INSTITUTE OF HUMAN VIROLOGY

ANNUAL REPORT 2021

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 Virology, Pathogenesis, and Cancer Division, Vaccine Research Division, Immunotherapy Division, 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 C virus, human T-cell leukemia viruses 1 and 2, human papillomavirus, herpes viruses, and cancer research. IHV's patient base has grown from just 200 patients to approximately 5,000 in Baltimore and Washington, D.C., and more than 2 million in African and Caribbean nations. In particular, IHV is internationally renowned for its basic science and vaccine research, which includes a preventive HIV vaccine candidate in human clinical trials and funded largely by the Bill & Melinda Gates Foundation.

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

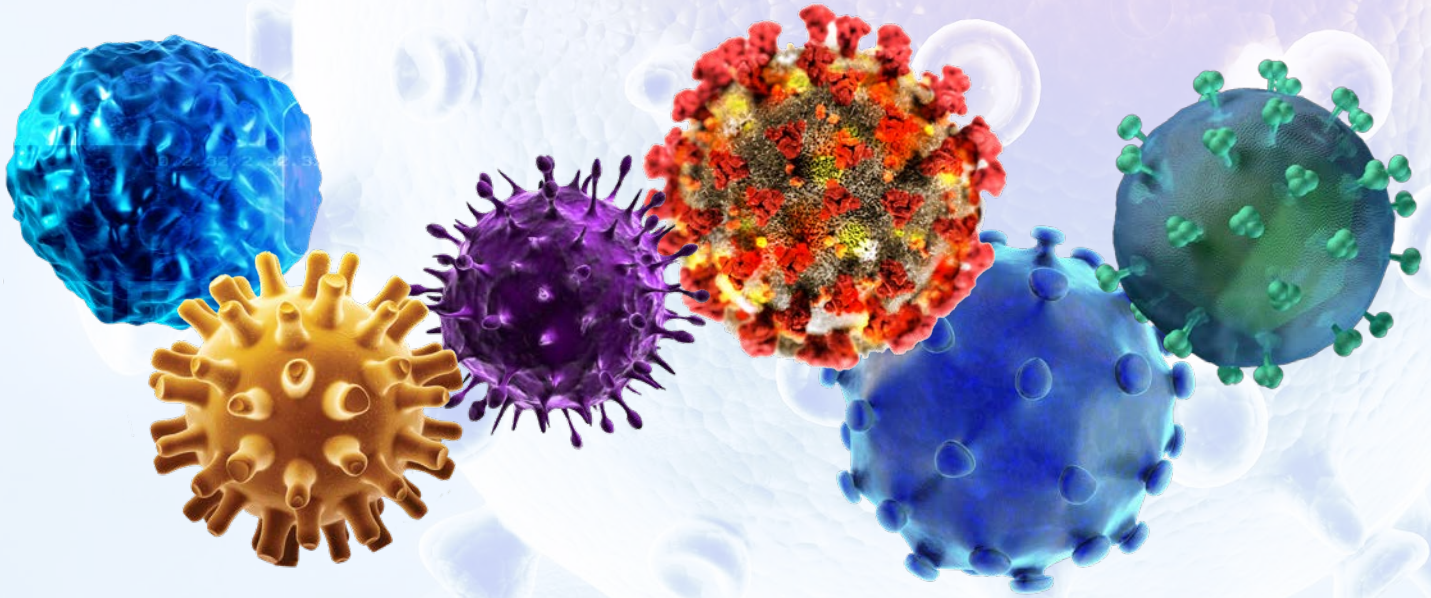
Our Mission

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

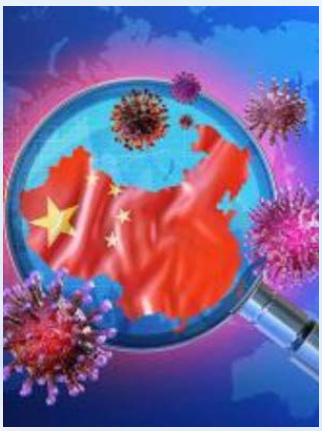
Robert C. Gallo, MD

This past fiscal year, the Institute of Human Virology at the University of Maryland School of Medicine pivoted much of its resources to battle the COVID-19 pandemic while simultaneously continuing to address challenges presented by viruses causing chronic infectious diseases. Also, as a result of the pandemic, IHV postponed its international annual meeting, where we plan to formally celebrate the 25th anniversary of the founding of the Institute.

Challenging Anti-Asian Sentiment

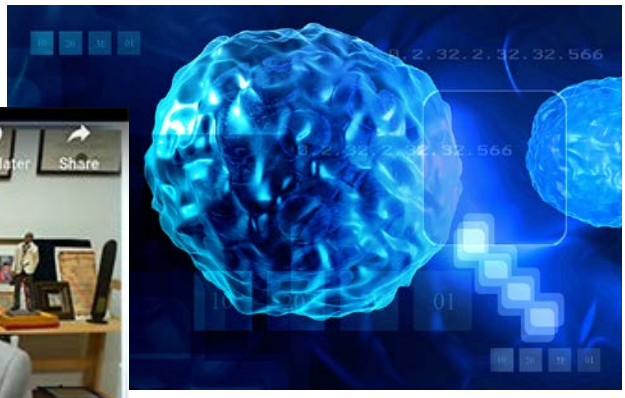
While the Divisions and Ciheb continued to advance their research and clinical programs, which you will read about more in depth later in this report, an important issue IHV leadership addressed was the continued anti-Asian sentiment that increased in the past year due to unfounded speculation about the virus' origin and some biased political sentiment, further resulting in assaults on private citizens, as well as smear campaigns against well-respected Chinese scientists.

IHV Board of Advisors Co-Chair Terry Lierman penned a letter to U.S. Representative Jamie Raskin, the Chair of the House Subcommittee on Civil Rights and Civil Liberties, requesting House Hearings to address racial profiling and investigations of Chinese and Asian descent scientists and scholars. The advocacy led Rep. Raskin and Rep. Judy Chu, Chair of the Congressional Asian Pacific American Caucus (CAPAC), this past summer to hold a roundtable entitled "Researching while Chinese American: Ethnic Profiling, Chinese American Scientists and a New American Brain Drain."



Despite the obstacles, or I should say even more so because of them, I firmly believe that we need to strengthen connections between China and the rest of the world, and one way to do this is through the Global Virus Network (GVN), which I co-founded and of which IHV is a leading Center of Excellence. GVN's mission includes bridging the world through scientific proven data without political influence. We can accomplish almost anything working together, such as ending the COVID-19 pandemic and preparing for any future viral threats.

Using Old Vaccines to Battle COVID-19 and Future Threats



Dr. Gallo suggests an oral polio vaccine could help fight coronavirus on Good Morning San Diego

Garnering international headlines this past year, was a research idea I pursued, in partnership with colleagues from the GVN, promoting the idea that live-attenuated vaccines (LAVs) such as measles, polio, and tuberculosis, may boost immunity to SARS-CoV-2 and provide some protection against future pandemics. We asserted in a perspective published in the Proceedings of the *National Academy of Sciences of the United States of America (PNAS)* that LAVs prospectively might offer a vital tool to bend the pandemic curve, averting the exhaustion of public health resources and preventing needless deaths, and merit being studied.

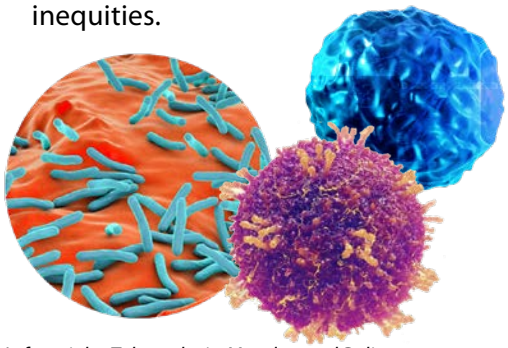
Our innate immune response is the first line of defense against invading, new pathogens. The outcome of any infection depends on the race between the pathogen and the host defense systems. The innate immunity and enhancing defense pathways provided by widely-used and well-recognized vaccines could substantially mitigate, or even prevent, infection from other pathogens such as SARS-CoV-2. This is especially valuable because LAVs can fill the gap until specific vaccines are available and, in particular, when they have not reached certain countries globally.

We very actively support the marvelous COVID-19-specific vaccines, and nothing in the *PNAS* publication conflicts with the development and use of these effective vaccines. This approach is worthy of prompt further study due to the probability of future pandemics. This could be a stop-gap before specific vaccines are made. But even in the current pandemic, they may be of use in non-affluent nations where the specific vaccines are not available.

Since the publication of our perspective in *PNAS*, studies by others have confirmed that LAVs such as MMR did help prevent severe COVID-19 disease progression. My esteemed colleagues and I continue to call

In this July 29, 1962 file photo, Mrs. Dayton George holds her son, Brian, 2, as she and her family take the Sabin oral polio vaccine in Richardson, Texas. Credit: Ferd Kaufman/Associated Press

on governments, philanthropy, and non-profit foundations to support testing of an LAV strategy to determine whether LAVs can protect high-risk populations, such as healthcare workers and the elderly, as well as low-income populations worldwide, thereby reducing social and economic inequities.



Left to right: Tuberculosis, Measles, and Polio

Mourning IHV Friends and Colleagues—

This past year, the Institute experienced significant losses of close friends and colleagues, who were also ***IHV Lifetime Achievement Awardees***.

Professor Yi Zeng, MD was presented the 2012 IHV Lifetime Achievement Award in Public Service for his lifetime of leadership in virology and cancer research

Dr. Zeng (left) and Gallo at a conference

Professor Yi Zeng, MD, Academician of the Chinese Academy of Sciences, former President of the Chinese Academy of the Preventive Medicine, and former Dean of the College of Life Science and Bioengineering at Beijing University of Technology, passed away in 2020. In 2012, IHV faculty unanimously voted to honor Prof. Zeng with the IHV Lifetime Achievement Award in Public Service for his lifetime of leadership in virology and cancer research. He was best known for establishing the relationship of Epstein-Barr virus (EBV) and nasopharynx cancer, developing EBV serologic tests for nasopharynx cancer early diagnosis, and discovering the first example of co-carcinogenesis in humans when a combination of EBV infection and particular carcinogenic products derived from Chinese medicines and foods common to Southern China caused nasopharyngeal carcinoma. Prof. Zeng was a founding Center Director of China's GVN Center of Excellence and hosted GVN's 7th International Meeting in Beijing, China in 2015. Prof. Yi Zeng's loss is a tremendous one not just for China, but for all of his colleagues around the world. We are saddened by this immense loss and extend our deepest sympathies to his family and friends.

In 2020, IHV Board of Advisors member **Harry Huge, JD,** passed away. He was co-founder and chairman of the Harry and Reba Huge Foundation and practiced law nationally and internationally in the areas of commercial litigation in federal and state courts, international business and transaction law, corporate matters, including securities, venture capital, biotechnology, communication, and investment transactions. Mr. Huge received his BA from Nebraska Wesleyan University and his JD from Georgetown University. During his law career, Mr. Huge was involved in several landmark cases too long to list. The Institute was pleased to honor Harry with the 2010 IHV Lifetime Achievement Award for Public Service held uniquely that

Harry Huge, JD

year in the ancient region of Calabria, Italy. Harry had a distinguished law career with, among others, American labor unions and the country of Estonia, and he was generous in his philanthropic work providing American students continued education scholarships, particularly in the area of science, through the Huge Foundation. We are most grateful for his profound support of advancing biomedical science, particularly for the IHV and the GVN, and we extend our deepest sympathies to his loving family.

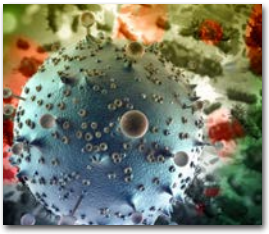
Harry Huge, JD, (right) with Dr. Gallo recieving the 2010 IHV Lifetime Achievement Award

John Martin, PhD, (left) with Dr. Gallo recieving the 2014 IHV Lifetime Achievement Award.

In 2021, **John Martin, PhD,** who was also a GVN Board of Directors member, passed away. John received IHV's 2014 Lifetime Achievement Award for Public Service and was IHV's 2017 Annual Marlene and Stewart Greenebaum Lecturer. He was a leader in supporting access to life-saving anti-HIV medications that although still under patent were made widely and affordably available to millions around the world infected with HIV, and for prevention through pre-exposure drug therapy. John was a tremendous clinical scientist, businessman, global public health leader, philanthropist, and good friend. The fields of medicine and science have many notable leaders who contribute to public health. But it is his leadership at Gilead Sciences that stands out and resulted in the successful development of antiviral therapeutics for the treatment of HIV, hepatitis B and C, and influenza. Further, the global public health response to HIV/AIDS was immensely facilitated by John, which is unique among the global pharmaceutical industry. His humanitarian leadership resulted in more than 10 million HIV-infected persons receiving lifesaving therapies with the best drugs available. His life's work lives on in those he mentored and in The John C. Martin Foundation, among many others. John Martin is irreplaceable, and his passing is a devastating loss to many.

Dr. John Martin speaks at IHV's annual meeting in 2019.

IHV At-A-Glance



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 inter-disciplinary Research Programs that cover numerous aspects of infection, immunity, and inflammation research, including: Microbial Pathogenesis, Cancer Biology, Immunity & Inflammation, Structural Biology & Molecular Biophysics, and Drug Discovery & Development. The Division is directed by **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Professor, Departments of Pharmacology, Microbiology & Immunology.

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 and Professor of Microbiology and Immunology. The Division of Vaccine Research faculty and collaborating faculty in the Division of Clinical Care and Research continue the development of an AIDS vaccine under the IHV "bench to the clinic" model of translational research. This model enables a strong multidisciplinary approach to AIDS vaccine development by combining the tools molecular and cell biology, virology, immunology, optical physics, structural biology, and state-of-the art clinical trials capacity, all within a single building housing the IHV. 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. The IHV-001 is a conformationally constrained protein comprised of HIV-1 gp120 linked to the first two domains of human CD4 by a flexible peptide spacer. This immunogen is denoted as the full-length single chain (FLSC) protein.

Division of Clinical Care and Research

The Division of Clinical Care and Research is the leader in providing the highest quality clinical care, clinical research, and medical education in the Baltimore and Washington, D.C. metropolitan area. The Division has 44 faculty members and more than 75 support personnel, who managed over 50 active grants and contracts this year. The Division is led by **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division and Head of the Clinical Care Research Unit, with clinical leadership by **Anthony Amoroso, MD**, Professor of Medicine, Associate Director of the Division, Head of Clinical Care Programs. Dr. Kottilil and Dr. Amoroso have built a clinical care and research program that provides both the most advanced medical care to our patients, while pursuing the research questions that will most impact their lives.

The Baltimore-based ambulatory clinical programs supported by the Division continue to provide premier care in the management and prevention of HIV infection, hepatitis comorbidities, and treatment of patients with other infectious diseases under the clinical leadership of Dr. Amoroso. The clinical research program under Dr. Kottilil's direction, continues to concentrate on studies focused on therapeutics and a cure for hepatitis B, HIV cure-related research, COVID-19, other infectious diseases, and the intersection of opioid-use disorder and 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, Director of Center for International Health, Education, and Biosecurity (Ciheb), continues a research focus. The division published 90 manuscripts in peer-reviewed journals in FY21, and the 12 faculty-led 21 federal research awards.

Division of Immunotherapy

The Division of Immunotherapy, currently led by **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology and Microbiology & Immunology, continues its fundamental research on cancer immunology and immunotherapy. This year, **Yang Liu, PhD**, former Professor of Surgery and Director of the Division of Immunotherapy, and **Pan Zheng, MD**, PhD, former Professor of Surgery and Immunotherapy faculty member, made a great achievement in combating COVID-19 based on their fundamental research of the CD24-Siglec innate immune checkpoint. In collaboration with Yong-Tang Zheng, PhD, Professor at the Chinese Academy of Science, they discovered that CD24Fc protects against viral pneumonia in simian immunodeficiency virus-infected Chinese rhesus monkeys. In collaboration with Dr. Su, they found that CD24Fc reduces T-cell lymphopenia and exhaustion in HIV-infected humanized mice. In a clinical trial, COVID-19 patients that received CD24Fc had a 60% higher probability of seeing improved clinical status. These findings led to the acquisition of Oncoimmune by Merck. In November 2020, Oncoimmune co-founders Dr. Liu and Dr. Zheng left IHV and established OncoC4. Following their departure, Dr. Su has taken leadership of the Division of 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 2020-2021, 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.

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

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

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

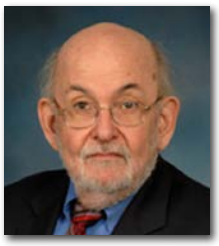
Financial Overview

IHV had yet another strong financial year in FY21, generating $112,500,000 of total revenue. This resulted from continued stability in all 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). Significant change can be expected year over year in Ciheb and Population-Based HIV Impact Assessment (PHIA) funding, as these amounts are fundamentally affected by U.S. government policy regarding awards of funds to indigenously based versus U.S. entities. This year and in years to come, 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 FY22. In FY20, IHV received funding in the amount of $48,000,000 for PHIA surveys in Nigeria, Zambia, and Botswana. We are currently awaiting decisions as to whether CDC will conduct PHIA HIV surveys in any number of new countries—decisions that will have well over a $10 million impact on our budget. IHV is working with foresight to prepare for reduced funding by establishing and supporting indigenous organizations to successfully compete to win relevant grants, for which they would seek our support. 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 & 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 & 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
Head, Clinical Research Unit
Institute of Human Virology
Professor, Medicine
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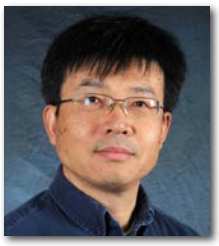


Lishan Su, PhD

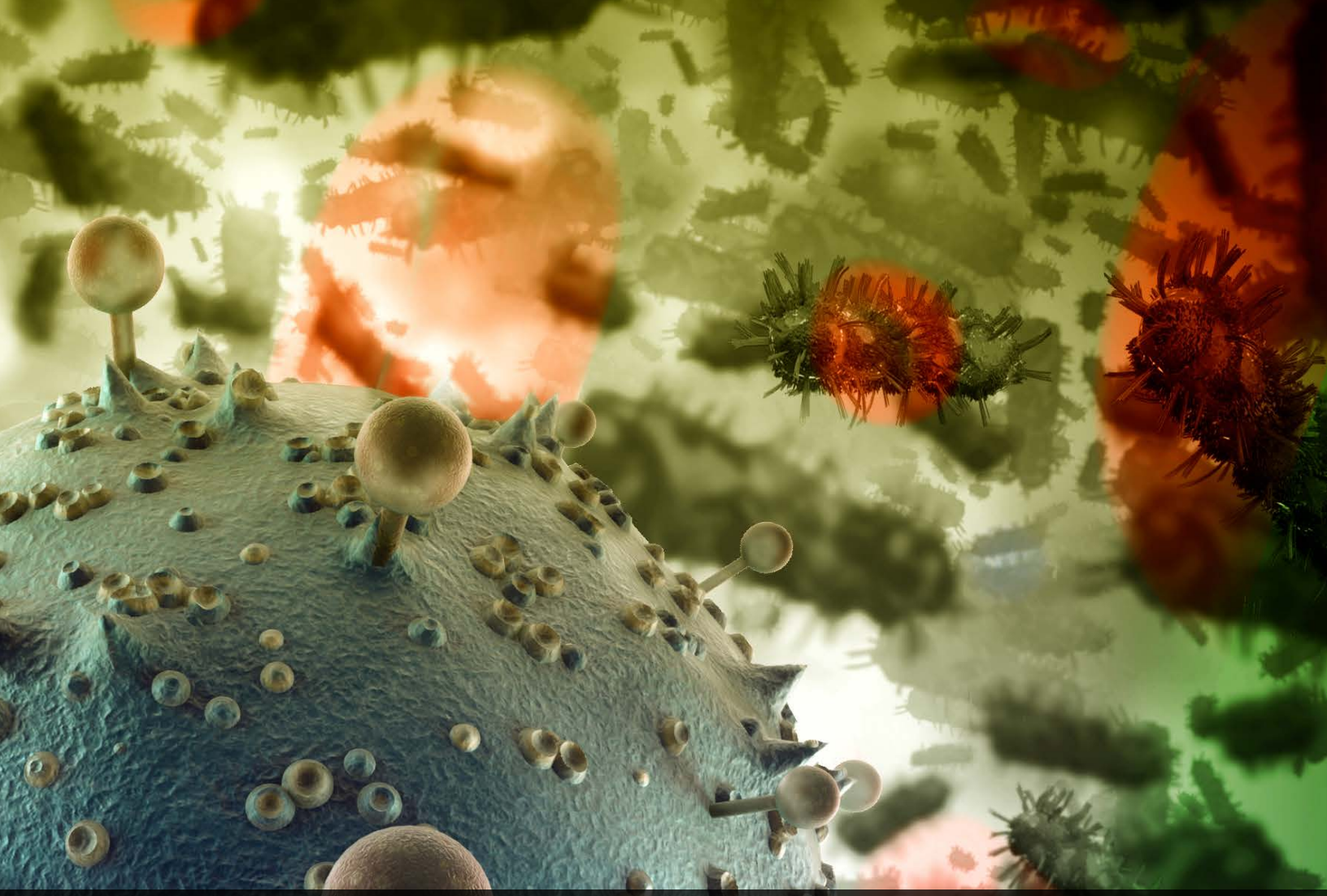
Director, Division of Virology, Pathogenesis, and Cancer,
Interim Director, Division of Immunotherapy
Institute of Human Virology
The Charles Gordon Smith Professor for HIV Research
University of Maryland School of Medicine

Anthony Amoroso, MD

Associate Director, Division of Clinical Care and Research
Head, Clinical Care Programs
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



The Division of Virology, Pathogenesis, and Cancer (VPC)

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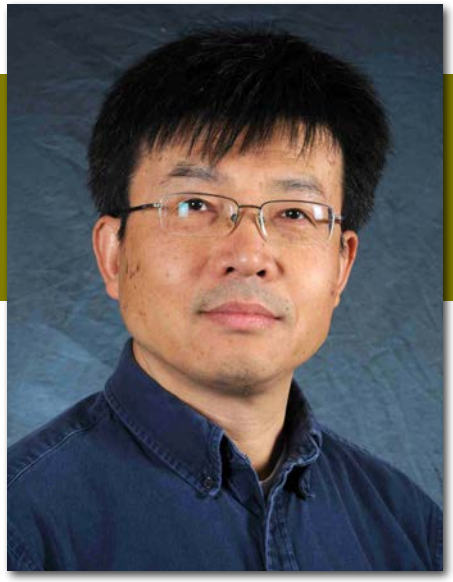
Virology, Pathogenesis, and Cancer (VPC)



Lishan Su, PhD

The division is directed by **Lishan Su, PhD**, The Charles Gordon Smith Professor for HIV Research, Professor, Departments of Pharmacology, Microbiology & Immunology. The Division was renamed the Division of Virology, Pathogenesis, and Cancer (VPC) this past year.

Hongshuo Song, PhD

As the PI of a currently on-going R21 grant, **Hongshuo Song, PhD**, Assistant Professor of Medicine, successfully led the viral genetic study of the therapeutic Ad26/MVA mosaic HIV vaccine trial (RV405) to its completion. A genetic analysis identifying a potential "rebound bottleneck" and viral phenotype characterization is currently ongoing, which is expected to provide important insights into HIV cure strategies. Dr. Song's lab successfully constructed the infectious molecular clone of the first CXCR4-tropic transmitted/founder (T/F) HIV-1. This is the first demonstration that X4-tropic HIV-1 without CCR5-using ability is transmissible through the mucosal route. Another major progression is that Dr. Song's group for the first time captured the de novo evolution process of a HIV-1 coreceptor switch in natural infection and demonstrated that "driver mutations" triggering the coreceptor switch is associated with immune escape to neutralization activity. Based on this finding, as well as the fact that the receptor binding regions of many viruses tend to overlap with antigenic epitopes, Dr. Song proposed a potentially paradigm-shifting concept: the "escape by shifting" model that for viruses with receptor flexibility, shift in receptor specificity can be an evolutionary mechanism of viral immune evasion in natural hosts with humoral immunity. The long-term goal is to explore the "escape by shifting" scenario in a wide variety of viral infections in relation with viral pathogenesis, disease outcome, and zoonotic potential, which may lead to entirely novel insights into therapeutic and preventative approaches.

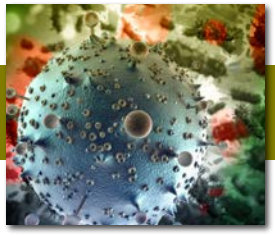
Alfredo Garzino-Demo, PhD

The lab of **Alfredo Garzino-Demo, PhD,** Associate Professor of Microbiology and Immunology, already has several cell lines that constitutively express the Spike protein of SARS-CoV-2, and the lab uses them to produce high titers of pseudotype virus, using an HIV backbone. Dr. Garzino-Demo's lab is now setting up a non-infectious SARS-CoV-2 entry fusion assay, which will make it possible to evaluate potency of anti-SARS-CoV-2 antibodies without the need for a BSL3 lab. The assay toolbox will be of great utility to clinical and basic sciences. Clinicians will be able to quickly determine the presence and potency of neutralizing antibody responses, informing the strategy for the care of the patients. Researchers will benefit tremendously from fast and accurate tools to identify and characterize neutralizing and ADCC-inducing antibodies. As added benefits, the assays for the toolbox can be used also to screen drugs, peptides, and aptamers for their activity against SARS-CoV-2. Dr. Garzino-Demo is a highlighted VPC faculty member for this year's report and detailed research activities will follow.

Olga Latinovic, PhD, MSc, MBA

The lab of **Olga Latinovic, PhD, MSc, MBA,** Assistant Professor of Microbiology and Immunology, research efforts focus on the chemokine coreceptor CCR5 and its role in HIV infection with different combined antiretroviral therapy designs. The goal of Dr. Latinovic's current research line is to investigate if T/F viruses enter primary cells via a distinct CCR5 subpopulation, and how these quantified subpopulations might differ from those bound by CI viruses. Dr. Latinovic's lab successfully developed a methodology for the detection and quantitative analysis of overlapping events between intracellular (CCR5 C-terminus-GFP fusion protein collaboration with **Yutaka Tagaya, BM, PhD,** Assistant Professor of Medicine) and extracellular (panel of various mAbs against N-terminus, ECL2, and multidomain) CCR5 epitopes. This methodology has allowed the group to characterize and quantify which CCR5 subpopulations are permissive for HIV-1 infection (including both, T/F, and CI viruses) *in vitro*.

Detailed research activities for VPC faculty are outlined on the following pages.

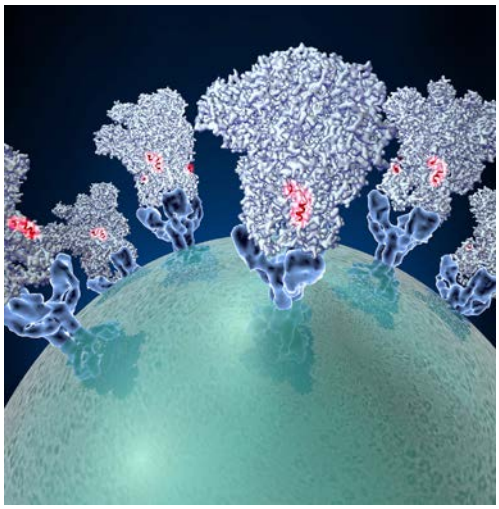


Garzino-Demo Laboratory

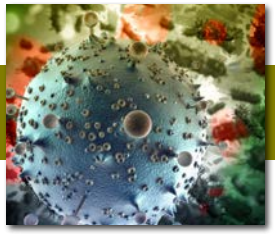
The **Laboratory of Virus-Host Interactions**, headed by **Alfredo Garzino-Demo, PhD,** Associate Professor of Microbiology and Immunology, studies the etiopathogenesis of viral infections with the aim of developing new therapeutic approaches. For many years, the laboratory has been focused on HIV infection, but in 2020 it started studies on SARS-CoV-2.

