilil, MBBS, PhD

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

Lishan Su, PhD

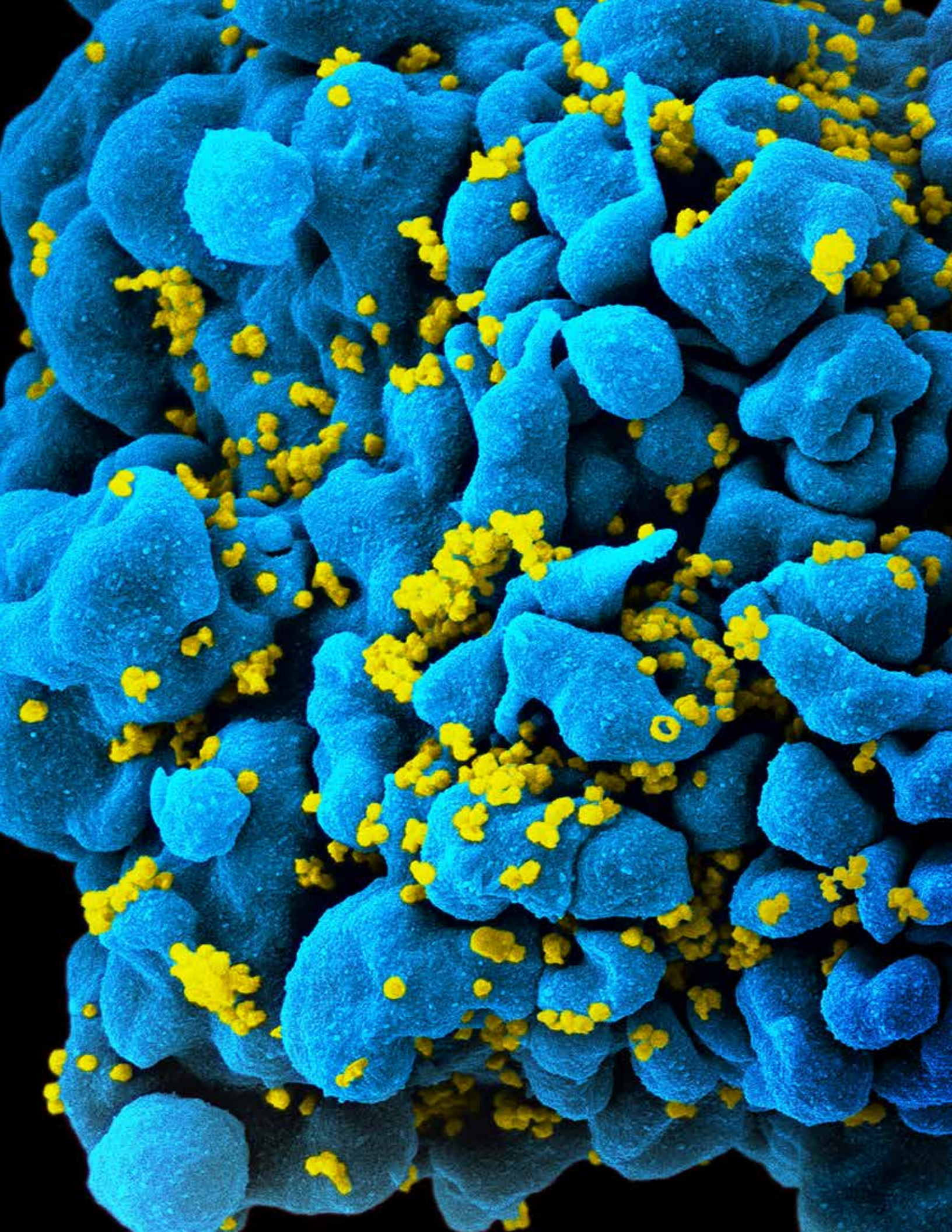
Director, Division of Virology,
Pathogenesis, and Cancer,
Interim Director, Division of Immunotherapy
Institute of Human Virology
The Charles Gordon Smith Professor for
HIV Research
University of Maryland School of Medicine

Anthony Amoroso, MD

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

Dave Wilkins

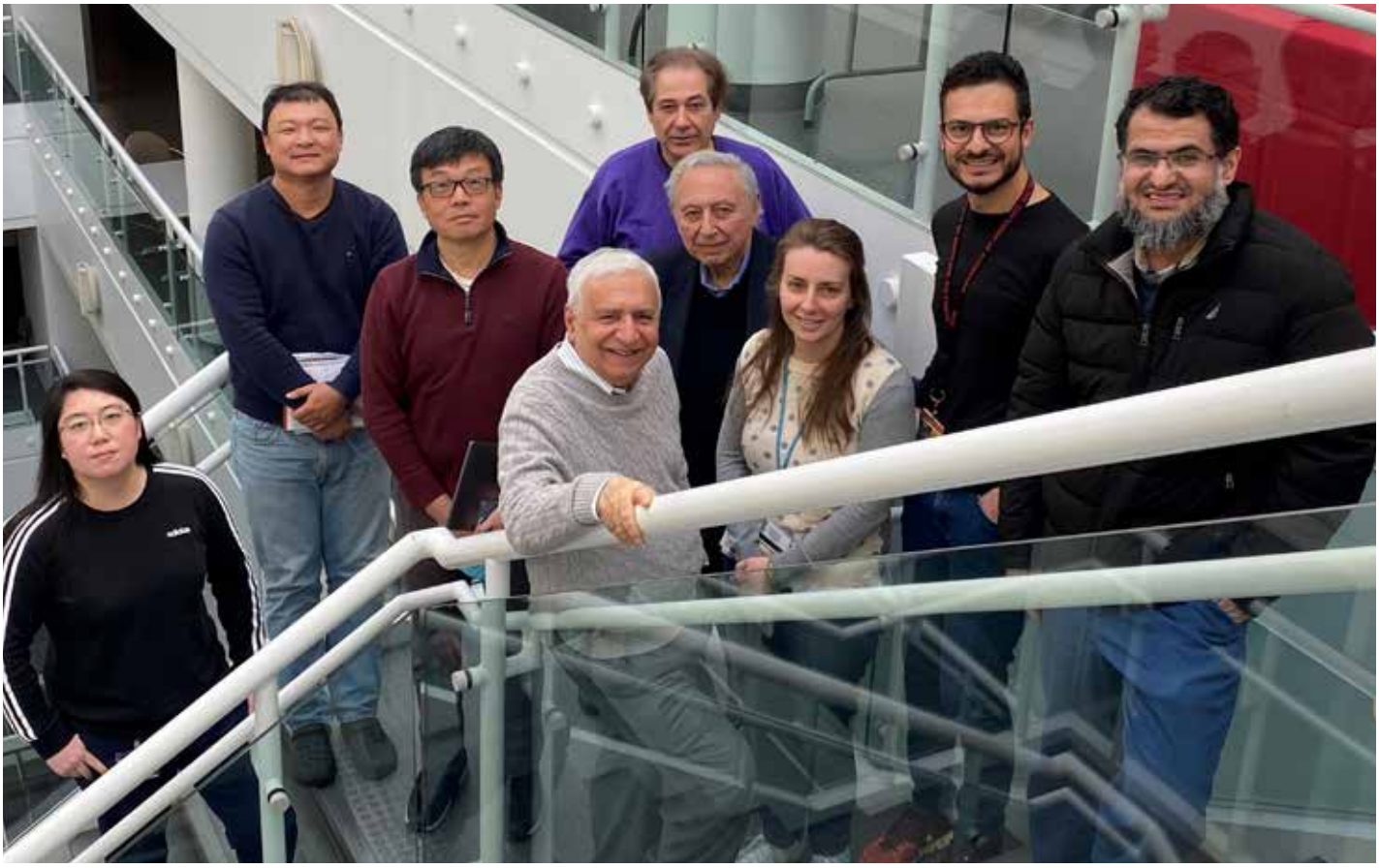
Chief Operating Officer
Institute of Human Virology
University of Maryland School of Medicine



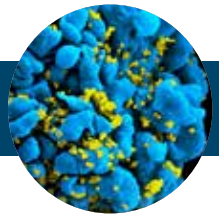
Virology, Pathogenesis, and Cancer (VPC)

Lishan Su, PhD

In the Division of Virology, Pathogenesis, and Cancer (VPC) at the Institute of Human Virology (IHV), more than a dozen faculty members lead research programs defining the molecular basis of infection and immunity and developing novel therapies and treatments for infectious disease, immune dysregulation, inflammatory disorders, and cancer. The Division scientists' research is supported by a diverse portfolio of federal, state, philanthropic, and industrial funds. The Division is organized into five interrelated and interdisciplinary 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 is directed by **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology and Microbiology & Immunology.



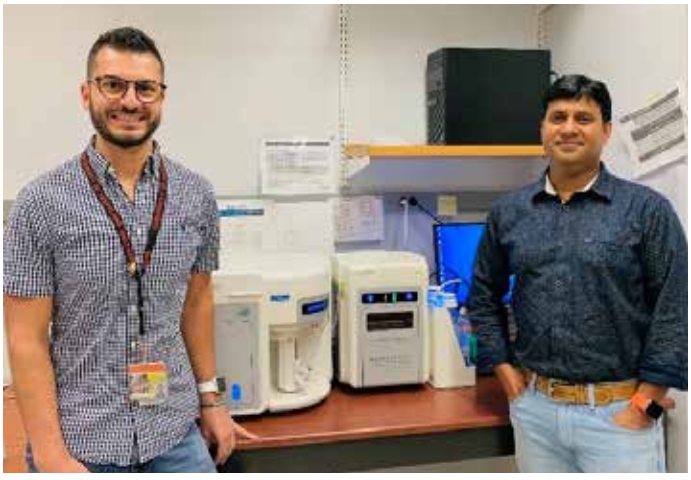
(L to R) Hongshuo Song, PhD, Guangming Li, PhD, Lishan Su, PhD, guest speaker Rafi Ahmed, PhD, of Emory University, Davide Zella, PhD, Robert C. Gallo, MD, Francesca Benedetti, PhD, Giovannino Silvestri, PhD, MS, and Musleh Muthana, PhD



Rathinam Laboratory

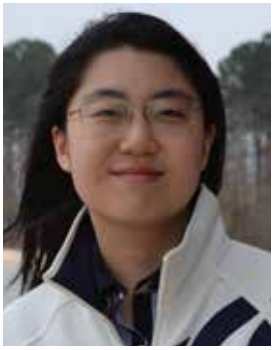
Chozha Rathinam, PhD

Chozha Rathinam, PhD, Associate Professor of Medicine, is continuing studies on the physiological consequences of inflammation mediators. A series of recent studies from the Rathinam laboratory demonstrated that exaggerated chronic inflammation leads to pancytopenia (a deficiency of blood cells), myeloproliferation (making new blood cells), bone marrow failure, and premature death. Currently, Dr. Rathinam, along with **Giovannino Silvestri, PhD,** Research Associate of Medicine, investigates the molecular machinery through which viral infections (such as HIV-1 and influenza), drive irregular development of blood cells and cause immune system deficiencies. In addition, the Rathinam lab has been enthusiastically involved in unraveling the "molecular mysteries" of neuroinflammation (brain inflammation). Particularly, Dr. Rathinam attempts to understand how traumatic brain injury (TBI)-induced neuroinflammation impairs the development and function of the body's immune system. To this end, the Rathinam laboratory has recently identified that the peripheral dendritic cells (DCs) are severely impaired at both acute and chronic phases of TBI, due to deregulated levels of stress hormones, which eventually leads to immunodeficiencies. Dr. Rathinam's ongoing studies are focused on decoding the cellular and molecular players that control the "neuro-immune crosstalk" and "brain-bone marrow" axis.



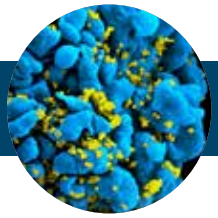
Dr. Silvestri (left) and Dr. Rathinam.

Song Laboratory



Hongshuo Song, PhD

Hongshuo Song, PhD, Assistant Professor of Medicine, is currently trying to understand how multiple virus mechanisms evolved together, such as how a virus forms antigens (i.e. the bits that can cause an immune response by the host), how a virus enters a host cell, and how severely the virus affects the host, with a particular focus on HIV-1 (in other words, this research direction aims to decipher the co-evolution of virus antigenicity, cellular tropism and the virulence). The fast-evolving nature and high genetic adaptability of RNA viruses mean that immune escape mutations in the virus inevitably occur in the face of the host immune defense. However, the impact of these immune escape mutations on infection severity of the virus and how host symptoms manifest is poorly understood. Recent studies in Dr. Song's lab demonstrated that virus antigen formation, what host coreceptor it uses to gain cell entry, and which cells it chooses to infect have all evolved together in natural HIV-1 infection. She found that a single, naturally selected mutation which confers complete escape of the V3-glycan broadly neutralizing antibody (which normally inactivates and kills HIV-1), can trigger a coreceptor switch in how the virus enters the cell, and consequently leads to an alteration in target cell specificity. These novel findings, together with the fact that the antibody binding region of many viruses overlap with receptor binding regions, prompted Dr. Song to propose a paradigm-shifting concept: "escape by shifting." The central hypothesis is that for viruses with receptor flexibility, alteration in which receptor they use represents an evolutionary mechanism of immune evasion in natural hosts with adaptive immunity. In this novel concept, Dr. Song for the first time coined the term "receptor tropism space" to describe the repertoire of receptors that can be used by a particular virus. Under immune pressure, a virus explores its receptor space while exploring the sequence space and fitness landscape. During this process, certain variants escape the immune system by altering which receptor it uses. This novel research direction is expected to have important implications for understanding virus pathogenesis, the potential spread between animals and humans (the zoonotic potential), as well as for vaccine and therapeutic design. In addition, Dr. Song's lab is also trying to determine the biological basis underlying the "virulence-transmission trade-off" of HIV from the perspective of virus CD4 T-cell subset tropism.



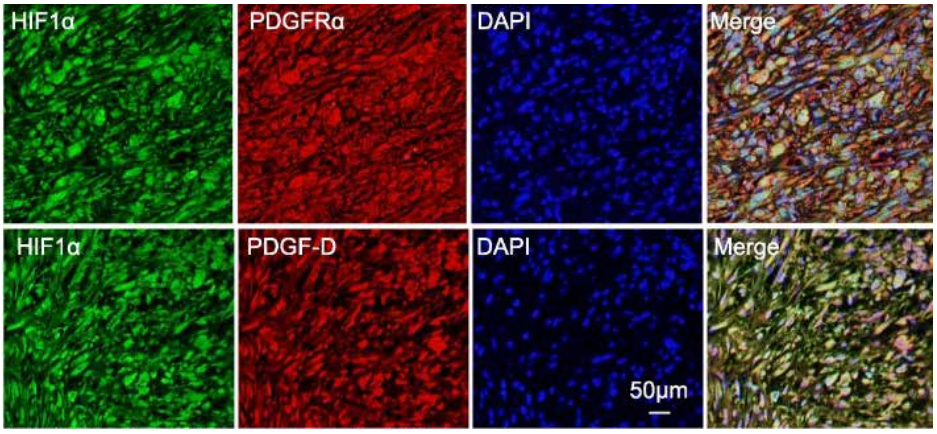
Laboratory of Viral Pathogenesis and Immunotherapy

The Laboratory of Viral Pathogenesis and Immunotherapy, led by Dr. Su has continued research programs on several areas of human immunology and virology, particularly in studying human immune system-pathology of chronic virus infections. He continues the research programs that use HIV and hepatitis B viruses as probes to dissect human immunity and inflammatory diseases, and to develop antibody and cell-based drugs targeting novel immune cells and signaling pathways. His lab has discovered and focused on the plasmacytoid dendritic cells (pDC)-interferon (IFN)-macrophage (M2 cells specifically) axis in the immune-pathogenesis and therapy of chronic HIV and hepatitis B infections. The lab has also started investigation of the pDC-IFN-M2 axis in tumor microenvironments and in cancer immunotherapy. The laboratory thus studies HIV-1 and hepatitis B (virology) and how their interactions with human innate immune cells cause inflammatory diseases (immunology) using various cell and organoid cultures, as well as humanized mouse models. In addition, we are developing novel drugs including antibodies, CAR-T, and therapeutic vaccines (immunotherapy) to treat human inflammatory diseases including virus infection and cancer.

Yutaka Tagaya, BM, PhD

Tagaya Laboratory

Yutaka Tagaya, BM, PhD, Assistant Professor of Medicine, will continue in FY21 his NIH-funded R21 work (PI: Yutaka Tagaya, 5R21AI1588556-02) to explore the small molecule Lipid II binder (precursor of the bacterial cell wall) as a new class of multidrug resistant pathogens including nontuberculous mycobacteria. This project is in collaboration with Erik de Leeuw, PhD, Msc, a former member of the IHV. The Tagaya lab has in the past worked on developing small molecule multi-cytokine inhibitors, and recently finished a phase I/II clinical trial testing the therapeutic potential of one of such inhibitors in treating T-cell malignancies (Large Granular Lymphocytic Leukemia and cutaneous T-cell lymphoma) in collaboration with several leading clinical Institutions in the U.S. They saw clinical response in 30-40% of enrolled patients who were refractory in previous treatments. A summary manuscript was submitted, and an attempt is being made to secure more funding to study the hypothesized molecular mechanism that distinguishes what responds and what does not to the treatment based on preliminary data collected from patients. This research is expected to provide a new treatment for T-cell malignancies without standard cure. His lab also studies HTLV-1 and is developing, in collaboration with Dr. Su's laboratory, a CAR-T (chimeric antigen receptor-T-cell)-based therapy for the fatal CD4 leukemia (adult T-cell leukemia) that is caused by HTLV-1.

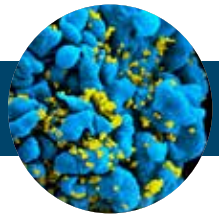


The HIF1α-PDGFD-PDGFRα axis controls glioblastoma growth. Co-expression of HIF1α with PDGFRα and PDGF-D in glioblastoma tissue arrays were examined by immunofluorescence co-staining. Journal of Experimental & Clinical Cancer Research 40, 278 (2021).

Laboratory of Tumor Cell Biology

Davide Zella, PhD

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 & Martha Gudelsky Distinguished Professor in Medicine, Co-Founder and Director of IHV, Co-Founder and Chair of the Scientific Leadership Board of the Global Virus Network (GVN), is continuing the studies elucidating the role of a mycoplasma chaperon protein, DnaK, in causing eukaryotic cells dysfunction. In the past year, in a newly generated model of a DnaK knock-in mouse, we observed



that the presence of DnaK increases DNA copy number variations (CNVs). DNA CNVs are considered important evolutionary factors assisting in the creation of useful complex genomic features. However, alterations caused by CNVs may also result in genomic disorders, including cancers. The overall influence of components of the cellular microenvironment on DNA CNVs formation is poorly understood. Our results indicate that embryonic cells' exposure to DnaK *in utero* is associated with increased chromosomal alterations, reduced fertility, and high rate of fetal abnormalities, highlighting a new connection between components of the human urogenital tract microbiota, namely Mycoplasmas, and embryogenesis. The major contributors to these studies have been **Francesca Benedetti, MBA, PhD**, Research Associate of Biochemistry and Molecular Biology, in collaboration with **Giovannino Silvestri, MS, PhD**, Research Associate of Medicine.

Dr. Su Investiture Ceremony

The Division of Virology, Pathogenesis, and Cancer (VPC) friends and colleagues gathered in Westminster Hall for the Investiture Ceremony Celebrating Donor's Generosity and Recognize of the Groundbreaking Research in Human Virology. **Lishan Su, PhD**, an internationally prominent virologist and immunologist at the University of Maryland School of Medicine's (UMSOM) Institute of Human Virology (IHV), was invested as the Charles Gordon Smith Endowed Professor for HIV Research.

Lishan Su, PhD, and Robert C. Gallo, MD

(L to R back row) Yang Liu, MD, Shuaikun Su, PhD, Yaoxian Lou, Jair Flores, Jiapeng "Michael" Wu, Amara Ejikemeuwa
(L to R front row) Pan Zheng, MD, PhD, Weirong Yuan, Kathryn Eclar, Mingyue Liu, PhD, Lishan Su, PhD, Guangming Li, PhD, Degui Geng, PhD

Virology, Pathogenesis, and Cancer (VPC) Publications

Angeletti S, Giovanetti M, Fogolari M, De Florio L, Francesconi M, Veralli R, Antonelli F, Donati D, Miccoli GA, Fonseca V, **Benedetti F**, **Zella D**, Riva E, Ciccozzi M (2022). Detection of a SARS-CoV-2 P.1.1 variant lacking N501Y in a vaccinated health care worker in Italy. *Journal of Infection* 84(1):94-118. DOI: **10.1016/j.jinf.2021.06.026**

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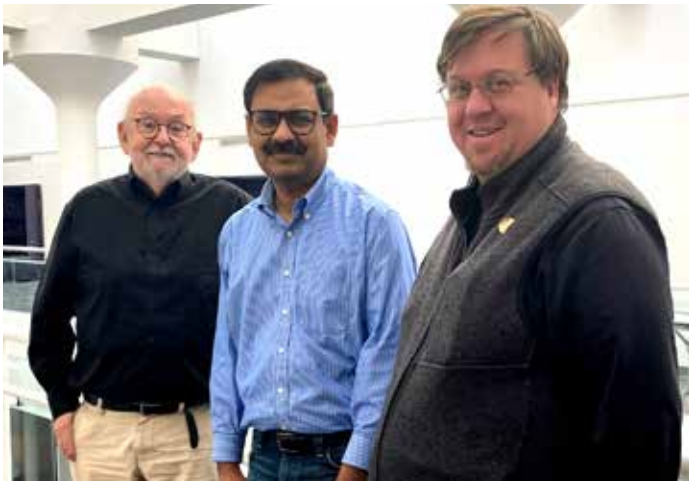
Vaccine Research

George K. Lewis, PhD

The Division of Vaccine Research is led by **George K. Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Professor of Microbiology and Immunology. The Division of Vaccine Research is pursuing the development of an AIDS vaccine under the IHV "bench-to-clinic" model of translational research. In this vein, The Division of Vaccine Research continues its 26-year search for a broadly protective AIDS vaccine. This search employs a robust multidisciplinary approach based on virology, immunology, cell biology, structural biology, molecular biology, optical physics, and translational medicine.

The Division collaborates closely with investigators of the IHV Division of Clinical Care and Research on developing the "in-house" HIV vaccine, Full Length Single Chain (FLSC) **(Figure 1)**, and on fundamental studies of protective antibody responses to HIV. Division of Vaccine Research members collaborate nationally and internationally with investigators at Duke University, Massachusetts Institute of Technology, University of Maryland College Park, Uniformed Services University of the Health Sciences, Emory University, Scripps Research, Harvard University, Dartmouth University, Northwestern University, University of Pennsylvania, University of West Virginia, Case Western Reserve University, the Military HIV Research Program, Royal Thai Army Armed Forces Research Institute of Medical Sciences (AFRIMS) in Thailand, and Mahidol University of Thailand. Division of Vaccine Research efforts are funded by grants from the National Institutes of Health (NIH), The Bill and Melinda Gates Foundation, The Defense Threat Reduction Agency as part of the Department of Defense, the Veterans Administration, and the Henry Jackson Foundation for Medical Research.



(L to R) George Lewis, PhD, Krishanu Ray, PhD, and Greg Snyder, PhD

The FLSC Vaccine Immunogen

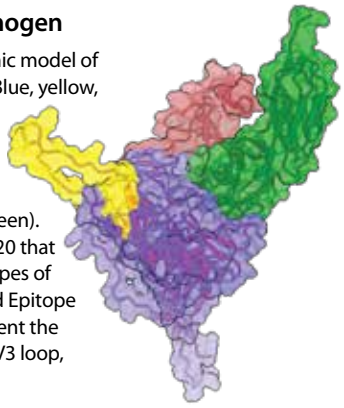


Figure 1. Current working atomic model of the FLSC vaccine immunogen. Blue, yellow, and red depict gp120 that is conformationally constrained by covalently occupying its CD4 binding site by the outer two domains of human CD4 (green). Blue represents the core of gp120 that exposes highly conserved epitopes of the co-receptor binding site and Epitope Cluster A. Yellow and red represent the highly variable V1/V2 loop and V3 loop, respectively.

The FLSC immunogen (molecule that triggers an immune response) **(Figure 1)** is a conformationally constrained (has limited flexibility) protein of HIV gp120 covalently linked to the first two domains of the human T-cell protein CD4 by a flexible peptide spacer. FLSC was developed in the Division of Vaccine Research shortly after establishing the IHV in 1996 **(Figure 2 on pg. 18)**. The FLSC vaccine concept was developed in 1996 by **Anthony DeVico, PhD,** Professor of Medicine, and Division collaborators. Its immunochemical and physical-chemical properties were published in *The Journal of Virology* in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research in collaboration with colleagues in the IHV Division of Clinical Care and Research, and The Military HIV Research Program. Drs. DeVico, **Robert C. Gallo, MD,** The Homer & Martha Gudelsky Distinguished

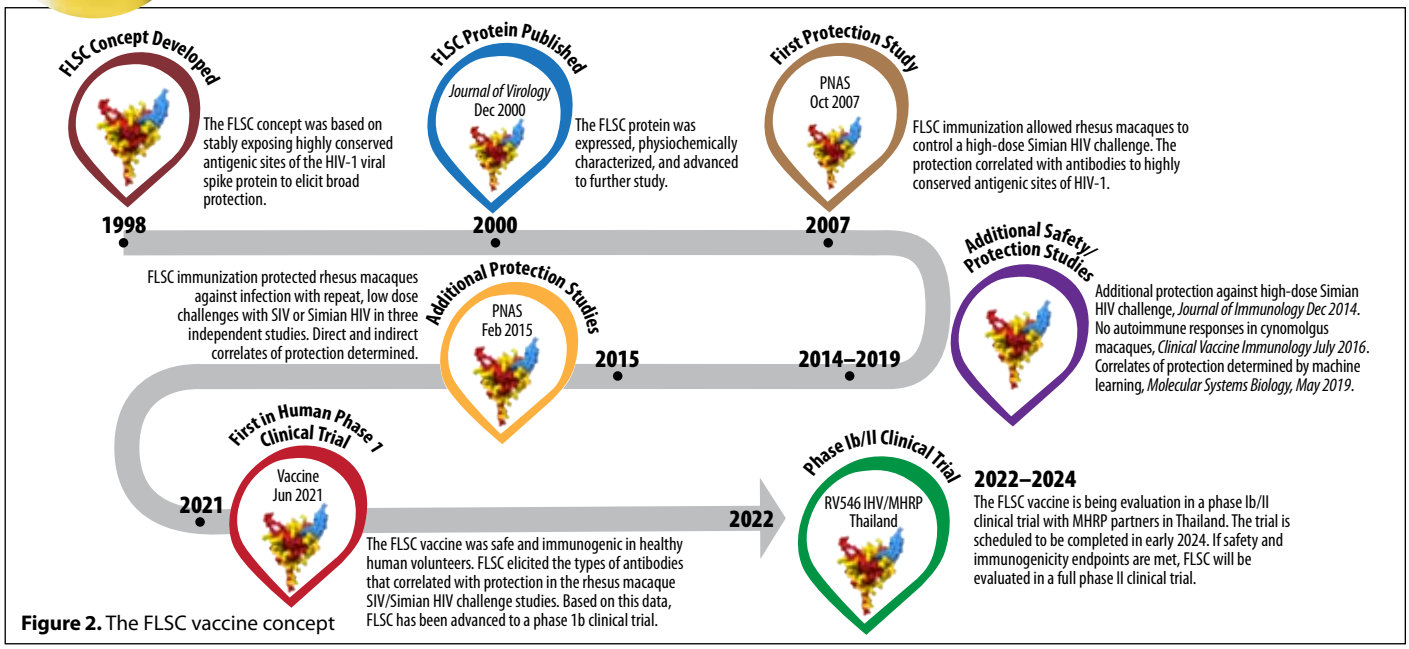


Figure 2. The FLSC vaccine concept

Professor in Medicine, Co-Founder and Director of IHV, Co-Founder and Chair of the Scientific Leadership Board at the Global Virus Network, and **George Lewis, PhD,** The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, IHV Deputy Director, Director of the Division of Vaccine Research, Professor of Microbiology and Immunology, have been involved with the FLSC vaccine program since its inception with crucial contributions made by all Division of Vaccine Research members past and present. Animal protection studies are essential for advancing any HIV vaccine to clinical trials. The first FLSC animal protection studies using stringent viral challenges were reported in the *Proceedings of the National Academy of Sciences* in 2007. Additional studies were published between 2014 and 2019 that confirmed the ability of FLSC immunization to elicit protection against model AIDS viruses in animals (*Journal of Virology* 2014, *Journal of Immunology* 2016, *Molecular Systems Biology* 2019, *Journal of Clinical Investigation* 2019). An additional animal study published in 2016 in *Clinical Vaccine Immunology* confirmed that the human CD4 component elicits autoimmune responses to this "self-protein."

