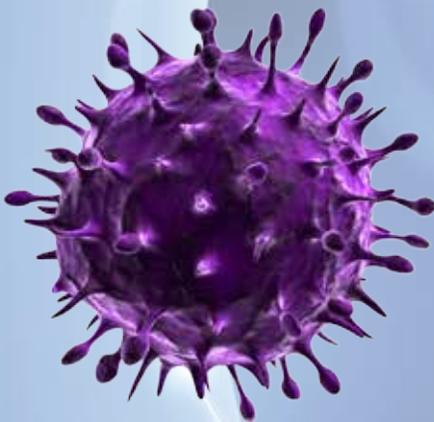


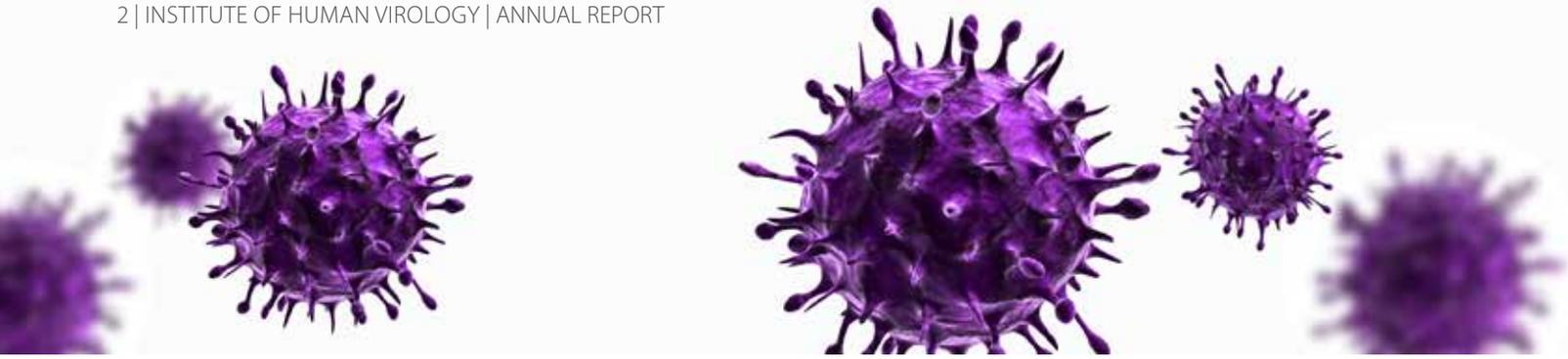
Institute of Human Virology

ANNUAL REPORT

2014



UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE



Our Mission

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

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 and co-director of IHV's Division of Basic Science and Vaccine Development, William Blattner, MD, associate director of the IHV and director of IHV's Division of Epidemiology and Prevention and Robert Redfield, MD, associate director of the IHV and director of IHV's Division of Clinical Care and Research.

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 70 faculty whose research efforts are focused in the area of chronic human viral infection and disease. At present, more than 75 percent of the Institute's clinical and research effort is targeted at HIV infection, but also includes the Hepatitis C virus, herpes viruses and cancer research. IHV's patient base has grown from just 200 patients to approximately 5,500 in Baltimore and close to 1,000,000 in 6 African and 2 Caribbean nations.

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

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

Director's Message

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine had an exciting year—particularly in its international presence. For the second time in history, the Annual IHV International Meeting was held outside the Washington, D.C./ Baltimore region and uniquely hosted in Moscow, Russia. The 15th Annual Meeting, in partnership with the Moscow Center for HIV/AIDS Prevention and Treatment and the Global Virus Network (GVN), attracted approximately 1000 scientists, clinicians and pharmaceutical representatives from around the world to explore the latest developments in the fight against HIV/AIDS, viral oncology and other infectious diseases. Uniquely this year, the Meeting included presentations from members of the GVN, thereby broadening the scope of the meeting to cover other important human viral diseases including hepatitis, measles, influenza, enterovirus, polio, and hemorrhagic fever, to name a few.

A Global Leader: Cultivating innovative basic science and vaccine research, providing holistic health care and treatment, and building public health infrastructure through prevention and training programs





Dr. Gallo with Lifetime Achievement Awardees Vadim Agol, MD, PhD, DSc and José Esparza, MD, PhD

Prior to the IHV Annual meeting, IHV faculty voted for the prestigious Lifetime Achievement Award in Public Service and Lifetime Achievement Award for Scientific Contributions. The esteemed winners included:

2013 IHV Lifetime Achievement Award for Public Service—José Esparza, MD,

PhD, Senior Advisor on Vaccines for the Bill & Melinda Gates Foundation. Dr. Esparza was honored for his lifelong commitment to preventing human viral diseases through the development of effective vaccines. He crafted important parts of the HIV/AIDS prevention strategy during his work with UNAIDS, the World Health Organization, and his position at the Bill & Melinda Gates Foundation. He helped to found the African AIDS Vaccine Initiative and the AIDS Vaccine for Asia Network. Dr. Esparza was honored for the discovery, development and delivery of HIV drug therapies and for his contributions to HIV vaccine development.

2013 IHV Lifetime Achievement Award for Scientific Contributions—Vadim Agol,

MD, PhD, DSc, a corresponding member of the Russian Academy of Sciences and the Chumakov Institute of Poliomyelitis and Viral Encephalitides of the Russian Academy of Medical Sciences, and an Honorary Scientist of Russia. Dr. Agol was honored for his outstanding contributions

to understanding chronic viral diseases and how virus components counteract host immunity. He is a leader of research on poliovirus evolution and how this impacts strategies for vaccination and polio eradication.

The science presented at the meeting recognized both our commitment to the global fight against HIV/AIDS as well as a focus on several other human viral diseases, and the critical roles played by the scientists, physicians, and public health officials in the Russian Federation. For

each disease discussed, we concentrated on the latest developments in antiviral drug treatment or preventive vaccines and addressed the roles for viruses in human cancer, how they cause diseases and how they are spread. Workshops provided practical lessons for managing co-morbidities of HIV/AIDS including hepatitis, cancer, tuberculosis and diabetes. The Meeting resulted in a clinical training partnership between IHV and the Moscow Center for HIV/AIDS Prevention and Treatment.

In November, the School of Medicine honored me as the first Homer & Martha Gudelsky Distinguished Professor in Medicine at the University of Maryland School of Medicine during a terrific ceremony that included family and friends. The Homer & Martha Gudelsky Family Foundation, Inc. established The Homer & Martha Gudelsky Distinguished Professorship in Medicine in December 2005 in recognition of the distinguished medical careers of Donald E. Wilson, MD, MACP, Dean Emeritus, and John A. Kastor, MD, professor and former chair of the Department of Medicine. Needless to say,



Speakers at the Homer & Martha Gudelsky investiture included (L to R): The late Reinhard Kurth, MD, Chairman of the Foundation Council, Ernst Schering Foundation; Max Essex, DVM, PhD, Chair, Harvard School of Public Health Initiative; Robert Gallo, MD; E. Albert Reece, MD, PhD, MBA, Dean, University of Maryland School of Medicine; Terry Lierman, Chair, Institute of Human Virology Board of Advisors; and Stephen Davis, MBBS, FRCP, FACP, The Dr. Theodore E. Woodward Chair in Medicine.



L to R: Drs. Robert R. Redfield, C. David Pauza, and Robert C. Gallo

I am very happy and honored by this distinction and very proud to wear the Gudelsky name.

In the Basic Science and Vaccine Development (BSVD) Division, led by Dr. George Lewis and me, we experienced significant progress this past year in our viral oncology, immunology, virology, and HIV-1 vaccine research programs. For example, we moved into the next phase of our Institute’s HIV vaccine candidate funded largely by the Bill & Melinda Gates Foundation, among other entities including the U.S. National Institutes of Health. We have collaborations to determine the role of the HIV-1 structural protein in the genesis of B cell lymphoma. And, Dr. Eric Sundberg’s team is investigating molecular

recognition in infectious diseases as a path to rationalizing novel therapeutic approaches to microbial pathogenesis, chronic inflammatory diseases, and infectious causes of cancer. These are just a few projects.

IHV Associate Director and Director of the Epidemiology and Prevention Division, Dr. William Blattner, continued to lead the Institute of Human Virology, Nigeria (IHVN) through funding from the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). IHVN’s impact is best measured in the clinical care, treatment, and prevention services to 944,004 Nigerians who were counseled and tested for HIV; 896,555 mothers who were screened to prevent infections of their babies; 139,857 patients who received antiretroviral therapy; and 32,749 health care workers who were trained.

IHV Associate Professor and Animal Models Division head, Dr. Joseph Bryant, led animal research on lymphoma associated with HIV and primate research on our HIV preventive vaccine candidate. IHV develops The Division developed a HIV-1 transgenic nude rat—a novel disease progressed animal model for HIV-1/AIDS.

During FY 2014, IHV’s basic research portfolio, at the heart of our mission, continued to thrive despite severe cuts to the U.S. National Institutes of Health (NIH) and U.S. Centers for Disease Control (CDC) funding levels. The Institute’s overall income continued to be influenced by the U.S. government’s decision to award international HIV care and treatment grants primarily to indigenous institutions as opposed to U.S. universities and institutes. However, the financial graph on page 30 depicts the large amount of funding now going to organizations that the Institute has spun-off both in the U.S. (Profectus Biosciences, Inc.) and in four African nations. IHV has also been able to provide significant financial support to the new Global Virus Network (GVN), established to organize the world’s top virus researchers. The technical assistance IHV provides these organizations brings a great deal of revenue back to the Institute. IHV continues to augment the world’s ability to fight chronic viral diseases in a meaningful and compelling way.



Prof. Ulrike Protzer, MD, Institute of Virology, TU Munich, presents during IHV’s Annual International Meeting held this year in Russia.

Dr. Robert Redfield, IHV Associate Director and Director of the Clinical Care and Research Division, reported another successful year, particularly as his team continued to build upon their PEPFAR programs in seven African and two Caribbean nations and their local outreach here in Baltimore. The Division supports more than 250 sites in 7 countries. In each of these locations, we have strong programs providing training, care and treatment. The Division provides care and treatment to more than 5,000 Baltimoreans living with HIV.



Participants during IHV’s Meeting

IHV Leadership



Robert C. Gallo, MD

Director, Co-Director, Division of Basic Science and Vaccine Research, Institute of Human Virology and Professor, Homer & Martha Distinguished Professor in Medicine, and Professor, Microbiology and Immunology, University of Maryland School of Medicine



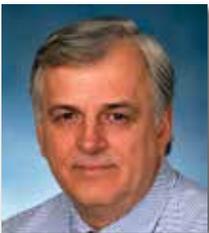
William A. Blattner, MD

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



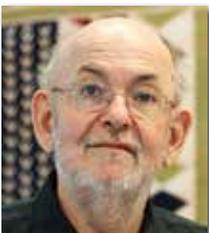
Robert R. Redfield, MD

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



C. David Pauza, PhD

Associate Director, Institute of Human Virology and Professor, Medicine, University of Maryland School of Medicine



George K. Lewis, PhD

Co-Director, Division of Basic Science and Vaccine Research, Institute of Human Virology and Professor of Microbiology and Immunology, University of Maryland School of Medicine



Joseph L. Bryant, DVM

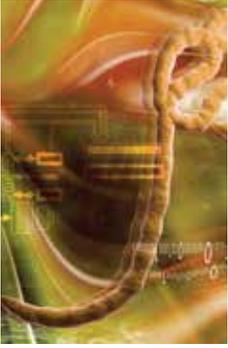
Director, Division of Animal Models, Institute of Human Virology and Professor, Medicine, University of Maryland School of Medicine



Dave Wilkins

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





Division of Basic Science and Vaccine Development

The Division of Basic Science and Vaccine Development faculty led by Division Directors Drs. Robert Gallo and George Lewis, draws upon a wide spectrum of disciplines including molecular and cell biology, virology, immunology, and structural biology to solve major problems facing cancer, immunology, and viral diseases. Over the last year the division has made significant progress in our oncology, immunology, virology, and HIV-1 vaccine research programs.