Alfredo Garzino Demo, PhD, discusses protein expression data with Virginia Carroll, PhD (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

I. Toolbox to detect SARS-CoV-2 antibodies: The emergence of SARS-CoV-2 in the human population has resulted in a pandemic disease, COVID-19, that has brought most of the developed world to a virtual standstill due to lockdowns to prevent further spreading of the infection. More than 209 million reported cases and more than 4 million deaths have occurred worldwide as of August 18, 2021. Currently diagnosed US COVID-19 cases stand at about 37 million, with more than 620,000 reported deaths. These figures do not take into account asymptomatic and non-diagnosed cases, which would significantly increase the toll of the disease on humanity. COVID-19 research progressed rapidly, starting with the identification of its causative agent, SARS-CoV-2, and its receptor within a month of the emergence of disease. The brisk pace of research and development resulted in the emergency use approval of several safe and effective vaccines. However, the emergence of variants of concern, including the rapidly spreading delta, which is less susceptible to the activity of antibodies elicited by currently available vaccines, calls for the rapid identification of new antiviral antibodies and drugs. The identification of antibodies that can neutralize infection, or that can induce antibody-dependent cellular cytotoxicity (ADCC) is currently based either on infections with replication competent virus (necessitating highly trained personnel and BSL3 facilities) or single-cycle pseudotype viruses (which are cumbersome to prepare and have variable batch-to-batch titers). In the laboratory, we are developing an advanced assay toolbox of robust, highly reproducible assays to detect neutralizing antibodies (or drugs that block entry and/or fusion), ADCC-inducing antibodies, and produce high-titer pseudovirions. The toolbox is composed of permutations of well-characterized reagents, adjusted to the needs of each assay. We are developing: 1) a non-infectious, high-throughput-ready assay detecting anti-SARS-CoV-2 neutralizing antibodies. We will use well-established cell lines engineered to express the viral Spike protein, or the cellular ACE2 receptor, and monitor fusion using GFP fluorescence as a reporter. We will use this assay to identify neutralizing antibodies from sera of convalescent patients; 2) an assay to detect anti-SARS-CoV-2 antibodies that can induce antibody-dependent cellular cytotoxicity (ADCC). We will use established cell lines resistant to NK cytotoxicity, to express viral Spike protein, to identify antibodies that induce ADCC; 3) a highly reproducible system to produce pseudotype viruses bearing the SARS-CoV-2 Spike protein. Besides developing new assays, the reagents that we will prepare in the course of the studies described above will be useful to improve and optimize pseudotype virus production, which is normally affected by variability due to the efficiency of co-transfecting different constructs. We will use cell lines permanently expressing viral Spike protein to produce pseudotype SARS-CoV-2 spike viruses at a reproducibly high titer. The pseudotypes will be



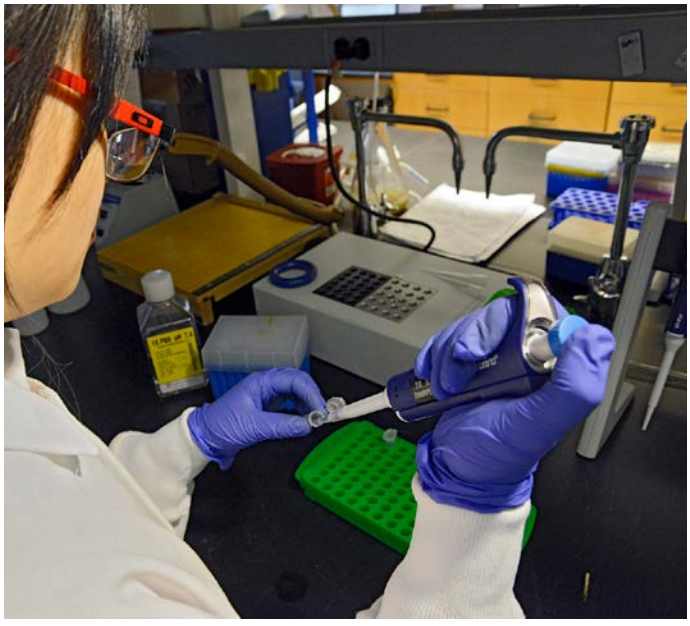
The illustration shows a SARS-COV viral membrane decorated with spike proteins; highlighted in red is a potential antibody neutralization site. Credit: NIGMS via David Veesler, University of Washington

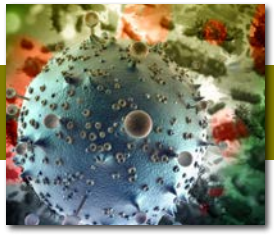


useful for infectivity and neutralization assays.

The toolbox will be of great utility to clinical and basic sciences. Clinicians will be able to quickly determine the presence and potency of neutralizing antibody responses, informing the strategy for the care of the patients. Researchers will benefit tremendously from fast and accurate tools to identify and characterize neutralizing and ADCC-inducing antibodies. As added benefits, the assays that will compose the toolbox can be used also to screen drugs, peptides, and aptamers for their activity against SARS-CoV-2. Part of these studies will be pursued in collaboration with **Joseph P.Y. Kao, PhD,** Professor of Physiology, and **Eric Legenzov, PhD,** Postdoctoral Fellow, in the Department of Physiology.

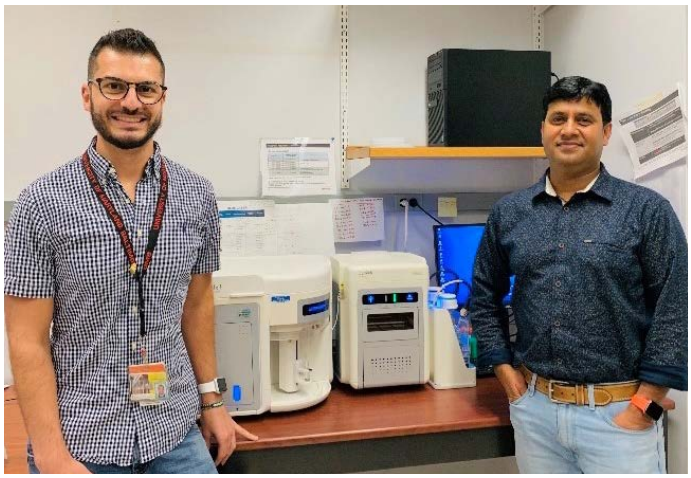
II. Pathogenesis of HIV infection: In the last decade, studies performed in the laboratory have characterized that HIV preferentially infects cells that express the CCR6 chemokine receptor. CCR6 is expressed on memory T-cells, Th17 cells (i.e., helper T-lymphocytes that produce Interleukin (IL)-17, macrophages,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





Rathinam Laboratory

In Fall 2016, **Chozha Rathinam, PhD,** Associate Professor of Medicine, joined the IHV. In the past five years at IHV, the Rathinam laboratory has trained two postdoctoral scientists (**Panjamurthy Kuppuswamy, PhD,** and **Ram Lakhan, PhD**), one medical student (**Huanwen (Alvin) Chen, MD**) and one undergraduate student (**Ms. Ashlee DeLeon**). **Giovannino Silvestri, MS, PhD,** is a Research Associate of Medicine in the lab. Research undertaken at the Rathinam lab in the past few years has made seminal contributions to the fields of both immunology and stem cell biology.



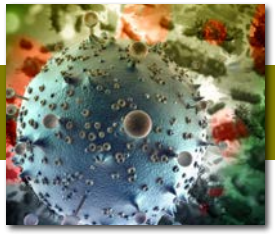
Dr. Silvestri (left) and Dr. Rathinam

In particular, studies have emerged from the Rathinam lab that have unequivocally proven the roles of infection and inflammation in the control of hematopoietic stem cell (HSC) development.

Inflammatory signals as key regulators of HSCs: The role of infection and inflammation in the control of hematopoiesis has gained a lot of attention in recent years. While it was believed that only lineage committed progenitors were involved in sensing and in responding to infections, it is now evident that HSCs are directly involved in the primary response of both acute and chronic infections. The direct response of HSCs to an immune insult might be a key determinant in the clearance of the pathogen, since HSCs can dictate cell fate decisions and can preferentially differentiate into a particular hematopoietic lineage, in order to clear the pathogen. While previous studies have elegantly and unequivocally demonstrated the significance of inflammatory signals in determining the outcome of hematopoiesis, mechanisms through which inflammatory signals govern HSC proliferation and differentiation remain totally unknown. A series of recent studies (Nakagawa MM, *Cell Reports*, 2018; Nakagawa MM, *Frontiers in Cell and Developmental Biology*, 2018; Nakagawa MM, *Stem Cell Research*, 2018; Nakagawa MM, *Scientific Reports*, 2019) from the Rathinam lab has indicated that decontrolled inflammation (through either a deficiency of an ubiquitin editing enzyme–A20 or constitutive activation of canonical NFκB pathway) results in pancytopenia, myeloproliferation, bone marrow failure, and premature death.

Notch signaling circuits in pathologic hematopoiesis: Misregulation or loss of Notch signaling underlies a wide range of human pathologies, from developmental defects to adult-onset diseases. Recent evidence supports a potent tumor suppressor role for Notch in both solid tumors and hematological malignancies. These links to human disease provide a compelling rationale for further investigation into molecular mechanisms through which Notch regulates hematopoiesis. Pioneering studies over the past two decades (including our own) established that overexpression of Notch1 causes increased self-renewal and immortalization of hematopoietic stem cells (HSCs). However, studies based on loss of functions approach demonstrated a dispensable role for Notch1 in HSCs. To understand the complex roles of the Notch pathway in HSCs and explain this molecular paradox, we ablated Rbpj-mediated canonical Notch signals in HSCs and studied the downstream consequences on HSC maintenance and functions. Our data specify that canonical notch signals play indispensable roles in the differentiation of lymphoid-primed multipotent progenitors (MPP4) and hematopoietic recovery following radiation-, genotoxic-, and cytokine-induced stress. Unexpectedly, our studies identified that Rbpj deficiency leads to activation of Notch target genes through Hif-1α mediated non-canonical Notch pathways in HSCs. In essence, our studies (Lakhan R, *Frontiers in Cell and Developmental Biology*, 2021) identified a previously unknown role for non-canonical Notch signaling and established a functional link between Hif and Notch pathways in hematopoiesis. In addition, our mechanistic studies provided novel insights and rationale as to how and why loss of canonical Notch signals might result in normal hematopoiesis under steady state hematopoiesis.

Molecular control of dendritic cell differentiation from HSCs: Dendritic cells (DCs) are essential to initiate and dictate both innate and adaptive immune responses. In particular, DCs are essential for antigen presentation and initiation of protective



T-cell responses. DCs are located throughout the body and form a sophisticated and complex network that allows them to communicate with different populations of lymphocytes. Intensive research in the past several years enriched our knowledge on the functional roles of distinct DC subsets in steady and pathologic states. However, molecular mechanisms that drive differentiation of hematopoietic progenitors into the DC lineage remain largely unknown. One of the major interests of the Rathinam lab is to identify novel transcriptional targets and molecular drivers of DC development and functions, which may allow to engineer DCs for immunomodulation and targeted vaccine approaches.

To this end, a recent study was focused on identifying the contribution of PI3K signaling pathways in DC differentiation. Our studies identified that a deficiency of p85α and p85β subunits of PI3K causes increased differentiation of cDC2 and pDC subsets in the spleen. On the other hand, DC numbers in the bone marrow (BM), thymus and lymph nodes were decreased in p85α and p85β mutant mice. Interestingly, non-lymphoid, resident tissue DCs remain unaffected in p85 deficient mice. Analysis of DC-specific progenitors and precursors indicated increased numbers of common DC progenitors (CDPs) in the BM and precursors DCs (pre-DCs) in the BM and spleen of p85 deficient mice. *In-vitro* differentiation studies demonstrated augmented DC-differentiation capacities of p85 deficient BM cells in the presence of GM-CSF and Flt3L. Molecular studies revealed increased proliferation of DCs and CDPs in the absence of p85 and altered signal transduction pathways in p85 mutant DC subsets in response to Flt3L. In essence, our studies, for the first time, unequivocally established that the regulatory subunits of class I_A PI3Ks play pivotal roles in the development and maintenance of DCs.

Dr. Silvestri is currently investigating the functions of an interesting protein that acts as both transcription factor and E3 ubiquitin ligase during the differentiation of DCs. Through a spectrum of gene specific mutant mice and selective ablation of the candidate genes at distinct stages of DC development, data of Dr. Silvestri document a striking reduction of DCs in all lymphoid organs. An intensive high throughput molecular analysis identified a novel signaling circuit in the regulation of DCs. Knowledge obtained from these studies will provide key insights into the cellular and molecular mechanisms through which early differentiation programs and functions of DCs are controlled.

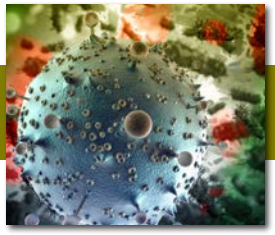
Su Laboratory

After joining The Institute of Human Virology at UMSOM in Oct. 2020, the laboratory of **Lishan Su, PhD,** The Charles Gordon Smith Professor for HIV Research, Professor, Departments of Pharmacology, Microbiology & Immunology, Director, Division of Virology, Pathogenesis, and Cancer, Interim Director Division of Immunotherapy, continues the research programs to investigate human immunity and inflammatory diseases, and to develop antibody and cell-based drugs targeting novel immune cells and signaling pathways. The laboratory thus studies how HIV-1 and HBV interact with human immune cells to cause inflammatory diseases (Immunology). Our group has discovered and focused on the plasmacytoid dendritic cell (pDC)-interferon axis in the immunopathogenesis and therapy of chronic HIV infection. The group has also started investigation of the pDC-IFN-Mac axis in tumor microenvironments (TME) and in cancer immune therapy. 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.

Virology and Immunopathogenesis

1. "HIV-1 Vpr disrupts the IFN-TET-ISG pathway to promote HIV-1 infection and persistence": The long-term goal of this investigation is to elucidate the mechanisms by which HIV-1 accessory protein Vpr alters the host defense pathway to enhance HIV-1 infection and persistence. We propose that the Vpr-TET2-IFN-ISG pathway modulates HIV infection, IFN signaling and the expression of a subset of ISGs. In the past year, we reported that Vpr enhanced HIV-1 infectivity associated with increased Env processing in macrophages. Vpr-enhanced Env processing depended on TET2 and IFITM3, which were constitutively expressed in human monocyte-derived macrophages (MDMs). We further showed that Vpr reduced IFITM3 expression by degrading TET2 in macrophages associated with reduced demethylation of the IFITM3 promoter. We conclude that HIV-1 Vpr enhances viral infectivity in macrophages by suppressing TET2-dependent IFITM3 expression. Therefore, the Vpr-TET2 axis reduced IFITM3 expression via TET2 dioxygenase-dependent and sustained IL6 induction via TET2 dioxygenase-independent mechanisms to contribute to elevated HIV-1 replication during HIV-1 infection.

2. HIV-1 Vpr modulates the TET2/IRF7 axis to impair IFN induction in pDCs to enhance HIV-1 replication: As one



of the abundant HIV-1 virion-associated proteins, Vpr remains the most enigmatic of HIV-1 accessory proteins that enhances HIV-1 replication via unclear mechanisms. We discovered that Vpr-facilitated viral replication in CD4+ T-cells when co-culture with pDCs via IFN-dependent mechanisms. We showed that Vpr impaired IFN-I induction in pDCs activated by HIV-1 or R848, correlated with Vpr activity that is dependent on its interaction with VprBP but not on G2 cell cycle arrest. We further demonstrate that Vpr reduced IFN regulatory factor 7 (IRF7) transcription in pDCs by degrading TET2. Vpr failed to further reduce IFN-I production and IRF7 transcription when TET2 was genetically depleted in pDCs. Finally, depletion of TET2 in pDCs by either Vpr or shRNA reduced the demethylation of IRF7 promoter. We conclude that Vpr can enhance HIV-1 replication by modulating IFN-I induction in pDCs and the Vpr-TET2-IRF7 axis may provide a novel therapeutic target to control HIV-1 infection.

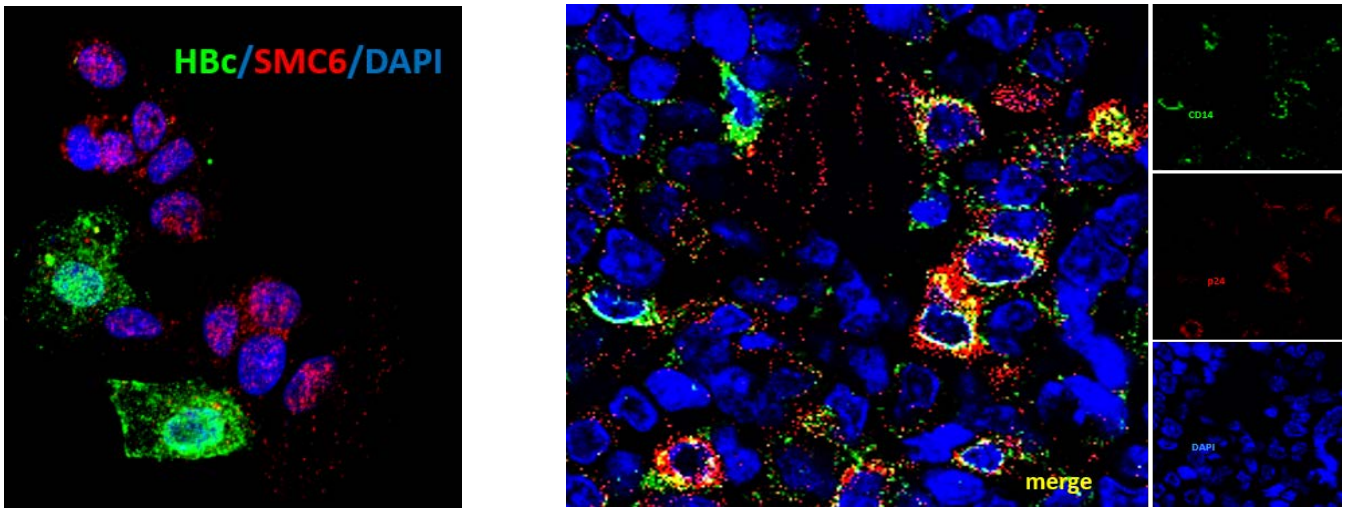
3. HIV-1 immunopathogenesis in the absence and presence of ART

a. **HIV-1 induced innate immune responses +/- cART/pDC depletion in vivo characterized by single cell RNAseq and CYTOF in the spleen and bone marrow of humanized mice:** We employed the single-cell RNA sequencing (scRNA-seq) technology to study HIV-induced transcriptomic change in innate/adaptive immune cells in lymphoid organs of hu-mice with HIV/ART +/- pDC depletion. We performed scRNA-seq on total human CD45+ and CD3-hCD19- human leukocytes isolated from spleens or bone marrow of HIV-infected humanized mice (NRG-hu HSC mice +/- HIV +/-ART). In summary, we characterized HIV-induced transcriptomic changes of innate immune cells in the spleen at single-cell levels and identified the pathogenic immune cells *in vivo* (Cheng et al. *JCI-Insight*, 2020).

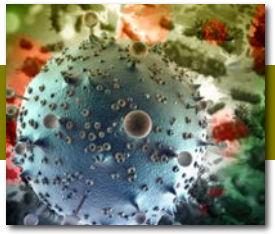
b. **pDCs/IFN contribute to anti-HIV T-cell exhaustion and HIV persistence through dysregulation of T-cell metabolism in lymphoid tissues with chronic HIV infection:** Individuals infected with human immunodeficiency virus type-1 (HIV-1) show metabolic alterations of T-cells through unclear mechanisms with undefined consequences. We analyzed the transcriptome of T-cells from patients or hu-mice with HIV-1 and revealed that the altered oxidative phosphorylation (OXPHOS) pathway is associated with immune pathology. Inhibition of OXPHOS by 2DG or the US Food and Drug Administration-approved drug metformin suppresses HIV-1 replication in human CD4+ T-cells and rescues T-cells in humanized mice. These studies uncover the glycolysis/OXPHOS pathways in T-cells as a target for HIV-1 therapy (Guo, Wang et al. 2021, *Nature Immunology).*

Immunotherapy of HIV Pathogenesis and Tumors

1. pDCs contribute to T-cell exhaustion and HIV persistence through induction of IDO+ mDC/Mac: We discovered that pDC-depletion during suppressive cART in humanized mice resolved HIV-associated inflammatory diseases and rescued anti-HIV-T cells. Importantly, pDC-depletion in HIV-infected mice under cART reduced HIV-1 reservoirs in lymphoid and other



Left: *Hepatitis B viral infected human and mouse liver cells. The viral protein HBx degrades the human/mouse protein SMC6. Credit: Dr. C. Murphy, Dr. N. Reszka-Blanco, and Dr. Lishan Su*
Right: *Using a drug to activate HIV reservoirs in immune system cells. Credit: Dr. G. Li and Dr. N. Reszka-Blanco*



tissues *in vivo*. In addition, we found that HIV-1 infection induced indoleamine 2,3-dioxygenase (IDO) expression in a pDC-dependent fashion *in vivo.* Furthermore, IDO inhibition reversed HIV-1 immune pathogenesis, rescued anti-HIV T-cells and reduced HIV reservoirs in cART-treated mice *in vivo*. We conclude that pathogenic pDCs contribute to residual inflammation via persistent IDO induction during effective cART *in vivo*. These pathogenic pDCs contribute to HIV/cART-associated inflammatory diseases, depletion, and exhaustion of anti-HIV T-cells, and HIV-1 reservoir persistence. Targeting the pDC-IFN-IDO axis may provide a novel strategy for treating HIV/cART-associated inflammatory diseases and for controlling HIV-1 reservoirs during cART (HIV-1 cure).

2. Virological and immune mechanisms of HIV-enhanced liver diseases

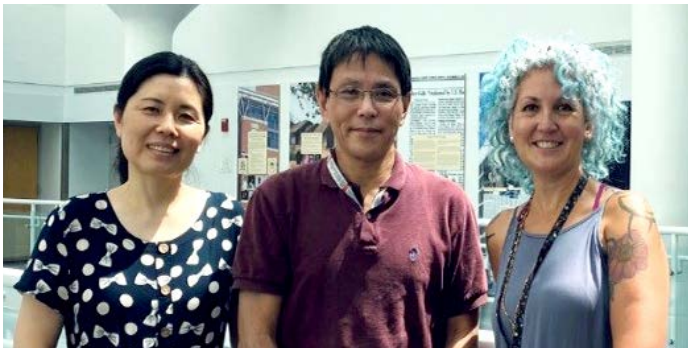
Liver diseases caused by HIV-1 infection under cART or HAART without HBV/HCV co-infection are generally understudied and pose a serious health problem because half of the estimated 38 million HIV-infected people are currently under cART. HIV-induced inflammation is not completely resolved during cART and may contribute to the increased risk of liver diseases.

We have discovered that HIV infection and cART in humanized mice induced hepatitis and an increase in collagen deposition and fibrosis-associated genes in the liver, correlated with an interferon signature. HIV-1/cART led to infiltration of human M2-like macrophages in the liver. In addition, we identified that type I IFNs directly activated hepatic stellate cells as well as enhanced TGF-β-induced activation of hepatic stellate cells through the elevated phosphorylation of Smad2/3 in hepatic stellate cells. Finally, blockade of type I IFN-α/β receptors reversed HIV/cART-induced hepatitis and liver fibrosis in humanized mice. These findings provide mechanistic insights related to the role of type I IFNs in liver fibrosis during chronic HIV-1 infection and raise the possibility of transiently blocking IFN-I signaling in PWH under cART would provide a novel strategy to treat HIV/cART-associated inflammatory liver diseases.

a. Chimeric antigen receptor (CAR) T cells in immunotherapy: Adoptive transfer of CAR-engineered immune cells represents an opportunity to provide virus- or tumor-specificity that does not require MHC-mediated antigen presentation and neoantigens. However, developing CARs for patients remains challenging because: (1) HIV-inflamed tissues and the TME of solid tumors are highly immunosuppressive. B7-H3 functions as an immune co-inhibitory molecule since it reduces type I interferon release by T-cells and cytotoxic activity of natural killer (NK) cells. With our collaborators, we have identified B7-H3 as a suitable CAR target antigen in multiple tumors. B7-H3 expression frequently correlates with faster cancer progression and poor clinical outcome. In addition to tumor cells, B7-H3 is also overexpressed by the tumor-associated vasculature and stroma fibroblasts. Fc-enhanced B7-H3-specific monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs) showed effective antitumor activity against B7-H3+ tumor cells in preclinical xenograft mouse models. These data prompted us to generate B7-H3-specific CAR-T cells (B7-H3-CAR-Ts) and to obtain remarkable antitumor activity in solid tumor models.

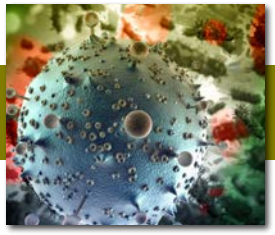
Tagaya Laboratory

The lab of **Yutaka Tagaya, BM, PhD,** Assistant Professor of Medicine, studies T-cell biology, cytokine/receptor structure and function in immune responses and human T-cell leukemia virus-1 (HTLV-1). Over the past several years, the research focus has been on exploiting small molecule inhibitors to understand the disrupted interaction of immune cell subpopulations via cytokines and their translational applications as therapeutics on select immune/inflammatory diseases, as well as in cancer.



Xiarong Wu (left), Dr Tagaya (center), and Felisa Diaz-Mendez

The first project involving small molecule drug development started back in 2011, when I was testing a hypothesis that a peptide that resembles in structure the shared portion of γc-cytokines (Interleukin (IL)-2, 4, 7, 8, 15, and 21) might block multiple family member cytokines, not just one. All γc-cytokines bind to the γc (CD132) molecule and use it as a signal transducing subunit in their receptors. Each one of them has critical function in hematopoiesis and in immune responses. We noted that all six cytokines show weak sequence homology (15-25%) at the amino acid level, but the conservation is higher



(50-80%) at the C-terminus region called the D-helix (i.e., most cytokines display a four α-helical bundle structure and the D-helix stands for the most C-terminal α-helix of the four). We designed D-helix resembling peptides (since there are several wobble positions when all six cytokines were aligned at the D-helix position, more than 2,000 variants of the peptides were possible) and screened them *in silico* using a docking algorithm to exclude those that do not bind to the cytokine-binding pocket of the γc-molecule. This process reduced the number of candidate peptides to less than 100, all of which were synthesized on a small scale and tested by a cytokine-specific proliferation assay using indicator cell lines. One of the resultant peptides showed potent inhibiting activity only against IL-2 and IL-15, and to a lesser degree to IL-9, but not to IL-4, 7, 21 of the γc-cytokines or non-γc-cytokines. Thus, this unique strategy gave rise to a series of new peptides, which inhibits the selected members (but not all members) of the γc-cytokines ***(Figure 1)***. By changing the amino acid sequences, we could also synthesize other inhibitors that are specific for IL-15 and IL-21 (but not for other γc- or non- γc-cytokines). To our knowledge, this is the first successful example of synthesizing inhibitors that block multiple members of cytokines that share structural similarity/ receptor components. It is of note that most cytokines belong to a certain cytokine family like the γc-family, so this technology can be expanded to synthesize inhibitors that block multiple and selective members of the other important cytokine families (*e.g.,* IL-6 family, IL-17 family, IFN family etc.).

The lead inhibitor blocks IL-2/IL-15 (and to a lesser degree IL-9), which

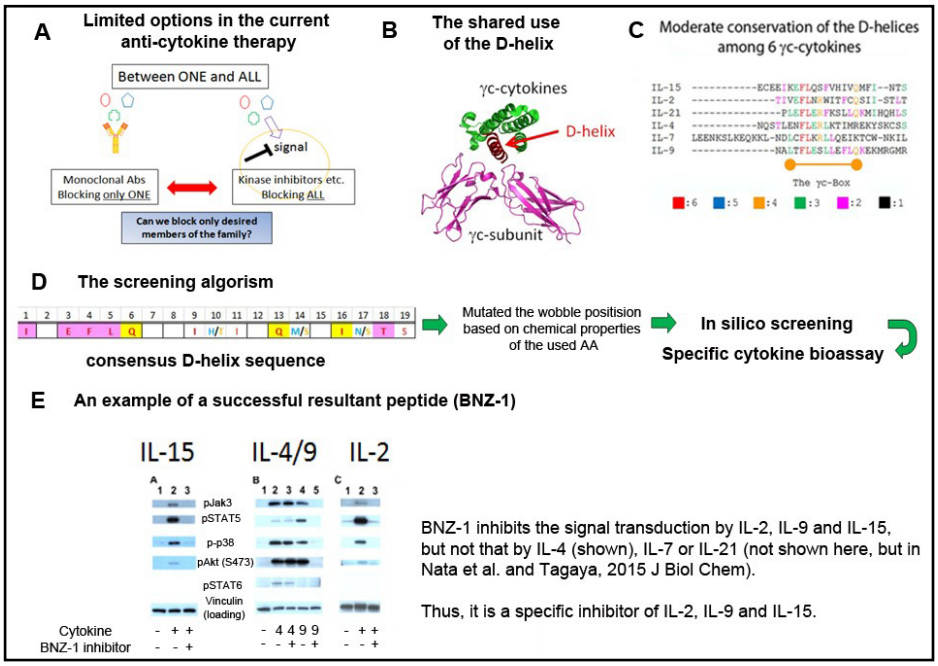
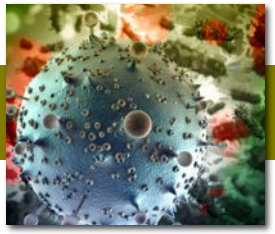


Figure 1: *Design of multi-cytokine inhibitor with selectable target spectrum*

is named BNZ-1. What is the value of co-inhibiting IL-2 and IL-15? In a normal immune response, these two cytokines are produced by activated T-cells (IL-2) and activated monocytes/ dendritic cells (IL-15) at different stages of the immune activation. Thus, there is little overlap between the role of IL-2 and IL-15, even if they share signaling components of their receptors (except for the non-signaling α-subunit). This is also exemplified by the non-overlapping phenotype of IL-2 and IL-15 knockout mice. However, under chronic activation of the immune cells under prolonged infection, immune/ inflammatory diseases, and cancer, the spatial/temporal segregation of IL-2 and IL-15 disappear. A mono-inhibition of either IL-2 or IL-15 becomes powerless under these conditions and a multiple-cytokine inhibitor is needed. Existing modalities to accomplish this goal may include the combinatorial use of neutralizing antibodies for each cytokine, a neutralizing antibody against the shared components of the IL-2 and IL-15 (β/CD122 and γ/ CD132) and Jak3 kinase inhibitors. The combined use of monoclonal antibodies for therapeutic application is challenging due to the high cost of antibody therapy. There is no neutralizing antibody binding to CD132 and antibodies against CD122 can only block trans-action of IL-15, but not the cis-action of IL-15. The Jak inhibitors block too many cytokines other than IL-2/15 and cause T-cell deficiency, immune suppression, anemia, and bleeding tendency upon chronic use. Thus, our new inhibitor specific for IL-2 and IL-15 may have significant value as a clinical drug. As IL-2/IL-15 act at the very early stage of T-cell activation during an immune response, we observed in our animal models that the blockade of IL-2/IL-15 has profound impacts on subsiding the production of an array of pro-



inflammatory and activating cytokines and chemokines and blocking the transition of naïve T-cells into inflammatory effector cells/cytotoxic cells. Co-inhibition of IL-2/IL-15 does not interfere with the TCR-mediated activation, so the antigen-driven part of the immune response is spared. In short, the inflammatory nature of chronic immune response will be attenuated.

BNZ-1 is IND (investigational new drug)-approved by the FDA and a phase I study involving healthy volunteers demonstrated that BNZ-1 blocks *in vivo* IL-2/IL-15 actions as demonstrated by the reduction in number of NK cells (of which the differentiation and peripheral homeostasis depends on IL-15), and regulatory T-cells (which is dependent on IL-2).

