19th Annual International Meeting of the Institute of Human Virology

OCTOBER 23-26th
Four Seasons Hotel
Baltimore, Maryland

Hosted by Institute of Human Virology
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Welcome

19th Annual International Meeting of the Institute of Human Virology at the University of Maryland School of Medicine

Dear Colleagues and Friends,

You are invited to join us for the 19th Annual International Meeting of the Institute of Human Virology (IHV) scheduled for Monday, October 23, 2017 through Thursday, October 26, 2017 at the Four Seasons Hotel in Baltimore, Maryland. This year, the Annual Meeting will feature presentations on the latest advances in: HIV “Cure” Research, Preventative and Therapeutic Vaccines, Immunology and Viral Pathogenesis, Viral Diagnostics, Emerging Concepts in Cancer Therapy, Cancer and Stem Cells, Infectious Agents and Cancer, Public Health Science and Responses - From Local to Global, Clinical Virology - Cardiovascular and Liver Complications of Viral Infections, Junior investigators are invited to submit research abstracts for oral or poster presentation, so please share this opportunity with your faculty and colleagues.

A special mini-symposium will honor this year’s IHV Lifetime Achievement Awardees: Lifetime Achievement Award for Public Service: Quarraisha Abdool Karim, PhD Associate Scientific Director, Centre for the AIDS Program of Research in South Africa (CAPRISA), Salim S. Abdool Karim, MBChB, PhD, DSc Professor for Global Health, Department of Epidemiology, CAPRISA; Lifetime Achievement Award for Scientific Contributions: Peter Palese, MD Horace W. Goldsmith Professor of Medicine, Chair of the Department of Microbiology, Professor of Microbiology and Medicine, Icahn School of Medicine at Mount Sinai

In addition to other prominent presenters, this symposium will feature the fourth annual Reinhard Kurth Memorial Lecture by Peter Palese, MD. The Annual Awards Gala will be held Wednesday, October 25 at the Four Seasons Hotel, Baltimore. A gala reception will begin at 6:00 p.m. followed by dinner at 7:00 p.m. We look forward to welcoming you to Baltimore this October as we continue our annual tradition of excellent science and provocative discussion.

Sincerely,

Robert C. Gallo, MD
Homer and Martha Gudelsky Distinguished Professor in Medicine
Director, Institute of Human Virology
Co-Founder and Director, Global Virus Network

Manhattan Charurat, PhD
Director, Division of Epidemiology and Prevention
Professor of Medicine, Institute of Human Virology
The Institute 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.

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Director, Division of Epidemiology and Prevention

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Co-Director, Division of Basic Science

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Co-Director, Division of Basic Science

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National Basketball Association Hall of Fame Coach and Player
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The Institute of Human Virology at the University of Maryland School of Medicine is grateful for the assistance provided by our International and Local Organizing Committees.

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  Director, Institute of Human Virology

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  San Raffaele Scientific Institute

- Sharon Lewin, FRACP, PhD
  The University of Melbourne

- Richard Wyatt, PhD
  The Scripps Research Institute

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  Director, Institute of Human Virology

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- Chozha V. Rathinam, PhD
  Institute of Human Virology
Communications and Press Policy

To enhance the exchange of information and communication among attendees of the Institute of Human Virology Annual International Meeting, the following must be adhered to by all participants:

- No coverage, reporting or publication of scientific data or presentations at the Institute of Human Virology Annual Meeting is permitted without the written consent of the presenter(s) and Nora Grannell (info below). This rule applies to all forms of media, including blogging, tweeting, etc.

- Alternatively, if the content does not contain information about non-published data, or comments made during the closed meeting, all forms of media are acceptable without written consent.

One-on-one interviews with scientists and media may be arranged by contacting Nora Samaranayake, Director of Public Relations and Marketing, Institute of Human Virology, (410) 706-1954 or NSamaranayake@ihv.umaryland.edu.

Those registering for the meeting as “press” must provide their credentials within 3 days to ihvmeeting@ihv.umaryland.edu.
Special Acknowledgements

The Institute of Human Virology at the University of Maryland would like to thank the following organizations. Without their continued and generous support, this meeting would not be possible.

*Funding for this conference was made possible, in part, by 5 R13 AI 046078 - 18 from the National Institute of Allergy and Infectious Diseases. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
The 2017 IHV Lifetime Achievement Award for Scientific Contributions

Peter Palese, PhD

Dr. Peter Palese is a Professor of Microbiology and Medicine, and the Chair of the Department of Microbiology at the Icahn School of Medicine at Mount Sinai. His research is in the area of RNA-containing viruses with a special emphasis on influenza viruses. He established the first genetic map for influenza A, B, and C viruses, identified the function of several viral genes, and defined the mechanism of neuraminidase inhibitors (which are now FDA-approved antivirals). He was also a pioneer in the field of reverse genetics for negative strand RNA viruses. His laboratory’s research is currently focused on the development of a universal influenza virus vaccine and oncolytic viruses.

Palese is a member of the National Academy of Sciences, the National Academy of Medicine (formerly IOM), and the American Academy of Arts and Sciences. He is also a corresponding member of the Austrian Academy of Sciences and a member of the German Academy of Sciences (Leopoldina). Palese is a recipient of the Robert Koch Prize, the Sanofi-Institut Pasteur Award, the Beijerinck Virology Prize, and the Maurice Hilleman/Merck Award; he has received honorary doctorate degrees from The Mount Sinai School of Medicine, Baylor College of Medicine and McMaster University. Dr. Palese serves on the editorial board for the Proceedings of the National Academy of Sciences and is a former president of the Harvey Society and the American Society for Virology.
Quarraisha Abdool Karim, PhD

Quarraisha Abdool Karim, PhD, Associate Scientific Director of CAPRISA, is an infectious diseases epidemiologist whose main research interests are in understanding the evolving HIV epidemic in South Africa; factors influencing acquisition of HIV infection in adolescent girls; and sustainable strategies to introduce antiretroviral therapy in resource-constrained settings. She holds Professorships in Clinical Epidemiology at the Mailman School of Public Health, Columbia University, USA and in Public Health at the Nelson R Mandela School of Medicine, University of KwaZulu-Natal in South Africa. She is also a visiting scientist at Massachusetts General Hospital and Visiting Lecturer at Harvard University. Since 1998 she has played a central role in building the science base in southern Africa through the Columbia University - Southern African Fogarty AIDS International Training and Research Programme that has trained over 600 scientists in southern Africa.

She was the Principal Investigator of the landmark CAPRISA 004 tenofovir gel trial which provided proof of concept for Microbicides, highlighted by Science as one of the Top 10 scientific breakthroughs in 2010. Professor Abdool Karim’s has over 170 peer reviewed publications and has authored several books and book chapters.

Professor Abdool Karim is currently chair of the South African National AIDS Council Prevention Technical Task Team, a member of the UNAIDS Scientific Expert Panel and Scientific Advisor to the Executive Director of UNAIDS. She is an advisory board member of the Higher Education and Training HIV/AIDS Programme (HEAIDS), Scientific Advisory Board member of the US President’s Emergency Pan for AIDS Relief (PEPFAR), Chair of the PEPFAR Adolescent Girls and Young Women Expert Working Group, a member of the HIV Centre Strategic Advisory Committee and the NIH OAR Microbicides Planning Group. She is a Foreign Associate member of the US US National Academy of Medicine, Fellow of the Royal Society of South Africa, Fellow of the Academy of Science of South Africa, Fellow of the African Academy of Sciences and Fellow of The World Academy of Sciences (TWAS). She is currently Vice-President (Southern African Region) of the African Academy of Sciences.
Salim S. Abdool Karim, MBChB, PhD, DSc (honoris causa) is a clinical infectious diseases epidemiologist widely recognised for his ground-breaking scientific contributions in HIV prevention and treatment. He is Director of CAPRISA - Centre for the AIDS Programme of Research in South Africa; Pro Vice-Chancellor (Research), University of KwaZulu-Natal; CAPRISA Professor of Global Health at Columbia University, Adjunct Professor of Medicine, Cornell University and Associate Member of The Ragon Institute of Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT) and Harvard University.

His contributions to microbicides for HIV prevention spans two decades and culminated in the CAPRISA 004 tenofovir gel trial which provided proof-of-concept that antiretroviral drugs can prevent sexually transmitted HIV infection and herpes simplex virus type 2 in women. He is co-inventor on patents which have been used in several HIV vaccine candidates and his clinical research on TB-HIV treatment has shaped international guidelines on the clinical management of co-infected patients.

He chairs the UNAIDS Scientific Expert Panel and is a member of both the WHO HIV-TB Task Force and the WHO Expert Panel on STIs and HIV. He is an elected Fellow of the World Academy of Sciences, African Academy of Sciences, Academy of Science in South Africa, Royal Society of South Africa and American Academy of Microbiology. He is a Foreign Associate Member of the US National Academy of Medicine. He serves on the Boards of Lancet-Global Health, Lancet-HIV and the New England Journal of Medicine.
Previous Recipients of IHV Lifetime Achievement Awards

LIFETIME ACHIEVEMENT AWARDS FOR SCIENTIFIC CONTRIBUTIONS

1999  George Klein, MD, Karolinska Institute, Stockholm, Sweden
2000  Maurice Hilleman, PhD, Merck Research Laboratories, Sumneytown, Pennsylvania, USA
2001  Hilary Koprowski, MD, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
2002  Alexander Rich, MD, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
2003  Jan Svoboda, PhD, DSc, Institute of Molecular Genetics, Prague, Czech Republic
2004  Paul Zamecnik, MD, Massachusetts General Hospital, Boston, Massachusetts, USA
2005  Manfred Eigen, PhD, Max Planck Institute, Göttingen, Germany
2006  Maxine Singer, PhD, National Institutes of Health, Bethesda, Maryland, USA
2008  Isaac P. Witz, PhD, Tel Aviv University, Tel Aviv, Israel
2010  Rino Rappuoli, PhD, Novartis Vaccines, Sienna, Italy
2011  Max Essex, DVM, PhD, Harvard AIDS Institute, Boston, Massachusetts, USA
2012  Thomas A. Waldmann, MD, National Cancer Institute, Bethesda, Maryland, USA
2013  Vadim I. Agol, MD, PhD, DSc, Russian Academy of Medical Sciences, Moscow, Russia
2014  William Paul, MD, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA
2015  Harald zur Hausen, MD, Nobel Laureate, Gelsenkirchen, Germany
2016  Peter Vogt, Ph.D., Scripps Research Institute, La Jolla, California, USA

LIFETIME ACHIEVEMENT AWARD FOR PUBLIC SERVICE

2004  Stewart Greenebaum, Greenebaum and Rose Associates, Inc., Baltimore, Maryland, USA
2006  Martin Delaney, Project Inform, San Francisco, California, USA
2008  John D. Evans, Evans Telecommunication Company, Miami, Florida, USA
2010  The Honorable Robert K. Gray, Gray and Company II, Miami, Florida, USA
2012  Yi Zeng, PhD, China Centers for Disease Control, Beijing, China
2013  José G. Esparza, MD, PhD, Bill & Melinda Gates Foundation, Seattle, Washington, USA
2014  John Martin, PhD, Gilead Sciences, Inc., Foster City, California, USA
2015  Anthony S. Fauci, MD, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA
2016  Ray Schinazi, Ph.D., Hon DSc, Emory University, Atlanta, Georgia, USA

ONE-TIME LIFETIME ACHIEVEMENT AWARD FOR EXCELLENCE IN TEACHING

2010  Michele LaPlaca, MD, Institute of Microbiology of the University of Bologna, Bologna, Italy

LIFETIME ACHIEVEMENT AWARD FOR EXCELLENCE IN MEDICAL EDUCATION, CLINICAL CARE AND CLINICAL RESEARCH

2012  John G. Bartlett, MD, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
Evening Events Schedule

Monday, October 23, 2017
6:30 – 8:30 pm
Opening Reception
Grand Prefunction

Tuesday, October 24, 2017
6:10 – 8:30 pm
Poster Session
Grand Prefunction

Wednesday, October 25, 2017
6:00 – 7:00 pm
Lifetime Achievement Awards
Gala Reception
Grand Prefunction

7:00 pm
Lifetime Achievement Gala
Banquet and Awards Ceremony
Cobalt Ballroom
Program Overview

Monday, October 23, 2017

8:30 am – 12:20 pm
Session A - HIV “Cure” Research

10:10 – 10:25 am
Coffee Break

12:20 – 1:35 pm
Lunch Break

1:35 – 3:40 pm
Session B – Emerging Concepts in Cancer Therapy

3:40 – 3:55 pm
Coffee Break

3:55 – 6:25 pm
Session C – Preventative and Therapeutic Vaccines

6:30 – 8:30 pm
Opening Reception

Tuesday, October 24, 2017

8:30 am – 12:05 pm
Session D – Immunology and Viral Pathogenesis

10:10 – 10:25 am
Coffee Break

12:05 – 1:20 pm
Lunch Break

1:20 – 2:35 pm
Session D – Immunology and Viral Pathogenesis (continued)

2:35 – 4:15 pm
Session E – Public Health Science and Responses - From Local to Global

4:15 – 4:30 pm
Coffee Break
Program Overview, continued

4:30 – 6:10 pm
6:10 – 8:30 pm

Wednesday, October 25, 2017

8:30 am – 12:05 pm

10:10 – 10:25 am
12:05 – 2:15 pm
2:15 – 5:55 pm

4:00 – 4:15 pm
6:00 – 7:00 pm
7:00 pm

Thursday, October 26, 2017

8:30 am - 12:30 pm

10:10 – 10:25 am
12:05 – 1:05 pm
1:05 – 3:30 pm
3:30 pm

Session F – Cancer and Stem Cells
Poster Session

Session G – Infectious Agents and Cancer
Coffee Break
Lunch Break
Session H – Lifetime Achievement Award Mini-Symposium
Coffee Break
Gala Reception
Lifetime Achievement Awards Banquet

Session I – Advances in Clinical Virology - Cardiovascular and Liver Complications of Viral Infections
Coffee Break
Lunch Break
Session J – Special Symposium on Advances in Viral Diagnostics
Adjourn
Monday, October 23, 2017

Session A:
HIV “Cure” Research
Grand Ballroom
Chairpersons and Discussants:
Diana Finzi, PhD, National Institutes of Health
Robert Siliciano, MD, Johns Hopkins University
Carl Dieffenbach, PhD, DAIDS

8:30 Monsef Benkirane, PhD, University of Montpellier
Understanding for targeting the HIV reservoir

8:55 Guido Ferrari, MD, Duke University
Antibody binding to HIV-1 infected cells as mechanism for treatment of HIV infection

9:20 Mirko Paiardini, PhD, Emory University
Combined immune-based strategies targeting viral persistence in ART-suppressed SIV-infected rhesus macaques

9:45 Douglas Nixon, MD, PhD, George Washington University
Immune Targeting of the Latent Reservoir

Coffee Break, 10:10 AM - 10:25 AM Grand Prefunction

10:25 Mary Kearney, PhD, National Cancer Institute
No evidence for HIV Replication in lymph nodes during ART

10:50 Kevin Morris, PhD, Beckman Research Institute of the City of Hope
Eradication of HIV; molecular therapeutic paths to a functional cure

11:15 Jintanat Ananworanich, MD, PhD, U.S. Military HIV Research Program
Early ART and HIV Remission: Experience from the RV254 and related HIV remission studies

11:40 Deanna Kulpa, PhD, Emory University
The Contribution of Memory CD4+ T cell subset phenotype to latency reversal efficiency

12:05 Early Stage Investigator: Ya-Chi Ho, MD PhD, Johns Hopkins University
Cytotoxic T lymphocytes shape the landscape of HIV-1 proviruses

Lunch Break, 12:30 PM – 1:35 PM
Session B:
Emerging Concepts in Cancer Therapy
Grand Ballroom
Chairpersons and Discussants:
Eduardo Sotomayor, MD, George Washington University
Isaac Witz, PhD, Tel Aviv University

1:35 Yutaka Tagaya, PhD, Institute of Human Virology
Shooting Many Cytokines with a Single Stone - a Novel Anti-cytokine Technology with Broad Clinical Application

1:55 Paul Frohna, MD, PhD, PharmD, Bioniz Therapeutics
Results from a First-In-Human Study with BNZ-1, a Novel, Selective Inhibitor of IL-2, IL-9, and IL-15 at the Common Gamma-Chain Receptor, in Clinical Development for the Treatment of HAM/TSP and T-Cell Malignancies

2:05 Michael Caligiuri, MD, Ohio State University
Fc Bridged Cellular Cytotoxicity (FcBCC): a novel mechanism by which NK cells recognize HSV

2:25 Roberto Accolla, MD, PhD, University of Insubria
Cancer Vaccine: Tumor Immunology meets...Immunology

2:50 Luigi Buonaguro, MD, National Cancer Institute Fondazione Pascale
Discovery to first-in-man studies of a multi-peptide-based hepatocellular carcinoma vaccine - HEPAVAC

3:15 Early Stage Investigator: Hua Cheng, PhD, Institute of Human Virology
Development of anti-tumor cytotoxic lymphocytes using engineered human primary blood dendritic cells

Coffee Break, 3:40 PM - 3:55 PM Grand Prefunction

Session C:
Preventative and Therapeutic Vaccines
Grand Ballroom
Chairpersons and Discussants:
William Blattner, MD, Salt Run Global
George Lewis, PhD, Institute of Human Virology

3:55 John Moore, PhD, Weill Cornell Medicine
Production and properties of SOSIP trimers

4:20 Ronald Desrosiers, PhD, University of Miami
Long-term delivery of antiviral monoclonal antibodies

4:45 William Schief, PhD, Scripps Research Institute
Germline-targeting vaccine design for HIV

5:10 Lai-Xi Wang, PhD, University of Maryland College Park
Defining the glycopeptide epitopes of broadly neutralizing antibodies for HIV vaccine design
5:35  Paolo Lusso, MD, PhD, National Institute of Allergy and Infectious Diseases
Quaternary Configuration of the HIV-1 Receptor-Binding Site

6:00  Early stage: Mohammad Sajadi, MD, Institute of Human Virology
Pan-neutralizing antibodies derived from human plasma targeting a new epitope

Opening Reception 6:30 PM - 8:30 PM Grand Prefunction

Tuesday, October 24, 2017

Session D:
Immunology and Viral Pathogenesis
Grand Ballroom
Chairpersons and Discussants:
Warner Greene, MD, PhD, Gladstone Institutes
Anthony Devico, PhD, Institute of Human Virology

8:30  Thomas Lehner, MD, Kings College London
The role of stress agents in immunization against HIV-1 infection and eliciting CD4+ memory stem cells

8:55  Guido Silvestri, MD, Emory University
Immune-based interventions for HIV cure: lessons from NHP models

9:20  John Mellors, MD, University of Pittsburgh
HIV Cure: Time to Rethink the “Shock and Kill” Strategy?

9:45  Mathias Lichterfeld, MD, Ragon Institute
Clonal proliferation of CD4 T cells encoding intact HIV-1

Coffee Break, 10:10 AM - 10:25 AM Grand Prefunction

10:25 Guido Poli, MD, Vita-Salute San Raffaele University
Reversible HIV-1 Latency Induced in Primary Human Monocyte-Derived Macrophages by Repeated M1 Polarization

10:50 Eric Verdin, MD, The Buck Institute
Chromatin Functional States Correlate with the Reversal of Latently HIV-1 Infected Primary CD4+ T cells

11:15 Richard Wyatt, PhD, Scripps Research Institute
HIV Env trimer immunogen design and modification to elicit neutralizing antibodies

11:40 Early Stage Investigator: Keith Reeves, PhD, Harvard Medical School
Innate-primed alternative signaling pathways enhance functional mucosal mobilization of memory-like NK cells in HIV/SIV infection

Lunch Break, 12:05 PM - 1:20 PM
**Session D:**

**Immunology and Viral Pathogenesis (continued)**

**Grand Ballroom**

Chairpersons and Discussants:
- **Anders Vahlne, MD, PhD**, Karolinska Institute
- **Alan Schmaljohn, PhD**, University of Maryland School of Medicine

1:20  
**Warner Greene, MD, PhD**, Gladstone Institutes  
*D-109*  
*Defining a Potent New Class of Latency Reversing Agents Devoid of Toxicity and Detrimental Cell Activation That Enhance CTL/NK Cell Killing*

1:45  
**Howard Gendelman, MD**, University of Nebraska Medical Center  
*D-110*  
*Combination of CRISPR-Cas9 and Long Acting Slow Effective Release Antiretroviral Therapy Eliminates HIV-1 Infection in Humanized Mice*

2:10  
**Savita Pahwa, MD**, University of Miami  
*D-111*  
*Influence of age on immune response to influenza vaccination in virologically suppressed HIV infected persons*

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**Session E:**

**Public Health Science and Responses - From Local to Global**

**Grand Ballroom**

Chairpersons and Discussants:
- **Erica Ollmann Saphire, PhD**, Scripps Research Institute
- **Kathleen Neuzil, MD, MPH**, Center for Vaccine Development, Institute of Global Health, University of Maryland School of Medicine

2:35  
**Boris Lushniak, MD, MPHd**, University of Maryland College Park School of Public Health  
*E-101*  
*Infectious Disease - Public Health Response*

3:00  
**The Honourable Isaac Adewole, MBBS(Ib), FWACS, FMCOG, FAS, FRCOG, DSc(Hons)**, The Federal Minister of Health of Nigeria  
*E-102*  
*Policy, Practice and Science in Nigeria: Implementing Evidence Based Research for HIV programming in Nigeria*

3:25  
**Kashef Ijaz, MD, MPh**, Centers for Disease Control and Prevention  
*E-103*  
*Global Health Security – Why is it important?*

3:50  
**Early Stage Investigator: Gytis Dudas, PhD**, Fred Hutchinson Cancer Research Center  
*E-104*  
*Virus genomes reveal factors that spread and sustain the Ebola epidemic*

**Coffee Break, 4:15 PM - 4:30 PM** Grand Prefunction
Session F:
Cancer and Stem Cells
Grand Ballroom
Chairpersons and Discussants:
Leonid Margolis, PhD, National Institute of Child Health and Human Development
Guido Poli, MD, Vita-Salute San Raffaele University

4:30 Stavroula Kousteni, PhD, Columbia University
Regulation of Leukemogenesis by the Bone Marrow Niche

4:55 Heinrich Jasper, PhD, Buck Institute for Research on Aging
Inflammation and immune modulation: tackling age-related stem cell dysfunction