Viral Oncology

The Viral Oncology program studies the etiology and pathogenesis of malignancies caused by virus infections, either by direct transformation by HTLV-1, or by indirect effects of HIV-1 infection, which greatly increases the likelihood that an infected individual will develop a malignancy over their life span.

Dr. Hua Cheng's group is investigating how human T cell leukemia virus type 1 (HTLV-1) causes adult T cell leukemia and lymphoma (ATL). ATL develops after a long incubation period and progresses aggressively leading to death in most cases. The genome of HTLV-1 encodes an oncogenic protein, Tax, that is essential for malignant transformation of human T lymphocytes. We have shown that HTLV-1-transformed T cells have increased autophagic flux due to the deregulation of autophagy by Tax, where it recruits essential molecules into lipid raft microdomains in I κ B kinase-dependent manner. Persistent autophagic flux is crucial for promoting survival and proliferation of HTLV-1-transformed T cells, leading to a new publication in the peer-reviewed journal *Oncogene* in the last year. Dr. Hua's group has also used Tax to establish a new model of T cell large granular lymphocytic leukemia that providing a new model to develop novel therapies for this disease.

Dr. Yutaka Tagaya's group is also investigating the mechanisms of HTLV-1 associated malignancies and as well as non-malignant pathologies associated with this viral infection. His group has developed a new peptide for the treatment of non-malignant diseases associated with HTLV-1 infection including HAM-TSP and select autoimmune disorders. His group is also investigating the role the RNA form of HBZ in Adult T cell Leukemia and the role of the IRF8 transcription factor in differentiation of NKG2C+CD94+ CD8 T cells (a subset of CD8 NK-T cells).

Other investigators of the Viral Oncology Program are studying the mechanism through which HIV-1 infection predisposes to B cell lymphoma. HIV-1 does not encode a viral oncogene and its oncogenic effects are indirect. Dr. Gallo leads a team comprised of

Dr. Sabrina Curreli, Dr. Davide Zella, Dr. Wuyuan Lu, and Dr. Alfredo Garzino-Demo of the Division of Basic Science and Vaccine Research in collaboration with Dr. Joseph Bryant from the Division of Animal Models and Dr. William Blattner of the Division of Epidemiology and Prevention Research to determine the role of the HIV-1 structural protein, p17, in the genesis of B cell lymphoma. This work is carried out in collaboration with Dr. Arnaldo Caruso and colleagues at the University of Brescia. This work has led to the identification of B cell lymphomas in HIV-1 transgenic mice. Drs. Curreli, Zella, and Bryant have characterized the tumors that arise spontaneously in these mice as pre-B cell lymphomas, which are similar to some B cell lymphomas that arise in HIV-1 infected people. Dr. Lu's group is studying the structure of p17 and Dr. Garzino-Demo's group is developing new transgenic mice expressing only p17. These basic science projects are supporting clinical studies of B cell lymphomagenesis by Dr. Blattner and his team.

Although it is a bacterium, Drs. Gallo, Zella, Curreli, and Bryant have discovered that certain strains of mycoplasma induce lymphomas in immunodeficient mice. Mycoplasmas are distinguished from



L to R: Drs. Robert Gallo, Wuyuan Lu, Alfredo Garzeno-Demo, Sabrina Curreli and Joseph Bryant

other bacterial species by their lack of a cell wall and they are the smallest known self-replicating organisms. Further, they preferentially grow in eukaryotic cells. Studies from this group have shown that primary and secondary tumors from mycoplasma-infected mice harbor mycoplasma DNA sequences and a direct interaction between a mycoplasma protein and p53, impairing its ability to respond to DNA damage and possibly leading to malignant transformation. The studies describe the first causal link between mycoplasma infection and the development of lymphomas.

Dr. Eric Sundberg's laboratory continues expansion of a research program focused on molecular mechanisms by which *Helicobacter pylori* causes gastric cancer. Infection with *H. pylori*, in particular strains that harbor the CagA oncoprotein and the Type IV Secretion System (T4SS) machinery used to inject this transforming protein into gastric epithelial cells, is the leading cause of human gastric cancer. Dr. Sundberg's group is investigating the structure and function of CagA, how it interacts with both bacterial and human proteins, and the mechanisms by which components of the T4SS engage host cell receptors. In FY2014, Dr. Sundberg and colleagues published a report describing the interaction between CagA and CagF, an *H. pylori* protein that chaperones and delivers CagA to the T4SS prior to its translocation into epithelial cells.

Immunology

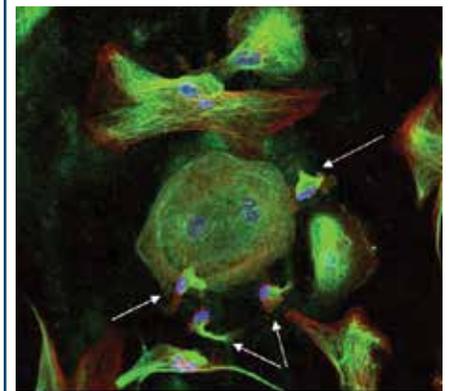
Immunology contributes in multiple ways to the IHV goal of eradicating infectious diseases and their associated malignancies.

Dr. David Pauza's group has made major scientific advances over the last year including:

1. Detailed analysis of gamma delta T cells in patients where HIV is suppressed by prolonged antiretroviral therapy;
2. Identification of a new function for gamma delta T cells defined by the licensing of NK cells to detect and destroy inflammatory dendritic cells;
3. Identification of a new structural defect in CD8 T cells, TIM-3 as a marker for immune exhaustion; and
4. Discovery of a new T follicular helper cell subset in human tonsil involved in the final stages of B cell maturation and immune memory.

Dr. Cristiana Cairo in collaboration with Dr. Pauza has been investigating the role of VgVd2 cells in the context of neonatal and infant immunity. Studies in Cameroon have shown that prenatal exposure to placental malaria causes depletion of pathogen reactive VgVd2 cells in the fetus leading to poor responses by this important subset in neonates, leading to a new publication in the *Journal of Infectious Diseases*. Her ongoing research in Malawi continues to explore the impact of maternal malaria on fetal immunity.

Dr. Suzanne Gartner's laboratory is continuing investigations of multi-lineage differentiation potential of novel small cells produced by nurse macrophages, which was published in *PLoS One* recently. A particular focus is the question of whether the nurse cells can generate erythroid progenitors and CD34+ hematopoietic stem cells. In addition, Dr. Gartner's group has continued the characterization of steps leading to the production of CD4+ T cells from then nurse macrophages. Studies are continuing in humans based on observations that nurse macrophages and their novel monocytoid progeny reside in human bone marrow. Dr. Gartner's group has also received new funding to investigate the role of bone marrow as a reservoir of HIV-1 infection.



CD11b Tubulin TOTO-3

Macrophages cultured from HIV+ bone marrow: Staining with CD11b identifies cells of the monocyte/macrophage lineage. A large, multinucleated macrophage with features characteristic of nurse macrophages, is seen in the center of the field. Nearby are four very small adherent cells, also CD11b positive (arrows). These two populations are highly reminiscent of the nurse macrophages and their progeny that Dr. Gartner and her colleagues culture from normal human blood. These findings suggest that bone marrow in HIV+ individuals may be a site where the nurse macrophage/small cell cycle can proceed. (Photo Credit, Dr. Yiling, Liu, IHV)



Dr. David Pauza's laboratory group

Dr. Erik de Leeuw's laboratory investigates anti-microbial effects of defensins, which are anti-microbial peptides with activities on bacteria and HIV-1. Dr. Leeuw's studies center on the role of defensins as signaling molecules that connect the innate and adaptive immune systems. In this regard, his group has shown that defensins interact synergistically with TNF- α , which is a key regulator in the immune system with strong



Dr. Eric Sundberg's laboratory group

proinflammatory and immunomodulatory properties. His group has identified new small molecule inhibitors of Lipid II that is a key element of defensin action. A lead compound, BAS00127538, binds to Lipid II, affects cell wall biosynthesis and acts protective in a mouse model for sepsis. Using a combination of Computer Aided Drug Design and medicinal chemistry, this compound is currently being optimized and examined for its potential as a novel, broad-range antibacterial in collaboration with researchers of the University of Maryland School of Pharmacy.

Dr. Eric Sundberg's group investigates molecular recognition in infectious diseases as a path to rationalizing novel therapeutic approaches to microbial pathogenesis, chronic inflammatory diseases, and infectious causes of cancer. Dr. Sundberg's group is elucidating the molecular basis of effector functions of antibodies with the goal of manipulating these functions for specific therapeutic purposes. In collaboration with Dr. Lai-Xi Wang, Dr. Sundberg's group has determined the crystal structure of Endoglycosidase S, a large enzyme that removes sugars specifically from IgG. This enzyme is used extensively for glycan engineering and plays a key role in bacterial evasion of the host immune response. This structure provides novel information on the catalysis mechanism of this enzyme that will be useful in further tailoring its activity and in the development of inhibitors to attenuate bacterial pathogenesis.

Virology

Fundamental virology remains a mainstay in HIV-1 research providing new windows on therapeutic targets and several investigators are pursuing different strategies to prevent or abrogate HIV-1 infection.

Dr. Alfredo Garzino-Demo's group focuses on the anti-HIV-1 activities of b-defensins with emphasis on signaling activity initiated by the binding of b-defensins to the chemokine receptor, CCR6. This

interaction leads to the activation of APOBEC3G, a cytidine-deaminase that is involved in the innate resistance to HIV-1 infection. Thus, b-defensins indirectly affect HIV-1 replication through the activation of this potent innate anti-viral pathway. Dr. Garzino-Demo's group is also investigating the role of b-defensins and the CCR6 signaling pathway in the protection of Th17 cells from HIV-1 infection. This subset is massively and selectively lost in the gut mucosa of humans infected with HIV-1 and rhesus macaques infected with SIV.

Dr. Fabio Romero's group investigates the basic biology of the CD4+ T cell reservoir for HIV-1. This work is significant in that the reservoir is refractory to anti-retroviral drugs and any attempt to cure HIV-1 must include reservoir eradication. Dr. Romero's group has used an in vitro reservoir model to show that reservoir CD4+ T cells have high levels of CD2. This enables enrichment of the reservoir population although it is still heterogeneous in phenotype. Additional studies are being carried out to identify more cell surface molecules that are expressed selectively on reservoir cells. Identification of the ultimate phenotype of reservoir CD4+ T cells will be important to ultimately curing HIV-1.

Dr. Olga Latinovic studies the synergistic effects of two molecules that inhibit HIV-1 infection in vitro. The first molecule is, Maraviroc, an FDA-approved drug that binds to CCR5 and blocking HIV-1 entry. The second molecule is FLSC-IgG1, which is a chimeric protein comprised of CD4-triggered gp120 fused to the heavy chain of IgG1 developed in the IHV by Dr. Tony DeVico who collaborates on this work. FLSC-IgG1 also binds to CCR5 but with a different mechanism than Maraviroc. Synergistic in vitro inhibition of HIV-1 infection is observed when these two molecules are combined. New imaging methods to define the mechanisms of inhibition at the single cell level have been developed with Dr. Joseph Lakowicz and an in vivo model for therapy by this drug combination have been developed together with Dr. Timothy Fouts of Profectus Biosciences and IHV's Drs. Joseph Bryant and Robert Redfield.

Dr. Joseph Lakowicz is developing new methods to quantify protein-protein interactions using intrinsic fluorescence that occurs from all proteins with novel photonic structures. This approach is being developed in collaboration with Dr. Tony DeVico and it will lead to a label free method for high-throughput screening of biological molecules. The approach is being developed for rapid screening of monoclonal antibodies. Dr. Lakowicz is also collaborating with Dr. Latinovic where they have developed a method based on plasmonic substrates to directly identify HIV-1 secreting cells in vitro. Finally, Krishanu Ray and Dr. Lakowicz in collaboration with Dr. DeVico and Dr. Lewis have developed a method to directly quantify the binding of antibody to HIV-1 virions in solution. This method employs Fluorescence Correlation Spectroscopy and it directly quantifies the binding of antibodies to virions, obviating the inherent problems encountered with typical plate capture assays. This information is being further pursued to define multiple epitope exposures throughout the HIV-1 replicative cycle using single molecule fluorescence approaches.

