17TH ANNUAL

INTERNATIONAL MEETING of the Institute of Human Virology

www.ihv.org

SEPTEMBER 27– 30, 2015 | BALTIMORE

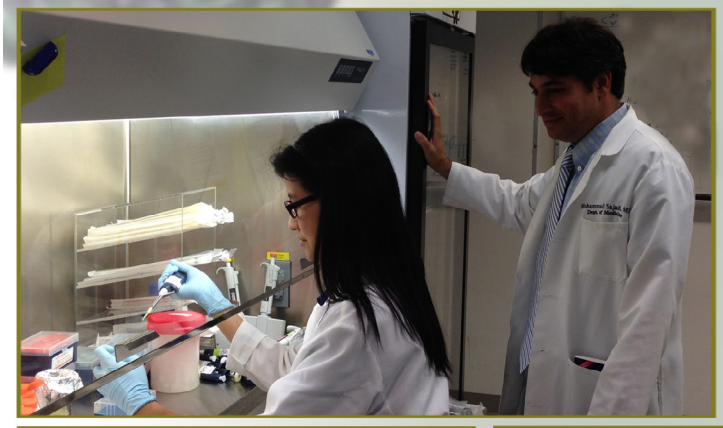
at the Baltimore Marriott Waterfront

Hosted by

INSTITUTE OF HUMAN VIROLOGY

www.ihv.org

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE



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Welcome

17th Annual Internaltional Meeting of the Institute of Human Virology at the University of Maryland School of Medicine

Welcome to the 17th Annual International Meeting of the Institute of Human Virology's (IHV) Awards Banquet. My colleagues and I are proud to present IHV's Lifetime Achievement Awards for Scientific Contributions & Public Service during this special evening. This year, IHV's faculty elected two very deserving, internationally renowned individuals who also happen to be my personal friends.

We are presenting for the first time two Lifetime Achievement Awards for Scientific Contributions & Public Service. This year, IHV's faculty elected Anthony S. Fauci, MD and Harald zur Hausen, MD to receive our annual honor, both of whom presented special lectures during the meeting today.

Dr. Fauci, as Director of the U.S. National Institute of Allergy and Infectious Diseases for more than 30 years, has administered a comprehensive research portfolio targeting the prevention, detection, and treatment of infectious diseases such as HIV/AIDS. He has made major contributions to the field of clinical immunology, such as in Wegner's granulomatosis, early in his career – culminating in his work on HIV/AIDS pathogenesis.

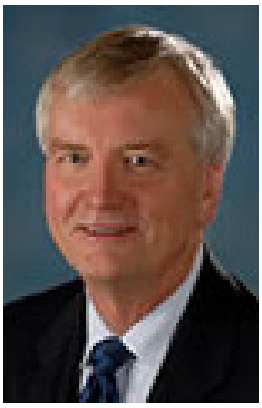
Prof. zur Hausen, a virologist and cancer researcher, was the Scientific Director of the German Cancer Research Center from 1983 to 2003. He has pioneered research in papillomaviruses most notably the link between human papillomaviruses (HPV) and cervical cancer. His research helped lead to the development of the HPV vaccine in 2006. In 2008, Prof. zur Hausen was awarded the Nobel Prize in Physiology or Medicine.

Uniquely at this year's Gala, we will premiere a seven minute film entitled "From Past to Future: Snapshots from the Institute of Human Virology" by Staffan Hildebrand, a Swedish film producer who has been documenting the AIDS pandemic since 1986.

Thank you for joining us as we honor these two pioneers for their achievements in human health and for your participation in IHV's Annual International Meeting.

Sincerely,

Robert C. Gallo, MD
Homer & Martha Gudelsky Distinguished Professor in Medicine
Director, Institute of Human Virology
University of Maryland School of Medicine
Co-founder & Scientific Director, Global Virus Network



William A. Blattner, MD
Professor and Associate Director, Institute of Human Virology

MISSION STATEMENT

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

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

Its unique structure seeks to connect cohesive, multi-disciplinary research and clinical programs so that new treatments are streamlined from discovery to patient. The IHV serves patients locally and the scientific community globally.