5:20 Ulrich G. Steidl, MD, PhD, Albert Einstein College of Medicine
Targeting Aberrant Transcription in Pre-Cancerous Stem Cells

5:45 Early Stage Investigator: Chozha Rathinam, PhD, Institute of Human Virology
Decoding the regulatory networks of Leukemic Stem Cells through Ubiquitylation

Poster Session 6:10 PM - 8:30 PM Grand Prefunction

Wednesday, October 25, 2017

Session G:
Infectious Agents and Cancer
Grand Ballroom
Chairpersons and Discussants:
Franco Buonaguro, MD, Istituto Nazionale Tumori “Fondazione Pascale”
Kevin Cullen, MD, University of Maryland School of Medicine

8:30 Massimo Tommasino, PhD, International Agency for Research on Cancer
Human papillomaviruses and carcinogenesis: well-established and novel models

8:55 Sam Mbulaiteye, MBChB, MPhil, MMed, National Cancer Institute
Endemic Burkitt lymphoma and infectious agents in cancer: new results from the EMBLEM study implicating falciparum malaria and Epstein-Barr virus in causation

9:20 Charles Bangham, ScD, FMedSci, Imperial College London
Regulation of HTLV-1 proviral latency

9:45 Eric Sundberg, PhD, Institute of Human Virology
The Helicobacter pylori adhesin protein HopQ exploits the dimer interface of human CEACAMs for oncoprotein translocation

Coffee Break, 10:10 AM - 10:25 AM Grand Prefunction
10:25  Giorgio Trinchieri, MD, National Cancer Institute  
*Role of Microbiome in Cancer*

10:50  Cynthia Sears, MD, Johns Hopkins University  
*Carcinogenic Potential of Bacterial Biofilms*

11:15  Cornelia Trimble, MD, Johns Hopkins University  
*HPV vaccines: where are we now, and where are we going?*

11:40  Nicolas Wentzensen, MD, PhD, National Cancer Institute  
*Molecular Etiology of Cervical Cancer, HPV and gene methylation*

**Lunch Break, 12:05 PM - 2:15 PM**

**Session H:**  
**Lifetime Achievement Award Mini-Symposium**  
**Grand Ballroom**  
Chairpersons and Discussants:  
**Robert Gallo, MD**, Institute of Human Virology  
**Manfred Dierich, MD**, Medical University Innsbruck  

2:15  Robert C. Gallo, MD, Institute of Human Virology  
*Introduction to Lifetime Achievement Awards*

2:20  Mary Klotman, MD, Duke University  
*Speaking in honor of Peter Palese: Potential of Integrase-defective Lentiviral Vectors for HIV vaccine delivery*

2:50  Bernard Roizman, ScD, University of Chicago  
*Speaking in honor of Peter Palese: The détente between herpes simplex viruses and their human host*

3:20  Peter Palese, MD, Mount Sinai Medical School  
*Reinhard Kurth Memorial Lecture: Towards a Universal Influenza Virus Vaccine*

**Coffee Break, 4:00 PM - 4:15 PM**  
**Grand Prefunction**

**Session H:**  
**Lifetime Achievement Award Mini-Symposium (continued)**  
Chairpersons and Discussants:  
**Robert Redfield, MD**, Institute of Human Virology  
**The Honourable Isaac Adewole, MBBS(Ib), FWACS, FMCOG, FAS, FRCOG, DSc(Hons)**, The Federal Minister of Health of Nigeria

4:15  Thomas Quinn, MD, MSc, NIAID, National Institutes of Health  
*Speaking in honor of Quarraisha Abdool Karim: The HIV Pandemic in Sub-Saharan Africa: Challenges, Successes and Leadership*

4:45  John Martin, PhD, Gilead Sciences  
*Speaking in honor of Salim Abdool Karim: Reflections on the Impact of Nucleotide Antiviral Drugs*
Thursday, October 26, 2017

Session I:
Advances in Clinical Virology - Cardiovascular and Liver Complications of Viral Infections
Grand Ballroom
Chairpersons and Discussants:
Shyam Kottilil, MD, Institute of Human Virology
Ed Tramont, MD, National Institute of Allergy and Infectious Diseases

8:30 Henry Masur, MD, National Institutes of Health
The Changing Natural History of HIV Infection: From Opportunistic Infections to Inflammation and Chronic Diseases

8:55 Robert Weiss, MD, Johns Hopkins University
Probing mechanisms of accelerated coronary atherosclerosis and heart disease in HIV+ people

9:20 Barry Peters, MBBS, MD, FCRP, Kings College London
The Metabolic Complications of HIV

9:45 Early Stage Investigator: Shashwatee Bagchi, MD, Institute of Human Virology
Cardiovascular Disease in HIV and Chronic Hepatitis C-Infected Patients

Coffee Break, 10:10 AM - 10:25 AM Grand Prefunction

10:25 Patrizia Farci, MD, National Institutes of Health
Advances in HCV-Associated Hepatocellular Carcinoma

10:50 Kenneth Sherman, MD, PhD, University of Cincinnati
Hepatitis Viruses in HIV Infection

11:15 Angus Dalgleish, MD, FMedSci, St. George’s, University of London
Optimisation of a therapeutic vaccine; the importance of immune modulation

11:40 Mario Stevenson, PhD, University of Miami Miller School of Medicine
Assessing the contribution of myeloid cells to HIV-1 persistence under ART

Lunch Break, 12:05 PM - 1:05 PM
### Session J:
**Special Symposium on Advances in Viral Diagnostics**
**Grand Ballroom**

**Chairpersons and Discussants:**
- **Niel Constantine, PhD**, Institute of Human Virology
- **Richard Zhao, PhD**, University of Maryland School of Medicine

| Time  | Speaker and Affiliation | Title and Presentation Details |
|-------|-------------------------|--------------------------------|
| 1:05  | Niel Constantine, PhD, Institute of Human Virology | Brief Introduction |
| 1:10  | Sheila Peel, MSPH, PhD, U.S. Military HIV Research Program | Special Lecture: Current Challenges in HIV Diagnostics – Time to Revise our Approach? |
| 1:50  | Mark Manak, PhD, U.S. Military HIV Research Program | Decreased levels of seroreactivity in individuals subjected to antiretrovirals early in acute HIV infection |
| 2:10  | Michael Reed, PhD, OraSure Technologies | Performance and usability of the OraQuick® HIV Self-Test, an oral fluid based HIV self-test, in South Africa |
| 2:30  | Kathy Shriver, PhD, Bio-Rad | Geenius HIV 1/2 Supplemental Assay: A Rapid, Reliable and Simple System for the Confirmation and Differentiation of Antibodies to HIV |
| 2:50  | Kevin Delaney, MPH, PhD, Centers for Disease Control and Prevention | Recent developments in HIV testing in the US: Where we are, what’s new, and where we hope to go |
| 3:10  | Rudy Ippodrino, PhD, Ulisse Biomed | Programmable nucleic acid nanoswitches for the rapid, single-step detection of antibodies in bodily fluids |
| 3:30  | Adjourn |
A-101 Monsef Benkirane, PhD, University of Montpellier
Understanding for targeting the HIV reservoir

A-102 Guido Ferrari, MD, Duke University
Antibody binding to HIV-1 infected cells as mechanism for treatment of HIV infection

A-103 Mirko Paiardini, PhD, Emory University
Combined immune-based strategies targeting viral persistence in ART-suppressed SIV-infected rhesus macaques

A-104 Douglas Nixon, MD, PhD, George Washington University
Immune Targeting of the Latent Reservoir

A-105 Mary Kearney, PhD, National Cancer Institute
No evidence for HIV Replication in lymph nodes during ART

A-106 Kevin Morris, PhD, Beckman Research Institute of the City of Hope
Eradication of HIV; molecular therapeutic paths to a functional cure

A-107 Jintanat Ananworanich, MD, PhD, US Military HIV Research Program
Early ART and HIV Remission: Experience from the RV254 and related HIV remission studies

A-108 Deanna Kulpa, PhD, Emory University
The Contribution of Memory CD4+ T cell subset phenotype to latency reversal efficiency

A-109 Ya-Chi Ho, MD, PhD, Johns Hopkins University
Cytotoxic T lymphocytes shape the landscape of HIV-1 proviruses

B-101 Yutaka Tagaya, MD, PhD, Institute of Human Virology
Shooting Many Cytokines with a Single Stone - a Novel Anti-cytokine Technology with Broad Clinical Application

B-102 Paul Frohna, MD, PhD, PharmD, Bioniz Therapeutics
Results from a First-In-Human Study with BNZ-1, a Novel, Selective Inhibitor of IL-2, IL-9, and IL-15 at the Common Gamma-Chain Receptor, in Clinical Development for the Treatment of HAM/TSP and T-Cell Malignancies

B-103 Michael Caligiuri, MD, Ohio State University
Fc Bridged Cellular Cytotoxicity (FcbCC): a novel mechanism by which NK cells recognize HSV

B-104 Roberto Accolla, MD, PhD, University of Insubria
Cancer Vaccine: Tumor Immunology meets...Immunology

B-105 Luigi Buonaguro, MD, National Cancer Institute “Fondazione Pascale”
Discovery to first-in-man studies of a multi-peptide-based hepatocellular carcinoma vaccine - HEPAVAC

B-106 Hua Cheng, PhD, Institute of Human Virology
Development of anti-tumor cytotoxic lymphocytes using engineered human primary blood dendritic cells

C-101 John Moore, PhD, Weill Cornell Medicine
Production and properties of SOSIP trimers
C-102 Ronald Desrosiers, PhD, University of Miami
Long-term Delivery of Antiviral Monoclonal Antibodies

C-103 William Schief, PhD, Scripps Research Institute
Germline-targeting vaccine design for HIV

C-104 Lai-Xi Wang, PhD, University of Maryland College Park
Defining the glycopeptide epitopes of broadly neutralizing antibodies for HIV vaccine design

C-105 Paolo Lusso, MD, PhD, National Institute of Allergy and Infectious Diseases
Quaternary Configuration of the HIV-1 Receptor-Binding Site

C-106 Mohammad Sajadi, MD, Institute of Human Virology
Pan-neutralizing antibodies derived from human plasma targeting a new epitope

D-101 Thomas Lehner, MD, Kings College London
The role of stress agents in immunization against HIV-1 infection and eliciting CD4+ memory stem cells

D-102 Guido Silvestri, MD, Emory University
Immune-based interventions for HIV cure: lessons from NHP models

D-103 John Mellors, MD, University of Pittsburgh
HIV Cure: Time to Rethink the “Shock and Kill” Strategy?

D-104 Mathias Lichterfeld, MD, Ragon Institute
Clonal proliferation of CD4 T cells encoding intact HIV-1

D-105 Guido Poli, MD, Vita-Salute San Raffaele University
Reversible HIV-1 Latency Induced in Primary Human Monocyte-Derived Macrophages by Repeated M1 Polarization

D-106 Eric Verdin, MD, The Buck Institute
Chromatin Functional States Correlate with the Reversal of Latently HIV-1 Infected Primary CD4+ T cells

D-107 Richard Wyatt, PhD, Scripps Research Institute
HIV Env trimer immunogen design and modification to elicit neutralizing antibodies

D-108 R. Keith Reeves, PhD, Harvard Medical School
Innate-primed alternative signaling pathways enhance functional mucosal mobilization of memory-like NK cells in HIV/SIV infection

D-109 Warner Greene, MD, PhD, Gladstone Institutes
Defining a Potent New Class of Latency Reversing Agents Devoid of Toxicity and Detrimental Cell Activation That Enhance CTL/NK Cell Killing

D-110 Howard Gendelman, MD, University of Nebraska Medical Center
Synergism between CRISPR/Cas9 and LASER ART leads to elimination of HIV-1 with no rebound in Humanized Mice
D-111 Savita Pahwa, MD, University of Miami
Influence of age on immune response to influenza vaccination in virologically suppressed HIV infected persons

E-101 Boris Lushniak, MD, MPH, University of Maryland College Park School of Public Health
Infectious Disease - Public Health Response

E-102 The Honourable Isaac Adewole, MBBS(Ib), FWACS, FMCOG, FAS, FRCOG, DSc(Hons), The Federal Minister of Health of Nigeria
Policy, Practice and Science in Nigeria: Implementing Evidence Based Research for HIV programming in Nigeria

E-103 Keshef Ijaz, MD, MPH, Centers for Disease Control and Prevention
Global Health Security – Why is it important?

E-104 Gytis Dudas, PhD, Fred Hutchinson Cancer Research Center
Virus genomes reveal factors that spread and sustained the Ebola epidemic

F-101 Stavroula Kousteni, PhD, Columbia University
Regulation of Leukemogenesis by the Bone Marrow Niche

F-102 Heinrich Jasper, PhD, Buck Institute for Research on Aging
Inflammation and immune modulation: tackling age-related stem cell dysfunction

F-103 Ulrich Steidl, MD, PhD, Albert Einstein College of Medicine
Targeting Aberrant Transcription in Pre-Cancerous Stem Cells

F-104 Chozha Rathinam, PhD, Institute of Human Virology
Decoding the regulatory networks of Leukemic Stem Cells through Ubiquitylation

G-101 Massimo Tommasino, PhD, International Agency for Research on Cancer
Human papillomaviruses and carcinogenesis: well-established and novel models

G-102 Sam Mbulaiteye, MBChB, MPhil, MMed, National Cancer Institute
Endemic Burkitt lymphoma and infectious agents in cancer: new results from the EMBLEM study implicating falciparum malaria and Epstein-Barr virus in causation

G-103 Charles Bangham, ScD, FMedSci, Imperial College London
Regulation of HTLV-1 proviral latency

G-104 Eric Sundberg, PhD, Institute of Human Virology
The Helicobacter pylori adhesin protein HopQ exploits the dimer interface of human CEACAMs for oncoprotein translocation

G-105 Giorgio Trinchieri, MD, National Cancer Institute
Role of Microbiome in Cancer

G-106 Cynthia Sears, MD, Johns Hopkins University
Carcinogenic Potential of Bacterial Biofilms
G-107 Cornelia Trimble, MD, Johns Hopkins Medical Institute
HPV vaccines: where are we now, and where are we going?

G-108 Nicolas Wentzensen, MD, PhD, National Cancer Institute
Molecular Etiology of Cervical Cancer, HPV and gene methylation

H-101 Mary Klotman, MD, Duke University
Potential of Integrase-defective Lentiviral Vectors for HIV vaccine delivery

H-102 Bernard Roizman, ScD, University of Chicago
The détente between herpes simplex viruses and their human host

H-103 Peter Palese, MD, Mount Sinai Medical School
Towards a Universal Influenza Virus Vaccine

H-104 Thomas Quinn, MD, MSc, NIAID, National Institutes of Health
The HIV Pandemic in Sub-Saharan Africa: Challenges, Successes and Leadership

H-105 John Martin, PhD, Gilead Sciences
Reflections on the Impact of Nucleotide Antiviral Drugs

H-106 Anthony Fauci, MD, NIAID, National Institutes of Health
Sustained ART-Free HIV Remission: Obstacles and Opportunities

I-101 Henry Masur, MD, National Institutes of Health
The Changing Natural History of HIV Infection: From Opportunistic Infections to Inflammation and Chronic Diseases

I-102 Robert Weiss, MD, Johns Hopkins University
Probing mechanisms of accelerated coronary atherosclerosis and heart disease in HIV+ people

I-103 Barry Peters, MBBS, MD, FCRP, King’s College London
The Metabolic Complications of HIV

I-104 Shashwatee Bagchi, MD, Institute of Human Virology
Cardiovascular Disease in HIV and Chronic Hepatitis C-Infected Patients

I-105 Patrizia Farci, MD, National Institutes of Health
Advances in HCV-Associated Hepatocellular Carcinoma

I-106 Kenneth Sherman, MD, PhD, University of Cincinnati
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I-107 Angus Dalgleish, MD, FMedSci, St. George’s, University of London
Optimisation of a therapeutic vaccine; the importance of immune modulation

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Assessing the contribution of myeloid cells to HIV-1 persistence under ART
J-101  Sheila Peel, MSPH, PhD, US Military HIV Research Program
Current Challenges in HIV Diagnostics – Time to Revise our Approach?

J-102  Mark Manak, PhD, US Military HIV Research Program
Decreased levels of seroreactivity in individuals subjected to antiretroviral therapy early in acute HIV infection

J-103  Michael Reed, PhD, OraSure Technologies
Performance and usability of the OraQuick® HIV Self-Test, an oral fluid based HIV self-test, in South Africa

J-104  Kathleen Shriver, PhD, Bio-Rad
Geenius HIV 1/2 Supplemental Assay: A Rapid, Reliable and Simple System for the Confirmation and Differentiation of Antibodies to HIV

J-105  Kevin Delaney, MPH, PhD, Centers for Disease Control and Prevention
Recent developments in HIV testing in the US: Where we are, what’s new, and where we hope to go

J-106  Rudy Ippodrino, PhD, Ulisse Biomed
Programmable nucleic acid nanoswitches for the rapid, single-step detection of antibodies in bodily fluids
P-A1  Mudit Tyagi, PhD, The George Washington University
CBF-1 promotes the establishment and maintenance of HIV latency by recruiting Polycomb repressive complexes, PRC1 and PRC2, at HIV LTR

P-A2  Takashi Okamoto, MD, PhD, Nagoya City University
Development of anti-Tat compound: MD Simulation of the Tat/Cyclin T1/CDK9 Complex Revealing the Hidden Catalytic Cavity within the CDK9 Molecule Upon Tat Binding

P-A3  Richard Apps, PhD, The George Washington University
Limitations of CD32a expression as a marker of the HIV latent reservoir

P-A4  Christopher Woldstad, PhD, University of Nebraska Medical Center
Multimodal theranostic tests for antiretroviral drug delivery

P-A5  Robert Furler, PhD, The George Washington University
HIV Infected Cells Have Depolarized Membrane Potentials and Increased Intracellular Calcium Levels

P-A6  Jianshi Yu, PhD, University of Maryland School of Pharmacy
A Possible Role for Retinoic Acid in the Functional Cure of SIV Infections in ART/α4β7 mAb-treated Monkeys

P-A7  Tracy Evans-Gilbert, MD,MPH,CTropMed®, Jamaica Perinatal and Paediatric HIV/AIDS Programme, Cornwall Regional Hospital
HIV disease history in perinatally HIV infected adolescents with interrupted care

P-A8  Hang Su, BS, University of Nebraska Medical Center
Establishing tissue reservoirs for the human immunodeficiency virus in humanized mice

P-A9  Mary Banoub, BS, University of Nebraska Medical Center
Transformation of Darunavir into a long acting Nanoformulated Prodrug

P-A10  Elizabeth Anderson, B.Sci, HIV Dynamics and Replication Program, National Cancer Institute
Accumulation and persistence of deleted HIV proviruses following prolonged ART

P-A12  Camille Lange, MSc, PhD, National Cancer Institute, National Institute of Health, Frederick, MD
Discordant HIV Populations with Discordant V3 Tropism in CSF and Plasma: Implications for Establishing HIV Reservoirs

P-C1  Peter Smith, PhD, St. Georges University of London
Development of HIV-1 Immunotherapy with Vacc4x and Vacc-C5

P-C2  Yongjun Sui, PhD, National Cancer Institute
Protection against or delay of intrarectal SHIV acquisition by mucosal vaccines in the absence of Env-antibody responses

P-C3  Camila Guzman, BS, Institute of Human Virology
A Modified Vaccinia Ankara vector expressing Lassa virus-like particles (MVA-LasVLP) protects mice from lethal challenge with a Lassa-Mopeia reassortant virus
P-C4 Walther Mothes, PhD, Yale University

Associating HIV-1 Env Trimer Structures with Functional Env Conformational States by smFRET Analysis

P-C5 Ursula Dietrich, PhD student, Georg-Speyer-Haus

Broadly neutralizing nanobodies selected from dromedary immune libraries with subtype C SOSIP Env glycoproteins: optimization and preclinical development

P-D1 John Williams, PhD, University of Pittsburgh

Differential pathogenesis of human metapneumovirus clinical isolates in C57BL/6 mice

P-D2 Roberto Accolla, PhD, University of Insubria

TRIM22 binds to CIITA and sequesters it into nuclear bodies containing TRIM19/PML and Cyclin T1. Implications for HIV-1 infection

P-D4 Orrianne Morrison, PhD, Food and Drug Administration

HIV-1 Env Trimer Conformational Implications of Peptide Fusion Inhibitor Resistance

P-D6 Jibreel Jumare, MBBS, PhD, University of Maryland at Baltimore

Elevated Plasma HIV RNA level is associated with impaired neurocognitive function among HIV-1 infected patients in Nigeria

P-D8 Chiara Orlandi, PhD, Institute of Human Virology

New insights on the human anti-HIV-1 Env antibody-mediated cell cytotoxicity (ADCC) against HIV-1 virus: Allosteric regulation of FcRs binding upon antigen engagement

P-E1 Richard Zhao, PhD, Institute of Human Virology

A novel way to test and discover new inhibitors against drug resistant HIV-1 proteases

P-E2 Nadia Sam-Agudu, MPH, International Research Center of Excellence, Institute of Human Virology Nigeria

The Impact of Structured Mentor Mother Support on Retention During the First 12 Months Postpartum among HIV Positive Women in Rural Nigeria

P-E3 Niel Constantine, PhD, Institute of Human Virology

Assessment of internationally-available HIV test kits for their suitability to meet manufacturers’ claims

P-E4 Nadia Sam-Agudu, MBBS, MPH, PhD, Institute of Human Virology

The MoMent Study: Correlates of Viral Suppression at 6 months Postpartum among HIV-Positive Women in Rural Nigeria

P-E5 Nicaise Ndembi, MPhil, PhD, Institute of Human Virology Nigeria

Whole Genome Deep Sequencing of HIV Reveals Extensive Multi-class Drug Resistance in Nigerian Patients Failing First-line Antiretroviral Therapy

P-E6 Janet Itelima, PhD, University of Jos, Nigeria

Hepatitis B and Hepatitis C viral infections among pregnant women in some Nigerian major Cities: A Review

P-G2 Juan Zapata, Msc, PhD, Institute of Human Virology

Development of engineered T-cell immunotherapy for treating Adult-T cell leukemia caused by HTLV-1
P-G3  Terry-Elinor Reid, PhD, Institute of Human Virology
Unravelling the Mechanism of Action of HLBT-100 Molecule against Adult T-Cell Leukemia

P-G4  Makar Tapas, PhD, Department of Neurology, University of Maryland
Molecular characterization of hippocampal changes in an animal model of HIV associated Primary Central Nervous System Lymphoma

P-G5  Franco Maria Buonaguro and AnnaLucia Tornesella, Istituto Nazionale Tumori – IRCCS Fondazione Pascale
Differential immune response to HCV peptides as cancer-progression biomarkers of HCV-infections

P-I1  Alonso Heredia, PhD, Institute of Human Virology
Monotherapy with Integrase Inhibitors Does Not Maintain Viral Suppression in Humanized Mice with Chronic HIV Infection

P-J1  Paul Lambotte, PhD, Chembio Diagnostic Systems, Inc.
Meta-analysis of laboratory and field studies of the DPP® HIV Syphilis Assay, a single-use, rapid combination test for the detection of HIV and syphilis antibodies at the Point of Care
A-101
Understanding for targeting the HIV reservoir
Monsef Benkirane, PhD, University of Montpellier

HIV infection is suppressed but not cured by Anti-Retroviral Therapy (ART). This is due to the establishment of a viral reservoir that is responsible for the persistence of low levels of plasma viremia in patients under ART. Viral rebound is observed immediately after ART interruption. HIV persistence may arise from ongoing residual virus replication and/or from latently-infected cells in which long-lived resting memory CD4+ T cells harbouring transcriptionally silent provirus represent the largest pool in the blood. Addressing the source of HIV persistence is required to achieve a cure for HIV. We will discuss our recent data showing that CD32a is marker of HIV persistent CD4 T cell.