Vaccine

A safe and effective vaccine is widely viewed as the best way to quell the HIV-1 epidemic; however, after over twenty-five years of intensive research, it remains elusive. IHV

investigators are actively pursuing several vaccine strategies with a lead vaccine candidate now poised for a Phase I clinical trial.

Dr. Gallo is leading a program to evaluate a conformationally constrained vaccine denoted as FLSC (Full Length Single Chain) in a Phase I Clinical Trial. The Bill and Melinda Gates Foundation and the Military HIV Research Program support this study and it involves member institutes including Dr. Tony DeVico, in whose group FLSC was originally developed, Dr. George K. Lewis who is Co-Principal Investigator, and Dr. Bruce Gilliam and Dr. Robert Redfield, who are responsible for the Phase I Clinical Trial. The project also includes collaboration with former IHV member Dr. Timothy Fouts of Profectus Biosciences, who is also a co-inventor of the vaccine. This program represents the cumulative efforts of a large group of investigators who were brought together by Dr. Gallo to work on an HIV-1 vaccine when the IHV was established seventeen years ago. It is emblematic of the original design of the IHV to go from bench to bedside inside a single institution. FLSC is a conformationally constrained fusion protein of gp120 and CD4 that stably exposes highly conserved epitopes that are targets of protective antibodies. A number of challenge studies in non-human primates carried out over the years show that FLSC elicits protective responses in rhesus macaques against a

model AIDS virus SHIV162p3. These studies have identified serological correlates of this protection in addition to identifying protein and adjuvant compositions that are key to protection. These key preclinical studies set the stage for the first evaluation of FLSC in humans scheduled for 2015.

In addition to his involvement in the development of FLSC, Dr. Lewis also leads a group of IHV collaborators in a program to understand the basis of antibody-mediated protection against HIV-1. This program is funded by the Bill and Melinda Gates Foundation and involves extensive collaborations among IHV members, Dr. Tony DeVico, Dr. Marzena Pazgier each of whom leads key projects of the program. This program tests the hypothesis that non-neutralizing antibodies that exhibit potent Fc-mediated effector function can protect rhesus macaques against SHIV162p3.

Dr. Tony DeVico's group has developed state of the art methods to quantify epitope exposure on free virions in solution and at the virion-cell surface interface during viral entry. Epitope exposure on free virions is determined by the fluorescence correlation spectroscopy method described earlier in the collaboration with Dr. Joseph Lakowicz. Epitope exposure at the virion-cell interface is determined by single viral particle imaging using conventional confocal microscopy as well as by super resolution microscopy. Information from these studies is being used in conjunction with a new ADCC assay developed in Dr. Lewis' group using target cells sensitized with entering virions to determine the relationship between epitope exposure and ADCC activity. These studies indicate that factors other than just epitope exposure dictate differences in potencies among mAbs that mediate ADCC.

Dr. Marzena Pazgier's group is determining the epitope footprints for mAbs that exhibit potent ADCC activity. Her group has used X-ray crystallography to solve co-crystal structures for three anti-gp120 mAbs that mediate potent ADCC. These mAbs recognize structures associated with the mobile regions of gp120 that communicate CD4-induced conformational changes to gp41 during viral entry (Figure X). Most importantly, the epitope footprint defined for these mAbs falls into the region of gp120 that was implicated in the RV144 vaccine trial as a target of potentially protective antibodies that mediate ADCC.

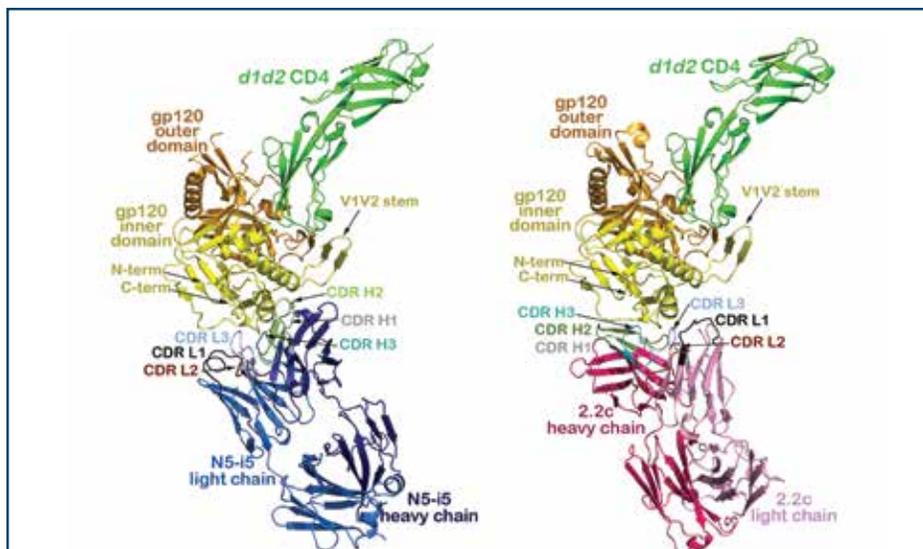


Figure X. Crystal structures of N5-i5 Fab-gp12093TH057 coree-d1d2CD4 and 2.2c Fab-gp12089.6P coree-d1d2CD4 complex. The light/heavy chain of N5-i5 Fab and 2.2c Fab are shown in light blue/dark blue and light pink/dark pink, respectively, and the complementarity-determining regions (CDRs) are shown in black (CDR L1), brown (CDR L2), light blue (CDR L3), grey (CDR H1), green (CDR H2), and cyan (CDR H3). The gp120 inner domain is shown in yellow, the outer domain in orange. Published in *J. Virol.* 2014 Nov 1;88(21):12895-906.

In addition to his involvement in the development of FLSC as a vaccine, Dr. Lewis' group is investigating the physical-chemical basis for ADCC. Studies are underway to determine the molecular basis of the bell-shaped dose-response curves seen in ADCC assays. These studies employ the information from the projects led by Drs. DeVico, and Pazzier in addition to flow cytometric methods to quantify the degree to which multivalent mAb binding and Fc orientation determine the binding of immune complexes on target cells to Fc receptors on effector cells. These interactions are major elements controlling ADCC potency *in vitro*. In addition, his group is testing the hypothesis that these effects determine the protective potency of mAbs in passive immunization studies in non-human primates. These studies will be carried over the next year using a passive immunization model.

Dr. Lai-Xi Wang's group is investigating carbohydrate scaffolds as potential HIV-



Members of IHV's Vaccine Group

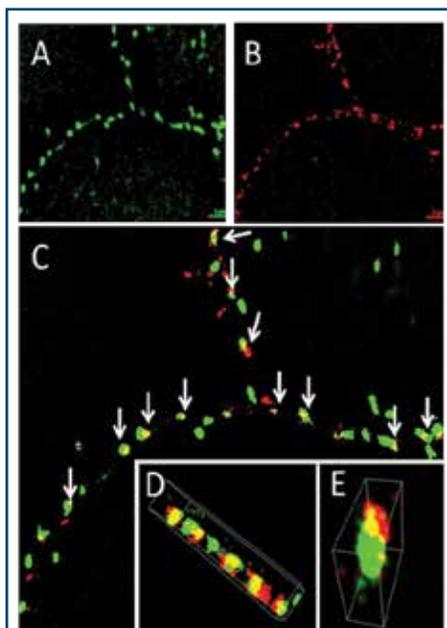


Figure 3. Contacts between FLSC IgG1 (developed by DeVico and group) and CCR5. FLSC IgG1 Zenon Alexa 488 (green- Panel A-staining assay from the Lewis group) binding to CCR5 stained with CCR5 mAb, clone 45523 and an Alexa 647 conjugated secondary antibody (red-Panel B), their overlap (yellow-Panel C) and a 3-D close up of direct contacts between CCR5 and FLSC IgG1 on the TZMbl cell membrane (Panels D and E) were imaged by super resolution microscopy and total internal reflection fluorescence methodology (TIRF) (Rust *et al.*, 2006). This is the first Super resolution microscopy (Nobel prize, 2014) work published from IHV (Latinovic *et al.*, 2014) together with Dr. Redfield.

1 vaccine candidates. His group has developed a series of cyclic glycopeptides corresponding the V1/V2 domain harboring epitopes recognized by broadly neutralizing mAbs that recognize glycan-dependent epitopes. This approach has extended to V3 domain glycopeptide epitopes. This work employs new method developed by Dr. Wang's group to install glycans selectively at predetermined glycosylation sites. This has led to new epitope scaffolds that strongly bind broadly neutralizing mAbs specific for glycan-dependent epitopes. Further, Dr. Wang's group is using these glycosylation methods to improve the functional activity of monoclonal antibodies that mediate ADCC. This work should lead eventually to more potent therapeutic mAbs and possibly new vaccine candidates.

Dr. David Pauza's group is developing Fc-targeted mucosal immunogens for HIV-1. His work targets the neonatal Fc receptor (FcRn) that mediates bidirectional antibody transport across mucosal epithelia. His has developed Env-Fc fusion proteins that can be used to vaccinate mucosally and is funded for these studies. These novel immunogens are delivered by spraying into the nose and are potent in nonhuman primate studies. Newer immunogens have also been produced that allow highly repetitive presentation of key portions within the HIV envelope

glycoprotein and they are advancing into animal testing and evaluation. These studies are done in collaboration with Drs. Sundberg, Maria Salvato, Wang, and Bryant of the IHV and Dr. Xiaoping Zhu from University of Maryland, College Park.

Dr. Maria Salvato's laboratory conducts research on the pathogenesis of viral hemorrhagic fevers, investigating host responses to virulent and benign infections by arenaviruses [lymphocytic choriomeningitis virus (LCMV) and Lassa fever virus (LASV)]. In addition to profiling the transcriptome and proteome of blood cells from rhesus macaques given lethal or benign infections, this team has also profiled human PBMC exposed to Lassa virus comparing it to the profile of a mild-attenuated version of Lassa virus, the reassortant virus ML29 (Zapata *et al* J Virol 2013). The profiles revealed that virulent arenaviruses suppress induction of IL6 and IL8 whereas mild infections do not; also that Lassa elicits high levels of thrombomodulin that could account for hemorrhagic signs in severe cases of Lassa fever. Studies on platelet development showed that inactivated virulent arenaviruses, but not mild arenaviruses, are able to bind platelets and block their function (Zapata, Cox, Salvato, PLoS NTD, 2014).





Division of Clinical Care and Research

The Division of Clinical Care and Research continues to develop its tripartite mission: Clinical Care, Clinical Research, and Medical Education, both domestically and around the world. Our clinical program continues to grow, especially with the expansion of the University of Maryland Medical System's Midtown Campus and expanded IHV ambulatory programs for the treatment of HIV, Hepatitis B (HBV), and Hepatitis C (HCV). In light of major advancements in HCV therapeutics, our clinical trials unit has enhanced its focus on the treatment of HCV. The division's laboratory based program continues to focus on targeting host cell pathways, both to develop novel strategies to target the HIV reservoir, as well as to provide new options in the setting of HIV antiretroviral resistance. Finally, our medical education programs continue to provide strong domestic medical educational activity, both at the IHV and the University, and throughout the state of Maryland, as well as our National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) funded international training programs in Sub Saharan Africa and the Caribbean.