Robert C. Gallo, MD
Director

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Associate Director
Director, Division of Epidemiology and Prevention

Robert R. Redfield, MD
Associate Director
Director, Division of Clinical Care and Research

Joseph L. Bryant, DVM
Director, Division of Animal Models

George Lewis, PhD
Co-Director, Division of Basic Science and Vaccine Research

Wuyuan Lu, PhD
Co-Director, Division of Basic Science

Eric Sundberg, PhD
Co-Director, Division of Basic Science

C. David Pauza, PhD
Associate Director of Faculty Development

Dave Wilkins
Chief Operating Officer

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Former National Football League Player

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Peter Palese, PhD
Mount Sinai School of Medicine

James Pinkerton
RATE Coalition

Ellen Ratner
Talk Radio News Service

The Honorable Stephanie Rawlings-Blake
Mayor of Baltimore

The Honorable Edward “Chip” Robertson, Jr.
Bartimus, Frickleton, Robertson & Gorny

The Honorable Kathleen Kennedy-Townsend
Retired Lieutenant Governor of Maryland

Jeffrey B. Trammell
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Lenny Wilkens
National Basketball Association Hall of Fame Coach and Player

Steve Wozencraft
John O’Donnell Associates, LLC

IHV Scientific Advisory Board

Organizing Committee

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.

Robert C. Gallo, MD, Chair

William Blattner, MD, Co-Chair

Luigi Buonaguro, MD, National Cancer Institute, "Fondazione Pascale"

Carl Dieffenbach, PhD, Division of AIDS, National Institute of Allergy and Infectious Diseases

Jose Esparza, MD, PhD, Institute of Human Virology

Salim Karim, MD, PhD, Centre for the AIDS Programme of Research in South Africa (CAPRISA)

Clara Lehmann, MD, University of Cologne

John Moore, PhD, Weill Cornell Medical College

Carlo Federico Perno, MD, PhD, University of Rome Tor Vergata

Robert Siliciano, MD, PhD, Johns Hopkins University

Sten Vermund, MD, PhD, Institute for Global Health, Vanderbilt University Medical Center

Local Organizing Committee

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Baltimore, Maryland

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Fabio Romerio, PhD

Eric Sundberg, PhD

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:

- All comments at sessions are off-the-record and are not for attribution.
- 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 Grannell, Director of Public Relations and Marketing, Institute of Human Virology, (410) 706-1954 or ngrannell@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.

Office of AIDS Research

National Institute of Allergy and Infectious Diseases*

Division of AIDS, NIH

Gilead

Sanofi Pasture

National Institute on Drug Abuse

AstraZeneca *
AZ support is for educational purposes only

Profectus BioSciences, Inc.

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Abbott Molecular

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Sysmex Global

The Marlene and Stewart Greenebaum Cancer Center

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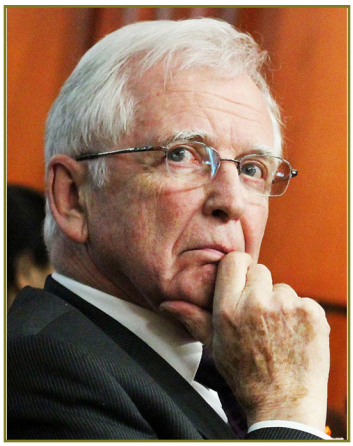
**Funding for this conference was made possible [in part] by 5 R13 AI 046078 - 16 from the National Institute of Allergy and Infectious Diseases. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.*

The 2015 IHV Lifetime Acheivement Award for Scientific Contributions and Public Service

Harald zur Hausen, M.D.