A-102
Antibody binding to HIV-1 infected cells as mechanism for treatment of HIV infection
Guido Ferrari, MD, Duke University; Jeffrey Nordstrom, PhD, Macrogenics; Scott Koenig, MD, Macrogenics; Julia Sung, MD, University of North Carolina - Chapel Hill; David Margolis, MD, University of North Carolina - Chapel Hill; Barton Haynes MD, Duke University Medical Center

Anti-HIV antibody function is not limited to capturing free virus but also includes the recognition of HIV-1 infected cells. Both neutralizing and non-neutralizing antibody responses recognizing HIV-1 envelope epitopes expressed on the cellular membrane can recruit Fc receptor-bearing cells and direct their cytotoxic activity against the infected cells. We can leverage on our ability to use monoclonal antibody and monoclonal antibody-based molecules to protect from and treat HIV-1 infection.

A-103
Combined immune-based strategies targeting viral persistence in ART-suppressed SIV-infected rhesus macaques
Mirko Paiardini, PhD, Emory University

Antiretroviral therapy (ART) suppresses viral replication in HIV-infected individuals, but does not eliminate an extremely durable reservoir of latently infected cells that is established early after infection. Understanding the phenotype and location of latently infected cells represents a critical challenge in designing a cure for HIV; furthermore, many HIV-infected individuals given ART exhibit residual inflammation, which may contribute to virus persistence. This presentation will discuss immune based strategies targeting HIV persistence developed over the past several years using the model of SIV infection in rhesus macaques. Recent work identified PD-1+ follicular helper CD4+ T-cells as an important cellular compartment for viral persistence. We have described that CTLA-4+PD-1- memory CD4+ T-cells, which share phenotypic markers with regulatory T-cells and localize outside the B-cell follicle of the lymph nodes, are significantly enriched in SIV-DNA; contain robust levels of replication-competent virus; and increase their contribution to the SIV reservoir with prolonged ART. Finally, we showed that Interleukin-21 and IFN-alpha administration in ART-treated, SIV-infected RMs reduces residual immune activation during ART and temporally delay viral rebound after ART treatment interruption.

These recent advancements highlight the complexity and diversity of the mechanisms and T-cell populations that can contribute to the residual reservoirs of virally infected cells. Developing a range of different interventions to target individual components of viral reservoirs represent both a formidable challenge and an exciting opportunity for the years to come.

A-104
Immune Targeting of the Latent Reservoir
Douglas F. Nixon, MD, PhD, The George Washington University

HIV is a human infectious exogenous retrovirus which is thought to have infected human populations from cross primate species transmissions. Within our genomes are remnants of past infectious retroviruses which have endogenized, called “endogenous retroviruses” (ERVs). We have previously shown that human ERVs (HERVs) can be transcribed in an HIV infected cell, but had not identified which sub-family or unique HERV was transcribed. Using a novel computational pipeline, Telescope, we have identified which HERVs are expressed in HIV infected cells.

We have received funding for a Martin Delaney Collaboratory grant called “Believe” in which we research towards HIV eradication based upon enhanced targeted cell therapy. As part of this program, we have investigated whether we can identify markers which uniquely identify the latent reservoir. New data will be presented on two putative markers, CD32a and IFITM1.

Funding: The NIH Martin Delaney Collaboratory, “Believe”, NIAID UM1 award AI126617, co-funded by NIDA/NINDS/NIMH/NIAID; and grants NCI CA 206488; NIAID AI 76059.
NO EVIDENCE FOR HIV REPLICATION IN LYMPH NODES DURING ART

William McManus, BS, National Cancer Institute - Frederick; Jonathan Spindler, BS, National Cancer Institute - Frederick; Michael Bale, BS, National Cancer Institute - Frederick; Ann Wiegand, MS, National Cancer Institute - Frederick; Andrew Musicik, BS, National Cancer Institute - Frederick; Xiaolin Wu, PhD, Liedos Biomedical; David Wells, BS, Liedos Biomedical; Stephen Hughes, PhD, National Cancer Institute - Frederick; Mary Kearney, PhD, National Cancer Institute – Frederick; et al

To better understand the mechanisms of HIV persistence and to further investigate the question on ongoing viral replication in lymph nodes, we characterized HIV proviral populations, their levels of expression, and their sites of host integration in paired lymph node mononuclear cells (LNMC) and peripheral blood mononuclear cells (PBMC) collected after long-term ART and compared to them to the HIV populations prior to ART initiation. Three donors initiated ART in chronic infection and had viremia suppressed for 4-12 years; one donor initiated ART in acute infection and had viremia suppressed for 18 years. Proviral populations and expression were characterized by single-cell analyses and expanded clones were identified using the integration sites assay (ISA). Populations were compared phylogenetically, using a test for panmixia (well-mixed or divergent), by determining the fraction of expressing vs. latent proviruses, determining the levels of expression in single cells with actively-transcribing proviruses, and by comparing the expanded clonal populations. Proviruses in LNMC and PBMC were well mixed and were not significantly divergence from the pre-ART populations. The fraction of proviruses that were latent vs. actively transcribing during ART were not different (5-8% in the PBMC and 2-20% in the LNMC) (p=0.4). The levels of expression in actively-infected cells were low in both compartments, typical of suppression of viral replication. The same clonal populations were detected in PBMC and LNMC (p=0.8). These findings are not consistent with continued viral replication during ART in either the peripheral blood or the lymph nodes. Our results also suggest that infected cells migrate freely between the peripheral blood and the lymph nodes and demonstrate that the HIV reservoir is long-lived and proliferating populations of cells that were infected prior to initiating ART.

Eradication of HIV; molecular therapeutic paths to a functional cure

Kevin Morris, PhD, The Beckman Research Institute at the City of Hope

The eradication of functional replicative HIV is within our collective grasp. Several emerging modes of targeted therapeutics, ranging from chimeric antigen receptor (CAR) T-cell targeted killing of virus infected cells to targeted genomic editing and/or excision of latent provirus, may prove promising with regards to eradicating the spread of functional HIV. We have recently developed two distinct molecular approaches that may facilitate the eradication of HIV. The first approach is the systemic activation of HIV followed by a polyvalent “swarm” of HIV-gp120 bi-specific CAR CD4+/CD8+ T-cells. Systemic activation of latent HIV can occur by removing anti-retroviral therapy (ART) and/or by targeted activation of provirus. To activate provirus we developed a biologically deliverable recombinant zinc finger protein activator (ZFP-362-VPR), that functionally activates HIV in an LTR directed and specific manner. Notably, ZFP-362-VPR can be used in combination with a swarm of differentially HIV-gp120 targeted bi-specific CAR CD4+/CD8+ T-cells, to specifically kill virus infected cells. A second approach to eradicate HIV is the targeted genomic editing and/or excision of integrated virus. The approach we describe here builds on biologically deliverable recombinant protein technologies to direct the excision and/or targeted mutations to loci in the provirus, ultimately rendering the virus non-replicative. Collectively, these emerging molecular therapeutic strategies juxtaposed with current antiretroviral therapy may one day result in the eradication of HIV.

Early ART and HIV Remission: Experience from the RV254 and related HIV remission studies

Jintanat Ananworanich, MD, PhD, US Military HIV Research Program (MHRP)

Early antiretroviral therapy (ART) is an important step in the path towards an HIV cure. Acute HIV infection studies have demonstrated the ability to identify and treat very early infection in adults, resulting in significantly smaller HIV reservoirs, preserved immune functions with little viral escape to immune pressure. These results have been illustrated in the ongoing RV254 acute HIV infection study in Thailand that has enrolled close to 500 individuals. It has served as a platform to learn the effects of early ART and recruit participants for HIV remission trials.

Despite the favorable qualities, the majority of early treated individuals do not achieve HIV remission. Indeed this has been the experience to date in the RV254 HIV remission trials, which include three completed studies and one ongoing, with others in development. The interventions have included latency-reversing agent, broadly neutralizing antibody and therapeutic HIV vaccine. However, there are important lessons to be learned that would inform the design of future HIV remission trials.

There continues to be exciting new development of immune-based interventions. It is highly likely that combination therapies that can generate persistent and effective immune responses to control HIV will be required for a durable ART-free sustained remission of HIV.
The latent HIV reservoir persists in individuals on ART predominantly in memory CD4+ T cells, a heterogeneous population comprised of central memory (CM), transitional memory (TM) and effector memory (EM) subsets. Current HIV eradication strategies that aim to reverse latency in this heterogeneous pool of cells have had limited success. To characterize HIV latency reversal in all memory CD4+ T cell subsets that contribute to the HIV reservoir in vivo, we developed LARA (Latency and Reversion Assay), a primary cell based in vitro model of HIV latency. To identify pathways associated with latency reversal in each subset, we exposed latently infected cells from both HIV-infected individuals and LARA to different classes of latency reversing agents (LRAs). Memory subsets showed distinct responses that resulted in varying efficiencies to the LRAs tested. Importantly, the most effective LRAs triggered the differentiation into cells that expressed an EM phenotype. Transcriptional profiling of CD4+ T cells from HIV-infected individuals exposed to bryostatin, the LRA that showed the highest latency reversal, identified several EM specific pathways that were significantly upregulated in both the CM and EM subsets, including genes encoding for cytokines and effector molecules such as IFN-γ, IL-2, IL-4, and TNF. Together, these results support LRA exposure triggering differentiation toward an EM subset phenotype to be linked to higher latency reversal efficiency. Identification of these pathways is a critical prerequisite to understand factors that influence latency reversal in vivo as well as contributing to the most effective design of regimens capable of comprehensive reactivation of the HIV reservoir in eradication strategies.

Cytotoxic T lymphocytes shape the landscape of HIV-1 proviruses

Despite antiretroviral therapy, HIV-1 persists in memory CD4+ T cells creating a barrier to cure. The majority of HIV-1 proviruses are defective due to packaging signal deletions, APOBEC-mediated G-to-A hypermutations, large internal deletions, and point mutations. These defective proviruses are considered clinically irrelevant. Using cells from HIV-1-infected individuals and reconstructed patient-derived defective proviruses, we show that defective proviruses can be transcribed to RNAs that are spliced and translated into viral antigens. Proviruses with defective major splice donors (MSDs) can activate novel splice sites to produce HIV-1 transcripts. Cells with HIV-1 proviruses containing defective MSDs can be recognized by HIV-1-specific cytotoxic T lymphocytes (CTLs). Surprisingly, cells with proviruses containing lethal mutations upstream of CTL epitopes can also be recognized by CTLs potentially through aberrant translation. Thus, expression of defective proviruses complicates the measurement of the latent reservoir. CTLs may change the landscape of HIV-1 proviruses by preferential targeting cells with specific types of defective proviruses. The scope of potential CTL targets may be bigger than the size of the latent reservoir.
Results from a First-In-Human Study with BNZ-1, a Novel, Selective Inhibitor of IL-2, IL-9, and IL-15 at the Common Gamma-Chain Receptor, in Clinical Development for the Treatment of HAM/TSP and T-Cell Malignancies

Paul Frohna, MD, PhD, PharmD, Bioniz Therapeutics; Yutaka Tagaya, MD, PhD, Institute for Human Virology; Anoshie Ratnayake, MD, Bioniz Therapeutics; Nick Doerr, PhD, Bioniz Therapeutics; Asjad Basheer, PhD, Bioniz Therapeutics; Laith Al-Mawsawi, PhD, Bioniz Therapeutics; Woo Jae Kim, PhD, Bioniz Therapeutics; Juan Zapata, PhD, Institute for Human Virology; et al

Aberrant signaling of IL-2, IL-9, and IL-15, members of the γc cytokine family, is involved in multiple human diseases (eg, T-cell malignancies, GvHD, HAM/TSP) that are not effectively or safely treated by the currently available anti-cytokine approaches.

BNZ-1 is a selective inhibitor of IL-2, IL-9 and IL-15 signaling through γc, without altering IL-4, -7, or -21. In this open-label, single-dose study (NCT03046459), 18 healthy adults (n=3/dose) received a single IV dose of 0.2, 0.4, 0.8, 1.6, 3.2 or 6.4 mg/kg and were monitored for 30 days. BNZ-1 was well-tolerated with a good safety profile (no serious/severe AEs, no DLTs, and no clinically-significant changes on labs, vital signs or ECGs).

BNZ-1 exposure was dose proportional with an elimination t1/2 of ~5 days, supporting weekly or every other week dosing. PD activity was characterized by flow cytometry of Tregs (IL-2), NK cells (IL-15) and CD8+ central memory T-cells (Tcm; IL-2 & IL-15) in PBMCs from Days 4, 15 & 31. Tregs were decreased by 50-60% after doses of 0.4-1.6mg/kg on Day 4 and by 80-93% at 3.2 and 6.4 mg/kg on Day 15. On Day 4 NK cells decreased by 20, 40 and 60% at 0.2, 0.4 and 0.8mg/kg, respectively, and plateaued at 70-80% decreases at doses ≥1.6 mg/kg. Tcm were decreased at Day 4 for the top 3 doses that continued to decline to Day 15 when all doses, except 0.2 mg/kg, showed a mean decrease ranging from 10 to 81% that trended with dose. Tregs, NK cells, and Tcm returned to/toward baseline by Day 31. CD4+ and CD8+ T-cells, B-cells, and monocytes were unchanged at all time points.

These clinical data suggest that BNZ-1 is a highly-active, selective immunomodulator that safely decreases Tregs, NKs and Tcm, while sparing the major leukocyte populations.

Fc Bridged Cellular Cytotoxicity (FcBCC): a novel mechanism by which NK cells recognize HSV

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The initial infection by herpes simplex virus 1 (HSV1) is usually a self-limited event, but the mechanism of this protection prior to the development of a primary humoral response is unknown. Individuals deficient in natural killer (NK) cells can suffer from overwhelming and at times fatal HSV1 infection. The NK cell surface is naturally coated with IgG that is bound to Fcy receptor CD16a. Here we show that human NK cells utilize the Fc portion of IgG bound to its cell surface to recognize gE, an HSV1-encoded glycoprotein that also binds the Fc portion of IgG but at a site distinct from that of CD16a. The Fc-bridge formed between the HSV1-infected cell and the NK cell results in NK cell activation and spontaneous lysis of the HSV-infected cell in the absence of HSV-specific antibody. In vivo, the absence of the Fc portion of human IgG, or of NK cells, results in death from primary HSV1 infection. This mechanism, which we call Fc bridged cellular cytotoxicity (FcBCC) may be broadly applicable to Fcy receptor-bearing immune cells and other pathogens encoding Fc-binding proteins.

Cancer Vaccine: Tumor Immunology meets...Immunology

Roberto Accolla, MD, PhD, University of Insubria

Although recent therapeutic approaches have revitalized the enthusiasm of the immunological way to combat cancer, still the comprehension of the immunity against tumors is largely incomplete. Due to their specific function, CD8+ T cells with cytolytic activity (CTL) have attracted the attention of most investigators because CTL are considered the main effectors against tumor cells. Nevertheless, CTL activity and persistence are largely dependent on the action of CD4+ T helper cells (TH). Thus establishment of tumor-specific TH cell response is key to the optimal response against cancer. I will describe emerging new strategies to increase the TH cell recognition of tumor antigens. In particular, I will present recent data indicating that tumor cells themselves can act as surrogate antigen presenting cells for triggering TH response if genetically modified to express the MHC class II transcriptional activator CIITA. Indeed, injection of CIITA-modified tumor cells of distinct histological origin and of distinct MHC genetic background triggering TH response if genetically modified to express the MHC class II transcriptional activator CIITA. Indeed, injection of CIITA-modified tumor cells of distinct histological origin and of distinct MHC genetic background into syngeneic recipients induces strong protective and long-lasting adaptive immune response that can be transferred to naive recipients by CD4+ TH cells. Depletion of dendritic cells does not modify the capacity to reject the tumor and to acquire immunological memory. These results challenge the immunological dogma that dendritic cells are the exclusive cells capable of inducing T cell priming. The strategy of modifying tumor cells with CIITA has been applied for the production of a novel generation of anti-tumor vaccine against human hepatocarcinoma that is now in clinical trial.
Luigi Buonaguro, MD, National Cancer Institute “Fondazione Pascale”

Hepatocellular (HCC)/normal adjacent tissue matched samples have been collected for HLA immunopeptidome analysis. 17 HCC samples from HLA-A*02+ patients and 15 samples from HLA-A*24+ patients have been analysed by mass spectrometry. RNA-expression profiles have been established for 12 HCC samples. HLA-presentation/expression of peptides on primary HCC samples (as well as mRNA expression) were compared to normal tissue samples from relevant organs (including heart, brain, lung, kidney, liver, nerve, skin etc.) present in the Immatics’ database.

A total of 16 peptides have been selected and confirmed for immunogenicity for the HepaVac vaccine and are currently synthesized according to GMP standard. Of these, 7 are restricted to HLA-A*02; 5 to HLA-A*24 and 4 to HLA class II.

A single-arm, first-in-man trial entitled HepaVac-101 is designed to investigate in patients with very early, early and intermediate stage of HCC the off-the-shelf multi-peptide-based HCC vaccine (IMA970) plus the CV8102 adjuvant (RNAdjuvant®) following a single pre-vaccination infusion of low-dose cyclophosphamide acting as an immunomodulator. The study drugs are applied without concomitant anti-tumor therapy with the intention to reduce risk of tumor recurrence/progression in patients who have received all indicated standard treatments. The primary endpoints are safety, tolerability, and immunogenicity. Secondary/exploratory endpoints are additional immunological parameters in blood (e.g. regulatory T-cells, myeloid-derived suppressor cells, impact of the standard therapy on the natural immune response), infiltrating T-lymphocytes in tumor tissue, biomarkers in blood and tissue, disease-free survival/progression-free survival and overall survival.

Long Wu, Huan Zhang, Yixing Jiang, Robert Gallo, Hua Cheng, Institute of Human Virology, University of Maryland Baltimore School of Medicine

Dendritic cell (DC)-based immunotherapy has achieved modest clinical benefits, however, several technical hurdles in DC preparation, activation and cancer-associated antigen (TAA) delivery limit its broad applications in cancer therapy. We have developed immortalized and activated human primary blood dendritic cell (DC) lines, ihv-DCs. Human primary blood dendritic cells can be immortalized from several cc of peripheral blood and can be expanded at large quantity at normal cell culture condition. The ihv-DCs are a subset of CD11c+/CD205+ DCs that persistently display co-stimulatory molecules and produce interferon gamma. These DCs are engineered to constitutively express a TAA such as hTERT, which prime donor-derived T cells to generate antigen-specific CTLs that induce cytolysis of hTERT-expressing target cells in an HLA-A2-restricted manner. In addition, the engineered DCs are able to induce simultaneous production of both anti-cancer CTLs and NK cells from naïve PBMCs. In NSG mouse model, infusion of the activated CTLs and NK cells that are generated from naïve PBMCs using the engineered DCs suppress lung metastasis of human lung cancer cells. Both CTLs and NK cells are found to infiltrate lung as well as lymphoid tissues, mimicking the in vivo trafficking patterns of cytotoxic lymphocytes. This new approach should facilitate the development of cell-based immunotherapy for human lung cancer.

John Moore, PhD, Weill Cornell Medicine

I will review the progress of our team’s projects to produce GMP-quality SOSIP trimers in amounts and quantities appropriate for human clinical trials. The BG505 SOSIP.664 GMP-project has now been completed successfully, yielding ~5 grams of trimers. A follow-up on effort to make the germline–bNAb targeting BG505 SOSIP.v4.1-GT1.1 trimer is well underway, using the same core methodologies. The latter trimer was designed at the Amsterdam Medical Center and is very similar to one recently described by Medina-Ramirez et al. in J Exp Med.