There are quite a few diseases in which IL-2/IL-15 co-inhibition might be useful, including several T-cell malignancies (because IL-2/IL-15 are T-cell growth factors), immune diseases such as alopecia areata and GvHD and we have tested these possibilities by using animal models and *ex vivo* patient-derived samples. We targeted two T-cell malignancies (Large-Granular Lymphocytic Leukemia (LGLL) and cutaneous T-cell lymphoma (CTCL)), chosen based on literature and our own animal model studies, and conducted a Phase I/II clinical trial (NCT03239392) by cooperating with six institutions (University of Virginia, Ohio State University, City of Hope, Moffitt Cancer Center, University of Pittsburgh, and Rochester Skin Cancer Center) to recruit patients and dosed BNZ-1 in its PEGylated form. The trial was sponsored by BIONIZ LLC (Irvine, CA) which I co-founded.

We recruited 20 LGLL patients and 30 CTCL patients, most of which were unresponsive to conventional and investigational treatments. In LGLL, BNZ-1 showed 30% overall response rate (ORR) and no major adverse effects. Remarkably, we saw prompt apoptotic death of LGLL leukemic cells in circulation within 48h after administering BNZ-1, which is in support of the working hypothesis that leukemic cells in this leukemia are dependent on IL-2/IL-15 *in vivo*. Responding and non-responding cases (judged by clinical criteria) show differences if the BNZ-1 effects persist over 4-weeks or longer or not, as demonstrated in ***Figure 2*** (a single-cell RNA-sequencing of the blood samples before and after BNZ-1 treatment). Thus, we now focus our research interests in delineating what makes leukemic cells maintain their response to IL-2/IL-15 co-inhibition. With CTCL, we saw 40% ORR, which was assessed by the standard modified Severity-Weighted Assessment Tool (mSWAT) that scores the area of the skin affected by the infiltration of the lymphoma cells compared to skin in various parts of the body. We also examined panels of surface, intracellular immune, lymphocyte, and cytokine using patients' blood undergoing the BNZ-1 treatment and saw some preliminary correlation between a few markers and the mSWAT improvements.

The trial has been approved by the FDA to move to Phase III (pending funding) and we are moving to initiate another clinical trial involving Alopecia areata.

The research on these leukemias is now focusing on the molecular analysis of the intracellular activation status/gene expression profiles using patients' specimens collected during the trial to discover what would make BNZ-1 treatment more effective, leading to the eradication of malignant T-cells from patients. We are also developing a humanized mouse model of LGLL using IL-15-transgenic NSG mice as there exists no good mouse model to study this disease. A few

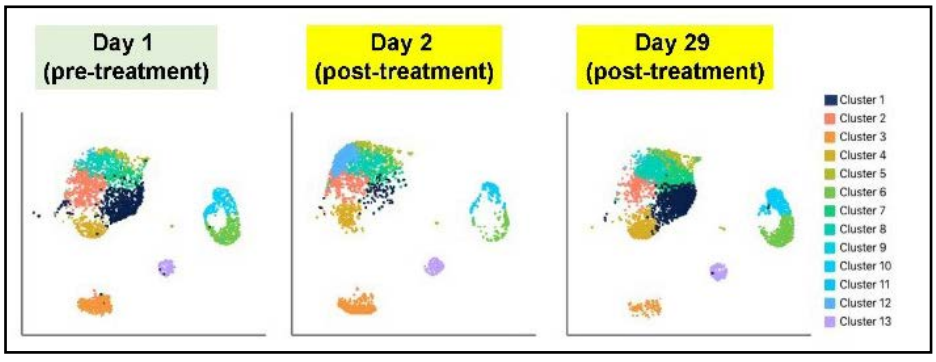
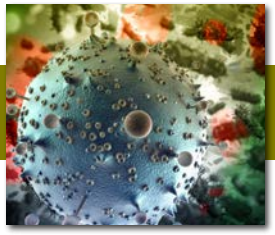


Figure 2: *BNZ-1 quickly eradicated leukemic cells in a non-responding LGLL case (tSNE analysis). PBMCs from an LGLL patient (UVA-002) were purified by the Ficoll-gradient and the cells were viably frozen immediately. One million frozen cells were brought back to ambient temperature before RNA extraction and the library was constructed using a kit from 10x Genomics. Single-cell sequencing and data analysis were performed by the single Cell Analysis Core of Columbia University (New York, NY)*

Some clusters such as cluster 1 robustly diminished 24 hours following the first administration of PEG-BNZ-1. However, the same cluster reappeared by day 29, suggesting that understanding how these cells lose response to IL-2/15 co-inhibition hold the key to improving the efficacy of BNZ-1 as a therapeutic drug treating LGLL.



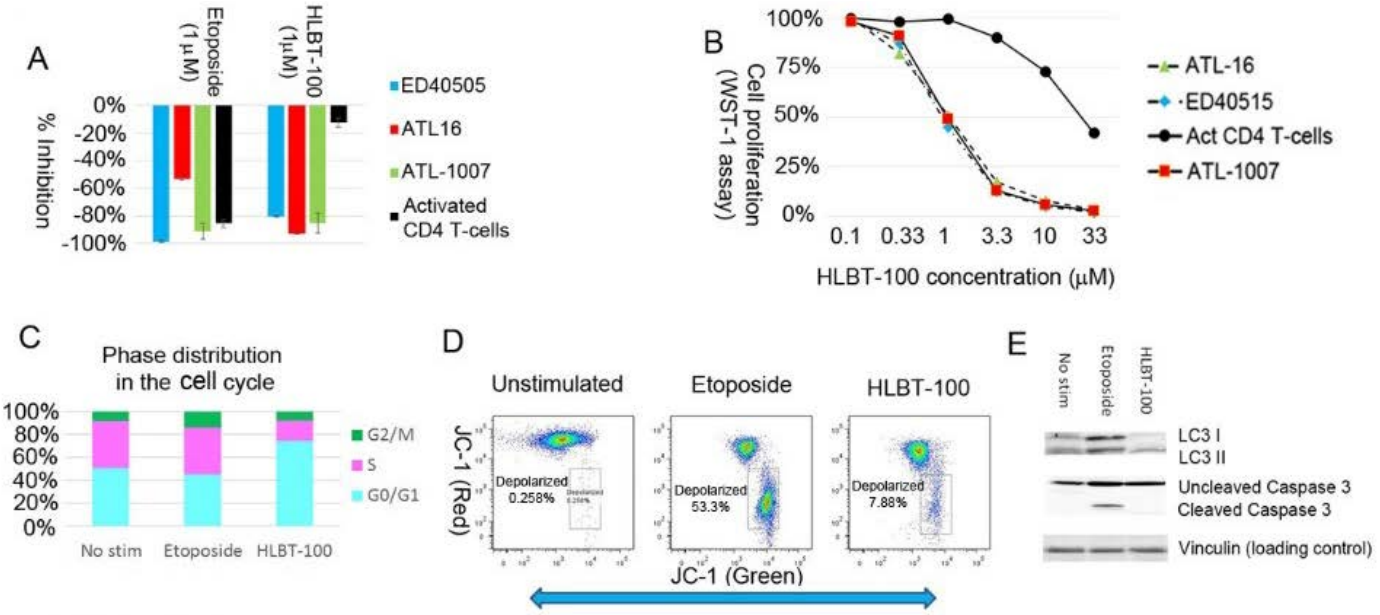


Figure 3. A) *Growth of ATL cells by HLBT-100. Cells were plated in a 96-well plate in their exponential growth phase at 10^6/mL in 200 μL medium containing the indicated concentration of inhibitors. ATL-16/ED are ATL cell lines while ATL 1007 are ex vivo ATL cells purified by cell sorting from an ATL patient. CD4 T-cells were expanded from human PBMCs by 2 days of PHA-P stimulation (5 μg/mL), followed by 5 days expansion with human IL-2 (1 nM). After a 12-hour incubation with inhibitors, 20 μL WST-1 reagent (Clontech) was added to the culture and OD450 was measured 2 hours later to monitor cellular proliferation. Cells incubated with 50 μM etoposide (large excess to completely stop cellular metabolism) was used as control for OD450. Percentage inhibition = (OD450 of inhibited growth — OD450 of 50 μM etoposide) / (OD450 of uninhibited growth — OD450 of 50 μM etoposide) —1) X 100. Experiments were performed in triplicate and repeated three times.*

B) *Dose response of cell proliferation of ATL and normal CD4 T-cells to HLBT-100. WST experiments described above. 100% cell proliferation; data without any inhibition/ 0%; data with 50 μM etoposide.*

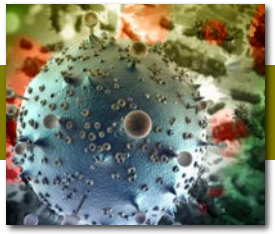
C) *Cell cycle arrest at G0/G1 to S phase transition by HLBT-100. ATL-16 cells were treated with 3 μM HLBT-100 for 16 hours, fixed in 70% ethanol, and stained with propidium iodide. RNA was degraded by included RNase A. Flow data was collected using FACS Aria II cell analyzer (BD Biosciences) and analyzed by FLowJo. Percentage of cells in G2/M phase (etoposide versus control, p=0.0015 / HLBT-100 versus control, p=0.542), percentage of cells in G0/G1 phase (HLBT-100 versus. control, 0.001 / etoposide versus control, 0.0653), percentage of S phase (HLBT-100 versus control, p=0.0001 / etoposide versus control, p=0.0152). Figure represents one of three repeated experiments.*

D) *Mitochondrial depolarization assay (JC-1 dye). ED cells were treated with 1 μM of indicated inhibitors for 12 hours and cells were stained with JC-1 dye (Invitrogen). Green and red fluorescence were analyzed by FACS Aria II.*

E) *Formation of LC3II, but no cleavage of Caspase 3 by HLBT-100 in ATL cells. ED cells were treated with 3 μM HLBT-100 / etoposide for 12 hours before cell lysis. Cellular proteins were electrophoresed and transferred to a PVDF membrane, which was probed with various antibodies sequentially. Equal loading was confirmed with Vinculin.*

manuscripts and resubmission of R21 funding is underway.

The second project involving small molecule drug development focuses on establishing a new treatment for a fatal adult T-cell leukemia, a CD4 T-cell leukemia caused by the human T-cell leukemia virus-1 (HTLV-1). HTLV-1 was discovered in 1979 by the Gallo group and was the first oncogenic retrovirus identified in humans. It is also arguably the most carcinogenic agent to humans. Globally 10-20 million people are infected by HTLV-1 and 5-10% of them manifest adult T-cell leukemia (ATL), which develops over 3-4 decades, and when entered to the aggressive phase (lymphomatous/ acute type) patients are expected to have less than 2 years of life left. ATL is highly resistant to conventional anti-leukemia therapy such as the combination of chemotherapy and radiation because HTLV-1 facilitates the accumulation of genetic mutations in host cells. Recent years have seen the emergence of a new treatment strategy, including anti-CCR4 therapy (because only ATL cells and normal regulatory T-cells express CCR4) and antiretroviral therapy (though difficulties in patient adherence and



adverse effects makes it less effective). However, ATL still represents an unmet medical need and the development of curative treatment is needed. Several years ago, **Joseph Bryant, DVM,** former Associate Professor of Pathology, Director of the Division of Animal Models, and **Ngeh Toyang, PhD,** former Research Associate, of the IHV have identified an anti-cancer activity with a flavonoid compound (HLBT-100) and we also observed that HLBT-100 shows potent anti-ATL activity *in vitro*. HLBT-100 strongly induced cell cycle arrest (at G0 phase) within 24 hours of treatment in several ATL cell lines (all derived from ATL patients, some retaining clonal consistency with the leukemic cells in the original patients) and one fresh ATL cell line from a patient. More interestingly, the mode by which HLBT-100 causes cell-cycle arrest is not by apoptosis (which is reported to occur in epithelial cancer cell lines in the original report, but by way of inducing autophagy *(**Figure 3** on the previous page)*. We found it interesting because reports conducting a whole-genome analysis of fresh ATL cells demonstrate frequent genetic alterations in leukemic cells associated with components of the TCR-signaling, p53 and associated molecules, anti-apoptotic genes (including the gain-of-function mutations in STAT3), but not with those in autophagy. Thus, we reasoned that alterations of the autophagy pathway may not be perceived by the ATL cells as a "critical stress."

Flavonoids have been drawing attention as drug candidates for quite some time, because they are naturally produced by plants and show anti-cancer/anti-inflammatory effects on a variety of cells. However, there are shortcomings that prevent efficient drug development of flavonoid compounds (so far, only flavopiridol/Alvocidib has made it to an FDA-approved drug). These include water insolubility, poor absorption, and rapid metabolism. The poor target nature of the compound makes it difficult to exert therapeutic effects, while avoiding off-the-target adverse effects. To circumvent these problems, we are formulating HLBT-100 encapsulated into liposomes/nanoparticles. We are also engineering the vehicle to express CCR4-ligands, so they will be specifically targeted to ATL cells. To know more about its mode of action (MOA), we are conducting gene expression profiling on ATL cells treated with HLBT-100 to identify target genes/pathways altered by HLBT-100, and CAD (computer associated design) reverse docking to identify potential intracellular binding partner protein of HLBT-100 (a collaboration with **Terry Elinor-Reid, PhD,** former member of the Animal Core Facility at the IHV, now a faculty member at the Concordia University of Wisconsin). Based on these data, we are preparing a manuscript and planning to re-submit an STTR grant (Dr. Tagaya as the PI, a collaborative work with Educational and Scientific LLC-members Dr. Toyang (CEO), Dr. Bryant and **Henry Lowe, PhD,** Adjunct Professor of Medicine).

The third project is the application of Lipid II-binding small molecules as a new type of antibiotics to control drug-resistant *Mycobacterium abscessus*. This is a collaborative project with **Erik de Leeuw, PhD,** former Assistant Professor of Biochemistry and Molecular Biology and member of the IHV, now with the FDA, to develop a new class of antibiotic therapeutics from a newly identified (by the de Leeuw group) Lipid II-binding small molecule into broad-range antibacterial activity. As a model of targets, we will choose nontuberculous mycobacteria (NTM) because these organisms possess excessive intrinsic and an adaptive resistance mechanism and represent a multidrug-resistant pathogen, a very difficult-to-treat target.

We will be optimizing a few candidates to produce validated drug compounds with reasonable IC50 values and lipid II-binding affinity. We will then verify the mode of action of the lead candidates using NMR-based lipid II interaction study and cell biology assays.

This project is funded by an NIH grant (1R21AI158856-01, April 2021-March 2023).

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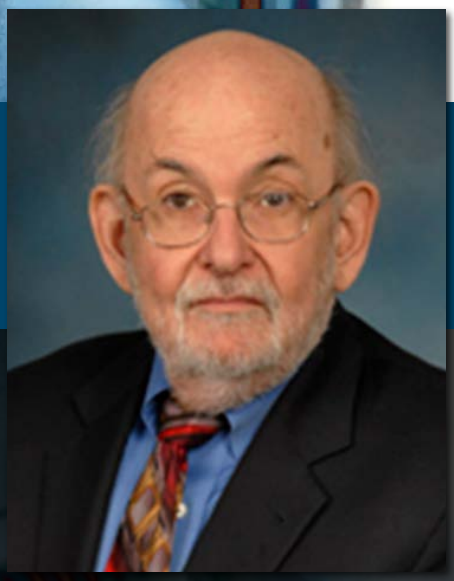
Vaccine Research



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 faculty and collaborating faculty in the Division of Clinical Care and Research continue the development of an AIDS vaccine under the IHV "bench to the clinic" model of translational research. This model enables a strong multidisciplinary approach to AIDS vaccine development by combining the tools molecular and cell biology, virology, immunology, optical physics, structural biology, and state-of-the-art clinical trials capacity, all within a single building housing the IHV.

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. The IHV-001 is a conformationally constrained protein comprised of HIV-1 gp120 linked to the first two domains of human CD4 by a flexible peptide spacer. This immunogen is denoted as the full-length single chain (FLSC) protein ***(Figure 1***). The group of **Anthony DeVico, PhD**, Professor of Medicine, developed the FLSC vaccine concept in the early years of the IHV with the first publication of its immunochemical and physical chemical profile in 2000. Since that time, FLSC development has been the principal focus of the Division of Vaccine Research (Dr. DeVico, Dr. Lewis, and **Robert C. Gallo, MD**, The Homer & Martha Gudelsky Distinguished Professor in Medicine and Professor of Microbiology and Immunology, Co-Founder and Director of the IHV) in collaboration with colleagues in the IHV Division of Clinical Care and Research (**Joel Chua, MD**, Professor of Medicine, and **Mohammad Sajadi, MD**, Professor of Medicine), The Military HIV Research Program, and the NIAID, NIH HIV Vaccine Trials Network.

Anthony DeVico, PhD

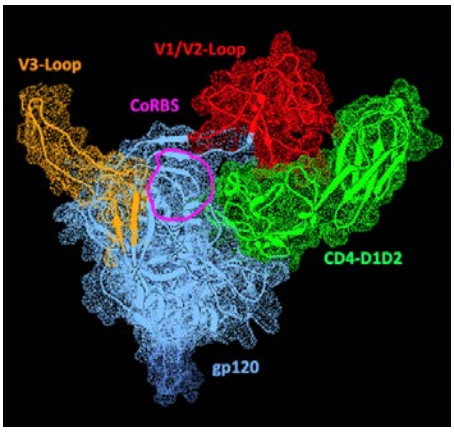
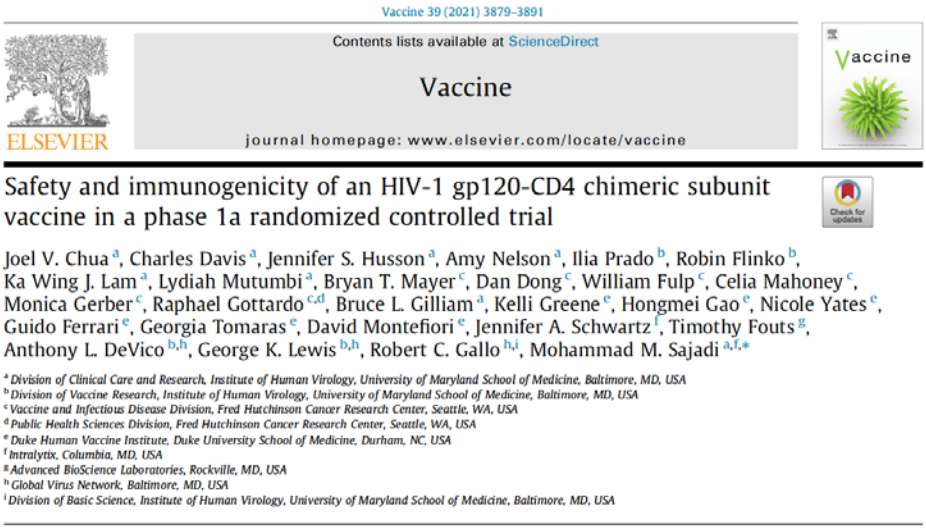


Figure 1. *Molecular model of the IHV-001 FLSC vaccine*

Results of this phase Ia clinical trial were published in the peer-reviewed journal Vaccine on June 29 of this year ***(Figure 2)***. This work represents over twenty years of basic research, preclinical research and development, and clinical trial execution by members of the Divisions of Vaccine Research and Clinical Care and Research. The initial design and publication of the IHV-001 FLSC vaccine concept in 2000 was followed by multiple studies demonstrating safety and protection against model AIDS viruses in animal models from 2007 to 2019. These combined safety, immunogenicity, and animal protection studies provided the scientific basis for the IHV-001 phase-1a clinical trial. This work was supported by multiple extramural grants from the NIAID/NIH, The Bill and Melinda Gates Foundation, and the Military HIV Research Program (MHRP). The IHV-001 vaccine was found to be safe and immunogenic in the phase 1a clinical trial where it elicited the same types of antibody responses that correlated with protection against model AIDS viruses in animal studies. Based on these encouraging results, the IHV-001 vaccine has been advanced to a phase-1b clinical trial, scheduled to begin in December 2021, in Thailand via collaboration with MHRP and colleagues at the Duke Human Vaccine Institute.

The Division of Vaccine Research is also pursuing basic science questions that emerged over the years of IHV-001 vaccine development. The Division



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Safety and immunogenicity of an HIV-1 gp120-CD4 chimeric subunit vaccine in a phase 1a randomized controlled trial

Joel V. Chua [a], Charles Davis [a], Jennifer S. Husson [a], Amy Nelson [a], Ilia Prado [b], Robin Flinko [b], Ka Wing J. Lam [a], Lydiah Mutumbi [a], Bryan T. Mayer [c], Dan Dong [c], William Fulp [c], Celia Mahoney [c], Monica Gerber [c], Raphael Gottardo [c,d], Bruce L. Gilliam [a], Kelli Greene [e], Hongmei Gao [e], Nicole Yates [e], Guido Ferrari [e], Georgia Tomaras [e], David Montefiori [e], Jennifer A. Schwartz [f], Timothy Fouts [g], Anthony L. DeVico [b,h], George K. Lewis [b,h], Robert C. Gallo [h,i], Mohammad M. Sajadi [a,f,*]

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[e] Duke Human Vaccine Institute, Duke University School of Medicine, Durham, NC, USA
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Figure 2. *"First in Humans" IHV-001 Clinical Trials*

is focusing on four key problems confronting the development of an HIV-1 vaccine: 1) identification of an immunogen that elicits broadly protective immunity; 2) identification of the correlates and mechanisms of broad protection elicited by IHV001; 3) ensuring that the broad, vaccine-elicited protection persists over long periods without repeated vaccination; and 4) understanding host factors such as innate immunity and vaccine elicited CD4+ T-cell responses that augment or attenuate broad, vaccine-elicited protection.

For example, both pre-clinical studies and our first phase I clinical trial of IHV-001 have shed new light on the correlates and mechanisms of protective immunity to HIV-1. In our pre-clinical studies, our team unexpectedly found that protection correlates largely with Fc-mediated effector function and not virus neutralization (problem #2, above). This team included Division members Dr. Lewis, **Dr. DeVico, Krishanu Ray, PhD**, Associate Professor of Biochemistry and Molecular Biology, **Marzena Pazgier, MS, PhD**, (now at USUHS, Bethesda), and **Greg Snyder, PhD**, Assistant Professor of Medicine, as well as Dr. Sajadi of the Division of Clinical Care and Research. This work was supported initially by a grant from The Bill and Melinda Gates Foundation, as well as two R01 grants to Dr. Lewis. More recently, the work is supported by a collaborative P01 grant with investigators at Duke University, Harvard University, Dartmouth University, Northwestern University, and the University of Pennsylvania. Drs. DeVico, Lewis, Snyder, and Ray are focusing on physicochemical and cell biology of Fc-mediated effector function for this program. These efforts are also supported by funding from the US Military Defense Threat Reduction Agency to Dr. Lewis, a R01 grant awarded to Dr. Krishanu Ray, as well as by a R01, and VA Merit Award to Dr. Sajadi.

Robin Flinko (left), Research Manager, Dr. Ray (center), and Dr. Lewis (Photo taken before the SARS-CoV-2/ COVID-19 pandemic)

This work led to the identification of the two most highly conserved epitope regions of gp120, the outer HIV-1 envelope glycoprotein, that are targets of potentially protective antibody responses. First, our FLSC studies led to the identification of Epitope Cluster A, which is a highly conserved target of non-neutralizing antibodies that exert Fc-mediated effector functions against CD4+ T-cells that have bound HIV-1 or infected CD4+ T-cells that are budding virus prior to CD4 down regulation by the viral proteins Nef and Vpu. Second, Dr. Sajdai's group in collaboration with Division members identified a highly conserved neutralization epitope in the CD4 binding site of gp120. Monoclonal (mAbs) specific for this epitope exhibit the broadest neutralization of HIV-1 reported to date and studies are underway to exploit this property to develop a vaccine based on this structure. Further, these mAbs offer significant possibilities for enhanced prophylaxis and therapy against HIV-1, the latter of which is particularly important for HIV-1 "cure" initiatives.

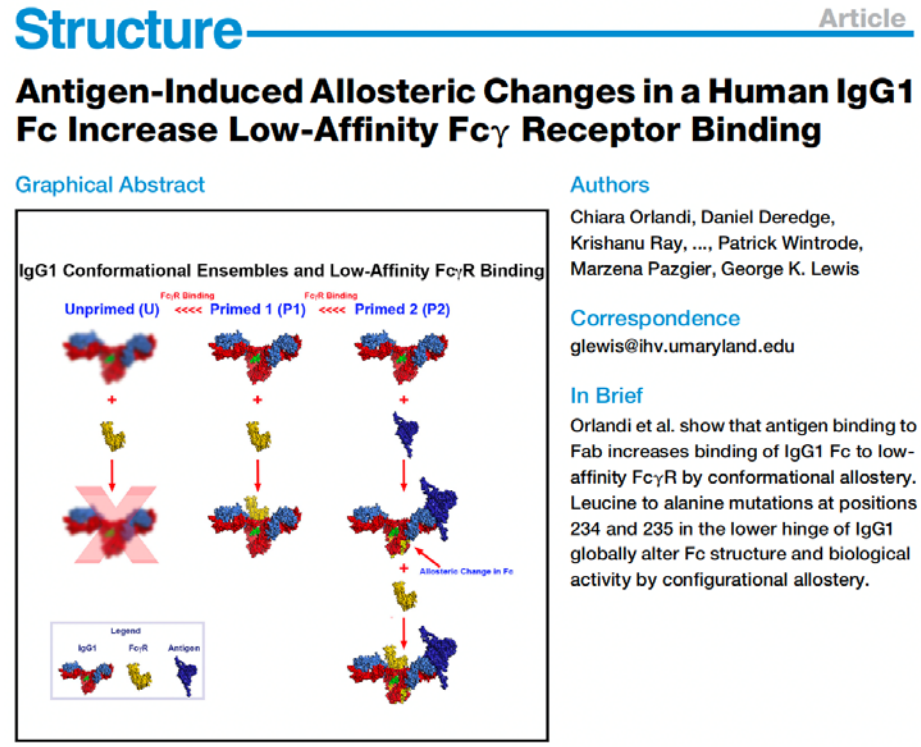
Dr. DeVico's group has developed new tools to characterize target epitopes on free virions, virions entering

target cells, and virions budding from infected cells for each type of mAb. This work is leading to an increasingly clear picture of temporal epitope exposure during different phases of the viral replicative cycle that defines windows of opportunity for antibodies to interfere with infection by neutralization, Fc-mediated effector function, or both. This work provides a virological and immunological explanation for the correlates of protection we have linked with the FLSC vaccine strategy. This research involves broad application of several cutting-edge technologies, including fluorescence correlation spectroscopy, fluorescence resonance energy transfer, confocal microscopy, and super-resolution microscopy.

Dr. Lewis's group has developed passive immunization models to evaluate the mechanisms of antibody-mediated protection *in vivo*. His group is also developing quantitative *in vitro* models to determine the relative potencies of mAb candidates to be evaluated in passive immunization studies *in vivo*. This work has led to the identification of "prozones" both in vitro and *in vivo* for Env-specific Fc-mediated effector function. His group is also exploring the mechanism of a novel pattern of mAb synergy in ADCC involving an allosteric effect through which the binding of antigen to the Fab region of a mAb causes a distal conformational change in the Fc-region that leads to increased Fc-receptor binding. This work was published last year in the peer-reviewed journal *Structure* ***(Figure 3)***. Dr. Ray's group has adapted fluorescence correlation spectroscopy and fluorescence resonance energy transfer to study the interaction of antibodies with Env on virions and in solution. These methods permit the solution-phase characterization of conformational effects that occur after antigen binding leading to increased binding to Fc-receptors. These methods permit co-localization of epitopes to single Env molecules on virions and in solution. He will continue these studies under the aegis his R01 and the collaborative P01 grant.

Dr. Snyder joined the Division of Vaccine Research as our structural biologist shortly after Dr. Pazgier's moving to USUHS. Dr. Snyder has extensive experience in the structural biology of components of the innate immune system that our Fc-receptor studies have implicated as potential correlates of protection elicited in animals by our FLSC vaccine concept. Although Dr. Snyder joined our group recently, his efforts have already played a key role in our successful competition for new funding from the Defense Threat Reduction Agency (Department of Defense) to predict protective immune responses against novel pathogens. This new collaboration also involves Dr. Ray of the Division, as well as investigators at West Virginia University and MIT.

Dr. Sajadi's group has developed new methods for the isolation of human


Structure Article

Antigen-Induced Allosteric Changes in a Human IgG1 Fc Increase Low-Affinity Fcγ Receptor Binding

Graphical Abstract

Authors
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In Brief
Orlandi et al. show that antigen binding to Fab increases binding of IgG1 Fc to low-affinity FcγR by conformational allostery. Leucine to alanine mutations at positions 234 and 235 in the lower hinge of IgG1 globally alter Fc structure and biological activity by configurational allostery.

Figure 3. *Graphical Abstract from publication in Structure, May 2020.*

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

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

Vaccine Research Publications

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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 and Ackerman ME (2021). "Diverse antiviral IgG effector activities are predicted by unique biophysical antibody features." *Retrovirology*, 18(1): p. 35. https://doi.org/10.1186/s12977-021-00579-9

Tolbert WD, Van V, Sherburn R, Tuyishime M, Yan F, Nguyen DN, Stanfield-Oakley S, Easterhoff D, Bonsignori M, Haynes BF, Moody MA, **Ray K**, Ferrari, **Lewis GK**, Pazgier M (2020). "Recognition Patterns of the C1/C2 Epitopes Involved in Fc-Mediated Response in HIV-1 Natural Infection and the RV114 Vaccine Trial." *mBio*, 2020. 11(3). https://doi.org/10.1128/mBio.00208-20

Tolbert WD, Sherburn R, Gohain N, Ding S, Flinko R, **Orlandi C**, **Ray K**, Finzi A, **Lewis GK**, Marzena Pazgier (2020). "Defining rules governing recognition and Fc-mediated effector functions to the HIV-1 co-receptor binding site." *BMC Biology*, 18(1): p. 91. https://doi.org/10.1186/s12915-020-00819-y

Riktegaran-Tehrani Z, Saadat S, Saleh E, Ouyang X, Constantine N, **DeVico AL**, Harris AD, **Lewis GK**, Kottilil S, **Sajadi MM** (2020). "Performance of nucleocapsid and spike-based SARS-CoV-2 serologic assays." *PLoS One*, 15(11): p. e0237828.