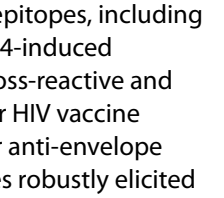
Based on these safety and protection studies, FLSC was advanced to a first-in-humans phase 1a clinical trial in healthy volunteers completed in 2019 (NCT02756208). The FLSC immunogen was formulated with alum as the adjuvant (something that helps boost the immune response even more) (IHV01 formulation) in that study. A phase 1a trial was carried out in collaboration with **Joel Chua, MD,** Associate Professor of Medicine, and **Mohammad Sajadi, MD,** Professor of Medicine, both in the Division of Clinical Care and Research Clinical Research Unit. The trial results were published in the peer-reviewed journal *Vaccine* in 2021. FLSC proved safe and immunogenic, eliciting immune responses similar to those observed in the performed animal protection and safety studies. Based on the safety and immunogenicity data, the IHV01 formulation is now in a phase Ib clinical trial, named RV546, in Thailand through a collaboration among investigators at IHV, U.S. Military HIV Research Program, Duke, Case Western Reserve, and AFRAMS/ Mahidol University (NCT04658667). The R546 trial will boost volunteers who were immunized in the original RV144 trial (NCT00223080) that demonstrated partial efficacy and who were boosted again in the RV305 (NCT01435135) and RV306 (NCT01931358) clinical trials. The IHV01 formulation will be evaluated in RV546 to determine whether it increases the breadth of the potentially protective antibody response to HIV from that of the previous trial RV144. In addition, RV546 will evaluate the ability of a new adjuvant developed by the U.S. Military HIV Research Program to increase immunogenicity. The first results of RV546 are anticipated in 2024, and if successful, it is possible that IHV01 could be advanced to a phase IIb safety/efficacy trial. FLSC development and advancement through animal protection studies to a phase 1b clinical trial is a prime example of the IHV bench-to-bedside approach to translational research established at the Institute's inception. Drs. DeVico, Gallo, and Lewis have been with the FLSC team since 1996. FLSC development was made possible by many Division of Vaccine Research

members and collaborators over the years. Although there are far too numerous of them to list here, their contributions are apparent in the key publications resulting from this work. FLSC development was made possible by continuous extramural funding from NIH including the National Institute of Allergy and Infectious Diseases' (NIAID) Division of Acquired Immunodeficiency Syndrome, National Heart, Lung, and Blood Institute, National Cancer Institute, National Institute of General Medical Sciences, The Military HIV Research Program/Henry Jackson Foundation for Medical Research, and The Bill and Melinda Gates Foundation.

The development of the FLSC vaccine centers on four fundamental problems confronting the development of an HIV vaccine: 1) identifying an immunogen that elicits broadly protective immunity; 2) identifying the correlates and mechanisms of broad protection; 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 enhance or weaken broad, vaccine-elicited protection. The current research efforts addressing these problems are described here for the Division of Vaccine research members.

DeVico Laboratory

Over the past 26 years, **Dr. DeVico's** laboratory has pursued the development of HIV vaccine concepts based on adaptive immunity against the viral envelope glycoproteins. This effort, involving the Director's Office, many members of the Vaccine Division, and a wide array of outside collaborators over the years, heavily utilized nonhuman primates and pioneered various different mucosal Simian HIV challenges in this model. Regarding human HIV vaccines, Dr. DeVico participated in efforts to reveal immune correlates of reduced risk in the partially efficacious RV144 trial which was published in the *New England Journal of Medicine* in 2012 (NCT00223080). The FLSC immunogen, developed in and patented from Dr. DeVico's laboratory as described in the publication in *Journal of Virology* in 2000, is based on transition state gp120 structures that form upon HIV attachment to the CD4 T-cell protein and present some of the most conserved and functionally important epitopes (attracts antibodies) on the viral envelope **(Figure 3)**. Antibody responses to these epitopes, including ones designated CD4-induced (CD4i), are highly cross-reactive and potentially useful for HIV vaccine development. Other anti-envelope response specificities robustly elicited by IHV01 match those determined to correlate with reduced risk in the RV144 efficacy trial. FLSC formulated with alum (IHV01) fully translated from bench-to-bedside in our first-in-humans" phase Ia trial (NCT02756208) published recently in *Vaccine* in 2021 As part of a longstanding forged partnership with the Military HIV Research Program (MHRP) and the Henry Jackson Foundation (HJF), this immunogen is currently being in RV546 described above, to assess the benefits of repeated boosting with heterologous immunogens and novel adjuvants (NCT04658667).



Anthony DeVico, PhD

For more than decade, Dr. DeVico has been collaborating with Dr. Sajadi on deconvoluting the plasma anti-HIV Env responses by the body's immune system. This work led to the discovery of a new family of extremely broad and potent broadly neutralizing antibodies that were described in published in the high-impact journal *Cell* in 2018. Drs. DeVico's and Sajadi's current efforts, in collaboration with a variety of investigators at NIAID (Paolo Lusso, MD, PhD), Scripps Research (Joe Jardine, PhD), and the University of Maryland (Brian Pierce, PhD, Assistant Professor Cell Biology and Molecular

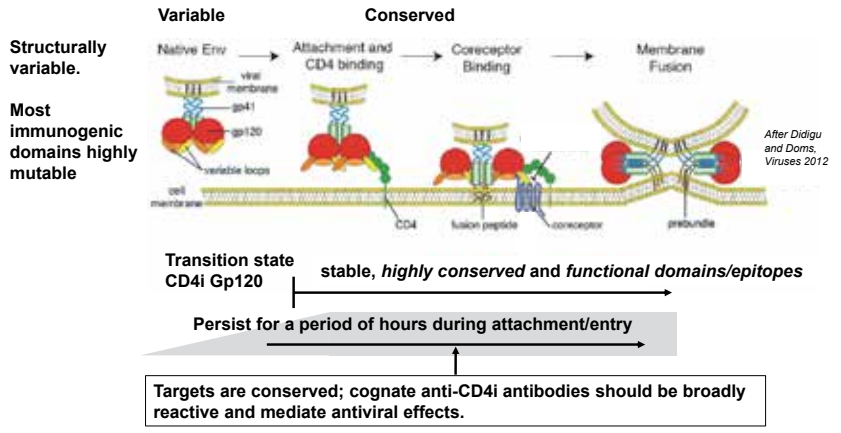


Figure 3. Strategy to identify an immunogen that elicits broadly protective immunity.

Genetics) are dedicated to generating new engineered versions of our broadly neutralizing antibodies individually and in combination with greater breadth, potency, and escape resistance. In collaboration with **Alonso Heredia, PhD,** Assistant Professor of Medicine, in the Division of Clinical Care and Research, Dr. DeVico is testing the new broadly neutralizing antibodies /mixtures for superior preventive and therapeutic effectiveness in newly developed humanized mouse models of HIV infection.

Ray Laboratory

Krishanu Ray, PhD

Krishanu Ray, PhD, Associate Professor of Biochemistry and Molecular Biology, has been working in fluorescence spectroscopy since 1994. Dr. Ray has applied state-of-the-art single-molecule fluorescent-based approaches, including FRET (fluorescence resonance energy transfer), to study protein-protein interactions, virion-antibody interactions, and viral assembly. Currently, his lab's research is focused on probing the nature of HIV-1 envelope interactions with human T-cell receptors, anti-envelope antibodies, and Fc receptors (receptors that bind to antibodies) using fluorescence correlation spectroscopy (FCS), single-molecule detection, time-resolved fluorescence, and super-resolution microscopy as novel tools.

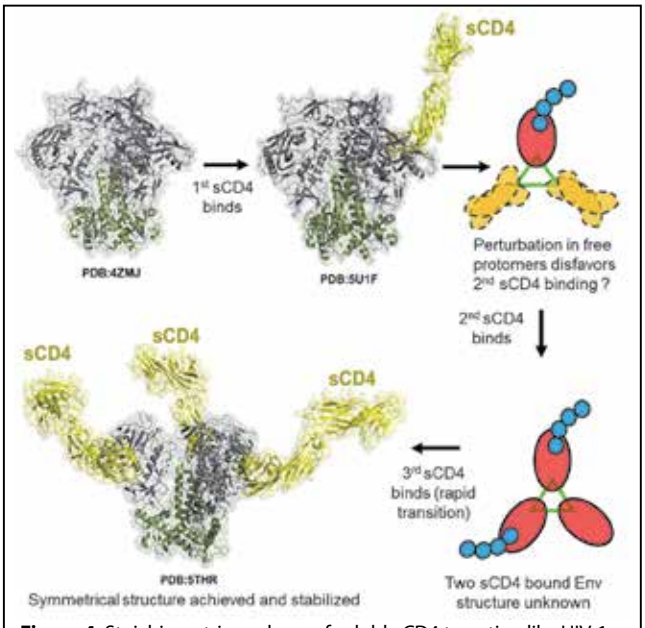


Figure 4. Stoichiometric analyses of soluble CD4 to native-like HIV-1 envelope by single-molecule fluorescence spectroscopy.

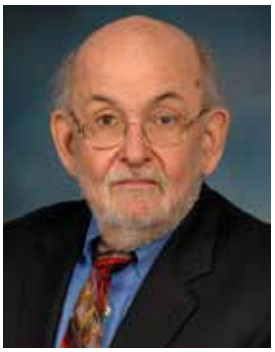
Through applications of FCS, Dr. Ray's work has provided a unique view of HIV virion-antibody interactions. Notably, these single-molecule fluorescence approaches enable assessing individual virions and virion trimers at a level of detail not achievable with standard analytical methods. For example, Dr. Ray's group reported the first solution-based assay studying antibody-virion interactions by FCS in 2014 in the *Journal of Virology*. More recently, Dr. Ray's group has developed new assays for the following problems: 1) a FRET-FCS assay to define the co-expression of different epitopes on the HIV envelope glycoprotein (*Frontiers in Immunology* 2019), 2) a single molecule fluorescence method to determine the stoichiometry (how many of each one bind to one another) of viral receptor-envelope interactions **(Figure 4)** (*Cell Reports* 2019), and an FCS assay to identify antigen-induced allosteric changes (how well it binds) in IgG1 Fc (a combination of these two proteins, IgGI and Fc, along with an antibody bind to FcgR receptor to initiate antibody triggered adaptive immune responses) leading to increased FcgR binding (*Structure* 2020).

Most recently, Dr. Ray, in collaboration with Drs. DeVico, Lewis, and Sajadi are applying single-molecule fluorescence methods to characterize broadly neutralizing antibody interactions and their combinations with single virions *in situ* in plasmas (blood without the cells) from HIV infected people with detectable viral loads or in viral outgrowth assays (viruses grown in cells) for antiretroviral therapy-suppressed HIV infected people. Optimizing breadth, potency, and virus escape resistance (viruses becoming resistant to antiretroviral therapies) are primary goals for clinical developing broadly neutralizing antibodies, which have distinct therapeutic advantages over conventional antiretroviral therapy in specific clinical settings. A significant issue is that all single broadly neutralizing antibodies exhibit limited coverage of epitope variability/mutability among HIV strains, allowing virus escape, and prompting the use of broadly neutralizing antibody combinations instead of single broadly neutralizing antibodies. Determining which broadly neutralizing antibodies or combinations to use in the clinic is challenging as there is heterogeneity in broadly neutralizing antibody neutralization of HIV from different individuals. Currently, there are no methods to directly census broadly neutralizing antibody reactivity with HIV in plasma swarms aside from virus neutralization assays. While standardized neutralization assays will remain essential tools, they can overestimate *in vivo* potency and escape resistance, fail to capture essential determinants of combination broadly neutralizing antibody action, and appear inconsistent with clinical outcomes in broadly neutralizing antibody

prevention or therapy trials. Dr. Ray's group has developed a single-molecule fluorescence approach toward faster and easier neutralization resistance testing based on the direct, quantitative detection of antibody-target binding within a subject's virus population. Dr. Ray received a new NIH grant and a fundable score on a second NIH grant to pursue this important new project.

Lewis Laboratory

Dr. Lewis has fifty-two years of published research experience with a background focusing on the structural basis of immunogenicity, the biological and structural basis of antibody function, and HIV vaccine design. Dr. Lewis has collaborated with Drs. DeVico and Gallo since 1996 on the development of the FLSC immunogen and more recently with Dr. Sajadi since FLSC entered the clinical development pipeline **(Figure 1 see pg. 17).**



George K. Lewis, PhD

Drs. Lewis, DeVico, and Gallo were the first in the literature to point out poor antibody persistence as a significant problem confronting HIV-1 vaccine development (*PNAS* 2014), which remains an important, understudied area. Drs. DeVico, Gallo, and Lewis have collaborated with investigators at Emory University and University of California San Francisco, where a deficit has been found in the generation of long-lived antibody responses to gp120-based immunogens. This work also identified an unexpected synergy between vaccination and antibody-mediated protection against AIDS-like viruses in an animal model. These studies were supported by an NIH program project grant and are being written up for publication. These findings are the basis for new human studies in collaboration with Dr. Sajadi on the poor persistence of antibody responses in HIV-infected people, people recovered from SARS-CoV-2, and people vaccinated against HIV or SARS-CoV-2. Preliminary data suggest deficits in long-lived antibody production in these settings similar to those observed in animal models. Several NIH funding avenues are being pursued to continue this work.

Pursuant to the FLSC animal studies **(Figure 1 see pg. 17)**, protective immunity correlated directly with Fc-mediated effector function specific for CD4-induced epitopes **(Figure 3 pg. 19)** and not neutralization (*Journal of Virology* 2014, *Journal of Immunology* 2016, *Molecular Systems Biology* 2019). During these studies, the IHV team developed the first quantitative metrics connecting antibody specificity with Fc-mediated effector function (*PNAS* 2014). These studies led to discovering the highly conserved gp120 epitope cluster A, an extremely potent target for anti-FLSC antibodies mediating Fc-mediated effector function (*PNAS* 2014). Subsequent studies mapped epitope cluster A to the gp41 docking site of gp120 in native Env (*Journal of Virology* 2014, *Structure* 2016, *Structure* 2017) that becomes exposed upon CD4 binding **(as depicted in Figure 3)**. Interestingly, similar cluster A antibodies were produced in the RV144 clinical trial demonstrating partial effectiveness (*mBio* 2020). As suggested in **Figure 3**, antibodies to the co-receptor binding site of gp120 also mediated strong Fc-mediated effector function, albeit somewhat less potent than antibodies to epitope cluster A (*PNAS* 2014, *BMC Biology* 2020). These studies define epitope cluster and co-receptor binding site epitopes as the primary targets of Fc-mediated effector function correlated with protection in the FLSC animal studies (*Journal of Virology* 2014, *Journal of Immunology* 2016, *Molecular Systems Biology* 2019).

Based on the studies above, Dr. Lewis's group is pursuing the question of how antibody specificity impacts Fc-mediated effector function. These studies led to the discovery of an antigen-driven allosteric network in human IgG1 that increases its binding to FcgR, enabling Fc-mediated effector function (*Structure* 2020). This work challenges the conventional concept that Fc-mediated effector function requires only the passive aggregation of antigen-antibody

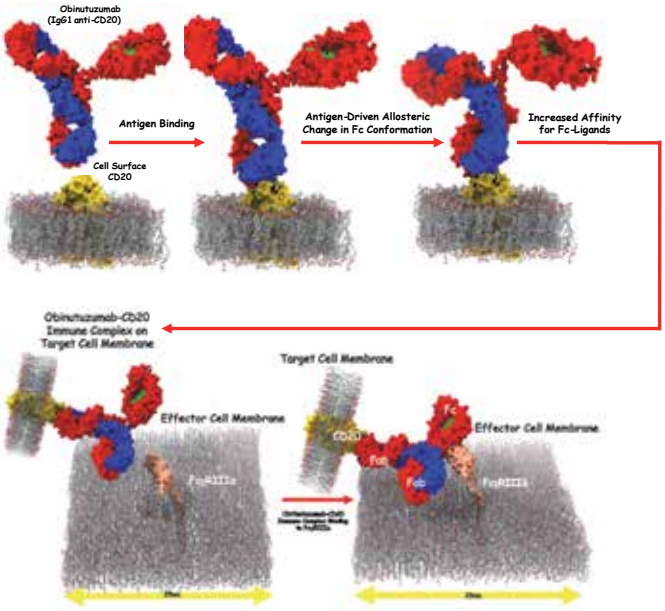


Figure 5. Model for membrane-oriented steps in anti-CD20 Fc-mediated effector function using the commercially licensed monoclonal antibody obinutuzumab. Based on Protein Data Bank structures IE4K.pdb, IgG1-all.pdb, and mAb867120210629.pdb.

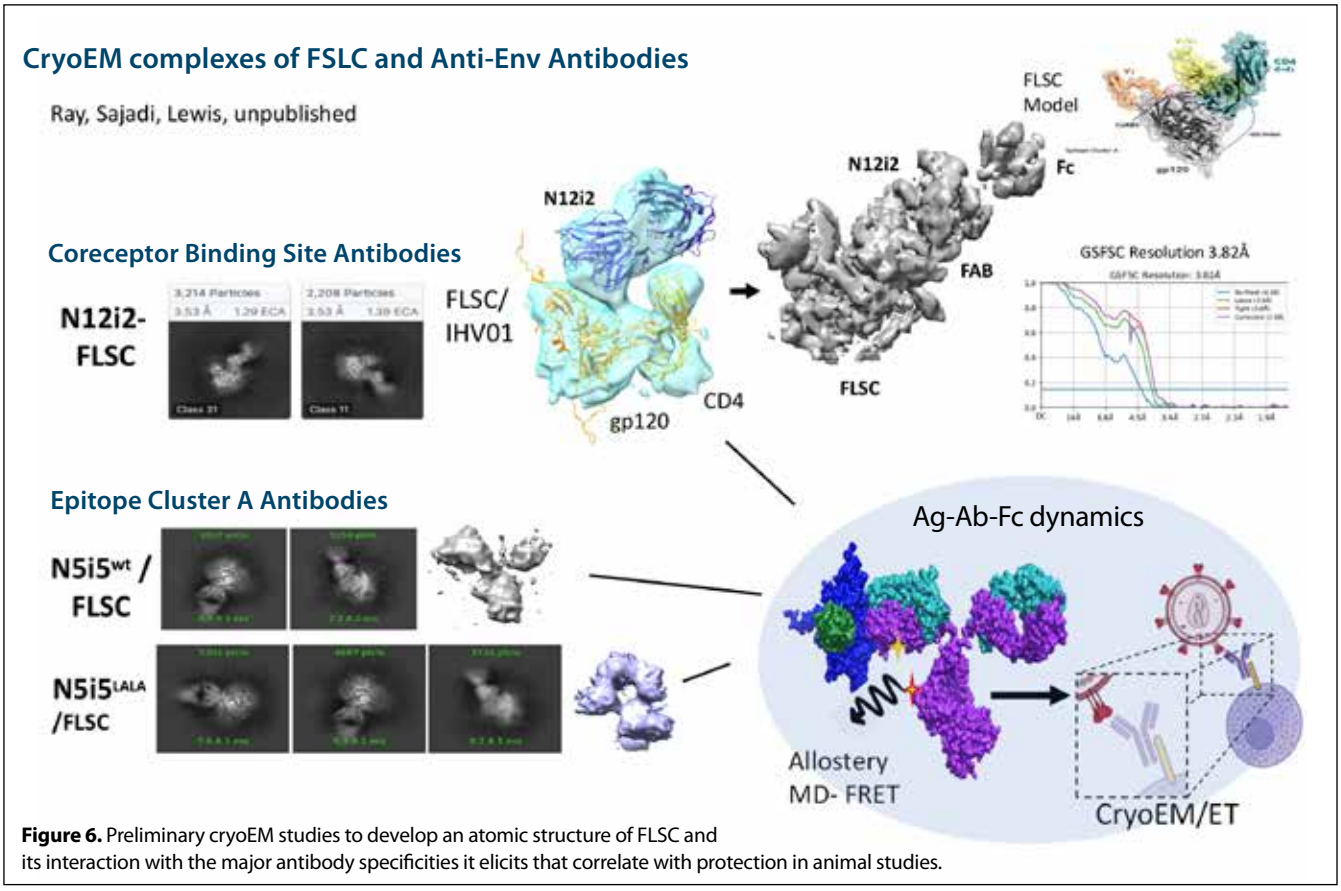


Figure 6. Preliminary cryoEM studies to develop an atomic structure of FLSC and its interaction with the major antibody specificities it elicits that correlate with protection in animal studies.

complexes without conformational changes in Fc. It is now the primary emphasis of Dr. Lewis's research efforts. These efforts are based on structural and computational biology to build membrane domain models of antigen-antibody complexes on target cells and how FcgR recognizes them on effector cells. These models incorporate epitope specificity as the basis for interpreting *in vitro* and *in vivo* biological assays for Fc-mediated effector function. **Figure 5 (on pg 21)** depicts a working model for the commercially licensed therapeutic anti-CD20 monoclonal antibody obinutuzumab. Studies are underway to develop a general model to predict Fc-mediated effector functions based on specificity, immunoglobulin class, and Fc-receptor class.

Greg A. Snyder, PhD

Snyder Laboratory

Greg A. Snyder, PhD, Assistant Professor of Medicine, joined the Division of Vaccine Research in 2019. Dr. Snyder's research focuses on understanding the immune system's recognition of self from non-self. To this end, Dr. Snyder has pursued molecular studies characterizing natural killer (NK) cell function, carbohydrate recognition by C-type lectins (proteins that bind to carbohydrates), and microbial and host recognition by Toll-like receptors. Dr. Snyder's earlier studies involving NK cells structurally defined a unique immunoglobulin domain hinge angle for one of the first identified NK cell inhibitor receptors (KIR2DL) and set the groundwork for determining NK-KIR-MHCI (major histocompatibility complex I) interactions (*PNAS* 1999). Dr. Snyder's structure and molecular modeling studies of the carbohydrate-binding protein DC-SIGN (CD209L) helped redefine its role in binding to the HIV-1 viral envelope glycoprotein, gp120, and cell adhesion protein ICAM-3. They developed a novel prediction algorithm for identifying additional DC-SIGN binding glycoproteins based on their predicted glycosylation footprint (*Journal of Molecular Biology* 2005). Our structural and molecular dynamic studies of Toll-like-Interleukin 1/18 receptors (TIR) domain-containing proteins, including MyD88, and subversive pathogenic bacterial TIR-like proteins have provided molecular insights for developing TIR-based therapeutics, immune evasion,

cancer, and metabolic regulation (*PNAS* 2013, *Journal of Biological Chemistry* 2014, *Innate Immunity* 2020).

Most recently, Dr. Snyder is continuing this line of research on bacterial TIR NAD+ hydrolases (PUMA and TirS), *Pseudomonas aeruginosa* (*Pa*) infected, and *Staphylococcus aureus* (*Sa*). TIR domains differ in infection establishment and subversion of TLR and MyD88 innate signaling. However, their respective NAD+ hydrolase activity and its effect on infection establishment, pathogenesis, and interaction with TLR and MyD88 signaling components have not been characterized. In collaboration with Dr. Ray, Alison Scott, PhD, Assistant Professor of Microbial Pathogenesis at the UM School of Dentistry, and Nathanial Archer, PhD, of Johns Hopkins Medicine, Dr. Snyder is using two-photon fluorescent imaging (2p-FLIM), mass spectrometry imaging, and structural biology to characterize two multidrug-resistant (MDR) bacteria-animal infection model systems *Pseudomonas aeruginosa* infected mouse lung and *Staphylococcus aureus* that express NAD+ hydrolases (*Pa*- PUMA and *Sa* - TirS). These studies are underway, and several grant applications are pending based on work being written up for publication.

In collaboration with Drs. Ray and Lewis, Dr. Snyder's group recently used in-solution single-molecule-fluorescence and molecular dynamics to identify and characterize discrete antigen-induced Fab (fragment antigen-binding region on an antibody) and Fc domain conformations. The in-solution single-molecule-fluorescence FRET and molecular-dynamics measurements allow rank ordering of HIV-1 antigens (Virion, SOSIP, FLSC, gp120) that induce unique patient antibody (Fab-Fc) domain conformations and stabilize Fc receptor binding on cells. To date, the only atomic-level structures of FLSC have been generated by computational modeling of glycans and variable domains missing in existing gp120 structures determined by X-ray crystallography or cryo-electron microscopy (cryo-EM). Thus far, all attempts to develop an FLSC structure by X-ray crystallography have failed. However, using cryo-EM, Dr. Snyder has made significant progress on this front with the identification of 2-D image classes and reconstruction of FLSC in combination with human monoclonal antibodies specific for epitope cluster A or co-receptor binding site epitopes. Preliminary data shown in **Figure 6** are being refined to achieve resolutions below 5.1 Å. This work has already led to several pending grant applications and the development of new manuscripts on the structural basis of Fc-mediated effector function.

Vaccine Research Publications

Caccuri F, Messali S, Zani A, Campisi G, Giovanetti M, Zanussi S, Vaccher E, Fabris S, Bugatti A, Focà E, Castelli F, Ciccozzi M, Dolcetti R, **Gallo RC**, Caruso A (2022). HIV-1 mutants expressing B cell clonogenic matrix protein p17 variants are increasing their prevalence worldwide. *Proceedings of the National Academy of Sciences USA* 119(27):e2122050119. DOI: **10.1073/pnas.2122050119**

Cheng HD, Dowell KG, Bailey-Kellogg C, Goods BA, Love JC, Ferrari G, Alter G, Gach J, Forthal DN, **Lewis GK**, Greene K, Gao H, Montefiori DC, Ackerman ME (2021) Diverse antiviral IgG effector activities are predicted by unique biophysical antibody features. *Retrovirology* 18(1):35. DOI: **10.1186/s12977-021-00579-9**

Fields JK, Kihn K, Birkedal GS, Klontz EH, Sjöström K, Günther S, Beadenkopf R, Forsberg G, Liberg D, **Snyder GA**, Deredge D, Sundberg EJ (2021). Molecular Basis of Selective Cytokine Signaling Inhibition by Antibodies Targeting a Shared Receptor. *Frontiers in Immunology* 12:779100. DOI: **10.3389/fimmu.2021.779100**

Gallo RC (2021). Some reflections on HIV/AIDS research after 40 years. *American Journal of Physiology: Lung Cellular and Molecular Physiology* 321(6):L1057-L1058. DOI: **10.1152/ajplung.00442.2021**

Gallo RC, Tagaya Y (2022). Reflections on Some of the Exceptional Features of HTLV-1 and HTLV-1 Research: A Perspective. *Frontiers in Immunology* 13:859654. DOI: **10.3389/fimmu.2022.859654**

Habibzadeh F, Sajadi MM, Chumakov K, Yadollahie M, Kottilil S, Simi A, Stafford K, Saeidimehr S, Rafiei M, **Gallo RC** (2021) COVID-19 Infection Among Women in Iran Exposed vs Unexposed to Children Who Received Attenuated Poliovirus Used in Oral Polio Vaccine. *JAMA Network Open* 4(11):e2135044. DOI: **10.1001/jamanetworkopen.2021.35044**

Habibzadeh F, Chumakov K, Sajadi MM, Yadollahie M, Stafford K, Simi A, Kottilil S, Hafizi-Rastani I, **Gallo RC** (2022). Use of oral polio vaccine and the incidence of COVID-19 in the world. *PLoS One* 17(3):e0265562. DOI: **10.1371/journal.pone.0265562**

Tolbert WD, Nguyen DN, Tuyishime M, Crowley AR, Chen Y, Jha S, Goodman D, Bekker V, Mudrak SV, **DeVico AL**, **Lewis GK**, Theis JF, Pinter A, Moody MA, Easterhoff D, Wiehe K, Pollara J, Saunders KO, Tomaras GD, Ackerman M, Ferrari G, Pazgier M (2021). Structure and Fc-Effector Function of Rhesusized Variants of Human Anti-HIV-1 IgG1s. *Frontiers in Immunology* 12:787603. DOI: **10.3389/fimmu.2021.787603**

Weichseldorfer M, Tagaya Y, Reitz M, **DeVico AL,** Latinovic OS (2022). Identifying CCR5 coreceptor populations permissive for HIV-1 entry and productive infection: implications for in vivo studies. *Journal of Translational Medicine* 20(1):39. DOI: **10.1186/s12967-022-03243-8**

Clinical Care and Research

Shyam Kottilil, MBBS, PhD

The Division of Clinical Care and Research continues to lead in providing the best clinical care, clinical research, and medical education in the Baltimore and Washington, D.C. metropolitan area. The Division has 38 faculty members and more than 60 support personnel who managed 58 active grants and contracts this year.

The Division was led by **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, with clinical leadership by **Anthony Amoroso, MD**, Professor of Medicine, for most of the year. In April 2022, Dr. Amoroso took on a new role as Director of the Clinical Innovations Program. Drs. Kottilil and Amoroso developed a clinical care and research program that enables delivery of the most advanced medical care to our patients while pursing the research questions that will most impact their lives.

Anthony Amoroso, MD

The Division supports a large Baltimore-based outpatient clinical program that provides exceptional care in managing and preventing HIV and hepatitis, the conditions that accompany these viral infections, as well as treating patients with other infectious diseases. The clinical research program under Dr. Kottilil's direction, continues to study therapeutics and cures for hepatitis B and HIV, COVID-19, infectious diseases associated with opioid use disorder, and other infectious diseases**.**

SARS-CoV-2 Pandemic Response

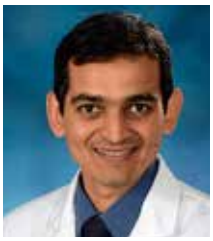
As we entered our second year of the COVID-19 pandemic, IHV's clinical faculty continued to be a leader in the front-line care in the COVID-19 pandemic. The Division continues to pair with urgent care centers and provide telemedicine support for high risk COVID-19 infected patients.

Dr. Kottilil in collaboration with Pan Zheng, MD, PhD, former Professor of Surgery, and Yang Liu, MD, former Professor of Surgery, both formerly of IHV's Division of Immunotherapy led a randomized controlled clinical trial using the CD24Fc molecule for severe to critical COVID-19 patients. The clinical trial was stopped early for effectiveness and was one of the very few therapies that have demonstrated efficacy in improving clinical outcomes of severe and critical COVID-19 patients. The results of this pioneering study were published earlier this year in *Lancet Infectious Diseases*.

IHV investigators continue to conduct COVID-19 research. **Jennifer Husson, MD,** Assistant Professor of Medicine, who led the Divisions' Clinical Research Unit (CRU), working in collaboration with Kirsten Lyke, MD, Professor of Medicine, from University of Maryland, Baltimore's (UMB) Center for Vaccine Development and Global Health, continued to implement the large National Institutes of Health (NIH)-funded multi-center trial, Mix and Match COVID-19 Booster study. The results of this study were published in *New England Journal of Medicine*.