This project stems from our NIH-funded HIVRAD grant program and the translation phase has been supported and managed by the BMGF and IAVI, reflecting the three funding agencies working together towards a common goal.
The current availability of an incredible array of monoclonal antibodies (mAbs) with potent neutralizing activity against a broad range of HIV-1 isolates creates attractive possibilities for treatment and prevention. An ability to achieve stable levels of protective mAb concentrations long-term via vector delivery has a number of distinct advantages over repeated passive administrations. These include cost, issues relating to adherence, and convenience. Using AAV as vector, we have achieved stable concentrations of authentic IgG mAb in monkeys in excess of 100 ug per ml of serum for as long as 3.5 years, the longest we have measured. In the one SHIV-infected monkey to which we have successfully delivered two anti-HIV mAbs, viral loads have been impressively suppressed from 11,000 at the time of AAV administration to below the limit of detection for more than 22 months in the absence any antiviral drug treatment. The main obstacle hindering development of this approach for use in humans is anti-drug antibodies, i.e. the development of an antibody response to the delivered antibody that can severely impair the concentrations of delivered antibody that can be achieved. These anti-antibodies are predominantly or exclusively directed to the variable domains, i.e. they are anti-idiotype. This is especially a problem because the mAbs with potent neutralizing activity that we want to deliver for the most part are highly divergent from germline and have unusually long CDR3 regions. We now appear to have found vector design and vector delivery conditions that allow consistent delivery of problematic anti-SIV/anti-HIV mAbs. Nonetheless, continued work is needed to effectively realize the full potential of this approach.
Mohammad M. Sajadi, Amir Dashti, Marzena Pazgier, William D. Tolbert, Michael S. Seaman, Xin Ouyang, Dongkyoon Kim, Guy Cavet, Robert R. Redfield, George K. Lewis, and Anthony L. DeVico

Using a new methodology to obtain the sequences of antibodies in circulation, we have discovered a family of antibodies of remarkable breadth and potency: the N49 P series. Some members of this family have the capability to neutralize 100% of isolates tested in a Tier 1-3 multiclade 117 pseudovirus panel, including all pseudoviruses that were resistant to other mAbs tested in the same panel (PGT121, GT 128, PGT 145, PGDM1400, PGT 151, 10-107 4, 10E8, PG9, PG16, 3BNC117, NIH 45-46, BANC195, VRC01, and VRC07). Elisa studies and sequence analysis show the N49 mAbs to have some characteristics of CD4-binding site antibodies. However, crystallographic studies show a bypassing of the CD4-binding site pocket in favor on the inner domain. The N49 P series has potential to be useful in passive immunization and prophylactic vaccine design for HIV-1.

Thomas Lehner, MD, Kings College London, University of London; Durdana Rahman, PhD, University of London; Yufei Wang, MD, University of London; Trevor Wittall, PhD, University of London

A robust immunological memory is critical for the longevity of any vaccine. We have demonstrated CD4+ T stem cell memory (TSCM) in the Thai RV144 HIV-1 vaccine clinical trial. Comparable TSCM were demonstrated in the mucosal vaccination of women, using HIVgp140-HSP70 conjugate administered by the vaginal route. TSCM can be upregulated by recombinant IL-15 or DC membrane associated IL-15 (maIL-15) by a variety of stress agents, such as thermal, oxidative or ionophore, which we studied in vitro. Recombinant IL-15 elicited >3-fold increase and DC maIL-15 >2-fold increase in CD4+ TSCM. Both systemic and mucosal immunization elicited lower TSCM than the in vitro activated cells. Surprisingly, recall of past exposure to immunogens, such as PPD, showed similar increase to PPD as that to the stress agent. This was shown for CD4 proliferative responses, Th1 cytokines and CC chemokines. As both the homeostatic and inflammasome pathways may be stimulated by stress agents, inhibition studies were carried out to validate this for TSCM. Indeed both pathways may be involved in CD4+ T cell proliferation, though the homeostatic pathway is more significant than the inflammasome one. These studies support the concept that stress agents are important in eliciting and maintaining CD4+ TSCM cell longevity in vaccination.

Guido Silvestri, MD, Emory University

While the availability of potent anti-retroviral therapy, ART, has dramatically reduced the mortality and morbidity associated with HIV infection, no intervention that can functionally “cure” the infection is yet available. This is due to a persistent reservoir of latently infected cells that is resistant to both ART (which targets specific phases of the “productive” virus life cycle) and immune-based interventions (which require expression of viral proteins as target antigens). Over the past few years, the non-human primate model of SIV/SHIV infection of rhesus macaques has been developed and validated for studies of HIV eradication in the setting of fully suppressive ART. In this presentation, I will review: (i) the opportunities presented by the SIV/SHIV macaque models to conduct studies aimed at developing and testing novel interventions to achieve a functional cure for HIV infection; (ii) the main immune-based strategies that are currently explored to reduce or eliminate the virus reservoir in the NHP model (i.e., shock & kill, block & lock; soothe & schmooze; push & vanish; as well as transplant and gene therapy); and (iii) the published and ongoing preclinical trials of immune-based interventions that are conducted by our team in ART-treated SIV-infected rhesus macaques with the goal of inducing a functional cure. Among the used interventions I will discuss type I interferons, interleukin-21, FTY720, check-point blockade inhibition (i.e., inhibitors of PD-1, CTLA4, and LAG-3), CD8+ T cell depletion, CD4+ T cell depletion, and autologous stem cell transplantation.

John Mellors, MD, University of Pittsburgh

The favored initial approach by many to depleting HIV reservoirs and achieving an HIV cure was the “shock and kill” strategy, consisting of “shocking” proviruses out of latency and killing the cells with newly expressed viral antigens, either by direct viral-mediated cytotoxicity or immune-mediated clearance. However, in vitro models showed that proviral latency reversal alone did not result in death of infected cells (Shan, et al. Immunity 2012). Ex vivo experiments revealed that only a small fraction of proviruses (~1.5%) can be reactivated to produce virions with maximum CD4+T-cell activation, and that <1% are reactivated with current, small molecule latency reversing agents (Cillo, et al. PNAS 2014). In addition, maximum CD4+T-cell activation can cause the expansion of clones carrying intact proviruses capable of sustained production of infectious virus (Bui, et al. PLoS Pathogens 2017). With regard to immune-mediated killing of infected cells, increasing antibody-dependent effector functions including ADCC, ADCP, and ADCF is a popular approach, but a recent trial (ACTG A5342) of two doses (40 mg/kg) of the bnMAb VRC01 revealed that is had no effect on persistent viremia and did not decrease the number infected cells in blood or the subset expressing viral RNA. Although many more approaches to “shock and kill” are in development and being tested alone and in combination, these initial data summarized above suggest that the goal of reservoir depletion may be more difficult to achieve than anticipated because of barriers to latency reversal and resistance of infected cells to immune-mediated clearance.
Clonal proliferation of CD4 T cells encoding intact HIV-1.

Mathias Lichterfeld, MD, Ragon Institute

HIV-1 causes a chronic, incurable disease due to CD4 T cells that contain replication-competent provirus but exhibit little or no active viral gene expression, and effectively resist combination antiretroviral therapy (cART). Such latently-infected CD4 T cells possess a remarkable long-term stability and typically persist life-long, for reasons that are not fully understood. We have used massive single-genome, near full-length next-generation sequencing of HIV-1 DNA derived from unfractionated PBMC, ex vivo-isolated CD4 T cells, and phenotypically complex memory CD4 T cells from peripheral blood and lymphoid tissues to characterize the dynamics and underlying mechanisms supporting viral persistence. These studies demonstrated multiple sets of independent, near full-length proviral sequences from cART-treated individuals that were completely identical, consistent with clonal expansion of CD4 T cells harboring intact HIV-1. Interestingly, we found that Th1 CD4 T cells, typically responsible for antiviral immune defense, seem to harbor the majority of such clonally-expanded intact proviruses in cells from peripheral blood. In addition, we noted that cells harboring clonally-expanded proviral sequences frequently expressed cell surface markers known to protect CD4 T cells during the vulnerable phase of clonal proliferation, suggesting that HIV-1-infected CD4 T cells rely on physiological mechanisms for maintaining viral reservoir stability through clonal expansion. A closer longitudinal analysis of intact proviruses in distinct CD4 T cell subsets in future studies will be highly informative for developing targeted interventions for viral reservoir manipulation in clinical settings.

Reversible HIV-1 Latency Induced in Primary Human Monocyte-Derived Macrophages by Repeated M1 Polarization

Francesca Graziano, PhD, Institut Curie, Paris, France; Giulia Aimola, MS, San Raffaele Scientific Institute, Milano, Italy; Greta Forlani, PhD, University of Insubria, Varese, Italy; Filippo Turrini, PhD, San Raffaele University, Milano, Italy; Roberto Accolla, MD, University of Insubria, Varese, Italy; Elisa Vicenzi, PhD, San Raffaele Scientific Institute, Milano, Italy; Guido Poli, MD, San Raffaele University, Milano, Italy.

The contribution of tissue-associated macrophages to the viral reservoir in HIV-1 infected individuals receiving cART remains highly debated. In this regard, we have previously reported that functional M1 polarization of primary human MDM by short-term (18 h) stimulation with pro-inflammatory cytokines (IFN-γ plus TNF-α) leads to a significant containment of virus replication. Here, we demonstrate that restimulation of infected M1-MDM with the same pro-inflammatory cytokines 7 days after infection (M12 MDM) leads to a superior containment of virus replication to near undetectable levels, as determined by RT activity released in culture supernatants, in comparison to both control (CTR) MDM and to M1-MDM that were not restimulated by polarizing cytokines. M12 MDM showed an upregulation of APOBEC3A and 3G, with a significant reduction of HIV DNA and viral lack of viral mRNA expression together with the expression of transcriptional inhibitors of proviral gene expression, namely CIITA and TRIM22, although expression and phosphorylation of transcriptional inducers of HIV-1 provirus, such as NF-kB and STAT-1, were not impaired. Latently infected M12-MDM harbored replication-competent virus that was promptly reactivated by allogeneic PHA blasts or their culture supernatant. Thus, our study provides a formal demonstration that a state of reversible latent HIV-1 infection can be established in primary human MDM upon their repeated M1 polarization by stimulation with pro-inflammatory cytokines before and after in vitro infection leading to a dominance of restrictive over permissive factors.

Chromatin Functional States Correlate with the Reversal of Latently HIV-1 Infected Primary CD4+ T cells

Emilie Battivelli, Matthew S. Dahabieh, Mohamed Abdel-Mohsen, J. Peter Svensson, Israel Tojal Da Silva, Lilian B. Cohn, Andrea Gramatica, Steven Deeks, Warner Greene, Satish K. Pillai, Eric Verdin

Current antiretroviral therapies (ART) do not allow for the eradication of the human immunodeficiency virus (HIV) due to the presence of latent proviruses in rare, long-lived resting CD4+ T cells. The main research efforts to eliminate the viral reservoir are focused on the use of latency reversing agents (LRAs) to force the reactivation of the latent provirus, while maintaining ART to prevent de novo infections. Subsequently, reactivation of HIV expression would kill reservoir cells via viral cytopathic effects and/or immune clearance (“shock and kill” strategy). So far, no LRAs tested in clinical trials have succeeded in reducing the reservoir. Furthermore, there is limited understanding as to why some latent proviruses are being induced, while others are not.

We used an improved dual-fluorescent HIV reporter (GKO), which distinguishes productively infected cells from the latent population, to investigate the efficacy of the “shock and kill” strategy. In addition, GKO provides a unique opportunity to (1) explore the impact of HIV integration site specificity on the fate of the infection, and to (2) characterize the inducible subpopulation of latently infected cells, since it allows the isolation of inducible latent and non-inducible latent populations from the productively infected majority.

We first showed that our patients’ data was consistent with previously published studies. However, we found that at most 5% of GKO latent proviruses were reactivated. Moreover, the analysis of HIV-1 integration sites from productively, non-inducible and inducible latently infected populations reveals heterogeneity within the latent infections. In contrast to non-inducible latent infections, the integration sites of inducible latent proviruses have similar features to those of productive proviruses, thus demonstrating a prominent role for the site of integration and its chromatin context for the fate of the initial infection as well as for latency reversal.

Our study shows an important roadblock for the “shock and kill” approach to reservoir eradication. Differences between inducible and permanently latent reservoir cells suggest that complete reservoir reactivation and eradication with LRAs may prove impossible, and that a multipronged “functional cure” approach may be necessary.
A major challenge in HIV-1 vaccine design is to generate antibodies directed toward conserved broadly neutralizing epitopes on the surface-exposed viral envelope glycoprotein (Env). Most conserved epitopes are masked by self N-glycans, limiting naïve B cell recognition of the underlying protein surface following Env vaccination or during natural infection. Recently, soluble faithful mimics of the HIV Env spike have been developed, including the stabilized cleavage-independent NFL (native flexible linked) trimers, but their capacity to elicit broadly cross-reactive tier 2 (clinical isolate) neutralizing responses has so far been limited. The conserved primary receptor, CD4 binding site, is a known neutralizing determinant, but is flanked by self-N-linked glycans, limiting B cell and antibody access to this site. Here, we eliminated up to four N-glycans surrounding the CD4 binding site of the NFL trimer without affecting trimer stability or conformation, as demonstrated by multiple biophysical methods and EM. Using these well-ordered trimers, we arrayed them at high density on synthetic liposomal nanoparticles because, as we have shown, this multivalent trimer array enhances B cell activation, germinal center formation and the elicitation of HIV neutralizing antibodies. We performed immunogenicity experiments in animal models, demonstrating that the N-glycan-deleted trimers elicited superior neutralizing responses as a prime for fully glycosylated trimers, compared to multiple immunizations with fully glycosylated trimers alone. The N-glycan deleted priming also resulted in detectable cross-neutralization of a small subset of tier 2-like viruses following boosting. The approach of N-glycan deletion as a prime, coupled with multivalent trimer array, is a promising means to elicit better HIV cross-neutralizing antibodies.

**D-108**

**Innate-primed alternative signaling pathways enhance functional mucosal mobilization of memory-like NK cells in HIV/SIV infection**

Keith Reeves, PhD, Harvard Medical School

Burgeoing evidence indicates a broader functional repertoire for NK cells beyond innate immunity including adaptive functions. Specifically, memory-like NK cells lacking the FcR γ-signaling chain (FcRΔγg-NK cells) still require antibody to grant antigen-specificity, but are pre-sensitized for rapid mobilization against viral antigens. Interestingly, FcRΔγg-NK cells require innate priming by CMV, but execute memory-like killing against HIV and SIV through poorly understood mechanisms.

Sixty rhCMV−, rhCMV+, and chronically SIV-infected macaques were studied and compared to thirty naïve and untreated HIV-infected humans. FcRΔγg-NK cells were systemically distributed but, correlating with viral load, increased four-fold in CMV+ and HIV/SIV-subjects, including in the G1 tract. Upregulated CD16 and CD56 suggested memory-like priming is required for both antibody-dependent functions and mucosal homing. FcRΔγg-NK cells exhibited two-fold more robust IFN-γ secretion and cytotoxicity in the presence of antibody, but reduced expression of Helios and Eomes — indicative of epigenetic modifications, and clustered independently from traditional NK cells in multidimensional t-SNE. The γ-chain adaptor, Syk was absent or dephosphorylated in FcRΔγg-NK cells, but ζ-chain, phosphorylated by adaptor Zap70, was significantly upregulated, indicating use of the alternative ζ-chain/Zap70 pathway to achieve greater functional potency.

Our work presents the first description of a combinatorial mechanism of innate-priming and alternative signaling to explain the memory-like phenomena of NK cells mobilized against HIV/SIV. Future studies harnessing memory-like NK cells could create exciting modalities for both vaccine and curative therapies.

**D-109**

**Defining a Potent New Class of Latency Reversing Agents Devoid of Toxicity and Detrimental Cell Activation That Enhance CTL/NK Cell Killing**

Andrea Gramatica1, Roland Schwarzer1, Mauricio Montano1, Eytan Herzig1, Thomas Packard1, and Warner C. Greene1,*

Despite long-term administration of antiretroviral therapy (ART), HIV-1 persists in a broadly distributed latent reservoir mainly comprised of resting CD4+ T cells. Cells harboring latent provirus typically display little to no HIV-1 gene expression and thus remain invisible to the immune system. To achieve a durable sustained viral remission in HIV-infected patients off ART (a functional cure), it will be important to both reduce the size of the reservoir and to control viral rebound by eliciting an effective immune response capable of restraining viral spread from the smaller reservoir. This approach will likely require the combined use of potent and safe latency-reversing agent (LRA) and a therapeutic HIV vaccine.

Our recent studies have shown that activators of the AKT/mTOR pathway form a promising group of LRAs. Our interest has focused on two small molecules, SB-216763 and Tideglusib that commonly inhibit glycogen synthase kinase-3 (GSK-3). This inhibition triggers a metabolic shift to glycolysis and results in sequential activation of mTORC2, AKT, and mTORC1. Both compounds are known to have high tissue penetration including the brain.

We found that these GSK-3 inhibitors potently activate latent HIV-1 in both a tissue-based model of HIV latency formed in primary CD4 T cells, and in CD4 T cells isolated from HIV-infected patients. In some experiments, these agents are more potent than anti-CD3/anti-CD28 antibodies even though the GSK-3 inhibitors do not appear to induce T cell activation (measured by changes in CD69 and CD25 expression). Finally, in contrast to the undesirable compromise of CTL/NK function associated with many first generation LRAs (PKC activators, HDAC inhibitors), the GSK-3 inhibitors actually enhance CTL and NK cell effector function.

In summary, our findings reveal GSK-3 inhibitors as an interesting new class of potent, safe, non-cell activating LRAs. Next, it will be key to define their activity in vivo using SIV-infected macaques on suppressive ART. The fact that tideglusib is already in phase II human trials for myotonic dystrophy and autism could accelerate its ultimate testing as an LRA in HIV-infected patients.

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D-110
Synergism between CRISPR/Cas9 and LASER ART leads to elimination of HIV-1 with no rebound in Humanized Mice

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Treatment with long acting slow effective release (LASER ART) rilpivirine, myristoylated dolutegravir, lamivudine and abacavir followed by CRISPR-Cas9 proviral DNA excision led to viral eradication in HIV-1 infected humanized mice. Ultrasensitive nested and digital droplet PCR and RNA scope assays failed to detect HIV-1 in blood, spleen, lung, kidney, liver, gut-associated lymphoid tissue and brain in twenty-nine percent of infected animals treated with the dual regimen. Excision of proviral DNA fragments spanning the LTRs and the Gag gene were identified without identifiable off target effects. The absence of viral rebound following cessation of ART with no progeny virus recovery served to verify HIV-1 eradication. In contrast, HIV-1 was readily detected in all infected animals treated with LASER ART or CRISPR-Cas9 alone. Thus, sequential application of LASER ART and CRISPR-Cas9 therapies administered to HIV-1 infected humanized mice provides the proof of concept that viral sterilization is possible.

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D-111
Influence of age on immune response to influenza vaccination in virologically suppressed HIV infected persons

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Background: Approximately 5–20% of the US population contracts influenza infection annually with >200,000 hospitalizations and >35,000 deaths that occur mainly in older adults. We investigated determinants of immune response to influenza vaccine in relation to aging and concurrent HIV infection.

Methods: 154 HIV infected (HIV+) virologically controlled persons on ART and 161 HIV uninfected (HIV−) grouped by age as young (<40 yrs), middle aged (40-59 yrs) and old (≥60 yrs) were given trivalent influenza vaccination. Serological responses to influenza vaccine antigens were correlated with cellular immune activation (IA), plasma markers of inflammation, and immune phenotype and function of peripheral leukocytes, including peripheral T follicular helper cells (pTfh).

Results: Absolute responders with >4 fold increase in titer to all the vaccine antigens were fewer in HIV+ (14%) than in HIV− (32%), lower in old compared to young, and inversely correlated with age for Ab to H1N1 and B antigen. Several immunologic markers were negative predictors of the vaccine response in HIV infection; these included higher levels of activated pTfh, monocytes expressing inflammatory marker CD11b, activated naïve B cells, checkpoint inhibitor Tim3 on CD4 T cells and high plasma sCD25. Positive correlations were found with frequencies of bulk and antigen specific pTfh cells exhibiting high IL-21 and low IL-2 expression and lacking in inflammatory cytokines (TNFa, IL17) production. Although more deficiencies were evident in HIV+ old compared to other groups, the differences between HIV+ and HIV− for Ab responses and immunologic markers were maximal in young age.

E-101
Infectious Disease - Public Health Response

Boris Lushniak, MD, MPHD, University of Maryland College Park School of Public Health

E-102
Policy, Practice and Science in Nigeria: Implementing Evidence Based Research for HIV programming in Nigeria

Isaac F. Adewole, MBBS(Ib), FWACS, FMCOG, FAS, FRCOG, DSc(Hons), Honourable Minister of Health, Federal Ministry of Health, Abuja, Nigeria

Nigeria with a population of over 180 million currently has a national estimate of 3% prevalence of HIV infection. Briefly, 3 million people are living with HIV; 160,000 pregnant women living with HIV and pediatric HIV infection account for about 30% of global burden. Following the assumption of office by President Muhammadu Buhari in 2015, the country initiated plan and began an aggressive drive in revitalizing the healthcare system towards attainment of Universal Health Coverage in the country.

This presentation will chronicle policies, practices and evidences generated in-country on biology of HIV infection, transmission and management as well other non-orthodox claims of cure. The socio-cultural interpretations, perceptions and behaviours as it affects HIV infection within Nigerian space will be highlighted. The concluding section of the presentation will focus on key priority areas of HIV programming and research that requires international collaborations.
Kashef Ijaz MD, MPH, Principal Deputy Director, Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA

Diseases know no boundaries; a health threat anywhere is a health threat everywhere. New viral and bacterial pathogens continue to emerge and in today’s tightly connected world a disease can be transported from an isolated rural village to any major city in as little as 36 hours. The recent Ebola epidemic clearly demonstrated that at majority of the countries (at least 70%) are not prepared to respond to disease events. It also emphasized the overdue and urgent need to implement core capacities of WHO’s International Health Regulations (IHR, 2005). This would help countries have the ability to prevent, detect and respond to infectious disease threats at source, which will not only reduce morbidity and mortality but also the economic impact for the developing countries as well as globally. At present, 65 countries have committed to implement the Global Health Security agenda that supports the implementation of IHR, 2005. Examples from its recent accomplishments and achievements have demonstrated the ability of countries to conduct timely disease surveillance and response to public health events.

E-104
Virus genomes reveal factors that spread and sustained the Ebola epidemic

Gytis Dudas, PhD, Fred Hutchinson Cancer Research Center

The 2013–2016 West African epidemic caused by the Ebola virus was of unprecedented magnitude, duration and impact. Here we reconstruct the dispersal, proliferation and decline of Ebola virus throughout the region by analysing 1,610 Ebola virus genomes, which represent over 5% of the known cases. We test the association of geography, climate and demography with viral movement among administrative regions, inferring a classic ‘gravity’ model, with intense dispersal between larger and closer populations. Despite attenuation of international dispersal after border closures, cross-border transmission had already sown the seeds for an international epidemic, rendering these measures ineffective at curbing the epidemic. We address why the epidemic did not spread into neighbouring countries, showing that these countries were susceptible to substantial outbreaks but at lower risk of introductions. Finally, we reveal that this large epidemic was a heterogeneous and spatially dissociated collection of transmission clusters of varying size, duration and connectivity. These insights will help to inform interventions in future epidemics.