Liu Q, Zhang P, Miao, Lin Y, Kwon YD, Kwong PD, Riktegaran-Tehrani Z, Seaman MS, **DeVico A, Sajadi MM**, Lusso P (2021) "Rational Engraftment of Quaternary-Interactive Acidic Loops for Anti-HIV-1 Antibody Improvement." *Journal of Virology*, 95(12). https://doi.org/10.1128/jvi.00159-21

The Division of Clinical Care and Research

The Division of Clinical Care and Research is the leader in providing the highest quality clinical care, clinical research, and medical education in the Baltimore and Washington, DC metropolitan area. The Division has 44 faculty members and more than 75 support personnel, who managed over 50 active grants and contracts this year. The Division is led by **Shyam Kottilil, MBBS, PhD**, Professor of Medicine, Director of the Division and Head of the Clinical Care Research Unit, with clinical leadership by **Anthony Amoroso, MD**, Professor of Medicine, Associate Director of the Division, Head of Clinical Care Programs. Drs. Kottilil and Amoroso have built a clinical care and research program that provides both the most advanced medical care to our patients, while pursuing the research questions that will most impact their lives.

Clinical Care and Research

Shyam Kottilil, MBBS, PhD

Anthony Amoroso, MD

The Baltimore-based ambulatory clinical programs supported by the Division continue to provide premier care in the management and prevention of HIV infection, hepatitis comorbidities, and treatment of patients with other infectious diseases under the clinical leadership of Dr. Amoroso. The clinical research program under Dr. Kottilil's direction, continues to concentrate on studies focused on therapeutics and a cure for hepatitis B, HIV cure-related research, COVID-19, other infectious diseases, and the intersection of opioid-use disorder and infectious diseases.

SARS-CoV-2 Pandemic Response

The IHV's clinical faculty continued to play a major role in front-line care in the COVID-19 pandemic throughout the year. As the intensity of the epidemic waned in Maryland, so did the intensity of patient-related care and hospital system support duties by our faculty. However, the work and care continue in efforts to manage and end the pandemic. One area of new focus for the Division was 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, PhD,** former Professor of Surgery, formerly of IHV's Immunotherapy Division and now at OncoC4 (formerly Oncoimune, Inc.), led a randomized controlled clinical trial using the CD24Fc molecule for severe to critical COVID-19 patients. The clinical trial was stopped early for efficacy and was one of the very few agents that have demonstrated efficacy in improving clinical outcomes of severe and critical COVID-19 patients. This molecule, developed by IHV's Dr. Zheng and Dr. Liu, is currently being developed by OncoC4 in collaboration with Merck, Inc.

During this year, IHV investigators including **Joel Chua, MD,** Assistant Professor of Medicine, **Shivakumar Narayanan, MD,** Assistant Professor of Medicine, Director of Hepatitis Research at the IHV, completed several clinical trials on COVID-19 in collaboration with the National Institutes of Health (NIH) and other major industry partners. **Rohit Talwani, MD,** Associate Professor of Medicine, completed a major COVID-19 vaccine clinical trial effort with the Johnson & Johnson vaccine at the Baltimore Veterans Affairs Medical Center. **Jennifer Husson, MD, MPH**, Assistant Professor of Medicine, Director of the Divisions' Clinical Research Unit, working in collaboration with **Kirsten Lyke, MD**, Professor of Medicine, from UMB's Center for Vaccine Development and Global Health, has initiated a large NIH-funded multi-center trial, Mix-and-Match COVID-19 Booster study.

From the laboratory side, Dr. Kottilil and **Bhawna Poonia, PhD,** Associate Professor of Medicine, continue working on their NIDA grant supplement to investigate COVID-19 progression and immunity in subjects with HIV infection and opioid use disorder. **Mohammad Sajadi, MD,** Professor of Medicine, **Kapil Saharia, MD**, **MPH,** Assistant Professor of Medicine, and **John Baddley, MD,** Professor of Medicine, are studying the vaccine immune response in immunocompromised patients. Dr. Sajadi continues to look at the humoral response in COVID-19 infection in addition to a collaboration with the NIH on COVID-19 infected lung tissue.

Clinical Care Program Overview

The IHV continues to provide state-of-the-art, high quality care to the citizens of Maryland, and beyond. Over the last three years under Dr. Kottilil and Dr. Amoroso's leadership, the IHV has taken a greater role in leading the Infectious Disease Division for the School of Medicine. 2020-2021 proved to remain a very difficult and stressful year for Infectious Disease physicians as they continued to provide front-line care in this pandemic.

Sarah Schmalzle, MD, Assistant Professor of Medicine, and her staff maintained an active ambulatory 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 a 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 mortality associated with drug use.

During this year the Division's two clinical practices were combined that allowed for significant synergies in clinical care and education. Led by **Dave Riedel, MD, MPH,** Associate Professor of Medicine, the Infectious Disease Fellowship that has 14 fellows remains one of the largest infectious disease Accreditation Council for Graduate Medical Education (ACGME) fellowship training programs in the country. With 42 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 and Solid Organ Transplant Program at University of Maryland Medical Center, led by Drs. Baddley and Sarahia, respectively. In addition, a new service was created, Critical Care Infectious Disease, led by **Wisna Jean, MD,** Assistant Professor of Medicine and Chief of Medical Critical Care Service, focused on optimizing care for critically ill patients.

Dr. Jean teaching a fellow

Financial Health Clinical Program

FY2021 is on target to exceed FY2019 and significantly better than FY2020 despite the ongoing COVID-19 pandemic. The combined clinical practices (IHV and ID) will exceed $7,000,000 in charges in FY 2021. After physician salary costs, administrative costs, billing costs, malpractice insurance costs, and operational costs the clinical practice is anticipated to realize a revenue that exceeds costs for this past year. However, losses incurred from FY2020 due to the COVID-19 pandemic remain.

HIV Care

The THRIVE program (Together Healing, Reaching, Inspiring, to achieve Victory over illness, and Embrace life), run by

L to R: The THRIVE Program's Robin Palmeiro, LCSW-C; Sarah Schmalze, MD; and Tiffany Moritz (Photo taken before the SARS-CoV-2/COVID-19 pandemic); pictured right, a bulletin board of photos celebrating THRIVE team members' COVID vaccinations

Dr. Schmalzle, Medical Director, 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 under-insured 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' and same day medication starts for HIV treatment and prevention, pap, colposcopy, anoscopy, a medication-assisted therapy program (buprenorphine and naltrexone), nutritionist evaluation and provision of free nutritional supplements and vitamins, and pharmD services for medication safety, education, and adherence. THRIVE is also newly offering the novel monthly injectable HIV medication and COVID-19 vaccination to its patients. 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 Divison'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 and outpatient parenteral antibiotic therapy (OPAT) follow up, and penicillin allergy skin testing.

In 2021, THRIVE is focusing on a planned relocation to the new ambulatory tower at Midtown Campus in late September, continued engagement and retention efforts including expansion of home-based support services, and building care models to adjust to the needs of an aging HIV population.

Health and Recovery Practice (HARP)
The University of Maryland School of Medicine's (UMSOM) HARP is a new joint venture between the IHV's Division of Clinical Care and Research and the Department of Psychiatry and Addiction Medicine. It continues to adapt and expand its services. The HARP program has expanded staffing capacity and services to meet the needs of vulnerable populations throughout the COVID-19 pandemic. Throughout the last year, HARP has centered its efforts on implementing an electronic medical record assessment to address the social determinants of health (SDOH) for all patients receiving care at 1001 W Pratt programs (site of HARP). Addressing the SDOH — the conditions under which people live, learn, work, and play —significantly impact patients' overall well-being. With the information gained from the SDOH assessment, HARP staff offer resources, such as patient assistance services to help reduce barriers to wellness. The HARP program joined the COVID-19 vaccination effort by holding vaccine clinics for all patients attending 1001 W Pratt programs. In partnership with FEMA and UMMS Addiction treatment programs, HARP has administered 270 doses of the COVID-19 vaccine to its patient population helping to reduce the spread of the virus among people hardest hit by the virus.

Outpatient Parenteral Antimicrobial Therapy (OPAT)
During the last year the University of Maryland OPAT Program under Dr. Narayanan's direction as Medical Director has managed over 650 patients through the program. The program has studied outcomes of OPAT in management of infectious syndromes in persons with opioid use disorder (OUD). This aim is to identify critical touch points during the medical care of such patients, including hospitalization, and transitions of care, and to leverage these as opportunities to intervene and optimize OUD treatment, including linkage to care, improve outcomes of treatment of infectious syndrome and overall health. The program plans to pilot use of long acting lipoglycopeptides linked and collocated with medication-assisted therapy for OUD for management of such infections, and to compare outcomes with standard of care.

Members of the Jacques team (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

The JACQUES Initiative
2020-2021 has been one of the most challenging periods for healthcare due to the COVID-19 pandemic; the JACQUES Initiative (JI) was not spared from its impact. The community work for which the JI program is best known was significantly limited. In accordance with the University of Maryland's guidelines and restrictions, the JACQUES Journey Center at Midtown closed to the public and staff in March of 2020. All face-to-face activities, such as HIV and HCV point-of-care, rapid testing, as well as the social support groups for clients living with HIV and the LGBTQ-focused The EXCHANGE Program were suspended in order to prevent the spread of the COVID-19 virus. It was a time of great anxiety, uncertainty, and fear, particularly before the first COVID-19 vaccines became available. Nevertheless, our team remained united and engaged with video conferences and phone calls. The JI team pivoted and implemented new ways to engage our clients remotely through social media and telephone. We referred clients to mail-based HIV testing coordinated by the Baltimore City Health Department and the State of Maryland, while our team personally delivered safe-sex kits to those who requested them online. Furthermore, JI continued providing linkage to nPEP services via phone for all clients that were referred from our partner Mercy Hospital in collaboration with the UMB's THRIVE clinic, Baltimore City Health Department (BCHD), and Chase Brexton. Our staff was also capable of responding remotely to all the linkage to care needs for patients newly diagnosed with HIV at UMMC and MTC hospitals, as well as the admitted patients who had fallen out of HIV care. We continued working with the Corrections Department to assist with its linkage to care needs for soon-to-be-released inmates living with HIV, although the volume of referrals and the capacity to visit them within the prison system decreased as well. Changes in the program's funding also challenged its capacity to plan future operations and growth. As a result, JI's leadership proactively moved the JACQUES Journey Center to a UMB-owned and managed space within its downtown campus, where activities are progressively returning to normal.

Clinical Programs in Chronic Viral Hepatitis
The Division's hepatitis B (HBV) and C (HCV) treatment programs continue to expand under **Lydia Tang, MB, BCh,** Assistant Professor of Medicine, **Eleanor Wilson, MD, MHS,** Associate Professor of Medicine, and **Angie Price, DNP, CRNP, MSN,** with locations at the Downtown and Midtown University of Maryland campuses, and the Veterans Affairs Maryland Health Care System (VAMHCS).

The Division has established a comprehensive clinical program to screen, link, and treat patients with chronic HBV infection, while simultaneously conducting translational research on

the immunopathogenesis of HBV persistence, with the aim of curing HBV chronic infection. In partnership with the Hepatitis B Initiative of Washington, D.C. (HBI-DC), the IHV continues to increase awareness and provide screening for patients at risk for chronic HBV in the Baltimore/District of Columbia metropolitan area, where a majority of patients have not been engaged in clinical care due to socioeconomic background. Since 2005, over 18,000 people in the D.C.-metropolitan area have been screened by HBI-DC, with prevalence rates of 6% for HBV. Those who tested positive are linked to care for further evaluation and treatment. Since 2016, Dr. Tang has received multiple grants to support the HBV clinical research program and successfully completed a single-site phase 2 clinical trial evaluating a new experimental drug for chronic HBV treatment. In 2020, Dr. Tang was awarded a career development grant from the Institute for Clinical and Translational Research/Clinical and Translational Science Award (ICTR/CTSA) to continue building on her basic and translational science work on correlates of response to immunomodulation in people with chronic HBV, with and without HIV coinfection. As an advocate for increased community engagement in HBV research, Dr. Tang is also the principal investigator for several clinical trials based in community health-care centers.

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

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

The IHV's clinical and research activities reach beyond the University campus through its D.C. Partnership for HIV/AIDS Progress Comorbidities Program (DC PFAP). Since 2015, this unique clinical research program has embedded Division providers and research staff in community-based settings such as a syringe service program, opioid treatment program, and federally qualified community health centers in Washington, D.C. and Baltimore. In these settings, Division staff and collaborators are able to engage populations generally excluded from research, such as minorities and people who use

Members of the RIIS team (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

Clinical Research Unit staff (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

drugs, and 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 individuals with infectious complications of opioid-use disorder and implement treatment models to improve both infectious and drug-use associated outcomes. This program is led by Co-Directors, **Sarah Kattakuzhy, MD,** Associate Professor of Medicine and **Elana Rosenthal, MD,** Assistant Professor of Medicine, with program management by **Rachel Silk, RN, MPH,** clinical and research support by **Britt Gayle, MD, MPH,** Assistant Professor of Family and Community Medicine, **Ashley Davis, CRNP,** and **Amelia Cover, CRNP,** and study coordination by **Rahwa Eyasu, MSN, FNP, Emade Ebah, MPH,** and **Onyinyechi Ogbumbadiugha, MPH.**

Dr. Kattakuzhy has expanded an opioid-use disorder (OUD) resident education initiative, AIROH, which trains residents in Family and Internal Medicine on OUD and harm reduction. AIROH has been incorporated into the Maryland Addiction Consult Service, a grant program of the Maryland Department of Health. Dr. Rosenthal serves as principal investigator for an NIH-sponsored, multi-site investigation to evaluate OUD, HIV, and HCV-related outcomes among adults who are hospitalized with infections associated with injection of opioids. In the last year, Dr. Rosenthal initiated a clinical program and research study of transgender individuals, utilizing 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 faculty mentors to several ID fellows.

Clinical Research Clinical Research Unit (CRU)

Angie Price, DNP, CRNP, MSN

The IHV Clinical Research Unit continues to grow under the direction of Dr. Husson. This year, the CRU formed a leadership team consisting of **Angie Price, DNP, CRNP, MSN**, who manages the CRU, **Amy Nelson, PhD, RN**, who manages our new study start up, and **Rachel Silk, RN, MPH**, who manages the CRU's revenue and expenses. Under the leadership team, the CRU is composed of a multidisciplinary team of one nurse coordinator, a pharmacist, a research nurse, one regulatory specialist, four study/research coordinators, three laboratory technicians, and a receptionist. During the past year, despite having to close to 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), 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, and liver transplantation. Additionally, the CRU has continued to play an active role in bringing clinical therapeutic trials to patients hospitalized with COVID-19. The CRU opened a 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 treatment of chronic viral infections in a variety of hosts.

Full-Length Single Chain (FLSC) Vaccine Program

The FLSC vaccine was developed by IHV scientists under the leadership of **Dr. Robert Gallo, George Lewis, PhD,** The Robert C. Gallo, MD Endowed Professorship in Translational Medicine and Director of the IHV Division of Vaccine Research, and **Anthony DeVico, PhD,** Professor of Medicine in the IHV Division of Vaccine Research. The clinical component of the FLSC vaccine program is currently headed by Dr. Sajadi. The phase 1a (dose escalation), randomized, placebo-controlled, double-blinded clinical trial designed to evaluate the safety and immunogenicity of a HIV vaccine called FLSC (full-length single chain) in healthy volunteers without HIV infection was carried out at the IHV and results recently published in *Vaccine*. This trial represents the true translational impact of IHV on meeting the needs of HIV-infected individuals. FLSC will also be tested in several upcoming vaccine trials at the HVTN (HVTN132 and HVTN 134) and MHRP (RV509 and RV546).

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

The collaborations between the IHV and with the NIAID intramural program of the National Institutes of Health (NIH) continue. NIAID clinical trials are still beingrecruited at the IHV CRU (Anthony Fauci, MD, Director of NIAID, and Tae-Wook Chun, PhD, Chief, HIV Immunovirology Unit). The Division has two NIH intramural bench-to-bedside grants; one to evaluate changes in immune activation using novel imaging techniques among patients undergoing therapy for hepatitis C with or without HIV coinfection and then compare radiological changes (MRI) in HCV mono-infected and HIV/HCV coinfected patients pre- and post-treatment, compared to HIV mono-infected patients (IHV's **Poonam Mathur, DO, MPH,** Assistant Professor of Medicine, and Henry Masur, MD, Chief, Critical Care Medicine Department, NIH). Second, is a novel artificial intelligence based algorithm development for improving clinical adherence of HIV patients at THRIVE clinic (also led by Dr. Mathur). Finally, the research collaboration continues between Adriana Marques, MD, Chief, Clinical Studies Unit, Laboratory of Clinical immunology and Microbiology, from NIAID and the Lyme disease program with an NIH IRB-approved protocol implemented at the UMB Waterloo infectious disease practice. The IHV is able to enhance its research capabilities with this collaboration.

Poonam Mathur, DO, MPH

Clinical Trials Program

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

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 HCV direct-acting antiviral treatment as an anchor to engage people who inject drugs (PWID) in uptake of HIV prevention strategies including PrEP, opioid substitution therapy, and safer injection practices. Dr. Rosenthal leads this study funded by a Gilead research grant for 100 courses of HCV therapy (sofosbuvir/velpatasvir) and 100 courses of PrEP, and a Merck investigator initiated grant that supports treatment (elbasvir/grazoprevir) for an additional 100 patients. Enrollment has completed for the Gilead supported study portion and participants are now in long-term follow-up. Additionally, for the second 100 participants, the study team also collaborated with National Institute of Drug Abuse to use their ecological momentary assessment (EMA) technology to assess cravings and adherence. This study has fully enrolled and completed.

Best HBV

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

Joel Chua, MD

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 1:1 to receive doses of CD24Fc 240 mg IV or placebo. This study is funded by an NHLBI SBIR grant (1 R44 HL145964-01A1) partnering with OncoImmune, Inc. and Dr. Nehal Mehta, Section of Inflammation 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 HCV in mono-infected and HIV co-infected individuals and compare inflammatory markers radiological changes (MRI) in HCV mono-infected and HIV/HCV coinfected patients pre- and post-treatment compared to HIV mono-infected patients. This study is funded through a Merck investigator-initiated grant and the National Institutes of Health Bench-to Bedside Award.

CoCrystal
Dr. Chua is also conducting a phase 2a study evaluating the safety and efficacy of combination treatment with two weeks of the non-nucleoside inhibitor CDI-31244 plus six weeks of sofosbuvir/velpatasvir in patients with HCV genotype 1. The study completed enrollment and findings were published this year.

Geomapping Resistance and Viral Transmission in Risky Populations (GRAVITY)
The goal of GRAVITY is to identify newly acquired cases of HIV and HCV in high risk populations, and to better understand characteristics associated with viral transmission in Washington, D.C. Dr. Rosenthal and Dr. Kattakuzhy have obtained NIH and Gilead Sciences funding to implement HIV and HCV screening programs in those who inject drugs, men who have sex with men, transgender individuals, and sex workers. This study is funded both by NIH and by an investigator-initiated clinical trial from Gilead Sciences led by Dr. Kattakuzhy. This study is fully enrolled and in the data analysis phase.

CHOICE
With pilot funding from NIAID, NIH, Dr. Rosenthal and Dr. Kattakuzhy are conducting a needs assessment of the care continuum of people with OUD 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.

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

HOPE in Action
Dr. Husson, along with our transplant surgery team and investigators from Johns Hopkins University, won an U01 award from NIAID to evaluate the use of HIV-infected donor kidneys for transplantation into HIV-infected kidney transplant recipients. Dr. Husson has been guiding the infectious disease management of UMB's program in HIV transplantation and is the site principal investigator for this multi-center study. Through this study, the first HIV-to-HIV kidney transplant at the University of Maryland was successfully completed and preliminary data 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 an NHLBI K23 grant.

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

Shyam Kottilil, MBBS, PhD, and Jennifer Husson, MD (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

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

LOOP
This investigator-initiated study funded by the JC Martin Foundation and led by Dr. Rosenthal is a natural history study following the long-term outcomes of persons with opioid-use disorder.

STOP-CO Clinical Trial
Dr. Husson, along with collaborators from NIH and UCSF completed enrollment for the NIAID/NIH funded study to treat HIV/HCV co-infected patients with sofosbuvir and ledipasvir. This was funded through a novel grant mechanism to foster intramural-extramural collaborations, and the findings were published in the *American Journal of Transplantation*.

TLR-8
Dr. Tang completed this phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and antiviral activity of GS-9688 in virally-suppressed patients with chronic hepatitis B in which the IHV/CRU was the only US site.

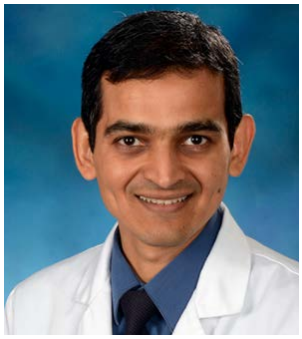
Direct Lysis of *Staph aureus* Resistant Pathogen Trial (Disrupt)
Dr. Baddley is the site investigator for Disrupt, a phase 3 study evaluating the efficacy and safety of exebacase, a novel direct lytic agent, in patients with staphylococcus bacteremia.

SOLAR
Dr. Narayanan was the site investigator for the multicenter trial comparing the long-acting injectable regimen of cabotegravir and rilpivirine to biktarvy 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 efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia, which completed enrollment and the findings were published in July 2021.

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

Regeneron Monoclonal 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.



Shivakumar Narayanan, MBBS, MD

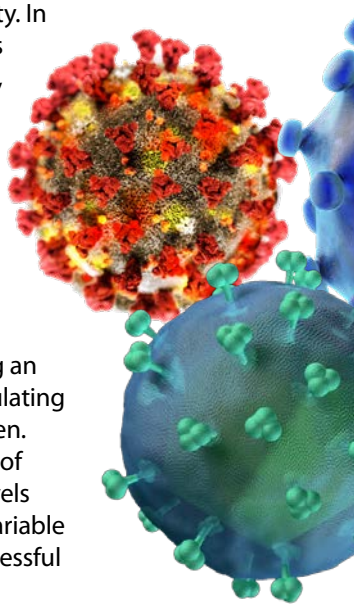
SARS-CoV-2 Vaccine Responses among Solid Organ Transplant Recipients
Dr. Saharia has built a cohort of transplant recipients who were vaccinated against SARS-CoV-2 either before or after transplant and collected samples to analyze their immune responses to the vaccine.

Clinical Care and Research Division Laboratory Based Programs
The Kottilil laboratory actively pursues two targeted research programs: "A Functional Cure Approach to Chronic Hepatitis B Infection" and "Hepatitis C Immunology Program."

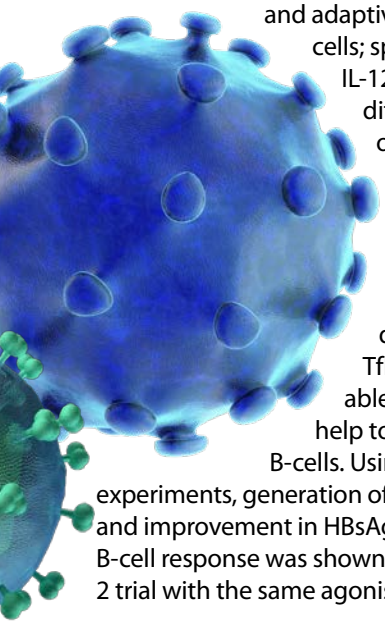
HBV Functional Cure Program

Currently available nucleoside/tide analog antiviral treatments are successful in achieving HBV suppression in the vast majority of patients. However, these treatments are required lifelong and do not result in viral clearance. Achieving HBsAg loss or seroconversion defines chronic hepatitis B (CHB) functional cure and is the goal of Dr. Kottilil's translational research program. Their ongoing efforts in this direction focus on multiple approaches that include targeting the viral, and/or host, factors required for viral persistence, and novel immune-based therapies, including immunomodulation and therapeutic vaccines.

These research efforts led by Dr. Poonia and Dr. Kottilil primarily delineate intrahepatic and peripheral T- and B-cell immune responses to HBV that correlate with development of protective immunity. Three separate projects are presently funded by research grants from Arbutus Pharmaceuticals and from Gilead Sciences. The goals of the Arbutus project are determining the mechanisms of massive immune dysfunction observed in CHB. The project focuses on the role HBsAg and exhaustion markers play in impairing antiviral immunity. In published results from this project, they identified correlation of HBsAg levels with inhibitory checkpoint molecule expression on helper CD4+ T-cells, indicating an immune dysregulating role of this antigen. Importantly, use of serum HBsAg levels as a stratifying variable determined successful



response to anti-PD-1 blocking for recovering anti-HBs immunity. In continuing work, they are investigating the importance of soluble inhibitory molecules and exosomes in HBV-mediated immune dysfunction. Using combinations of HBV-infected cell lines and patient sera they are characterizing exosomes derived from HBV-infected samples for their expression of immunomodulatory molecules with the goal of identifying targets for intervention. Their preliminary results indicate that exosomes from infected samples are able to inhibit TCR-mediated cytokine production. They hypothesize that these exosomes express inhibitory molecules such as PD-L1; the next steps are to identify these molecules using high throughput methods. Under the projects funded by Gilead Sciences, the central question was exploring the TLR8 pathway as a viable strategy to recover an HBV-specific immune response with the goal of achieving a functional cure. In two recently submitted manuscripts from these projects, they described immune pathways modulated by this agonist. Induction of the proinflammatory cytokine IL-12 led to activation of innate and adaptive lymphoid cells; specifically, IL-12 led to differentiation of HBsAg-specific follicular helper T-cells. These TLR8-differentiated Tfh were then able to provide help to cognate B-cells. Using co-culture experiments, generation of plasma cells and improvement in HBsAg-specific B-cell response was shown. In a phase 2 trial with the same agonist, modest reduction in HBsAg was observed in a subset of patients. Further work will attempt to identify if antigen specific Tfh induction correlates with HBsAg decline. The lab continues in depth investigation of the mechanism of Tfh help to B-cells in CHB. Recently, they identified a novel IL-27-mediated pathway for supporting B-cells. In published results, they show that Tfh-derived IL-27 effectively compensates the function of IL-21 by supporting Tfh-B-cell function required for a protective antibody response and may contribute to viral clearance, thereby providing potential target for achieving a functional cure.



Hepatitis C Immunology Program

This highly productive translational/bench research portfolio focuses on A) unraveling biological correlates of protective immunity to hepatitis C virus (HCV) for informing vaccine approaches and B) examine immune reconstitution or perturbations in successfully cured patients. Using samples collected from various clinical trials, Dr. Poonia and Dr. Kottilil continue their investigations into determinants of sustained virologic response (SVR) with directly acting antiviral (DAA) therapy. Previously they compared patients that had successful viral clearance versus failed cases. Immune phenotypes that predicted SVR included CD8+ and CD4+ T-cells expressing multiple inhibitory receptors including PD-1, LAG-3, and Tim-3 and containing HCV specific cells, indicating role of activated antigen specific cells in antiviral response. Their recent published work identified terminally differentiated CD8+ T-cells as another correlate of failed SVR with short duration DAA. These studies are aimed at understanding the role the immune system plays in an HCV cure which will inform vaccine approaches. Another lab focus is a detailed understanding of which immune functions repair and which persist immune defects in cured individuals. This knowledge has ramifications for HCV reinfection or relapse or for complications including hepatocellular carcinoma (HCC). They continue to publish on adaptive and innate immune defects that persist in cured individuals, including CD8+ T-cell gamma delta T-cells, MAIT cells and NK cell defects. On the other hand, defects in Tfh-B-cells are evidently repaired upon cure with DAA. Ongoing research will determine the relevance of such an altered immune landscape for complications like fibrosis and HCC. Despite highly effective DAA treatments, there is a need for a prophylactic vaccine; this is primarily due to many individuals being unaware of their infected status and limited to access to treatments due to costs. The knowledge of persisting immune defects in cured individuals adds another incentive for discovering a vaccine; it is still not clear whether patients that are cured develop protective immunity which will be effective in preventing re-infections. This is especially relevant in patients with continued high-risk behavior such as injection drug use and those with HIV co-infection. There is limited data on HCV reinfection after successful DAA mediated treatments, however rates are reported to be higher in PWIDs. These questions are being answered in projects funded by investigator-initiated clinical research studies by Gilead Sciences and an NIH R01 grant from National Institute of Drug Abuse to study the immune correlates of protection from reinfection among people at the highest risk of acquisition of HCV namely, those with HIV infection and people who inject drugs. Preliminary results indicate that approximately 15% patients in this cohort got re-infected after initially achieving SVR. Ongoing work is identifying immune cell differences in those who got re-infected compared to the rest with the expectation of identifying correlates

of protection. Although immune activation is a feature of chronic HCV infection, their results show significantly higher levels of immune activation along with higher levels of PD-1 expression on both CD4+ and CD8+ T-cells among PWIDs. Importantly, DAA-mediated virus clearance led to normalization of immune activation among non-PWIDs only. The significance of this continued immune activation despite virus clearance is being investigated currently. Their recent work showed that chronic viral hepatitis results in accelerated epigenetic aging; interestingly an immune clock composed of activation markers defined this biological age. Currently, they are investigating the mechanisms behind immune activation-mediated biological aging. Preliminary work shows a link between immune activation and mitochondrial dysfunction in T-cells with possible implication for T-cell function. As a result of these observations, a novel area of investigation is being developed in the lab: the link between persistent immune activation in chronic viral infection, mitochondrial dysfunction, and antiviral immunity, for which a combination of humanized mouse models and clinical samples from various cohorts of chronically infected patients are being utilized. Finally, they received a supplement to this grant for investigating COVID-19 progression and immunity in subjects with HIV infection and opioid-use disorder. There is a potential to identify immune deficiencies in this subset of patients that contribute to more severe disease progression.