Clinical Research

The clinical research activity within the division continues to focus on several key areas: therapeutic research, targeted cohort development for multi-investigator use, and a transitional international education footprint to support a targeted clinical research program. Therapeutic research priorities include: 1) to develop therapeutic strategies to target the HIV reservoir and promote the potential of a functional cure; 2) to target host cell pathways, especially CCR5 as a primary HIV therapeutic and preventive target, as well as a strategy to overcome antiretroviral resistance; and 3) to evaluate new approaches to using approved HIV antiretroviral (ARV) drug therapy to achieve better outcomes, and evaluate new antiviral agents to treat HCV in phase 1-3 trials. Targeted clinical cohorts have been developed for a cohort of patients who naturally suppress HIV without ARV treatment; a cohort of patients who express HIV but persistently control HIV expression to low levels (> 50 but $< 5,000$ copies/ml); a cohort of HIV patients with cancer; a cohort of perinatally HIV infected patients who are now adults; a cohort of HIV infected patients characterized by HIV proviral copy number; and a cohort of HIV HCV co-infected patients. Each of these cohorts provides valuable clinical material for hypothesis generating investigations by members of the IHV.

Laboratory Based Research Efforts

The laboratory based research efforts within the Division of Clinical Care and Research continue to focus on targeting host cell pathways; both a potential strategy to attack the HIV

reservoir, as well as an approach to outcome resistance of currently approved ARVs.

Working together, Dr. Alonso Heredia and Dr. Redfield continue to investigate new approaches to targeting CCR5. Their working hypothesis is that there is a threshold of CCR5 density required to sustain the HIV reservoir in the setting of ARV induced HIV suppression. Of particular interest are ongoing studies characterizing the relationship between CCR5 density and HIV proviral copy number.



L to R: Dr. Alonso Heredia, Nhut Le, Dr. Redfield and Sandra Medina Moreno

Building on years of research targeting host cell pathways in enhanced approved ARV antiviral activity, as well as defining new antiviral targets, Dr. Heredia recently received an R21 grant titled "Long Term Inhibition of HIV Transcription by Targeting Cellular CDK9". This work is an extension of earlier work by Dr. Heredia and Dr. Redfield where they demonstrated that Indurubin-3'-monoxime inhibits HIV infection by blocking CDK9 activity (AIDS 2005) and suppresses replication of multidrug resistant HIV in the humanized mouse model (Heredia A, Natesan S, Nhut L, Medina Moreno S, Zapata J, Reitz M, Bryant J, Redfield RR. Indirubin 3'-monoxime, from a Chinese Traditional Herbal Formula, Suppresses Viremia in Humanized Mice Infected With Multidrug-resistant HIV AIDS Research and Human Retroviruses, AIDS Research and Human Retroviruses 2014, Vol 30, No 5, p. 403-406

In addition, this year Dr. Heredia and Dr. Redfield extended their earlier observation that specific targeting of key pathways in purine biosynthesis and cell cycle enhances antiviral activity of Tenofovir in the setting of drug resistance, as well as further extended these finding to include bioavailable derivatives of Resveratrol, an S phase inhibitor with anti ribonucleosidase reductase activity. (Heredia A, Davis CE, Reitz MS, Le N, Wainberg MA, Foulke JS, Wang L, Redfield RR. Targeting of the Purine Biosynthesis Host Cell Pathway Enhances the Activity of Tenofovir Against Sensitive and Drug Resistant HIV-1. *J Infect Dis*, 2013 Dec; Vol 208 (12), pp. 2085-94; and (Heredia A, Davis C, Amin M, Le N, Wainberg MA, Oliveira M, Deeks S, Wang L, Redfield RR. Targeting Host

Nucleotide Biosynthesis with Resveratrol Inhibits Emtricitabine Resistant HIV-1. *AIDS*, 2014 January 28, 28:317-323)

Dr. Olga Latinovic is also working with Dr. Redfield on developing different combinatorial approaches to enhance potency of agents that target HIV viral entry. They are currently using the clinically approved CCR5 antagonist Maraviroc (MVC), in combination with a fusion protein (FLSC IgG1) originally designed by Drs. DeVico, Lewis, and Gallo of the Basic Science Division, containing gp120BAL, the D1 and D2 domains of human CD4, and the hinge-CH2-CH3 region of human IgG1 fusion protein. The two reagents bind to distinct domains of CCR5, and both have relatively high anti-viral activities that strongly synergize when tested with different cell types, including primary CD4+ T cells [Figure 1]. They observed that MVC induces allosteric changes on the CCR5 molecule in a way that significantly increases FLSC IgG1 binding to the CCR5 molecule. Based on these in vitro data and preliminary in vivo data in the humanized mouse model, Drs. Latinovic and Redfield believe that the combined FLSC IgG1-Maraviroc activity may have therapeutic potential, especially in light of the extended half-life of FLSC IgG1 and industry interest in long acting antiretroviral drugs for both treatment and for pre-exposure prophylaxis.

Dr. Latinovic is also attempting to better understand the conformational states of the cellular co-receptor, CCR5. To that end, Dr. Latinovic has used different monoclonal antibodies (MAbs) that are able to distinguish different CCR5 conformations.

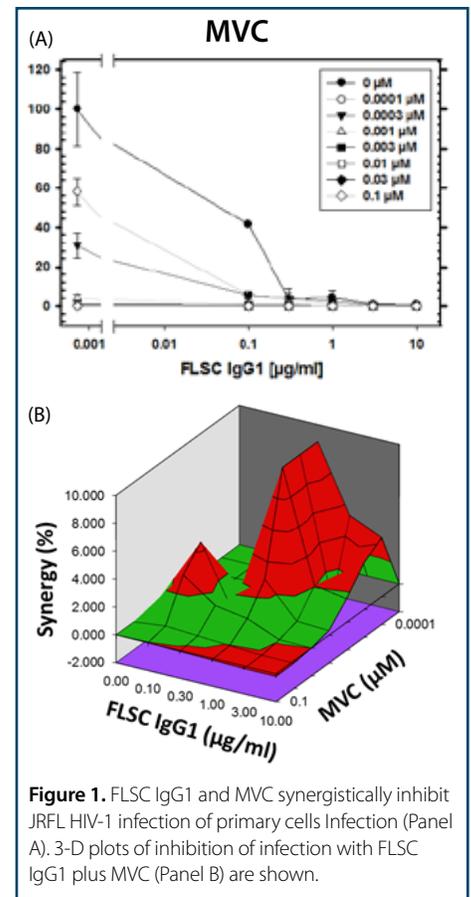


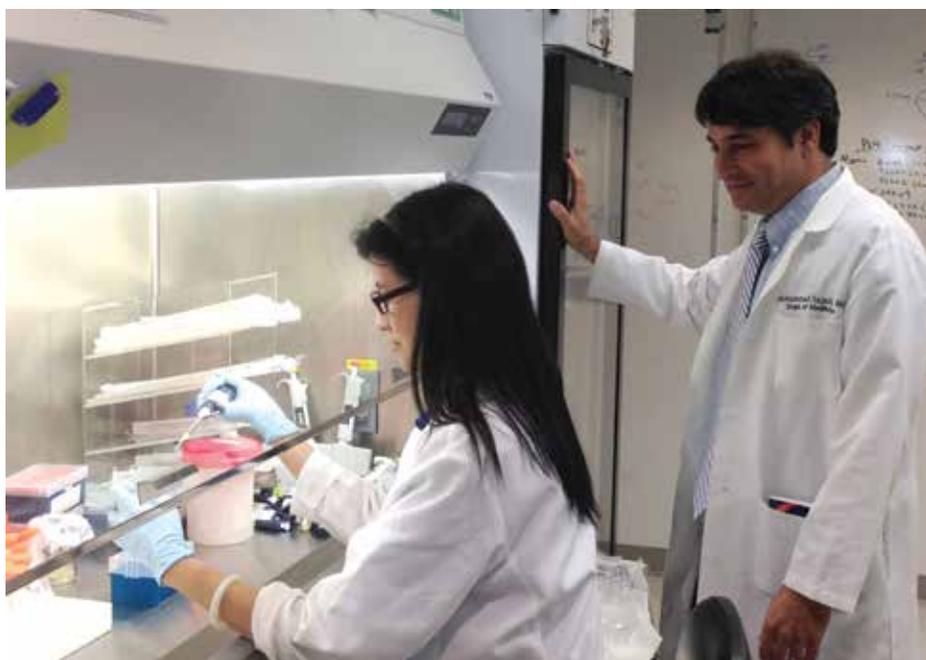
Figure 1. FLSC IgG1 and MVC synergistically inhibit JRF1 HIV-1 infection of primary cells Infection (Panel A). 3-D plots of inhibition of infection with FLSC IgG1 plus MVC (Panel B) are shown.

This will allow for utilization of them as probes, in order to distinguish different CCR5 populations. The rationale is that not all CCR5 MABs are able to reduce HIV-1 entry (and consequently, infection); suggesting that only some CCR5 populations are permissive for entry. Understanding the nature of CCR5 conformations and the identification of specific CCR5 populations, (which are dynamic and modulated by localization, G protein association, and trafficking), may lead to understanding their selective targeting by HIV-1 virions. That may hopefully facilitate development of inhibitors to block CCR5 usage by HIV-1.

Dr. Mohammad Sajadi is currently making the transition from a mentored K23 awardee to an independent investigator. As part of his mentored grants, he was able to build a cohort of Natural Viral Suppressors (NVS), HIV-1 infected patients who control viral replication in the absence of HIV therapy. Collaborating with the Division of Epidemiology, he provided molecular evidence that these NVS patients have evidence of hypermutation suggestive of effective immune pressure (Eyzaguirre L, Charurat M, Redfield RR, Blattner W, Carr J, Sajadi M. Elevated Hypermutation Levels



Kate Schneider and Dr. Olga Latinovic



Xin Ouyang and Dr. Mohammad Sajadi

in HIV-1 Natural Viral Suppressors. *Virology*, 2013; 443:306-312). Working with Dr. Talwani he used the NVS cohort to study a subgroup of HIV/HCV co-infected patients to evaluate immune defects secondary to HCV in this unique population. (Sajadi MM, Redfield RR, Talwani R. Altered T Cell Subsets in HIV-1 Natural Viral Suppressors (Elite Controllers) With Hepatitis C Infection. *AIDS*, 2013 May 8, 27: 1989-1995, PMID: 23660578).

Building on this work, Dr. Sajadi has expanded his NVS work with the addition of a cohort of HIV patients with detectable, but persistently low viral loads. He is using both of these cohorts to investigate anti HIV humoral immunity and HIV neutralization activity. He was recently awarded the 2014-15 Passano Foundation Clinician Investigator Award, for "early contribution to scientific research." He has also been successful in obtaining independent funding, with a recently successful VA Merit award titled, "Discovery of acidic epitopes for HIV-1 broadly neutralizing sero-antibodies." In addition, he has recently obtained a high priority score (7%) on his first NIH R01 grant titled, "HIV-1 acidic epitope discovery from broadly neutralizing sero-antibodies". Dr. Sajadi's efforts have benefited from his strong collaboration with Drs. Lewis and DeVico from the Division of Basic Science and Vaccines. In collaboration with them, Dr. Sajadi oversees a project to directly sequence antibodies from patient plasma, as well as studying the common characteristics

of antibodies (and gene families) that mediate the neutralization response in HIV infection.