F-102
Inflammation and immune modulation: tackling age-related stem cell dysfunction

Heinrich Jasper, PhD, Buck Institute for Research on Aging

In aging and diseased tissues, regeneration and regenerative therapies are limited by stem cell dysfunction and unfavorable tissue environments. Promising strategies to improve success include interventions that enhance stem cell function and that harness and boost endogenous tissue repair mechanisms. We study stem cells and tissue repair in barrier epithelia and the retina of Drosophila and mice to explore the causes and consequences of age-related regenerative dysfunction. These studies have led to the discovery of interventions targeting age-related inflammation, stem cell proliferation, stem cell metabolism, innate immune responses, and the commensal microbiota as strategies to enhance regeneration and extend lifespan. I will discuss these strategies and provide perspectives for the development of targeted interventions to improve tissue function in the elderly. I will highlight strategies to improve stem cell activity by targeting endogenous proliferation, differentiation and nutrient response pathways, and strategies to improve tissue repair by modulating innate immunity and host/commensal interactions. Combining such strategies is likely to significantly improve tissue homeostasis and regenerative therapies in the elderly, ultimately extending the healthy years of life.

F-103
Targeting Aberrant Transcription in Pre-Cancerous Stem Cells

Ulrich G. Steidl, MD, PhD, Albert Einstein College of Medicine

Relapse continues to be the most common cause of death in acute myeloid leukemia (AML) and many other cancers. Recent evidence has shown that the accumulation of stepwise genetic and epigenetic changes in tissue-specific stem cells lead to the formation of pre-cancerous/pre-leukemic stem cells (pre-LSC) that play a pivotal role not only in disease origination but also in relapse. While the existence and essentiality of such pre-cancerous cell states has been demonstrated in mice and humans, still very little is known about the molecular mechanisms driving pre-LSC origination and progression. We have recently performed molecular studies of pre-leukemic cell states in mouse genetic models as well as primary cells from patients, and discovered new transcription factors and regulatory mechanisms in pre-LSC in myelodysplastic syndromes (MDS) and AML. We have uncovered critical roles for several transcription factors in pre-LSC, and found that enhancer haplodeficiency and resulting minimal reduction of key transcription factors can be sufficient to induce pre-LSC formation and subsequent progression to MDS and AML. Such models provide novel tools for mechanistic study of pre-LSC and their progression to overt MDS and AML, and for the development and testing of pharmacological approaches to therapeutically interfere with these processes.

In summary, recent studies have started to shed light on pre-cancerous stem cell states as the earliest origin of various malignancies including MDS and AML, as well as molecular mechanisms driving their formation and progression. These advances provide a basis for the specific therapeutic targeting of pre-cancerous stem cells for the causative treatment of MDS and AML and other cancers.
F-104
Decoding the regulatory networks of Leukemic Stem Cells through Ubiquitylation

Chozha Rathinam, PhD, Institute of Human Virology, University of Maryland Baltimore School of Medicine

In the recent years, it has become increasingly evident that hematopoietic stem cells (HSCs) are directly involved in the recognition of both acute and chronic infections. HSCs sense immune insults by both cell intrinsic, through the pattern recognition receptors (PRRs), and extrinsic, mediated mainly by the pro-inflammatory cytokines, mechanisms. However, prolonged exposure of HSCs to inflammatory conditions results in defective differentiation of the immune cells. Even though earlier studies suggested that a tight control on inflammatory signals is essential for proper development of the immune system, precise molecular mechanisms that control inflammatory signals in HSCs and the effects of individual pro-inflammatory cytokines on HSC fate decisions have not been elucidated. In this study, we utilized several animal models including mice that either lack the ubiquitin editing enzyme-A20, that functions as a negative regulator of NF-κB, or express a constitutively active form of IKK2, which results in augmented NF-κB signals, in the presence or absence of specific pro-inflammatory cytokines, to study the impact of inflammation in the determination of HSC fate. Our data indicate that deregulated NF-κB signals in HSCs lead to pathologic hematopoiesis, including a striking loss of lymphoid differentiation and skewing towards the myeloid lineage. Furthermore, NF-κB mediated lymphopenia was caused by both cell intrinsic (changes in genetic and molecular signatures) and extrinsic (elevated expression of pro-inflammatory cytokines) mechanisms. At this annual meeting, we would be discussing the precise molecular pathways through which inflammatory signals affect the development of Normal and Leukemic Stem Cells.

G-102
Endemic Burkitt lymphoma and infectious agents in cancer: new results from the EMBLEM study implicating falciparum malaria and Epstein-Barr virus in causation

Sam Mbulaiteye, MBChB, MPhil, MMed, National Cancer Institute

The human leukaemia virus HTLV-1 causes chronic inflammatory disease or an aggressive T-cell malignancy in about 10% of infected people. The risk of these diseases is strongly correlated with the proviral load, which frequently exceeds 10% of peripheral blood mononuclear cells. The high proviral load is limited by a strong, chronically activated host immune response. HTLV-1 does not release cell-free virions, but propagates both within and between hosts by cell-to-cell contact, via the virological synapse. Until recently, HTLV-1 was thought to be latent in vivo, and persisted chiefly by continuous oligoclonal proliferation of about 100 clones of HTLV-1-infected CD4+ T cells. However, we have shown that a typical individual carries between 10^4 and 10^5 clones, and the proviral load – the chief correlate of disease – is determined by the number of clones, not by oligoclonal proliferation. We recently discovered that HTLV-1 alters host chromatin structure in the infected cell, by binding the chromatin architectural protein CTCF, which regulates higher-order chromatin structure and gene expression in vertebrates. Thus, HTLV-1 does a remarkable experiment of nature, by changing the conformation of chromatin in tens of thousands of different ways in each infected host. Two broad questions are raised: first, how does CTCF benefit the virus? Second, how does the change in chromatin structure affect the host? I will show that the abnormal chromatin looping caused by CTCF can deregulate host gene expression and so may act as an oncogenic driver. I will also present evidence that HTLV-1 plus-strand is expressed in intense, intermittent bursts, and that expression minus strand is not, as is currently believed, constitutive.

G-101
Human papillomaviruses and carcinogenesis: well-established and novel models

Massimo Tommasino, PhD, International Agency for Research on Cancer

Human papillomaviruses (HPVs) infect the cutaneous or mucosal epithelia. More than 200 HPV types have been isolated so far, and they are classified phylogenetically as genera and species. Persistent infections by the mucosal high-risk (HR) HPV types from genus alpha have been clearly associated with cancer development of the genital and upper respiratory tracts. The products of two early genes, E6 and E7, are the major HR HPV oncoproteins, being essential in all steps of the carcinogenic process. They exert their functions by interacting with a large number of cellular proteins, including the products of tumour suppressor genes, and altering their properties. Biological and epidemiological data indicate that beta HPV types, together with ultraviolet (UV) radiation, promote non-melanoma skin cancer development. However, in contrast to the HR mucosal HPV types, cutaneous beta HPV types appear to be required only at an early stage of carcinogenesis, facilitating the accumulation of UV-induced DNA mutations. Several findings also suggest that these HPV types and other carcinogens may synergize in the induction of malignancies at different anatomical sites.
Role of Microbiome in Cancer

Giorgetto Trinchiero, MD, National Cancer Institute

Commensal microorganisms colonize barrier surfaces of all multicellular organisms, including those of humans. For more than 500 million years, commensal microorganisms and their hosts have coevolved and adapted to each other. As a result, the commensal microbiota affects many immune and non-immune functions of their hosts, and de facto the two together comprise one metaorganism. The commensal microbiota communicates with the host via biologically active molecules. Recently, it has been reported that microbial imbalance may play a critical role in the development of multiple diseases, such as cancer, autoimmune conditions, and increased susceptibility to infection. The commensal microbiota not only may affect the development, progression and immune evasion of cancer but it has also important effects on the response to cancer immune- and chemo-therapy. Myeloid cells are a major component of the tumor microenvironment where they play a dual role inducing anti-tumor immune responses but mostly promoting immune evasion, tumor progression and metastases formation. Myeloid cells respond to environmental factors including signals derived from commensal microbes that modulate their function and reactivity thus impacting the response to cancer therapy.

Carcinogenic Potential of Bacterial Biofilms

Cynthia Sears, MD, Johns Hopkins University

The colonic microbiome is hypothesized to contribute to the induction and progression of colon cancer. While select bacterial species have been implicated in colon carcinogenesis, recent data also suggest that bacterial community organization and composition are carcinogenic. Studies of paired surgical CRC samples and normal colon mucosa as well as colon biopsies of healthy controls undergoing screening colonoscopy revealed that sporadic colon tumors located proximal to the hepatic flexure are characterized by invasive polymicrobial biofilms that extend to normal colon tissue far distant from the tumor. In contrast, colon mucosal biofilms occur much less frequently in individuals with colon cancer distal to the hepatic flexure and in only about 15% of mucosal samples from healthy colonoscopy controls. This talk will present an update on the intersection of individual microbes, biofilms and mechanisms of colon carcinogenesis. Together our studies support a model by which specific bacteria with their virulence genes as well as microbiota organization act with host immune responses to contribute to colon cancer pathogenesis.

HPV vaccines: where are we now, and where are we going?

Cornelia L. Trimble, MD, Johns Hopkins University School of Medicine

On a global scale, at least 20% of human malignancies are caused by known infectious pathogens. Most are viruses; of these, human papillomavirus (HPV) causes more cancers than any other. In populations which do not have herd immunity because of insufficient uptake of the preventive vaccines, HPV infections are endemic, in part, because they are asymptomatic. In the cervix, disease is clinically indolent. In immune-competent persons, a transition from the intraepithelial cancer precursor lesion, cervical intraepithelial neoplasia 3 (CIN3) or high grade squamous intraepithelial lesion (HSIL), to invasive carcinoma is thought to take on the order of 10-15 years. Moreover, not all HSILs progress to cancer; in a relatively short observational window, we and others have reported spontaneous regression of biopsy-confirmed cervical HSIL in a subset of women. The current standard of care treatment is surgical resection. In women who are HIV seropositive, less is known. Persistent infections are common, and the incidence of cervical cancer is three-fold that of immune-competent women.

HPV lesions are relatively accessible, thereby providing a clinical setting in which to better understand the immunobiology of disease, and to test proof-of-principle of potential non-surgical interventions. The infectious etiology presents an opportunity to manipulate immune responses to viral antigens. Indeed, the preventative HPV vaccines, Gardasil and Cervarix, are nearly (100%) effective in vaccinated persons. Immune-based therapies for established HPV disease would address two significant clinical settings: (1) in eradicating established cancer precursor lesions (CIN3/HSIL), and (2) in recurrent or metastatic HPV cancers. Early studies have established proof-of-principle in both. Challenges presented in eradicating HPV disease will be discussed, as well as strategies moving forward.
Most cervical cancers are caused by persistent infections with one of a dozen carcinogenic human papillomaviruses (HPV). The cancer risk differs by HPV genotype, with HPV16 and HPV18 accounting for over 70% of all cervical cancers. E6 and E7, are potent oncoproteins that inhibit apoptosis by disabling p53 and activate the cell cycle by disrupting the pRB pathway. In addition, the viral oncogenes cause major chromosomal instability already at precancerous stages and may induce integration of the viral genome into the host cells. Despite these strong oncogenic features of HPV, only a small subset of HPV infections ever progress to precancer or cancer. Recently, the important role of host and viral methylation in the molecular etiology of cervical cancer has been recognized. We recently conducted a discovery effort that yielded a set of host gene methylation markers that showed promising performance to detect cervical precancer. Similarly, we recently showed that regions of the HPV genome of 11 carcinogenic types are highly methylated in women with CIN3 compared to women with transient infections, suggesting that methylation is a general phenomenon in the transition from infection to precancer. Methylation patterns were found to be similar between closely related HPV genotypes. These findings may improve our understanding of the molecular basis for viral persistence and increase our ability to identify women who are more likely to progress to cervical cancer. Measuring host or HPV DNA methylation could serve as a specific marker for cervical precancer in cervical cancer screening.

Potential of Integrase-defective Lentiviral Vectors for HIV vaccine delivery

Mary Klotman, MD, Duke University

The key mission of viruses is to spread within its ecological niche. To achieve their mission viruses must multiply efficiently, be available at appropriate body sites for transmission and yet not kill the host since extreme virulence that kills the host curtails the spread of viruses in a population as illustrated by SARS and Ebola viruses. HSV infects a very large fraction of human population and is therefore a successful pathogen. To achieve its mission the virus encodes functions of omission that fail to block host immune responses and functions of commission that specifically curtail its replication. The net effect is the evolution of a pathogen that controls its replication so as to maintain a high level of contacts between infected and uninfected individuals.

Towards a Universal Influenza Virus Vaccine

Peter Palese, PhD, Icahn School of Medicine at Mount Sinai

Despite FDA-approved vaccines and antivirals, seasonal and pandemic influenza remains a serious threat associated with substantial morbidity and mortality. While annual seasonal influenza virus vaccination is frequently effective – albeit underutilized in most countries – a safe universal influenza virus vaccine providing broad and long-lasting immunity would represent a major breakthrough. We have developed vaccine constructs which express chimeric hemagglutinins resulting in the redirection of the immune response away from the immunodominant (variant) head domain of the hemagglutinin toward the much more conserved stalk of the hemagglutinin and the highly conserved neuraminidase. Such vaccine constructs work well in animal challenge models and await extensive clinical trials in humans. The mechanism by which these novel vaccines mediate protection is via antibodies which do not rely on hemagglutination inhibitory (HI) activity but rather on ADCC (antibody-dependent cell-mediated cytotoxicity) effects, activation of complement and/or inhibition of virus replication through directly binding to viral proteins. It is hoped that the universal influenza virus vaccine based on chimeric hemagglutinins will provide long-lasting protection against all seasonal and pandemic influenza virus strains in the future with the possibility of eventually eliminating influenza B.
H-104
The HIV Pandemic in Sub-Saharan Africa: Challenges, Successes and Leadership

Thomas Quinn, MD, MSc, NIAID, National Institutes of Health

There are 36.7 million people living with HIV, of whom 19.4 million (53%) live in eastern and southern Africa. Last year, 1.8 million people became newly infected, with 43% residing in eastern and southern Africa. South Africa has over 7 million people infected (20% of the global total), the largest number of infected people in any country. In 2016, 380,000 new infections occurred in South Africa, along with 180,000 AIDS-related deaths. Currently one of every 10 individuals are infected, and in some areas, one of every three young women are infected. By 2005, South Africa had the highest incidence in the world. This led to a vigorous response by the scientific community to study and advocate for a more intensive public health and governmental response. Drs. Quarraisha Abdool and Salim Abdool Karim responded by building the Centre of AIDS Programme of Research in South Africa (CAPRISA), one of the most respected research entities in the continent. They documented very high rates of infection in young women, described social patterns and risk factors of high transmission, identified mucosal factors associated with increased susceptibility, and implemented the first successful trial of Tenofovir microbicide, effective in decreasing acquisition of both HIV and HSV-2 in women. They implemented antiretroviral access programs responsible for a 29% decline in new infections in adults and a 56% decline in neonatal infections since 2010. Their efforts along with others have led to the largest number of people on antiretroviral therapy at over 7 million people infected in any country. The largest number of people on antiretroviral therapy at 3.5 million people. Drs. Q. and S. Karim have demonstrated the scientific leadership that will be necessary to fully control the HIV pandemic in South Africa.

H-105
Reflections on the Impact of Nucleotide Antiviral Drugs

John Martin, PhD, Gilead Sciences

Antiviral nucleotide prodrugs have benefitted patients suffering from HIV and viral hepatitis, providing for the possibility to live longer, healthier lives. In addition, tenofovir has allowed for pre-exposure prophylaxis to prevent HIV infection. This is an example of the pioneering work of Salim and Quarraisha Karim.

H-106
Sustained ART-Free HIV Remission: Obstacles and Opportunities

Anthony Fauci, MD, NIAID/NIH

Profound and durable suppression of HIV by antiretroviral therapy (ART) represents a major accomplishment in HIV research. However, HIV persists in patients despite long-term ART therapy and if ART is withdrawn, the virus almost invariably rebounds. Lifelong ART treatment is associated with toxicity, residual chronic inflammation, and the accelerated onset of diseases associated with aging. Therefore, alternatives to lifelong ART are being pursued, with the goal of achieving sustained, ART-free HIV remission. The first pathway to sustained ART-free HIV remission is to completely eradicate the replication-competent HIV reservoir – a classic “cure.” The second pathway is to control HIV rebound without eradication of the virus – referred to as “sustained virologic remission.” Three potential avenues to achieving sustained virologic remission will be discussed. The first approach involves the preservation of natural HIV-specific natural immunity without additional immune enhancements. A key challenge is to determine why the time to HIV rebound following interruption of ART has varied so widely. The second approach involves therapeutic vaccination; in this regard, the results of a recently completed, placebo-controlled therapeutic vaccine trial will be discussed. The third approach is the passive transfer of HIV-specific antibodies. Recent data on the passive transfer of broadly neutralizing anti-HIV antibodies (bNAb) to individuals whose viremia is suppressed by ART and the effect of these bNAb in suppressing viral rebound will be presented. In addition, the role of passive transfer of anti-α4β7 antibody in inducing long-term, post-ART remissions in non-human primates will be discussed.

I-101
The Changing Natural History of HIV Infection: From Opportunistic Infections to Inflammation and Chronic Diseases

Henry Masur, MD, Clinical Center, National Institutes of Health, Bethesda, Maryland

Clinicians are well aware of the changing natural history of HIV infection in regions where antiretroviral therapy is accessible. Clinical investigations of HIV in the first 20 years of the epidemic focused on the diagnosis, treatment and prevention of opportunistic infections. While there has always been a need to improve management strategies, effective approaches were developed for most opportunistic infections, although the quality and duration of survival were short until antiretroviral therapy became effective and durable. As patients have live longer, morbidity due to comorbidities related to viral diseases (HCV, HBV, HPV, CMV), metabolic disorders, chronic inflammation, and neoplastic processes have become more prevalent. Health care systems have had to augment and expand their screening programs for such morbidities, and develop more comprehensive health care for HIV infected patients who survive with these co morbidities. Washington, D.C. is an example of a city which is realigning its resources to focus on these emerging comorbidities and to integrate care. Data on these comorbidities provide insight into research challenges that must be met.
Robert G. Weiss, Allison G. Hays, Micaela Iantorno, Shashwattee Bagchi, Gary Gerstenblith, Johns Hopkins and IHV, University of Maryland

Since the advent of effective ART in the 1990’s, HIV+ people are living longer and developing chronic diseases including cardiovascular disease that is currently the cause of death in 8%-15% of HIV+ people. HIV+ people have accelerated atherosclerosis and an approximate 50%-70% increase in the risk of myocardial infarction as compared to a comparable, age-matched population. Several factors are thought to contribute to this increased CAD risk including over-representation of traditional risk factors, chronic inflammation, and vascular activation in HIV+ people. However, the importance and interaction of these factors are very poorly understood.

This presentation will review the literature on this topic and discuss very recent studies showing that HIV+ people on contemporary ART with viral suppression have severely abnormal coronary endothelial function, a marker of early atherosclerosis and independent predictor of future events, before the development of heart disease. The presentation will review evidence that inflammation may contribute to accelerated atherosclerosis in HIV+ people and discuss new studies investigating contributing mechanisms and potential future therapies for reducing cardiovascular risk in HIV+ people.

Barry Peters, MBBS, MD, FRCP, Kings College London

Some conditions of metabolic origin are, at least in part, considered to be associated or driven by HIV infection or its treatment. These include hyperlipidaemia, lipodystrophy, type 2 diabetes, non-alcoholic fatty liver disease (non-ALFLD), fragility fractures, and some elements of cardiovascular disease.

There are several behavioural factors, particularly diet exercise, alcohol, smoking, and there are some antiretroviral drugs, that contribute to the high incidence of metabolic disease in people living with HIV (PLWH). Some fundamental biological and cellular mechanisms may be important in driving metabolic abnormalities in PLWH. Irisin, a cleaved part of a protein encoded by the FNDCS (Fibronectin type III domain-containing protein 5) gene, has been correlated in PLWH with adiposity, and inversely correlated with fat free mass and some strength parameters. HIV may disrupt fundamental metabolic host cell processes and further enable a preferential environment for virion assembly. The metabolic syndrome and obesity appear to be key for many cases of liver fibrosis in PLWH with concomitant hepatitis virus infection. The METAFIB study found that adipokines and SCD163 (a soluble form of Cluster of Differentiation receptor163), were significantly associated with fibrosis of the liver.

To improve metabolic health outcomes in PLWH, we need further studies to increase our evidence base and develop better therapies. Therapeutic strategies include the identification of risk factors for metabolic disease in PLWH, such as fatty liver, and screening for diabetes, affording the opportunity to encourage behavioural change such as diet and exercise, and the selection of appropriate antiretroviral medication.

Shashwattee Bagchi, MD, IHV, University of Maryland School of Medicine, Division of Infectious Diseases

Use of antiretroviral therapy has markedly reduced morbidity and mortality associated with human immunodeficiency virus (HIV) infection. Nonetheless, all-cause mortality rates remain high in HIV-infected patients compared to the general population, with non-AIDS conditions comprising almost half of deaths. Rates of coronary artery disease (CHD) are over twice as high in HIV-infected compared to matched uninfected controls, with rates anticipated to increase as this population ages. Factors contributing to increased risk of CHD in HIV-infected patients remain to be clearly elucidated. While some studies have strongly suggested that hepatitis C (HCV) co-infection is associated with increased rates of CHD in HIV-infected patients, results in all studies have not been consistent. Since HIV, HCV, and atherosclerosis are all associated with chronic inflammation and immune activation, it can be challenging to understand relative disease pathogenesis when found concurrently in individual patients. Identifying predictors of CHD progression from overlapping pathways has the potential to suggest novel preventive and therapeutic intervention strategies to mitigate CHD progression. In addition, if HCV infection is confirmed to confer additional risk for CHD among HIV-infected patients, this would provide further justification to treat HCV early and aggressively in this population irrespective of liver fibrosis stage.