Harald zur Hausen was born on March 11, 1936 in Gelsenkirchen-Buer, Germany. He studied Medicine at the Universities of Bonn, Hamburg and Düsseldorf and received his M.D. in 1960. After his internship he worked as postdoc at the Institute of Microbiology in Düsseldorf, subsequently in the Virus Laboratories of the Children's Hospital in Philadelphia where he was later appointed as Assistant Professor. After a period of 3 years as a senior scientist at the Institute of Virology of the University of Würzburg, he was appointed in 1972 as Chairman and Professor of Virology at the University of Erlangen-Nürnberg. In 1977 he moved to a similar position to the University of Freiburg. From 1983 until 2003 he was appointed as Scientific Director of the Deutsches Krebsforschungszentrum (German Cancer Research Center) in Heidelberg. He retired from this position in 2003.

He received a number of national and international awards, among them the Robert-Koch-Price, the Charles S. Mott Price of the General Motors Cancer Research Foundaton, the Federation of the European Cancer Societies Clinical Research Award, the Paul-Ehrlich-Ludwig Darmstädter-Price, the Jung-Price, Hamburg, the Charles Rudolphe Brupbacher Price, Zürich, the Prince Mahidol Award, Bangkok, the Raymond Bourgine Award, Paris, the Coley-Award, New York, the Life Science Achievement Award of the American Association for Cancer Research, San Diego, and the Nobel-Prize for Medicine, 2008.

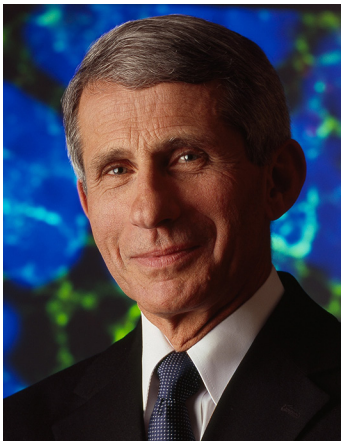
He received 32 honorary doctorates from the Universities of Chicago, USA, Umeå, Sweden, Prague, Czech Republic, Salford, UK, Helsinki, Finland, Erlangen-Nürnberg and Würzburg, both Germany, Ferrara, Italy, Melbourne, Australia, Buenos Aires, Argentine, Salerno, Italy, Warsaw, Poland, Madrid, Spain, Bucamaranga, Columbia, Los Angeles, USA, Jerusalem, Israel, Besancon, France, Valdivia, Chile, Ljubljana, Slovenia, Antwerp, Belgium, Pisa, Italy, New York, USA, Ioanina, Greece, Ho Chi Minh City (Saigon), Vietnam, Porto Allegre, Brazil, Athens, Greece, Guadalajara, Mexico, Patras, Greece, Nishny Nowgorod, Russia, Pleven, Bulgaria, Tomsk, Siberia and Warwick, UK.

He is an elected member of various academies (LEOPOLDINA, Heidelberg Academy of Sciences, Polish Academy of Sciences, Venezuela National Academy of Medicine, American Philosophical Society, National Academy of Medicine (USA), Foreign Member of the US National Academy of Sciences and of the research organizations EMBO andHUGO, and became an Honorary Member of a number of biomedical scientific societies. A large number of Special Lectures and Visiting Professorships, Memberships in Editorial Boards and active involvements in the organization of international meetings complement his curriculum.

From 1989-1991 he was chairing the Association of National Research Centres, in Bonn, Germany. From 1993-1996 he was President of the Organization of European Cancer Institutes. From 2000-2009 zur Hausen was Editor-in-Chief of the International Journal of Cancer, and from 2006-2009 he was member of the Board of Directors of the International Union against Cancer (UICC). From 2003-2009he was Vice-President of the German National Academy for Natural Sciences and Medicine LEOPOLDINA in Halle. Since 2006 he is a member of the National Science Tansfer and Development Agency in Bangkok, Thailand.

The 2015 IHV Lifetime Acheivement Award for Scientific Contributions and Public Service

Anthony S. Fauci, M.D.