The research in Dr. Nicholas Stamatou's laboratory is directed toward understanding how modulation of the carbohydrate content of cell surface proteins influences the functional capacity of cells of the immune system. Projects in the laboratory are focused on elucidating the role of sialic acid (N-acetylneuraminic acid) in regulating the responses of peripheral blood mononuclear cells (PBMCs) to infectious agents and inflammatory stimuli. His focus has been to study this carbohydrate as its terminal location on glycans, and its hydrophilic and electronegative features grant it an important role in regulating cellular interactions with ligands, microbes and neighboring cells, and in controlling cellular activation, differentiation, transformation, and migration. In his early work, Dr. Stamatou demonstrated that monomers of sialic acid on the surface of permissive PBMCs, as well as polysialic acid (polySia; a unique linear homopolymer of sialic acid), on a protein on the surface and/or extracellular milieu of activated CD4 T lymphocytes influence infection with HIV-1. Removal of the polySia moiety from this protein reduces productive infection by HIV-1. Thus, the enzymes that modulate expression of cell surface sialic acid content, and this polysialylated protein in particular, are potential targets for therapeutic agents

during infection. He has also shown that neuropilin-2 (NRP-2) is expressed on the surface of human dendritic cells (DC) and is polysialylated. Neuropilin-2 is a cell surface receptor for the semaphorin family of chemokines and helps guide migration of neurons on which it has been studied. The polySia moiety on NRP-2 expressed on the surface of DCs binds CCL21, a ligand for the CCR7 chemokine receptor, and influences DC migration. Thus, this multi-functional protein influences DC migration via interactions with at least these two families of chemokines. Dr. Stamatou has recently extended his initial finding by demonstrating that myeloid cell activation and differentiation that occur during cell recruitment and migration, during an inflammatory response are associated with stage-specific polysialylation of select proteins, and that polysialylation reduces macrophage capacity to phagocytize *Klebsiella pneumoniae* (Stamatou, N.M., Zhang, L., Jokilampi, A., Finne, J., Chen, W.H., El-Maarouf, A., Cross, A.S. and Hankey, K.G. (2014). Changes in polysialic acid expression on myeloid cells during differentiation and recruitment to sites of inflammation: Role in phagocytosis. *Glycobiology*, Sep;24(9):864-79; PMID: 24865221). It is expected that modifying the expression of polySia and/or carrier protein(s) in leukocytes will represent a novel approach to regulating immune responses during inflammation and infection. He has received funding from the Research and Education Foundation, Inc. (BREF) Award, VA Maryland Health Care System (VAMHCS) for the study of the function of Polysialic Acid Glycan in Immune Cell Activity.

Clinical Research and Clinical Trials

Recent major advancements have occurred in antiviral therapeutics for both HBV and HCV infection, and clinical research in HBV and HCV have been recently prioritized within the Division. This September, Dr. Shyam Kottitil and his team joined the Institute from the Laboratory of Immunoregulation of the National Institute of Allergy and Infectious Diseases, and expand our clinical and translational research activities in viral hepatitis. Together with Dr. Rohit Talwani, this group is positioned to continue to make important contributions in the field of viral hepatitis. Recently, Sreetha Sidharthan, Kerry Townsend, and Jack Masur joined this



L to R: Dr. Rohit Talwani, Sreetha Sidharthan, Kerry Townsend and Jack Masur

team of young researchers, who will work alongside of Dr. Talwani and Dr. Kottlilil. This year, Dr. Anuoluwapo Osinusi led the important evaluation of interferon free antiviral therapy in HCV patients with unfavorable treatment characteristics (Osinusi-Adekanmbi O, Stafford K, Ukpaka A, Salami D, Ajayi S, Ndembu N, Abimiku A, Nwizu C, Gilliam B, Redfield RR, Amoroso A. Long Term Outcome of Second Line Antiretroviral Therapy in Resource Limited Settings. *Journal of the International Association of Providers of AIDS Care (JIAPAC)* 2014 March 25). Dr. Talwani has continued to expand the IHV's clinical trial activity in the area of therapeutics for viral hepatitis. In partnership with the NIAID intramural program, the IHV has collaborated on several key interferon sparing phase 1 and 2 hepatitis C clinical trials (SPARE GS7977+RBV in treatment naïve HCV; ERADICATE HIV/HCV treatment with GS7977+GS5885; and SYNERGY GS7977+GS5885 in HCV mono-infection). In addition, Dr. Talwani is the Principal Investigator on a number of additional industry sponsored clinical trials at the IHV Clinical Research Unit (ACTG 5294-Phase 3 HCV/HIV; Vertex 950-115-Phase 3 HCV/HIV; BI 124.20 phase 3 HCV ; BI 124.20 phase 2 HCV; MK 047 phase 2 HCV). Dr. Talwani is also the PI on the evaluation of a new agent for the treatment of HBV (GS 110 phase 3 HBV). Dr. Talwani was recently awarded a bench to bedside NIH award, in collaboration with the NIAID, evaluating novel anti-fibrotic therapeutic strategies. The Clinical Division is excited about the expanded clinical research activity that will come in the years ahead.

Dr. Charles Davis and Dr. Bruce Gilliam serve as the co-directors of the IHV Clinical Research unit. Active trials are ongoing in the therapeutic areas of HIV, HBV, and HCV. Preference is given to investigator initiated trials and trials of investigational new therapeutic agents for HIV and Hepatitis C. Dr. Gilliam recently completed a novel antiviral strategy trial using Raltegravir and Maraviroc in HIV treatment naïve patients, as a proof of concept of a NRTI/PI sparing regimen. Dr. David Riedel and Dr. Gilliam recently initiated a follow up study evaluating this regimen as a simplification regimen with a focused goal to also evaluate a hypothesis related to the impact of ARV agents on telomere length, and telomerase activity, which may have an impact on the occurrence of cancer, and aging co-morbidities associated with an increased frequency in HIV infection.

Dr. Gilliam also serves as the Principal Investigator on ongoing studies related to the evaluation of the IHV's prototype preventive HIV vaccine developed by Drs. Gallo, DeVico, and Lewis, along

with Profectus Biosciences. Pre-clinical toxicity studies are being completed, with the phase 1 safety and immunogenicity trial initiation projected for the 2nd quarter of 2015.

In addition, valuable cohort studies are maintained by the Clinical Research Unit. These include a cohort of patients who naturally suppress HIV without ARV treatment; a cohort of patients who express HIV but persistently control HIV expression to low levels (> 50 but < 5,000 copies/ml); a cohort of HIV patients with cancer; a cohort of perinatally HIV infected patients who are now adults; a cohort of HIV infected patients characterized by HIV proviral copy number; a cohort of HIV infected post solid organ transplant patients, and a cohort of HIV/HCV co-infected patients. Each of these cohorts continues to provide valuable clinical material for hypothesis generating investigations by members of the IHV.

Clinical Research Focused on HIV co-mortalities

The research of Dr. David Riedel, a K12 awardee, is focused on HIV related cancer, and in particular, trying to understand the biologic differences between cancers in HIV infected patients compared to those in HIV uninfected patients. His current project centers on elucidating the involvement of the CCR5 axis in malignant progression of cancers in HIV-infected patients. It is important to understand the reasons leading to advanced stage cancer at diagnosis, so that new strategies can be developed for earlier detection and treatment, so as to improve the poor oncologic outcomes in HIV infected patients with cancer (Riedel DJ, Mwanji EI, Fantry LE, Alexander C, Hossain MB, Pauza CD, Redfield RR, Gilliam BL. High cancer-related mortality in an urban, predominantly African-American, HIV-infected population. *AIDS* 2013;27:1109-1117).

One of the most important clinical problems facing HIV-infected persons today is the rising rate of cardiovascular disease (CVD). Most of the literature describing risk factors and outcomes for CVD include data on HIV infected patients who are on older antiretroviral regimens that may have higher atherogenic potential. There is also a particular dearth of literature on women and African Americans who are often underrepresented in existing studies.

Dr. Shash Bagchi's research on cardiovascular health in HIV infected patients aims to evaluate the change in coronary heart disease risk, assessed by the Framingham risk score (FRS), in

HIV-infected patients entering the Evelyn Jordan Center (EJC) clinic from June 1, 2008 through December 31, 2012, and to identify socio-demographic and clinical factors that are associated with the change of the FRS in that time period. The study will also determine if specific antiretroviral medications were associated with the change in FRS in this patient population. Describing the cardiovascular health of patients at the EJC in the era of newer ART will not only make a contribution to the current literature, but also will help identify relevant research questions about CVD in the current era of HIV therapeutics.

Studies of chronic viral infections have shown that changes in T cell function and phenotype correlate with changes in antigen burden. Dr. Kapil Sahara has been studying the expression of inhibitory molecules (CTLA-4, PD-1), maturation markers, and cytokine profiles of TB-specific CD4 T cells in persons with different stages of TB infection, to determine whether mycobacterial burden correlates with functional and phenotypic changes in TB-specific CD4 T cells. Previous work during his post-doctoral fellowship at the NIH demonstrated that TB-specific CD4 T cells from HIV-TB co-infected individuals had reduced expression of CTLA-4 and PD-1, following treatment of TB disease. Furthermore, these cells had a less differentiated maturation profile, and had higher frequencies of cytokine subsets producing IL-2 following TB treatment. Similar trends were noted when comparing the profile of TB-specific CD4 T cells in persons with active and latent TB infection. Despite these differences, it remains unclear whether such changes in the immunological profile of TB-specific CD4 T cells can serve

as biomarkers of TB disease progression. To answer this, I am collaborating with researchers from the Infectious Disease Clinical Research Program (IDCRP) of the Uniformed Services University of the Health Sciences (USUHS) to study functional and phenotypic changes in TB-specific CD4 T cells in a cohort of individuals with latent TB infection, who have progressed to active TB disease. By studying these parameters longitudinally, we will be able to determine whether changes in TB-specific CD4 T cell function or phenotype precede the clinical diagnosis of active TB disease, and hence serve as biomarkers of disease progression.

Clinical Program

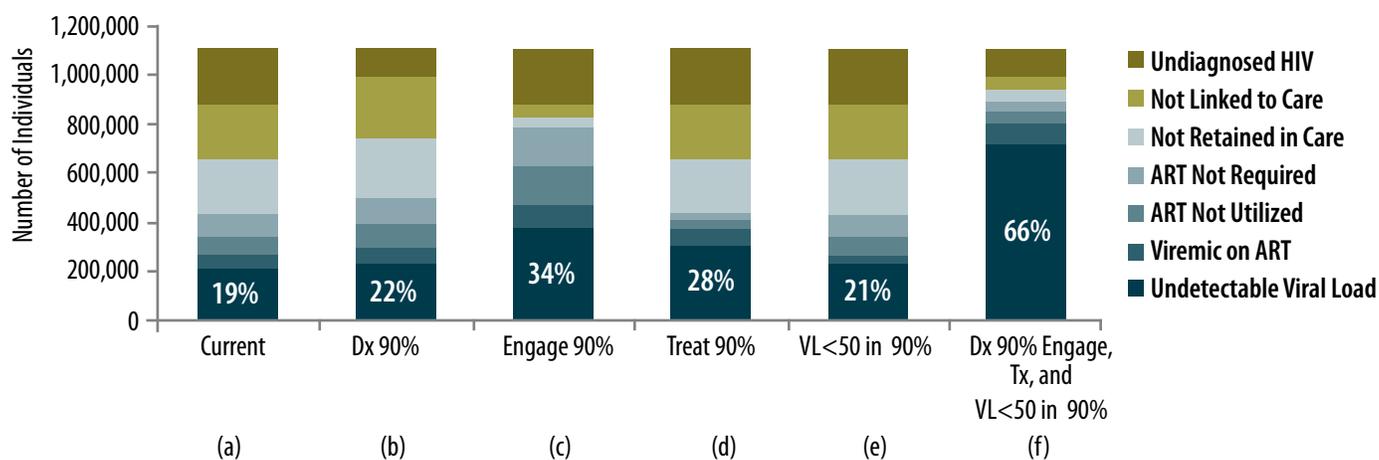
The IHV continues to operate a robust clinical program serving the citizens of Maryland and beyond, by providing care to more than 5,000 patients. The IHV, in partnership with UMMS, now operates ambulatory care services for patients living with HIV at the Evelyn Jordan Center Downtown campus (directed by Dr. Lori Fantry); the Family Health Center Midtown campus (directed by Dr. Mariam Khambaty), the JACQUES Clinic at the Midtown campus (directed by Derek Spencer, NP) and the ID Clinic at the Midtown campus (directed by Dr. Janaki Kuruppu). In partnership with the Baltimore VA, the IHV provides clinical care at the VA in the HIV/ID clinic directed by Dr. Anthony Amoroso, and in the Hepatitis Clinic, directed by Dr. Rohit Talwani. In addition, this fall the IHV, in partnership with UMMS, will open a clinic dedicated to the treatment of HBV and HCV at the Midtown campus under the direction of Dr. Talwani, as well as a new anoscopy clinic at Midtown to improve care for patients with HIV and HPV co-infection. Finally, IHV faculty also provide acute care to hospitalized patients living

with HIV and other complicated infectious diseases on two inpatient units located at the downtown UMMS campus.