The presentation will review the data on the individual contribution of HIV and chronic hepatitis C infection on the development of cardiovascular disease and the proposed mechanisms for these observations. Finally, new research investigating the intersections of these three disease processes with potential for future preventive and therapeutic interventions will be discussed.
I-105
Advances in HCV-Associated Hepatocellular Carcinoma
Patrizia Farci, MD, Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, NIAID

Over the past two decades, the incidence of HCC has more than tripled in the United States, and this alarming trend is due primarily, if not exclusively, to HCV infection. However, the role of HCV in hepatocarcinogenesis is still unknown. Whether HCV elicits liver cancer indirectly through chronic inflammation and fibrosis, or directly through the expression of viral proteins in a manner analogous to other human oncogenic viruses, remains to be established. In particular, there is limited information on the level of HCV replication within malignant hepatocytes and the molecular interactions between virus and tumor. We found a significant decrease in HCV RNA in the tumor compared to surrounding non-tumorous tissues, whereas no differences were observed in multiple areas of control non-HCC cirrhotic livers. Diminished HCV replication was not associated with changes in miR-122 expression. Tracking of individual variants demonstrated changes in viral population between tumorous and non-tumorous areas, the extent of which correlated with the decline in HCV RNA, suggesting HCV compartmentalization within the tumor. In contrast, compartmentalization was not observed between non-tumorous areas and serum, nor in controls between different areas of the cirrhotic liver or between liver and serum. Our findings indicate that HCV replication within the tumor is restricted, with viral compartmentalization suggesting segregation of specific viral variants in malignant hepatocytes. Our results provide new insights for understanding the role of HCV in HCC and may give new impetus to investigate whether malignant hepatocytes express or more likely have lost expression of factors that restrict viral replication.

I-106
Hepatitis Viruses in HIV Infection
Kenneth Sherman, MD, PhD, University of Cincinnati College of Medicine

Viral hepatitis represents an important comorbidity among those with HIV infection. The epidemiology and pathophysiology is often altered compared to the general population with increased prevalence, increased risk of chronicity, alteration of viral setpoints, and more rapid progression of hepatic fibrosis in many co-infected individuals. Recently, outbreaks of hepatitis A among MSM with HIV have been reported. Hepatitis B infection is often unrecognized and represents an important contributor to morbidity through both liver failure and increased risk of hepatocellular carcinoma. Hepatitis C is also associated with higher rates of chronicity following acute infection, and rapid hepatic fibrosis leading to liver related death. Treatment of HCV is efficacious but must take into account the underlying antiretroviral regimen. Hepatitis D may be more frequent among HBV/HIV infected persons than has been previously recognized, and also represents an independent risk of HCC. Hepatitis E infection can lead to chronic infections in those with HIV and other immunosuppressed states. Standard vaccination practices that are highly effective in the general population to prevent hepatitis A and B are of lower utility among those with HIV and alternative vaccine strategies should be employed.

CONCLUSION: Co-infection of hepatitis viruses with HIV leads to alterations in natural history, as well as prevention and treatment strategies. Care providers must be cognizant to these differences in order to provide optimal care for the HIV-infected patient.
Assessing the contribution of myeloid cells to HIV-1 persistence under ART

Mario Stevenson, PhD, University of Miami Miller School of Medicine; Viviane Machado, PhD, University of Miami

Assessing whether myeloid cells support HIV-1 persistence in the face of effective ART represents a significant technical challenge. As a result, there is as yet, no direct evidence that myeloid cells play any role in viral persistence in ART-suppressed individuals. As a consequence, research on myeloid cell reservoirs is falling into obscurity. Infection of macrophages can only be initiated by HIV-1 variants that have the ability to use low levels of CD4 on the cell surface. Therefore, if a functional myeloid reservoir contributes to viral persistence under effective ART, we would predict that viremia that rebounds following analytic treatment interruption (ATI), would contain viral variants that have a high affinity for CD4. We have developed an approach that allows identification of low frequency macrophage-tropic variants in rebounding viremia post ATI. Through single genome amplification (SGA), we cloned a large number of viral envelopes from plasma of individuals who underwent ATI. Furthermore, we have assessed whether macrophage-tropic viruses contributed to viral rebound in individuals who exhibited prolonged remission after receiving reduced intensity bone marrow transplant. When these envelopes were used to construct recombinant molecular clones, they conferred the ability to fuse with, and replicate within primary macrophages. We believe that these results provide strong evidence for the existence of a myeloid cell reservoir in infected individuals on suppressive ART and furthermore, that this reservoir contributes to viral rebound when ART is interrupted. The longevity and the anatomic source of the reservoir from which these macrophage-tropic viruses originate, is under investigation.

Decreased levels of seroreactivity in individuals subjected to antiretroviral therapy early in acute HIV infection

Mark Manak, PhD, Henry M Jackson Foundation, MHRP; Ashley Shutt, MA, Henry M Jackson Foundation, MHRP; Leigh Eller, PhD, Henry M Jackson Foundation, MHRP; Merlin Robb, PhD, Henry M Jackson Foundation, MHRP; Linda Jagodzinski, PhD, Walter Reed Army Institute for Research, MHRP; Jintanat Ananworanich, PhD, Henry M Jackson Foundation, MHRP; Sheila Peel, PhD, Walter Reed Army Institute of Research, MHRP

WHO guidelines recommend antiretroviral treatment (ART) of all HIV infected individuals regardless of CD4 count. Early treatment minimizes the risk of HIV transmission, lowers the natural reservoir of the virus, and reduces subsequent serious AIDS related events, but may also disrupt emergence of HIV diagnostic markers.

High-risk individuals at early stages of HIV infection, (HIV-1 RNA positive, Western Blot negative or indeterminate), were enrolled into an IRB approved study to examine the outcomes of early HAART initiation. Plasma samples collected at Week 0, 2, 12, and 24 were tested by EIA 1/2 Plus O, HIV-1/2 Ag/Ab Combo, HIV-1/2 MultiSpot (MS), and HIV-1 Western Blot (WB) (all from Bio-Rad, Redmond, WA). HIV Viral Load was determined by Abbott m2000 HIV-1 RT PCR (Chicago, IL). Stage of HIV infection was based on the Fiebig staging system.

Of individuals treated at Fiebig I and II, 63.6 and 59.1%, respectively, were antibody negative at 12 weeks. At week 12, MS was reactive in 18.2%, 53.7% and 35.0% of individuals treated at Fiebig I, II, and Fiebig III/IV, and decreased to 9.1%, 48.4% and 30.0%, respectively, by week 24. 52.9% of individuals treated at Fiebig III/IV were negative at Week 24. In contrast, all untreated individuals were highly reactive by EIA, WB, MS and RNA by week 2-3 after infection and remained reactive thereafter.

Absence of serological markers in individuals treated early in infection presents challenges in determining status of infection, as some individuals under therapy may test serologically non-reactive and RNA negative, but are infected. These findings may also have implications in monitoring individuals on Pre-exposure Prophylactics (PrEP) by serological tests alone.

Current Challenges in HIV Diagnostics – Time to Revise our Approach?

Sheila A. Peel, MSPH, PhD, US Military HIV Research Program (MHRP)

HIV infection remains a public health challenge; HIV testing serving as the gateway to entrance into the HIV care, treatment, and prevention cascade. Whether laboratory evidence of infection is generated by Point of Care test algorithms or highly sophisticated 4th and 5th generation immunoassay/supplemental serological and/or molecular confirmatory algorithms, diagnostic accuracy, correct classification of HIV infection status, is now challenged by the HIV field’s most notable advances in the arenas of HIV Prevention and Intervention. Paradigms such as Test and Treat, Treatment as Prevention, Pre-exposure Prophylaxis (PrEP), and Post-exposure Prophylaxis (PEP) reduce viral burden, viral reservoir constitution, the potential for onward HIV transmission, and decrease the risk of serious AIDS related health outcomes. These highly effective strategies however, have also been shown to cause the delay, reduction, or reversal of evolution of serological responses to infection and/or reduce molecular markers to below limits of detection by currently employed assay. Lack of evolution and/or suppression of markers long used by the laboratory to generate evidence confirming or refuting HIV infection can thus lead to misclassification of status. This talk will focus on current HIV testing modalities, challenges of HIV testing under the aforementioned scenarios, presentation of case studies, and considerations for a revised approach.
Performance and usability of the OraQuick® HIV Self-Test, an oral fluid based HIV self-test, in South Africa

Michael Reed, PhD, OraSure Technologies, Inc.; Mohammed Majam, MBA, BSc, Wits Reproductive Health and HIV Institute

With 30% of persons living with HIV globally still not knowing their status, increasing access to HIV testing is an approach to achieving the United Nations' target goal of diagnosing 90% of all people living with HIV by 2020. The OraQuick® HIV Self-Test is an oral fluid based self-test providing results in as little as 20 minutes and is the first self-test to receive WHO Prequalification (July 2017). WHO Prequalification allows access to high quality, easy to use, accurate HIV self-testing in countries wishing to broaden their HIV testing and treatment programs.

This talk describes the results and observations of studies conducted in South Africa to demonstrate ease of use and generation of accurate results in the hands of a lay user. The OraQuick® HIV Self-Test results were compared to results from a 4th Gen EIA with sensitivity of 100% (n=76) and specificity of 99.1% (n=324). A separate comprehension study was conducted to assess lay users’ ability to understand information provided on the outer packaging and product insert. Comprehension scores were high 99.5% (n=200) for all critical and safety related concepts. Understanding of the next steps for positive results was 97.5% (n=200)[1].

Many studies have shown and continue to demonstrate that the OraQuick® HIV Self-Test is a robust test that provides accurate and reliable results. Incorporating an easy to use oral fluid test into current HIV testing strategies can increase the number of individuals testing, especially those hard to reach high risk populations currently not accessing testing.

Geenius HIV 1/2 Supplemental Assay: A Rapid, Reliable and Simple System for the Confirmation and Differentiation of Antibodies to HIV

Kathleen Shriver, PhD, Bio-Rad Laboratories; Muriel Cardona, PhD, Bio-Rad Laboratories; Stephanie Gadelle, PhD, Bio-Rad Laboratories; Patrice Sarfati, PhD, Bio-Rad Laboratories

INTRODUCTION: In 2017 Bio-Rad Laboratories completed launching the FDA-approved Geenius HIV-1/HIV-2 Supplemental assay to replace Multispot HIV-1/HIV-2 in the current CDC HIV Diagnostic Algorithm. The Geenius cassette contains antibody-binding protein A, which is conjugated to colloidal gold dye particles; HIV-1 (p31, gp160, p24, gp41) and HIV-2 (gp36, gp140) antigens are bound to the membrane solid phase. Serum, plasma, or whole blood may be tested. Geenius uses an automated cassette reader and proprietary software to interpret HIV-1 and HIV-2 results. We report more recent performance data for this system, as well as an investigational protocol for testing dried blood spot (DBS) specimens.

METHODS: (1) WHO evaluated the Geenius HIV-1/HIV-2 Supplemental testing system with a panel of 1117 specimens. (2) DBS specimens were tested on Geenius using an investigational procedure (40 µL of DBS eluate and one drop of assay buffer). Samples included established infections (131 HIV-1, 31 HIV-2, one dual), 60 seroconversion specimens, and 106 DBS collected by CDC during HIV surveillance.

RESULTS: (1) Geenius sensitivity in the WHO evaluation was 100% and specificity was 97.4%. Seroconversion samples were detected +0.875 days vs. the benchmark. All the mixed titer and reference specimens were correctly classified. (2) Geenius DBS correctly detected HIV-1 and HIV-2 DBS with minor exceptions. DBS seroconversions showed slightly reduced sensitivity vs. plasma.

CONCLUSIONS: (1) The Geenius HIV-1/2 Confirmatory Assay was accepted for the WHO list of prequalified diagnostics (March 17, 2017). (2) Results of an investigational Geenius DBS procedure appear promising for settings without capacity for venipuncture.
Programmable nucleic acid nanoswitches for the rapid, single-step detection of antibodies in bodily fluids

Rudy Ippodrino, PhD, Ulisse Biomed

Antibody detection plays a pivotal role in the diagnosis of pathogens and monitoring the success of vaccine immunization. However, current serology techniques require multiple, time-consuming washing and incubation steps, which limit their applicability in point-of-care (POC) diagnostics and high-throughput assays. We developed here a nucleic acid nanoswitch platform able to instantaneously measure Immunoglobulins of type G and E (IgG and IgE) levels directly in blood serum and other bodily fluids. The system couples the advantages of target-binding induced co-localization and nucleic acid conformational-change nanoswitches. Due to the modular nature of the recognition platform the method can potentially be applied to the detection of any antibody for which an antigen can be conjugated to a nucleic acid strand. In this work we show the sensitive, fast and cost-effective detection of four different antibodies and demonstrate the possible use of this approach for the monitoring of antibody levels in HIV+ patients immunized with AT20 therapeutic vaccine.
CBF-1 promotes the establishment and maintenance of HIV latency by recruiting Polycomb repressive complexes, PRC1 and PRC2, at HIV LTR

Mudit Tyagi, PhD, The George Washington University; Sonia Zicari, PhD, The George Washington University; Kalamo Farley, PhD, The George Washington University; Lin Sun, PhD, The George Washington University; Gary Simon, MD, PhD, The George Washington University

The type of chromatin structure around the LTR promoter of integrated HIV provirus provides critical signals that regulate transcription during both productive and latent HIV infections. The C-promoter binding factor-1 (CBF-1) is a potent and specific inhibitor of the HIV-1 transcription, which performs its function after binding to specific sites at HIV LTR. Here we demonstrate that the knockdown of endogenous CBF-1 in latently infected primary CD4+ T cells, using specific small hairpin RNAs (shRNA), resulted in the reactivation of latent HIV proviruses. By performing Chromatin immunoprecipitation (ChIP) assays, using latently infected primary T cells and Jurkat T-cell lines, we demonstrated that CBF-1 induces the establishment and maintenance of HIV latency by recruiting Polycomb Group (PcG/PRC) corepressor complexes or Polycomb repressive complexes 1 and 2 (PRC1 and PRC2). Knockdown of CBFB-1 resulted in the dissociation of PRCs corepressor complexes and enhanced the recruitment of RNA polymerase II (RNAPII) at HIV LTR. Knockdown of certain components of PRC1 and PRC2 leads to the reactivation of latent proviruses. Similarly, treatment of latently infected primary CD4+ T cells with the EZH2 inhibitor, 3-deazaneplanocin A (DZNep), led to their reactivation.

Importance: Instead of inhibiting individual enzymes, targeting factors such as CBF-1, which mediate the establishment of multiple repressive epigenetic changes, could be more beneficial in designing strategies to reactivate and subsequently eliminate latent HIV reservoirs.

Development of anti-Tat compound: MD Simulation of the Tat/Cyclin T1/CDK9 Complex Revealing the Hidden Catalytic Cavity within the CDK9 Molecule Upon Tat Binding

Takashi Okamoto, MD, PhD, Nagoya City University; Kaori Asamitsu, PhD, Nagoya City University; Takatsugu Hirokawa, PhD, National Institute of Advanced Industrial Science and Technology (AIST)

We applied molecular dynamics (MD) simulation to analyze the dynamic behavior of the Tat/CycT1/CDK9 tri-molecular complex and revealed the structural changes of P-TEFb upon Tat binding. We found that Tat could deliberately change the local flexibility of CycT1. Although the structural coordinates of the H1 and H2 helices did not substantially change, H1', H2', and H3' exhibited significant changes en masse. Consequently, the CycT1 residues involved in Tat binding, namely Tat-recognition residues (TRRs), lost their flexibility with the addition of Tat to P-TEFb. In addition, we clarified the structural variation of CDK9 in complex with CycT1 in the presence or absence of Tat. Interestingly, Tat addition significantly reduced the structural variability of the T-loop, thus consolidating the structural integrity of P-TEFb. Finally, we deciphered the formation of the hidden catalytic cavity of CDK9 upon Tat binding. MD simulation revealed that the PITALRE signature sequence of CDK9 flips the inactive kinase cavity of CDK9 into the active form by connecting with Thr186, which is crucial for its activity, thus presumably recruiting the substrate peptide such as the C-terminal domain of RNA pol II. These findings provide vital information for the development of effective novel anti-HIV drugs with CDK9 catalytic activity as the target.

Limitations of CD32a expression as a marker of the HIV latent reservoir

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It was recently reported that CD32a accurately marks CD4+ T cells from peripheral blood of ART suppressed people which harbor replication competent HIV. A direct marker of these latently infected cells may be expected to associate with reservoir size, but we find that expression levels of CD32 measured on CD4+ T cells isolated from the blood of 12 ART-suppressed participants did not correlate with measurements of cell-associated DNA or inducible virus in these individuals. We also examined genetic variation in CD32a, characterizing polymorphisms in 93 virally suppressed people on ART. Our analysis of all SNPs observed, including those reported to impact IgG binding and HIV disease progression, found no association of any CD32a variants with levels of HIV provirus. Given these results we attempted to repeat the primary cell sorting experiments described in the original report of CD32 as a marker of latently infected cells. CD4+ T cells with highest CD32 staining were sorted by flow cytometry from peripheral blood of ART suppressed people. These populations were not enriched in viral DNA compared to CD4+CD32- populations, in contrast to the original report. The lack of correlation we observe between variation in CD32 expression or genotype and reservoir size, and failure to replicate isolation of latent cells by sorting of CD4+ T cells based on CD32 staining, indicate CD32 may not be a direct marker of replication competent HIV in CD4+ T cell populations.
**P-A4**

**Multimodal theranostic tests for antiretroviral drug delivery**

Bhavesh Kevadiya, PhD, UNMC; Christopher Woldstad, BS, UNMC; Brendan Ottmann, BS, UNMC; Prasanta Dash, PhD, UNMC; Balasrinivasa Saibaba, PhD, UNMC; Benjamin Lamberty, BS, UNMC; Brenda Morsey, MS, UNMC, Ted Kocher, BS, UNMC

**ABSTRACT:** Long acting slow effective release antiretroviral therapy (LASER ART) was developed to improve patient regimen adherence, prevent new infections and facilitate drug entry into human immunodeficiency viral reservoirs. To speed LASER ART development “multimodal imaging theranostic nanoprobes” were created. These europium (Eu3+) doped cobalt ferrite (CF) dolutegravir (DTG) (EuCF-DTG) nanoparticles were used as platforms for drug-particle biodistribution. After parenteral injection of EuCF-DTG, to rats and rhesus macaques, measured drug and cobalt levels by florescence and magnetic resonance imaging tests were found to be coordinate to iron levels. Moreover, EuCF-DTG was found to be a log order-of-magnitude more sensitive than equivalent amounts of particle encased iron oxide. Folic acid decoration facilitated drug particle cell uptake. We posit that theranostic nanoprobes can facilitate LASER ART drug delivery and be used as part of a precision nanomedicine treatment strategy.

**P-A5**

**HIV Infected Cells Have Depolarized Membrane Potentials and Increased Intracellular Calcium Levels.**

Robert Furler, PhD, The George Washington University

**Introduction/Background:** Ion distribution between the extracellular, cytoplasmic, and organelar spaces creates membrane potentials which drive many of life’s processes. This bioelectric membrane potential, driven by ion channel and pump activity, can be harnessed to allow or prevent entry of signaling mediators like Ca2+ into the cytoplasm. Several HIV proteins have been reported to function as ion channels or alter ion channel activity. This activity likely influences cell fate including activation and apoptosis. Hypothesis: HIV depolarizes the plasma membrane and alters intracellular calcium levels. Changing the polarization of the plasma membrane would alter the levels of HIV infection.

**Methods:** HIV infected cells were identified using anti-Env antibody PG9-AF647. Membrane potential measurements were done by flow cytometry using the DiBAC4(3) dye as previously reported. Intracellular Ca2+ measurements were also done by flow cytometry using the Fluo-4 dye. Ionomycin and PMA were used to show the contrast in intracellular Ca2+ levels between infected and uninfected cells. To assess the effects of membrane potential changes on HIV replication, 200μM diazoxide was added to cells during infections.

**Results:** HIV infected cells consistently had depolarized membrane potentials in both primary cells and cell lines. Additional depolarization increased infection. Membrane depolarization was accompanied by increased intracellular Ca2+. Ionomycin induced a drastic difference in Ca2+ flow between uninfected and HIV-infected cells. In uninfected cells, ionomycin induced an influx of Ca2+ while PMA had little effect. In contrast, both ionomycin and PMA induced a large efflux of Ca2+ from HIV infected cells.