Anthony S. Fauci, M.D., is director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health. Since his appointment as NIAID director in 1984, Dr. Fauci has overseen an extensive research portfolio devoted to preventing, diagnosing, and treating infectious and immune-mediated diseases. Dr. Fauci also is chief of the NIAID Laboratory of Immunoregulation, where he has made numerous important discoveries related to HIV/AIDS and is one of the most-cited scientists in the field. Dr. Fauci serves as one of the key advisors to the White House and Department of Health and Human Services on global AIDS issues, and on initiatives to bolster medical and public health preparedness against emerging infectious disease threats such as pandemic influenza. He was one of the principal architects of the President's Emergency Plan for AIDS Relief (PEPFAR), which has already been responsible for saving millions of lives throughout the developing world.

Dr. Fauci is a member of the US National Academy of Sciences and is the recipient of numerous prestigious awards for his scientific and global health accomplishments, including the National Medal of Science, the Mary Woodard Lasker Award for Public Service, and the Presidential Medal of Freedom. He has been awarded 38 honorary doctoral degrees and is the author, coauthor, or editor of more than 1,200 scientific publications, including several major textbooks.

Previous Recipients of IHV Lifetime Acheivement 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, D.Sc., Russian Academy of Medical Sciences, Moscow, Russia

2014 William Paul, MD, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, 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
The Honorable Robert K. Gray, Gray and Company II, Miami, Florida, USA

2010 Harry Huge, Esq., The Harry and Reba Huge Foundation, Charleston, South Carolina, USA

2011 Bernadine Healy, MD, In Memoriam, Former Director National Institutes of Health, Bethesda, MD, 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

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

Sunday, September 27, 2015

6:30 – 8:15 pm

Opening Reception/Poster Session
Kent A, B & C

Tuesday, September 29, 2015

6:15 – 7:00 pm

Lifetime Achievement Awards Gala Reception
Harborside Foyer

7:00 – 9:00 pm

Lifetime Achievement Gala Banquet and Awards Ceremony
Harborside Ballroom C

Program Overview

Sunday, September 27, 2015

2:00 - 2:30 pm	**Coffee and Gathering**
2:30 pm	**Session A - Comorbidities and Hepatitis C**
6:30 - 8:15 pm	**Opening Reception and Poster Session**

Monday, September 28, 2015

8:20 am	**Session B – Status of HIV Cure Research**
10:40 – 11:00 am	**Coffee Break**
12:20 – 2:00 pm	**Lunch**
2:00 pm	**Session C – Molecular Epidemiology: Viruses and Cancer**
4:00 – 4:20 pm	**Coffee Break**

Tuesday, September 29, 2015

8:20 am	**Session D – HIV Structural Biology, Immunology and Vaccines**
10:40 - 10:55 am	**Coffee Break**
11:45 am - 1:00 pm	**Lunch**
1:00pm	**Session E - Global Virus Threats: Translation of Basic Science to Public Health Practice**

Program Overview, cont.

Tuesday, September 29, 2015

3:40 - 4:10 pm	**Coffee Break**
6:15 am	**Gala Reception**
7:00 pm	**Lifetime Achievement Awards Dinner**

Wednesday, September 30, 2014

8:30 am	**Session F – Pathogenesis Research: Viruses, Cancer and Host Factors**
10:30 - 10:50 am	**Coffee Break**
11:45 am - 12:45 pm	**Lunch**
12:45 pm	**Session G – Immunology and Inflammation**
3:15 - 3:40 pm	**Coffee Break**
4:55 pm	**Meeting Adjourns**

Speaker Schedule

Sunday, September 27, 2015

Coffee and Gathering 2:00 - 2:30 PM - Harborside Foyer

Session A:
Comorbidities and Hepatitis C

Harborside Ballroom D&E
Chairpersons and Discussants:
Robert R. Redfield, MD, Institute of Human Virology University of Maryland School of Medicine
John Bartlett, Johns Hopkins University
Alexey Mazus MD, Moscow Center for HIV/AIDS Prevention and Treatment
Franco Buonaguro, MD, National Cancer Institute "Fondazione Pascale"

2:30 Shyam Kottilil, MD, PhD, Institute of Human Virology University of Maryland School of Medicine
Introduction to Hepatitis C Mini-Symposium *A-101*

2:40 Kristen Marks, MD, Weill Cornell Medical College
HCV treatment as prevention *A-102*