Alonso Heredia, PhD

Due to combination antiretroviral therapy (cART), patients with HIV are living longer, but increasingly often they necessitate treatment for comorbidities such as cancer. Currently, lung cancer is the leading cause of cancer death in patients with HIV. In the project entitled, "*Impact of concomitant chemotherapy on HIV resistance to cART and reservoir size,*" funded by NCI, the **Alonso Heredia, PhD,** Associate Professor of Medicine, laboratory is investigating drug interactions between chemotherapeutic drugs and antiretrovirals with the goal of improving treatments in the growing population of HIV-infected patients with cancer. In a related project, also funded by NCI, Dr. Heredia, in collaboration with Kevin Cullen, MD, The Marlene and Stewart Greenebaum Distinguished Professor in Oncology at the University of Maryland Greenebaum Cancer Center, and Dr. Sajadi are investigating the replacement of 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**, formerly of the Division of Basic Science in the IHV, 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 of Diagnostic Radiology & Nuclear Medicine 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. In another related project, Dr. Heredia, in collaboration with Tae-Wook Chun, PhD, (of NIAID) and Yuxing Li, PhD, Professor of Microbiology and Immunology and member of the Institute for Bioscience and Biotechnology (IBBR) Research, is investigating suppression of HIV reactivation in cells from cART-treated patients using various combinations of antibodies.

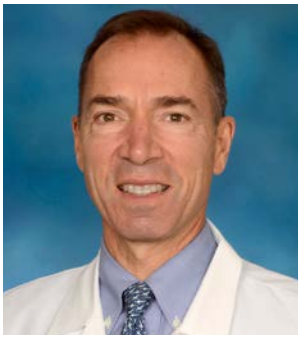
Yet another area of research in Dr. Heredia's laboratory is the development of effective antibodies against HIV. In collaboration with Dr. Sajadi, he is a Co-Investigator in the project "*Engineering of broadly reactive seroantibodies against HIV-1,*" funded by the Bill and Melinda Gates Foundation. 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 Dr. DeVico, Dr. Lewis and **Krishanu Ray, PhD,** Associate Professor, Biochemistry and Molecular Biology, Division of Vaccine Research at 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. Also, in collaboration with **Olga Latinovic, PhD, MSc**, Division of Virology, Pathogenesis, and Cancer in the IHV, he is investigating approaches to enhance the anti-HIV activity of entry inhibitors.

More recently, Dr. Heredia has begun a collaboration with Dr. Gallo, **Lishan Su, PhD,** The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology, Director of the Division of Virology, Pathogenesis, and Cancer, Dr. Daniel Zagury, and Dr. Helene Le Buanec (from Université de Paris, Institut de Recherche Saint-Louis, F-75010, Paris, France) to develop a mucosal vaccine against HIV that is based on the induction of specific CD8 T-cells responses that target infected CD4 T-cells.

Dr. Sajadi and his lab focus on humoral immunity in HIV-infected individuals with broadly neutralizing antibodies. He

works closely with Dr. Lewis and Dr. DeVico in the Division of Vaccine Research. Dr. Sajadi has five active grants, and is funded by the NIH, the Bill and Melinda Gates Foundation, and the VA. Dr. Sajadi has isolated several anti-HIV broad neutralizing antibodies that are among the most potent and broad described to date, which are currently undergoing preclinical development. He is also working on a project to understand the humoral response in COVID-19 infection.

Dr. Bagchi continues her focus on investigating the cardiovascular complications of patients who have chronic hepatitis C infection, HIV infection, or both, and 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 retrospective cohort studies of our outpatient HIV-infected patients in Baltimore, MD, a prospective cohort study among HIV and HCV mono-infected, and HIV/HCV co-infected to evaluating inflammatory mechanisms in HIV and/or HCV patients. Dr. Bagchi has a NIH K23 grant *"Elucidating Chronic Hepatitis C Infection as a Risk Factor for Coronary Heart Disease in HIV-Infected Patients,"* and recently completed an Accelerated Translator Incubator Pilot award from the University of Maryland Institute of Clinical and Translational Research *"Systemic and Epicardial Fat Inflammation and Local Coronary Atherosclerosis in HCV and HIV Patients."*



Nicholas Stamatos, MD, PhD

The laboratory of **Nicholas Stamatos, MD, PhD,** Associate Professor of Medicine, continues to conduct research focused on understanding how modulation of the carbohydrate content of cell surface proteins influences the functional capacity of cells of the immune system. In particular, his laboratory is studying how changes in the polysialic acid (polySia) content of specific cell surface glycoproteins on lymphocytes, monocytes, monocyte-derived dendritic cells, and macrophages influence the immune capacity of these cells. Experiments are being conducted using a murine model of pneumonia to test the hypothesis that regulated expression of polysialylated proteins on leukocytes helps direct cell homing and a well-orchestrated immune response during infection with *pneumococcus* and influenza virus. These experiments have indeed 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. 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 National Institute of Allergy and Infectious Diseases in the amount of $2,562,639 over 5 years. The grant entitled "*Influence of polysialic acid on leukocyte migration*" was awarded under the High Priority Immunology Grants program of National Institutes of Allergy and Infectious Diseases.

Although much is known about glycosylation of human immunodeficiency virus envelope proteins, relatively little is known about how glycosylation of proteins on the surface of permissive lymphocytes affects infection. Work from our laboratory previously demonstrated that removal of sialic acid from the surface of peripheral blood mononuclear cells using an exogenous bacterial neuraminidase promoted infection with HIV-1. Recently, we have demonstrated that activated human lymphocytes express not only monomeric sialic acid, but also polySia, and that removing this glycan enzymatically diminishes infection by HIV-1. Experiments are underway to identify a novel polysialylated protein(s) expressed by activated lymphocytes and to define the mechanism by which it promotes binding of HIV-1 to the cell surface. We are collaborating with the Heredia 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 our studies are expected to identify a novel target for treatment of HIV infection and provide a blueprint for down-regulating the expression of polySia or modified protein(s) in cells susceptible to infection with HIV-1.

Polysialic acid has provided a useful handle for 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 we identify on immune cells will have equally significant roles in cell function.

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The Division of Epidemiology and Prevention

The Division of Epidemiology and Prevention, led by **Man Charurat, PhD, MHS**, Professor of Medicine, Epidemiology and Public Health, Director of Center for International Health, Education, and Biosecurity (Ciheb), continues a research focus. The division published 90 manuscripts in peer-reviewed journals in FY21, and the 12 faculty-led 21 federal research awards.

Epidemiology and Prevention

Man Charurat, PhD, MHS

Rebecca Nowak, PhD, Assistant Professor of Epidemiology and Public Health, continued in FY21 to make progress on her NIH-funded K award, *"Role of anal microbiota, local cytokines and HIV in persistence of high-risk human papillomavirus (HR-HPV),"* (PI: Dr. Nowak, K07CA225403)**.** Dr. Nowak reported a high prevalence of multiple HPV infections among MSM who underwent anal cancer screening, suggesting that high-grade precancer's low detection rates were from screening inexperience rather than a low burden of HR-HPV. In addition, she and her collaborators at Johns Hopkins University (PI: Susan Tuddenham, MD, MPH), were awarded R21AI156765, "*The Rectal Microbiome and Incident Rectal Sexually transmitted Infections,*" which leverages archived longitudinal rectal samples from the TRUST/Building TRUST NIH Studies (PI: Dr. Charurat). The objective of this study is to examine differences in the rectal microbiota for MSM who acquire rectal *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) as compared with those who do not. This study will further compare longitudinal changes in the rectal microbiota that may be associated with increased risk for NG and CT, while accounting for risky behaviors such as number of sexual partners and condom use.

Rebeca Nowak, PhD

In FY21, **Alash'le Abimiku, PhD,** Professor of Medicine, Division of Geographic Medicine and Executive Director of the International Research of Excellence at the IHV-Nigeria (IHVN), was appointed to the Coalition for Epidemic Preparedness Innovations (CEPI) Scientific Advisory Committee. Dr. Abimiku joins a prestigious panel of experts to advise CEPI on the design and implementation of vaccine development, including protective *Betacoronavirus* vaccines, to protect against SARS-CoV-2 variants, other beta coronaviruses, and potentially novel coronaviruses that have yet to emerge. Dr. Abimiku will continue working as Chair of the African Society of Laboratory Medicine (ASLM) Board of Directors, as well as continue working to grow the IHV-N research platform and her NIH-funded independent research. Her research includes: "*Breast Milk Microbiota Influence on Infant Immunity and Growth (**BEAMING**),*" (PI: Dr. Abimiku, U01HG009783), "***SickleGenAfrica***," (U54HL141011) and "*Institute of Human Virology Nigeria-H3Africa Biorepository Initiative (**I-HAB**),*" (PI: Abimiku, U24HG007008). Continuing the tradition of building high quality laboratory infrastructure in countries that we serve and partner with, Dr. Abimiku's CDC-funded grant in Malawi (PI: Dr. Abimiku, NU2GGH002198) supported the accreditation of six laboratories in Malawi for the first time. She has expanded her expertise into supporting SARS-CoV-2 diagnosis and surveillance in Malawi, as well as in Mozambique (PI: Dr. Abimiku, NU2GGH002201), and under her CDC-funded Global Health Security grant in Nigeria (PI: Dr. Abimiku, NU2HGH000020).

Alash'le Abimiku, PhD

Nadia A. Sam Agudu, MD

Nadia A. Sam Agudu, MD, Associate Professor of Pediatrics, is multi-PI of the NIH-funded study, *"Adolescent to Adult Patient-centered HIV Transition (**ADAPT**),"* (MPI: Vicki Tepper, PhD, Professor of Pediatrics/Dr. Charurat/Dr. Sam-Agudu, R01HD089866). In FY21, ADAPT has reached 99% enrollment of the target sample size of 300 adolescents living with HIV (ALHIV) across six study sites in North-West and North-Central Nigeria. ADAPT examines the impact of tailored peer support on successful transition and viral suppression for ALHIV transitioning to adult care. As of the end of July 2021, ALHIV participant transition has reached 90%, and follow-up and data collection continues as the study enters its last year. Additionally, Dr. Sam Agudu began working on a project funded by the UMB President's Global Impact Fund (MPI: Dr. Sam-Agudu and Dr. Abimiku), and she is leading the Central and West Africa Implementation Science Alliance (**CAWISA**), which is tasked with providing mentoring and developing a toolkit for early investigators from Cameroon, DRC, Ghana, and Nigeria. Finally, with the onset of the COVID-19 pandemic, Dr. Sam-Agudu is collaborating with the NIH-funded **AFREhealth** (African Forum for Research and Education in Health, R25TW011217, (PIs:

Nelson Sewankambo, MBChB, MMed, MSc, Makerere University, Uganda; Prisca Adejumo, RN, PhD, of the University of Ibadan, Nigeria; Jean Nachega, MD, PhD, MPH, of Stellenbosch University, South Africa; and Fatima Suleman B.Pharm, M.Pharm, PhD, of the University of KwaZulu-Natal, South Africa to rapidly generate rigorous evidence on COVID-19 to inform policy and practice in African countries, especially for pregnant women, children, and adolescents.

Kristen Stafford, PhD, MPH, Associate Professor of Epidemiology and Public Health, and Deputy Director, Center for International Health, Education, and Biosecurity, and Director of the Master of Science in Epidemiology and Clinical Research program, completed a five-state population-based household survey of COVID-19 in Nigeria in FY21. The first phase of the survey was conducted from September to October of 2020; it found that the seroprevalence of SARS-CoV-2 antibodies ranged from about 9–24%. The second phase of the survey conducted in May and June of 2021 found a seroprevalence of almost 40%. Active PCR-confirmed infection was less than 0.2% in both periods. In Stafford's big data grant **SHIELD** (PI: Dr. Stafford, NUGGH001976), which is responsible for the development and management of the Nigeria National Data Repository (NDR), she and the team are working to incorporate predictive algorithms using machine learning into the NDR in an implementation science approach to better identify patients in need of enhanced support to maintain engagement in care. She has also led the development of an analytic database sourced from NDR to enable the government of Nigeria and partners to execute quantitative assessments to improve treatment models and patient outcomes.

Dr. Stafford in the field for the BAIS V project

Dr. Dakum on a construction tour for one of the International Research Centers of Excellence

Patrick Dakum, MBBS, MPH, Associate Professor of Epidemiology and Public Health and Chief Executive Officer at the IHV-Nigeria (IHV-N), continued to lead the implementation of the CDC-funded PEPFAR public health program in Nigeria (PI: Dr. Dakum, **ACHIEVE**, NU2GGH002099). In addition, under Dakum's leadership, IHV-N was awarded one of the largest USAID single country grants for tuberculosis. Under the USAID "local organizations networks," IHV-N will seek to drastically increase the level of tuberculosis (TB) cases detected and treated in Nigeria over the next five years (72062020CA00008). IHV-N was awarded $15 million to establish a Tuberculosis Local Organizations Network (TB-LON 3) grant in four states. IHV-N is working rapidly to improve TB case detection and treatment in communities using a differentiated model approach while strengthening resilient and sustainable systems for tuberculosis control. As of March 2021, after one year of project implementation, more than 2.1 million individuals were screened for tuberculosis, and 11,134 people were notified for tuberculosis and placed on treatment. Dakum's research is focused on establishing a long-term research cohort of persons living with HIV in Nigeria. He is working to characterize the burden, risk profile, pathogenesis, trends, and clinical outcomes of chronic non-communicable diseases among PLHIV.

Peter Memiah, DrPH, MSc, Associate Professor of Medicine, commenced an adolescent mental health initiative in Kenya in FY21 dubbed Reaching, Engaging Adolescents and Young Adults for Care Continuum (**REACH-Mental Health**). REACH-MH is a collaboration between the University of Maryland, Baltimore's (UMB) Schools of Medicine and Social Work, LVCT Health, and Kenya's Ministry of Health (Award number: 10PMPGIF: Presidential Global Impact Fund). REACH-MH is a two-year study that will adapt adolescent-led participatory research and complement it with secondary data analyses using one of the largest online service providers for adolescent health in Africa to: 1) identify key mental health risk factors among adolescents using digital technology to solicit information, and 2) identify barriers to and facilitators of mental health services for adolescents by conducting targeted qualitative interviews. REACH-MH will provide needed evidence on the burden of adolescent mental health and will inform the design of age-appropriate mental health services for adolescents in Kenya. In FY21, REACH-MH held its first partnership meeting (July 2021)

Dr. Memaih and the REACH team in Kenya

that brought together more than 50 national stakeholders also representing Nairobi, Mombasa, and Kisumu counties, including a majority representation from adolescent youth groups in Kenya. The adolescent-led first partnership meeting developed the road map for implementing the REACH-MH study, which will also create a new collaborative community; this community will provide valuable growth opportunities to students and faculty while helping develop innovative strategies to improve the mental health and well-being of adolescents in Kenya.

Shenghan Lai, MD

Shenghan Lai, MD, Professor of Epidemiology and Public Health, has developed a cohort of African American adults in Baltimore to investigate individual and combined effects of HIV infection, long-term ART exposure, chronic cocaine use, and other factors on subclinical coronary artery disease (CAD) in his NIH-funded study *"Effects or HIV, Cocaine, and Prolonged ART use on Subclinical Cardiovascular Disease (**HEART**),"* (PI: Dr. Lai, U01DA040325). Lai and team found that cocaine use may induce/accelerate subclinical CAD and other HIV-associated comorbidities, and in FY21 they conducted COVID-19 interviews with the cohort to identify COVID-19-associated factors related to morbidity and mortality in the study population. In FY22, Dr. Lai and his team will examine whether and how cocaine use influences HIV/ART-associated cardiovascular and neurocognitive comorbidities. Additionally, he continued his work with **Hong Lai, PhD, MPH,** Associate Professor of Epidemiology and Public Health, who 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,"* (PI: Dr. Lai, R21DA048780). Recently, Dr. Lai published a radiomics-based analysis indicating conventional risk factors, cocaine use, and HIV infection each have different effects on changes in coronary atherosclerosis over time. This study showed cocaine use was significantly associated with almost a quarter of the radiomics features; HIV infection, in contrast, was linked to only slightly more than 1% of radiomics features. The study also revealed that HIV infection had a more profound effect on coronary artery disease in younger individuals. This study echoed an NHLBI-funded HIV-associated sudden cardiac death investigation, demonstrating one-third of apparent sudden cardiac deaths in HIV-infected persons were due to occult drug overdose.

Hong Lai, PhD, MPH

Cristiana Cairo, PhD

Cristiana Cairo, PhD, Assistant Professor Medicine, continued her NIH study of the *"Impact of* in-utero *HIV exposure on infant T- and B-cell responses in Malawi"* (MPI: Dr. Cairo/Miriam Laufer, MD, Professor of Pediatrics, U01HD092308) in FY21. Her study involves characterizing T- and B-cell responses to routine immunization antigens in infants born to three different cohorts of women: women with undetectable HIV viral load before conception and through pregnancy; women with HIV high viremia, diagnosed late in pregnancy; and women with no HIV infection. The goal is to determine whether the extent of immune perturbations in HEU infants correlates with the degree of exposure to HIV viral replication during gestation. Overall, more than 1,100 women were screened for eligibility, and approximately 600 enrolled. Four hundred eighty-five infants were enrolled out of 528 births in the study, and 262 completed the 9-month follow up. The clinical activities for the study have been completed, and the experimental activities have begun. Due to a broad and prolonged disruption of ultra-low temperature shipping (caused by a world-wide COVID-19-related disruption of flight schedules), shipping of infant specimens had to be postponed with substantial experimental delays. The first experiments conducted on cord blood cells suggest that the frequency of Vdelta2 T-cells producing pro-inflammatory cytokines — in particular polyfunctional cells — is higher in HEU neonates, which aligns with phenotypic results previously observed for neonates recruited in Dr. Charurat's MARGIN project. Dr. Cairo is also involved in a study led by Dr. Laufer to assess neurocognitive development in the same cohort of Malawian HEU infants (R01HD100235). The experiments led by Dr. Cairo, which will help investigate a potential link between monocyte activation at birth and neurocognitive outcomes in young children are planned to begin in the fall. In the effort to further build her expertise in the field of fetal-maternal immunology, Dr. Cairo joined a large multidisciplinary team lead by Marcela Pasetti, PhD, Professor of Pediatrics, to study "*Maternal Immunization and Determinants of Infant Immunity"* in the context of a P01 (Contact PI: Pasetti), which will begin before the end of summer 2021. Dr. Cairo will help with experiments aimed at assessing T- and B-cell responses to TdaP and influenza vaccination administered during pregnancy.

Clement Adebamowo, BM, ChB, ScD, FWACS, FACS, Professor of Epidemiology and Public Health, Director for Global Health Cancer Research and Associate Director Population Science Program, Marlene and Stewart Greenebaum Comprehensive Cancer Center, conducts research in the genetics of breast, colon, and prostate cancers and research ethics education. In FY21, Dr. Adebamowo built on his *"African Female Breast Cancer Epidemiology study (**AFBRECANE**),"* (PI: Adebamowo, U011HG009784) study investigating the genomics and epidemiology of molecular subtypes of breast cancer in indigenous African populations and was awarded a new NIH grant*, "Point of Care Diagnostic test for Molecular Subtyping of Breast Cancer (**PoCBreCA**),"* (PI: Dr. Adebamowo, R21CA255835).

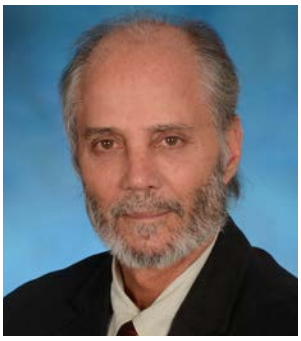
In the PoCBreCA study, Dr. Adebamowo will work with collaborators to combine nanotechnology, photonics, miniaturization, and cell phone networks to develop a point-of-care diagnostic technology and kits to overcome the limitation of molecular subtyping of breast cancer in low- and middle-income countries.

Dr. Adebamowo was also awarded the grant *"Eastern Nigeria Research Ethics Training (**ENRICH**)"* (PI: Dr. Adebamowo, R25TW011811) by NIH in FY21. ENRICH is a collaborative research ethics training program that partners with University of Nigeria, Nsukka (UNN) and the Center for Bioethics and Research (CBR) to provide 40 master's degrees and 225 short- and medium-term trainings in research ethics. The program will rapidly scale up bioethics expertise and research capacity in eastern Nigeria and ensure that trainees conduct innovative, culture-specific bioethics research projects, and expand contributions to the global research ethics discourse. ENRICH is an extension of one of Dr. Adebamowo's training programs, *"Entrenching Training and Capacity in Research Ethics in Nigeria (**ENTRENCH**),"* (PI: Dr. Adebamowo, R25TWE010514) and Western African Bioethics Training Program (R25TW007091).

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

Since 2004, Dr. Adebamowo has been working to strengthen research ethics in Nigeria. He helped establish and continues to strengthen the National Health Research Ethics Committee (NHREC) and 35 institutional health research ethics committees in Nigeria. He has implemented more than 20,000 online courses; conducted 82 onsite courses for research ethicists, biomedical researchers, and members of ethics committees; and has admitted 43 Master's in Bioethics students into our training programs.

Niel Constantine, PhD, Professor of Pathology at the Institute of Human Virology, has been active in the diagnostic arena for more than 40 years. His accomplishments during the past



Niel Constantine, PhD

two years include: 1) Fulfilling requirements with an ongoing contract with USAID through FHI360 to evaluate diagnostic test systems for the detection of infection by HIV, HBV, HCV, Cryptococcus, syphilis, and for hCG. International locations from more than ten counties have sent test kit lots for evaluation for use with well-characterized sample panels under good laboratory practices. Reports of the assessments are sent to FHI360 monthly, with further assessments as necessary; 2) assessments of antibody tests' utility for COVID-19, including the in-house developed tests and commercial rapid assays; and 3) collaboration with UMB researchers (Psychiatry Department) for the investigation of infectious agents and their effect with a variety of psychiatric disorders.

Dr. Charurat is Principal Investigator of five research awards. Dr. Charurat's **Building TRUST** (PI: Dr. Charurat, R01AI120913) award was built on his NIH TRUST (R01MH099001) grant, which was originally funded in 2012. These awards allowed for the development of cohort of 1,200 men who have sex with men (MSM) in Nigeria that has been followed for the last decade. The Building TRUST study achieved the target enrollment goal of 1,200 MSM using respondent-driven sampling (RDS). The Building TRUST study made formative contributions to the key population research with more than 30 publications. The study found that MSM marginalization continued unabated and further increased the stigma, and there was a spectrum of stigma severity among MSM. Indeed, there was a dose-response pattern in the association between stigma level and incident HIV. The study found an extremely high prevalence and incidence of HIV and STIs, especially among the young (15-19 years old) MSM, and that engagement in care improved condom and lubricant use. Furthermore, the study found social network support was strongly associated with a better HIV care cascade and HIV prevention cascade. Additionally, the study found a shift in rectal microbiota towards more pathogenic bacteria among HIV-positive individuals. Also, delving deeper into the molecular analyses, the study discovered a unique, new subtype B recombinant HIV-1 that characterizes the HIV epidemic among MSM, and that not being on antiretroviral therapy (ART) was associated with membership in a genetically linked cluster. Finally, the study observed that stigma is commonly experienced in clusters where community members perceived a higher level of stigma. In FY22, Dr. Charurat plans to continue his research with the MSM cohort on stigma, non-communicable disease, and optimizing PrEP.

Dr. Charurat with a team member in the field

In FY21, Dr. Charurat continued to lead the population-based HIV impact assessment (**PHIA**) in Zambia (**ZAMPHIA 2020**) and Botswana (**BAIS V**), *"Regional Strengthening of HIV-focused Population-base National Surveys and Size Estimations* (***RESPONSE***)," (PI: Dr. Charurat, NUGGH002172).

Unlike other HIV population-based surveys, RESPONSE provides direct estimates of HIV prevalence, incidence, and drug resistance through biomarker sample collection. With more than 600 survey team members currently in the field in Zambia and Botswana interviewing and collecting specimens, data from more than 50,000 individuals will be used to publish the national and sub-national epidemic data for Zambia and Botswana in FY22. The information will be used to guide PEPFAR programming towards achieving the UNAIDS 95/95/95. In FY21, the Nigeria PHIA, **NAIIS** (PI: Dr. Charurat, NU2GGH00218), made significant progress towards archiving the dataset for public use and completed reliable estimates for key populations in Nigeria through the data analysis and triangulation of game of contracts and the network scale-up method (NSUM) PHIA data.

In FY21, Dr. Charurat and his study team concluded the analyses for the *"The Microbiome Affects Risk of Growth in HIV-exposed but Uninfected Infants—Nigeria* (***MARGIN***)" (PI: Dr. Charurat, R01DE025174) study. The study focuses on the gut and oral microbiota of HIV-exposed uninfected infants and HIV-unexposed infants and examines how those microbiota relate to early childhood co-morbidities among HIV exposed uninfected infants. In FY22, he will work towards publishing the data in three manuscripts.

Finally, Dr. Charurat and Dr. Abimiku continue to guide and mentor three PhD candidates from Nigeria enrolled in the Department of Epidemiology and Public Health at the University of Maryland, Baltimore as they make progress toward their degree supported by **Epi-Nigeria** (MPI: Dr. Charurat/Dr. Abimiku, D43TW010051), an NIH Fogarty International Center award.

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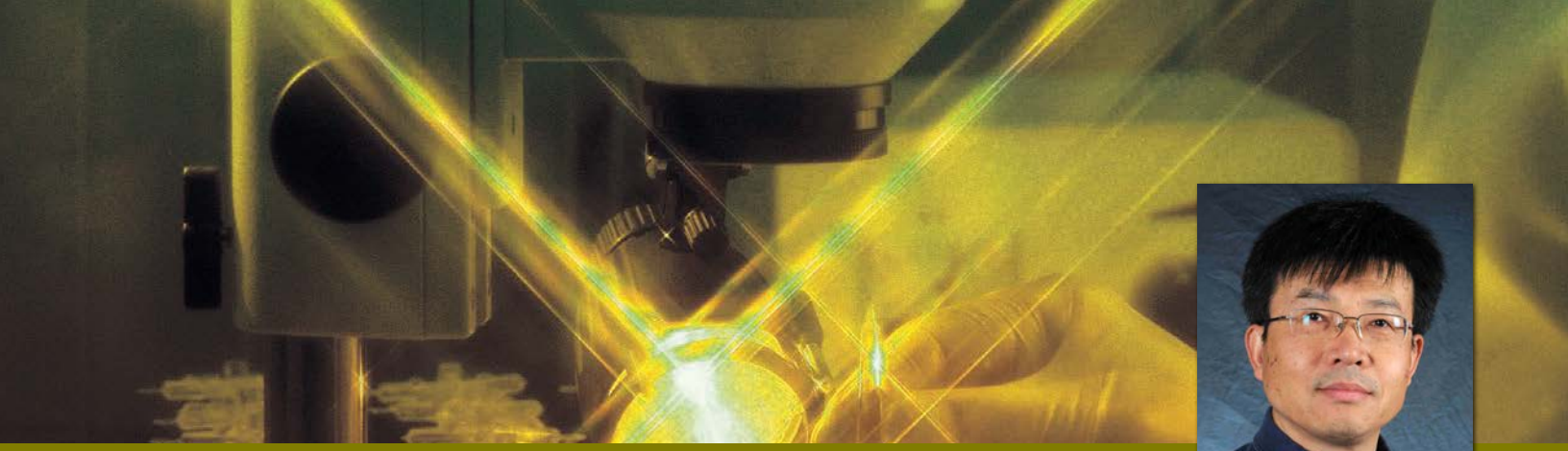


Lishan Su, PhD

Immunotherapy

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

This year, **Yang Liu, PhD**, former Professor of Surgery and Director of the Division of Immunotherapy, and **Pan Zheng, MD, PhD**, former Professor of Surgery and Immunotherapy faculty member, made a great achievement in combating COVID-19 based on their fundamental research of the CD24-Siglec innate immune checkpoint. In collaboration with Yong-Tang Zheng, PhD, Professor at the Chinese Academy of Science, they discovered that CD24Fc protects against viral pneumonia in simian immunodeficiency virus-infected Chinese rhesus monkeys. In collaboration with Dr. Su, they found that CD24Fc reduces T-cell lymphopenia and exhaustion in HIV-infected humanized mice. In a clinical trial, COVID-19 patients that received CD24Fc had a 60% higher probability of seeing improved clinical status. These findings led to the acquisition of Oncoimmune by Merck. In November 2020, Oncoimmune co-founders Dr. Liu and Dr. Zheng left IHV and established OncoC4. Following their departure, Dr. Su has taken leadership of the Division of Immunotherapy.

Yang Liu, PhD

Pan Zheng, PhD

Three major strikes in revealing novel mechanisms of immunotherapy have been made in the Division of Immunotherapy. One of the major areas of focus has been to understand the mechanism by which CTLA-4 can be targeted for cancer immunotherapy. It has long been established that the soluble CTLA-4 (sCTLA4) molecule is protective against autoimmune diseases in mice. Through the work of Dr. Yang and Dr. Zhang, and now under leadership of Dr. Su, this project has led to data showing strong correlation between the levels of sCTLA4 and immune-related adverse events (irAEs) in the clinic. They established a striking correlation between high binding to soluble CTLA4 protein and the severity of irAEs in human CTLA4 knockin (KI) mice. Current efforts are devoted to testing roles for both cell surface and sCTLA-4 in conferring protection against irAEs, and the hypothesis that sCTLA4, which evades clearance by irAE-inducing anti-CTLA-4 antibodies, can be a potential therapeutic for prevention and treatment of irAEs. These studies will have a transformative impact in immune-oncology research, as they may offer prophylaxis and treatment for irAEs associated with the most effective immunotherapy in use in the clinic.