This year the UMMS began to transition specific programs targeted for expansion to its Midtown campus location. The IHV's clinical care programs, along with other infectious disease clinical programs, have been defined as anchor programs for the new University of Maryland Midtown ambulatory care center. One of the key IHV clinical programs is the JACQUES Initiative.

In 2011, Gardner identified gaps in the continuum of HIV care that depict poor engagement and retention in care. These gaps include patients not tested for HIV, not linked or retained into care, and those not on or non-adherent to antiretroviral (ART) medications. Nationally, only 19-25% of persons living with HIV are virally suppressed. Gardner also presented a model in the same article which indicated that improvement in any single component of engagement in care will have minimal impact on the proportion of HIV-infected individuals in the United States with an undetectable viral load. Improvement in the entire continuum of engagement in care is required for test-and-treat strategies to substantially increase the proportion of persons with undetectable viral loads (Gardner EM, 2011). Considering the impact of viral suppression on reduced mortality, morbidity and transmission, closing the gaps in the continuum of care is essential to stopping the epidemic of HIV in the United States. Furthermore, in the past five years, policy has aligned with this science to support a goal, which 20 years ago was unimaginable.

This evidence has motivated the JACQUES Initiative (JI) to approach comprehensive





2013–2016 Infectious Disease Fellows

HIV care delivery through four key components that will more effectively identify, link, and retain our citizens in high quality HIV care and supportive services, providing more opportunities to suppress virus and consequently prevent the spread of HIV. Community engagement is the cornerstone of the JI approach, and involves the faith-based community, the academic and clinical campuses of the University of Maryland and other local providers, our local policy makers, as well as collaboration with the arts and entertainment industry. These four components are: 1) Outreach and Testing: JI is working with an interdisciplinary team at UMMC to create a standardized approach to routine HIV testing and linkage to care. In 2013, UMMC began routine HIV testing in the Department of Medicine. This approach yielded diagnosis of 15 new positives, and over 80 previously diagnosed positives that were out of care at the time of their inpatient admission. Through a collaborative effort, these individuals were linked to HIV care and supportive services. This approach is being expanded in 2014 to the Department of Surgery and the Emergency Department. These efforts are complemented by targeted community-based outreach in areas disproportionately impacted by HIV. 2) Linkage to Care: The JACQUES Initiative's five day per week, no appointment necessary Connect 2 Care Clinic sees patients who are newly diagnosed, or out of HIV care that self-refer, or are encountered through outreach efforts. The multidisciplinary JI staff will assess the patient's medical and psychosocial needs on the spot, and fulfill immediate needs. The patient is linked to JI, or another HIV clinic that best suits their needs. This model is successful in linking 70% of new and previous positives to HIV care and treatment. 3) Early Treatment: The JI clinic uses a highly supportive approach to aim for high rates of retention and viral suppression. This approach utilizes a multidisciplinary approach, where all levels of staff are involved in the plan of care of the patient. 4) Adherence and Retention: The JI Treatment Adherence Center (TAC) includes daily, weekly, and monthly observed therapy at an integrated pharmacy for patients who experience anticipated barriers to successful antiretroviral therapy. JI's TAC staff, including a licensed pharmacist, HIV providers,

and treatment coaches, liaise with each patient's HIV provider to monitor adherence regularly. A daily no-show list assures communication between JI's TAC staff and the patient, when a patient does not present for a scheduled medication pick up. JI is also engaged in incorporating the latest prevention evidence into practice. JI is working with campus and policy partners to develop strategies to implement pre and post exposure prophylaxis in non-occupational settings, in addition to engaging high-risk HIV negative citizens into the medical care system to increase education, and utilize pharmaceutical risk reduction resources.

Medical Education

The Division of Clinical Care and Research is deeply engaged in medical education at all levels; teaching medical students, medical residents, fellows in infectious diseases, state health care professionals, and health care professionals in sub Saharan Africa and the Caribbean.

All University of Maryland medical students are enrolled in the Host Defenses and Infectious Diseases (HDID) course during their 2nd year of medical school training. This 10 week course incorporates faculty from various departments, divisions, and institutes in the School of Medicine to include the IHV, Microbiology, Infectious Diseases, Transplant Surgery, the Center for Vaccine Development (CVD), Emergency Medicine, Pediatric Infectious Diseases, Epidemiology, and Rheumatology, just to name a few. Dan Schulze, PhD, from the Department of Microbiology, and Devang Patel, MD, from the IHV Clinical Division are the course directors, and many of the IHV faculty from both the Basic Science and Vaccine Division, and the Clinical Division participate in teaching the course.

The IHV in partnership with the Division of Infectious Disease offers a 2 year fellowship program in infectious diseases with the opportunity to extend 1-3 more years for post doctoral clinical research training. This year the Division has a group of 14 first and second year fellows, plus 3 additional fellows, Dr. Bork, Dr. Husson, and Dr. Tang, who elected to complete a third year of advanced clinical/clinical research training.

The IHV clinical programs have developed one of the largest cohorts of HIV patients with cancer, as well as post solid organ transplant patients with chronic HIV infection. Dr. Jacqueline Bork's and Dr. Jennifer Husson's efforts will focus on immunocompromised hosts; Dr. Bork with HIV and Cancer, and Dr. Husson with a focus on HIV and transplantation. Additionally, building on the expansion of the IHV's HBV/HCV clinical research program, Dr. Lydia Tang's efforts will focus on viral hepatitis therapeutics.

The IHV clinical program oversees the University of Maryland Local Performance Site of the Pennsylvania/Mid Atlantic AIDS Education and Training Center (AETC) provides HIV/AIDS education, consultation, technical assistance, and resource materials to health care professionals throughout the State of Maryland. We are also committed to improving the HIV knowledge and education of providers across the state. Led by Dr. Redfield and Dr. Bruce Gilliam, the AETC is entering its 13th year of funding and activity at the IHV/University of Maryland as a leading education outlet for the greater Baltimore and Mid Atlantic regions.

International

The international activities of the Clinical Division continue to grow under the direction of Deus Mubangizi, with a focus on building sustainable clinical capacity through advanced clinical training programs in HIV and other infectious diseases, and building

operational research capacity within our African and Caribbean institutional partners. The Clinical Division continues to make broad strides toward improving medical education at pre and in-service levels, as well as patient care outcomes in countries across Sub-Saharan Africa and the Caribbean. As an awardee of the NIH funded MEPI grant, the IHV, in partnership with the University of Nairobi, established the first clinical skills lab in Kenya to be accredited by the Society for Simulation in Healthcare. In addition, 4 fellows of the University of Nairobi master's program in implementation science were hosted at the IHV/UMB for three month trainings in research methodologies with mentorship for identified research projects by key IHV/UMB faculty and staff. In Rwanda, the IHV has developed a CDC funded year long curriculum in Infectious Diseases for post graduate medical training. This Postgraduate Diploma in Infectious Diseases and HIV Medicine for the National University of Rwanda (NUR) was formally approved by the President and Cabinet of the Government of Rwanda in 2013. In Zambia, the IHV's partnership with the University of Zambia is in its sixth year of offering a 18 month program in infectious diseases training for physicians, and in its second year of a NIH funded 4 year internal medicine infectious diseases training program. In Tanzania, the IHV collaborated with the Catholic University of Health and Allied Services of Bugando to host a national symposium in March 2014, as

part of the 2014 scientific updates series. In the Caribbean, the IHV has developed CDC funded post graduate infectious disease training programs in Haiti and Guyana, which are being successfully transitioned to the full local ownership and management of our key partners in each country.

This year the Clinical Division completed CDC funded nation-wide surveillance studies of antiretroviral drug resistance in both pediatric and adult patients in Kenya and Tanzania. Also, while working with the CDC in Kenya, the IHV rolled out Kenya's first inner city methadone treatment program for drug addicts within Nairobi. In addition, the IHV designed and implemented a model for laboratory service which has now been scaled up by the Kenyan Ministry of Health to the entire country.

In Tanzania, the Clinical Division received additional funding from the World Health Organization (WHO) to implement innovative approaches to TB case finding and the evaluation of molecular technology to improve TB diagnosis in rural Tanzania. Also in West Africa, the IHV recently received additional WHO funding for a novel program reaching wandering herdsmen and homeless children with TB diagnostic and treatment services in Nigeria. Implemented in collaboration with the WHO, this program will provide valuable insight regarding best practices for reaching these underserved populations.



L to R: Dr. Jackie Bork, Dr. Lydia Tang and Dr. Jennifer Husson





Division of Epidemiology and Prevention

The Division continues to implement research projects and research training largely focused in Nigeria, built upon its established PEPFAR infrastructure but is also targeting Baltimore-based studies, particularly among underserved populations experiencing negative health disparities and key populations at high risk for HIV. Currently, Dr. William Blattner and the six faculty members in the Division implement fourteen research grants with an annual direct funding level of over \$4.6M, seven training grants with an annual direct funding level of almost \$4M and five implementation grants at an annual direct funding level of \$54.4M.

Studies with Key HIV-affected Populations

The TRUST Study (multi-PI leadership Drs. William Blattner and Man Charurat) is an NIH-sponsored R01 implementation science research grant investigating optimal strategies for addressing gaps in

treatment and prevention services among a key population, men who have sex with (MSM) in Nigeria. The project engages an innovative research strategy to apply network theory to improve recruitment of marginalized and highly stigmatized MSM and to understand how social and sexual networks impact behavior and treatment and prevention outcomes. As Nigeria has a “mixed” epidemic where HIV transmission is driven and sustained by both the general population and key populations such as MSM, the 10-fold HIV prevalence and high incidence among the MSM community provide an important target



Dr. William Blattner



Dr. Man Charurat

for innovative interventions. The January 2014 decision by Nigerian President Goodluck Jonathan to sign an anti-gay law prohibiting public show of same sex relationships and up to 10 years imprisonment for persons or groups that witness, abet and aid the solemnization of a same sex marriage or supports the registration, operation and sustenance of gay clubs, societies, organizations, processions or meetings in Nigeria has had significant negative impacts in blocking access of MSM for much needed HIV

services. Fortunately, Professor John Idoko, the head of Nigerian National Agency for the Control AIDS and the Chairman of the UM-IHV Fogarty Training Advisory Group, declared on January 20,

2014 that the law shall not affect healthcare center delivering care to this population allowing the TRUST clinic to continue to provide services. A scientific oral presentation (“Discrimination among Men Who Have Sex with Men in Nigeria: Assessment of the immediate HIV-related impact of anti-gay laws”) was made at the 2014 International AIDS Society Meeting that documented the negative impacts on prevention services that this draconian law has had on client service uptake. Despite this barrier the TRUST project has enrolled 882 participants with 51% of all participants testing positive for HIV at the clinics in Abuja and Lagos as presented at the recent AIDS conference (“Respondent-driven Sampling as an Implementation Science Approach to Accrue Men who have Sex with Men (MSM) into a Prospective HIV Prevention, Treatment, and Care Study in



Dr. Rebecca Nowak

Trust Study Prevalence and Incidence of Sexually Transmitted Infections

Total	Prevalence (%)	Incidence/100 person-years among HIV+	Incidence/100 person-years among HIV-
HIV	44.1%	HIV Incidence Rate= 9.8/100 person-years	
Rectal Gonorrhoea	21.1%	40.3 (20.2–80.7)	29.0 (7.2–115.9)
Rectal Chlamydia	12.2%	18.5 (7.3–49.4)	14.0 (2.0–99.6)
Syphilis	0.7%	10.2 (1.4–72.5)	3.8 (0.5–27.1)
Hepatitis B (HBsAg)	8.8%	35.0 (17.5–70.0)	31.5 (10.2–72.5)

Nigeria"). Participants who test positive for HIV are immediately enrolled in treatment preparation to evaluate the impact of Treatment as Prevention (TasP). In longitudinal follow up, clients in the study exhibit high incidence rates of multiple sexually transmitted diseases including a 9.8% annual HIV incidence. An important new finding is that 57% of the MSM participants report sexual relationships with women as well as men representing an important "bridge" to the general population epidemic, a research topic to be pursued in future research submissions including studies of risk for high risk human papilloma virus, the cause of cervical cancer among female partners a focus of new faculty member Dr. Rebecca Nowak. Lessons learned in the Nigeria project are a focus of future research projects planned for study in Baltimore where MSM represent a major driver of the local epidemic.