3:00 Camilla Graham, MD, Harvard Medical School
Price, Cost-Effectiveness and Affordability of Hepatitis C Drugs: How Did We Get Into This Mess? *A-103*

3:20 Kenneth Sherman, MD, University of Cincinnati
Comorbidities and Hepatitis C *A-104*

3:40 Barry Peters, MD, Kings College London
The metabolic and cardiovascular complications of HIV *A-105*

4:00 John Bartlett, MD, Johns Hopkins University School of Medicine
HIV Infection: What's New Novel and Exciting *A-106*

4:20 Alexey Mazus, MD, Head of Moscow Center for HIV/AIDS Prevention and Treatment
HIV/HCV coinfection: modern treatment strategies, problems in Eastern Europe *A-107*

4:40 Franco Buonaguro, MD, National Cancer Institute 'Fondazione Pascale'
Viral and cellular biomarkers in HPV-related cancers *A-108*

5:00 Joel Palefsky, MD, University of California, San Francisco
Pathogenesis of anal cancer *A-109*

5:20 Corey Casper MD, MPH, Fred Hutchinson Cancer Research Center
Translational Research to Advance the Prevention and Treatment of HIV-Associated Malignancies *A-110*

5:40 Richard Chaisson, MD, Johns Hopkins Center for Tuberculosis Research and Center for AIDS Research
Controlling the Impact of HIV-related Tuberculosis *A-111*

6:00 Tracy Sparkes, Pharm.D., University of Maryland School of Pharmacy
Impact of Antiretroviral Regimen on Renal Transplant Outcomes in HIV-Infected Recipients *A-112*

Opening Reception (Harborside Foyer) and Poster Session (Kent A, B & C) 6:30 - 8:15 pm

Monday, September 28, 2015

Session B:
Status of HIV Cure Research

Harborside Ballroom D&E
Chairpersons and Discussants:
George Shaw, MD, PhD, University of Pennsylvania
Anders Vahlne, MD, PhD, Karolinska Institutet

8:20 Robert Siliciano, MD, PhD, Johns Hopkins University
Unique features of effector to memory transition render CD4+ T cells permissive for latent HIV infection *B-101*

8:40 Guido Poli, MD, Vita-Salute San Raffaele University
Towards Achieving a State of Reversible HIV-1 Latency in Primary Monocyte-Derived Macrophages (MDM) by M1 Polarization *B-102*

9:00 Keith Jerome, MD, PhD, University of Washington Lab Medicine
Genome-directed antiviral endonuclease therapy: promise and perils *B-103*

9:20 David Margolis, MD, University of North Carolina at Chapel Hill
HIV Cure Research: a status report *B-104*

9:40 John Frater, MD, PhD, University of Oxford
Post Treatment Control: what predicts long-term HIV remission? *B-105*

10:00 Julie Overbaugh, PhD, Fred Hutchinson Cancer Research Center
Characterizing the basis for the broad and potent HIV-specific neutralizing antibody response of infants *B-106*

10:20 Jonathan Karn, PhD, Case Western Reserve University
Distinct mechanisms of hormonal control of HIV latency in T-cells and microglial cells *B-107*

Coffee Break 10:40 - 11:00 AM - Harborside Foyer

11:00 Stephen H. Hughes, PhD, National Cancer Institute
Specific HIV integration sites are linked to clonal expansion and persistence of infected cells *B-108*

11:20 Deborah Persaud, MD, Johns Hopkins Children's Center
HIV Latency and Perinatal Infection *B-109*

11:40 Fabio Romerio, PhD, Institute of Human Virology University of Maryland School of Medicine
The HIV-1 antisense transcript AST promotes latency by recruiting PRC2 to the 5'LTR *B-110*

12:00 Paolo Lusso, MD, PhD, National Institute of Allergy and Infectious Diseases
Sulfotyrosine-Mediated V2-V3 Interaction Stabilizes the HIV-1 Envelope Trimer Facilitating Immune Evasion *B-111*