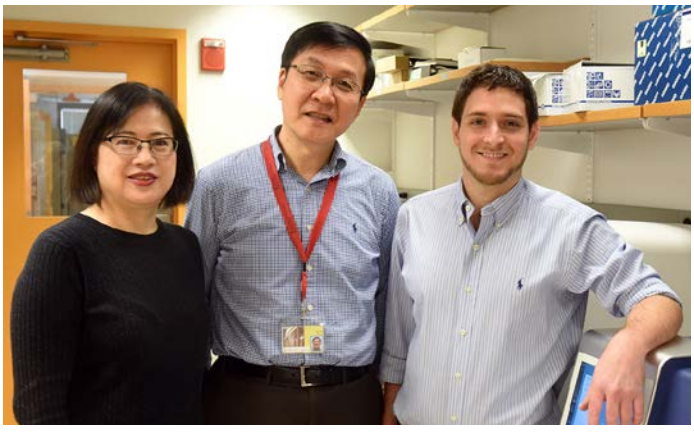
A second major research focus has involved studies of a preclinical model for assessing long-term immunotherapy-related adverse effects in children. These studies, initiated by Dr. Zheng and currently led by **Yin Wang, PhD**, Assistant Professor of Surgery, take advantage of the established novel mouse model developed by Dr. Zheng and Dr. Liu. The model is unique in that it faithfully recapitulates irAEs in major organs in immunotherapy. Using this model, current studies are devoted to addressing

the central hypothesis that irAEs reflect the malfunction of checkpoints in the cellular response to tissue injury and can be corrected by fortifying the checkpoint.

The third major research direction at the Division of Immunotherapy is focused on the novel concept of targeting of HIF-1α to abrogate the PD-L1-mediated immune evasion checkpoint in the tumor microenvironment, while promoting immune tolerance to the host. A combination of Anti-CTLA-4 and anti-PD-1/PD-L1 is the most effective cancer immunotherapy but causes high incidence of irAEs. These studies, led by Dr. Wang, have shown that targeting HIF-1α suppresses PD-L1 expression on tumor cells and tumor-infiltrated myeloid cells, but paradoxically induces PD-L1 in normal tissues via an IFNγ-dependent mechanism. Targeting the HIF-1α-PD-L1 axis in tumor cells reactivates tumor-infiltrating lymphocytes and causes tumor rejection. The HIF-1α inhibitor echinomycin potentiates cancer immunotherapeutic effects of anti-CTLA-4 therapy with efficacy comparable to anti-PD-1 antibodies. Their data has demonstrated that, while anti-PD-1 exacerbates anti-CTLA-4-induced irAE, echinomycin protects mice against these irAEs by increasing PD-L1 levels in normal tissues. Their data suggest that targeting HIF-1α fortifies the immune tolerance function of the PD-1:PD-L1 checkpoint in normal tissues, but abrogates its immune evasion function in the tumor microenvironment, to achieve safer and more effective immunotherapy.

Liu Laboratory

Yan Liu, PhD, Assistant Professor of Surgery, works on signal transduction and gene dysregulation-associated diseases including cancers and neurodegenerative disorders. She has special expertise in studies of molecular mechanisms underlying diseases. Currently, she supervises projects related to proliferative and metastatic mechanisms of solid tumors including Wilms tumor, colorectal cancer, glioblastoma. and medulloblastoma. She also studies the effects of abnormal glycogen metabolism in neurodegenerative disorders and aging, and exploiting targeting therapies via exosome-based gene delivery. Her long-term goals are to develop novel, gene-targeting therapies to treat these diseases in humans. Wilms tumor (WiT) is a kidney cancer that primarily affects children. For patients with anaplastic WiT, metastasis and recurrence are common, and prognosis is generally poor. Novel therapies are needed to improve outcomes for patients with this high-risk WiT. A potential contributor to WiT development is constitutive activation of AKT by insulin-like growth factor 1 (IGF1) and its receptor (IGF1R) signaling pathway, but the complete underlying mechanism has remained unclear. Dr. Liu's work has demonstrated that the hypoxia-inducible factor 1α (HIF-1α)-IGF binding protein 2 (IGFBP2) axis and tumor-specific IGF1A are key players for constitutive activation of IGF1-AKT signaling leading to WiT malignancy. Their studies showed that HIF-1α and IGFBP2 are highly expressed in a majority of WiT patient samples, and that deficiency of HIF-1α, IGFBP2, or IGF1 in WiT cells significantly impairs tumor growth and nearly abrogates metastasis in xenografted mice. Moreover, they found that pharmacologic targeting of HIF-1α by echinomycin delivered via nanoliposomes efficiently restrained growth and metastasis of patient-derived relapsed anaplastic WiT xenografts, and was more effective than vincristine in an anaplastic WiT mouse model, where it eliminated metastasis via suppressing HIF-1α targets and the HIF-1α-IGFBP2 axis governing IGF1-AKT signaling.



Dr. Yan Liu (left), Dr. Yin Wang (center), and Dr. Chris Bailey

Glioblastoma multiforme (GBM), a lethal brain tumor, remains the most daunting challenge in cancer therapy. Overexpression and constitutive activation of PDGFs and PDGFRα are observed in most GBM; however, available inhibitors targeting isolated signaling pathways are minimally effective. Therefore, better understanding of crucial mechanisms underlying GBM is needed for developing more effective targeted therapies. Some of Dr. Liu's most recent work has demonstrated that HIF-1α binds the PDGFD proximal promoter and PDGFRA intron enhancers in GBM cells to induce their expression and maintain constitutive activation of AKT signaling, which in turn increases HIF-1α protein level and activity. They found that knockout of HIF-1A, PDGFD or PDGFRA in U251 cells inhibits cell growth and invasion *in vitro* and eradicates tumor growth *in vivo*, and that HIF-1A knockdown in GBM cells extends survival of xenograft mice, whereas PDGFD overexpression shortens survival. They found that the HIF-1α inhibitor echinomycin induces GBM cell apoptosis and effectively inhibits growth of GBM *in vivo* by simultaneously targeting the HIF-1α-PDGFD/PDGFRα-AKT feedforward pathway.

Her work revealed that HIF-1α orchestrates expression of PDGF-D and PDGFRα for constitutive activation of the

AKT pathway and is crucial for GBM malignancy, suggesting that therapies targeting HIF-1α may provide an effective treatment for GBM.

Wang Laboratory

Led by Dr. Wang and also including Dr. Liu and **Christopher Bailey, PhD**, Postdoctoral Fellow, the Wang lab devotes its efforts to the identification of novel molecular pathways and targets underlying human disease, and the development of novel targeted therapies with high translational potential to address unmet needs in clinical care. The disease areas that Dr. Wang's lab focuses on are diverse and range from cancer to autoimmune diseases, as well as neurological disorders, COVID-19, and immunotherapy-related adverse events. Their lab has made great achievements in understanding critical roles of the transcription factor hypoxia-inducible factor 1α (HIF-1α) in human disease, including hematopoietic malignancies, breast cancer, Wilm's tumor, and brain tumors. Several of their publications have highlighted central roles for HIF-1α in cancer and demonstrate the safety and efficacy of HIF-1α-targeted therapy with echinomycin in mouse models of cancer.

HIF-1α in hematological malignancies

One major achievement of Dr. Wang's lab has been their discovery that HIF-1α, under normoxia, is constitutively active in leukemia initiating cells of human AML. They demonstrated an essential role of HIF-1α in maintaining leukemia initiating cells, providing an effective approach to targeting leukemia initiating cells in the treatment of hematological malignancies. The HIF-1α-inhibitor echinomycin showed a strong therapeutic effect by eliminating leukemia-initiating cells and preventing the recurrence of leukemia. They further demonstrated that echinomycin has a significant therapeutic effect on relapsed AML at doses that are 30-50-fold lower than what are considered maximally tolerable in humans. Recently, they tested if HIF-1α activity is the converging point of the major cancer stem cell maintenance programs and if HIF-1α activity is also regulated by common recurrent genetic alterations in AML, to find a novel approach for the treatment of both recurrent and TP53-mutated AML by targeting HIF-1α. They found that echinomycin was broadly effective against xenografts from multiple AML samples *in vivo*, and more effective than combined cytarabine and daunorubicin chemotherapy. Using TP53-mutated AML cell line THP1 and patient-derived AML cells, they tested a new echinomycin formulation with longer half-life and significantly improved therapeutic effect. Their data suggest a novel approach to treat AML with TP53 mutations.

Dr. Yan Liu (left), Dr. Yin Wang (center), and Dr. Chris Bailey

Liposomal formulation of echinomycin

For over a decade, Dr. Wang's lab has studied the function of HIF-1α in cancer. As the first group to renew the effort of exploring echinomycin for cancer therapy, another major contribution of Dr. Wang's lab has been the development of a new liposomal formulation of echinomycin. Echinomycin, a bifunctional intercalating agent and quinoxaline antibiotic from *Streptomyces echinatus*, is a potent small-molecule inhibitor of HIF-1α, functioning by competitively inhibiting HIF-1α binding to DNA hypoxia-response elements (HRE) in a sequence-specific manner. In the late 1980's, long before being identified as an HIF-1α inhibitor, echinomycin was evaluated in multiple phase I/II clinical trials for solid tumors led by the National Cancer Institute for multiple phase I/II trials. Although echinomycin exhibited manageable toxicity profiles in these trials, its clinical development was discontinued because it was not consistently effective for patients refractory to all available frontline therapies. However, a small subset of patients experienced complete or partial responses to echinomycin in nearly all of the trials. Dr. Wang's lab hypothesized that these mixed responses may have been attributable to heterogeneity in HIF-1α expression, which could not have

been meaningfully assessed at that time, since echinomycin was clinically discontinued before HIF-1α was identified as an important molecular target for cancer therapy. To explore this notion, Dr. Wang's lab investigated whether HIF-1α expression in solid tumors could serve as a predictive biomarker for echinomycin therapeutic effects in mouse models of cancer. Their studies revealed that, while cancer cells expressing high HIF-1α were more sensitive to echinomycin treatment in cell culture, therapeutic effects of echinomycin in mice bearing the same tumors was formulation-dependent. They found that the traditional Cremophor EL (CrEL) based echinomycin formulation previously employed in clinical trials was similarly ineffective in mouse models of HIF-1α-expressing solid tumors. In contrast, reformulation of echinomycin using a liposomal delivery platform could rescue the potent HIF-1α inhibitory action of the drug *in vivo*, leading to significant improvement of therapeutic effects. Compared to the same dose of CrEL-echinomycin, liposomal echinomycin provided superior inhibition of breast cancer growth, metastasis, and HIF-1α target gene expression, and was significantly safer in preclinical toxicology studies. Taking advantage of liposomal echinomycin as an enabling technology, the Wang lab has completed several other projects focusing on therapeutic targeting of HIF-1α, including TP53-mutated AML and Wilms tumor. Their ongoing studies continue to develop this paradigm in glioblastoma multiforme, medulloblastoma, early T-cell precursor ALL, and in the context of cancer immunotherapy with anti-CTLA-4 antibodies.

The study of HIF-1α in immunotherapy

Monoclonal antibodies (mAbs) targeting CTLA-4 and PD-1/PD-L1 immune checkpoints have risen as curative options for many cancer patients, including those with advanced disease. In terms of therapeutic efficacy, the superiority of anti-CTLA-4 and anti-PD-1/PD-L1 combination therapy over monotherapy is well-documented. However, dual-immune checkpoint blockade is severely limited by high incidence of immune-related adverse events (irAE), which can result in discontinuation of immunotherapy and, in some cases, even cause death. A major challenge for cancer immunotherapy is to eliminate irAE without compromising the synergistic cancer immunotherapeutic effect of dual-immune checkpoint blockade. HIF-1α has emerged as a prime target for human cancer. However, no HIF-1α inhibitors have received regulatory approval for commercial use in cancer patients. A third major focus of the Wang lab has involved studies showing that targeting HIF-1α suppresses PD-L1 expression on tumor cells and tumor-infiltrated myeloid cells, but unexpectedly induces PD-L1 in normal tissues by an IFNγ-dependent mechanism. Their recent studies have shown that targeting the HIF-1α-PD-L1 axis in tumor cells reactivates tumor-infiltrating lymphocytes and causes tumor rejection. The HIF-1α inhibitor echinomycin potentiates cancer immunotherapeutic effects of anti-CTLA-4 therapy with efficacy comparable to anti-CTLA-4 and anti-PD-1 antibodies. However, while anti-PD-1 exacerbates irAE triggered by ipilimumab, echinomycin protects mice against irAEs by increasing PD-L1 levels in normal tissues. Their data suggest that targeting HIF-1α fortifies the immune tolerance function of the PD-1/PD-L1 checkpoint in normal tissues but abrogates its immune evasion function in the tumor microenvironment to achieve safer and more effective immunotherapy. Aside from these studies, Dr. Wang's group is also investigating the clinical dilemma of irAEs from a different angle by taking over the R01-funded project initiated by Dr. Zheng, *"A mouse model to assess long-term immunotherapy-related adverse effects in children."* Building on their work using the mouse model of irAE developed by Dr. Liu and Dr. Zheng, Dr. Wang's ongoing studies will make a substantial contribution to knowledge by characterizing long-term irAEs in mice and by examining the role of damage-related molecular patterns (DAMPs)-binding protein CD24 and Siglecs in irAE pathogenesis.

Immunotherapy Publications

Liu Y, Nelson MV, Bailey CM, Zheng P, Dome JS, Liu Y, **Wang Y** (2021). "Targeting the HIF-1a-IGFBP2 axis therapeutically reduces IGF1-AKT signaling and blocks the growth and metastasis of relapsed anaplastic Wilms tumor." *Oncogene*, Jun 21. doi:10.1038/s41388-021-01907-1. DOI: 10.1038/s41388-021-01907-1

Huang X, Liu Y, **Wang Y**, Bailey CM, Zheng P, Liu Y (2021). "Dual Targeting Oncoproteins MYC and HIF1α Regresses Tumor Growth of Lung Cancer and Lymphoma." *Cancers (Basel)*, Feb 9;13(4):694. DOI: 10.3390/cancers13040694

Scarpa M, Singh P, Bailey CM, Lee JK, Kapoor S, Lapidus RG, Niyongere S, Sangodkar J, **Wang Y**, Perrotti D, Narla G, Baer MR (2021). "PP2A-activating Drugs Enhance FLT3 Inhibitor Efficacy through AKT Inhibition-Dependent GSK-3β-Mediated c-Myc and Pim-1 Proteasomal Degradation." *Molecular Cancer Therapeutics*, Apr;20(4):676-690. DOI: 10.1158/1535-7163.MCT-20-0663

Bailey CM, Liu Y, Peng G, Zheng P, Liu Y, **Wang Y** (2020). "A Liposomal Formulation of HIF-1α Inhibitor Echinomycin Inhibits Growth and Metastasis of Experimental Model of Breast Cancer." *Nanomedicine NBM*, Jul 29:102278. DOI: 10.1016/j.nano.2020.102278

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

The Center for International Health, Education, and Biosecurity (Ciheb) has made key advances in addressing critical needs in health system capacity that improve the prevention, care, and treatment of HIV and other infectious and noncommunicable diseases. In 2020-2021, Ciheb improved and expanded programs in Botswana, Kenya, Malawi, Mozambique, Nigeria, Rwanda, Tanzania, and Zambia.

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

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.

Kristen A. Stafford, PhD, MPH

Man Charurat, PhD, MHS

In 2020-2021, Ciheb crossed a new sustainability threshold by supporting the establishment of three indigenous non-governmental organizations committed to advancing public health in Botswana, Kenya, and Zambia. These three organizations will further strengthen the long-term impact of Ciheb's programmatic initiatives. 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 Acting Country Director **Reson Marima, MD,** Ciheb is implementing precision programming and data-driven programs toward achieving HIV epidemic control in Botswana. Ciheb is supporting 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 (MOHW) and has been helping to care for approximately 118,000 HIV patients on antiretroviral treatment (ART).

The Bummhi team, led by **Ndwapi Ndwapi, MD**, consists of 525 staff members. A physician and pioneer in establishing publicly funded ART 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 FY 21, Ciheb supported five programs in Botswana including BPACE, 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 UMB is a subrecipient.

Projects

Botswana Partnership for Advanced Clinical Education (BPACE)

In 2021, the Botswana team closed out the BPACE project, which had been supporting 52 high-volume facilities of the MOHW in 12 districts. During its five years, BPACE helped the government of Botswana implement key strategies to attain the UNAIDS 95-95-95 targets. Overall, BPACE supported more than 120,000 clients on HIV treatment with more than 30,000 HIV positive clients being newly enrolled on ART since the beginning of the program; overall, 98% were virally suppressed. Throughout BPACE's implementation, the indicators for retention, viral load coverage, and viral suppression remained above 97%.

BPACE helped strengthen health facilities' personnel with delivering client-centered services, including facility case tracking officers and expert clients, the latter of which are HIV-positive persons who have openly declared their status. Expert clients have provided peer navigation, health talks, and psychosocial support to newly diagnosed HIV-positive individuals to support linkage to treatment. Additionally, BPACE supported the national efforts to eliminate mother-to-child transmission (MTCT) of HIV through high testing and treatment coverage for over 99% of clients, with MTCT holding at 0.6% throughout the year.

COVID-19 Response

In 2021, the team also closed out the initial COVID-19 response grant. The first case of COVID-19 was detected in Botswana in March 2020, and the Botswana government imposed a strict country-wide lockdown and social distancing on April 2. Bummhi focused on implementing two immediate measures at the clinics it supports to ensure continued treatment of HIV patients: 1) decongesting waiting areas and 2) expediting clinic visits so that patient exposure would be limited. Bummhi also deployed mobile testing clinics, assisted with contact tracing, and supported the development of COVID-19 surveillance measures.

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

The Botswana team began implementing year-one 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 prioritizes index testing; prevention through tuberculosis preventive treatment (TPT) and PrEP; case-based surveillance with recency testing; full transition to 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 MOHW 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 delivered 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 began 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 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 to cultivate 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 MOHW to strengthen monitoring and evaluation activities at the national, district, site, program, and laboratory levels; 2) Strengthen data warehouse data management and analytics to support tracking of outcomes for HIV-positive individuals; 3) Strengthen HIV case-based surveillance for tracking of outcomes for HIV-positive individuals — including recency and drug resistance; 4) Support the Health Statistics Unit on quality improvement and quality assurance for international classification of diseases coding and capturing of morbidity and mortality data to improve tracking of patient outcomes; and 5) Strengthen lab surveillance and monitoring and evaluation systems, including support for capturing of viral load results and other HIV lab-related data at all viral load laboratories.

Fifth Botswana AIDS Impact Survey (BAIS V)

A member of Botswana's BAIS V team

Members of Botswana's BAIS V team

This CDC survey is among the population-based HIV impact assessments (PHIAs) being conducted in select nations. BAIS V is a cross-sectional, household-based, nationally representative survey that is assessing the prevalence of HIV as well as key HIV-related health indicators, such as incidence, viral load suppression, and risk behaviors, and will describe uptake of key HIV prevention, care, and treatment services.

The preparation for BAIS V survey implementation began in 2019 prior to the onset of the COVID-19 pandemic. In early 2021, with the development and implementation of guidelines for safe working and return-to-work policies by the Botswana Presidential COVID-19 Task Force, the survey and field work officially launched. In August 2021, the field work ended, and the two-stage cluster survey reached nearly 20,000 participants, more than 13,500 households, and completed more than 10,000 household interviews. The BAIS V survey is in the post-household survey data collection phase, and datasets are being analyzed to provide valuable information for HIV and global health policymakers and program planners. The BAIS summary sheet and final reports are slated to be released by August 2022.

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

Kenya

Under the leadership of Country Director **Caroline Ng'eno, MD,** and supported by a senior management team that includes Finance and Administration Director **Mr. Mathew Kimani** and grant program managers, Ciheb continues to make progress in Kenya in building health systems capacity and in expanding prevention efforts for HIV and TB.

Projects

Partnership for Advanced Care and Treatment (PACT) Endeleza and Timiza PACT Endeleza, under the leadership of Project Director **Rebecca Wangusi, MBBS**, collaborates with Nairobi City County health management teams to provide comprehensive quality HIV services that are integrated with existing county structures and systems with a focus

PACT Endeleza staff celebrate one of the Health Service Delivery awards

on government ownership for sustainability of supported services. PACT Timiza has been implemented in partnership with Kisii and Migori County Health Departments to support 248 healthcare facilities. PACT Timiza, led by Country Director **Caroline Ng'eno, MD**, aims 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 have been able to provide HIV testing services to hundreds of thousands of

Members of Ciheb Kenya's TRACK team

individuals, nearly 16,000 of whom were identified as HIV-positive and linked to treatment services this year. In FY21, PACT Endeleza supported nearly 31,000 people living with HIV (PLHIV) on ART in Nairobi County, and PACT Timiza supported 92,501 PLHIV on ART in Kisii and Migori Counties.

Technical Assistance for Public Health Impact in Kenya (TAPHIK)

The University of Maryland, Baltimore (UMB), in partnership with the Kenya Medical Research Institute (KEMRI), is supporting HIV and TB program implementation, laboratory testing, and surveillance systems in Western Kenya. This includes 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, 1,307 PLHIV case reports were captured, of which 490 (37%) were newly diagnosed from October 2020 to present day. The project continues to help develop standard operating procedures, instruction manuals, job aids, routine data quality assessment plans, and data dictionaries.

Technical Assistance to Ready and Accelerate Capacities of Public Health Programs in Kenya (TRACK)

Ciheb Kenya, the local indigenous organization, has been working with the CDC, the Kenya Ministry of Health, and the National Vaccines and Immunization Programme (NVIP) to support COVID-19 vaccine preparedness through the ongoing TRACK project. Kenya received its first shipment of vaccines in the spring of 2021, and more than 1 million Kenyans have since been vaccinated against COVID-19.

TRACK provided technical assistance in eight priority counties, including Nairobi, Kisumu, Siaya, Migori, Homa Bay, Busia, Nyeri, and Mombasa Counties. The assistance included facility assessments and renovations in readiness for the vaccine rollout, community messaging, and healthcare provider trainings to ensure quality service delivery.

Exactly 1,075,808 first doses have been administered, and 674,452 second doses have been administered as of September 2021. Of those in priority groups who received the second dose of the vaccination, 207,768 were aged 58 years and above, 117 were healthcare workers, 98,019 were teachers, and 53,969 were security officers. The proportion of adults fully vaccinated was 2.5%. The TRACK program continues to work with the Ministry of Health, NVIP, and county leadership to support the COVID-19 vaccination rollout, specifically with policy development, trainings, and technical assistance on data use for improved services.

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 is led by **Emily Koech, MPH, MMed**, CEO of Ciheb Kenya. Smoking significantly impacts the progression and outcome of HIV disease and has been identified as the leading contributor to premature mortality among people with HIV. The study hypothesizes that the combined use of pharmacological and behavioral interventions may improve the chances of maintaining long-term abstinence and will provide needed efficacy data regarding best treatment approaches for sustained tobacco abstinence for PLHIV in Nairobi, Kenya. To date, the trial has enrolled 104 of the 300 targeted participants and is pending IRB approval for a sub-study on including alcohol cessation use messaging in PSF materials.

Key Population Investment Fund (KPIF)

Impact Research and Development Organization (IRDO), a Kenyan NGO, selected UMB to receive funding through a memorandum of understanding to implement the KPIF

program, which aims to provide innovative and effective HIV prevention, care, and treatment services to key populations (KPs) in Kenya. UMB, through Ciheb, was identified as a sub-grantee to take the lead in implementing KPIF in Kisii County because of its experience in providing HIV prevention, treatment, and care among KPs, and it is currently serving 1,645 KPs across the three sites. The funds are intended to help identify previously undiagnosed HIV infections among KPs, link them to care, retain them in care, and ensure they adhere to medication until they are (and remain) virally suppressed to not contribute towards HIV transmission to their partners.

Reaching, Engaging Adolescents and Young Adults for Care Continuum in Health (REACH)-Mental Health

A collaboration between UMB, LVCT Health, and Kenya Ministry of Health aims to identify mental health protective and risk factors among adolescents and young people using an established mobile app called REACH. The project is led by **Peter Memiah, DrPH, MSc**, Associate Professor of Medicine and Ciheb's Director of Continuous Quality Improvement, and Fernando Wagner, DSc, Professor of Social Work at UMB. The project will adapt innovative multimodal adolescent-led strategies to engage adolescents and young adults into mental healthcare. This project will be conducted in three counties in Kenya: Kisumu, Nairobi, and Mombasa, which were selected to ensure geographic, cultural, and environmental variation in the project sample.

Malawi

Under the leadership of Principal Investigator **Alash'le Abimiku, PhD**, Professor of Medicine, Division of Epidemiology and Prevention, Executive Director of the International Research Centre of Excellence at the Institute of Human Virology Nigeria, which she co-founded; and a Principal Investigator and Director for Laboratory Services at Ciheb, and Deputy Country Director **Visopo Harawa, PhD, MSc**, Ciheb's work in Malawi is registering significant impact in building health systems capacity and in expanding prevention efforts for HIV, TB, and COVID-19.

Accelerating Malawi's PEPFAR Laboratory Logistics and InFrastructure for QualitY (AMPLIFY)

This laboratory strengthening grant aims to strengthen laboratory efficiency, capacity, and quality through improving laboratory infrastructure, laboratory data use for decision making, training human resources, and adhering to quality management systems. AMPLIFY has been providing technical assistance at the national and county level to strengthen the capacity of molecular laboratories in Malawi and increase access to quality laboratory services. Dr. Harawa directs AMPLIFY, and the program is supported by a senior management team that includes the Finance and Administration Director Mr. Tokha Manyungwa and technical leads.

Dr. Abimiku attends a ceremony celebrating four Ciheb-supported Malawian laboratories receiving international accreditation

In 2021, four Malawi laboratories supported by Ciheb through AMPLIFY received accreditation from the Southern African Development Community Accreditation Service (SADCAS), becoming the first laboratories in the country to attain this status. These four laboratories are primarily providing molecular diagnostic services for the PEPFAR-supported HIV program (viral load and early infant diagnosis testing), and more recently diagnosing SARS-CoV-2. AMPLIFY is currently supporting seven other HIV molecular laboratories and one TB laboratory to get accredited.

SADCAS
SOUTHERN AFRICAN DEVELOPMENT COMMUNITY ACCREDITATION SERVICE

Mozambique

Mozambique, led by **Dr. Abimiku** and Country Director **Dinis Jaintilal, PG DPH**, is the newest addition to Ciheb's country portfolio. Ciheb primarily operates in Mozambique under the Laboratory Systems Enhancement for AIDS Pandemic Control (LAPSEC) project to support the Ministry of Health (MOH) in strengthening the laboratory systems for diagnosing HIV and TB and expanding COVID-19 testing to the sub-national level.

Projects

Laboratory Systems Enhancement for AIDS Pandemic Control (LAPSEC)

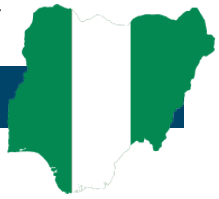
In FY21, Ciheb worked with MOH to improve TB detection, running workshops to train 75 clinicians and 80 lab technicians in five provinces in systematic TB screening and TB diagnostic algorithms, and visiting 82 health facilities in nine provinces for on-site TA. Ciheb strengthened the PEPFAR laboratory system by implementing quality management systems in seven labs. Thus far, one of the labs has received ISO 15189 accreditation.

While supporting rapid testing CQI implementation, Ciheb revised the national HIV rapid testing algorithms and conducted 11 trainings of 228 participants to establish district CQI committees in 45 districts across seven provinces. The district CQI committees conduct trainings and testers' certification, implement internal quality control for HIV testing, and ensure participation in external quality assurance (EQA). To keep track of testers' training and certification, Ciheb is finalizing a training database that will be deployed to MOH.

To support sustainable quality assurance program for HIV- and TB-related testing, Ciheb worked with the Mozambique National Institute of Health (INS) to implement an EQA program for early infant diagnosis (EID), viral load (VL), and Xpert Mycobacterium TB complex/rifampin testing based on proficiency testing panels prepared at INS ensuring all EID, VL, and TB testing sites participate in EQA and supported expansion of HIV rapid testing EQA to increase coverage. Ciheb supported proficiency testing prep trainings, provided technical assistance, and managed supplies procurements.

The CDC provided supplemental funding to support the government's efforts to increase COVID-19 testing availability in all provinces. Ciheb supported sample transportation to testing laboratories, procurement of swabs and other supplies for sample collection and testing, and training and site activation for COVID-19 testing using GeneXpert in seven sites.

Finally, as a sub-recipient to CDC on the Antenatal Care (ANC) COVID Serosurveillance project, Ciheb is supporting procurements, logistics, and data management related to measuring the seroprevalence of antibodies to COVID-19 in the population of pregnant women attending first ANC in three provinces in Mozambique.



Nigeria

In FY21, 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, Dr. Stafford) and Nigeria AIDS Indicator Impact Survey (NAIIS—Principal Investigator, **Dr. Charurat**) grants, as well as Project ECHO.

Projects

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

In its fifth and final year, the SHIELD grant has continued to support the government of Nigeria and implementing partners in providing quality HIV services using real-time data through developing and using interoperable health information systems. The SHIELD project continued to manage and enhance the National Data Repository (NDR), including the creation of an analytical database of de-identified, patient-level data that can be requested for analysis. The database currently contains longitudinal de-identified data for approximately 2.1 million patients who have received HIV care and treatment services. In addition, Ciheb finalized a data quality review dashboard to display scores and trends in completeness, consistency, and validity of partner facility data, which is used for data quality improvement. Surveillance is another major component of

A member of Nigeria's SHIELD team looking at a data dashboard

the SHIELD grant, with 186 facilities actively participating in the first phase of case-based surveillance (CBS) roll out across 18 states. A total of 788 healthcare workers have been trained in CBS since August 2020. There are also 217 facilities trained and engaged in recency surveillance, and training for the mortality surveillance pilot across eight states has started.

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 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)

During its fourth year, following the formal handover of the NAIIS 2018 National Technical Report to the government of Nigeria at the end of September 2020, Ciheb finalized the NAIIS public use data set and made it available on the National Bureau of Statistics data portal and continued to support the use of NAIIS samples stored in the National Reference Laboratory biorepository for other disease burden estimation.