Jennifer Husson, MD

Joel Chua, MD



Shivakumar Narayanan, MBBS, MD

Joel Chua, MD, Associate Professor of Medicine, conducted a study on the safety of canakinumab for COVID. Dr. Chua and **Shivakumar Narayanan, MBBS, MD,** Assistant Professor

of Medicine, Director of Hepatitis Research, were the site Principal Investigators for two studies using Regeneron's monoclonal antibodies. These studies conducted at IHV's CRU were published in leading medical journals including *New England Journal of Medicine*, *The Lancet*, *The Lancet Infectious Diseases*, *JAMA*, and *JAMA Internal Medicine*.

Elana Rosenthal, MD

From the laboratory side, Dr. Kottilil continued working on his National Institute on Drug Abuse (NIDA) grant supplement to investigate COVID-19 progression and immunity in subjects with HIV infection and opioid use disorder with **Elana Rosenthal, MD,** Associate Professor of Medicine, Co-Director of the DC Partnership for HIV/AIDS Progress Hepatitis Clinical Research Program.

Mohammad Sajadi, MD, Professor of Medicine, **Kapil Saharia, MD, MPH,** Associate Professor of Medicine, Chief of the Solid Organ Transplant Infectious Diseases Service, and **John Baddley, MD,** Professor of Medicine, are studying vaccine immune response in immunocompromised patients. Dr. Sajadi continues to look at the antibody response in COVID-19 infection in addition to a collaboration with the NIH examining COVID-19 infected lung tissue.

Mohammad Sajadi, MD

Kapil Saharia, MD, MPH

John Baddley, MD

First-in-Human Xenotransplant

On January 7, 2022, University of Maryland School of Medicine (UMSOM) surgeon-scientists performed a first-in-human xenotransplant using a genetically modified pig heart which was successfully transplanted into a 57-year-old patient with terminal heart failure. Physician-researchers from the Division of Clinical Care and Research, Drs. Saharia, Baddley, Husson, and **Katya Prakash-Haft, MD**, Assistant Professor of Medicine, played collaborative roles in caring for this patient and/or developing infection control measures to safeguard against possible pathogens that may originate from the pig heart. The study was published in *New England journal of Medicine*.

Dr. Saharia, **Alip Ghosh, PhD, MSc,** Research Associate in Medicine, and **KiSeok Lee, PhD,** Research Assistant of Medicine, worked with other IHV researchers to develop several in-house tests to monitor the xenotransplant recipient for porcine (pig) viruses, including porcine endogenous retrovirus (PERV) and porcine cytomegalovirus (PCMV). These assays are also being used for surveilling healthcare workers that were involved in the care of the xenotransplant recipient.

As plans move forward for potential clinical trials, Division researchers will continue to work closely with the University of Maryland School of Medicine's xenotransplant team to develop more sophisticated test for screening organ-source animals for potential porcine pathogens and to monitor future xenotransplant recipients for any evidence of porcine pathogen transmission.

Clinical Care Program—The IHV continues to provide state-of-the-art, high-quality care to the citizens of Maryland, and beyond. Over the last four years under Drs. Kottilil and Amoroso's leadership, the IHV has taken a greater role in leading the Division of Infectious Disease for UMSOM.

Sarah Schmalzle, MD, Associate Professor of Medicine, Medical Director of The THRIVE Program, and her staff, maintained an active outpatient HIV program for more than 2,500 patients in our Baltimore clinics with creative efforts and expansion of telemedicine. The IHV continues to identify unmet patient needs and expand services to address them with the development of new clinical program Health and Recovery Program (HARP) in partnership with the Addiction Medicine Program at UMSOM to address the other enormous epidemic of infections and deaths associated with drug use.

Sarah Schmalzle, MD

David Riedel, MD

The Division's clinical practices allow for optimal clinical care and education. The Infectious Disease Fellowship, led by **Dave Riedel, MD, MPH,** Associate Professor of Medicine, has 14 fellows and remains one of the largest infectious disease Accreditation Council for Graduate Medical Education (ACGME) fellowship training programs in the country. With 38 Infectious Disease clinical faculty providing clinical care, this has allowed for growth in the IHV's Immunocompromised Host Program including care and research in the Greenebaum Comprehensive Cancer Center led by Dr. Baddley and the Solid Organ Transplant Program at University of Maryland Medical Center led by Dr. Saharia.

THRIVE staff examine a patient

Financial Health Clinical Program

FY22 is expected to be a strong year. The combined clinical practices (IHV and Infectious Diseases) will exceed $7,800,000 charges in FY22. After physician salary costs, administrative costs, billing costs, malpractice insurance costs, and operational costs the clinical practice anticipates reaching a revenue that exceeds costs for this past year, well toward a complete recovery from previous years.

HIV Care

The THRIVE program (Together Healing, Reaching, Inspiring, to achieve Victory over illness, and Embrace life), run by Medical Director Dr. Schmalzle continues to stand out for its commitment to providing patient-centered, comprehensive, compassionate, interprofessional team-based, comprehensive care in one center. THRIVE provides care to approximately one quarter of the people living with HIV in Baltimore City, receiving private and federal funding to provide care otherwise not available to underinsured patients and to expand available services to meet the needs of our patients. Key HIV services offered include HIV specialty and primary care, HIV prevention services (PEP and PrEP), same day "Connect 2 Care" visits and same day medication initiation for HIV treatment and prevention, Pap (cervical cancer screening), colposcopy (visual examination of the cervix), anoscopy (examination of the rectum and anus), a medication-assisted therapy program (buprenorphine and naltrexone), and Pharm D drug information specialist services to ensure medication safety, education, and adherence (patients keep taking their medicine as prescribed). THRIVE also offers injectable HIV medication for HIV treatment and HIV prevention, as well as COVID-19 vaccines. Integrated mental health care and counseling, housing coordination, substance use counseling, employment counseling, transportation assistance, food vouchers, and emergency rent/utilities assistance, all coordinated through a highly dedicated and competent social work team directed by Division's **Robyn Palmeiro, LCSW-C**, round out THRIVE's patient-centered HIV services. Infectious disease care at THRIVE includes hepatitis C evaluation and management, infectious disease consultations, hospital discharge, outpatient parenteral antibiotic therapy (i.e., intravenous (IV) antibiotics) follow up, and penicillin allergy skin testing. In September 2021, the THRIVE Program moved to the new outpatient tower at the University of Maryland Medical Center's (UMMC) Midtown Campus. Areas of focus for 2022 include continue engaging and retaining patients with efforts such as expanding home-based support services and implementing the STRIVE to 100 (Strengthening THRIVE's Resilient Individuals to liVE to 100) model of care for adults more than 50-years old living with HIV.

Robyn Palmeiro, LCSW-C

HARP (Health and Recovery Practice)

UMSOM's Health and Recovery Practice is a joint venture between the IHV's Division of Clinical Care and Research and the Department of Psychiatry and Addiction Medicine. Launched in Fall 2019, HARP provides primary care, urgent care, wound care, and infectious disease treatment for active patients at Psychiatry's Drug Treatment Programs located at 1001 West Pratt. This is a population-based initiative to improve care for our patients and curb the costs of avoidable emergency department and inpatient stays. The HARP program focused on staffing capacity and services to meet the needs of vulnerable populations to ensure appropriate use of hospital and medical resources. Last year, HARP onboarded two community health workers to provide non-medical case management to patients. Additionally, the HARP program was awarded a grant from the Maryland Department of Health's Center for Harm Reduction Services to reduce substance use related disability and deaths. This grant allowed HARP to become an Overdose Response Program, which allows the program to provide overdose education and prevention, such as naloxone distribution.

OPAT (Outpatient Parenteral Antimicrobial Therapy)

During the last year, the University of Maryland's Outpatient Parenteral Antimicrobial Therapy Program, which provides intravenous (IV) antibiotics, under Dr. Narayanan's direction as Medical Director, has managed more than 700 patients through the program. The program has collaborated with transitional care services to optimize monitoring and treatment

outcomes in patients discharged on antibiotics to skilled nursing facilities. Ongoing collaboration with the Department of Pharmacy looks at opportunities for antimicrobial stewardship for patients discharged on IV antibiotics. Data on OPAT outcomes in patients with substance use was published recently and presented at ID Week 2022.

OPAT collaborates with the HARP program to implement sequential treatment with long acting lipoglycopeptides (a kind of antibiotic) prescribed along with medication for opioid use disorder for patients hospitalized with infections related to opioid use. The group has initiated a new research study to use long-acting oritavancin (a lipoglycopeptide antibiotic) infusions to optimize care for patients with opioid use disorder funded by Melinta Therapeutics. This program continues to identify critical touch points during the medical care of such patients, including hospitalization and transitions of care to leverage these as opportunities to intervene and optimize treatment including linking patients to care, and improving outcomes infection treatment and overall patient health.

The JACQUES Initiative

FY22 has been the continuation of a post-COVID transition process within our program. The JACQUES Journey Center at UMMC Midtown Campus that closed to the public and staff in March 2020 due to COVID reopened within UMB's downtown campus at 520 W. Fayette St. The new space is open to the public by appointment, and its new location is in close proximity to the UMMC allowing easy access to patients at the hospital.

In accordance with the University of Maryland's guidelines, the JACQUES team resumed most face-to-face activities, such as HIV and hepatitis C rapid testing and prevention, as well as linking patients to medical services for clients living with HIV,

Care providers at THRIVE consult with a patient

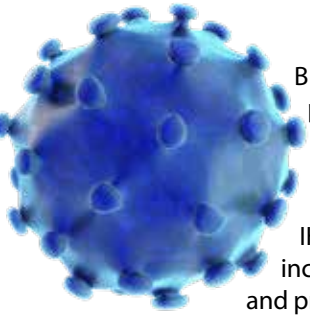
Members of THRIVE and the JACQUES Initiative at Baltimore's Pride parade

specifically focusing on newly diagnosed and patients who have fallen out-of-care. In collaboration with the Baltimore City Health Department, the JACQUES Initiative continues to link patients released from the Corrections Department (SOAR Program) to care services, as well as nPEP (non-occupational post-exposure prophylaxis; prevent HIV after being exposed to it) services for all clients referred from Mercy Medical Center in collaboration with the UMB's THRIVE clinic and other partner clinical programs. This year, new working collaborations were established that resulted in great opportunities to provide targeted HIV testing and education. Our new partners include the BD Health substance abuse treatment programs, the UMB Community Engagement Center, the Baltimore City Community College, Morgan State University, and the No Struggle No Success program (a program that combats prison recidivism), among others. There is no better way to end the fiscal year for The JACQUES Initiative than to supporting the LGBTQ+ community of Baltimore by participating in the Annual PRIDE parade, organizing a PRIDE celebration with the THRIVE clinic at UMMC Midtown in June.

Clinical Programs in Chronic Viral Hepatitis

The Division's hepatitis B and C treatment programs continue to expand under **Lydia Tang, MB, Bch**, Assistant Professor of Medicine, **Eleanor Wilson, MD,** Associate Professor of Medicine, and **Angie Price, DNP,** Director of the Clinical Research Unit, with locations at the Downtown and Midtown University of Maryland campuses, and the U.S. Veterans Affairs Maryland Health Care System (VAMHCS).

The Division has established a comprehensive clinical program to screen, connect, and treat patients with chronic hepatitis B infection, while simultaneously conducting translational research on the immune response during disease progression of hepatitis B viral persistence, with the aim of curing hepatitis



B chronic infection. In partnership with the Hepatitis B Initiative of Washington, D.C. (HBI-DC), IHV continues to increase awareness and provide screening for patients at risk for chronic hepatitis B in the Baltimore/D.C. metropolitan area, where a majority of patients have not been engaged in clinical care and due to their socioeconomic background. Since 2006, more than 20,000 people in the D.C.-metropolitan area were screened for hepatitis B and C by HBI-DC, with prevalence rates of 5% for hepatitis B and 3% for hepatitis C. 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 successfully completed a single-site phase 2 clinical trial evaluating a new experimental drug for chronic hepatitis B treatment. Dr. Tang's research, supported by a career development grant from the Institute for Clinical and Translational Research/Clinical and Translational Science Award (ICTR/CTSA), focuses on the effect of HIV and hepatitis B coinfections on response to controlling hepatitis B-specific immune responses in people with chronic hepatitis B. As an advocate for increased community engagement in hepatitis B research, Dr. Tang collaborates with primary care providers in the D.C. metropolitan area and established research clinics within community health care centers improving access to clinical trials.

As Director of the Hepatitis Clinic at the VAMHCS, Dr. Wilson participated in one of the largest hepatitis C treatment initiatives in Maryland, with more than 90% of VA patients treated in just over four years. In ongoing collaborative projects, she investigated post-hepatitis C treatment outcomes, including hepatitis B reactivation, fibrosis (liver scarring) progression, diagnosis of malignancies, and cardiovascular events in her VA patient group. Given the recent outbreak of hepatitis A in Baltimore City, Dr. Wilson participated in quality improvement efforts to ensure transplant patients, who are immunosuppressed and therefore at disproportionate risk of developing chronic hepatitis A infection, are protected against infections or these infections being transmitted to health care workers. At IHV, Dr. Wilson completed the largest single-site phase 2b clinical trial of an investigational combination of direct-acting antiviral drugs for treating relapsed hepatitis C, with more than 75 patients recruited from the Baltimore/D.C. area. Her ongoing projects include investigating outcomes of vaccination against viral hepatitis in patients with chronic viral infections, including HIV and hepatitis C, launching initiatives to expand screening and treatment access for at risk patients, and investigating methods to identify liver cancer (hepatocellular carcinoma) early in at-risk patients who have been cured of hepatitis C.

Community-Based Programs for Infectious Diseases and Opioid Use Disorder

The IHV's clinical and research activities reach beyond the University campus through its Research Initiative in Infectious Diseases and Substance Use (RIIS). RIIS is a grantee of the Partnership for HIV/AIDS Progress Comorbidities Program (PFAP) sponsored by the NIH Office of AIDS Research. Since 2015, this unique clinical research program has embedded Division providers and research staff in community-based settings such as a syringe service program in Washington D.C., an opioid treatment program in Baltimore, and a buprenorphine mobile treatment unit on the Eastern Shore. In these settings, Division staff and collaborators engage populations generally excluded from research, such as people who use drugs and gender and sexual minorities. They enact studies across the spectrum of translational research, including the *ANCHOR*, *GRAVITY*, *PATCH*, and *LOOP* protocols. These investigations seek to better understand the continuum of care of marginalized populations with or at risk for infectious diseases and implement treatment models to improve both infectious diseases and overall health outcomes. Clinical care and clinical research occur alongside translational investigations aimed at better understanding the impact of patient specific factors (such as opioid use disorder treatment and gender affirming hormone therapy) on infectious disease risk and outcomes. This program is led by Co-Directors, **Sarah Kattakuzhy, MD, MPH,** Associate Professor of Medicine, and **Elana Rosenthal, MD,** Associate Professor of Medicine, with program management by **Rachel Silk, RN, MPH,** clinical and research support by **Ashley Davis, NP, Amelia Cover, NP**, and Max Spaderna, MD, Assistant Professor of Psychiatry, and study coordination by **Rahwa Eyasu, NP**, **Emade Ebah, MPH,** and **Onyinyechi Ogbumbadiugha, MPH**.

Sarah Kattakuzhy, MD, MPH (L) and Elana Rosenthal, MD (R)

Dr. Kattakuzhy has expanded an opioid use disorder education initiative, obtaining SAMHSA (Substance Abuse

and Mental Health Services Administration) funding with the Schools of Nursing and Graduate Studies to bring opioid use disorder education and training to health professional students across UMB. Dr. Rosenthal serves as Principal Investigator for an NIH-sponsored, multi-site investigation to evaluate infectious diseases, opioid use disorder, HIV, and hepatitis C-related outcomes among adults who are hospitalized with infections associated with injection of opioids. Over the past two years, Dr. Rosenthal initiated a clinical program and research study of transgender individuals, using gender-affirming hormone therapy as a bridge to HIV treatment and prevention.

Drs. Kattakuzhy and Rosenthal, along with Dr. Narayanan, developed the Addictions and Associated Infections Track within the Infectious Disease Fellowship Program, and serve as research mentors to several faculty in the Division of Infection Diseases.

Clinical Research Unit (CRU)

The IHV Clinical Research Unit under the direction of Dr. Husson, Director, and Dr. Price, Deputy Director, continues to conduct high-impact research. The CRU leadership also includes **Amy Nelson, PhD, RN,** who manages new study start up, and Ms. Silk who manages the CRU's revenue and expenses. Under the leadership team, the CRU is comprised of a multidisciplinary team of one nurse coordinator, a pharmacist, a research nurse, one regulatory specialist, two study/research coordinators, three laboratory technicians, a phlebotomist/medical assistant, and a receptionist. During the past year, despite having to close research per UMB COVID-19 research restrictions, the CRU continued to manage a portfolio of 38 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, i.e., fatty liver disease), and COVID-19 with 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, hepatocellular carcinoma (liver cancer), and liver transplant. Additionally, the CRU continues to play an active role in bringing clinical therapeutic trials to patients hospitalized with COVID-19. The CRU has negative pressure space within the clinic in order to facilitate outpatient COVID-19 studies. The CRU continues to support the IHV's mission of advancing the understanding and treating chronic viral infections in a variety of people.

HIV Vaccine Program

The full-length single chain (FLSC) HIV vaccine was developed by IHV scientists under the leadership of **Robert C. Gallo, MD,** The Homer & Martha Gudelsky Distinguished Professor in Medicine, Co-Founder and Director of the IHV, Co-Founder and Chair of the Scientific Leadership Board at the Global Virus Network, **George Lewis, PhD,** The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, Director of the IHV Division of Vaccine Research, and **Anthony DeVico, PhD,** Professor of Medicine, in IHV's Division of Vaccine Research. The clinical component of the FLSC vaccine program is currently headed by Dr. Sajadi. The phase 1a (dose escalation), randomized, placebo-controlled, double-blinded clinical trial designed to evaluate the safety and immune response of the HIV vaccine in healthy volunteers without HIV infection was carried out at IHV and results were published in *Vaccine*. A phase 1b study using this vaccine is currently being carried out with the U.S. Military HIV Research Program in Thailand (study code RV546). These trials represent the true translational impact of IHV on meeting the needs of HIV-infected individuals.

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

The collaborations between IHV and the NIAID Intramural Program of the NIH continued during this academic year. NIAID clinical trials are recruited at IHV's CRU (Anthony Fauci, MD, Director of NIAID and Tae-Wook Chun, PhD, Chief of the HIV Immunovirology Unit). The Division has two NIH intramural bench-to-bedside grants.

The first grant aims to evaluate changes in immune activation using novel imaging techniques among patients undergoing therapy for hepatitis C with or without HIV coinfection and then compare radiological changes (through MRI) in people only infected with hepatitis C with HIV/hepatitis C coinfected patients before and after treatment, compared to patients only infected with HIV (IHV's **Poonam Mathur, DO, MPH,** Assistant

Professor of Medicine, and Henry Masur, MD, Chief of Critical Care Medicine Department at NIH).

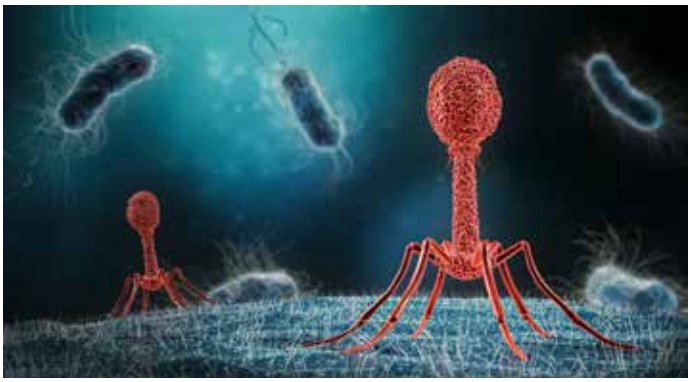
The second grant is a novel artificial intelligence-based algorithm developed for improving HIV patients' clinical adherence THRIVE clinic (also led by Dr. Mathur).

Finally, the research collaboration continues between Adriana Marques, MD, (Chief of Clinical Studies Unit, Laboratory of Clinical Immunology and Microbiology) from NIAID and the Lyme disease program at the Waterloo location's infectious diseases practice with an NIH IRB- (institutional review board)-approved protocol implemented at the UMB Waterloo practice. The IHV can enhance its research capabilities with this collaboration.

James Doub, MD

Bacteriophage Therapy

James Doub, MD, Assistant Professor of Medicine, Director of the Infectious Diseases Ambulatory Practice, is studying the use of bacteriophage (viruses that infect and kill bacteria) therapy in prosthetic joint infections to reduce the disability and death associated with these infections. He has treated 11 chronic prosthetic joint infection cases with bacteriophage therapy through the U.S. Federal Food and Drug Administration's (FDA) expanded access pathway with good success. However, many aspects of this novel therapeutic continue to be poorly understood. Consequently, he is collaborating with Ken Urish, MD, PhD, at the University of Pittsburgh and the NIH has awarded them an R01 to study the ramifications of sugar composition in the cell wall of *Staphylococcus aureus* on bacteriophage activity and ability to infect the bacteria.



Clinical Trials Program—The Division continues its rapid growth of clinical research initiatives that focus on novel, investigator-initiated clinical trials and remains to be one of the most dynamic clinical research programs. The major investigator-initiated clinical trials are highlighted here.

A Novel Model of Hepatitis C Treatment to Prevent HIV, Initiate Opioid Substitution Therapy, and Reduce Risky Behavior (ANCHOR)

ANCHOR is designed to evaluate the efficacy of using hepatitis C direct-acting antiviral treatment as an anchor to engage people who inject drugs in taking HIV prevention strategies including taking PrEP, opioid substitution therapy, and safer injection practices. Dr. Rosenthal leads this study funded by a Gilead research grant for 100 courses of hepatitis C therapy (sofosbuvir/velapasvir) and 100 courses of PrEP. A Merck investigator-initiated grant 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 NIDA to use their ecological momentary assessment (EMA) technology to assess cravings and adherence. This study is completed and in final analysis.

Best HBV (Hepatitis B Virus)

Dr. Chua is conducting a single center, open-label phase 4 study to evaluate the effiectiveness, safety, and tolerability of treatment with a fixed dose combination of bictegravir/emtricitabine/tenofovir alafenamide in adults with HIV and hepatitis B coinfection who are currently on antiretroviral therapy, with consistently low HIV viral levels for at least six months. This year he expanded the study to add an additional site with the Philadelphia Department of Public Health. This study was funded by Gilead Sciences as an investigator-initiated clinical trial.

CD24Fc Administration to Decrease LDL and Inflammation in HIV Patients, Both as Markers of Efficacy and Cardiovascular Risk Reduction (CALIBER)

Dr. Mathur is the Principal Investigator 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 to receive either doses of CD24Fc 240mg IV or placebo. This study is funded by an National Heart, Lung, and Blood Institute (NHLBI) Small Business Innovation Research grant (1 R44HL145964-01A1) partnering with OncoImmune, Inc with Nehal Mehta, MD, MSCE, FAHA, MS, Section of Inflammation

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Clinical Trials Program (continued)

and Cardiometabolic Diseases, NHLBI. OncoImmune successfully sold their product to Merck this year and the study has completed enrollment.

Cardiovascular Disease in HIV and Hepatitis C: Risk Outcomes after Hepatitis C Eradication (CHROME)

CHROME, led by Dr. Mathur is a study to follow the treatment of only hepatitis C and HIV/hepatitis C co-infected individuals. The study compared inflammatory markers and radiological changes (through MRI) in only hepatitis C-infected and HIV/hepatitis C co-infected patients before and after treatment, compared to only HIV-infected patients. This study is funded through a Merck investigator-initiated grant and an NIH Bench-to-Bedside Award.

Geomapping Resistance and Viral Transmission in Risky Populations (GRAVITY)

The goal of *GRAVITY* is to identify newly acquired cases of HIV and hepatitis C in high-risk populations, and to better understand the characteristics associated with viral transmission in Washington, D.C. Drs. Rosenthal and Kattakuzhy have obtained funding from NIH and Gilead Sciences in this investigator-initiated clinical trial to implement HIV and hepatitis C screening programs in those people who inject drugs, men who have sex with men, transgender individuals, and sex workers. This study is fully enrolled and in its data analysis phase.

CHOICE

With pilot funding from NIAID, NIH, Drs. Rosenthal and Kattakuzhy conducted a needs assessment of the care continuum of people with opioid use disorder admitted in four major hospitals in the USA for infectious diseases complications. Participating institutions include George Washington Hospital, Washington D.C., University of Maryland Medical Center, Baltimore, MD, Emory University Hospital, Atlanta, GA, and University of Alabama at Birmingham, Birmingham AL. The final analysis is in progress.

PATCH

Dr. Rosenthal has initiated a new clinical trial focused on combining care for transgender populations in Washington, D.C., and Baltimore. **Melanie Malave Sanchez, MD**, Assistant Professor of Medicine, has received NHLBI K12 funding for studying immune-mediated end organ disease in transgender people living with HIV on hormone replacement therapy.

HOPE in Action

Dr. Husson, along with the transplant surgery team and investigators from Johns Hopkins University, won an U01 award from NIAID to evaluate using 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 multicenter study. Through this study, the first HIV positive to HIV positive kidney transplant at the University of Maryland was successfully completed and preliminary data was published this year.

HIVCAT

Shashwatee Bagchi, MD, Assistant Professor of Medicine, is the Principal Investigator for a study investigating the cardiovascular complications of patients who have chronic hepatitis C infection, HIV infection, or both. She is supported by NHLBI K23 grant.

HIVTR CCR5 Clinical Trial

Dr. Kottilil in collaboration with other investigators from the University of California San Francisco received a U0-1 award from NIAID to evaluate using CCR5 blockade in HIV-infected kidney transplant recipients to increase kidney graft survival. This study completed enrollment this year and is continuing to follow study participants and collect data.

LOOP

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

Direct Lysis of Staph aureus Resistant Pathogen Trial (Disrupt)

Dr. Baddley is the site investigator for a phase 3 study evaluating the effectiveness and safety of exebacase, a novel direct lytic agent (breaks open the membranes of bacteria to kill it), in patients with Staphylococcus infection.

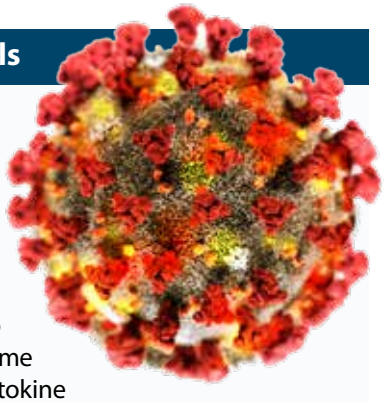
Salvage

Dr. Husson was the site investigator for the multicenter trial treating patients with HIV who have failed multiple treatment regimens. The study remains open.

SOLAR

Dr. Narayanan was the site investigator for the multicenter trial comparing the long-acting injectable HIV drug regimen of cabotegravir and rilpivirine to biktarvy alone for patients with well-controlled HIV. This study successfully completed enrollment this year.

COVID-19 Clinical Trials



CAN-COVID

Dr. Chua is the site investigator for a phase 3 randomized, double-blind, placebo- controlled study to assess the effectiveness and safety of canakinumab on cytokine release syndrome (colloquially known as a cytokine storm) in patients with COVID-19-induced pneumonia. The study completed enrollment and the findings were published in *JAMA* last year.

SAC-COVID

This study led by Dr. Kottilil uses the novel drug CD24Fc to examine if it may help to reduce multiple inflammatory cytokines (MIS-C) and protect lung tissue from the injuries and damage caused by an over reactive immune system. The results were published in the prestigious journal *The Lancet Infectious Diseases* in 2022.

Regeneron Monoclonal and Antibodies

Dr. Narayanan was the site investigator for the inpatient Regeneron study evaluating the efficacy of the monoclonal antibody casirivimab and imdevimab in patients hospitalized with COVID-19. Dr. Chua was the site investigator for the outpatient study evaluating the use of the monoclonal antibody to prevent COVID-19 infection in exposed, close contacts of persons infected with COVID-19.

SARS-CoV-2 Vaccine Responses among Solid Organ Transplant Recipients

Dr. Saharia has built a study group of transplant recipients who were vaccinated against SARS-CoV-2 either before or after their transplant. He collected samples to analyze their immune responses to the vaccine.

Laboratory-Based Programs

The Division's laboratory research program has three research aims: 1) Strategies to achieve a functional cure of viral infections (hepatitis B, HIV, etc.), 2) treat/prevent end organ disease due to chronic inflammation (liver, heart, brain), and 3) curtail co-occurring health conditions to improve disability caused by viral diseases. To achieve these aims, they conduct translational research using samples collected from subjects enrolled in various clinical protocols. They are funded by multiple sources, including NIH, the pharmaceutical industry, philanthropy, and institutional grants. Functional cure projects involve expanding understanding of the pathogenesis of viral persistence and immune dysfunction (**Alip Ghosh, PhD, MSc,** Research Associate of Medicine, **Arshi Khanam, PhD,** Research Associate of Medicine, and **Natarajan Ayithan, PhD,** Research Associate in Medicine) in patients with chronic hepatitis B and HIV infection. These projects are supported by clinical study groups of patients with chronic diseases (Drs. Tang, Wilson, and Schmalzle). Most patients with chronic viral infections suffer from ongoing end organ damage, an area of high clinical and scientific relevance. In this regard, their translational research is focused on studying metabolic dysfunction triggered by receptor dysregulation that leads to immune dysfunction and activation. Together, these processes contribute to accelerated aging and end organ damage. In this regard, they study approaches to improve metabolic and mitochondrial function by enhancing NAD levels, improving antiviral immune function, and dampening inflammation (Drs. Mathur and Ghosh). Finally, patients with chronic viral infections also have co-occurring medical conditions that contribute to increased death and disability. Their research uses samples collected from a well-characterized study group of people living with infectious diseases (Drs. Kattakuzhy and Rosenthal) and evaluates immune function against the pathogen, as well as characterizes immune dysregulation (Drs. Ghosh and Khanam) that could put them at heightened risk for reinfection, poor vaccine response, and bad outcomes from COVID-19. These projects are supported by multiple NIH grants (NIAID, NIDA, National Institute on Alcohol Abuse and Alcoholism (NIAAA), and NHLBI and pharmaceutical support (Arbutus Pharmaceuticals, Gilead Sciences Inc.)