Lunch 12:20 – 2:00 PM

Session C:
Molecular Epidemiology: Viruses and Cancer

Harborside Ballroom D&E
Chairpersons and Discussants:
Stanley Weiss, MD, FACP, FACE, Rutgers New Jersey Medical School
Douglas Blayney, MD, Stanford Cancer Center
Alash'le Abimiku, PhD, Institute of Human Virology University of Maryland School of Medicine
Warren Johnson, MD, Weill Cornell Medical College
James Goedert, MD, National Cancer Institute

2:00 Mark K. Slifka, PhD, Oregon National Primate Research Center at Oregon Health & Science University
Vaccines and Mechanisms of Host Defense *C-101*

2:20 Beatrice Hahn, MD, Perelman School of Medicine, University of Pennsylvania
Dissecting HIV-1 Transmission: Understanding Transmitted Founder Virus Biology C-102

2:40 Man Charurat, PhD, Institute of Human Virology University of Maryland School of Medicine
Genetic Diversity of HIV Reveals the Epidemiological Role of High Risk Groups in Nigeria *C-103*

3:00 Esther H. Chang, PhD, Georgetown University
A Tumor-Targeting Delivery Platform for p53 Therapy: Translation and Clinical Applications *C-104*

3:20 Gloria Yuen Fun Ho, PhD, Albert Einstein College of Medicine
Insulin and IGFBP-3 Associated with Lung Cancer Susceptibility In Current Smokers *C-105*

3:40 Myron Essex, DVM, PhD, T.H. Chan School of Public Health, Harvard University
The Botswana Combination Prevention Project (BCPP): Addressing the UN 90-90-90 Targets *C-106*

Coffee Break 4:00 - 4:20 PM - Harborside Foyer

4:20 Sten Vermund, MD, PhD, Institute for Global Health, Vanderbilt University Medical Center
Stigma and Depression Among Newly Diagnosed HIV Infected MSM in China *C-107*

4:40 Howard Strickler, MD, Albert Einstein College of Medicine
Recent Cohort Data Suggest Revising US Cervical Cancer Screening Practices in HIV+ Women *C-108*

5:00 Clement Adebamowo, BM, ChB, ScD, FWACS, FACS, Institute of Human Virology University of Maryland School of Medicine
HPV Associated Cervical Cancer in HIV negative African Women *C-109*

5:20 Edward L. Murphy, Jr., MD, MPH, University of California, San Francisco
Human T lymphotropic virus types 1 and 2 (HTLV-1 and -2) and hepatitis C virus (HCV) epidemiology: lessons from studies of blood donors *C-110*

5:40 John Vertefeuille, PhD, Centers for Disease Control and Prevention
Progress toward poliomyelitis eradication - Nigeria, January 2014-July 2015 *C-111*

Tuesday, September 29, 2015

Session D:
HIV Structural Biology, Immunology and Vaccines

Harborside Ballroom D & E

Chairpersons and Discussants:
Robert C. Gallo, MD, Director, Institute of Human Virology University of Maryland School of Medicine
Georgia Tomaras, PhD, Duke Human Vaccine Institute
José Esparza MD, PhD, Adjunct Professor, Institute of Human Virology University of Maryland School of Medicine
Nina Russell, MD, Bill and Melinda Gates Foundation
Thomas Lehner, CBE, MD, Kings College London

8:20 Rogier Sanders, PhD, Weill Cornell Medical College
HIV-1 neutralizing antibodies induced by native-like envelope trimers *D-101*

8:40 Kwinten Sliepen MSc, University of Amsterdam
Presenting native-like HIV-1 envelope trimers on ferritin nanoparticles improves their immunogenicity *D-102*

9:00 John Moore, PhD, Weill Cornell Medical College
Studies on native-like SOSIP.664 trimers and other forms of Env *D-103*

9:20 Heather Desaire, PhD, University of Kansas
Molecular-level analysis of Env: What's on native trimers and how can we reproduce it in a vaccine? *D-104*

9:40 Theresa L. Chang PhD , Rutgers University
Integrin a4b7 expression increases HIV susceptibility in activated cervical CD4+ T cells via an HIV attachment-in dependent mechanism *D-105*