Mr. Charles Mensah

HIV Treatment, Care and Support Program

While PEPFAR funding has shifted from the University to indigenous organizations, the Division of Epidemiology and Prevention benefits from the ongoing support of IHV-Nigeria by the CDC through their funding of the ACTIONPlusUp grant led by Dr. Patrick Dakum and Mr. Charles Mensah that has since 2004 cumulatively established 167 antiretroviral treatment, 950 PMTCT venues, 193 TB centers and 1030 testing sites to provide HIV testing to over 3.2 million, care and support to 283,000 individuals, treatment to over 183,000 patients including 10,000 children and 8,000 pregnant women in Nigeria. This clinical care infrastructure has been a vital resource for the research mission of the Division. Additionally faculty from the Division provide technical support to ACTIONPlusUp and also receive direct funding for several technical assistance

grants that support multiple partners and the Government of Nigeria.

Dr. Dakum is also Principal Investigator of IHVN's Global Fund Multi-Drug Resistant TB (MDR TB) Grant which seeks to strengthen MDR TB prevention and control in Nigeria through developing MDR TB treatment centers and diagnostic laboratories and capacity building for healthcare workers to diagnose and treat MDR-TB. To date, 25,179 clients suspected of drug resistant TB have been tested and 706 MDR-TB patients placed on second-line anti-TB drugs.

Studies of ARV Resistance

Nigerian Researcher, Dr. Nicaise Ndembi, along with Drs. Abimiku and Dakum, have conducted several studies of adults on treatment have evaluated the challenges of emerging drug resistance to antiretroviral drugs (ARV). One of our analyses of 175 samples of patients with elevated viral load showed that Tenofovir-based regimens were less



Dr. Nicaise Ndembi

likely to have multiple nucleoside reverse transcriptase inhibitor (NRTI) mutations compared to other regimens and are more likely to have more active NRTI drugs available for second-line regimens. In another study investigated whether patients were appropriately receiving second-line ART. Of 56 with putative virological failure 9 contained no drug resistance mutations while 32% had lost first- and second line regimens options for currently available drugs. The only option for these patients will be access to next generation drugs that are currently not available at reduced pricing supported by PEPFAR. Employing regular viral load testing and applying treatment support interventions for those failing to take medication and when early drug resistance is detected employing viral genotype to guide therapy has the potential for reducing the need for access to next generation medications.

Monitoring ARV Resistance in Nigerian Children

In 2013, 60,000 Nigerian children were infected with HIV. Nigeria has the highest number of children with the virus in the world, according to the latest report by the United Nations. Furthermore, as countries like Nigeria move to universal access to ART, it is imperative that HIV drug resistance is monitored particularly among children who are more vulnerable. In a study conducted by Drs. Nadia Sam-Agudu and Nicaise Ndembi, among 100 HIV-infected children starting ART 21.4% had pretreatment HIV drug resistance NNRTIs meaning that a substantial number of children starting treatment are receiving sub-optimal treatment a finding that is helping guide national ART policies for pediatric treatment in Nigeria.



Dr. Nadia Sam Agudu

The INSPIRE-MoMENT Study

With funding from the World Health Organization through the INSPIRE initiative, Dr. Nadia Sam Agudu is the Nigerian PI for this multi-country program to identify best strategies for implementing effective Prevention of Mother to Child Transmission (PMTCT). In

Nigeria the prevalence of HIV is relatively low (3.6%) among pregnant women and with a high infant mortality from Malaria, and infant diarrhea the emphasis of resources is not on HIV prevention. To address this issue, Dr. Sam Agudu investigates how to close the gap in PMTCT uptake by adapting a previously developed approach from South Africa, engagement of mother mentors to support pregnant HIV positive mothers in accessing suitable preventative intervention and monitoring of the infant for evidence of infection. Mother mentors are HIV-positive women who have successfully engaged the PMTCT cascade and who now are hired to support other women. The study is a matched prospective cohort to investigate the best option for engaging Mother Mentors in a low prevalence environment. The study has completed its qualitative phase for identifying best practices and the intervention phase has enrolled 960 participants in prospective follow up.

The NeuroAIDS Study



Dr. Blattner and Dr. Ernest Ekong

Correlates of Monocyte-Associated Virus in HIV Neurocognitive Impairment, a NIH-funded research projects is co-lead by Drs. William Blattner and Walter Royal, a faculty from the Department of Neurology and HIV collaborator. This prospective longitudinal cohort study is designed to determine the frequency and nature of neurocognitive impairment among treatment naïve Nigerian HIV positive subjects and to identify clinical, laboratory and virologic risk factors and progression over time. A particular focus is on studying the

relationship of monocyte-derived virus from these patients in relationship to neurocognitive impairment. A total of 336 subjects have been recruited, 221 cases (treatment-naïve HIV-1 positive) and 115 controls (HIV-1 negative) all of which have had their baseline visit and on neuropsychological testing approximately 20% show evidence of mild neurocognitive impairment. Virological analysis is currently ongoing. Preliminary analysis of immune markers documents that specific markers of monocyte activation are associated with this neurocognitive impairment.

The Strategic Timing of AntiRetroviral Treatment (START) Study

Dr. Ernest Ekong, leads The Strategic Timing of Anti-retroviral Treatment (START) study a multi-country, randomized study funded by the NIH through the INSIGHT network that aims to determine whether starting ART early (before CD4 drops to < 500 cells/mm³), rather than waiting until CD4 drops to < 350 cells/mm³ (when evidence from randomized trials supports starting ART), reduces the occurrence of serious morbidity and mortality among HIV-infected persons. The START began enrollment in Nigeria in September 2012 and initial results show a greater proportion of participants beginning ART in the early arm report good adherence and achieving undetectable viral load (< 20 copies/ml) within 6 months of ART initiation and a retention rate of close to 100%. The results from this study are important for informing international treatment guidelines in the context of PEPFAR and other expanded treatment access programs.

The leDEA Network

The leDEA collaboration is a multi-country cohort study funded by the National Institutes of Health and comprises of 17 adult centers and 11 pediatric cohorts in 10 countries. Dr. Man Charurat is the PI for the Nigerian site through the West Africa Database on Antiretroviral Therapy (WADA) collaboration. WADA is a unique collaboration among several clinical centers in West Africa with several years of experience in the care and treatment of people living with HIV and

AIDS. The overall goal of WADA is to conduct epidemiological research on the prognosis and outcomes of HIV-1 and HIV-2-infected adults, pregnant mothers, and children and HIV- exposed infants in care at these collaborating clinical centers. The Nigerian adult cohort has a total of 16,621 people living with HIV with 9,124 at University of Abuja Teaching Hospital and 7,497 at University of Benin Teaching Hospital. A multi-regional leDEA study on 'Survival among HIV-infected Individuals with Kaposi's Sarcoma in Sub-Saharan Africa in the Era of Potent Antiretroviral Therapy' is also currently ongoing at 2 Nigerian sites in collaboration with faculty member Dr. Clement Adebamowo.

Studies of Breast Milk

Dr. Alash'le Abimiku is the Nigerian PI for this multi-country Canadian Institutes of Health-funded study of breast milk from HIV-infected and uninfected women. The study is evaluating levels of soluble Toll-Like Receptor 2 (sTLR2),



Dr. Alash'le Abimiku

pro-inflammatory cytokines and viral antigenemia. Results, thus far, show that breast milk from HIV-infected women have significantly higher levels of sTLR2 than uninfected breast milk. Further, sTLR2 levels correlated with HIV-1 p24 and interleukin (IL)-15, thus suggesting a local innate compensatory response in the HIV infected breast. The study also demonstrated that sTLR2 physically interacts with p17, p24 and gp41 and inhibits HIV-induced nuclear factor kappa-light-chain-enhancer of activated B cells activation, and inflammation. Importantly, binding of sTLR2 to HIV-1 proteins inhibited a TLR2-dependent increase in chemokine receptor 5 expression, thus resulting in significantly reduced HIV-1 infection. These results indicate novel mechanisms by which sTLR2 plays a critical role in inhibiting mother-to-child HIV transmission.



Dr. Alash'le Abimiku receives biorepository research project award.

HIV Vaccine Preparedness Studies

This Canadian HIV Vaccine Initiative in Nigeria is led by Dr. Alash'le Abimiku. A cohort of 534 HIV-exposed, seronegative individuals are in their second year of follow up to understand risk factors for infection from ongoing collection of behavioral data, medical history and physical examinations. Results show consistent condom use at baseline was 40% and remained low during the 2-year follow up reaching only 47%. 27 of the women (10.5%) became pregnant during the course of the study. HIV incidence was low at 1.1% but Hepatitis C prevalence was significant at 7%. For vaccine trials the finding that 40.3% of participants have hypertension is a major barrier for enrollment particularly in early phase trials that require medically health volunteers.



Dr. Clement Adebamowo

Genomic Research in Cancer and Viral Diseases

The Human Heredity and Health in Africa H3Africa is a major focus of the NIH and Wellcome Trust for advancing the capacity of African scientists to be at the forefront of the genomics revolution. Dr. Clement Adebamowo received one of seven collaborative research center grants to form the African Collaborative Center for Microbiome and Genomics Research (ACCME) at IHV-Nigeria. The proposed

research applies genomic analysis of the HPV virus, the vaginal microbiome and the host genome to apply an integrative epidemiological approach to investigate how these factors contribute to persistent high risk HPV infection on the path to cervical cancer. The study also applies epigenomic and somatic cervical cancer genomics analyses to understand the role that these factors play in pathogenesis. The study is being implemented in Abuja, Nigeria and Lusaka, Zambia affording an opportunity for cross cultural comparative studies given the higher rates of cervical cancer in Zambia compared to Nigeria, despite high rates of high risk HPV exposure in both locales. Enrollment is currently above 120% of the

target and transfer of HPV DNA based testing technology from collaborating partner in the Netherlands has been successful. ACCME has conducted 2 training programs, one on Manuscript and Scientific Writing, and Introduction to Biostatistics using SAS and R. These courses were attended by participants from other African countries and the United States.

IHV-Nigeria H3Africa Biorepository (I-HAB)



H3 Africa Biorepository

Dr. Alash'le Abimiku received one of the four biorepository research projects awarded through NIH H3Africa initiative to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. The I-HAB has been implemented according to International Society for Biological and Environmental Repositories (ISBER) best practices. I-HAB is now positioned to support multiple centers among H-Africa research projects and research centers in the conduct of genomics research. The biorepository is set up to ensure the safety of all specimens with a highly secured environment. I-HAB is currently supporting multiple researchers in the collection, processing, storage and shipping of samples. Dr. Abimiku is taking leadership within the H3Africa consortium and among its investigators on developing an integrated Laboratory Information Management System for promoting seamless access of information on stored samples and exchange of information between repositories and investigators.

Nigerian Alliance for Health System Strengthening

The CDC-awarded Nigerian Alliance for Health Systems Strengthening (NAHSS) grant is led by Dr. William Blattner and implemented by Ms. Chinenye Ugoji. NAHSS is a technical assistance award designed to support the Nigerian Federal Ministry of Health (FMOH) in the development of a national Quality Management (QM) program. Since the



Ms. Chinenye Ugoji

NAHSS award in 2012, the Division has successfully engaged the leadership of the FMoH and all implementing partners in Nigeria, 10 State Ministries of Health (SMoH), NEPWHAN and other relevant stakeholders in Nigeria in the development of a unified and nationally accepted QM Program (NigeriaQual). The NAHSS project has built capacity of more than 1500 healthcare, FMoH, SMoH and IP personnel for different components of NigeriaQual implementation. Of these, 100 are certified Master Trainers who support the amplification of NigeriaQual in the country. NigeriaQual software was developed to support local capacity for implementing NigeriaQual and using the data to guide local site quality improvement and the capacity of government officials to use information to guide “smart investment” of health care dollars for maximal impact.