Alonso Heredia, PhD

Heredia Laboratory

Due to combination antiretroviral therapy (cART), patients with HIV are living longer, but increasingly often they necessitate treatment for co-occurring conditions, 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 the laboratory of **Alonso Heredia, PhD**, 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. In a related project, also funded by NCI, Dr. Heredia, in collaboration with Kevin Cullen, MD, Marlene and Stewart Greenebaum Distinguished Professor of Oncology, of the University of Maryland Greenebaum Cancer Center, and **Mohammad Sajadi, MD**, Professor of Medicine, is investigating replacing cART with broadly neutralizing antibodies to enable effective lung cancer immunotherapy in HIV-infected patients.

Another area of active investigation in Dr. Heredia's lab is to find a cure for HIV. In collaboration with Fabio Romerio, PhD, from Johns Hopkins University, Dr. Heredia is a Co-Investigator in the NIAID funded project "*Sustained HIV remission via sequence-specific epigenetic silencing of latent proviruses.*" In this project, Dr. Heredia is assessing the impact of HIV antisense transcript expression on silencing of HIV proviruses both in tissue culture and in humanized mice. In a related project, Dr. Heredia is collaborating with the team of **Linda Chang, MD, MS**, Professor Diagnostic Radiology and Nuclear Medicine in UMSOM and IHV affiliate, on a NIDA-funded project that seeks to eliminate HIV in the brain by a novel technology that transiently opens the blood-brain barrier to allow efficient delivery of cART and CRISPR to the brain.

Yet another area of research in Dr. Heredia's laboratory is developing effective antibodies against HIV. In collaboration with Dr. Sajadi, he is a Co-Investigator in the project "*Engineering of broadly reactive seroantibodies against HIV-1,*" 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 pan-neutralizing monoclonal antibodies in humanized mice. In another similar project, "*Impact of antibody effector function diversity on antiviral activity in situ,*" funded by NIAID, he is collaborating with **Anthony DeVico, PhD**, Professor of Medicine, **George Lewis, PhD**, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, IHV Deputy Director, Director of the Division of Vaccine Research, Professor of Microbiology and Immunology, and **Krishanu Ray, PhD**, Associate Professor of Biochemistry and Molecular Biology, from the Division of Vaccine Research in the IHV. 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.

More recently, Dr. Heredia has begun a collaboration with Dr. Gallo, **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Director of the Division of Virology, Pathogenesis, and Cancer, Interim Director of the Division of Immunotherapy, Drs. Daniel Zagury and Helene Le Buanec, both of the Université de Paris, Institut de Recherche Saint-Louis, Paris, France, to develop a vaccine against HIV that is based on inducing of specific CD8 T-cells responses that target infected CD4 T-cells.

Sajadi Laboratory

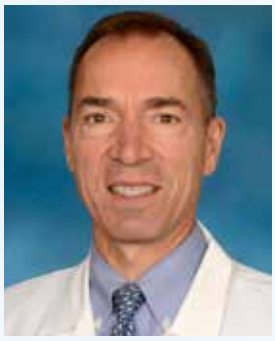
Mohammad Sajadi, MD

Dr. Sajadi and his lab focus on adaptive immunity in HIV-infected individuals with broadly neutralizing antibodies. He works closely with Drs. Lewis and DeVico in the Division of Vaccine Research. Dr. Sajadi has five active grants, 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 lack of durable antibody responses in infections such as HIV-1 and SARS-CoV-2.

Bagchi Laboratory

Dr. Bagchi continues her focus on investigating the cardiovascular complications of patients who have chronic hepatitis C infection, HIV infection, or both. She collaborates widely with numerous investigators from multiple institutions throughout the United States. She has multiple projects she is engaged in to address this clinical problem and consequent research questions, ranging from a group study looking back over data collected from outpatient, HIV-infected patients in Baltimore, a prospective study among HIV or hepatitis C infected and HIV/hepatitis co-infected individuals to evaluate inflammatory mechanisms. 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's Institute of Clinical and Translational Research "*Systemic and Epicardial Fat Inflammation and Local Coronary Atherosclerosis in HCV and HIV Patients.*"

Stamatos Laboratory



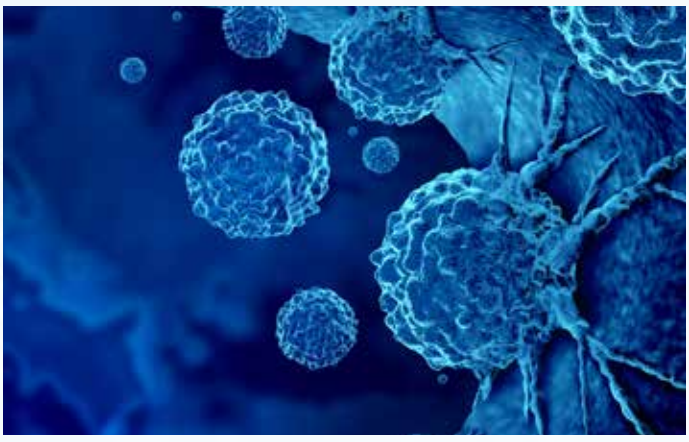
Nicholas Stamatos, MD, PhD

The laboratory of **Nicholas Stamatos, MD, PhD,** Associate Professor of Medicine, conducts research focused on understanding how controlling the carbohydrate content of cell surface proteins influences the functional capacity of cells of the immune system. In particular, his laboratory studies how changes in the polysialic acid (polySia) content of specific cell surface glycoproteins on neutrophils, lymphocytes, monocytes, monocyte-derived dendritic cells, and macrophages influence the immune capacity of these cells. He conducts experiments using a mouse 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 have 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. One possible explanation is more efficient phagocytosis by alveolar (in the lungs) macrophages and neutrophils that lose their cell surface polySia during early stages of pneumococcal infection. Microfluidic chamber migration assays and intravital microscopy of the pulmonary vascular bed of infected mice are some of the methods being used to elucidate the role of polySia in leukocyte recruitment. The overriding 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 NIAID 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.

Aberrant glycosylation is a hallmark of malignant cells and increased polysialylation has been associated with metastasis and aggressiveness of various brain and lung tumors. Dr. Stamatos' laboratory has also begun evaluating the expression of polySia in acute myeloid leukemia patient samples and in breast cancer cell lines with the goal determining a potential role in disease progression. His lab has shown that letrozole resistance leads to an upregulated expression of polySia in MCF-7 breast cancer cells and that this glycan promotes migration in migration assays. The polySia carrier in these cells is not known, but does not appear to be one of the few known polysialylated proteins. They expect that identifying this polySia carrier protein will help reveal the role of polySia in regulating its function.

Although much is known about glycosylation of HIV envelop proteins, relatively little is known about how glycosylation of proteins on the surface of permissive lymphocytes affect infection. Work from his laboratory previously demonstrated that removal of sialic acid from the surface of peripheral blood mononuclear cells using an enzyme from bacteria that cuts it off the surface promoted infection with HIV-1. Recently, they 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 novel polysialylated protein(s) expressed by activated lymphocytes and to define the mechanism by which it/they promote(s) binding of HIV-1 to the cell surface. Dr. Stamatos' lab is collaborating with Dr. Heredia's lab to determine whether humanized mice that are transplanted with human lymphocytes, in which polySia expression is silenced, are relatively resistant to infection with HIV. The results from their studies are expected to identify a novel target for treating 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. To date, only eight mammalian proteins are known to carry this unique glycan. 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 they identify on immune cells will have equally significant roles in cell function.



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Epidemiology and Prevention

Man Charurat, PhD, MHS

The Division of Epidemiology and Prevention, led by **Man Charurat**, **PhD, MHS,** Professor of Medicine, and Epidemiology and Public Health and Director of the Center for International Health, Education, and Biosecurity (Ciheb), continues a focus on research. The Division published 91 manuscripts in peer-reviewed journals in FY22 and 14 faculty led 20 federal research awards.

Alash'le Abimiku, PhD

Alash'le Abimiku, PhD, Professor of Medicine, Executive Director of the International Research of Excellence at the IHV-Nigeria (IHV-N), received an NIH data science research award under NIH's new initiative for Harnessing Data Science for Health Discovery and Innovation in Africa (DS-I Africa). Under the program, the NIH has issued 19 awards to support research, ethics, and training activities. Dr. Abimiku's award entitled "*Role of Data Streams in Informing infection Dynamics in Africa (**INFORM AFRICA**)* (U54TW012041)," is a research hub involving data from Nigeria and South Africa to study SARS-CoV-2 and HIV with the goal of using data to improve pandemic preparedness. Dr. Charurat is a Principal Investigator of this award as well, along with esteemed investigators Tulio de Oliveira, PhD, of Stellenbosch University, Chenfeng Xiong, PhD, MA, MS, of Villanova University, and Vivek Naranbhai, MD, PhD, DPhil, of the Centre for the AIDS Programme of Research in South Africa. Finally, Dr. Abimiku is continuing her NIH research "*Breast Milk Microbiota Influence on Infant Immunity and Growth* (***BEAMING***)" (U01HG009783), "***SickleGenAfrica***" (U54HL141011), and "*Institute of Human Virology Nigeria -H3Africa Biorepository Initiative (**I-HAB**)*" (U24HG007008). She has been successful in getting additional funding as supplements to these grants to continue those research activities (U24HG007008-09S1, U01HD094658-05S1), as well as expanding effects of environmental factors and climate change (U54TW012041-02S1) and studying SARS-COV-2 immune responses in vaccinated Nigerian women (U01HD094658-05S2).

Rebeca Nowak, PhD

Rebecca Nowak, PhD, Assistant Professor of Epidemiology and Public Health, received two new NIH awards in FY22. She was awarded "*Integrated Model for the Prevention of Anal Cancer using Screen and Treatment for HSIL*" (U01CA275053) from NIH's National Cancer Institute (NCI). On this award, Dr. Nowak will be working with Sylvia Adebajo, MBBS, MS, MPH, Maryland Global Initiatives Corporation-Nigeria Country Director, to adopt training procedures to transfer knowledge and conduct anal cancer screening and treatment as intended in men who have sex with men living with HIV in Nigeria. Dr. Nowak was the first to introduce screening and treatment of anal precancer, high-grade squamous intraepithelial lesions (HSIL), in Nigeria four years ago.

Building on her prior research, she uses implementation science to develop a systematic approach for evaluating HSIL screening and treatment in an HIV care setting for a low-to-middle-income country. Additionally, Dr. Nowak was awarded "*Evaluating immunity of oral HPV to understand lower oropharyngeal cancer risks among MSM*" (R21DE31516). For this study, she is leveraging archived samples collected from 620 participants from the TRUST study group started by Dr. Charurat and the U.S. Department of Defense U.S. Military HIV Research Program RV368 study group of men who have sex with men and transgender women in Nigeria. This study will evaluate whether high exposure via mucus membranes contributes to systemic immunity and alters the prevalence of human papillomavirus infection in the mouth. Dr. Nowak has completed data collection and is in the analysis phase of her

NIH-funded K award, "*Role of anal microbiota, local cytokines, and HIV in the persistence of high-risk human papillomavirus (**HR-HPV**)*" (K07CA225403).

Nadia Sam-Agudu, MD

Nadia Sam-Agudu, MD, Associate Professor of Pediatrics, Senior Technical Advisor of Pediatric HIV at IHV and International Senior Technical Advisor of Pediatric and Adolescent HIV at IHV-N, working with Dr. Abimiku, received an NIH Fogarty International Training grant "*Expanding the pool of Independent Investigators in implementation Science in Nigeria through HIV Research Training*" (D43TW01228). This award builds upon 15 years of a UMB-IHV-N partnership to train Nigerian researchers to build capacity in West Africa in HIV/AIDS research. Dr. Sam-Agudu continued in FY22 to work on "*Adolescent Adult Patient-centered HIV Transition (**ADAPT**)*" along with Co-Principal Investigators Vicki J. Tepper, PhD, Professor of Pediatrics and Division Head of Immunology and Rheumatology Pediatrics of the University of Maryland School of Medicine (UMSOM), and Dr. Charurat (R01HD089866). The *ADAPT* study has enrolled 300 adolescents living with HIV across six study sites in North-West and North-Central Nigeria to examine the impact of a tailored peer support transition to adult HIV care. Finally, in FY22, Dr. Sam-Agudu continued the study "*Central and West Africa Implementation Science Alliance (CAWASI)*" funded by CRDF Global (formerly the U.S. Civilian Research and Development Foundation) (G202012-67153) work to develop an implementation science toolkit for early investigators from Cameroon, Democratic Republic of the Congo, Ghana, and Nigeria.

Cristina Cairo, PhD

Cristiana Cairo, PhD, Assistant Professor Medicine, continued her NIH study with Miriam Laufer, MD, Professor of Pediatrics, "*Impact of in-Utero HIV exposure on infant T- and B-cell responses in Malawi*" (U01HD092308) in FY22. The study characterizes T- and B-cell responses to routine immunization antigens in infants born to three different study groups of women: women with undetectable HIV viral load before conception and through pregnancy; women with high HIV virus levels, diagnosed late in pregnancy; and women with no HIV infection. The goal is to determine whether the extent of immune perturbations in HIV-exposed uninfected infants correlates with the degree of exposure to HIV viral replication during gestation. Dr. Cairo is also working with Marcela Pasetti, PhD, Professor of Pediatrics, on an NIH study that Dr. Pasetti leads, "*Mechanisms of protection against Shigellosis in Children*" (R01AI167367). Shigella species are a major global cause of diarrhea and dysentery, and this study investigates the continuum of Shigella immunity in children to define maternal antibodies (Ab) that help prevent shigellosis during the first months of life and the immune responses the children acquire post-exposure that reduce the risk of infection after the 2-year-old mark. In the context of these studies that rely on precious newborn and infant samples, Dr. Cairo and David Rach, a PhD candidate in the Molecular Microbiology and Immunology graduate program, employ a state-of-the-art full-spectrum cytometry (measuring numbers and characteristics of cells) platform to enable detailed and comprehensive analyses with limited cell numbers. Mr. Rach developed cytometry panels that allow the simultaneous assessment of 25-30 markers and provide critical information on activation, differentiation, and function for multiple T- and B-cell populations (including rare subsets), thus maximizing the use of clinical specimens.

Marie-Claude Lavoie, PhD, MSc

Marie-Claude Lavoie, PhD, MSc, Assistant Professor of Epidemiology and Public Health, is the Director of Strategic Information and Evaluation for Ciheb. As a new faculty member in FY22, Dr. Lavoie recently joined the ***LIVE*** project or the Living Analysis of HIV Implementation Science in low-to-middle-income countries led by Elvin Geng, MD, MPH, at Washington University in St. Louis. The *LIVE* project aims to generate methodologically robust rapid and living reviews evaluating the effects of HIV intervention implementation strategies on the HIV cascade to advance implementation science evidence synthesis and to contribute to the HIV response.

Kristen Stafford, PhD, MPH, Associate Professor of Epidemiology and Public Health, Deputy Director of Ciheb, initiated a Centers for Disease Control and Prevention (CDC)-funded study in Botswana entitled "*COVID-19 Vaccine Implementation & Evaluation*" led by Principal Investigator and Botswana Country Director Ndwapi Ndwapi, MD, (NU2GGH002258) in FY22. With the demand for COVID-19 vaccination decreasing, understanding current barriers

Kristen Stafford, PhD, MPH

to vaccination is necessary. Hence, this study conducts rapid community assessments using focus group discussions with groups of vaccinated and unvaccinated people to develop a tool kit to assist healthcare workers in their conversations with patients, to develop clear messaging to the general public. Twelve focus group discussions have been conducted with household heads, young adults 18-24 years living with parents and guardians, healthcare workers, and community leaders. Data is currently being analyzed. In FY22, Dr. Stafford also continued to guide the population-based HIV impact assessment (***PHIA***) in Zambia (***ZAMPHIA***) and Botswana (***BAIS V***) under the award "*Regional Strengthening of HIV-focused Population-base National Surveys and Size Estimations* ***(RESPONSE)***." Dr. Charurat is the Principal Investigator and Dr. Stafford is the Technical Director of this study (NUGGH002172). The *PHIA* household-based HIV surveys identify the prevalence and incidence of HIV, assess the coverage and impact of HIV services, characterize HIV-related risk behaviors, and assess progress towards achieving the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 targets (HIV testing, treatment, and viral control rates) on national and regional levels using a nationally representative sample of adults aged 15 years and older. Approaches that link people to care ensure that people who test positive for HIV through the survey are efficiently connected to care and treatment. The *BAIS V* data shows that among adults (15-64 years old) in Botswana living with HIV, 95.1% were aware of their status, 98% of those aware of their status were on antiretroviral therapy, and 97.9% of those on antiretroviral therapy achieved viral load suppression. Based on these results, Botswana has met the more ambitious 95-95-95 targets set as a fast-track strategy to end the HIV/AIDS epidemic by 2030. The *ZAMPHIA* data will be released in FY23.

BAIS V Project

Patrick Dakum, MBBS, MPH

Patrick Dakum, MBBS, MPH, Associate Professor of Epidemiology and Public Health, Chief Executive Officer at IHV-N, continued to lead the CDC-funded U.S. President's Emergency Plan for AIDS Relief (PEPFAR) public health program in Nigeria through the CDC-funded award *"ACTION to Control HIV Epidemic through Evidence (**ACHIEVE**)"* (NU2GGH002099). In FY22, through the *ACHIEVE* award, Dr. Dakum continued to deliver HIV services to four states in Nigeria, worked with the *DREAMS* initiative to reduce HIV/AIDS in adolescent girls and young women, brought HIV services to almost 10,000 men who have sex with men and transgender individuals in Nigeria between the ages 10-24 years old, and expanded HIV services to pregnant people in their communities.

Dr. Dakum's DREAMS program in Ciheb Zambia trained mentors to identify gender-based violence

Lottie Hachaambwa, MB, ChB, Assistant Professor of Medicine, Chief Executive Officer at Ciheb Zambia, investigates the feasibility of an integrated intervention to reduce advanced HIV deaths in the study "*Inpatient Package to Reduce HIV and AIDS-related death in Zambia (**IPADZ**)*" led by Principal Investigator Michael Vinikoor, MD, of the University of Alabama in Birmingham (R34MH121103). In the Adult Acute Flaccid Paralysis Prevalence and Etiologies in Lusaka (***APPEL***) study, he collaborates with Michelle Kvalsund, DO, MS, at the University of Rochester to address knowledge gaps in the common causes and common risk factors for adult acute flaccid paralysis in Zambia.

Lottie Hachaambwa, MB, ChB

Dr. Hachaambwa and Dr. Claassen, both working in Zambia, were instrumental in developing a national COVID-19 case-management guidelines for the Zambian Ministry of Health.

Cassidy Claassen, MD, MPH, Associate Professor of Medicine, Ciheb's Global Health Fellowship Director, is Principal Investigator of "*The Re-engagement at Discharge (**Re-Charge**)*" (R34MH122265). The *Re-Charge* study seeks to better understand the barriers to HIV care for patients after being discharged from the hospital. He will then translate these findings to adapt a community health worker intervention to support the post-hospital continuum of care by addressing patient- and system-level barriers. Finally, he will test this intervention in a pilot implementation study. Ultimately findings from this study are expected to help maintain HIV treatment adherence and prevent loss of follow-up.

Cassidy Claassen, MD, MPH

Peter Memiah, DrPH

Peter Memiah, DrPH, Associate Professor of Medicine, Director of Continuous Quality Improvement for Ciheb, continued investigating adolescent mental health in Kenya in FY22. His study is entitled "*Reaching, Engaging Adolescents and Young Adults for Care Continuum*" (***REACH-Mental Health***). His other study in Kenya, which he co-leads is ***AGILE***, "*Accelerating access to Gender-Based Violence Information and Services Leveraging on Technology Enhanced Chatbot*." *AGILE* is a messenger chatbot that can converse with users via WhatsApp. The *AGILE* chatbot will screen for gender-based violence symptoms, quiz users on their risk, and, if needed, immediately recommend services. The chatbot is built around the nationwide adolescent One2one platform that includes a call center hotline operated by counselors that enable wrap-around services, such as referral to other services, including post-exposure prophylaxis and psychological counseling. The chatbot will deliver tailored self-care conversations to gender-based violence survivors and those at risk. The study will use implementation science frameworks to measure outcomes. Both studies are conducted in collaboration with the University of Maryland, Baltimore's (UMB) Schools of Medicine and Social Work, LVCT Health, and Kenya's Ministry of Health.

Shenghan Lai, MD, Professor of Epidemiology and Public Health, has recruited and followed approximately 1,500 African American adult men and women in Baltimore since 2000, 950 of whom are HIV infected, to investigate the effects of HIV and cocaine use on HIV-associated co-occurring health conditions in an NIH-funded study "*Effects or HIV, Cocaine, and Prolonged ART use on Subclinical Cardiovascular Disease (**HEART STUDY**)*" (U01DA040325). Dr. Lai and his team found that cocaine use may induce/accelerate undetected coronary artery disease and other HIV-associated co-occurring health conditions. **Hong Lai, PhD, MPH,** Associate Professor of Epidemiology and Public Health, continued her quantitative work on the NIH award "*Evaluate the Data on the Impact of Cocaine Abstinence or Reduced Use on Radiomic Features of Noncalcified Coronary Plaques in HIV-Infected Cocaine Users with Silent Coronary Artery Disease*" (R21DA048780). Recently, working with Dr. S Lai, she began investigating the impact of cocaine use on the differences in male/female HIV-associated neurocognitive disorders.

Niel Constantine, PhD, Professor of Pathology, has been active in the diagnostic arena for more than 43 years. His work includes evaluating diagnostic test systems for detecting infection by HIV, hepatitis B and C, Cryptococcus, and syphilis, and recently assessing COVID-19 in-home and commercial rapid assays. He also investigates the effect of infectious agents on various psychiatric disorders and assists in developing unique assays using antibodies from sharks.

Niel Constantine, PhD

Man Charurat, PhD, MHS

Dr. Charurat is the Principal Investigator of five new NIH awards in FY22. Through NIH Fogarty International Center's ***LAUNCH*** initiative (Launching Future Leaders in Global Health), Dr. Charurat was awarded "*Integrated Networks of Scholars in Global Health Research Training (**INSIGHT**)*" (D43TW012274). *INSIGHT*, a UMB-led consortium with Janet Turan, PhD, of the University of Alabama, Anna Maria Mandalakas, MD, PhD, MSEpi, of Baylor School of Medicine, and Vishwajit Nimgaonkar, MD, PhD, of the University of Pittsburgh, joined Fogarty's flagship global health scholars program with six other university consortia to develop or expand global health research training programs for U.S. postdocs, U.S. pre-docs, and low- and middle-income country postdocs. Dr. Charurat also received in FY22 the award "*Impact of Non-B*

Nicaise Ndembi, PhD, MSc

*HIV-1 Subtype on Second Line Protease Inhibitor Regimens in Africa (**INSPIRE**)"* with **Nicaise Ndembi, PhD, MSc,** Adjunct Associate Professor of Medicine (R01AI147331). *INSPIRE* aims to advance understanding of the effects of drug resistance mutations and naturally occurring polymorphisms in regions other than reverse transcriptase or protease in non-B subtype HIV-1 strains. The study intends to identify factors that predict when and how medications fail to suppress HIV for patients on protease inhibitor antiretroviral medications that may increase their risk of developing resistance on a third-line treatment regimen. In FY22, Dr. Charurat was awarded "*Synergistic epidemics of non-communicable diseases, stigma, and economic inequalities among sexual and gender minorities (SGM) living with HIV in Nigeria"* (R01HL65686). This study, in collaboration with Co-Principal Investigators Typhanye Dyer, PhD, MPH, Associate Professor of Epidemiology and Biostatistics of the University of Maryland College Park, and Rachel Robinson, PhD, MA, of American University, uses syndemic (adverse interactions between diseases and social conditions) frameworks to explain elevated HIV risk in sexual and gender minority populations. The study builds on Dr. Charurat's ***MSM TRUST*** study group and will examine the association between syndemic factors and HIV non-communicable disease outcomes, assess whether and how community-level and structural-level factors exacerbate the syndemic, and determine whether the syndemic characterized for HIV non-communicable disease prevalence and outcomes is associated with risk of disengaging from care continuums. Dr. Charurat will also lead Project 1 for *INFORM AFRICA* (details above under Dr. Abimiku). *INFORM AFRICA* Project 1 will look at COVID-19 transmission and risks. Dr. Charurat and his team are analyzing to assess viral phylogenetic changes and population structure over time within select Sub-Saharan African counties; measuring the networks of asymptomatic-indexed case finding, their characteristics, and contribution to transmission potential, and establishing spatially explicit relationships between environmental conditions, population density, and spatial drivers for multi-scale (e.g., regional to village) transmission and risk. Finally, in FY22, Charurat received funding from NIH's National Cancer Institute for *"Botswana Smoking Abstinence Reinforcement Trial (**BSMART**)"* (U01CA275048). Along with Dr. Ndwapi, Dr. Charurat will investigate smoking cessation interventions in Botswana for HIV clients. *BSMART* uses a type 2 hybrid effectiveness-implementation study design to implement the SBIRT (screening, brief intervention, and referral to treatment) intervention in HIV clinics, followed by treatment with a smoking cessation medication. The tobacco epidemic is one of the most significant public health threats facing Botswana, which has the highest HIV and tobacco use prevalence in Sub-Saharan Africa. With lung cancer the most common non-AIDS-defining malignancy among people living with HIV, accounting for 20% of the cancer burden, *BSMART* is poised to assist the Government of Botswana in smoking cessation goals for its citizens.

Data Science for Health Discovery and Innovation in Africa (DS-I Africa) Consortium meeting for a presentation as part of the INFORM Africa project.

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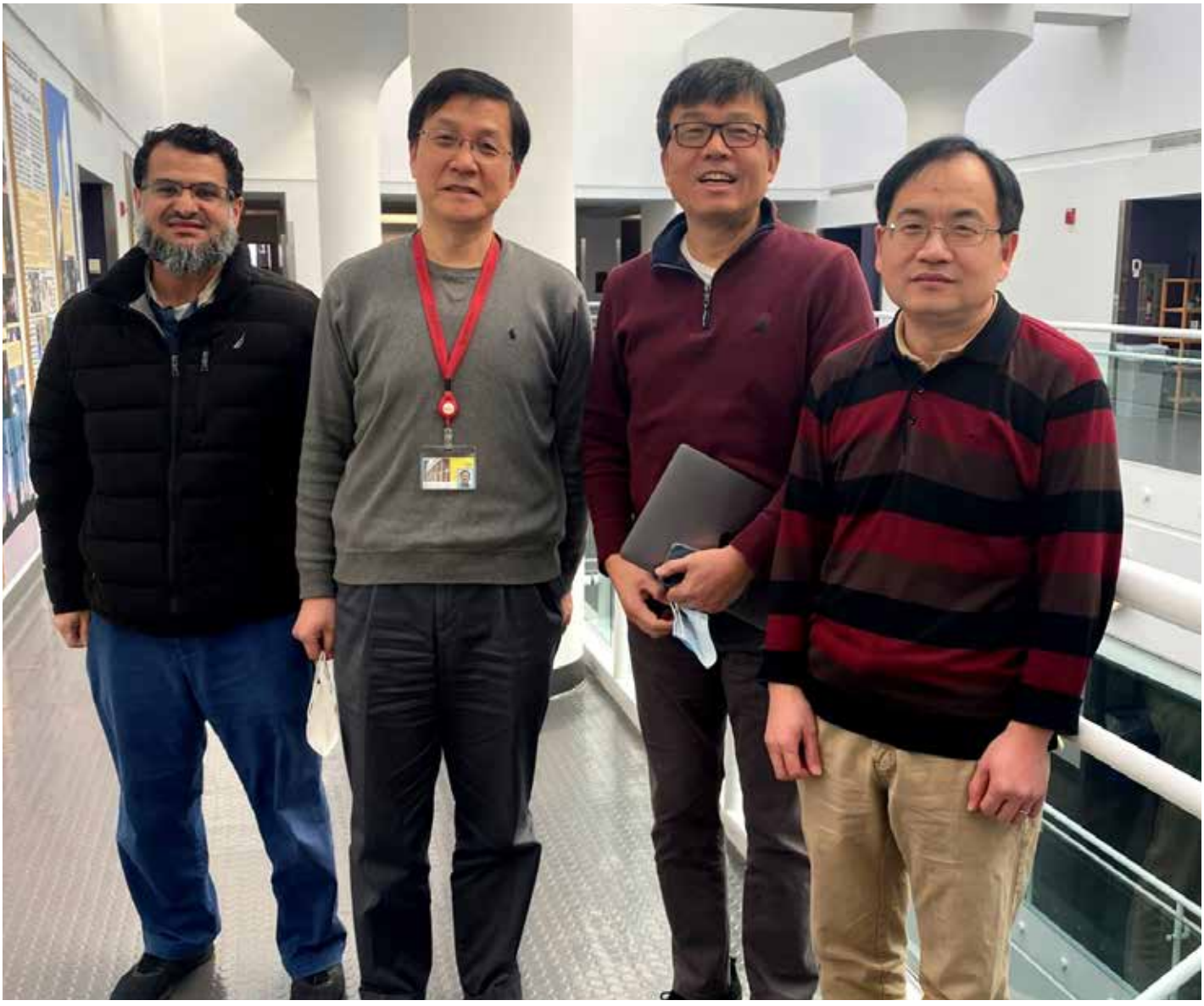
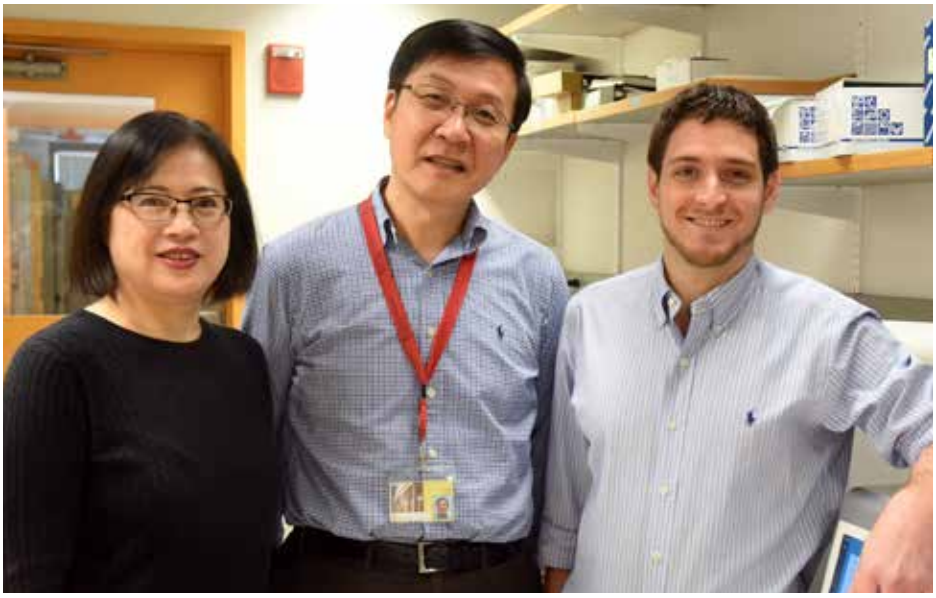
Immunotherapy

Lishan Su, PhD

The Division of Immunotherapy, currently led by Acting Director **Lishan Su, PhD,** The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology and Microbiology and Immunology, continues its fundamental research on cancer immunology and immunotherapy.