**P-A6**

**A Possible Role for Retinoic Acid in the Functional Cure of SIV Infections in ART/α4β7 mAb-treated SIV Monkeys**

Jianshi Yu, PhD, University of Maryland School of Pharmacy; Jace Jones, PhD, University of Maryland School of Pharmacy; Aftab Ansari, PhD, Emory University School of Medicine; Neil Sidell, PhD, Emory University School of Medicine; Maureen Kane, PhD, University of Maryland School of Pharmacy Mass Spectrometry Center

Our team of collaborators has recently reported that combining short term antiretroviral therapy (ART) with the in vivo administration of a primatized monoclonal antibody against the α4β7 integrin (α4β7 mAb) in SIV-infected macaques resulted in sustained control of viremia without need for continued therapy. We have determined that acute SIV infection caused a rapid and sustained drop in plasma retinoic acid (RA) levels that was not corrected upon ART-mediated control of viral replication, but was restored soon after start of α4β7 mAb treatment. This was followed by the rebound of certain CD8α+ NK lymphocytes, cells known to be regulated by RA. Depletion studies of the α4β7 mAb-treated “SIV controllers” with anti-CD8α and anti-CD8β Abs have indicated that rebound of viremia and return to suppression tracks most closely with the depletion and reappearance of NK and NKT cells. In parallel in vitro studies using a cell line model of latent SIV infection (Hut78 and SIV-Hut78), we determined that SIV infection inhibited RA production, while α4β7 mAb treatment can stimulate RA production. The data indicated that SIV-Hut78 cells showed a marked reduction in RALDH2 expression (the key regulatory enzyme in RA biosynthesis). The retinol chaperone protein RBP1 was also reduced in SIV-Hut78 cells. Together, these in vivo and in vitro studies indicate that an increase in RA levels is an early sign of the efficacy of α4β7 mAb treatment and suggests that ligation of the α4β7 integrin leads to intra-cellular signaling events that include the restoration of RA production by select RALDH-expressing cells, and signals that induce NK cell activation/re-distribution that may in concert play a fundamental role in sustained control of viremia.
P-A7

HIV disease history in perinatally HIV infected adolescents with interrupted care

Tracy Evans-Gilbert, MD, MPH, CTropMed®, Jamaica Perinatal and Paediatric HIV/AIDS Programme, Cornwall Regional Hospital; Shelly Ann Williams, BSc Nursing, Jamaica Perinatal and Paediatric HIV/AIDS Programme; Gail Reid, BSc Social Work, Western Regional Health Authority; Celia Christie, MBBS, DM Peds, MPH, FAAP, FIDSA, FRCP (Edin), Jamaica Pediatric and perinatal HIV/AIDS Programme, University of the West Indies

Early initiation of HAART preserves the robust immune system of perinatally HIV infected children and limits viral reservoir size. Our aim was to study the current immune and virological status of perinatally infected adolescents who returned after defaulting care. A retrospective analysis was conducted on laboratory outcomes stratified by defaulters and non-defaulters and among age bands at HAART commencement. Among 78 patients, the median age was 14 years [IQR 13.17], HAART was commenced at a median age of 6 years [IQR 3.8] with 45 (57%) at ≥6 years. Among 27 defaulters the median time of default was 22 months. Total time on HAART was a mean of 8.5 years ±3 years and 56 (71%) were on protease inhibitors. Zenith HIV RNA load was a median of 4.8 log10 copies/ml [IQR 4.2, 5.2]. Nadir CD4 cell count was 368 [IQR 61,648]. Median current CD4 percent was 33.5% [IQR 18,46 ]. Duration of CD4 of 15-25% was 12 months [IQR 4,32] for defaulters compared with 4 months [IQR 0.8] for non-defaulters. The mean duration of viral load < 500 copies /ml was 1.48± 1.68 years among defaulters, 3.6± 3.2 years among non defaulters (p<0.0001); 3.9±3 for those commencing HAART at age 1-5 yrs, and 2.4±2.6 for ≥6 years (p<0.05). Seventy percent of adolescents commencing HAART at 1-5 years versus 43% at age ≥6 year had a current CD4 count >500 (p<0.03). Virologic suppression was 67% in the 1-5 year band versus 27% in the > 6 year band (p <0.0001). Defaulters and non defaulters did not differ with current virologic or immunologic markers. Late age at starting HAART had a greater negative influence on final outcome than interrupted therapy. These results suggest the potential in HIV remission research of interrupting HAART after early initiation of treatment.

P-A8

Establishing tissue reservoirs for the human immunodeficiency virus in humanized mice

Hang Su, BS, UNMC; Prasanta Dash, PhD, UNMC; Santhi Gorantla, PhD, UNMC; Larisa Poluektova, MD, PhD, UNMC; Howard Gendelman, MD, University of Nebraska Medical Center

Due to extraordinary challenges of early viral detection and restricted access to anatomical sites, it remains imperative to track early temporal dynamics of viral latency establishment. The development of humanized mice has provided new insights into the immunology, pathogenesis, treatment, prevention, and measured eradication. In the current study, we applied two widely used humanized mouse models of HIV/AIDS; human CD34+ hematopoietic stem cells (HSC) and peripheral blood lymphocytes (hu-PBLS)-transplanted NOD.Cg-PkdcdscidIl2r^tm1Wjl/SzJ mice, to investigate early events in HIV latency. Twenty hu-HSC or hu-PBLS mice were injected intraperitoneally with HIV-1AΔA at 104 TCIΔ50. Infected animals were randomly separated into 4 groups and sacrificed at day 3, 5, 7 and 14 after infection. Blood and tissues were harvested for immunohistochemistry and semi-nested PCR tests for HIV-1 DNA and RNA. Peripheral CD4+ T cells were reduced by around 10% after HIV-1 infection in hu-HSCs mice but over 20% in hu-PBLS mice. IHC tests showed HIV-1p24 expressing cells only in 14-day infected hu-HSCs mice but in all infected hu-PBLS mice. HIV-1 RNA and DNA were observed in 14-day infected hu-HSCs mice from spleen, liver and gut at 106-8 copies/106 hCD45+ cells, whereas detected in 2/5 animals (~106 copies) at early time points. They were observed in all infected hu-PBLS mouse tissues (~106copies/106 hCD45+ cells in 3-day group and 106-8 copies in other time points). HIV-1 was detected in both hu-HSCs and hu-PBLS models as early as 3 days after infection but more robust within the latter. This may be related to various host restriction factors. Targeting these host factors may provide stronger clues about establishment of HIV persistence.

P-A9

Transformation of Darunavir into a long acting nanoformulated prodrug

Mary Banoub, BS, UNMC; Aditya Bade, PhD, UNMC; JoEIllyn McMillan, PhD, UNMC; Benson Edagwa, PhD, UNMC; Howard Gendelman, MD, UNMC, et al

Antiretroviral therapy (ART) has improved the quality and longevity of HIV-1 patients. Despite such advances limitations in drug bioavailability, resistance, and secondary toxicities abound affecting regimen adherence. We posit that such pharmaceutical limitations may be overcome by drug transformation into long acting slow effective release ART (LASER ART); a pharmaceutical approach that improves cell and tissue drug penetration and depot formation leading to extended dosing intervals and improved antiretroviral responses. To this end, a hydrophobic bioreversible derivative prodrug of darunavir (DRV) was synthesized by medicinal chemistry. Modified DRV (MDRV) was synthesized by covalent linkage of a 14-carbon hydrophobic fatty acid moiety to the parent drug through a hemiaminal bond. A stable poloxamer 407 coated prodrug DRV nanofomulations (NMDRV) produced by high-pressure homogenization. Physicochemical properties of NMDRV and resultant particle cell uptake, antiretroviral efficacy pharmacokinetic and biodistribution studies were performed with subsequent comparisons made between prodrug and native drug formulations. Laboratory and pharmacokinetic tests were performed in monocyte derived macrophages (MDM) and BALB/c mice, respectively. NMDRV displayed up to 86 mg per 106 cells in 24 hours and retention up to 2 weeks compared to undetectable levels in the native DRV treatment. Effective plasma DRV concentration was detected in the prodrug arm through day 7 following a single dose of 40 mg/kg compared to undetectable levels in the parent drug treatment arm. The results highlight opportunities for LASER ART to achieve improved ART distribution and dissolution with limited toxicity for long-term HIV/AIDS treatments.
Accumulation and persistence of deleted HIV proviruses following prolonged ART

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HIV-1 immunotherapy offers an alternative to cART or as a ‘functional cure’ by eliminating reactivated viral reservoirs. Both cellular and antibody mediated immune responses have been identified which are capable of reducing either HIV-1 infection risk or severity of infection. We present data on both T-cell based (Vacc4x) and antibody based (vacc-C5) vaccine antigen under development for HIV-1 immunotherapy. Vacc4x has undergone phase II trials demonstrating reductions in viral load and sustained anti-HIV-1 T-cell responses. Additional immune modulation, such as that used in cancer immunotherapy, may have utility in HIV-1 Immunotherapy. For this reason we combined Vacc4x with the immune modulator Lenalidomide both in vitro and in a phase I trial of 24 subjects in order to assess the ability of this combination to enhance CD4+ T cell responses. The combination was safe, well tolerated and demonstrated increases in CD4+ T-cell counts after a two week vaccine protocol. We have identified that antibodies specific for a heterodimeric peptide construct comprising the C5501-512 and gp41732-744 regions of the HIV envelope protein (Vacc-C5) are correlated with slow disease progression, lower viral load and markers of immune function in HIV-1 patients and are capable of mediating antibody dependent cytotoxicity. We conducted a phase I/II trial of 36 ART treated patients vaccinated with Vacc-C5 antigen. Vacc-C5 was safe, well tolerated and increased anti-Vacc-C5 titre in a subset of patients. These data support the continued development of Vacc4x, Lenalidomide and Vacc-C5 in an HIV-1 immunotherapeutic setting.

Discordant HIV Populations with Discordant V3 Tropism in CSF and Plasma: Implications for Establishing HIV Reservoirs

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CNS reservoirs of HIV are established early in infection and may be distinct from HIV populations in peripheral lymphoid organs, but the mechanisms responsible for compartmentalization are not well understood. To determine if HIV compartmentalization occurs during CNS infections, we investigated HIV populations in plasma and CSF in patients with active cryptococcal meningitis (CM). HIV infected patients with CM (N=73) from the COAT, ASTRO-CM studies, had lumbar punctures and phlebotomy. HIV RNA was quantified in plasma and CSF prior to initiating anti-CM or antiretroviral therapy. A subset (N=9) with CSF RNA>plasma RNA and another subset (N=9) with plasma RNA>CSF RNA underwent single genome sequencing (SGS) of HIV env from plasma and CSF. SGS of cellular DNA was also performed on a subset of patients (N=5) with lymphocytic pleocytosis. 992 SG sequences were obtained. Sequences were aligned and subjected to phylogenetic analyses, compartmentalization analyses (panmyxia) and cell tropism of the V3 loop in env for R5/X4 predictions (GENO2PHENO). Patients with CSF pleocytosis (WBC>5 cells/µl), had higher levels of HIV in CSF than in plasma (p<0.05). In general, proportions of R5 and X4 variants in CSF and plasma were similar, but there was strong discordance in 4 patients, reflecting compartmentalization. Sensitive population analyses revealed viral compartmentalization between CSF and plasma (N=5). In patients with pleocytosis, HIV variants in CSF-derived cells were distinct from those in CSF, but were indistinguishable from PBMC-derived HIV. Overall, CSF compartmentalization of HIV was detectable in the majority of patients with CM. CSF pleocytosis does not contribute substantially to establishing HIV populations in CNS.
Development of HIV-1 Immunotherapy with Vacc4x and Vacc-C5

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Vacc4x has undergone phase II trials demonstrating reductions in viral load and sustained anti-HIV-1 T-cell responses. Additional immune modulation, such as that used in cancer immunotherapy, may have utility in HIV-1 immunotherapy. For this reason we combined Vacc4x with the immune modulator Lenalidomide both in vitro and in a phase I trial of 24 subjects in order to assess the ability of this combination to enhance CD4+ T cell responses. The combination was safe, well tolerated and demonstrated increases in CD4+ T-cell counts after a two week vaccine protocol.

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Protection against or delay of intrarectal SHIV acquisition by mucosal vaccines in the absence of Env-antibody responses

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To identify the protective mechanisms of an HIV mucosal vaccine similar to RV144, we carried out a pilot study in which we mucosally immunized rhesus macaques with HIV/SIV peptides, SIV-expressing MVA, and full-length single chain protein of HIV-gp120 fused to CD4. In the macaques that received this combination, 3/14 were sterilely protected after high-dose SHIVSF162P4 intrarectal challenge, compared to 0/29 controls (p=0.03).

We observed mucosal antigen-specific T cell responses, but not antibody responses. We then tested efficacy of this HIV mucosal vaccine against repeated low-dose intrarectal challenge with SHIVSF162P4. With 21 vaccinees and 7 controls, we achieved 44% vaccine efficacy (p = 0.028). Consistent with the pilot study, the vaccine did not induce Env-specific antibody responses in the plasma or rectal mucosa. It induced gag- and Env-specific T cells in colorectal mucosa/MLN, but the magnitude did not correlate with delay of viral acquisition. Interestingly, the vaccine led to accumulation of myeloid-derived suppressor cells in the PBMCs and CD14+ monocytes in the colorectal intraepithelial compartment, which correlated with delay of viral acquisition. The vaccine also decreased rectal gp41 antibody, total rectal mucosal plasma cells, and gut microbiome richness. The bacterial PCA-1 correlated with number of exposures to achieve infection, suggesting gut microbiome’s possibly influencing HIV susceptibility. Overall, the mucosal vaccine had different protective mechanisms from the RV144 trial. Thus, a vaccine inducing mucosal T cells without antibodies can protect against mucosal SHIV acquisition. Combination with a systemically-delivered antibody-inducing vaccine might improve protection.

A Modified Vaccinia Ankara vector expressing Lassa virus-like particles (MVA-LasVLP) protects mice from lethal challenge with a Lassa-Mopeia reassortant virus.

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The Lassa-endemic areas of West Africa, including the embattled areas of northern Nigeria have been experiencing more frequent outbreaks of Lassa fever (early 2016 through the summer of 2017). Consequently an international effort has been launched to produce a Lassa vaccine, including a test of the MVA-LASV-VLP (GEO-LM02). The MVA vector has been developed by Dr. B. Moss’ lab at NIH in collaboration with GeoVax to deliver a variety of vaccine antigens. The GeoVAX-MVA-HIV-1VLP has been used in human trials involving more than 500 participants, it has the capacity to express large recombinant antigens, it elicits robust T and B cell responses, and is relatively safe due to its inability to replicate in mammalian cells. Of all the current Lassa vaccine candidates, GEO-LM02 is the only one that produces VLP in vivo.

Our experiments tested the optimum route of vaccination. We used young CBA/J mice that were challenged two weeks after vaccination with an intrarectal (ic) dose of a Lassa-Mopeia reassortant virus. Mice were given a single dose of GEO-LM02 by subcutaneous (sc), intraperitoneal (ip), and intramuscular (im) routes. 100% of those given im vaccine survived the lethal challenge, whereas the other routes were slightly less protective. All unvaccinated mice died within 8d post challenge. A second round of experiments confirmed the previous results and demonstrated a robust cell-mediated immunity after a single dose im vaccination. Again 100% of the un-vaccinated mice succumbed to lethal challenge and experienced erosion of their blood-brain-barrier. Subsequent experiments will test the durability of immunity in surviving mice.
P-C4

Associating HIV-1 Env Trimer Structures with Functional Env Conformational States by smFRET Analysis

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The HIV-1 envelope glycoprotein (Env) trimer mainly exists in a closed conformation (State 1), which is driven by CD4 binding through an intermediate conformation (State 2) to the open CD4-bound conformation (State 3). These functional Env states can be visualized by single-molecule Fluorescence Resonance Energy Transfer (smFRET). A breakthrough in the structural characterization of the HIV-1 Env trimer has been the generation of recombinant cleaved soluble gp140 SOSIP.664 trimers. Parallel cryoelectron microscopy studies have been performed with the mature HIV-1 JR-FL Env in complex with the PGT151 neutralizing antibody. Both approaches resulted in similar structures. It is currently generally assumed that these structures represent the ground state of HIV-1 Env (State 1). Here we apply smFRET to probe the conformational state of HIV-1 Env in these constructs and antibody complexes. Fluorophores were introduced at the identical positions in the HIV-1 Env proteins used for structural studies and the native Env on the surface of virions, and the resulting smFRET values compared. Surprisingly, smFRET data reveal that both the soluble gp140 SOSIP.664 and PGT151-HIV-1 JR-FL Env structures correspond to the State 2 gp120 conformation observed on the virus. Our data suggest that the all-important structure of State 1 of HIV-1 Env, which is the target of the majority of broadly neutralizing antibodies, remains unknown. Determining the structure of this additional conformation observed on native virions should allow the design of second generation immunogens that specifically present the State 1 conformation of HIV-1 Env.

P-C5

Broadly neutralizing nanobodies selected from dromedary immune libraries with subtype C SOSIP Env glycoproteins: optimization and preclinical development

Sarah Kalusche, PhD Student, Georg-Speyer-Haus; Felix Lehmann, master student, Georg-Speyer-Haus; Kathrin Koch, PhD, Georg-Speyer-Haus; Florian Klein, Professor, University of Cologne; Jonathan Torres, PhD, The Scripps Research Institute; Robyn Stanfield, PhD, The Scripps Research Institute; Andrew Ward, Professor, The Scripps Research Institute; Ian Wilson, Professor, The Scripps Research Institute; Ursula Dietrich, PhD, PI, Georg-Speyer-Haus; et al

Nanobodies or VHH are the smallest naturally occurring antibody fragments derived from heavy chain only antibodies from Camelidae. Due to their physicochemical properties (high stability, high affinity and target specificity, extended CDR3 loops and their small size allowing to enter into protein cavities), nanobodies are very suited for preventive and therapeutic applications. We recently selected nanobodies with broad neutralizing capacity against primary HIV-1 strains of different subtypes from phage immune libraries generated from dromedaries immunized with HIV-1 subtype C gp140 SOSIP Env glycoproteins (Koch et al., 2017, in press). Two nanobodies with complementary neutralization pattern neutralized 19 out of 21 pseudoviruses in the standard TZM-bl assay. Epitope mapping by data competition ELISAs as well as negative-stain EM reconstructions with trimeric SOSIPs identified the CD4 binding site as the major target. A new selection performed on a next-generation optC SOSIP.664 plus sCD4 with libraries generated at a late timepoint (7 months after the initial 7 weeks immunization cycle) identified two new nanobodies, which are currently being analyzed for neutralization. We further proved functionality of the nanobodies at acidic pH (as found in the vagina) and identified nanobody combinations resulting in increased breadth of neutralization in vitro. In view of preventive applications at vaginal sites of HIV-1 transmission, we are expressing the best nanobodies in a membrane-bound form and as a secreted version from lactobacilli (L. rhamnosus), which colonize the human vagina. Finally, nanobodies will be analyzed in a humanized mouse model of HIV-1 infection for their HIV-neutralizing capacity in vivo.

P-D1

Differential pathogenesis of human metapneumovirus clinical isolates in C57BL/6 mice

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Introduction. Human metapneumovirus (HMPV) is a member of the Pneumoviridae, formerly a subfamily of Paramyxoviridae. HMPV is a leading cause of lower respiratory infection in infants, children, and adults. The disease outcome of HMPV infection ranges from mild upper respiratory infection to severe pneumonia. Despite the clinical and economic burden, mechanisms of HMPV pathogenesis are not fully understood. In addition, no licensed vaccines or anti-viral drugs are available. Results. Most published HMPV studies use a few laboratory-adapted strains of the A2 lineage. Here, we tested eight HMPV clinical isolates from different genetic lineages in comparison to a laboratory reference strain in an established C57BL/6 mouse model. The clinical isolates induced variable disease severity. While mice infected by laboratory strain TN/94-49 (A2) did not lose weight, mice infected by clinical strains showed significant weight loss and greater lung histopathology. Several clinical isolates caused lethal disease, which is unusual in mouse models of HMPV. Viral replication in lungs was variable, but peak lung viral titer did not correlate with disease outcome. Higher proinflammatory cytokine production in mouse lungs was associated with more severe disease and death. Virulent clinical isolates of HMPV exhibited diminished innate immune responses and decreased antigen-presenting cells, suggesting active inhibition of innate immunity. The findings were confirmed in BALB/c and DBA/2 inbred mice.

Conclusion. Our results indicate that severe disease caused by HMPV clinical isolates was due to exuberant immune response and immunopathology. These data suggest that distinct HMPV strains may engage host immune mediators differently.
Host restriction factors represent a defence mechanism of the innate immune system against viral pathogens, such as HIV-1. Many studies focused on the interplay between restriction factors and HIV-1 have greatly improved our knowledge about the biology of the virus and the response of the host, but to date there is no evidence on a possible interaction between host restriction factors to counteract the virus. Here we show that TRIM22 and CIITA, two cellular proteins previously shown by us to inhibit HIV-1 proviral transcription with different mechanisms, interact in vivo and co-localize in nuclear bodies whose formation is hierarchically controlled by TRIM22. Importantly, TRIM19/Promyelocytic Leukemia (PML) protein, another repressor of HIV-1 transcription also acting before proviral integration, co-localized in these nuclear bodies upon TRIM22 expression induced by IFN-γ. Finally, TRIM22 nuclear bodies also contained CyclinT1, a crucial elongation factor of HIV-1 primary transcripts. These findings show that TRIM22 and CIITA, two cellular proteins previously shown by us to inhibit HIV-1 proviral transcription with different mechanisms, interact in vivo and co-localize in nuclear bodies whose formation is hierarchically controlled by TRIM22. Importantly, TRIM19/Promyelocytic Leukemia (PML) protein, another repressor of HIV-1 transcription also acting before proviral integration, co-localized in these nuclear bodies upon TRIM22 expression induced by IFN-γ. Finally, TRIM22 nuclear bodies also contained CyclinT1, a crucial elongation factor of HIV-1 primary transcripts. These findings show that TRIM22 nuclear bodies are a site of recruitment of factors crucial for the regulation of HIV-1 transcription and highlight the potential existence of a concerted action between TRIM22, CIITA and TRIM19/PML to maintain a state of proviral latency at least in myeloid cells.

**P-D4**

**HIV-1 Env Trimer Conformational Implications of Peptide Fusion Inhibitor Resistance**

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Viral entry of HIV-1 is mediated by the envelope glycoprotein (Env), which consists of gp120 and gp41 trimer subunits. Entry begins when gp120 binds the CD4 receptor on the host cell. This induces conformational changes that expose the binding site for the CCR5 or CXCR4 chemokine co-receptors. Subsequently, heptad repeat 1 (HR1) and heptad repeat 2 (HR2) of gp41 self-assemble to form a six-helix bundle (6HB) that drives membrane fusion needed for viral entry. Previously, we identified HR1 peptide resistant Envs with key resistance mutations in HR1 or HR2 of gp41 that impact 6HB stability. These key gp41 resistance mutations defined two resistance pathways that were each associated with additional mutations in gp120 and gp41. Here, we further characterized the relative contribution of individual gp120 and gp41 mutations on Env conformational structure and sensitivity to CD4-induced conformational changes. Mutant Envs were assessed using a panel of conformation-dependent broadly neutralizing antibodies, temperature sensitivity studies, and soluble CD4-mediated entry into CD4-CCR5+ cells. Our data show that Envs from both resistance pathways have relaxed (more open) trimer conformations in their native state that is primarily mediated by individual mutations in gp120. Despite increased sensitivity to CD4 neutralization, gp41 mutations decrease conformational reactivity to CD4 binding by altering the transition of Envs from a fusion-competent to the inactive form. Our findings identify gp41 residues, particularly those in HR1, as important regulators of Env conformational transitions.

**P-D6**

**Elevated Plasma HIV RNA level is associated with impaired neurocognitive function among HIV-1 infected patients in Nigeria**

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Introduction: Plasma HIV RNA level has been shown to correlate with HIV disease progression, morbidity and mortality. We examined the association between levels of plasma HIV RNA and cognitive function among patients in Nigeria.

Methods: A total of 179 HIV-1 infected participants with available plasma HIV RNA results and followed longitudinally for up to 2 years were included in this study. Blood samples from participants were used for the measurement of plasma HIV RNA and CD4+ T cell count. Utilizing demographic and practice effect adjusted T scores obtained from a 7-domain neuropsychological test battery, cognitive status was determined by the global deficit score (GDS) approach, with a GDS ≥ 0.5 indicating cognitive impairment.