Rwanda

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.

Projects

IMAKAZA

Under IMAKAZA (i'makaza in the local language of Kinyarwanda means "to sustain"), Ciheb has been providing technical expertise in information technology to the National Reference Lab (NRL) to enhance HIV eLab system technology to support laboratory technicians and clinicians to improve quality management and lab clinical interface. Ciheb provided a stepwise process for improving the quality of HIV rapid testing and an electronic proficiency testing training of trainers to four provinces and Kigali City. Ciheb also supported Abbott interfacing in six facilities. Supporting 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 (RBC) HIV Division to plan, coordinate, and implement patient-centered services for PLHIV through capacity building in CQI. Ciheb has integrated CQI into HIV clinical mentorship guidelines and standard operating procedures by integrating CQI HIV quality indicators to be reported by all district health facilities. In collaboration with CDC, the Rwanda Ministry of Health, and RBC, the team has showcased their efforts to establish CQI teams to drive improvement in Rwanda, specifically for PEPFAR priorities such as increasing index HIV testing, viral load suppression, and retention.

The CQI digital platform developed in Tanzania has now been adapted to Rwanda, and Ciheb is now strengthening CQI in 111 health facilities. More than 170 ongoing CQI initiatives are from health facilities. The methodology implemented for CQI in Rwanda includes initial site visits, mentorship and support, follow-up visits, and peer learning and experiential learning sessions. Finally, Ciheb has been providing ongoing program management support through program administration and closeout.

Addressing HIV in Young Women and Children

In Kigali, under funding from UNICEF, Ciheb works with RBC in supporting 18 facilities on CQI 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 non-HIV clinic spaces. More than 24 quality improvement projects are in implementation. Interventions have resulted in improvements in the proportion of women receiving antenatal 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.

Tanzania

Ciheb's team in Tanzania is comprised of more than 50 clinical and supporting 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.

Selian Arusha Town Clinic

Projects

Reaching, Engaging, and Acting for Health (REACH) In 2021, the Tanzania team completed the fifth year of the PEPFAR-funded REACH project, which worked in 11 regions of Tanzania. REACH was a national-level technical assistance program focused on improving uptake of data and evidence for faster HIV epidemic control achievement. REACH supports the government of Tanzania and CDC-funded local clinical implementing partners in minimizing systemic and structural barriers that impede the development of quality HIV/AIDS services. The program supported more than 250 health facilities and mentored more than 400 healthcare providers on CQI methodologies to improve PEPFAR clinical cascade indicators.

The Ciheb team developed a digital CQI platform that supports real-time data quality checks, SMS weekly report, CQI reporting, and in-depth patient level data analytics (through the Data Analytics Companion). This platform was scaled up to other PEPFAR implementing partners and the government of Tanzania through the National AIDS Control Program. It is being used in 273 facilities and has more than 650 quality improvement projects targeting different areas of HIV/AIDS service delivery. Under REACH, the Tanzania team has developed other technology, including an Android application (IQSMS), DHIS-2 Realtime data quality assurance tools, an index contacts tracking tool, and the Monthly Portal reporting tool.

Afya Kamilifu

Afya Kamilifu (which means "complete health" in Swahili) is a comprehensive HIV care and treatment program being 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 CQI, cutting across all departments and thematic areas in the project.

Through district-based mentorships, data-driven site visits by project staff, and by building the technical capacity of facility healthcare workers, Ciheb has improved performance across numerous key indicators. For example, isoniazid preventative therapy completion rates improved from 32% to above 90%, viral load suppression in children and adolescents improved from 54% to 91%, and the proportion of children in an optimized antiretroviral regimen has remarkably improved (98% of all children and adolescents are in optimized regimens). Also, Ciheb has initiated CQI projects across all key indicators across CDC tier I to III facilities.

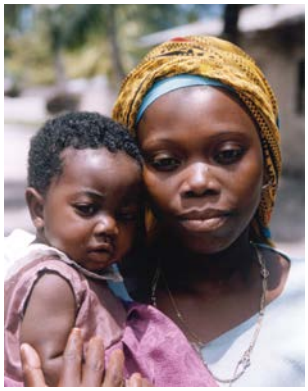
Zambia

Ciheb's team in Zambia is led by Country Director and Assistant Professor of Family 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 95-95-95 goals. Dr. Sheneberger was a significant contributor to the Zambian National ART Guidelines. These guidelines were the first in Africa to adopt tenofovir-based first-line antiretroviral therapy and the first to incorporate discordant couples into antiretroviral eligibility. Dr. Sheneberger has continued to provide guidance to Zambia as the

Nurse weighing a child at a Zambian clinic

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 diseases through spearheading the Master of Medicine & Infection Diseases at the University of Zambia School of Medicine. **Cassidy Claassen, MD, MPH**, Assistant Professor of Medicine, has been a major 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 (MOH) response to COVID-19.

Projects



Stop Mother and Child HIV Transmission (SMACHT)
In FY21, the team submitted final close out reports for the SMACHT project. SMACHT began as a prevention of MTCT grant and expanded to a comprehensive HIV care and treatment grant. It peaked in its fourth year with support to over 300 facilities in the Southern Province. The community approach to improving outcomes for patients with HIV that is used in Ciheb's other two community grants was designed and first implemented through SMACHT. The project also provided technical assistance to the Southern Provincial Health Office in four districts.

Zambia Community HIV Epidemic Control for Key Populations (Z-CHECK)

In 2021, the team finished the fifth year of the Z-CHECK project and began the close out process. Z-CHECK focused on providing community interventions to interrupt HIV transmission by identifying and linking each HIV-positive individual along a supported pathway to achieve viral suppression. Using effective interventions, Z-CHECK aimed to improve the targets for UNAIDS 95-95-95 goals in the Southern and Lusaka Provinces. Z-CHECK focused primarily on target populations, including adolescents, pregnant women and their children, young men, men who have sex with men (MSM), female sex workers, transgender people, injection drug users, and prisoners. Z-CHECK has also been the leader in PrEP in Zambia.

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 UNAIDS 95-95-95 epidemic control. It focuses on adolescents; key populations, including MSM, female sex workers, and prison populations; men under 30 and transient populations; pregnant and breastfeeding women and their families; as well as the general population. Based on significant success, the CIRKUITS project continued into its third year in 2021 and expanded to include new implementation of DREAMS centers. In year-four, CIRKUITS will continue its ongoing work in Eastern and Western Provinces as well as the Z-CHECK 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 with respect to COVID-19 and HIV via tele-mentoring 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 been supporting the Ministry of Health's (MOH) Expanded Program on Immunization in the COVID-19 vaccine rollout. Ciheb Zambia also worked with the World Health Organization and CDC to support MOH in carrying out an intra-action review for the Vaccine Pillar.

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

IPADZ aims to better understand and pilot an intervention to alter system-based factors that impact the inpatient HIV care received by patients, including provisioning ART, monitoring CD4 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 a hospitalization; the long-term goal is to develop and evaluate effective interventions to lower HIV-related mortality in the post-discharge period.

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

Treatment-experienced HIV patients in Zambia suffer high rates of mortality 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 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 to follow-up.

Second Zambia Population-based HIV Impact Assessment (ZAMPHIA)

This survey, funded by PEPFAR through the CDC, is one of the ongoing PHIAs being conducted in select countries. ZAMPHIA's goal is to estimate the prevalence and incidence of HIV in the Zambian population, to assess the coverage and impact of HIV services at the population level, and to characterize HIV-related risk behaviors using a nationally representative sample of adults aged 15 years and older. The data will be used to focus HIV services and resources to the areas of greatest need and help move Zambia closer to HIV epidemic control. The preparation for the ZAMPHIA survey began in 2019, prior to the onset of the COVID-19 pandemic, and was launched in February 2020. The survey was paused shortly after due to COVID-19. The national survey and field work officially relaunched in May 2021 and phase 1 of data collection ended July 2021 to allow for a pause for elections in Zambia. The survey reached 50% completion in phase 1 of data collection, and ZAMPHIA has so far enrolled 10,775 participants from 6,040 households. Currently, mapping and listing and community mobilization for the next waves of the survey has started and teams will return to the field for data collection in late September. Phase 2 of data collection is targeted for completion by December 2021 and final reports and data sets are expected to be released by December 2022.

Community mobilizers put up survey posters across Zambia in key locations to generate awareness and support participation in ZAMPHIA.

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Scientific Core Facilities

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

Scientific Core Facilities

Animal Core Facility

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

Harry Davis, BS, 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, Cynomologus, and Papio species) pigs, goats, sheep, rabbits, and, of course, mice, and rats. The Core for the past few years has shifted to primarily a mouse facility. This was due to the shift from a conventional mouse facility 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) and (nude mice) and specialize 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 into the second-generation humanized mouse models. The development of these new models has required a stricter barrier-type housing to prevent any pathogens that will interfere in studies. With this shift from a conventional and partial barrier type facility to a barrier type facility, I have had to redesign the housing and provide a more technically trained staff to meet the needs of the care of these special mice, and I have had to develop standard operating procedures (SOP) to ensure no contamination or loss of any research data. I have perceived that the observation of the NSG mice and the transgenic and knockout mice requires a trained staff to look for specific phenotypes that in many cases are an important component of the research. I have continued to maintain an up-to-date knowledge of these observations and to train my staff.

I have included a listing below of the investigators at IHV using animals and the titles of their approved IACUC approved protocols. I have also listed the specific type of models used. As I have in the past in keeping with the history of our relationship with the Divisions, the following are the list of collaborative and assistance with specific protocols.

In addition to the above, the Core continues to maintain animal models developed at IHV that are being used as models for HIV studies (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 over 50 funded investigators are using this model for studying chronic HIV/AIDS, and comorbidities such as HIV heart disease, HIV kidney disease, and HIV-associated neurocognitive disease.

Joseph Bryant, MS, DVM, the retired Director of the Animal Model Division and the IHV Animal Core facility since 2017, remains as a consultant to me and the Animal Core facility. His historical knowledge of the animal models has been invaluable to the Core and the IHV investigators.

Facility and Caging Improvements and AAALAC Accreditation

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

We have also upgraded our rodent housing units. We have purchased new individual ventilated caging systems (IVCs). These new units provide biocontainment individuality to each cage and monitoring system that can be monitored 24 hours a day though an internet capable system.

We are scheduled to undergo an AAALAC accreditation inspection in November 2021. I have prepared the IHV Program Description that has been submitted in conjunction with the School of Medicine. We have developed a very good working relationship with the comparative medicine division and its veterinarian's that provide the IHV with an attending veterinarian. This accreditation will ensure 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. I have a staff of nine animal research care personnel and one Research Associate, who are responsible for the care of animals at IHV, as well as assisting investigators on various scientific endeavors by providing technical support and technical services.

Development of a Special Program in the Animal Core Facility

HIV-1 Transgenic Rat Distribution Program

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

Collaborative efforts between the Division of Virology, Pathogenesis, and Cancer and the Animal Core Facility include the development of Animal Models. Projects include:

HIV/AIDS Non-Hodgkin Lymphomas

a. Pathogenesis studies
b. Development of animal models for AIDS/NHL
c. HIV-1 matrix protein p17 implicated in virally-associated lymphomas
d. Mycoplasma and cancer

Collaborators in the Division of Virology, Pathogenesis, and Cancer include:

Robert Gallo, MD, The Homer & Martha Gudelsky Distinguished Professor in Medicine and Co-Founder and Director of the IHV

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

Francesca Benedetti, PhD, Research Associate of Medicine in the Division of Virology, Pathogenesis, and Cancer (VPC)

Chozha V. Rathinam MSc, PhD, Associate Professor of Medicine, Head of the Laboratory of Stem Cell & Cancer Biology

DnaK and Mycoplasma Project

Continuing the studies on the relationship between Mycoplasma and cancer, Dr. Zella and Dr. Gallo together with Dr. Bryant, Dr. Benedetti**, Giovannino Silvestri, PhD,** Research Associate in the Division of Virology, Pathogenesis, and Cancer (VPC), and **Saman Saadat, PhD,** Postdoctoral Fellow. Human *Mycoplasma fermenta* was isolated and characterized. This strain of *ns* is able to induce lymphoma in a severe combined immuno-deficient (SCID) mouse model, similar to a previously described lymphomagenesis, dependent upon reduced p53 activity. Mycoplasma was abundantly detected early in infected mice, but only low copy numbers of mycoplasma DnaK DNA sequences were found in primary and secondary tumors, suggesting a "hit and run/hide" mechanism of transformation, in which the critical events have occurred before cancer detection. We demonstrated that this mycoplasma's DnaK binds to human USP10 (ubiquitin carboxyl-terminal hydrolase 10, a regulator of p53 stability), reducing p53 stability and anti-cancer functions, potentially increasing the likelihood of

DNA mutations and consequent malignant transformation. We also showed that mycoplasma DnaK reduced PARylation activity of PARP1 following DNA damage. PARP 1 is one of the most studied members of the family of PARP proteins, involved in the recognition and subsequent repair of single and double-strand breaks in DNA. We are currently extending these results and validating the underlying mechanisms in an *in vivo* model of DnaK knockin mouse designed in our laboratory. DnaK was inserted at the locus of ROSA26 in C57BL/6 mice by CRISPR/Cas-mediated genome editing. The DnaK gene is under the control of the CMV promoter for constitutive expression and carries a V5 Tag for convenient detection. It is important to note that our previous results in vitro show that the V5 tag does not affect the ability of DnaK to reduce protein binding or p53-dependent anti-cancer activities. These animals are currently housed in our animal facility and are currently used to i) test for higher spontaneous tumor incidence in mice expressing DnaK; and ii) assess for increased susceptibility to non-hematopoietic cancers and development, function, and response to DNA-damaging agents of peripheral B- and T-cells *ex vivo*.

Stem Cell and Cancer Biology

Dr. Rathinam 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 are being performed in the Animal Core.

Collaborators in the Division of Clinical Care and Research include:

Alonso Heredia, PhD, Associate Professor of Medicine

Nicholas Stamatos, MD, PhD, Associate Professor of Medicine

Mohammad Sajadi, MD, Professor of Medicine

Evaluating Treatment with CCR5

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

Humanized Mice for HIV Studies

Since the **Division of Vaccine Research** developed the full-length single chain Fc protein (FLSC 1IgG1), 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

Dr. Stamatos is evaluating the function of polysialic cell activity through the development and characterization of transgenic mice.

Other Collaborative efforts with the Animal Core Facility include:

Henry Lowe, PhD, Adjunct Professor of Medicine

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

Tapas Makar, PhD, former Assistant Professor of Neurology

Development of Natural Plants as Anti-Cancer Drugs

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

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

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

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

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

PI/Project Title Imaging Facility

Joel Chua, MD, Assistant Professor of Medicine

- Development of a humanized mouse model for Dengue virus infection

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

- Increasing the durability of Anti-HIV-1 Gp120 antibody responses
- DNA vaccinations using a gene gun

Choza Rathinam, Dr. rer. nat., Associate Professor of Medicine

- 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

Lishan Su, PhD, The Charles Gordon Smith Professor for HIV Research, Professor of Pharmacology, Director of the Division of Virology, Pathogenesis, and Cancer, Interim Director of the Division of Immunotherapy

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

Core Facilities Publications

Worthington M, Denaro F, **Benedetti F**, Williams S, Bryant J, **Zella D, Davis H** (2020) "An Immunohistochemical Analysis of Free Radical Stress in the Heart of the HIV-1 Transgenic Rat." *Microscopy and Microanalysis*, 26(S2):1-3. DOI: 10.1017/S1431927620017778

Denaro F, **Benedetti F**, Worthington MD, Scapagnini G, Krauss CC, Williams S, Bryant J, **Davis H, Latinovic O, Zella D** (2020). "The HIV-1 Transgenic Rat: Relevance for HIV Noninfectious Comorbidity Research." *Microorganisms*, 8,1643,1-25. DOI: 10.3390/microorganisms8111643

IHV Flow Cytometry Core

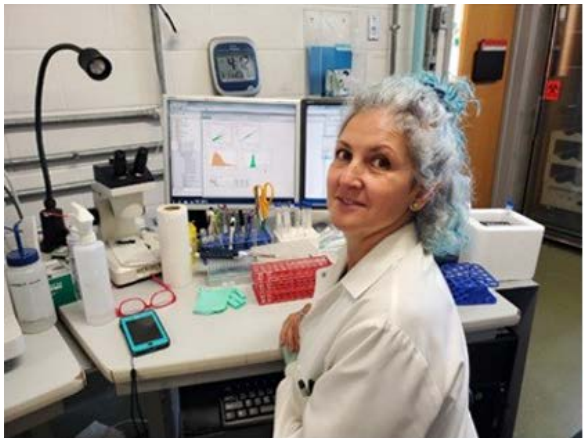
The IHV Flow/Sorting Core is located on the 6th floor of the IHV building. The purpose of the Core is to offer IHV users (and those from other organizations) with technical help for planning, implementing, conducting, and analyzing flow-cytometry experiments, including polychromatic flow analysis and fluorescence activated cell sorting (FACS). It has been operational under the leadership of **Yutaka Tagaya, BM, PhD**, Assistant Professor, Division of Virology, Pathogenesis, and Cancer since 2011. Currently it is mainly operated by **Felisa Diaz-Mendez, PhD**, (FDiazMendez@ihv.umaryland.edu, 410-706-1363) of the IHV.

1. Our main machine (Becton Dickinson FACSAria II) is located inside the BSL3 facility (Room N664).
2. It can be used in a pay-per-use fashion and open for users outside of the IHV (for the payment, we currently use the conventional invoice system, but we are joining the iLAB system of the University).
3. Scheduling can be done online (if you do not have access to the IHV Flow-CORE calendar, please send a request to the IHV Helpdesk @ www.ihv.org/helpdesk). For the first time use, please contact Dr. Diaz-Mendez by e-mail/phone.
4. The machine is only run by operators (Dr. Diaz-Mendez/ Dr. Tagaya) has three lasers (405nm, 488 nm, 635nm) with 12 fluorescence channels.
5. Our CORE is **the only infectious sorting facility in the entire University of Maryland Baltimore (UMB) Campus.** Because of this reason, we often receive referrals of users requesting infectious sorting from other flow cytometry facilities of the UMB. We have protocols approved for sorting cells with viruses such as HIV-1, HTLV-1, HCV, HBV, and influenza and a few parasitic organisms. **We also have a protocol to analyze/sort blood cells collected from SARS-CoV-2 positive patients.**
6. The core also has a 11-color GUAVA flow analyzer on the 5th floor (north common equipment corridor) that is accessible to all IHV users upon scheduling (using a calendar that is posted in front of the machine).

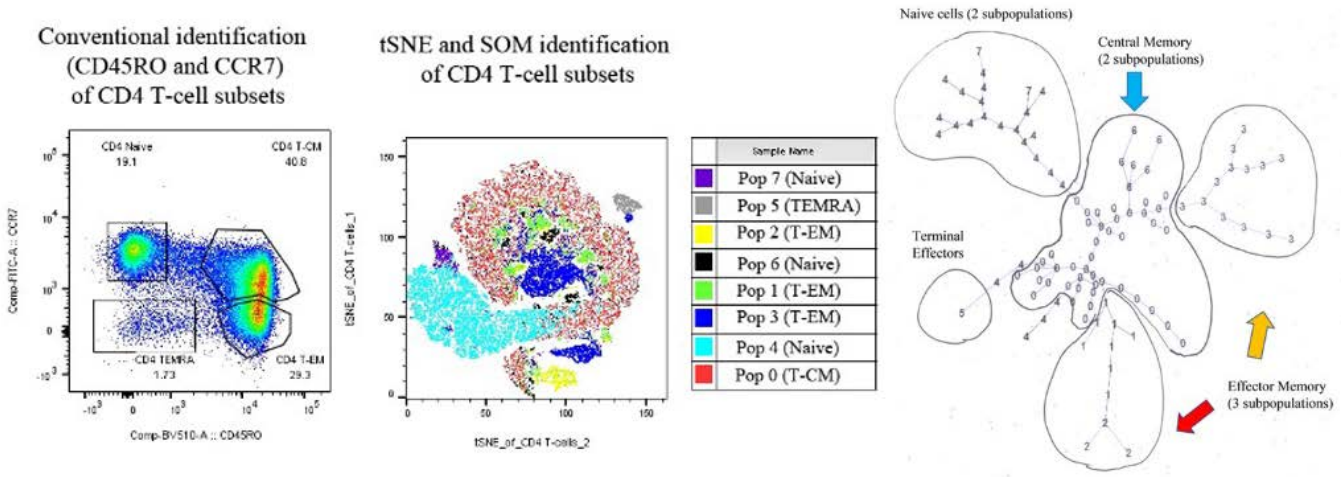
During the COVID pandemic, we have seen a severe decline of the activity (5-20% compared to normal years) of the Core's operation. However, the usage of the Core is coming back to previous levels in recent months. The Core has been working with mainly PIs from the Division of Virology, Pathogenesis, and Cancer (VPC) of the IHV, but also works with those from the Clinical and Epidemiology divisions (PIs: **Bhawna Poonia, PhD**, former Professor of Medicine, **Alonso Heredia, PhD**, Associate Professor of Medicine, **Shash Bagchi, MD**, Assistant Professor of Medicine, and **Cristiana Cairo, PhD**, Assistant Professor of Medicine).

Because the protocol requests that the Aria II in the BSL3 can only be operated by the Core's personnel, it enables the machine being to be used by consistent protocols and operational procedures. In addition, we perform weekly/bi-weekly beads calibration to ascertain that the machine is under optimal conditions. When signs of poor machine condition are observed (such as increased PMT values for scatter/ fluorescence, as well as increased CV values for each fluorescence channel), we will contact BD's engineer for unscheduled maintenance involving laser/flow-chamber alignment. We are thus confident that we maintain the machine in top condition most of the time. With our recent collaboration with the group of **Hongshuo Song, PhD**, Assistant Professor of Medicine, in the Division of VPC to sort-purify subsets of human CD4+ memory cells from HIV patients, we are constantly seeing greater than 97% purity of the sorted populations.

In cell sorting, we are helping users not only from IHV, but also from UMB and outside organizations because of the reasons mentioned above. We helped a New York-based company to



Dr. Diaz-Mendez (left) and Dr. Tagaya (right)—FlowCore personnel in action



Shown on the left is the conventional flow definition of CD4+ subsets (e.g., naive, central memory (T-CM), effector memory (T-EM), terminal effector (TEMRA)). On the right is the definition of eight distinct subsets of CD4+ T-cells using the self-organizing map (SOM) algorithm. It still retains the classical four subsets, but each subset contains subpopulations each of which is distinguishable from the other by one or two surface/intracellular markers. For example, naive cells can be further divided into two subpopulations based on the expression of CD38 and the ratio between these two subpopulations may change depending on the status of immune activation or disease conditions. Effector memory cells appear consisting of two rather distinctly related subpopulations (defined by the expression of CD28 and lytic enzymes). The t-SNE mapping allows the visualization of each subpopulation and links each group with expression levels of the markers used in the analysis.

sort their cells, and recently a company in Gaithersburg in sorting yeast cells expressing human genes. In the past, we helped IHV investigators engage in a yeast two-hybrid screening.

The needs for flow cytometry are constantly changing. With more publications coming out to demonstrate the heterogeneity of once-thought a 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 to analyze a complex mixture of cells, but our machines (11-12 channels) seem still satisfactory to many users studying hematopoietic cells. However, the expansion of available channels would be critical in the next several years to keep up with the technical progress and demands, including the replacement of current machines.

The ongoing changes in flow cytometry include the analysis methodology. In the past, the Flow-Core helped IHV users to install the site-license for the FlowJo software and provided basic training for users in the IHV and UMB. Unfortunately, we no longer offer this service. However, those within the IHV who wish to obtain a FlowJo license can still do so by contacting IHV-IT (with a cost). We have used newer analysis algorithms for multi-dimensional flow-data such as t-distributed stochastic neighbor embedding (tSNE) and self-organizing mapping (SOM). Shown in Figure 1 is a recent example of human CD4+ T-cells from a leukemia (large granular lymphocytic leukemia) patient representing the complexity of T-cell subsets, which is a part of an on-going clinical trial to test the therapeutic potential of a new multi-cytokine inhibitor (BNZ-1) that Dr. Tagaya's lab has developed. These experiments are designed to examine the drug effect of reducing the numbers of inflammatory T-cells that are causing disease-burden in the leukemia patients. Multiple markers (e.g., surface and intracellular) were used to characterize the inflammatory nature of each subset/subpopulation of non-leukemic T-cells from the patient. The t-SNE algorithm is already included in the recent version (Ver 10.5 and later) but the FlowSOM algorithm needs to be added-in together with the R-script. IHV-IT and FlowCORE can help IHV flow users to install and use these tools.

Imaging Facility

The Imaging Facility was established in 2012 as the first IHV Imaging Facility. **Olga S. Latinovic, PhD, MSc,** Assistant Professor of Microbiology and Immunology, Division of Virology, Pathogenesis, and Cancer, Head of the Lab for Pathogen-Cell Interactions and Head of the IHV Imaging Facility, established IHV's Imaging Facility. Dr. Latinovic led the facility since its conception. The laboratory was equipped with a newly launched Confocal LSM 800 Airyscan Microscope by Carl Zeiss AG in summer 2017, and recently, with Nikon's Fluorescence Microscope in summer 2020. Both systems have been utilized by various IHV and international investigators.

The facility is primarily focused on quantitative image analyses of pathogen and host cell interactions that contribute to various IHV projects. The demand for imaging studies significantly increased in the year of 2019 which resulted in numerous published works and projects. In late 2019, Nikon's team hosted a highly informative demo session showing the potential of the new generation of fluorescence microscopes, the Eclipse Ti2. This Eclipse Ti2 Inverted Research Scope system is perfect for the 3D imaging of precious tissue samples and it includes a motorized stage, options for live and fixed cell imaging, a detectable far-red 730 nm excitation wavelength (in addition to the existing four colors detectable on the confocal system), large diameter observation optics, a microarray imaging option, and additional cameras for large-volume data acquisition with a 4.5 times bigger imaging field than the one on the existing confocal system (needed for tissue imaging). This Nikon system is the most recent addition to IHV's Imaging Facility and was launched at full capacity during the national lockdown, in June 2020. The facility also operates with online scheduling as of June 2019 which provides efficient usage for numerous investigators. Some of the current projects of the facility are listed below:

Mycoplasma project

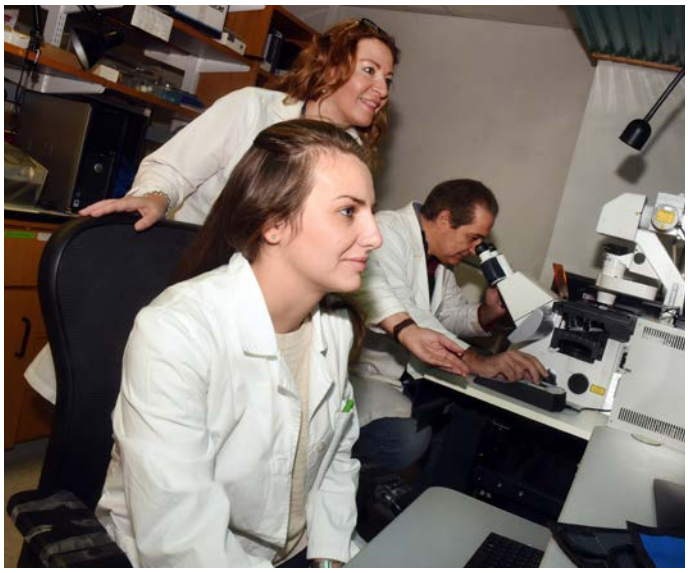
Dr. Latinovic was involved in the Mycoplasma project working originally with **Davide Zella, PhD,** Assistant Professor of Biochemistry and Molecular Biology and Co-Head of the Laboratory of Tumor Cell Biology in the Division of Virology, Pathogenesis, and Cancer, and the team in 2009. Their initial observations demonstrated the resetting patterns of mycoplasma interactions with human lymphocytes. The imaging part of the mycoplasma project is related to the direct visualization and quantitative studies of mycoplasma DnaK protein, focusing on its cytoplasmic and perinuclear intracellular location and its interactions with p53. The entire project is directed by Drs. Zella and Gallo, and the imaging parts of the project were included in:

1) *Proceedings of National Academy of Science* publication in 2019, "Mycoplasma promotes malignant transformation *in vivo* and its DnaK has broad oncogenic properties" (**Figure 1** *on the following page*).

2) *International Journal of Molecular Sciences,* in 2020, "Role of Mycoplasma Chaperone DnaK in Cellular Transformation."

CCR5 determinants for the HIV transmitted founder phenotype project

The goal of Dr. Latinovic's current research line is to investigate if transmitted founder (T/F) viruses enter primary cells via distinct CCR5 subpopulations, and how these quantified subpopulations might differ from those bound by (chronic infection) CI viruses. Dr. Latinovic's lab successfully developed a methodology for the detection and quantitative analysis of overlapping events between intracellular (CCR5 C-terminus-GFP fusion protein, a collaboration with **Yutaka Tagaya, BM, PhD,** Assistant Professor of Medicine), and extracellular (panel of various mAbs against N-terminus, ECL2, and multidomain) CCR5 epitopes (**Figure 2** *on the following page*).This methodology has allowed the group to characterize and quantify which CCR5 subpopulations



Olga Latinovic, PhD, MSC, and Davide Zella, PhD, and fellow working in the lab (Photo taken before the SARS-CoV-2/COVID-19 pandemic)

are permissive for HIV-1 infection (including both, T/F and CI viruses) *in vitro*. The main part of the project includes collaborative efforts with **Anthony DeVico, PhD,** Professor of Medicine in the Division of Vaccine Research, and his lab. The project's concept will allow measuring of the frequency, internalization dynamics, and trafficking/recycling rates of the CCR5 coreceptor. This project's outcomes will provide identification of the total CCR5 (internalized plus surface events) in donor cells upon productive infection to obtain a complete picture of all conformational subpopulations of selected CCR5 events involved in HIV entry and infection. The manuscript on this CCR5 conformational change study addressing selective populations in HIV+ PBMCs is in preparation and to be submitted for publishing.