(L to R) Musleh Muthana, PhD, Yin Wang, PhD, Lishan Su, PhD, and Degui Geng, PhD



(L to R) Yan Liu, PhD, Yin Wang, PhD, and Chris Bailey, PhD

Liu Laboratory

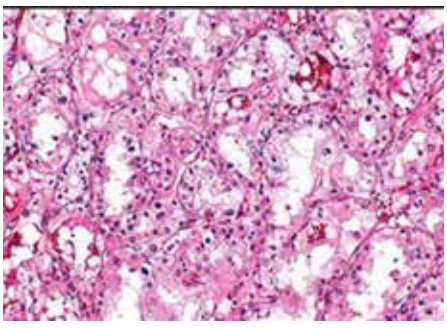
Yan Liu, PhD, Assistant Professor of Surgery, focuses primarily on cancer research, with an emphasis on understanding key signaling pathways associated with cancer malignancy and progression. Her research has covered multiple types of cancers including brain tumors, pediatric cancers, leukemia, and breast cancer. In FY22 alone, she has published three papers, and she has served as corresponding author on two of them.

HIF-1α-PDGF-D-PDGFR Axis in Glioblastoma

Glioblastoma multiforme (GBM) remains the most daunting challenge in cancer therapy. The Liu laboratory showed that hypoxia-inducible factor 1α (HIF-1α) binds to the PDGF-D proximal promoter and PDGFRα intron enhancers in GBM cells to induce their expression and maintain constitutive activation of the PDGF-D/PDGFR signaling pathway. PDGF-D-PDGFRα interaction increases protein levels and activity of HIF-1α, which governs the expression of growth factors, receptors, and substrates for constitutive AKT activation in U251 GBM cells under normal oxygen conditions. The Liu lab's data has shown that HIF-1α governs the constitutive activation of the PDGF-D-PDGFRα-AKT signaling pathway in an autocrine feed-forward manner, which could integrate with the EGFR-ERK pathway and the tumor microenvironment in GBM malignancies. Liposomal echinomycin, a DNA-binding competitive inhibitor of HIF-1α, induces apoptosis of GBM cells and inhibits tumor growth in xenograft models of GBM. Her data revealed that HIF-1α is a hub for GBM malignancy and suggests that single-agent targeting of HIF-1α alone may provide an effective therapy for GBM. These observations have been published in *Journal of Experimental & Clinical Cancer Research*.

HIF-1α-IGFBP2-IGFA Axis in Wilm's Tumor

Pediatric cancers, such as Wilm's tumor, a rare kidney cancer, have been another major area of interest for Dr. Liu. For patients with anaplastic (cells divide rapidly and do not resemble healthy cells) Wilms tumor (WiT), metastasis and recurrence are common, and prognosis is generally poor. Novel therapies are needed for patients with this type of WiT. Work by Dr. Liu showed that the HIF-1α-IGF binding protein 2 (IGFBP2) axis and the tumor-specific IGF1A are key players for constitutive activation of IGF1-AKT signaling leading to the tumor's malignancy. HIF-1α and IGFBP2 are highly expressed in the majority of WiT patient samples. Pharmacologic targeting of HIF-1α by echinomycin delivered via nanoliposomes could efficiently restrain growth and metastasis of patient-derived relapsed anaplastic WiT xenografts. In her studies, liposomal echinomycin was more potent and effective in inhibiting WiT growth than vincristine in an anaplastic WiT mouse model and eliminated metastasis by suppressing HIF-1α targets and the HIF-1α-IGFBP2 axis, which governs IGF1-AKT signaling. Her studies also introduced the first mouse model of metastatic WiT. The data have been published in *Oncogene*.



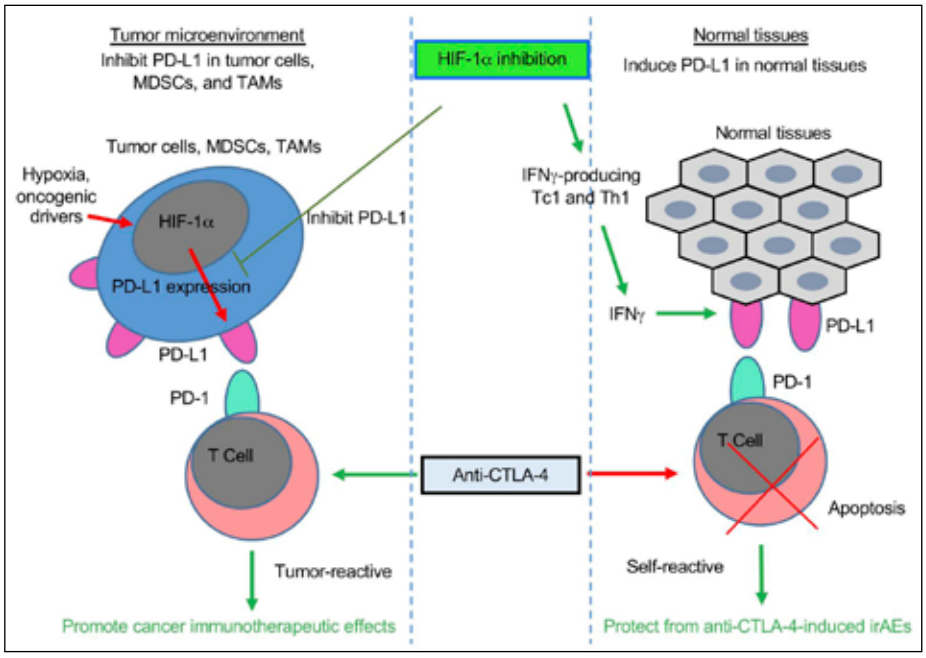
Wilm's Tumor

Wang Laboratory

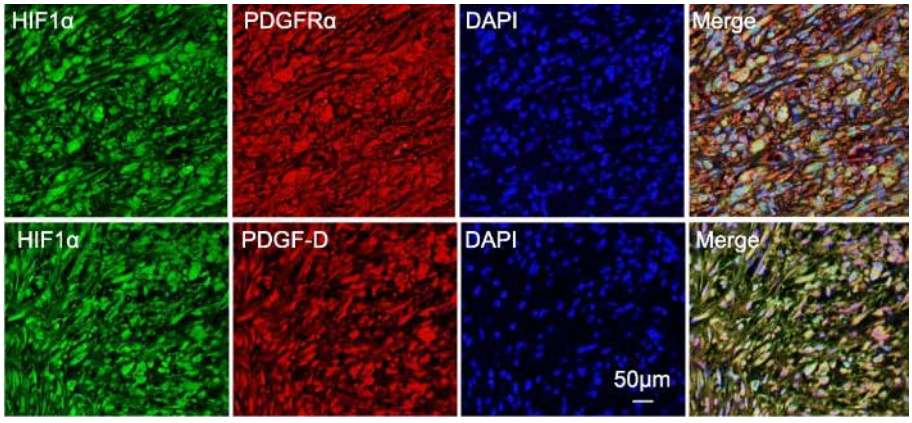
Led by **Yin Wang, PhD**, Assistant Professor of Surgery, the Wang laboratory's research has focused primarily on understanding underlying mechanisms of cancer and applying their discoveries to identify and develop novel therapeutic strategies with high translational potential. Dr. Wang's lab has made great achievements in understanding critical roles of the transcription factor hypoxia-inducible factor 1α (HIF-1α) in human disease. The Wang Lab has published four papers in this last year with most of the publications highlighting central roles for HIF-1α in cancer therapy and cancer immunotherapy. A summary of the accomplishments and progress for FY22 is as follows, including current research.

HIF-1α in Immunotherapy

A combination of cancer immunotherapy using anti-CTLA-4 plus anti-PD-1/PD-L1 antibodies is the most effective but cause a high incidence of immune-related adverse events (irAEs). Dr. Wang's group reported that targeting of HIF-1α suppressed PD-L1 expression on tumor cells and tumor-infiltrating myeloid cells, but unexpectedly induced PD-L1 in normal tissues by an IFN-γ-dependent mechanism. Targeting the HIF-1α/PD-L1 axis in tumor cells reactivated tumor-infiltrating lymphocytes and caused tumor rejection. The HIF-1α inhibitor echinomycin strengthens the cancer immuno-therapeutic effects of anti-CTLA-4 therapy, with effectiveness comparable to that of anti-CTLA-4 plus anti-PD-1 antibodies. However, while anti-PD-1 worsened the adverse events triggered by ipilimumab, echinomycin protected mice against these events by increasing PD-L1 levels in normal tissues. The Wang lab's data suggests that targeting HIF-1α fortifies immune tolerance of the PD-1/PD-L1 checkpoint in normal tissues but reverses its immune evasion function in the tumor microenvironment to achieve a safer and more effective immunotherapy. Their observations were published in *Journal of Clinical Investigation* this year. Dr. Wang is happy to report that his lab's work was featured in the June 2022 issue of *JCI This Month*, which highlights publications of particular impact. Their new concept—differential PD-L1 expression—was also discussed in a special commentary in *JCI* alongside **work by** HIF-1α discoverer and Nobel Laureate Greg Semenza, MD, PhD.



Targeting HIF-1α abrogates PD-L1–mediated immune evasion in tumor microenvironment but promotes tolerance in normal tissues. Journal of Clinical Innovation 2;132(9):e150846.



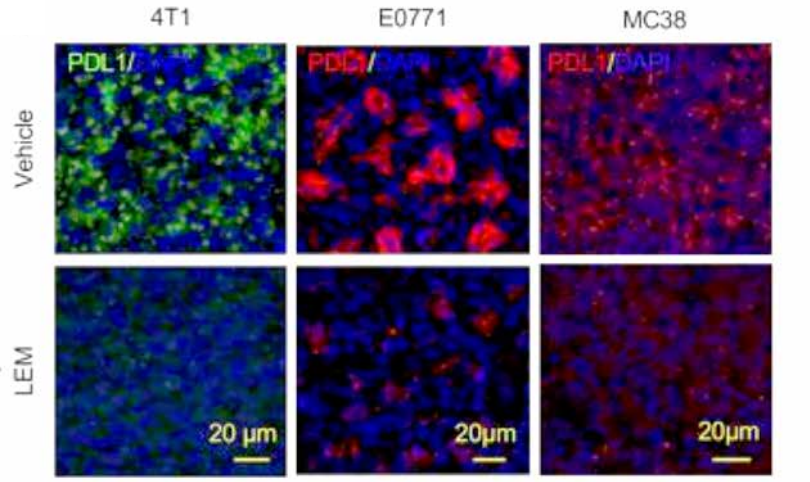
The HIF1α-PDGFD-PDGFRα axis controls glioblastoma growth. Co-expression of HIF1α with PDGFRα and PDGF-D in glioblastoma tissue arrays were examined by immunofluorescence co-staining. Journal of Experimental & Clinical Cancer Research 40, 278.

HIF-1α Is a Molecular Switch from GVHD to GVL Effect by Differential Regulation of PD-L1

PD-L1(B7-H1):PD-1 interaction preserves self-tolerance while restraining cancer immunity. Predictably, global blockade of this pathway confers strong cancer immunity but not without the major caveat of immunotherapy-related adverse events. In both xenogeneic and allogeneic models of bone-marrow transplantation to leukemia-bearing mice, Dr. Wang showed that targeting HIF-1α induces PD-L1 on host tissue while suppressing PD-L1 on leukemia cells and thus enhances graft versus leukemia (GVL) effect while abrogating graft versus host diseases (GVHD). Taking advantage of the xenograft model (which has compartmentalized human versus mouse PD-L1 expression), the Wang Lab found overlapping but distinct roles of PD-L1 on T-cells versus non-T cells. T-cell-associated PD-L1 promoted CD8 expansion in lymphoid organs, while PD-L1 on host cells limited GVHD. Their current data shows that PD-L1 inhibition on malignant tissues by targeting HIF-1α may normalize the tumor microenvironment, whereas induction of PD-L1 on host tissues by HIF-1α inactivation confers resistance to GVHD by fortifying the PD-L1(B7-H1): PD-1 checkpoint. The data have been summarized and will be submitted for publication.

Targeting HIF-1α Prevents Potential Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a fatal and incurable form of interstitial lung disease in which persistent injury results in scar tissue formation. Fibrotic disease, which is characterized by increased extracellular matrix (ECM) deposition and widespread blood vessel damage, has the prominent trait of chronic hypoxia (low oxygen). HIF-1α stimulates excessive ECM production and upregulates vascular remodeling and excessive angiogenesis (formation of new blood vessels), which further worsens chronic hypoxia and scar tissue formation. HIF-1α coordinates these changes in endothelial (cells lining the blood vessels) biology by regulating genes involved in oxygen sensing, glucose and lipid metabolism, angiogenesis, the expression of soluble growth factors, and extracellular matrix components. Current studies on COVID-19 acute respiratory distress syndrome (ARDS) have revealed an accumulation of monocyte-derived macrophages that acquired a profibrotic transcriptional phenotype. Gene set enrichment and computational data integration revealed a significant similarity between COVID-19-associated macrophages and profibrotic macrophage populations identified in idiopathic pulmonary fibrosis. COVID-19 ARDS was associated with clinical, radiographic, histopathological, and ultrastructural hallmarks of pulmonary fibrosis and SARS-CoV-2 triggers profibrotic macrophage responses and pronounced scar tissue formation in ARDS. Dr. Wang's lab analyzed single-cell transcriptomes of bronchoalveolar lavage (BAL) cells in patients with COVID-19-associated ARDS and found that HIF-1α target genes were primarily detected within profibrotic macrophage populations. This data demonstrated that fibrosis-associated macrophage gene signatures and HIF-1α target gene signatures were specifically enriched in SARS-CoV-2-exposed monocytes/macrophages. Macrophages play a critical role in wound healing and fibrosis by releasing cytokines that regulate fibroblast function and angiogenesis into the wound bed. However, the oxygenation status of macrophages during pathofibrogenesis in the niche of new fibrotic lesions, as well as the reasons for elevation in HIF-1α target genes in macrophages during pathofibrogenesis, have not been studied. Using the bleomycin mouse model of lung fibrosis and pimonidazole (a molecular probe for detecting hypoxia), Dr. Wang's lab discovered that the macrophages in new fibrotic lesions in the lung



HIF-1α drives PD-L1 expression in tumor cells. Journal of Clinical Investigation 2022;132(9):e150846.

are under hypoxic conditions. Immunofluorescence staining of the lung tissues showed that the number of macrophages and myofibroblasts found in the new fibrotic lesions were significantly reduced in mice that were treated with the HIF-1α inhibitor liposomal echinomycin. Flow cytometry showed a corresponding reduction in the frequencies of inflammatory macrophages in BAL fluid and lung tissues from liposomal echinomycin treated mice. Liposomal echinomycin reduced fibrotic lesions and αSMA expression in myofibroblasts in fibrotic lesions examined by Masson trichrome staining and immunofluorescence staining. Nintedanib (BIBF 1000), one of two FDA approved drugs for idiopathic pulmonary fibrosis, was identified as a selective inhibitor of the family of VEGF-, PDGF-, and FGF-receptor tyrosine kinases. In one of their current publications this year, Drs. Liu and Wang demonstrated that HIF-1α directly regulates PDGFD and PDGFRα in glioblastoma. Building on the earlier discovery, current data from Dr. Wang's lab shows that liposomal echinomycin significantly decreased macrophage PDGFD protein expression in the bleomycin fibrosis model. They plan to look at VEGF as well, which is a prominent HIF-1α target gene. Based on their data, they propose a HIF-1α centered model for COVID-19-associated lung fibrosis, wherein targeting HIF-1α may provide an effective therapeutic and/or prophylactic intervention for pulmonary fibrosis. This is an ongoing project in Dr. Wang's lab.

Immunotherapy Publications

Bailey CM, **Liu Y**, **Liu M**, Du X, Devenport M, Zheng P, Liu Y, **Wang Y** (2022). Targeting HIF-1α abrogates PD-L1-mediated immune evasion in tumor microenvironment but promotes tolerance in normal tissues. *Journal of Clinical Investigation* 132(9):e150846. DOI: **10.1172/JCI150846**

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Zhang X, Liu H, He J, Ou C, Donahue TC, **Muthana MM, Su L**, Wang LX (2022). Site-Specific Chemoenzymatic Conjugation of High-Affinity M6P Glycan Ligands to Antibodies for Targeted Protein Degradation. *ACS Chemical Biology* DOI: **10.1021/acschembio.1c00751**

Zhu JY, Huang X, Fu Y, **Wang Y**, Zheng P, Liu Y, Han Z (2022). Pharmacological or genetic inhibition of hypoxia signaling attenuates oncogenic RAS-induced cancer phenotypes. *Disease Models & Mechanisms* 15(2):dmm048953. DOI: **10.1242/dmm.048953**

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

Man Charurat, PhD, MHS

The Center for International Health, Education, and Biosecurity (Ciheb) has made key advances in addressing critical needs in health system capacity that improve the prevention, care, and treatment of HIV and other infectious and noncommunicable diseases. In FY22, Ciheb improved and expanded programs in Botswana, Kenya, Malawi, Mozambique, Nigeria, Rwanda, Tanzania, and Zambia.

Kristen A. Stafford, PhD, MPH

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 Deputy Director **Kristen Stafford, PhD, MPH,** Associate Professor of Epidemiology and Public Health, Division of Epidemiology and Prevention, Ciheb has conducted rigorous disease surveillance, employed data for action, enhanced professional education, developed robust information management systems, expanded continuous quality improvement processes, and deployed essential infrastructure.

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 U.S. Centers for Disease Control and Prevention (CDC) under the President's Emergency Plan for AIDS Relief (PEPFAR), the National Institutes of Health (NIH), and UNICEF. Below are select highlights from the past year.

BOTSWANA

Under Country Director **Lillian Okui, MD**, Ciheb is implementing precision, data-driven programs toward achieving HIV epidemic control in Botswana. Ciheb supports 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). It is the largest HIV treatment partner of the Botswana Ministry of Health and Wellness and has been helping to care for approximately 118,000 HIV patients on antiretroviral treatment.

The Bummhi team, led by **Ndwapi Ndwapi, MD**, consists of 525 staff members. A physician and pioneer in establishing publicly funded antiretroviral treatment with extensive experience in tuberculosis (TB) treatment and programming, Dr. Ndwapi is the former Director of Clinical Services at the Botswana Ministry of Health.

In FY21, Ciheb supported five programs in Botswana, including COVID-19 Response, *ABLE*, *BISHOP*, and *BAIS V*. The team closed out both the *BPACE* and COVID-19 projects in 2021. Bummhi, the new local indigenous organization, received the awards for *ABLE* and *BISHOP*, and University of Maryland Baltimore (UMB) is a sub-recipient.

Accelerating Botswana through the Last Mile to Epidemic Control (ABLE)

The Botswana team began implementing year two of ***ABLE***, which builds off the successes of ***BPACE***, but with greater efficiency and precision. *ABLE*'s scope of work was aligned with PEPFAR's COP21 guidance and prioritized index testing; prevention through tuberculosis preventive treatment and HIV pre-exposure prophylaxis (PrEP); case-based surveillance with recency testing (determining if an infection happened in the past six months); complete transition to antiretroviral therapies

tenofovir, lamivudine, and dolutegravir; retention; and viral load suppression. Ciheb helps *ABLE* achieve its HIV and TB epidemic control aims by providing data-driven, technical assistance to the Botswana Ministry of Health and Wellness and its National Strategic Framework. *ABLE* operates in 12 different PEPFAR health districts, 53 health facilities (13 hospitals and 40 clinics), and laboratory services that support all health districts. The services are tailored to underserved sites and populations and use quality patient-centered approaches.

Botswana Information Systems for Health Inter-Operability (BISHOP)

Over the last year, the Botswana team continued implementing the ***BISHOP*** program to support systems' interaction and use, data management and analyses, monitoring and evaluation, data quality improvement, and use of surveys and surveillance systems at the facility, district, and national levels in Botswana. The team brings significant technical expertise in health information systems and will continue leveraging their understanding of user challenges as a service delivery partner and user of the Patient Information Management System to support training and mentorship in the Government of Botswana electronic medical records (EMR) while monitoring EMR usage for feedback and remediation.

BISHOP will continue cultivating a culture of data demand and information use for decision-making through user-friendly visualization platforms and routine collaborative data review meetings. The program is organized under five strategic objectives: 1) Support the Botswana Ministry of Health and Wellness to strengthen monitoring and evaluation activities at the national, district, site, program, and laboratory levels; 2) Strengthen data management and analytics to support tracking outcomes for HIV-positive individuals; 3) Strengthen HIV case-based surveillance for tracking outcomes for HIV-positive individuals — including recency and drug resistance; 4) Support the Health Statistics Unit on quality improvement and assurance for international classification of diseases coding and capturing of death and disability data to improve tracking patient outcomes; and 5) Strengthen lab surveillance and monitoring and evaluation systems, including support for capturing viral load results and other HIV lab-related data at all laboratories that collect this information.

COVID-19 International Vaccine Implementation and Evaluation Program (CIVIE)

Since 2020, the goal of ***CIVIE*** has been to help ensure that low- and middle-income countries can effectively implement and evaluate COVID-19 vaccination programs, with the broader aim of establishing and strengthening sustainable programs for immunizations across the lifespan. *CIVIE* plans to continue and expand its support to ministries of health for COVID-19 vaccination program implementation and evaluation.

The Government of Botswana implemented phase 3 of *CIVIE* in September 2021 with the vaccination of persons aged 18-29, and phase 4 on December 2021 with vaccination of persons under the age of 18 years. Although COVID-19 vaccines are now readily available in the country, as of March 28, only 63.4% of the total population were fully vaccinated with 72.5% receiving the first dose. Only 270,738 booster vaccinations have been reported. These data points will allow *CIVIE* to adapt and refine vaccination provider toolkits from the Centers for Disease Control and Prevention (CDC) and UNICEF (originally the United Nations International Children's Emergency Fund) for Botswana.

Botswana Smoking Abstinence Reinforcement Trial (BSMART)

Tobacco use is highly prevalent among people living with HIV/AIDS, especially in southern Africa, where HIV is most heavily concentrated. Among people living with HIV/AIDS, tobacco use impacts HIV-related co-occurring health conditions and is the leading cause of premature death from non-HIV-related malignancies (cancer), such as lung cancer which account for 20% of the cancer burden. Integrating an evidence-based intervention, such as Screening, Brief Intervention, and Referral to Treatment into an HIV care system presents a significant opportunity to establish and evaluate a modifiable cancer prevention strategy in a low- and middle-income country setting where both lay health workers and non-physician clinicians are widely used. Botswana, where the UMB has worked since 2015, oversees a vast network of HIV care clinics for its citizens. Demographic Health Surveys from Sub-Saharan Africa show that smoking prevalence among people living with HIV/AIDS ranges from 12.5-44.3%. Yet, based on our pilot data,

the system of care is highly unprepared to meet the challenge of integrating evidence-based smoking cessation treatment into routine HIV care. The Government of Botswana wants more to be done to assist its citizen in smoking cessation. To meet this challenge, ***BSMART*** proposes to use a type 2 hybrid effectiveness-implementation study design to evaluate the effectiveness and implementation of a well-established Screening, Brief Intervention, and Referral to Treatment intervention consisting of the 5As (Ask, Advise, Assess, Assist, Arrange) delivered by trained lay health worker case managers, followed by referral to treatment with varenicline (a medication demonstrated to be effective for smoking cessation among people living with HIV/AIDS and on the list of covered medications in Botswana) prescribed and monitored by trained nurse prescribers-dispensers in the network of outpatient HIV care facilities in Botswana. The specific aims guided by the RE-AIM framework and informed by an implementation governance structure are to:

1. Assess the Reach and Effectiveness of *BSMART*.
2. Assess the Adoption and Implementation indexed by quality and consistency of intervention delivery.
3. Assess whether the intervention becomes Maintained as part of routine practices.
4. Determine the preliminary cost-effectiveness of *BSMART*.

Under the leadership of the Country Director **Caroline Ng'eno, MD,** and supported by a Senior Management Team that includes Senior Technical Advisors **Shelly Okumu, MBBS**, Dr. **Cornelia Ochola**, and **Violet Makokha**; Program Manager **Elijah Gichora**; and Finance Manager **Brian Awiti**; Ciheb continues to make progress in Kenya in building health systems capacity and in expanding prevention efforts for HIV and TB.

In October 2021, under the leadership of the Chief Executive Officer (CEO) **Emily Koech, MD,** Associate Professor of Medicine, Ciheb-Kenya, the new local, indigenous organization, began three new HIV prevention, care, and treatment grants (*CONNECT*, *ENTRENCH*, and *PACT Imara*), continuing on the efforts of the two previous UMB-led grants, *PACT Timiza* and *Endeleza*, with UMB now providing support as a sub-recipient. The program currently offers antiretroviral therapy for approximately 260,797 people living with HIV across 479 facilities in Nairobi, Kisumu, Migori, Machakos, Makueni, and Kitui counties in Kenya working in partnership with UMB.

Partnership for Advanced Care and Treatment (PACT) Endeleza and Timiza

PACT Endeleza, under the leadership of Project Director, **Rebecca Wangusi**, collaborated with Nairobi Metropolitan Services Health Management Teams to provide comprehensive quality HIV services integrated with existing county structures and systems with a focus on government ownership for the sustainability of supported services. In its final year, *PACT Endeleza* led infection prevention and control measures for the mitigation of SARS-CoV-2 infection in healthcare workers and clinic patients by building upon existing TB infection prevention and control platforms and utilizing the continuous quality improvement model. At the end of the project in September 2021, the rate of client screening for COVID-19 had increased from 66% to 82% at triage centers placed at the entry points of facilities. ***PACT Timiza***, led by the Country Director Dr. Ng'eno, was implemented in partnership with Kisii and Migori County Health Departments to support 241 healthcare facilities. The project aimed to support the respective County Health Management Teams and designated facilities to deliver an enhanced and integrated high-impact package of sustainable HIV prevention and treatment services towards achieving HIV epidemic control. Both *PACT Endeleza* and *PACT Timiza* provided HIV testing services to hundreds of thousands of individuals with a testing yield of approximately 3% and a rate of 92-95% for linking people to care by the end of the projects in September 2021. Additionally, *PACT Endeleza* supported nearly 31,134 people living with HIV on antiretroviral therapy in Nairobi County, and *PACT Timiza* supported 92,956 in Kisii and Migori counties. Ciheb-Kenya led the follow-on grants, *CONNECT* in Nairobi County and *ENTRENCH* in Kisumu and Migori counties with UMB as a sub-recipient.

Clinician inspects a box

Technical Assistance for Public Health Impact in Kenya (TAPHIK)

The UMB in partnership with the Kenya Medical Research Institute (KEMRI),

supported HIV and TB program implementation, laboratory testing, and surveillance systems in Western Kenya. This included building TB and HIV laboratory capacity for provisioning high-quality, specialized tests for the region; support of quality assurance, biosafety, and infection control practices; and using population-based surveillance approaches like the Health Demographic Surveillance System platform. ***TAPHIK*** supported case-based surveillance with the rollout of scan forms and open data kit platforms to collect HIV case-based reports from facilities in Kenya. Cumulatively, 4,353 HIV case reports were captured, of which 2,064 (47%) had newly identified HIV-positive individuals between October 2020 and September 2021. The previously supported components were split across existing implementing partners and memorandums of understanding with KEMRI for continuation at the end of 2021.