Results: In a longitudinal multivariable linear regression analysis, adjusting for CD4 cell count, Beck’s depression score, age, gender, years of education, and antiretroviral treatment status, global T scores decreased by 0.35 per log10 increase in Plasma HIV RNA [P=0.0328]. Adjusting for the same variables in a multivariable logistic regression, the odds of neurocognitive impairment were 30% higher per log10 increase in plasma HIV RNA (OR: 1.28 [95% CI: 1.08, 1.51]; P=0.0048). There were statistically significant associations for the speed of information processing, executive and verbal fluency domains in both linear and logistic regression analyses.

Conclusion: We found a significant association between plasma HIV RNA levels and cognitive function in both baseline (cross-sectional) and longitudinal analyses. However, the latter was significantly attenuated, and appeared to be driven largely by strong associations among antiretroviral naive individuals.
New insights on the human anti-HIV-1 Env antibody-mediated cell cytotoxicity (ADCC) against HIV-1 virus: Allosteric regulation of FcRs binding upon antigen engagement

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HIV-1 vaccine field is rapidly evolving and a deeper knowledge of the mechanisms of defense against HIV-1 infection is needed. In this regard, several studies highlighted the relevance of the antibody-mediated cell cytotoxicity (ADCC) in the context of HIV-1 infection, linking Fc-effector functions to protection against HIV-1 acquisition. The current model for ADCC activation is based on the concept that antibodies, bound to their respective antigens on the surface of HIV-1 sensitized cells, form aggregates which engage the FcRs, activating the effector cells. Our aim is to understand the molecular basis of ADCC and to identify the critical factors that lead to the triggering of the cytotoxicity against HIV-1 virus. Utilizing multiple approaches, such as ELISA, FCS (Fluorescence Correlation Spectroscopy), H/DX MS (Hydrogen/Deuterium Exchange Mass Spectroscopy) and crystallography, we studied the very first step of ADCC activation: the monovalent binding of viral antigen. Here, we demonstrate an allosteric regulation in anti-HIV gp120 Cluster A mAbs resulting from immune complex (IC) formation with a monomeric gp120-CD4 chimera antigen. We established that IC formation dramatically increases the efficiency of Ab interaction to low affinity FcRs compared to free IgG, impacting, in turn, the activation of the cytotoxicity against HIV-1 positive targets. In conclusion, we believe that monomeric antigen-antibody IC formation might be the very first step of HIV-1-specific ADCC triggering that likely precedes the IgG aggregation required for Fc receptors binding and in turn, effector cell activation. This might be a mechanism that enables the fine tuning of Fc-effector functions in vaccine regimens or HIV-1 passive treatments.

A novel way to test and discover new inhibitors against drug resistant HIV-1 proteases

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HIV-1 protease (PR) inhibitor (PI) is one of the most potent anti-HIV drugs. When it is used in combination with other drugs, if could suppress HIV to an undetectable level. However, successful treatment is often threatened by emergence of viral drug resistance of PRs (vdrPRs). Three vdrPRs were isolated from HIV-infected patients that carry seven (M7PR), ten (M10PR) and eleven (M11PR) PR gene mutations, respectively. They were expressed in a gene-inducible fission yeast system to allow the measurement of PR-specific activities. All three vdrPRs proteolyzed natural HIV viral substrates and conferred drug resistance to Indinavir in the fission yeast, suggesting they maintained the same proteolytic and drug resistant activities in the fission yeast as in mammalian cells. Moreover, the viral enzymatic activities of these vdrPRs coupled with the induction of growth inhibition and cell death, which could potentially be used as endpoints to test the efficacy of PI activities. In this study, five investigational PIs were used to test the utility of the PR-producing yeast system with Darunavir (DRV) as a control. All six compounds suppressed the wildtype PR and the M7PR-mediated activities. However, none of them suppressed activities conferred by M10PR or M11PR. The fact that M10PR and M11PR were resistant to all of the existing PI drugs including DRV, underscores the importance of continued searching for new PIs against vdrPRs. The described fission yeast cell-based system might be suitable for future testing or discovery of new PIs through high-throughput drug screening. Because this yeast cell-based method is function-driven. It has no presumption of what kind of PI will be found. It has the potential to uncover novel PIs.

The Impact of Structured Mentor Mother Support on Retention During the First 12 Months Postpartum among HIV Positive Women in Rural Nigeria.

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INTRODUCTION: With the advent of lifelong therapy, interventions that sustain long-term engagement with PMTCT services are needed. We evaluated the impact of a structured peer support program on postpartum PMTCT retention among rural Nigerian women.

METHODS: This prospective cohort study enrolled HIV+ pregnant women from 20 primary healthcare centers (PHCs). Ten PHCs with structured mentor mother (MM) support (training, supervision, client tracking, standard documentation & performance evaluation) were pair-matched with 10 routine unstructured peer support (PS) PHCs. Participants received viral load at 6 months and were followed up to 12 months postpartum. Viral suppression was defined as <20 copies/ml. Retention assessment was based on monthly & bi-monthly clinic visits in the 1st & 2nd six month postpartum periods respectively. Participants with ≥5 of 9 expected visits were considered retained. A logistic regression model with generalized estimating equation was used to evaluate the effect of PS & other factors on retention.

RESULTS: Of 497 women enrolled, 260 & 237 were exposed to MM & routine PS respectively. Women with MM support (aOR=6.8, 95% CI 3.4 – 13.1) & viral suppression at 6 months (aOR= 3.1, 95% CI 1.8 – 5.6) had higher odds of retention during the 12 month postpartum period. Age, distance from PHC, religion, gravidity, disclosure & time of diagnosis had no effect on retention.

DISCUSSION: Structure in peer support programs improved retention. Also, viral suppression had an independent effect on retention, indicating a strong link between adherence & sustained engagement; both being essential for PMTCT.

CONCLUSION: Built-in structure can significantly enhance the impact of PS interventions on PMTCT outcomes.
**P-E3**

Assessment of internationally-available HIV test kits for their suitability to meet manufacturers’ claims

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Background: HIV test kits, particularly rapid HIV tests, are used throughout the world as a primary measure to protect the blood supply and provide diagnosis to save lives. The US government purchases large numbers of HIV tests at considerable expense, and expects them to perform adequately. Objective: To assess a large number and variety of HIV test kits to determine if they meet the claims of the manufacturers.

Methods: From September 2010 through July 2017, a total of 1,123 lots of HIV test kits from 14 manufacturers and representing 11 different tests from 26 countries, were received for evaluation at the INSTITUTE OF HUMAN VIROLOGY. Each test kit was assessed for performance characteristics using panels of sera (n=30 or 160) that included positives for HIV-1 and HIV-2 (n=8 or 80), and negatives (n=22 or 80). Several HIV-1 positive samples were weak positives derived from seroconversion panels (SeraCare). Test kits were also assessed for precision using several HIV-1 weak positive samples tested in replicate.

Results: Of the HIV test kit lots evaluated, 99.2% successfully passed the evaluation with perfect performance. Of the 9 lots that did not pass, 3 were found to produce high background that interfered with reading, 2 performed inadequately with high-temperature testing, and 4 exhibited greater than one false-positive result. In one assessment, a country had reported poor performance of a test kit, but the test kit passed the evaluation; this resulted in a visit to the country to assess the laboratory’s activities.

Conclusion: In our evaluation of a large number and variety of HIV test kit lots from 14 manufacturers, nearly all performed as expected and met the manufacturers’ claims.

**P-E4**

The MoMent Study: Correlates of Viral Suppression at 6 months Postpartum among HIV-Positive Women in Rural Nigeria

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INTRODUCTION: The risk of mother-to-child transmission of HIV (MTCT) reduces with sustained pre & postpartum administration of suppressive maternal ARVs. The MoMent study evaluated for maternal viral suppression & its correlates among HIV+ Nigerian women.

METHODS: This prospective cohort study compared structured Mentor Mother (MM) vs unstructured peer support (PS) for PMTCT outcomes. Pregnant women were recruited at 20 matched Primary Healthcare Centers in rural North-Central Nigeria. Structured PS included daily MM supervision, standardized documentation, client tracking, & MM performance evaluations. Maternal viral load (VL) was performed at 6 months postpartum; women lost to followup were tracked back for VL tests. Viral suppression was defined as VL <20 copies/ml. All participants were on ART for ≥6 months. Multivariate logistic regression with generalized estimating equations was used to account for clusters and for adjusting confounders.

RESULTS: Among 497 enrollees, 296 (59.6%) presented for VL; 273/296 (92.2%) had samples collected. Of the 238/273 (87.2%) with available results, 138 (58%) were suppressed. Correlates of suppression were structured MM support (aOR 4.9, CI 2.6-9.2); age >30 years (aOR 2.3, CI 1.0-4.9); secondary education (aOR 2.0, CI 1.2-3.3); Christian religion (aOR 1.4, CI 1.1-2.1); PI-based ART (aOR 4.6, CI 1.3-16.0), and retention (aOR 3.7, CI 2.5-5.5). Marital/disclosure status & distance from facility were not significant.

DISCUSSION: Organized PS, older age, education, potent ARVs & retention supported viral suppression in our study. The role of religion is unclear & should be further explored.

CONCLUSION: Structured PS should be targeted to young & lesser educated women to reduce MTCT risk.

**P-E5**

Whole Genome Deep Sequencing of HIV Reveals Extensive Multi-class Drug Resistance in Nigerian Patients Failing First-line Antiretroviral Therapy

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BACKGROUND: Whole genome deep sequencing (WGS) could improve understanding of treatment failure and the emergence of resistance by revealing the distribution of mutations throughout the viral population over time.

METHODS: Adult patients receiving 1L ART (two NRTI and one NNRTI) at the University of Abuja Teaching Hospital, Nigeria, were included if they had experienced virological failure (HIV-1 RNA >1000 copies/mL, at least 6 months after ART initiation, confirmed by clinician-driven testing), and had a stored plasma sample available for WGS.

RESULTS: Sixty participants were sampled during 1L failure (73% female; median age 30 (interquartile ratio [IQR] 28-35); median CD4+ cell count 110 cells/mm3 (IQR 63-191); median 28 months after ART initiation (IQR 18-41)). At 1L failure, 57% of participants had thymidine analogue mutations (TAMs), with 30% harbouring 3 or more TAMs, 95% had other (non-TAM) NRTI mutations and 100% had NNRTI mutations. The most common mutations were M184V, Y181C, G190A, K65R and K103N. Overall, 17% (61/367) of the mutations identified were low-level minority variants (present at 2-20% of the intra-host viral population), which would not have been detected by standard resistance testing methods, 24% (88/367) were present at 20-90% frequency, and 59% (218/367) were dominant majority variants representing >90% of the participant’s viral population.

CONCLUSIONS: Diverse Nigerian HIV clades exhibit multi-class drug resistance at 1L ART failure. The predominance of high-frequency mutations suggests that emergent resistance had become fixed in the viral population by the time of sampling.
**P-E6**

*Hepatitis B and Hepatitis C. Viral Infections Among Pregnant Women in Some Nigerian Major Cities: A Review*

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Background: Worldwide, viral hepatitis is the commonest cause of hepatitis dysfunction in pregnancy. During pregnancy, viral hepatitis is associated with high risk of maternal complications and has become a leading cause of foetal death.

Aim: This review was done to assess the status of hepatitis B and hepatitis C viral infection among pregnant women in some Nigerian major cities.

Methodology: The information used for this review was from published works in Nigeria and elsewhere. The information was extracted over the period of seven months from November 2015 to June 2017.

Results: In Nigeria, the prevalence of hepatitis B and Hepatitis C viral infection is on the increase and the nation has been classified among the group of countries endemic for the infection with about 18 million of the populace infected. The prevalence of hepatitis B viral infection among pregnant women in many parts of the country has been reported; with Port Harcourt having the prevalence of (4.9%), Yenagoa (5.3%), Benin (12.5%) Jos (10.3%, 15.9% and 23.9%), Ibadan (21.3%). Anti- HCV antibody prevalence among pregnant women has also been reported in various parts of Nigeria; with Benin having the prevalence of (3.6%), Yenagoa (0.5%), Osogbo (9.2%), Enugu (14.9%), Jos (5.2%), Kaduna (11.9%), Kano (7.3%) and Zaria (18.2%). In Nigeria, the transmission of hepatitis B and Hepatitis C viral infections occur mainly during childhood as a result of maternal-neonatal transmission and by other risk factors like blood transfusion, sexual promiscuity, history of sharing of toothbrush, sharp objects such as razor blades, nail cutters and scissors and instruments for pedicure and manicure. Other modes of the viral infection common in the country include high risk groups such as health care workers, poor socioeconomic status. Thus, all the risk factors implicated elsewhere in the spread of the viral infections in the general population also play role in Nigeria.

Conclusion: The prevalence of hepatitis B virus (HBV) and Hepatitis C virus (HCV) among pregnant women in Nigeria is of intermediate endemicity. Therefore, there is the need to institute public health measures such as routine screening of all pregnant women’s blood and blood products for HBV and HCV, personal and environmental sanitation, and the discouragement of unsupervised injections to reduce disease burden and transmission in the population.

**P-G2**

*Development of engineered T-cell immunotherapy for treating Adult-T cell leukemia caused by HTLV-1.*

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HTLV-1 is perhaps the most oncogenic virus in humans. 5 to 10% of individuals infected by HTLV-1 develop a fatal T-cell leukemia (ATL) after 2-3 decades of latency. Conventional chemotherapy only creates escape mutants in ATL. Novel treatments including retroviral drugs, Arsenic Trioxide/IFNa combination, or Allogeneic stem cell transplantation have increased the 5-year survival, but there is still need to establish a cure. We chose an immunotherapy approach because all leukemic cells express some HTLV-1 viral proteins allowing to distinguish normal and HTLV-1 infected cells by the host immune system. In addition, anti-HTLV-1 immunity is suppressed in ATL patients. We aim to target HBZ (an antisense protein of HTLV-1) for this purpose because; 1) the frequency of T cells recognizing HBZ correlates well with low HTLV-1 proviral loads in contrast to T cells against Tax-1 or Env. 2) Unlike Tax-1, HBZ is constantly expressed by all stages of ATL cells. The challenge is that HBZ is an extremely weak immunogen. We identified a few epitopes of HBZ that stably find to Class I HLA molecules. We tested them using an in vivo model of ATL in immunized mice. Immunization by HBZ showed little therapeutic effects in these mice. DC immunization showed prolonged survival, but did not protect mice from ATL. Thus, we grew anti-HBZ CD8 T cells by immunizing normal T cells ex vivo, enriched them by HBZ-tetramer sorting. T-cell therapy involving anti-HBZ CD8 T cells successfully protected host mice, prompting us to rely on an “engineered T cell” strategy as novel treatment of acute/lymphomatous ATL cases.

**P-G3**

*Unravelling the Mechanism of Action of HLBT-100 Molecule against Adult T-Cell Leukemia*

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Adult T-cell leukemia-lymphoma (ATL) is a leukemia of mature CD4 T cells that develops after long-term infection of human T-cell leukemia virus (HTLV-1). The prognosis for patients living with the disease is poor, with chronic ATL median survival is 2 years. Once they are diagnosed with acute/lymphomatous ATL, patients have less than one year of life left. Current standard of care involves chemotherapy, combination of zidovudine (AZT) and IFN-a or Arsenic Trioxide and IFNa, antibody therapy (CD25, CCR4) and/or allogeneic stem cell transplantation, all of which will improve the median survival but are not effective for long term treatment. Hence there is an unmet need to discover and develop new and effective treatments against ATL. Strategies targeting signaling networks activated in ATL has been tried with some success. We have been testing a novel targeting of the JAK-STAT pathway with our novel small molecule inhibitor HLBT-100. In vitro experiments showed that HLBT-100 enhances serine-threonine phosphorylation of STAT3 by blocking the tyrosine phosphorylation of this molecule. In normal cells, this would allow mitochondrial translocation of the phosphorylated STAT3 after which STAT3 sustains homeostasis of cells and/or allogeneic stem cell transplantation, all of which will improve the median survival but are not effective for long term treatment. Therefore there is an unmet need to discover and develop new and effective treatments against ATL. Strategies targeting signaling networks activated in ATL has been tried with some success. We have been testing a novel targeting of the JAK-STAT pathway with our novel small molecule inhibitor HLBT-100. In vitro experiments showed that HLBT-100 enhances serine-threonine phosphorylation of STAT3 by blocking the tyrosine phosphorylation of this molecule. In normal cells, this would allow mitochondrial translocation of the phosphorylated STAT3 after which STAT3 sustains homeostasis of cells through the enhancement of mitochondrial energy generation. However this pathway seems non-functional in ATL cells. Thus, we hypothesize HLBT-100 seems to preferentially induce apoptotic death of ATL cells without damaging normal cells. We are currently validating this using a novel in vivo mouse model of ATL.
Primary Central Nervous System Lymphoma (PCNSL) is a rare form of extra nodal non-Hodgkin's lymphoma. HIV patients are more prone to PCNSL. It may arise from a systemic lymphoma that seeds multiple organs, including the brain. The predominant histology of PCNSL is large B-cell lymphoma. Molecular studies on systemic AIDS/NHL is well characterized, however, information on molecular studies of PCNSL is limited due in part to accessibility of tissue and lack of animal model. To date, no animal model has been developed, which recapitulates both histopathological and molecular features of this disease, including the immune phenotypic state. We recently developed an animal model of PCNSL. The observation of a phenotype of a HIV-1 transgenic mouse model that develops a B-cell lymphoma that mimics the disease is seen in AIDS patients with NHL. Brain lymphoma patients. HIV associated B-cell lymphoma patients as well as HIV infected patients suffer from cognatic impairment. Brain hippocampus region regulates cognatic behavior. Therefore, we were interested in finding the cellular and molecular changes in the hippocampus of these animals. Interestingly, we identified a significant increase of infiltrating leucocytes, T cells, B cells, and macrophages/microglial cells in the hippocampal region of these mice. Astroglisis is also observed. Aquaporin-4 (AQP4) is the predominant water channel expressed by astrocytes. The regulation of AQP4 has been extensively investigated in various neuropathological conditions; however, the functional role of AQP4 in synaptic plasticity, learning, and memory is only beginning to be elucidated. We have explored the role of AQP4 and its influence on hippocampus and its potential relationship with synaptic plasticity of these mice. Recent in vitro and in vivo studies using AQP4-null and wild-type mice, in particular, the impairment of cognatic function observed in the hippocampus of these animals. This suggests that AQP4 plays an important role in regulating synaptic plasticity in the hippocampus of these mice. Astrocytes play a role in synaptic plasticity. However, there are only a few studies that implicate a direct relationship of AQP4 in synaptic plasticity. All together, these studies highlight the potential influence of AQP4 in synaptic plasticity and memory of these animals probably due to compensatory mechanism.

HIV infections are the main cause of chronic liver disease and in part of lymphoproliferative disorders. Most HCV infections (>90%) determine chronic hepatitis, 30% of which progress to liver cirrhosis and 3% annually to Hepatocellular Carcinoma (HCC). The progression rate is mainly articulated in low (>40 years) and high (<10 years) speed progressors, with the latter being associated to male gender, <40 years of age, >150ml daily alcohol consumption. Current progression markers are mainly based on biochemical evaluation of liver damage (elevation of alanine and aspartate transaminases) and inflammation (elevation of alpha-fetoprotein). Such markers are not specific and elevated also for other infections (i.e. HBV and HCMV) or metabolic disorders (i.e. steatosis). Specific HCV-related markers would be relevant to identify HCV co-factors and to select high priority people for direct anti-viral treatment.

To identify HCC progression markers, samples from HCV+ patients at different infection stage have been analyzed on the HCV-peptide platform newly developed by JPT Peptide Technologies GmbH (Germany). It covers the complete HCV-protein arrays with >3000 overlapping 15-amino-acid-long peptides from all structural and non structural HCV proteins. The currently available data (from 7 HCV+ asymptomatic, 5 HCV+ with cirrhosis/HCC and 5 HCV- patients) demonstrates that in asymptomatic patients the level of anti-HCV is in general very low (including anti-capsid/core proteins), while high levels of immunoresponse anti-non-structural proteins is present in patients with liver cancer. Confirmation of such data would support the anti-non structural response as biomarker of cancer progression in HCV+ patients.
Monotherapy with Integrase Inhibitors Does Not Maintain Viral Suppression in Humanized Mice with Chronic HIV Infection

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Introduction and Methods: Simplification of current triple ART to dual ART or monotherapy may suffice to maintain HIV suppression while sparing drug toxicities. We evaluated and compared the efficacy of 20-week monotherapy with dolutegravir or raltegravir in humanized mice (HSC-NSG) infected with HIVBaL. Plasma HIV RNA was measured by qRT-PCR (limit of detection of 150 copies/40 µL plasma) and drug levels by LC/MS/MS. Escape viruses were genotyped and analyzed for replication capacity and drug susceptibility in tissue culture.

Results: Drug untreated control mice maintained constant viremia throughout the study. Virus isolates from these mice were susceptible to both raltegravir (EC50 < 8 nM) and dolutegravir (EC50 < 1 nM). Mice treated with raltegravir or dolutegravir had plasma drug levels comparable to those in humans. Monotherapy with raltegravir initially suppressed HIV viremia, but failed to maintain suppression in 4/4 mice. Viruses from raltegravir failing mice had the G140S and Q148H/K substitutions, and were resistant to both raltegravir (EC50 values of > 100 nM) and dolutegravir (EC50 values ranging 8.8-13.3 nM) in drug susceptibility assays using human PBMCs. Monotherapy with dolutegravir suppressed viremia in 5/5 of mice, but viremia rebounded in one animal after 12 weeks of treatment. The virus from this mouse had mutations E138K, G140S, Q148H, N155H and S230R, was highly resistant to both raltegravir (EC50 > 1000 nM) and dolutegravir (EC50 of 550 nM), and replicated to high levels in PBMCs.

Discussion: Raltegravir or dolutegravir monotherapy does not ultimately maintain HIV suppression in humanized mice, suggesting that dual therapy will most likely be required for simplification of ART treatment. 11 (OR=10.93) & 7 (OR=6.53) times more likely respectively, to have HIV negative infants compared to prophylaxis regimen.

Conclusion: HAART prior to and during pregnancy is associated with an increased likelihood of achieving a favorable EID result.