International collaboration—Cauliflower Mosaic Virus TAV

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

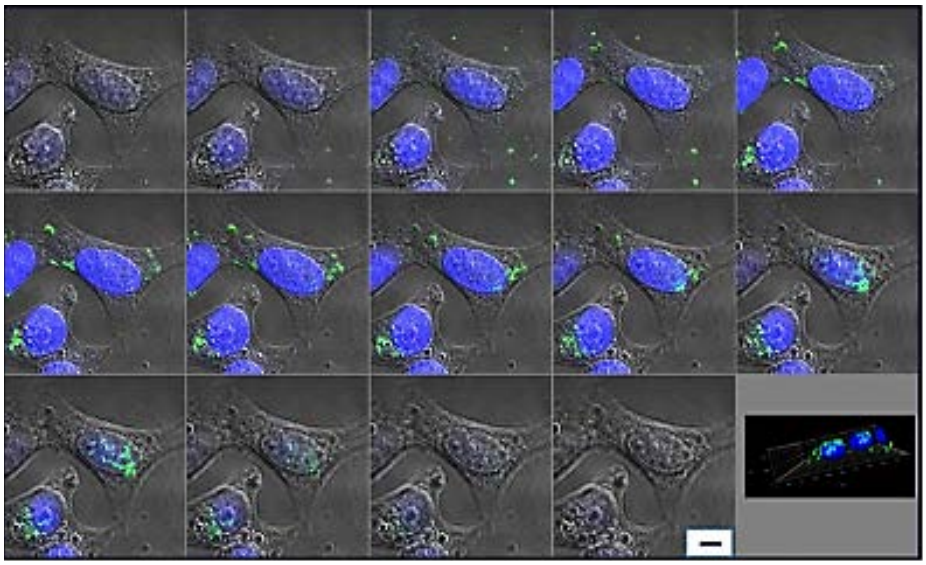


Figure 1. *Intracellular uptake of exogenous DnaK-V5 by mycoplasma-free HCT116 cells. Confocal images of exogenous DnaK-V5 protein of M. fermentans in HCT116 cells treated with DnaK-V5 protein (nuclear localization). The figures show the collected Z-stacks of the corresponding gallery of images, each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

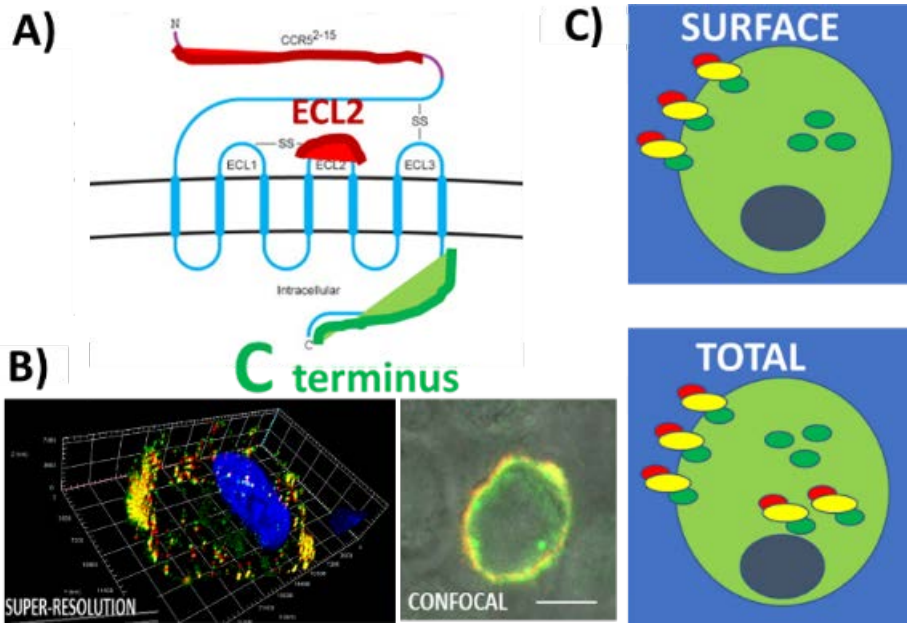


Figure 2. *A) A cartoon showing our dual staining model for labeling CCR5 C-terminal (GFP) and extracellular epitopes (the red color). B) A confocal microscopy image (right) and 3D super-resolution microscopy image (left) of a U87.CD4.CCR5-GFP cell expressing CCR5 C-terminus-fused GFP and a far-red Alexa 647 nm dye conjugated to the primary CCR5 mAbs against ECL2. C) A cartoon showing an example comparison of CCR5 labeled using mAbs at the cell surface only or in total, throughout the target cell.*

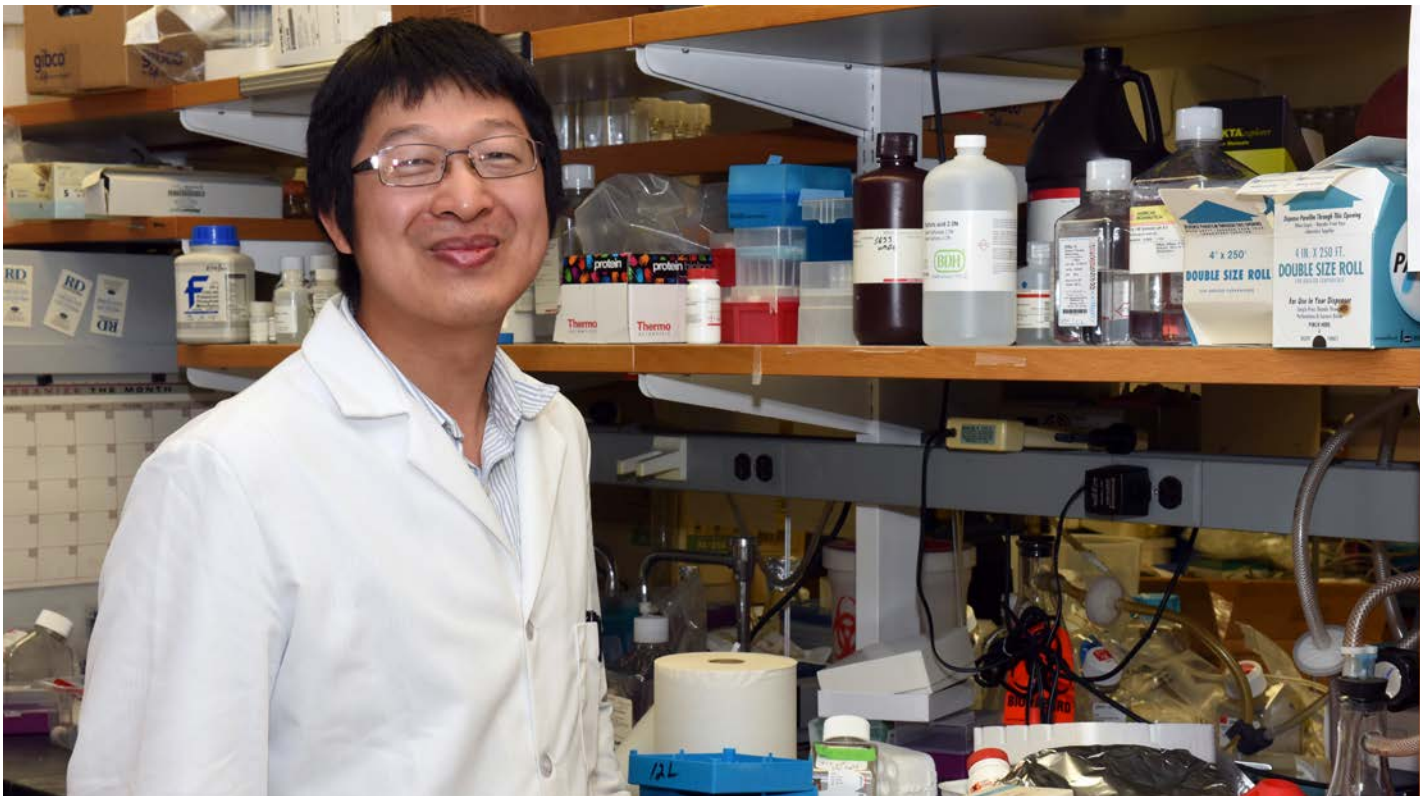
µQUANT Core Facility

The µQUANT Core Facility began with the co-founding of the Institute of Human Virology (IHV) in 1996. The Core provides quality immunological and biological services to researchers at IHV, the University of Maryland Baltimore (UMB), and to other collaborators locally and nationally. **Ping-Hsin "Rex" Lin, MS**, runs the daily operations of the core with academic oversight from **Anthony DeVico, PhD**, Professor of Medicine in the Division of Vaccine Research. IHV founded the µQUANT Core Facility to include a variety of centralized cores to provide both cost savings and standardized methods. The Core has devoted significant time to trouble-shooting all protocols utilized and has developed laboratory standard operating procedures. Its aim is to provide consistent, cost effective services that allow researchers to compare results generated within a week. The Core has been very successful in meeting these goals, and as such, its existence has optimized the pace and scope of research at IHV.

Core services include:

- Routine immunoassays (e.g. ELISA); endotoxin testing; monoclonal antibody and recombinant protein screening, production, purification, and labeling
- Production and maintenance of virus and cell stocks
- 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 at ihv.org/Research/Core-Facilities/Quant-Core/. The µQUANT Core Facility is heavily involved in supporting many IHV programs and projects. This past year, the Core supported scientific projects by providing routine testing and customized experiments to 14 research groups at IHV, and three UMB groups outside of IHV.



Ping-Hsin Lin, MS, working in the lab

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 with a major role in its formation and the subsequent continued success it experiences today. Since the HIV/AIDS outbreak of the early 1980's, it has been the goal of IHV Co-Founder and Director **Robert Gallo, MD**, also The Homer & Martha Gudelsky Distinguished Professor in Medicine, to promote a global collaborative network to overcome gaps in research during the earliest phases of viral epidemics and to ensure that sufficient numbers of medical virologists are trained to meet these challenges.

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 GVN's International Scientific Advisor, and his colleagues William Hall, MD, PhD, and the late Reinhard Kurth, MD. Dr. Hall is Professor of Microbiology at the University College Dublin (UCD) in Dublin, Ireland. Dr. Kurth was the former Director of the Paul Ehrlich Institute and the Robert Koch Institute and Chairman of the Foundation Council at Ernst Schering Foundation in Berlin, Germany in addition to serving as a member of the IHV Board of Advisors. At the inaugural meeting in 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.

COVID-19 Vaccine Development

In the fall of 2020, the world received the results of the Pfizer and BioNTech data and thereafter the Moderna data, of the development of effective vaccines against COVID-19. The GVN supported continuing studies of the duration of protection, safety, and protective efficacy of vaccines in preventing viral transmission. The GVN emphasized the need to provide vaccine availability to all countries. While news of the vaccine rollout has been an uplifting one, the scientists and virologists of the GVN remain concerned about anti-vaccination sentiments in the global population.

Institute of Human Virology Leadership Contributes to Global Virus Network Analysis Suggesting Measles, Polio, and Tuberculosis Vaccines May Boost Immunity to Coronavirus

This past year, IHV scientists co-published a perspective with GVN colleagues proposing that live attenuated vaccines (LAVs), such as those for tuberculosis, measles, and polio, may induce protective innate immunity that mitigate other infectious diseases, triggering the human body's natural emergency response to infections including COVID-19, as well as future pandemic threats. The scientists suggested that LAVs prospectively might offer a vital tool to bend the pandemic curve, averting the exhaustion of public health resources and preventing needless deaths, and merit being studied. The perspective was published in the *Proceedings of the National Academy of Sciences (PNAS)* of the United States of America in May 2021. The authors said that because of the huge toll that the current pandemic has taken on a global basis, looking into all possible options is essential. Despite the unprecedented brief time that it took to develop, test, and deliver the current vaccines, it still took a year and a half and if LAVs could help stimulate innate immunity, they could help delay the global impact of a new pandemic while a new vaccine is being developed.

GVN and USF Launch Joint

Dr. Gallo on Bloomberg Asia discusses the timeline and safety of COVID-19 vaccine trials

Online Course

Also, in the fall of 2020, the GVN and the University of South Florida launched the self-paced online course "Microbiomes and Their Impact on Viral Infections." Taught by world-renowned instructors, this course provides students, academics, and health professionals with the latest knowledge of the importance and role of microbiomes in preventing, mitigating, and treating diseases. The initiative also supports GVN's mission to train the next generation of virologists and better prepare mankind for future viral threats. Microbiomes and Their Impact on Viral Infections is a non-credit course comprised of two sessions. The first, "Introduction to Microbiomes," consists of 11 modules while the second, "Symbiotic Evolutions in the Microbiome World," comprises nine modules and is available to students for up to eight weeks after the start date. With a transdisciplinary approach, students will have access to lectures and complementary material, and will receive a certificate and a digital badge upon course completion.

GVN awarded four course scholarships to investigators working in various stages of viral infection prevention, including, Joseph Osega, a Kenya-based technical advisor and national HIV recency coordinator, who has extensive knowledge of HIV, malaria, and TB diagnostics to build capacity and develop public health infrastructure in Kenya; Nanma Cosmas, a lecturer and a doctoral candidate at the University of Jos, Nigeria, who focuses on prevention of HPV and other sexually transmitted infectious diseases among adolescent and young adults through studies of the microbiome in various parts of the body; Onyekachukwu Okeke, a doctoral candidate at the University of Jos, Nigeria, who works at a medical laboratory and has been on the front line during the COVID-19 crisis; and, Sophia Osawe, a doctoral candidate at the University of Jos, who researches the effects of maternal HIV infection and prenatal immunization on the immune responses and growth of infants.

GVN and IHV Co-Founder Dr. Robert Gallo Honored by China and Italy

In December 2020, Dr. Gallo was awarded the "VCANBIO Award for Biosciences and Medicine," a significant and authoritative award in the life sciences and medicine field of China. The elite Prize is jointly presented by the University of Chinese Academy of Sciences and the VCANBIO CELL & GENE ENGINEERING CORP, LTD to push forward scientific research, technological innovation, and continuous development in the life sciences and medicine field of China. "The Prize also serves to facilitate the industrial development and application of innovative life science achievements," said George F. Gao, DVM, DPHIL (OXON), Director General of the Chinese Center for Disease Control and Prevention (China CDC), Director, CAS Key Laboratory of Pathogenic Microbiology and Immunology, Professor, Institute of Microbiology, Dean of the Medical School of the Chinese Academy of Sciences and Director of China's Global Virus Network Center of Excellence. "Dr. Gallo is a pioneer in virus research and most worthy of this Prize. We are pleased to see him recognized by many members of the Chinese Academy of Sciences."

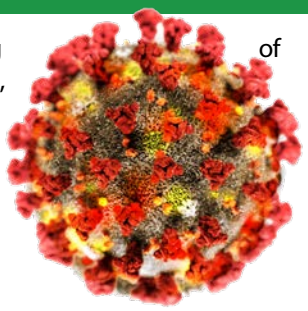
George F. Gao, DVM, DPHIL (OXON), courtesy of 中国新闻网, CC BY 3.0, Link

"Hosted by the Medical School of the University of Chinese Academy of Sciences, this award commends outstanding and innovative Chinese and foreign scientists, who have accomplished innovation achievements and breakthroughs in the life sciences and medicine field," said Yiming Shao, MD, the Chief Expert on AIDS, China CDC, Director of the Division of Research on Virology and Immunology, National Center for AIDS/STD Control and Prevention, China and Member of the GVN SARS-CoV-2 Task Force and China GVN. "I have worked with Dr. Gallo through the decades and admire his intellect and leadership, which have led to discoveries that have broad implications in protecting mankind from viral threats. I am delighted that my Chinese colleagues are recognizing him with this significant honor."

"Prof. Gallo has made a great deal of contribution to promote the Sino-American friendship and collaboration, especially for medical talent training and public health in China," said Prof. Guanhua Xu, Chairman of the selection committee of the VCANBIO Award for Biosciences and Medicine.

In December, Dr. Gallo was awarded Italy's "Magna Graecia International Prize," an award created in 1997 by the Magna Graecia Foundation that is bestowed to the most influential Italians and Italians of origin who have embodied and symbolized, in the most diverse sectors, the best qualities of Italy by extending Italian culture beyond national borders. "Dr. Robert Gallo's contribution to the whole of humanity derives precisely from his roots in Magna Graecia, the ancient incubator of Western civilization and medical science were figures of gigantic proportion such as Alcmeone and Pythagoras laid the foundations of the Krotonian school of medicine and the Italic Pythagorean School, respectively. It was these two geniuses who with their revolutions covered the birth of science and sprouted the bud of the human personality, an indication of a new approach to investigation and research, a rational anxiety aimed at the love of knowledge and the renaissance of nature. The innate feeling of the state of health animated the desire to understand the morbid phenomena and the causes that generated them. 'Knowing oneself,' as Socrates liked to repeat, through the modern exploration of origins is certainly a goal worth fighting for. Dr. Robert Gallo is the living testimony inherited from this origin in the past, the legacy of those ancient experiences, a monumental knowledge that today helps us

to understand the profound meaning of one's own attitude towards life, death, and destiny."



COVID-19 Variants Emerge

By January 2021, the rapid global spread of SARS-CoV-2 variants that emerged from the UK and South Africa brought great concern. GVN experts emphasized the need to urgently obtain data and evidence-based decisions on the strategy to extend the second vaccine dose timing to 12 weeks, or beyond what had already been tested in clinical trials due to several concerns about protective efficacy, vaccine safety, and generation of new variants. Thus, GVN recommends additional and innovative studies to address several other possibilities for overcoming the shortage of vaccines and also to reinforce vaccine efficacy and duration of effect, such as using:

1. Half the amount of vaccine for prime and boost vaccinations,
2. Heterologous prime and boost immunization by a combination of a COVID-19 vaccine and a non-specific effect of vaccine (i.e., BCG and oral poliovirus vaccine), and
3. Heterologous prime and boost immunization by a combination of different COVID-19 vaccines (i.e., use of Pfizer/BioNTech and Oxford/AstraZeneca vaccines).

GVN suggested launching well-designed clinical studies immediately so that the world could quickly learn which strategy is most effective. Experts in GVN Centers and Affiliates stood ready to collaborate and evaluate these vaccine strategies and extend their collective efforts to

Philanthropist Donates US $1M to GVN: Gift Supports Educational & Training Initiatives

In March 2021, announced the donation of US $1 million to support GVN's Academy, an initiative that fosters global collaborations by providing training and mentoring programs for rising junior virologists. With the new funds, GVN launched the GVN Postdoctoral Fellowship Program and the GVN Rising Star Program. The charitable contribution is especially meaningful as the GVN marked ten years since top virologists from more than a dozen countries ratified their participation in, and support of, the then newly created GVN at the inaugural meeting held March 1-3, 2011 at the Embassy of Italy in Washington, D.C. The GVN Postdoctoral Fellowship Training Program will train two postdoctoral researchers during a two-year term with the option to rotate among two GVN Centers of Excellence. Participants of the program will engage in GVN annual and regional meetings during their two-year term, exposing them to top virology experts and cutting-edge research initiatives. Fellows may also collaborate with GVN's growing list of industry partners. The GVN Rising Star Program will mentor 15 bright, junior scientists over the course of two years and match each mentee with a GVN senior virologist to provide one-on-one research and career guidance. Participants of the program will also engage in the elite GVN annual and regional meetings.

GVN Catalyzes WHO to Officially Recognize HTLV-1 as Threatening Pathogen to Humans

During GVN's 9th International Meeting in Melbourne, Australia on September 25-27, 2017 in partnership with the Peter Doherty Institute and the Institut Pasteur, researchers held impressive sessions on one of the most potent human carcinogens, human T-cell leukemia virus-1 (HTLV-1). The sessions were organized by Dr. Sharon Lewin, Director of The Peter Doherty Institute for Infection and Immunity and Director of Doherty's GVN Center of Excellence and Dr. Damian Purcell, member of GVN's HTLV-1 Task Force and Head of the Molecular Virology Laboratory in the Department of Microbiology and Immunology at Doherty. In particular, Dr. Lloyd Einsiedel, a member of the GVN HTLV-1 Task Force and of Baker Institute in Australia, reported serious HTLV-1 endemic cases in Central Australia.

The group of renowned scientists and activists were moved by the presentations to call on the World Health Organization (WHO) to support the promotion of proven, effective transmission prevention strategies on this debilitating and deadly virus. An abbreviated version of the letter, Time to eradicate HTLV-1: an open letter to WHO, co-authored by Dr. Robert Gallo; Dr. Fabiola Martin, member of GVN's HTLV-1 Task Force and a Sexual Health, HIV and HTLV Physician and scientist based in Brisbane/Australia; and Dr. Yutaka Tagaya, member of GVN's HTLV-1 Task Force and Assistant Professor of Medicine, Institute of Human Virology, University of Maryland School of Medicine, was published in *The Lancet* online and in the print

May 12, 2017 issue. The full letter, with many signatories, was published on the GVN website. The call-to-action was covered by major global media and scientific journals including *CNN, ABC, The Guardian, Science,* and *Nature Medicine,* among others.

Since 2017, GVN members such as Dr. Eduardo Gotuzzo, member of GVN's HTLV-1 Task Force and GVN Center Director of the Instituto de Medicina Tropical "Alexander von Humboldt" IMTAvH of the Universidad Peruana Cayetano Heredia (UPCH), have worked with Ministers of Health around the globe to also call on the WHO to recognize HTLV-1 as a threatening pathogen to humans.

In late 2018, the WHO organized a review on HTLV-1, including on its epidemiology, pathogenesis, and clinical impacts and invited the scientific community to assist. Dr. John Kaldor of the Kirby Institute of Australia, and a member of the GVN HTLV-1 Task Force, was chosen by the WHO to assemble a team and provide a review on the issue. Dr. Andrew Ball, the Senior Strategy and Operations Adviser in the Department of HIV/AIDS of WHO, subsequently organized a meeting in Tokyo in March 2019 and invited over 50 researchers/clinicians/patient representatives to the meeting to discuss a consensus on recommendations for the WHO relating to HTLV-1. The meeting was chaired by Dr. Toshiki Watanabe of University of Tokyo, the President of the International Retrovirology Association (IRVA) and a member of the GVN HTLV-1 Task Force. The meeting was published in February 2021.

Finally, in March 2021, catalyzed by GVN's initiative and commitment by its members, the WHO published several articles recognizing HTLV-1 as a relevant pathogen to humans.

While the sudden outbreak of the SARS-CoV-2 pandemic has slowed down the process, the WHO has finally properly recognized the threat of HTLV-1 to humans. We expect that this action will influence the scientific community, public health agencies in many countries, the pharmaceutical industry, and even investors to focus their attention and funding in support of research, drug development, clinical treatment, and social environment to combat HTLV-1.

GVN Adds New Members and Grows Its Reach

This past year, the GVN added five new academic Centers of Excellence (COE), two new corporate COEs, and one Affiliate. The new academic COEs include, Wuhan Institute of Virology (WIV), part of the Chinese Academy of Sciences, Radboud University Medical Center in the Netherlands, the Harvard T.H. Chan School of Public Health in the United States of America (USA), Institut Pasteur Korea (IPK), and Senegal's Institut de Recherche en Santé, de Surveillance Epidémiologique et de Formation [Institute for Health Research, Epidemiological Surveillance and Training], or the IRESSE. The GVN announced Sanofi Pasteur, the vaccines global business unit of Sanofi, and Gilead Sciences as its latest members of the GVN Healthcare and Pharma Center of Excellence Coalition, a groundbreaking, pioneering, and collaborative strategic initiative that brings together and harnesses the expertise and resources of the world's leading pharmaceutical companies to lead the war against viruses that pose a clear and present threat to public health and mankind. The new Affiliate is the University of the West Indies at St. Augustine in Trinidad and Tobago through GVN's Center of Excellence in HIV and HCV Clinical Pharmacology Laboratory in the Center for Integrated Global Biomedical Sciences, at the University at Buffalo, The State University of New York (SUNY), USA.

GVN Members represent expertise covering every class of human virus, and currently comprise virologists from 65 Centers of Excellence and 10 Affiliates in 35 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.

This past year the GVN also announced that USF Health, at the University of South Florida (USF) in Tampa, Fla., will serve as GVN's Southeast United States Regional Headquarters. USF Health is the first regional headquarters named by GVN to provide organizational and leadership support to GVN's Global Headquarters in Baltimore, Md. In that capacity, USF Health will help strengthen GVN's initial research response to emerging and re-emerging infectious diseases, such as COVID-19, and its collaborative efforts to plan for, and defend against, future epidemics and pandemics.

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, Shin-Hee Lee, PhD, Program Director, Marcus Gallo, MS, Research Analyst & Center Outreach Coordinator, and Kevin Kishpaugh, Operations Associate. IHV faculty and staff contributed time generously to the GVN throughout the year, including most notably Robert Gallo, MD, who, as mentioned,serves as Co-Founder and International Scientific Advisor of the GVN, Dave Wilkins, who oversees GVN's finances, and Nora Samaranayake, who serves as GVN's Senior Advisor on Public Relations. Other contributors include Mohammad Sajadi, MD; Anthony Amoroso, MD; Davide Zella, PhD; Shyam Kottilil, MBBS, PhD; Man Charurat, PhD; Yutaka Tagaya, PhD; Alash'le Abimiku, MON, PhD; Clement Adebamowo, BM, ChB, ScD, FWACS, FACS; Marv Reitz, PhD; Niel Constantine, PhD, MT(ASCP); George Lewis, PhD; Lishan Su, PhD; and Anthony DeVico, PhD. IHV also appreciates its own Board of Advisors for donating time and energy towards the advancement of the GVN mission.

INSTITUTE OF HUMAN VIROLOGY

IHV Faculty

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Lishan Su, PhD, Director, Virology, Pathogenesis, and Cancer (VPC)

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University of Maryland School of Medicine

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

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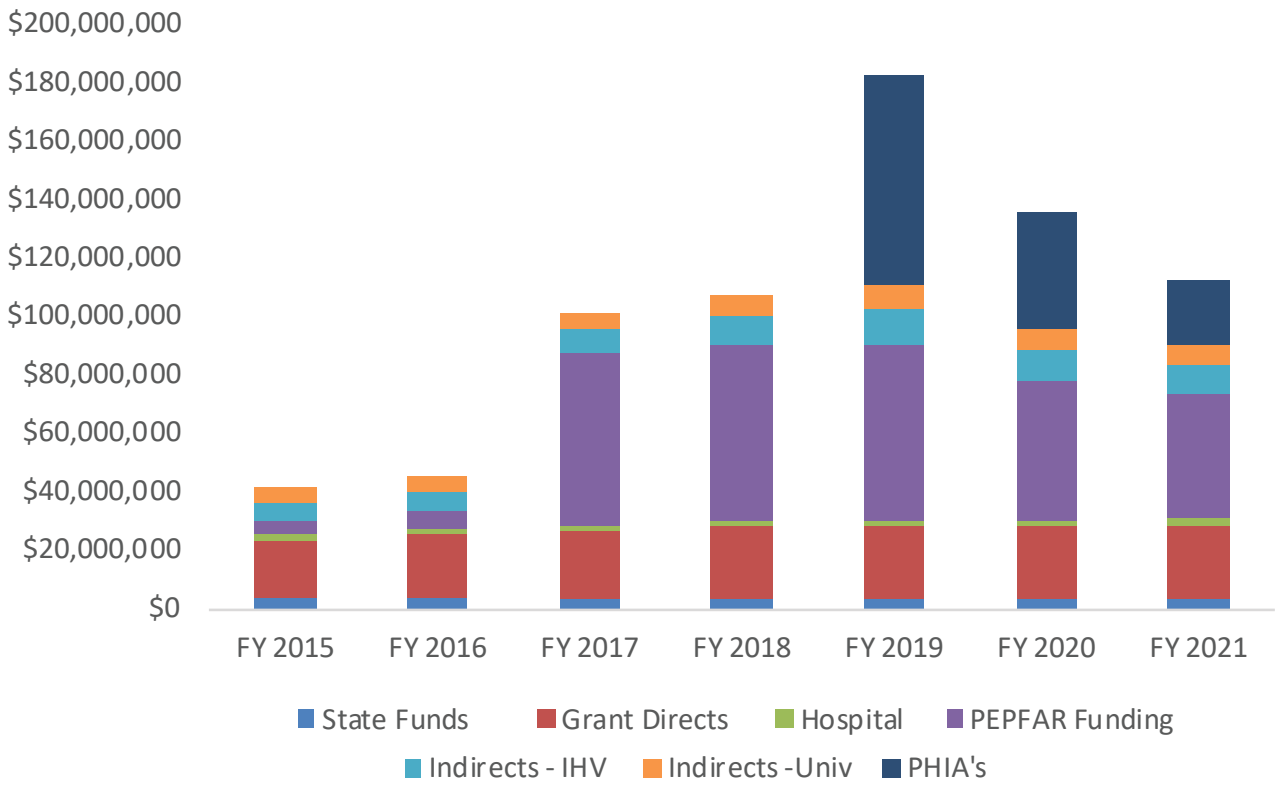
Financial Overview

IHV had yet another strong financial year in FY21, generating $112,500,000 of total revenue. This resulted from continued stability in all 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). Significant change can be expected year over year in Ciheb and Population-Based HIV Impact Assessment (PHIA) funding, as these amounts are fundamentally affected by U.S. government policy regarding awards of funds to Indigenously based versus U.S. entities. This year and in years to come, 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 FY22. In FY20, IHV received funding in the amount of $48,000,000 for PHIA surveys in Nigeria, Zambia, and Botswana. We are currently awaiting decisions as to whether CDC will conduct PHIA HIV surveys in any number of new countries—decisions that will have well over a $10 million impact on our budget. IHV is working with foresight to prepare for reduced funding by establishing and supporting indigenous organizations to successfully compete to win relevant grants, for which they would seek our support. The Immunotherapy; Vaccine Research; and Virology, Pathogenesis, and Cancer Divisions continue to deliver significant basic science and vaccine development grants.



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