County Ownership and Network to Maintain Nairobi Epidemic Control (CONNECT), Enhancing Technical Responses to the HIV Epidemic Control through Nimble County Health Systems (ENTRENCH), and Partnership for Advanced Care and Treatment (PACT) Imara

The UMB team continues to support Kenya's prevention, care, and treatment programs as sub-grantees to Ciheb-Kenya. Specifically, UMB provides technical support to facility staff, county, and sub-county health management teams, and Ministry of Health/ National AIDS and STIs Control Programme in Nairobi County (***CONNECT***), Kisumu, and Migori counties (***ENTRENCH***), and Makueni, Machakos, and Kitui counties (***PACT Imara***). UMB's support primarily focuses on health management and information systems; strengthening teaching and referral hospital Centers of Excellence for advanced HIV, TB,

Healthcare workers train at Pumwani Hospital

and gender-based violence recovery; continuous quality improvement; health systems strengthening aimed at ensuring transition and sustainability of donor-funded programs; and medication-assisted treatment for people who inject drugs. In this first year, UMB has supported Ciheb-Kenya in successfully building a central data repository, the Ciheb Reporting Information Management System (CRIMS), for program data from all 533 supported facilities monitoring both client-level and aggregate program data for reporting and program improvement. UMB also supported the scale-up of electronic records to facilities that did not have them and initiated migrating these records to a cloud-based platform. As part of *ENTRENCH*, the UMB team led Nyanza/ Western (NYAWEST) Technical Working Group monthly continuing medical education and case reviews, supporting 323 persons living with HIV on third line and salvage treatment (when an antiretroviral therapy regimen fails to control HIV and alternative regimens are used), as well as the 5th NYAWEST Annual Best Practices Forum, which nearly 300 participants attended. In addition, the medication-assisted treatment program reported 143 clients active at Jaramogi Oginga Odinga Teaching & Referral Hospital (JOOTRH) medication-assisted treatment clinic in Kisumu and 1,422 clients at Mathari and Ngara clinics in Nairobi.

NIH Smoking Cessation Study

UMB is conducting a five-year smoking cessation randomized control trial among HIV-positive people who inject drugs in Nairobi, Kenya, which Dr. Koech leads. Smoking significantly impacts the progression and outcome of HIV disease and has been identified as the leading contributor to premature death among people with HIV. The study hypothesizes that combining pharmacological and behavioral interventions may improve the chances of maintaining long-term abstinence and will provide needed data regarding the best treatment approaches for sustained tobacco abstinence for people living with HIV in Nairobi, Kenya. To date, the trial has enrolled 295 of the 300 targeted participants, received IRB (institutional review board)-approval for a sub-study to include alcohol cessation messaging in the positively smoke-free materials. Albeit delayed, the alcohol sub-study has enrolled 14 individuals. The team aims to complete enrollment by the end of this year.

Accelerating Access to Gender-Based Violence Information and Services Leveraging on Technology Enhanced Chat bot (AGILE)

The ***AGILE*** project is a collaboration between UMB's Schools of Medicine and Social Work, LVCT Health (a non-profit and prime awardee), and Kenya's Ministry of Health. The *AGILE* chatbot will use WhatsApp to converse with users, screen for gender-based violence symptoms, quiz users on their risk, and immediately recommend services if needed. The chatbot is built around the nationwide adolescent One2one platform that includes a call center hotline operated by counselors that offer services, such as referral to benefits, including HIV post-exposure prophylaxis and psychological counseling. The chatbot will deliver tailored self-care conversations to survivors of gender-based violence and those at risk. The study will utilize implementation science frameworks to measure outcomes. The team is currently using human-centered designs to build the prototype and have conducted several focus groups and in-depth discussions with potential users and relevant stakeholders.

Accelerating Malawi's PEPFAR Laboratory Logistics and Infrastructure for Quality (AMPLIFY)

AMPLIFY strengthens laboratory efficiency, capacity, and quality by improving laboratory infrastructure, laboratory data utilization for decision-making, training human resources, and adhering to quality management systems in Malawi. Program achievements this past year include:

- 180,593 COVID-19 tests conducted countrywide
- 627,027 viral load samples tested in ten molecular labs and 49 GeneXpert sites.
- 33,288 early infant diagnosis samples tested in ten molecular and 67 point-of-care testing sites.

Malawi COVID testing

STaRT

The UMB 201 team, a team of web developers in Sub-Saharan Africa to provide health Informatics solutions to all UMB PEPFAR countries, supported the design and development a Sample Tracking and Result Return/Reporting System (***STaRT***) system. The *STaRT* application utilizes data blending concepts, i.e., combining data from multiple sources into a single structure to effectively track, monitor, report, and inform decision-making in sample transportation and return of results in Malawi. The application has two main components: (1) the web component, which combines several interactive modules, functions, and an interactive user interface and dashboards for data queries, monitoring, visualizations, and ticket tracking. And (2) a graphical wallboard displays real-time statistics and alerts on sample transportation and handling at different designated locations. *STaRT* is being used by data monitors, the Ministry of Health of Malawi, and other stakeholders to monitor and track sample movement from health facilities to laboratories and return of results from laboratories to health facilities. Other features include a ticketing and alert function for any delayed sample processing in the diagnostic network that generates hourly, weekly, bi-weekly, and monthly data reports.

LIMS

The UMB 201 team supported the design and development of the new reception and dispatch module on the early infant detection viral load Laboratory Information Management System (LIMS). Development of this module is part of the optimization plan of the LIMS system that tracks samples and returns results in the Malawi sample transportation and diagnostics network. The module incorporates location scanning (using barcode/QR code scanners) to ensure real-time confirmation of receipt and delivery of samples/results at the various locations (i.e., the hub and molecular labs). The module has two primary user interfaces: (1) an interface for receiving and dispatching samples or results and (2) an interactive dashboard for displaying samples/results that have been received and dispatched.

The UMB 201 team is also upgrading the tech stack consisting of the programming languages, frameworks, database structure, and front-end and back-end tools of the early infant detection viral load LIMS system. This process will address functionality issues with the system, upgrade the user interface and experience of the system, implement data validation checks to address data quality issues, and add some new features and functions to the system.

Ciheb, led by **Alash'le Abimiku, MON, PhD**, Professor of Medicine, and Country Director **Dinis Jaintilal, PG DPH,** primarily operates in Mozambique under the Laboratory Systems Enhancement for AIDS Pandemic Control (*LAPSEC*) project to support the Ministry of Health in strengthening the laboratory systems for diagnosing HIV and TB.

Laboratory Systems Enhancement for AIDS Pandemic Control (LAPSEC)

In FY22, Ciheb worked with the Ministry of Health and CDC to implement point-of-care viral load testing using m-PIMA and GeneXpert (machines that process HIV tests) to monitor HIV treatment in priority populations such as pregnant and breastfeeding women and infants. The intervention allows for quick detection of high viral loads, immediate adherence sessions, and early changes in antiretroviral therapy if needed. Ciheb conducted training in nine out of 11 provinces and activated 31 sites for point-of-care viral load testing. Ciheb will expand point-of-care training and testing to the remaining provinces in the upcoming year.

To improve health outcomes for patients with advanced HIV disease, Ciheb supported implementing screening for opportunistic infections (TB and cryptococcal meningitis) using the flow urine lipoarabinomannan assay (LF-LAM) and a blood test that looks for cryptococcal antibodies. Ciheb conducted three regional workshops to train 99 clinicians and lab technicians from 27 health facilities selected to implement the AHD package of care in Mozambique. Ciheb continues working with the health facilities to ensure those diagnosed with opportunistic infections receive appropriate lifesaving treatment.

Ciheb continued supporting the Ministry of Health, strengthening TB detection towards the World Health Organization's End of TB strategy, training clinicians and lab technicians from all districts of Mozambique on sample collection of induced sputum (saliva and mucus coughed up) and gastric lavage (stomach pumping) for TB diagnosis, especially for children and people with HIV that have difficulties producing spontaneous sputum. For proper monitoring of TB treatment, Ciheb continued providing technical assistance to the National TB reference lab and to Nampula TB reference lab to implement drug susceptibility testing, including new second-line drugs (bedaquillin and linezolid), resulting in early detection of resistant strains and timely shifting of treatment regimens.

Ciheb strengthened the PEPFAR laboratory system by implementing quality management systems in six labs. Thus far, three labs are applying for ISO 15189 accreditation (the international standard for testing laboratories), one with 4-stars and two with 3-stars using the Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA) checklist.

To support the sustainable external quality assessment program for HIV and TB-related testing, Ciheb worked with the Mozambique National Institute of Health (INS) to establish local capacity to prepare proficiency panels for early infant detection and Xpert MTB/Rif (*Mycobacterium tuberculosis*/ resistance to rifampin) and to expand HIV rapid testing panel preparation to the provincial level to improve coverage and identify sites that require remediation towards continuous improvement.

Staff analyze data in Mozambique.

Training Database

The UMB 201 team supported the Mozambique Ministry of Health in designing and developing a Certified Tester Training Database application for managing trainings and certifications for healthcare workers across the country. The training management application provides a more efficient way for training organizations to manage, track, and issue certificates to training participants. The training database is currently being used to manage the trainings of health workers from different levels (i.e., from facility, district, province, and national) across Mozambique from one central hub. The application allows for creating and managing courses, training venue, certificates, participants, and a facilitator's directory. Certificates management of the training database includes auto-generated certificates with QR code verification, automated alerts for expiring certificates (which are sent to both course administrators in the Ministry of Health and participants). The training database provides an efficient way of managing, tracking, and ensuring that all health care workers are up to date with their required trainings and certifications.

Supervision Checklist Tool

The UMB 201 team supported the Mozambique Ministry of Health to

design and develop a supervisory checklist application to assist health facility supervisors in carrying out their periodic supervision visits. This supervisory checklist application is a simple web-based and mobile application that digitized paper-based forms to electronic forms allowing for easy administration of the questionnaire/checklist during a supervision visit to a health facility. The application not only allows recording of question responses, but it also allows capture and upload of images and PDF documents, automated calculation of final scores of assessments, real time report generation, and corrective actions ticketing and tracking. The application incorporates an interactive user interface and dashboard to display real time assessment scores from supervision visits. The mobile version of the tool has offline access which allows users to fill out the supervision checklist in the field without internet access and sync later to the web system. The supervision checklist tool is currently being used in the administrating supervision checklist for two thematic areas (TB and advance diseases), and it will be expanded to include another disease areas as well.

GeneXpert Logistic Management Information System Extract, Transform, and Load Tool

The UMB 201 team supported the Mozambique Ministry of Health to design and develop a data management tool for GeneXpert (machine that processes HIV test samples) monthly reporting. The GeneXpert logistic management information system reporting tool is a solution developed to automate the reporting and reports aggregation process for the Mozambique consumption report of reagents and consumables for microbiology/bacilloscopy (looks for rod-shaped bacteria) for GeneXpert. The tool uses the extract, transform, and load process to get reports from Excel templates, combines data from different laboratories into a single, consistent data store that aggregates and presents the data for the different reporting levels (i.e., from district to national). This tool cut off lags in data transition from emails to paper-based communication, addresses data errors from manual aggregation, ensures timely reporting, and improves overall efficiency in reporting. The tool also includes automated reminders/notifications sent out to laboratories and district/province supervisors and an interactive user interface and dashboard to display real time reporting rates across the various levels (facility, districts, province, and national). This tool is currently being used for managing GeneXpert reports but will be expanded to include other laboratory reports in the country.

NIGERIA

In FY22, under the leadership of Country Director **Sylvia Adebajo, MBBS, MPH, MSc, PhD,** and Deputy Country Director and Director of Strategic Information **Oluwasanmi Adedokun, MBBS, MPH, MWACP,** Ciheb-led the CDC-funded, Strengthening HIV Field Epidemiology, Infectious Disease Surveillance and Diagnostics (*SHIELD:* Principal Investigator **Kristen Stafford, MPH, PhD,** Associate Professor of Epidemiology and Public Health, Deputy Director of Ciheb) grant and the Nigeria AIDS Indicator Impact Survey (*NAIIS*: Principal Investigator, **Man Charurat, PhD, MHS,** Professor of Medicine, Director of Ciheb) grant. The team also provided technical Health Management Information System assistance as a subrecipient of several grants led by implementing partners, primarily Institute of Human Virology-Nigeria (IHV-N). These subgrants included Strengthening Global Health Security in Nigeria (*IHVN-prime*: Principal Investigator, **Dr. Abimiku**), Action to Control HIV Epidemic through Evidence (*ACHIEVE*: IHV-N Principal Investigator **Patrick Dakum, MBBS, MPH,** Associate Professor of Epidemiology and Public Health, CEO of IHV-N.

Strengthening HIV Field Epidemiology, Infectious Disease Surveillance, and Lab Diagnostics (SHIELD)

The ***SHIELD*** grant supported the Government of Nigeria and its implementing partners in providing quality HIV services using real-time data through developing and using interoperable health information systems. The *SHIELD* project managed and enhanced the National Data Repository, including creating an analytical database of de-identified, patient-level data that can be requested for analysis. As of September 2021, the database contained 5.3 million longitudinal de-identified patient records, of which 1.6 million patients were on antiretroviral therapy, and more than 3,000 facilities were uploading patient data to the system. In addition, Ciheb developed a National Data Repository Analytic Database, along with an online data request portal hosted on the National Association for State Community Services Programs website, which also contains guidelines for data use and publications and serves as an archive for publications developed using National Data Repository data. Surveillance was another major component of the *SHIELD* grant with case-based surveillance scaled up to 1,304 facilities, recency scaled up to 247 facilities, and pilot phase death surveillance in 60 facilities by the end of September 2021. The *SHIELD* project, including the National Data Repository and analytic database, was successfully handed over to the Government of Nigeria and the incoming project managers in December 2021.

Under the *SHIELD* grant, Ciheb was awarded an additional $3 million to work in collaboration with the CDC and the Nigeria Centre for Disease Control to estimate SARS-CoV-2 seroprevalence (number of people who test positive) in select states of Nigeria. Ciheb completed a two-phase population-based household seroprevalence study. The first phase took place in September 2020 in the states of Enugu, Nasarawa, and Gombe, and the second phase took place in June 2021 in Federal Capital Territory (FCT)-Abuja and Kano. Blood samples were collected from more than 12,000 individuals residing in a representative sample of households in the five states. The blood samples were then tested for the presence of SARS-CoV-2 antibodies using locally validated laboratory tests. Individuals who provided blood samples also answered a brief questionnaire that enabled the study team to characterize factors related to positivity and identify which population groups were most affected. The seroprevalence of SARS-CoV-2 found in each state was higher than had been reported through the Nigerian national surveillance system, which was expected based on limited initial testing, symptomatic testing strategies, and the ratio of symptomatic to asymptomatic cases worldwide.

Nigeria AIDS Indicator and Impact Survey (NAIIS)—Cohort Event Monitoring (CEM) for Safety Signal Detection After Vaccination with COVID-19 Vaccines in Nigeria

During its fourth year, Ciheb completed and disseminated the Lagos State ***NAIIS*** Report, uploaded all of the *NAIIS* datasets and related documents onto the National Bureau of Statistics data portal, and trained Federal Ministry of Health staff on using the data portal which led to a successful transition of custodianship to the Government of Nigeria. In addition, Ciheb conducted a manuscript workshop to build capacity of the Government of Nigeria to use the *NAIIS* public access dataset and continues to mentor them through the analysis and writing processes. Furthermore, Ciheb has been leading cohort event monitoring for adverse events after COVID-19 vaccinations, which is now in data collection for phase 2. Data collection for phase 1 was conducted between September 2021 and March 2022, and more than 12,000 participants were enrolled across six states and followed up for an average of three months following the first and second doses of a COVID-19 vaccine.

Nigeria NAIIS handover

Strengthening Global Health Security in Nigeria (Secure-Nigeria)

For the ***Secure-Nigeria*** project, Ciheb provides technical assistance in surveillance data management, visualization, analysis, and quality for key stakeholders, especially the Nigeria Centre for Disease Control, and builds capacity at the state level by providing national tools that display state-level surveillance information. In FY22, UMB finalized the Data Analysis Visualization System Tool for visualizing surveillance data and monitoring data quality. As part of the project, Ciheb also supports acute febrile (fever) illness sentinel surveillance with more than 80% enrollment thus far, and adverse events following immunization surveillance for COVID-19 vaccinations. The tool also includes dashboards developed by Ciheb for monitoring both of these surveillance efforts.

Nigeria's Data Analytics Visualization System Tool for disease surveillance

Action to Control HIV Epidemic through Evidence (ACHIEVE)

Ciheb's role in the ***ACHIEVE*** project has been to provide technical assistance for data management, surveillance implementation, and staff training for supported SURGE (PEPFAR initiative of surveillance) facilities in Rivers, Nasarawa, and FCT. In the fifth and final year of the project, the team started developing a central database for supported states, assisted implementing the Nigeria Medical Records System and reporting of HIV testing services and prevention of mother-to-child HIV transmission data to the provided patient-level data monitoring and quality reviews, supported facilities to report surveillance data and conduct real-time reviews, and provided capacity building and mentorship for facility staff on monitoring and evaluation, Nigeria Medical Records System reporting, and National Data Repository reporting. Ciheb will continue to work with IHV-N as a sub-grantee in the follow-on grant Action to Sustain Precision and Integrated HIV-Response towards Epidemic Control (***ASPIRE***).

In FY21, under the leadership of Country Director **Cyprien Baribwira, MD,** Adjunct Assistant Professor of Pediatrics, Ciheb supported three major initiatives as part of the five year, PEPFAR-funded *IMAKAZA* project. Through a UNICEF partnership, Ciheb also worked to lower HIV in young women and children.

IMAKAZA

Under ***IMAKAZA*** ("to sustain" in the local language of Kinyarwanda), Ciheb has been providing technical expertise in information technology to the National Reference Lab to enhance HIV eLab system technology supporting laboratory technicians and clinicians to improve quality management and the lab clinical interface. Ciheb provided a stepwise process for improving the quality of HIV rapid testing and electronic proficiency testing training for trainers to four provinces and Kigali City. Ciheb also supported Abbott interfacing in six facilities. Assisting HIV integration with outpatient departments, Ciheb is mentoring and training three healthcare centers in Rwamagana and Kamonyi Districts. Ciheb has been assisting Rwanda Biomedical Centre's HIV Division to plan, coordinate, and implement patient-centered services for people with HIV through capacity building in continuous quality improvement.

Ciheb has integrated continuous quality improvement into HIV clinical mentorship guidelines and standard operating procedures by integrating HIV quality indicators to be reported by all district health facilities. In collaboration with the CDC, the Rwanda Ministry of Health, and Rwanda Biomedical Centre, the team has showcased their efforts to establish continuous quality improvement teams to drive improvement in Rwanda, specifically for PEPFAR priorities such as increasing index HIV testing, viral load suppression, and retention. The continuous quality improvement digital platform developed in Tanzania has now been adapted to Rwanda, and Ciheb is now strengthening improvement in 111 health facilities. More than 170 ongoing continuous quality improvement initiatives are from health facilities. The methodology implemented for continuous quality improvement in Rwanda includes initial site visits, mentorship and support, follow-up visits, peer learning, and experiential learning sessions. Finally, Ciheb has been providing ongoing program management support through administration and closed out the project in November 2021.

Addressing HIV in Young Women and Children

In Kigali, with funding from UNICEF, Ciheb works with the Rwanda Biomedical Centre in supporting 18 facilities on continuous quality improvement projects to contribute to Rwanda's elimination of mother-to-child transmission efforts including family testing for children 2-14 years old born to mothers with HIV at clinic spaces not specializing in HIV care. More than 24 quality improvement projects are being implemented. Interventions have resulted in improvements in the proportion of women receiving prenatal care during the first trimester increasing from 22% to 31% and the proportion of children tested according to the national guidelines increasing from 95% to 98%, among others.

Ciheb's team in Tanzania is comprised of more than 50 clinical and support staff led by Country Director **Abubakar Maghimbi, MD**, Adjunct Assistant Professor of Medicine. Dr. Maghimbi has 18 years of experience in infectious diseases and more than eight years working on PEPFAR-funded projects. Dr. Maghimbi has helped to expand Ciheb's work and impact, and he is leading the ongoing implementation of its projects.

Afya Kamilifu

Afya Kamilifu ("complete health" in Swahili) is a comprehensive HIV care and treatment program implemented in partnership with Amref Health Africa in Zanzibar Islands, Tanga, and Simiyu regions. As a subgrantee, Ciheb supports TB/HIV and TB clinics and pediatric and adolescent HIV care. It also leads the project's overall continuous quality improvement cutting across all departments and thematic areas.

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 TB-preventative therapy completion rates improved from 32% to above 95% (**Figure 1**), HIV viral load suppression in children and adolescents improved from 54% to beyond 94% (**Figure 2**), and the proportion of children and adolescents on an optimized antiretroviral regimen has remarkably improved to 99% **(Figure 3**). Also, Ciheb has initiated continuous quality

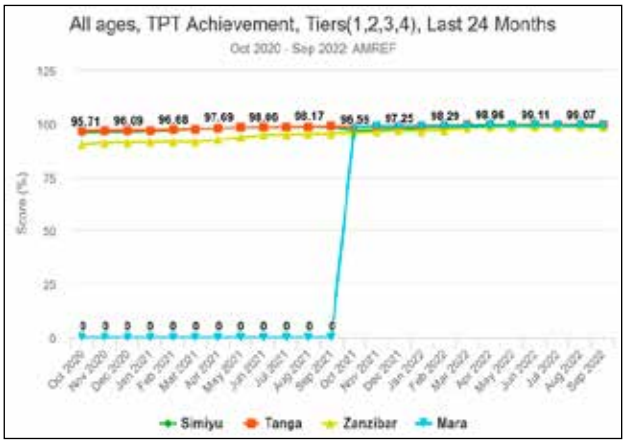

Figure 1. *TB-Preventative Therapy Achievement in All Ages*

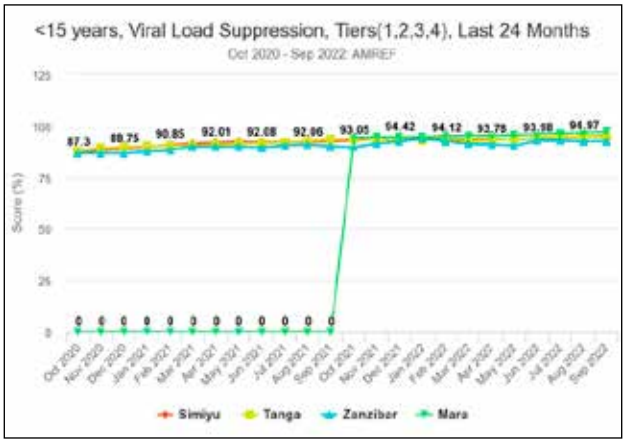

Figure 2. *Pediatric Viral Suppression*

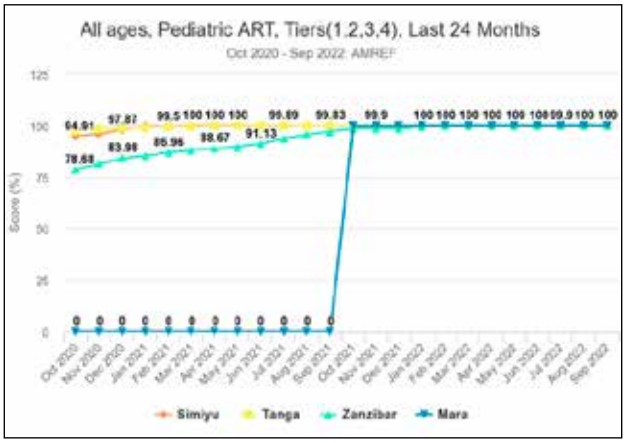

Figure 3. *Pediatric HIV Antiretroviral Therapy Optimization*

improvement projects across all key indicators across CDC tier I to III facilities.

MDH (Management and Development for Health) Support

UMB developed a patient-level data continuous quality improvement root cause analysis dashboard that focuses on improving performance on quality improvement indicators by helping the technical team to identify site-level issues and missed opportunities by specific health care professionals. The dashboard has successfully been integrated with the MDH CARE system, and technical teams have been oriented. Currently, the dashboard has included all indicators as per the scope of work. These include:

- HIV viral load coverage (clients missed sample collection based on clinician, HIV viral load uptake analysis – pediatric, HIV viral load uptake analysis - site trend, HIV viral load results in turnaround time, HIV viral load results not back, HIV viral load sample rejection).
- Enhanced adherence counselling (high viral load delayed enhanced adherence counselling initiation based on clinician, high viral load delayed enhanced adherence counselling trend, high viral load suppression trend).
- Isoniazid preventive therapy (TB screening missed opportunity analysis by staff, TB presumptive cascade, isoniazid preventive therapy eligible, initiation, and completion analysis by staff).
- Prevention of mother-to-child HIV transmission/early infant diagnosis (infants missed first HIV test within two months of age by trend and clinician, infants missed HIV confirmatory test at 18 months of age by trend and clinician, infants missed HIV test within 12 months of age by trend and clinician).
- Multi-month dispensing (3 multi-month dispensing eligible missed opportunity by clinician and trend, 6 multi-month dispensing eligible missed opportunity by clinician and trend).
- Retention indicators (monthly appointment adherence, monthly lost to follow-up analysis).
- Dolutegravir (first-line HIV antiretroviral therapy) uptake.
- Eligible missed opportunity by clinician and trend.

Trained MDH technical staff at headquarters and in all supported regions in continuous quality improvement indicator performance gap identification for improving program performance. (Kagera-72 staff, Geita-41 staff, Tabora-42 staff). Trained MDH quality improvement managers on continuous quality improvement processes including root cause analysis, standard evaluation system form documentation, and electronic quality improvement reporting. Conducted site visit to improve quality improvement performance in HIV continuous quality improvement indicators in selected tier I facilities. Trained R/CHMTs (government employees who supervise, monitor, and coordinate health service delivery) in Kagera on data use and root cause analysis based on new guidance according to "Data Use and Quality Improvement in Tanzania. Guidance for Councils Using a Situation Room Approach, QI/QI Initiatives, Version 1 September 2021."

Penta Training

The team coordinated Penta Training Zambia-Tanzania 2022 sponsored by ViiV Healthcare in collaboration with Penta. ViiV Healthcare provided funding through an independent medical education grant covering all costs related to running the online course. The training was held in a hybrid mode (online and face-to-face) to approximately 300 healthcare workers from local and regional HIV/AIDS centers and other healthcare facilities in Zambia, Tanzania, and neighboring countries such as Uganda, Zimbabwe, and Namibia.

The program was split into three days, from Monday, July 18, to Wednesday, July 20, 2022. The training course was delivered via the Zoom Pro video-conferencing platform in five different regional hubs in Tanzania, namely Tanga, Morogoro, Mwanza, Mbeya, and Dodoma.

ZAMBIA

Ciheb's team in Zambia is led by Country Director and Assistant Professor of Family and Community Medicine **Robb Sheneberger, MD**. Dr. Sheneberger has been leading IHV/UMB initiatives in Zambia since 2004 and has assisted the Republic of Zambia's government by serving on multiple partnership working groups and developing differentiated care systems to support the Joint United Nations Programme on HIV/AIDS 95-95-95 goals (HIV testing, treatment, and viral suppression rates in percentages. Dr. Sheneberger was a significant contributor to the Zambian National ART (antiretroviral therapy) Guidelines. These guidelines were the first in Africa to adopt tenofovir-based first-line antiretroviral therapy and the first to incorporate discordant couples (one partner has HIV and the other does not) into antiretroviral eligibility. Dr. Sheneberger has continued to guide Zambia as the country expanded to a test-and-start approach. **Lottie Hachaambwa, MB, ChB,** Assistant Professor of Medicine, has been instrumental in supporting advanced clinical education for HIV and infectious

Zambia HTCT

diseases by spearheading the Master of Medicine & Infection Diseases at the University of Zambia School of Medicine. **Cassidy Claassen, MD, MPH,** Associate Professor of Medicine, has been a significant contributor to the development and implementation of pre-exposure prophylaxis (PrEP) and differentiated service delivery for HIV testing and prevention in Zambia. Both Drs. Claassen and Hachaambwa have been leaders in supporting the Ministry of Health's response to COVID-19.

Community Impact to Reach Key and Underserved Individuals for Treatment and Support (CIRKUITS)

The ***CIRKUITS*** project uses a targeted community approach to improve HIV prevention, care, and treatment outcomes in Lusaka, Eastern, and Western Provinces to achieve Joint United Nations Programme on HIV/AIDS 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; and the general population. Based on the significant success, the *CIRKUITS* project continued into its third year in 2021 and expanded to include a new implementation ***DREAMS*** (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe) centers. In year four, *CIRKUITS* will continue its ongoing work in Eastern and Western Provinces, as well as the ***Z-CHECK*** (Zambia Community HIV Epidemic Control for Key Populations) work in Southern Provinces. Furthermore, it will focus on key population service delivery via collaboration with local key population civil society organizations.

COVID-19 Pandemic Response

In response to the COVID-19 pandemic, Ciheb helped develop 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 concerning COVID-19 and HIV via telementoring sessions. In addition, Ciheb's local indigenous partner, Ciheb Zambia, led a community response to develop and create locally made personal protective equipment for hospital healthcare workers in Lusaka. Ciheb Zambia has supported the Ministry of Health's Expanded Program on Immunization in the COVID-19 vaccine rollout. Ciheb Zambia also worked with the World Health Organization and CDC to support the Ministry of Health in conducting an intra-action review for the Vaccine Pillar.

Inpatient Package to Reduce HIV and AIDS-related Death in Zambia (IPADZ)

IPADZ aims to understand better and pilot an intervention to alter system-based factors that impact the inpatient HIV care received by patients, including provisioning antiretroviral therapy, monitoring CD4 T-cells and viral load, and screening for coinfections. The short-term goal is to assess the feasibility of an inpatient package to reduce system barriers to advanced HIV disease care during hospitalization. The long-term goal is to develop and evaluate effective interventions to lower HIV-related deaths after hospital discharge.