10:00 Douglas Nixon, MD, PhD, George Washington University
Cellular Immune correlates Analysis of an HIV-1 Pre-exposure Prophylaxis Trial *D-106*

10:20 Antje Heit, MD, PhD, Fred Hutchinson Cancer Research Center
Vaccination establishes CXCR5+PD1+CD4+ peripheral blood germinal center T follicular helper cell relatives in humans *D-107*

Coffee Break 10:40 - 10:55 - Harborside Foyer

10:55 Michel Nussenzweig, MD, PhD, The Rockefeller University
Special Lecture: Human Antibodies to HIV-1 *D-108*

11:20 Jeffrey Ravetch, MD, PhD, The Rockefeller University
Special Lecture: Fc Effector functions in the anti-viral response *D-109*

Lunch 11:45 AM - 1:00 PM

Session E:
Global Virus Threats: Translation of Basic Science to Public Health Practice
Harborside Ballroom D & E
Chairpersons and Discussants:
Carl Dieffenbach, PhD, Division of AIDS, National Institute of Allergy and Infectious Diseases
Prof. Bernhard Fleckenstein, Universitätsklinikum Erlangen
Susan Buchbinder, MD, University of California, San Francisco
John Idoko, MD, National Agency for the Control of AIDS, Abuja, Nigeria

1:00 Robert C. Gallo, MD, Director, Institute of Human Virology University of Maryland School of Medicine
Introduction to Reinhard Kurth Memorial Lecture

1:05 Harald zur Hausen, MD, Nobel Laureate, German Cancer Research Center in the Helmholtz Association
Reinhard Kurth Memorial Lecture: Zoonotic Origin of Some Common Human Cancers and Multiple Sclerosis? *E-101*

1:50 Robert C. Gallo, MD, Director, Institute of Human Virology University of Maryland School of Medicine
Introduction to Lifetime Achievement Awards

1:55 Anthony Fauci, MD, National Institute of Allergy and Infectious Diseases
Ending the HIV/AIDS Pandemic: The Convergence of Treatment and Prevention *E-102*

2:40 Barton Haynes, MD, Duke Human Vaccine Institute
The Pathway to HIV Vaccine Development *E-103*

3:10 Larry Corey, MD, Fred Hutchinson Cancer Research Center
Can non neutralizing antibodies be the basis for an effective HIV vaccine? Can we determine if RV 144 is "real or Memorex" ? *E-104*

Coffee Break 3:40 – 4:10PM - Harborside Foyer

4:10 Erica Ollmann Saphire, PhD, The Scripps Research Institute
Antibodies Against Ebola Virus: Results of the Viral Hemorrhagic Fever Immunotherapeutic Consortium *E-105*

4:40 Cliff Lane, MD, National Institute of Allergy and Infectious Diseases
Establishment of a Clinical Research Program in the Setting of the Ebola Outbreak in West Africa *E-106*

5:10 Salim Abdool Karim, PhD, Director, Centre for the AIDS Programme of Research in South Africa (CAPRISA)
Advancing Global Health: Lessons from the response to the HIV epidemic *E-107*

6:15 PM Gala Reception - Harborside Foyer

7:00 PM Lifetime Achievement Awards Dinner - Harborside Ballroom C

Wednesday, September 30, 2015

Session F:
Pathogenesis Research: Viruses, Cancer and Host Factors

Harborside Ballroom D & E
Chairpersons and Discussants:
Anders Vahlne, MD, PhD, Karolinska Institutet
Eduardo Sotomayor, MD, George Washington University School of Medicine & Health Sciences
Kevin Cullen, MD, Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine

8:30 Mario Stevenson, PhD, University of Miami
Pharmacologic inhibition of the HIV-1 vif:apobec axis *F-101*

8:50 Alfredo Garzino-Demo, PhD, Institute of Human Virology
HIV-1 matrix protein p17 promotes lymphangiogenesis by autophagy-mediated unconventional proteins secretion *F-102*