SHaRING



Group discussion exercise during SHaRING Training

Under the leadership of Dr. Alash'le Abimiku with funds from the CDC PEPFAR, the Division has collaborated with the Nigerian Federal Ministry of Health and Federal Ministry of Education, the Medical Lab Science Council of Nigeria, the Association of Medical Laboratory Scientists of Nigeria, and the two US agency: Association of Public Health Laboratories and the Clinical and Laboratory Standards Institute to create a program for laboratory quality improvement. To date SHaRING has built the capacity of 19 universities and 47 colleges of health technology offering medical laboratory science through training of the faculty in adult learning principles, Good Clinical and Laboratory Practice, Quality Management System and

advanced HIV/TB molecular techniques. Shown in the figure are the faculty engaged in training.

CADRE

The Capacity Development for Research into AIDS Associated Malignancies (CADRE) is a National Cancer Institute funded training grant to Dr. Clement Adebamowo to build capacity of Nigerian researchers to conduct AIDS Associated Malignancy Research. Since the grant was awarded 3 years ago, CADRE has trained 26 pre-doctoral and post-doctoral trainees. These trainings have contributed to the resuscitation of cancer registration in Nigeria with the formation of the Nigerian System of Cancer Registries. There are now 6 Population Based Cancer Registries and 21 Hospital Based Cancer Registries in Nigeria as a result of this training. After a more than 30 years absence, Nigerian cancer registration data is now being collated as part of the World Health Organization Cancer data and contributed to the Globocan 2012 database. So far 3 papers on cancer registration in Nigeria have been published and 7 more are in various states of publication. Another outcome of this grant is the conduct of research training on vaginal microbiome, high-risk HPV infection and risk of cervical cancer. This training generated the pilot data that led to the successful competition for a \$4.25 million H3Africa NIH grant to the IHV-Nigeria and a second grant application to the NCI/NIH that is currently being reviewed. CADRE is also supporting the development of clinical trials capacity at the National Hospital, Abuja, Nigeria in



AITRP trainee researching pediatric drug resistance

order to qualify this site as an international site for AIDS Associated Malignancies research.

AIDS International Training and Research Program from the NIH Fogarty Center



AITRP Trainee Performing Sequence Analysis

Funded since 1998 the IHV-UM AITRP research training grant has been led by Dr. William Blattner to develop research capacity within IHV-Nigeria and partner universities. The focus has been on HIV/AIDS and viral cancer research and related infections and outcomes. This has led to the growth of a sustainable research platform within IHV-Nigeria. Engaging a mentorship approach Division faculty have partnered with local investigators and trainees to conduct a variety of research training projects that have often spawned new research funding from NIH, CDC, WHO and other international research foundations. In the past decade, twenty one students have received advanced degrees (MS, MPH or PhD) and twenty four long-term post-docs have been trained in HIV research. Currently, we have three PhD candidates, two MPH candidates and one Post-doc conducting research in the areas of NeuroAIDS, Pediatric HIV, Lassa Fever/HIV, Prevention of Mother to Child Transmission, Adolescent HIV, and HIV transmission to the female partners of Men having Sex with Men.



IHV Supports Global Virus Network (GVN) Developments



The Institute of Human Virology (IHV) at the University of Maryland School of Medicine, led by Dr. Robert Gallo, has been working to create, develop and launch the Global Virus Network (GVN). Since the HIV/AIDS outbreak of the early 1980's, it has been Dr. Gallo's goal 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.



Drs. Kurth, Gallo and Hall co-founded the GVN at the Italian Embassy in Washington, DC in 2011.

GVN was officially co-founded in 2011 at the Italian Embassy in Washington, D.C. by Dr. Gallo and his colleagues William Hall, MD, PhD, and the late Reinhard Kurth, MD. Dr. Hall is Chair of Medical Microbiology and Director of the Centre for Research in Infectious Diseases at University College Dublin's (UCD) School of Medicine and Medical Science in Dublin, Ireland, and 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. At the inaugural meeting in DC, attendees from more than a dozen countries affirmed and ratified GVN's goals and objectives. Since that three day meeting, GVN worked to become incorporated as a non-profit, 501(c)(3) organization, which was granted by the U.S. government in March 2013. In 2012, GVN appointed Sharon Hrynkow, Ph.D. as President of the GVN. Its members represent

expertise covering every class of human virus, and comprise more than 20 countries. GVN has held subsequent meetings in Ireland, Italy, USA, Germany, and Russia. GVN will hold its next meeting in Beijing, China in May 2015.

In 2013, nearly two dozen journalists participated in GVN's first Virology Workshop for Journalists in partnership with St. George's University (SGU) and the Windward Islands Research and Education Foundation (WINDREF) in Grenada, West Indies January 30—February 1 to minimize the glaring information gap between medical researchers and mainstream media. On World Health Day, GVN announced the formation of the GVN Chikungunya Task Force, which focuses on issues related to more rapid identification of infections, improved treatment options and development of an effective vaccine. GVN also formed the GVN HTLV Task Force to speed the pathway to discovery of drugs that will stop virus transmission or progression from infection to disease, in addition to educating the public about the nature of these viruses, the diseases they cause, and how to prevent their spread. GVN's Ebola researchers, including Erica Sapphire of The Scripps Research Institute and Tom Geisbert of University of Texas Medical Branch at Galveston, received U.S. National Institutes of Health funding to find an antibody "cocktail" to fight the deadly Ebola virus.



GVN Scientific Director Robert Gallo lectures during this summer's Rina Shah Short-Term Exchange Program (STEP) session.



Last Fall, GVN launched two new training and education exchanges through the Rina Shah Short-Term Exchange Program (STEP), to support travel for post-doctoral level scientists and assistant professors in order to enhance medical virology skills or knowledge sets, or to develop collaborative proposals among GVN Centers of Excellence with the goal of maintaining the funding recipient's interest in medical virology as a career. GVN and the global community lost Reinhard Kurth, Ph.D. this year. In his name the GVN established the Global Virus Network Reinhard Kurth Scholarship Fund to support long- and short-term training opportunities for the next generation of

medical virology leaders who will be on the front lines of pandemic preparedness and who will help us tackle viral diseases which threaten countries worldwide today.

IHV continues to support the GVN as it matures as an independent organization. Dr. Gallo is GVN's Scientific Director. IHV staff also contribute time generously to the GVN, including most notably Dave Wilkins and Nora Grannell, who also serves as GVN's PR Director on a part-time basis, and IHV faculty, Drs. Robert Redfield, Bill Blattner, Dave Pauza, Maria Salvato, Mangalasseril Sarngadharan, and Alash'le Abimiku.

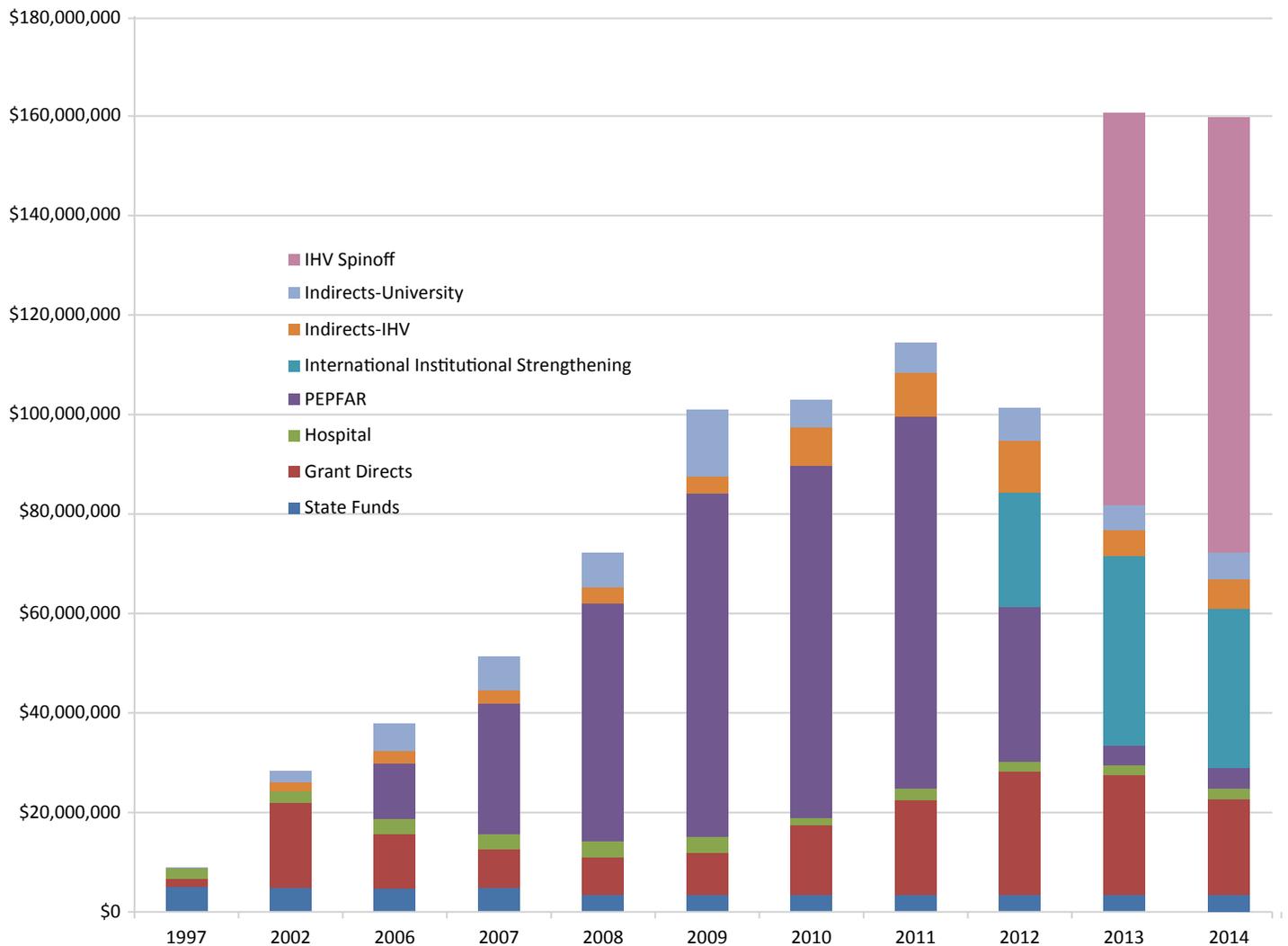


Participants gather for a picture during this past summer's STEP session.

Financials and Related Charts

IHV's success in driving basic research, vaccine development, clinical trials, patient care and international institutional strengthening in the fields of HIV and other chronic viral diseases positions the Institute as a successful model in the research community.

During FY 2014, IHV's basic research portfolio, at the heart of our mission, continued to thrive despite severe cuts to the U.S. National Institutes of Health (NIH) and U.S. Centers for Disease Control and Prevention (CDC) funding levels. The Institute's overall income continued to be influenced by the U.S. government's decision to award international HIV care and treatment grants primarily to indigenous institutions as opposed to U.S. universities and institutes. However, the graph below depicts the large amount of funding now going to organizations that the Institute has spun-off both in the U.S. (Profectus Biosciences, Inc.) and in four African nations. IHV has also been able to provide significant financial support to the new Global Virus Network (GVN), established to organize the world's top virus researchers. The technical assistance IHV provides these organizations brings a great deal of revenue back to the Institute. IHV continues to augment the world's ability to fight chronic viral diseases in a meaningful and compelling way.



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