Re-engagement at Discharge (Re-Charge): Improving Post-Hospital Outcomes for HIV-infected Adults in Zambia

Treatment-experienced HIV patients in Zambia suffer high death rates following hospital discharge in Zambia. The ***ReCharge*** study seeks to better understand the barriers to HIV care for patients after being discharged from the hospital. Ciheb will then translate these findings to an adapted community health worker intervention to support the post-hospital continuum of care by addressing patient- and system-level barriers. Finally, Ciheb will test this intervention in a pilot implementation study. Ultimately findings from this study are expected to help maintain treatment adherence and prevent loss of follow-up with patients.

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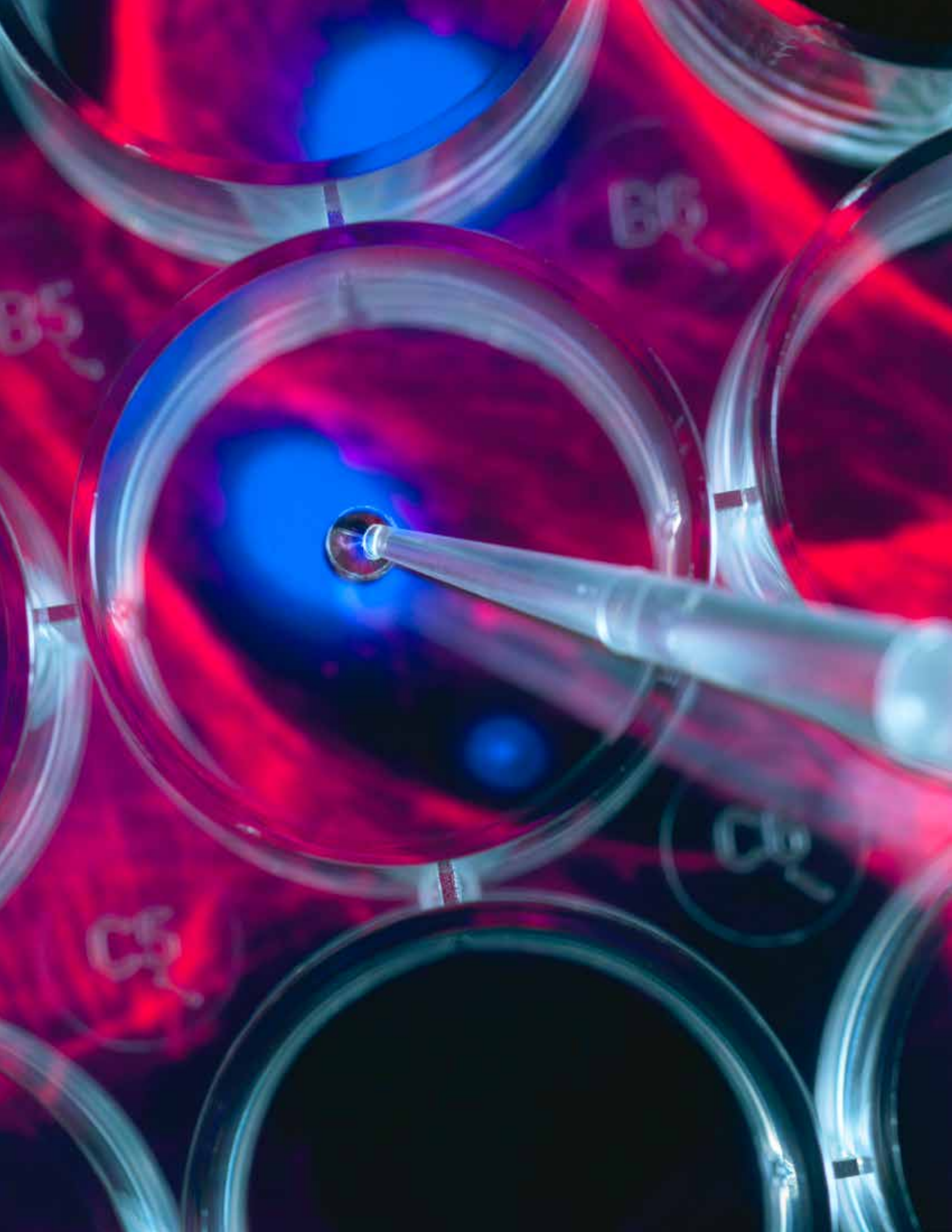


Scientific Core Facilities

Animal Core Facility

Harry Davis, MS, is Director of the Animal Core facility at the Institute of Human Virology (IHV). The facility is located in the IHV building on the first floor. It occupies 20,000 square feet and is a well-designed and equipped animal facility for housing laboratory animals used in biomedical research at IHV. Over the past five years, the Core has undergone changes based on the type of research using animals at IHV. Currently, the Core houses and supports rodents, primarily mice, but also rats. This contrasts with the past 20 years, where we housed non-human primates (*Rhesus macaques*, *Cynomolgus*, and *Papio* species) pigs, goats, sheep, and rabbits and, of course, mice and rats. The Core over the past few years has shifted primarily to a mouse facility due to the use of humanized and specialized transgenic and knockout mice. These models have become an important workhorse model for HIV research for viral studies, cancer studies, and immunotherapy studies. The transgenic and knockout mice have continued to play important roles in HIV and molecular studies. This shift has required a change in providing an environment for immunodeficient mice (NSG, SCID mice [severe combined immunodeficient], and Nude mice) and specialize in genetically modified mice. Today, one of the most popular immunodeficient mouse models in the field of cancer biology, as well as immune oncology is the NSG mice. We are also on the second-generation humanized mouse models. Developing these new models has required a stricter barrier-type housing to prevent any pathogens that can interfere in studies. With this shift from a conventional and partial barrier-type facility to a barrier-type facility I have required redesigning the housing and providing a more technically trained staff to meet the needs and care of these special mice. Mr. Davis developed standard operating procedures (SOP) to ensure that there is no contamination or loss of any research data. He has observed that examining these NSG mice, transgenic, and knockout mice requires a trained staff to look for specific phenotypes that, in many cases, are important component of the research. Mr. Davis continues to maintain an up-to-date knowledge of these observations and train his staff.

As in the past in keeping with the history of the Core's relationship with the Divisions, the following are the list of collaborations and assistance with specific protocols.

In addition, the Core continues to maintain animal models developed at IHV that are being used as models for HIV studies, such as the HIV-1 transgenic mouse and the HIV transgenic rat model. Both models are still being used and funded by NIH. This is especially true for the HIV transgenic rat model, which was developed here at IHV, and the model is only available from the Animal Core facility here at IHV. The model listed under NIH Reports from NIH shows that more than 50 funded investigators use this model for studying chronic HIV/AIDS and their co-occurring health conditions, such as heart disease, kidney disease, and HIV-associated neurocognitive disease.

Joseph Bryant, DVM, MS, Adjunct Associate Professor of Pathology, the retired Director of the Animal Model Division and the IHV Animal Core facility since 2017, remains a consultant to Mr. Davis and the Animal Core Facility. His historical knowledge of the animal models has been invaluable to the Core and IHV investigators.

Facility and Caging Improvements and AAALAC Accreditation

The Core has just completed the installation of the bulk sterilizer that replaces a 27-year-old unit. Installation of this unit will ensure that the Core will be able to provide the highest quality sterilized rodent housing systems on a consistent basis, which is critical to the success of the humanized mouse and other research programs. The Core also resurfaced the cage wash floors and expanded the exterior entrance that allows safer and cleaner deliveries that will enhance the biocontainment program. These and other improvements along with painting will insure our facility's functionality for the next 10 years.

The Core also upgraded its rodent housing units. They purchased new individually ventilated caging systems (IVCs).

These new units provide biocontainment individually to each cage and a monitoring system that can be monitored 24 hours a day though an internet capable system.

We were scheduled to undergo an Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accreditation inspection in November 2021. Mr. Davis prepared the IHV program description that was submitted in conjunction with the School of Medicine. The Core has developed a very good working relationship with the Division of Comparative Medicine and its veterinarian that provide the IHV with an Attending Veterinarian. This accreditation ensured continued approval of animal-based research from all federal funding programs, along with the ability to perform work for private groups seeking accredited research facilities.

Research Support at the Animal Core Facility

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. Mr. Davis has a staff of nine Animal Research Care Personnel and one Research Associate, who are responsible for the care of animals, as well as assisting investigators on various scientific endeavors by providing technical support and technical services.

HIV-1 Transgenic Rat Distribution Program

The Animal Core maintains the only source of HIV-1 transgenic rat animal models in the U.S. The Core currently works with the University to distribute the model to other researchers. The Core have provided a plethora of letters of support for NIH-funded research submissions.

Collaborative Projects with the Division of Virology, Pathogenesis, and Cancer

The Core has developed animal models for studying HIV/AIDS non-Hodgkin lymphomas with projects including 1) pathogenesis studies, 2) developing animal models for AIDS/non-Hodgkins lymphoma, 3) HIV-1 matrix protein p17, which is implicated in virally-associated lymphomas, 4) and mycoplasma and cancer.

DnaK and Mycoplasma Project

Continuing the studies on the relationship between mycoplasma and cancer are **Davide Zella, PhD,** Assistant Professor of Biochemistry and Molecular Biology, and **Robert Gallo, MD,** The Homer & Martha Gudelsky Distinguished Professor in Medicine; Co-Founder and Director of IHV, Co-Founder and Chair of the Scientific Leadership Board at the Global Virus Network, together with Dr. Bryant**, Francesca Benedetti, PhD,** Research Associate of Biochemistry and Molecular Biology, **Giovannino Silvestri, PhD, MS,** Research Associate of Medicine, and **Saman Saadat, PhD,** Postdoctoral Fellow.

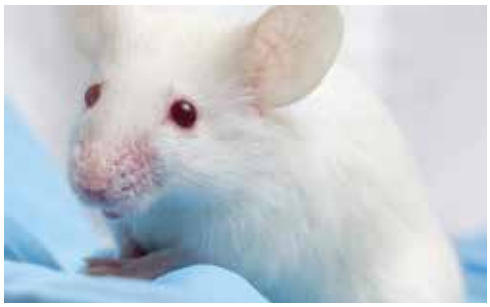
Human *Mycoplasma fermenta* was isolated and characterized for this strain of *ns* able to induce lymphoma in a severe combined immuno-deficient (SCID) mouse model similar to previously described lymphoma formation dependent upon reduced p53 activity. Mycoplasma was abundantly detected early in infected 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 had occurred before cancer detection. The team 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. 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-stranded breaks in DNA. The team is currently extending these results and validating the underlying mechanisms in an *in vivo* model of a *DnaK* knock-in mouse designed in the Core. *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 the 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 the Animal Core facility and are currently used to: 1) test for higher spontaneous tumor incidence in mice expressing *DnaK*; 2) 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*.

Stem Cell and Cancer Biology

Chozha Rathinam, Dr rer nat, Associate 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.

Modeling human immunopathology and therapy to infectious diseases in mice engrafted with human cells and tissues

The Core is assisting **Lishan Su, PhD,** The Charles Gordon Smith Professor for HIV Research, Director of the Division of Virology, Pathogenesis, and Cancer, Interim Director of the Division of Immunotherapy, Professor of Pharmacology, with developing breeding colonies of specialized strains of mice for a humanized mice program.



Collaborative Projects in the Division of Clinical Care and Research

Evaluating Treatment with CCR5

Alonso Heredia, PhD, Associate Professor of Medicine, is evaluating treatment with a CCR5 antagonist to slow tumor progression in HIV transgenic mice with early states of tobacco-induced non-small cell lung cancer. The Animal Core has recently developed a mouse model for studying lung cancer in the setting of HIV infection. The mouse model may allow 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), Dr. Heredia is 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

Nicholas Stamatos, MD, PhD, Associate Professor of Medicine, is evaluating the function of polysialic cell activity through developing and characterizing transgenic mice.

Other Collaborative Efforts with the Animal Core Facility

Development of Natural Plants as Anti-Cancer Drugs

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

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

Walter Royal, III, MD, Professor and Chair 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) in suppressing nervous system inflammation and other neuropathological abnormalities mediated by HIV-1 infection. For these studies, the Core will use 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 of Neurology, is collaborating with the Core to study HIV primary central nervous system lymphoma 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 this cancer's pathogenesis and investigating potential therapeutic strategies. The HIV-1 Tg26 mouse model develops this cancer similar to what is seen in in people with HIV who develop the cancer. The Core has evaluated the HIV-1 transgenic mouse model at the molecular level.

Institutional Animal Care and Use Committee-Approved Projects

Joel Chua, MD, Associate Professor of Medicine

- Development of a Humanized Mouse Model for Dengue Virus Infection

George Lewis, PhD, The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, Director of the Division of Vaccine Research, IHV Deputy Director, Professor of Microbiology and Immunology

- Long Lived Bone Marrow Plasma Cell Responses to HIV-1 Vaccines
- DNA Vaccinations Using a Gene Gun

Dr. Rathinam

- Breeding and Continuing Development of the HIV-1 Transgenic Rat Model
- Role of Post-Translational Modifications in Normal and Leukemic Hematopoiesis
- Breeding and Continuing Development of the HIV-1 Transgenic Mouse Model

Mohammad Sajadi, MD, Professor of Medicine

- Engineering of Broadly Reactive Seroantibodies

Dr. Stamatos

- Function of Polysialic Acid in Immune Cell Activity

Dr. Su

- Modeling Human Immunopathology and Therapy to Infectious Diseases in Mice Engrafted with Human Cells and Tissues

Yutaka Tagaya, BM, PhD, Assistant Professor of Medicine, Head of the IHV FlowCore

- Cytokine Co-Inhibition in Controlling Infectious-Associated Cytokine Release Syndrome

Yin Wang, PhD, Assistant Professor of Surgery

- Targeting Hypoxia-Inducible Factor 1 Alpha for Cancer Therapy
- Host Response to DAMP in Metabolic Syndrome
- Molecular Pathogenesis and Immunotherapy of Rheumatoid Arthritis
- Selective Modulation of Graft Versus Host Diseases and Graft Versus Leukemia Response
- Tumor Immunotherapy and the Mechanisms of Immunotherapy Related to Adverse Events

Animal Core Publications

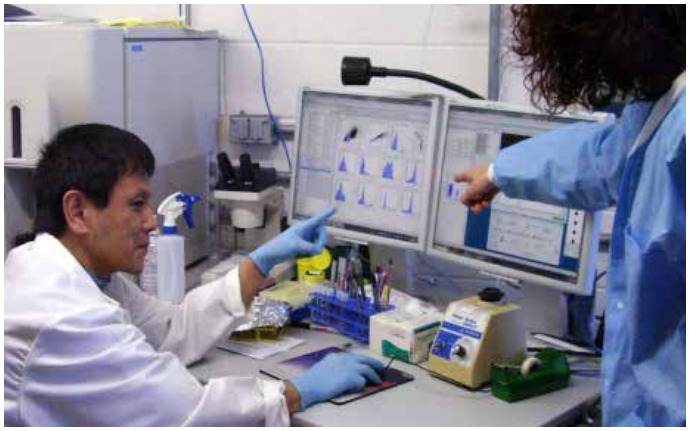
Gutierrez-Barbosa H, Medina-Moreno S, **Davis H,** Bryant J, Chua JV, Zapata JC (2022). Humanized Mice for the Study of Dengue Disease Pathogenesis: Biological Assays. *Methods in Molecular Biology* 2409:271-289. DOI: **10.1007/978-1-0716-1879-0_19**

Royal W 3rd, Bryant J, **Davis H,** Guo M (2022). Cigarette smoke and nicotine effects on behavior in HIV transgenic rats. *Behavioral Brain Research* 417:113591. DOI: **10.1016/j.bbr.2021.113591**

IHV Flow/Sorting Core

The IHV Flow/Sorting Core is located on the sixth floor of the IHV building. The purpose of the Core is to offer IHV and non-IHV users with technical help for planning, implementing, conducting, and analyzing flow-cytometry experiments such as polychromatic flow analysis and fluorescence activated cell sorting (FACS). It has been operational under the leadership of **Yutaka Tagaya, BM, PhD,** Assistant Professor of Medicine, since 2011. Currently, the main operator is **Felisa Diaz-Mendez, PhD,** of the IHV who is also Head of the µQUANT Core Facility.

- The Core's main machine, a Becton Dickinson FACSAria II, is located inside the Biosafety Level 3 facility in Room N664. Because of this, the Core offers sorting of infectious cells, a unique service they specialized in.
- The Core's services can be used in a pay-per-use fashion and is open for users outside of the IHV. For payment, the Core currently uses the conventional invoice system, but they plan to join the iLAB system of the University.
- Scheduling can be done by online through the IHV Flow-CORE calendar. If a client does not have access, please send a request to the **IHV Helpdesk**. For first-time use, please contact Dr. Diaz-Mendez by e-mail/phone.
- The machine is only run by operators Dr. Diaz-Mendez or Dr. Tagaya. It has three lasers (405 nanometers, 488 nanometers, and 635 nanometers) with 12 fluorescence channels.
- As mentioned above, the Core sort cells infected by hazardous microbes and cells of non-mammalian nature. The Core has protocols approved for sorting cells with viruses such as SARS-CoV2, HIV-1, HTLV-1, hepatitis C, hepatitis B, and influenza and a few other parasitic organisms. The Core will work with users who wish to sort infectious cells with organisms that are not currently covered by the protocols by acquiring new Institutional Biosafety Committee (IBC) approval. Please feel free to contact the Core, should you have any need.
- The Core also has a 11-color GUAVA flow analyzer on the fifth floor, North common equipment corridor of the IHV. This flow analyzer is accessible to all IHV users upon scheduling using the calendar posted in front of the machine.



FlowCore personnel in action

The Core works with investigators from the various divisions of the IHV. In cell sorting, the Core helps users not only from the IHV, but also from UMB and outside organizations and are open to inquiries from new users.

The needs for flow-cytometry are constantly changing. With more publications coming out demonstrating the heterogeneity of a once-thought single subset of cells and the relevance of minor cellular subpopulations in controlling infectious diseases or fighting against cancer, more surface markers are needed to identify and purify those minor target subsets. New technologies such as mass cytometry have been introduced to revolutionize the way of analyzing complex mixture of cells, but the Core's machines (11-12 channels) seem still satisfactory to many users studying immune/hematopoietic cells. However, expanding available channels would be critical in the next several years to keep up with technical progress and demands, including replacing the current machines.

Imaging Core

The Imaging Core Facilty at IHV includes several microscopes: from a turnkey system to the state-of-the-art single molecule fluorescence imaging, super-resolution microscopy, and 3-D volumetric tissue imaging microscope systems. The Core is currently managed by **Krishanu Ray, PhD,** Associate Professor of Biochemistry and Molecular Biology, and **Anthony DeVico, PhD,** Professor of Medicine, both in the Division of Vaccine Research. The facility is focused on quantitative fluorescence imaging and molecular analyses of protein-protein, antibody-virion, pathogen-host cell interactions and tissue imaging from various projects across the four IHV Divisions: Virology, Pathogenesis, and Cancer; Vaccine Research; Immunotherapy; and Clinical Care and Research. The facility operates with online scheduling of Core instruments and provides training and guidance on demand.

Krishanau Ray, PhD

Anthony DeVico, PhD

The primary instrument of this facility is the Zeiss Confocal LSM 800 Airyscan Microscope. In addition to providing multi-color standard confocal imaging from blue to the far-red spectral region, this microscope also provides lateral and axial resolution improvements of 1.7-fold and 4X sensitivity improvement by using AiryScan detectors. The system is equipped with four lasers: 405, 488, 561, and 640 nanometers, which assure multi-color event imaging, and GaAsP detectors which yield higher sensitivity, better image quality, and higher acquisition speed compared to regular confocal systems. Zen Blue software is available for the image analysis (size, volumes, colocalization rates, distance between the events, and their intensity rates). In addition, the system is equipped with a large scanner that enable tiling procedures for performing multi-color imaging with tissue samples. The system is also fully equipped with incubation systems allowing both temperature and carbon dioxide control, allowing real time live-cell imaging tasks needed for physiologically relevant studies.

A recently acquired Nikon Eclipse Ti2 Inverted Microscope system with 25-millimeter field of view (FOV) allows 3-D imaging of tissue samples. It includes multiple lasers, a motorized stage, options for live and fixed cell imaging, a microarray imaging option, and additional cameras for large-volume data acquisition. The Ti2 utilizes the sensor area of large-format CMOS cameras, thus significantly improving data throughput. Data analyses are accomplished with Nikon's NIS-Elements software.

The facility also includes a Nikon super resolution microscope with dSTORM and PALM imaging (and a 3-D option) that offer lateral resolution of 20 nanometers and axial resolution of 50 nanometers. The super resolution system is equipped with four solid-state lasers: 405, 488, 561, and 640 nanometers that offer multi-color event imaging with a back-illuminated EMCCD Andor iXon Ultra 897 camera and a sCMOS Hamamtsu Orca Flash camera. The system is also capable of performing total internal reflection fluorescence (TIRF) imaging. Nikon Elements and N-STORM software allow various data analysis procedures.

Additionally, Dr. Ray supervises instruments of his own design, which provide customized time-resolved scanning confocal microscopy with single-molecule detection sensitivity, fluorescence correlation spectroscopy (FCS), FRET measurements, single molecule imaging, two-photon imaging, label-free imaging, metabolic imaging, near-infrared imaging, and fluorescence lifetime imaging microscopy (FLIM). These systems include a picosecond pulsed supercontinuum laser and a femtosecond pulsed laser that can be adapted to several configurations for *in vitro*, *ex vivo*, and *in situ* measurements of protein-protein and protein-virion interaction at the molecular levels, cell-based imaging, and label-free tissue imaging. Multiple IHV faculty members are using these state-of-the-art instruments and techniques, including Dr. DeVico, **George Lewis, PhD,** The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, IHV Deputy Director, Director of Vaccine Research, Professor of Microbiology and Immunology, **Greg Snyder, PhD,** Assistant Professor of Medicine, **Shyam Kottilil, MBBS, PhD,** Professor of Medicine, Director of the Division of Clinical Care and Research, **Mohammad Sajadi, MD,** Professor of Medicine, **Alonso Heredia, PhD,** Associate Professor of Medicine, **Poonam Mathur, DO, MPH,** Assistant Professor of Medicine, **Hongshuo Song, PhD,** Assistant Professor of Medicine, **Nicholas Stamatos, MD,** Associate Professor of Medicine, and **Chozha Rathinam, Dr rer nat,** Associate Professor of Medicine, across IHV divisions.

µQUANT Core Facility

Felisa Diaz-Mendez, PhD

The µQUANT Core Facility was co-founded with 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. **Felisa Diaz-Mendez, PhD,** runs the daily operations of the core with academic oversight from **Anthony DeVico, PhD,** Professor of Medicine. 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 and cost-effective services that allow researchers to compare the 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.
- Maintenance of common use equipment. The latter includes a BIACORE T200, a SpectraMax M2 ELISA plate reader, an ABI simpliAmp PCR 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's 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 on the IHV website for the **µQUANT Core**. The µQUANT Core Facility is heavily involved in supporting many IHV programs and projects.

After two years of low activity due to the pandemic, the Core is now getting back to its normal activity level.

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

Christian Bréchot, MD, PhD, President of GVN

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine is a Center of Excellence of the Global Virus Network (GVN) 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,** 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 enough medical virologists are trained to meet these challenges.

Robert Gallo, MD

GVN was officially co-founded in 2011 at the Italian Embassy in Washington, D.C. by Dr. Gallo, who also serves as Chair of GVN's Scientific Leadership Board, with 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, 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 D.C., 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.

A Media Briefing Addressing the Exploding International COVID-19 Crisis: GVN Ideas for a Global Vaccination Strategy

In summer 2021, GVN leadership including Drs. Gallo, Bréchot, Sharon Lewin, MBBS, PhD, and Amadou Sall, PhD, hosted a media briefing to discuss ideas for a COVID-19 global vaccination strategy. Vaccination is one of the most effective control measures for human infectious diseases. COVID-19 vaccines, particularly mRNA vaccines, have been very effective, even against the current SARS-CoV-2 variants. Thus, successful vaccination has resulted in mitigating SARS-CoV-2 infection in countries, such as Israel, the U.K., and the U.S. Yet there had been evidence for a new surge of infection in those countries, thus stressing the need to really vaccinate most of the population. However, a vaccination campaign was slowed down in many countries mostly due to limited supplies and vaccine hesitance. On the other hand, many countries in Africa, South America, and Southeast Asia did not have access to vaccines. However, to end the pandemic, at least 70% of the population needed to be vaccinated, thus requiring 11 billion doses. Therefore, collective efforts were required to provide much needed vaccines to these countries. In addition to a specific vaccine, the GVN scientists advocated use of broadly effective, existing live vaccines (i.e., polio and Bacillus Calmette–Guérin used for tuberculosis) based on their stimulation of innate immunity. Overall, insufficient global vaccination and spread of more contagious, transmissible variants suggest that GVN needed to design a global approach including preventive strategies, rapid diagnostics, therapeutics, and viral genomic surveillance, in parallel with a vaccine for current and future pandemics. It was also important to provide infrastructure to African countries to develop and manufacture their own vaccines and to build up surveillance program to prevent future pandemics.

The GVN scientists emphasized prioritizing a vaccination strategy. In many countries, older populations (greater than 65 years old) and health care providers were a priority for vaccination, leading to successful reduction of severe cases of COVID-19. Vaccination was expanded to younger populations. However, for a successful global worldwide vaccination, GVN advocated that vaccination should be initiated later, when low- and middle-income countries would have been given the possibility to vaccinate their populations. This was not only a moral obligation and a case of vaccine equity; stopping the circulation of the virus is the only way to end the pandemics,

reopen the borders, and halting generation of novel variants. Many low- and middle- income countries continue to face a surge of COVID-19 with very low vaccination rates. COVAX and other health organizations were shipping the needed vaccines, but these were not enough. The Biden administration and the members of the G7 announced distribution of vaccines to countries in need, a major step in the right direction. More collaborative efforts will be required to help vaccinate low- and middle-income countries, including developing local capacities for vaccine production, while the positive impact of a waiver on licensing was a debated issue. Also, various vaccines with different platforms were getting approved and might facilitate global vaccination efforts.

Inaugural Cohort of Rising Star Mentorship Program

The Rising Star Mentorship Program, launched in August 2021, was created to identify and support promising, early career investigators helping them become leaders in the field of infectious diseases, as well as supporting development of innovative diagnostic and interventional approaches to fight human pathogens. The GVN Rising Star Mentorship Program offers a rare opportunity for future virology leaders to collaborate with key researchers, medical practitioners, and decision makers driving scientific, evidence-based solutions for some of today's largest challenges in public health. The five awardees for the inaugural cohort of the program include:

M. Jana Broadhurst, MD, PhD, DTM&H, Assistant Professor of Pathology and Microbiology, University of Nebraska Medical Center, USA

Kizzmekia S. Corbet, PhD, Assistant Professor of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, USA

Adeola Fowotade, MBBS, PhD, Msc, Instructor of Medical Microbiology and Parasitology, University of Ibadan, Nigeria

Vineet Menachery, PhD, Assistant Professor of Microbiology and Immunology, University of Texas Medical Branch, USA

Piya Paul Mudgal, PhD, Associate Professor of Virology, Institute of Virology, Manipal Institute of Virology, India

Inaugural Participants of Postdoctoral Fellowship Program

The GVN Postdoctoral Fellowship Program, funded by a private donor and Sanofi, was created to identify and support promising, postdoctoral researchers and engage them with top virology experts and cutting-edge research initiatives. The Fellowship Program offers a rare opportunity for future virology leaders to collaborate with key researchers, medical practitioners, and decision makers driving scientific, evidence-based solutions for some of today's largest challenges in public health. The three awardees and the three hosting GVN Centers of Excellence for the inaugural group of the program include:

Rubaiyea (Ruby) Farrukee, PhD, (Australia), The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Australia, GVN Center of Excellence

Birendra Prasad Gupta, PhD, (Nepal), IHV at University of Maryland School of Medicine, USA, GVN Center of Excellence

William Marciel de Souza, PhD, MS, (Brazil), Institute for Human Infections and Immunity and the Department of Microbiology and Immunology at the University of Texas Medical Branch, USA, GVN Center of Excellence

Back in March 2021, the GVN received a private donation of U.S. $1 million to support the GVN Academy, an initiative that fosters global collaboration by providing training and mentoring programs for rising junior virologists. With these funds, the organization launched the GVN Rising Star Program, which will mentor 16 scientists over the course of two years, as well as connect each mentee with a GVN senior virologist who can help provide one-on-one research and career guidance. The funds also support the GVN Postdoctoral Fellowship Program, which will train three postdoctoral researchers during a two-year term with the option to rotate among two GVN Centers of Excellence. Sanofi provided funding for a third awardee to be trained under the GVN Postdoctoral Fellowship Program. Participants of the program take part in exclusive GVN meetings and other professional development opportunities in virology.

Rising Stars 2022 Participants

GVN-Abbott Launch Pandemic Defense Postdoctoral Fellowship Program

Launched this past fiscal year, the GVN-Abbott Pandemic Defense Coalition Postdoctoral Fellowship Program aims to build the pipeline of virus hunters to improve pandemic preparedness and health security across the world. The program provides the latest scientific training in new pathogen discovery, genomic sequencing, and laboratory analysis led by leading virologists and clinicians from across GVN's 68 centers of excellence and 11 affiliates in 39 countries. The Fellowship supports one-year post-doctoral training fellowship for applicants with an MD, PhD, or DVM degree(s) with the potential to extend to a two-year program. GVN Centers of Excellence and Affiliates host participants who will complete comprehensive laboratory training to develop skills and contacts within GVN's international community of medical virologists. They also master the skills of identifying new pathogens and increasing research capacity.

GVN and Monaco COVID-19 Diagnostic Conference

Amid global spread of the Omicron variant, under the High Patronage of H.S.H. Prince Albert II of Monaco, the GVN, the Centre Scientifique de Monaco, the Fondation Prince Albert II de Monaco, the Fondation Merieux, and the Princely Government of Monaco, hosted the international conference: GVN & Monaco COVID-19 Diagnostic Conference: "Promises and Challenges: Towards the deployment of a global and collaborative diagnostic arsenal to detect and fight against pandemics" from Thursday, December 2 to Friday, December 3, 2021. This conference brought together academia, industry, and government to boost innovative technologies for meaningful collaborations with a focus on developing countries. This two-day workshop demonstrated that diagnostics are a central element in controlling pandemics by identifying cutting-edge technologies and platforms to be used for emerging pathogens, and by addressing how such novel technologies can readily inform public health strategies.

(L to R) Dr. Christian Bréchot (President, Global Virus Network), Prince Albert II of Monaco, and Dr. Patrick Rampal (President, Monaco Scientific Center) at the GVN and Monaco COVID-19 Diagnostic Conference in December 2021

Specific achievements and outcomes of this workshop include:

- Providing progress of cutting-edge technologies for COVID-19 diagnostics and platforms to be readily available for controlling the ongoing COVID-19 pandemic and for future pandemic preparedness
- Applying such novel diagnostic systems for implementing global health strategies
- Presenting approaches for sharing resources and technologies, especially with developing countries

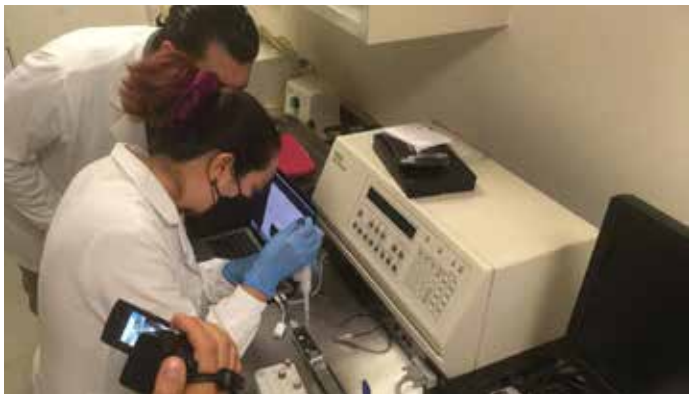
Testing: Immunology, Saliva, and Rapid Testing

In responding to emerging pathogens, it is critical to understand the dynamics of viral shedding in different individuals to identify the most vulnerable time point for viral transmission, to select efficient diagnostic tests, such as molecular and immunology tests, and to prevent super spreader events. Regarding testing, developing a neutralizing antibody test has been very useful in understanding the protective immunity against SARS-CoV-2 in naturally infected and vaccinated people, so as to predict the levels of protection against the virus in the context of waning immunity and breakthrough infections in order to implement public health policy. The presentations from Monaco offered a first proof-of-concept plan on how one can test a whole population of vaccinated individuals for their neutralizing antibodies with the potential of a stewardship personalized strategy for future boosts.

Using saliva samples has become a realistic and most useful strategy in COVID-19 diagnostics. Saliva-based detection assays can decrease cost and turnaround time. Different assays with different demographic samples demonstrated its usefulness and broad applications. Importantly, saliva may be superior to nasal swabs for early detection of infection. Rapid tests for COVID-19 can be particularly useful, not only in developed countries, but also in developing countries. Various advanced technologies and platform (i.e., CRISPR and biosensor-based assays) are now available for sensitive and cost-effective COVID-19 diagnostics. These advanced techniques are adaptable and deployable in the field with point-of-care testing and massive throughout.

Biomarkers and Genomic Sequencing

Identifying and monitoring biomarkers in patients have the potentials for predicting disease status and severity, identifying a target for antiviral drugs, and developing personalized treatments. Advanced genomic sequencing analysis facilitates rapid identification of emerging variants and predominantly circulating variants, leading to implementation of public health measures. Interestingly, water-waste surveillance approaches also have the potential to quickly identify circulating emerging variants and provide various valuable information required



Expanding genomic surveillance of SARS-CoV-2 in public health labs at local universities in Mexico

to protect the community. Sharing data and availability of database systems for SARS-CoV-2 genome sequencing enables experts to track variants of concern and to predict the impact of mutations in the variants on the effectiveness of existing vaccines, therapeutics, and diagnostics. Specifically, a risk assessment algorithm is facilitating tracking emerging variants and analyzing the functional impact of these mutations. In particular, such programs predict that the Omicron variant could be of great concern due to the many mutations found in the receptor binding domains of the virus and their impact on the efficacy of vaccines and therapeutics.

Implementation of Diagnostic Tests in a Global Health Strategy

Global collaboration, partnership, and leadership are critical in mitigating the current pandemic and in preventing future ones. Health organizations, such as FIND and Unitaid, have worked to accelerate breaking the chains of transmission and providing public health intervention measures by distributing affordable, accountable, and rapid diagnostic kits to developing countries. Yet, lack of testing in these countries (especially, remote and rural areas) have greatly hindered in mitigating the current pandemic. Important steps toward future pandemic preparedness will not only rely on providing access to inexpensive, rapid diagnostics and genome sequencing capacity, but also on providing education and training, as well as regional manufacturing capacity with technical knowledge transfer. Further, establishing global partnerships for sharing samples (biobanking) and available database systems are enhancing efforts to rapidly develop diagnostics for infectious diseases.

Conclusions

Diagnostics will be vital in preparing for future pandemics. For the next pandemic preparedness, new levels of partnerships between academia, industry, and government will be necessary with a globalized vision. In addition, the world needs comprehensive approaches for engineering, medicine, public health, and virology. Overall, GVN need an "Operation Warp Speed program" for diagnostics so as to accelerate the development, clinical testing, manufacturing, and procurement of novel tests. The GVN continuously establishes global partnerships, such as that with Monaco and Fondation Merieux, and merges the best experts worldwide in a science-driven and independent spirit to provide better strategies to mitigate current pandemics and to prepare for future ones. GVN's ongoing effort is to define the impact of the Omicron variant by global collaboration with the experts in protein structure, genomic surveillance and bioinformatics, virology, and clinical analysis by disseminating scientific findings, and by providing advice on global public health measures. The GVN is fluid in their specific research goals as the pandemic continues to evolve.

A Statement from the Global Virus Network on the 2022 Russian Invasion of Ukraine

The Global Virus Network (GVN) is an apolitical global organization comprised of the world's leading scientists, including those from Russia and Ukraine, who specialize in education and research for the purpose of protecting mankind from viral proliferation and viruses that cause pandemics. The scientists of the GVN collaborate to alleviate the pain and suffering caused by viral pathogens and to mitigate the threat they pose to mankind.

The members, including IHV, of GVN are motivated by the fundamental tenet of medicine; "to do no harm" and are dedicated to honoring the sanctity of life irrespective of culture, ethnicity, nationality, or race. We are scientists, not politicians, but we are compelled to raise our voices in unison to protest the invasion and wanton destruction of Ukrainian cities and the savage killing of innocent civilians and members of the military who are defending their homeland in the name of freedom and autonomy. They seek only peace. Mr. Putin, grant them peace. Mr. Putin, cease the armed hostilities immediately and enter into negotiations conducted in accord with respect for human life and dignity. We are committed to universal moral principles that govern the humane treatment of human beings and dictate the norms of civilized relations between nations. The current invaders of Ukraine are not exempted from the unequivocal adherence to these principles, for all members of humanity, "are not islands separate and apart, but part of the main." Mr. Putin, stop the aggression now!

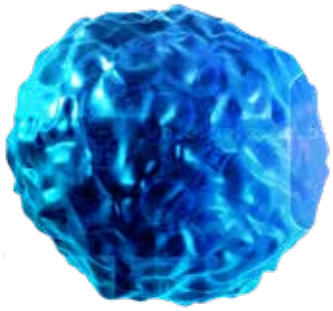
In the spirit of interconnectedness, we urge the combatants to cease hostilities and engage in negotiations to peacefully resolve their armed conflict. May this war in which the bitterest

enmities have been invoked, be terminated with "malice toward none and justice for all." May the sacrifices and suffering already endured be an impetus for peace, and may our common humanity provide the moral imperative by which the sanctity of life and human dignity take precedence over the bristling antagonisms which provided an incitement to force.

Let peace not be cast as a victory or defeat for either side, but as a triumph of morality arrived at by ethical individuals acting on behalf of their respective nations. When morality emerges as victorious, we can rest assured that mankind endures and prevails as the ultimate beneficiary.

IHV Contributes to GVN Studies Suggesting that the Oral Polio Vaccine Can Protect People in Developing Nations that Do Not Yet Have Access to COVID Vaccines

In April 2022, IHV and GVN announced two new studies in partnership with the Petroleum Industry Health Organization of Iran, providing evidence that getting the oral polio vaccine made from live, weakened poliovirus may protect people from COVID-19 infection by stimulating the immune system.



One of these studies demonstrated a lower incidence of COVID infections in countries in which people received the 'live' polio vaccine compared to countries that only received the polio vaccine that does not contain a live virus. These findings were published on March 17, 2022, in *PLOS One*.

Another report from the research team showed that when young children received the 'live' polio vaccine, their mothers, who were indirectly exposed to the poliovirus vaccine, did not get infected with COVID. This study was published late last year in *JAMA Network Open*.

Within a few hours of exposure to any pathogens—including weakened viruses like those in the oral polio vaccine—the immune system activates its first line-of-defense. This defense produces an immune response to a broad variety of pathogen-related molecules and ramps up the immune system's readiness for invaders—a process sometimes called 'trained innate immunity.' The outcome from one of these newest studies indicate that this trained innate immune response spurred by vaccination using the live poliovirus may provide protection for up to 6 months against COVID infection.

Child receives the oral polio vaccine

"Although countries like the U.S. and those in Europe are dropping pandemic restrictions, many people in lower income countries remain unvaccinated due to lack of supply. Individuals in these countries are still at high risk for COVID infection and potential complications, particularly since these regions still lack the latest treatments and enough ventilators for those who need them," said co-author **Shyam Kottilil, MBBS, PhD**, Professor of Medicine and Director of the Division of Clinical Care and Research at IHV, Chief of the Division of Infectious Diseases at the University of Maryland School of Medicine, and Senior Advisor to the GVN. **"These live vaccines may provide a stop gap to reduce hospitalizations and deaths until we can get these people COVID vaccines."**

Senior author on the studies, **Robert Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine, Co-Founder and Director of the Institute of Human Virology at the University of Maryland School of Medicine, a GVN Center of Excellence, and Co-Founder of the GVN and Chair of the GVN's Scientific Leadership Board, said, **"Early in the COVID-19 pandemic, prior to development of effective vaccines we proposed using live attenuated vaccines as a temporary solution to boost immunity until the vaccine could be developed. This idea directly stemmed from my GVN colleague and co-author Dr. Konstantin Chumakov, whose parents were vaccine researchers in the 1970s Soviet Union. His parents observed that flu rates seemed to drop in those people given the oral polio vaccine. Other GVN colleagues joined us in advocating for studies to determine if these live attenuated vaccines would be a feasible strategy during the coronavirus pandemic. Now we have some of the first evidence that they do offer protection. I hope funders take notice and**

increase support for these types of trials that study the innate immune response and provide significant hope in mitigating future pandemics."

The researchers say that this implies that these live vaccines, technically known as live attenuated vaccines, may be used temporarily to protect people in low-income countries that do not yet have access to COVID vaccines.

Co-author Konstantin Chumakov, PhD, a GVN Center of Excellence Director, said, **"These observations are yet another confirmation that live vaccines induce broad protection against infections caused by pathogens other than their direct target. They urgently call for the direct prospective clinical studies of this phenomenon that could lead to the development of a novel class of vaccines based on stimulation of trained innate immunity. Such vaccines could become the badly needed universal countermeasure against emerging infections."**

In the *PLOS One* study, the researchers compared infection rates per 100,000 people in 146 countries that received both the live and the injectable polio vaccine, which does not contain live virus, compared to 56 countries that only used the injectable, non-live version. They found infection rates in countries that did not use the live polio vaccine were about three times higher than those that did use the live polio vaccine.

For the *JAMA Network Open* study, the researchers followed 419 mothers in Iran whose young children were given the live polio vaccine compared to 3,771 mothers whose children did not receive the live polio vaccine. None of the mothers whose children received the live polio vaccine developed COVID, whereas 28 mothers whose children did not receive the live polio vaccine did contract COVID within 9 months. Researchers know that poliovirus and even the weakened virus from the vaccine can be shed in the stool. The researchers surmise that the mothers were exposed to virus when caring for their children through bathing and diaper changing.

"It is heartening to find similar study results obtained from very different approaches strengthening our hypothesis that using the oral vaccine may provide protection against SARS-CoV-2, the virus that causes COVID," said the first author on the studies, Farrokh Habibzadeh, MD, Special Consultant on Public Health for the GVN and the Managing Director of the Research and Development Unit of the Petroleum Industry Health Organization of Shiraz, Iran. He added that, **"This hypothesis should be tested in additional quality clinical trials, preferably conducted in countries where the oral polio vaccine is currently in use as part of their national immunization for polio."**

Co-author **Kristen Stafford, PhD, MPH**, Associate Professor of Epidemiology and Public Health at IHV at the University of Maryland School of Medicine and member of the GVN, said, **"Some high-income countries declare pandemics over when in fact they just transition to only affecting low-income countries. We do not want this pandemic to become like the HIV-epidemic, where years and years of delays led to millions of excess deaths because the antiretroviral medications were too limited in supply or expensive to reach those disproportionately affected. We need to find simpler, inexpensive solutions to protect people until they can get their full doses and boosters of the COVID vaccines."**

"The important observations that the oral polio vaccine may protect against different infections such as COVID-19 is crucial for future pandemic preparedness. Understanding the mechanisms of protection induced by the oral polio vaccine and other live attenuated vaccines can open the door for the development of improved vaccination strategies to protect against broader infections, and thus provide partial protection against new pathogens during a pandemic until specific vaccines can be developed," said Mihai Netea, MD, PhD, of the Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, a GVN Center of Excellence, and GVN Center Director.

One of the limitations of the live, weakened vaccines, is that they are not recommended for people with suppressed immune systems, as it could lead to infection.

Additional authors on the studies include **Mohammad Sajadi, MD**, Professor of Medicine at the IHV at the University of Maryland School of Medicine and member of the GVN; and Mahboobeh Yadollahie, MD, Ashraf Simi, BScN, Saeid Saeidimehr, MD, (*JAMA Network Open* only), Mohammad Rafiei, MD, (*JAMA Network Open* only), and Iman Hafizi-Rastani, MSc (*PLoS One* only) of the Petroleum Industry Health Organization of Iran.

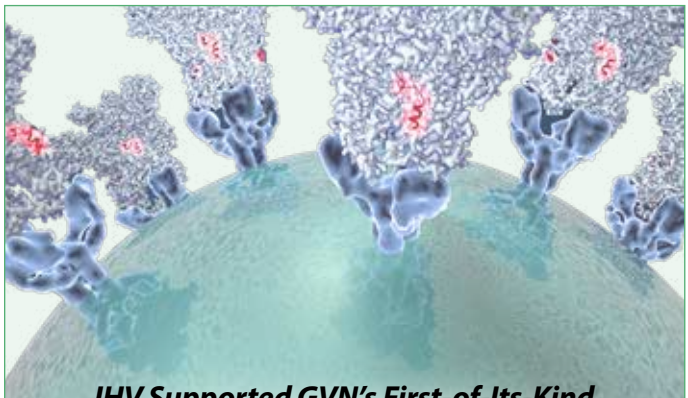
Seven Distinguished International Appointments to Board of Directors World Leaders in Academia, Business, Government, Healthcare, Philanthropy, and Science Commit Their Expertise to Advancing the Development and Expansion of GVN

This past year, the individuals elected to the Board of Directors of the GVN include Christian Bréchot, MD, PhD, President of the GVN, Associate Vice President for International Partnerships and Innovation at University of South Florida (USF), and Professor in the of Division of Infectious Disease in the Department of Internal Medicine at the USF Health

Morsani College of Medicine, the GVN Southeast U.S. Regional Headquarters; Brett P. Giroir, MD, CEO, Altesa BioSciences, USA; John Pottage, Jr, MD, Former Senior Vice President, Chief Scientific and Medical Officer of ViiV Healthcare and Non-Executive Director of Spero Therapeutics, USA; Juliette M. Tuakli, MD, MPH, Chair of the Board of Trustees of United Way Worldwide; Rosarii Griffin, MEd, MSc, DPhil, FRSA, DDVS, Director of the Centre for Global Development at the University of Cork College, Ireland; Stephen Israel, Vice Chairman for Biotechnology and Pharmaceuticals, Korn Ferry, USA; Steven Phillips, MD, MPH, Vice President of Science and Strategy of the COVID Collaborative, USA. The GVN also announced that Mathew L. Evins, Chairman of Evins Communications, Ltd, and a founding Board Member of the organization, was unanimously elected to serve as Chairman of the GVN's Board of Directors, as well as reelected to the position of Treasurer of the organization. David Scheer, President of Scheer & Company, Inc., was elected to serve as Vice Chairman and Secretary and Timothy Moynahan, Esq, the previous Chairman of the GVN Board of Directors, was honored as Chairman Emeritus for his outstanding leadership and service to the organization. Former general counsel of the U.S. Department of Health and Human Services (HHS), Robert P. Charrow of Greenberg Traurig, LLP, now serves as GVN's legal counsel.

GVN Launches Task Force to Combat Monkeypox Global Outbreak

This year, a higher incidence of human-to-human monkeypox transmission in varying geographical regions alarmed global health officials. While the transmission of monkeypox from animals to humans is established and known, the growing number of community transmission cases worldwide posed a potential pandemic threat. The GVN announced the formation of the GVN Monkeypox Task Force to urgently bring together GVN researchers to explore the growing number of monkeypox cases worldwide.



IHV Supported GVN's First-of-Its-Kind Conference to Evaluate the Public Health Magnitude of Long COVID and Define a Global Research Roadmap to Address the Crisis

This past summer, the GVN led a two-day meeting on the 'Science of Long COVID,' which was hosted at the University of Maryland, Baltimore. The first-of-its-kind conference reviewed the wealth of cohort (study group) data on long COVID, constructed a framework to characterize and define the conditions, and identified the most critical and urgent areas of research needed to better understand, diagnose, and treat this developing public health crisis (*See Director's Message for more information*).

Dr. Christian Bréchot is joined by GVN's chairs to discuss a research roadmap addressing long COVID

GVN Adds New Members and Grows Its Reach

This past year, the GVN added five new academic Centers of Excellence (COE) and one Affiliate. The new academic COEs include, the Institute of Biomedical Systems and Biotechnologies at Peter the Great St. Petersburg Polytechnic University, Russia; Scientific Platform Pasteur-University of São Paulo (SPPU), Brazil; Centre for the AIDS Programme of Research in South Africa (CAPRISA); Aegis Consortium at the University of Arizona Health Sciences, USA; and, Mahidol University, Thailand. The new Affiliate includes Centre Scientifique de Monaco (CSM).

GVN Members represent expertise covering every class of human virus, and currently comprise virologists from 68 Centers of Excellence and 11 Affiliates in 39 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.

Scientific Platform Pasteur-University of São Paulo is one of GVN's latest Centers of Excellence

IHV Faculty and Staff Support GVN Mission

In addition to Dr. Bréchot, GVN's staff headquartered at IHV includes Linman Li, MBA, MPH, PMP, CPH, Vice President, Alfredo Garzino-Demo, PhD, Program Director, Marcus Gallo, MS, Research Analyst and Centers Manager, Kevin Kishpaugh, Operations Manager, Avita Ukpabia, GVN Academy Program Coordinator, Cameron Eubank, Digital Marketing and Graphic Design Manager, Uchenna Mildred Udeh, Administrative Assistant, Marv Reitz, PhD, and Caroline Vega. 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 Chair of GVN's Scientific Leadership Board, **Dave Wilkins**, IHV's Chief Operating Officer, who serves as GVN's Senior Advisor and Chief Operating Officer, and **Nora Samaranayake**, IHV's Chief Communications and Public Affairs Officer, who serves as GVN's Senior Advisor on Public Relations. Other contributors include **Mohammad Sajadi, MD,** Professor of Medicine, Division of Clinical Care and Research, **Anthony Amoroso, MD,** Director of Clinical Innovations Program in the Division of Clinical Care and Research, Professor of Medicine, **Davide Zella, PhD,** Assistant Professor of Biochemistry and Molecular Biology, Division of Virology, Pathogenesis, and Cancer, **Shyam Kottilil, MBBS, PhD,** Director of the Division of Clinical Care and Research, Professor of Medicine, **Man Charurat, PhD, MHS,** Director of the Division of Epidemiology and Prevention, Director of Center for International Health, Education, and Biosecurity (Ciheb), Professor of Medicine, **Yutaka Tagaya, BM, PhD** Assistant Professor of Medicine, Head of the IHV Flow Core, Division of Virology, Pathogenesis, and Cancer, **Alash'le Abimiku, MON, PhD,** Professor Medicine, Division of Epidemiology and Prevention, Ciheb, **Niel Constantine, PhD, MT(ASCP),** Professor of Pathology, Division of Epidemiology and Prevention, **George Lewis, PhD,** The Robert C. Gallo, MD Endowed Professorship in Translational Medicine, IHV Deputy Director, Director of the Division of Vaccine Research, Professor of Microbiology and Immunology, **Lishan Su, PhD,** The Charles Gordon Smith Professor for HIV Research, Director, Division of Virology, Pathogenesis, and Cancer, Interim Director of the Division of Immunotherapy, Professor of Pharmacology, and **Anthony DeVico, PhD,** Professor of Medicine, Division of Vaccine Research. IHV also appreciates its own Board of Advisors for donating time and energy towards the advancement of the GVN mission.

IHV Faculty

DIVISION OF VIROLOGY, PATHOGENESIS, AND CANCER

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

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

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Hongshuo Song, PhD—Head of the Laboratory of Molecular Virology, Assistant Professor, Medicine

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

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

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

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

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Eleanor Wilson, MD—IHV, Associate Professor, Medicine

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Yan Liu, PhD—IHV, Assistant Professor, Surgery

Yin Wang, PhD—IHV, Assistant Professor, Surgery

Xu Wang, PhD— IHV, Research Associate, Pharmacology

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University of Maryland School of Medicine

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Shenghan Lai, MD, MPH—IHV, Professor, Epidemiology and Public Health

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Habib R. Omari, PhD, MPH —IHV, Research Associate, Epidemiology and Public Health

Nadia Sam-Agudu, MD—IHV, Associate Professor, Epidemiology and Prevention

Kristen Stafford, PhD, MPH—IHV, Associate Professor, Epidemiology and Public Health

IHV Faculty

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Abubakar Maghimbi, MD—IHV, Adjunct Assistant Professor, Medicine
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David Riedel, MD, MPH—IHV, Associate Professor, Medicine
Brenna Roth, MD, MPH—IHV, Assistant Professor, Medicine
Robb Sheneberger, MD—IHV, Assistant Professor, Family Medicine

SCIENTIFIC CORE FACILITIES

Animal Core Facility

Harry Davis, MS—Head of the Animal Core Facility (non-faculty member)
Joseph Bryant, DVM, MS—Adjunct Associate Professor, Pathology, Animal Core Facility

Flow Cytometry and Cell Sorting Core Facility

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

Imaging Core Facility

Krishanu Ray, PhD—IHV, Associate Professor, Biochemistry and Molecular Biology
Anthony DeVico, PhD—IHV, Head of the Laboratory of Viral Envelope Studies, Professor, Medicine

µQuant Core Facility

Felisa Diaz-Mendez, PhD—Head of the µQuant Core Facility (non-faculty member)
Anthony DeVico, PhD—Professor, Medicine

FORMER IHV FACULTY NOW ADJUNCT

Jason Bailey, DO—IHV, Clinical Assistant Professor, Clinical, Division of Clinical Care and Research
Joseph Bryant, DVM, MS—Adjunct Associate Professor, Pathology, Animal Core Facility
Ulrike Buchwald, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Farley Cleghorn, MD, MPH—IHV, Adjunct Assistant Professor, Medicine, Division of Clinical Care and Research
Joanna Cole, MD—IHV, Visiting Clinical Instructor, Medicine, Division of Clinical Care and Research
Guesly Delva, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
John Farley, MD, MPH—IHV, Adjunct Associate Professor, Medicine, Division of Epidemiology and Prevention
Suzanne Gartner, PhD—IHV, Adjunct Associate Professor, Medicine, Division of Basic Science
Bruce Gilliam, MD—IHV, Clinical Professor, Medicine, Division of Clinical Care and Research
Luciano Kapelusznik, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Olga Latinovic, PhD, MSc—IHV, Adjunct Assistant Professor, Microbiology and Immunology, Division of Virology, Pathogenesis, and Cancer
Michael Levin, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Otha Myles, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Nicaise Ndembi, PhD—IHV, Adjunct Associate Professor, Medicine, Division of Epidemiology and Prevention
Chidi Nwizu, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
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Anuoluwapo Osinusi, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Mikulas Popovic, MD, PhD—IHV, Adjunct Professor, Medicine, Division of Basic Science
Marvin Reitz, PhD—IHV, Adjunct Professor, Medicine, Division of Basic Science
Alan Schmaljohn, PhD—IHV, Adjunct Professor, Microbiology and Immunology
Nathaniel Smith, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Leonard Sowah, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research

ADJUNCT FACULTY

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Cyprien Baribwira, MD—IHV, Clinical Assistant Professor, Medicine, Division of Clinical Care and Research
Luigi Buonaguro, MD—IHV, Adjunct Associate Professor, Medicine, Division of Basic Science
Arnaldo Caruso, MD, PhD—IHV, Adjunct Professor, Medicine, Division of Basic Science
Prakash Chandra, Dphil—IHV, Adjunct Professor, Medicine, Division of Basic Science
José G. Esparza, MD, PhD—IHV, Adjunct Professor, Medicine, Division of Vaccine Research
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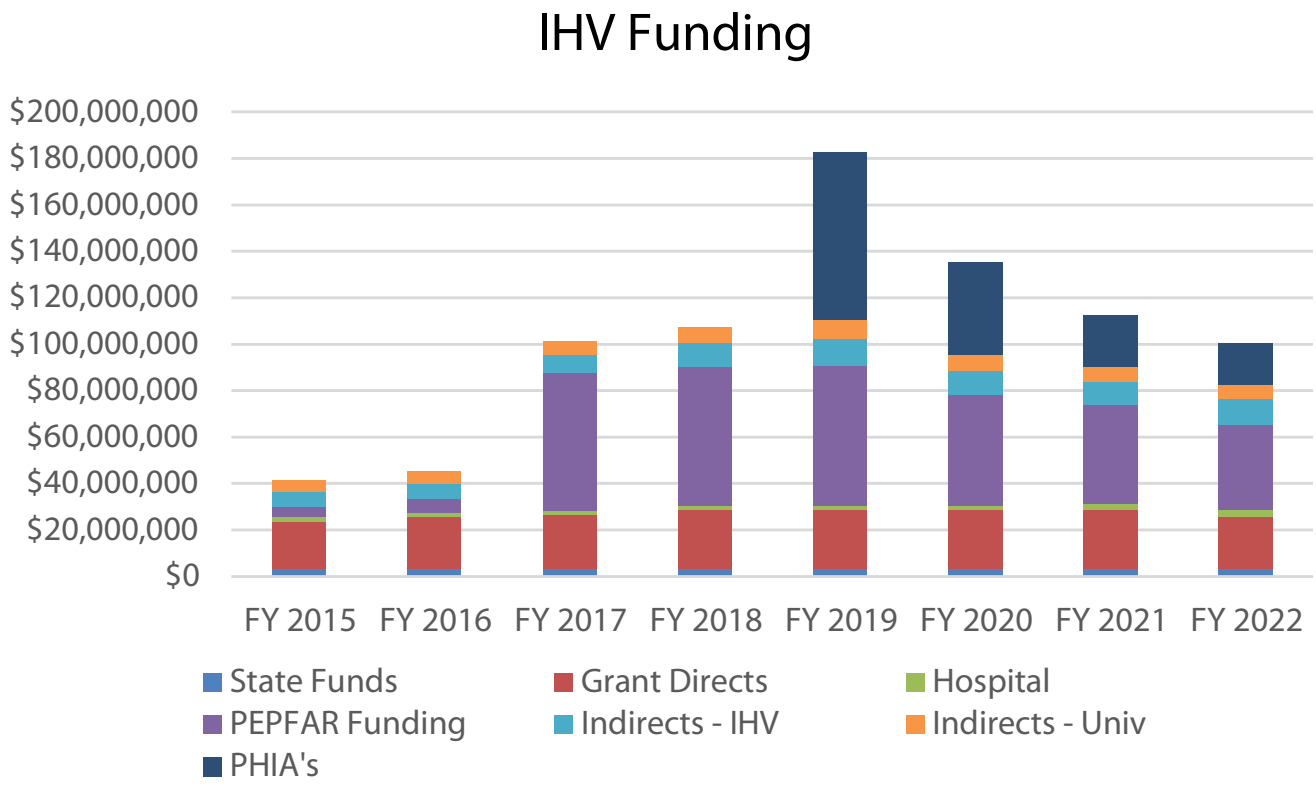
Financial Overview

IHV's grants and contracts portfolio was again significant in FY22, generating $100,500,000 of total revenue. All of IHV's five Divisions and one Center, including Virology, Pathogenesis, and Cancer, Immunotherapy, Vaccine Research, Clinical Care and Research, Epidemiology and Prevention, and the Center for International Health, Education, and Biosecurity (Ciheb), performed significant basic research, clinical care, clinical research, and epidemiology programs. In the international arena, the trend for more awards to indigenous organizations will continue, and this is reflected in funding drops in each of these areas—a trend that will likely continue in FY23. IHV has been established and is supporting indigenous organizations in four countries (Kenya, Botswana, Zambia, and Tanzania) to successfully compete to win relevant grants. The Immunotherapy, Vaccine Research, and Virology, Pathogenesis, and Cancer Divisions continue to deliver significant basic science and vaccine development grants.



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