9:10 Wuyuan Lu, PhD, Institute of Human Virology
A conformational switch that turns on the B cell growth-promoting activity of the HIV-1 matrix protein p17 *F-103*

9:30 Luigi Buonaguro, MD, National Cancer Institute, "Fondazione Pascale"
Hepatitis virus associated liver cancer: pathogenesis and immunotherapeutic strategies *F-104*

9:50 Isaac Witz, MD, PhD, Tel Aviv University
Site-Specific Metastasis Revisited *F-105*

10:10 Anthony DeVico PhD, Institute of Human Virology
Transition State Gp120 Structures as HIV Vaccines *F-106*

Coffee Break 10:30 - 10:50 AM - Harborside Foyer

10:50 Genoveffa Franchini, National Cancer Institute, Bethesda
Adjuvant dependant RAS activation and mucosal envelope antibody to V2 correlate with reduced risk of Sivmac251 acquisition *F-107*

11:10 Thomas Lehner, CBE, MD, Kings College London
The role of a dual pre- and post- entry innate and adaptive immune mechanism in protection against HIV-1 infection *F-108*

11:30 Krishanu Ray, PhD, University of Maryland School of Medicine
Antigenicity of the Human Immunodeficiency Virus Envelope on Virions in Solution by Fluorescence Correlation Spectroscopy *F-109*

Lunch 11:45 AM – 12:45 PM

Session G:
Immunology and Inflammation

Harborside Ballroom D & E

Chairpersons and Discussants:
Luigi Buonaguro, MD, National Cancer Institute, "Fondazione Pascale"
William Hall, PhD, University College Dublin
George Pavlakis, MD, PhD, National Cancer Institute
Leonid Margolis, PhD, National Institute of Child Health and Human Development

12:45 Ellis L. Reinherz, MD, Dana-Farber Cancer Institute
Special Lecture: The T cell receptor is a mechanosensor *G-101*

1:15 Andrés Finzi, PhD, University of Montreal
Modulating Env conformation: a new approach to eliminate HIV-1-infected cells *G-102*

1:35 Richard Koup, MD, Vaccine Research Center, National Institute of Allergy and Infectious Diseases
Use of bnAbs and bnAb-based bispecific antibodies to target HIV-expressing cells in vivo *G-103*

1:55 Margaret Ackerman, PhD, Thayer School of Engineering at Dartmouth College
Breaking the species barrier: IgG subclasses in man and macaques *G-104*

2:15 Galit Alter, PhD, Harvard Medical School, Ragon Institute of MGH, MIT and Harvard
Defining protective antibody profiles against HIV utilizing systems serology *G-105*

2:35 Falk Nimmerjahn, PhD, Lehrstuhl Genetik, Friedrich-Alexander Universität Erlangen-Nürnberg
The pro- and anti-inflammatory effector functions of IgG *G-106*

2:55 Eric Sundberg, PhD, Institute of Human Virology
Enzymatic manipulation of antibody Fc-mediated effector functions *G-107*

Coffee Break 3:15 - 3:40 PM - Harborside Foyer

3:40 Leonid Margolis, MD, National Institute of Child Health and Development
Some HIV-1 virions are more equal than others: Mosaics of Envs on individual HIV virions as evaluated with flow virometry *G-108*

3:55 Hua Cheng, PhD, Institute of Human Virology
TBK1/IKKε, the non-canonical IκB kinases, promote survival and proliferation of HTLV-1-transformed T cells by maintaining Stat3 activity *G-109*

4:10 Ira Berkower MD, PhD, Lab of Immunoregulation, FDA
Live attenuated rubella vectors stably express SIV Gag and HIV Env proteins in a highly immunogenic vaccine platform *G-110*

4:25 Kenneth Bagley, PhD, Profectus Biosciences
DNA prime/subunit boost using SIVE660 based rhFLSC yields 75% efficacy against cross clade SIVmac251 intrarectal challenge *G-111*

4:40 Closing Remarks from Dr. Gallo - **Meeting Adjourns 4:55pm**

A-101 *Introduction to Hepatitis C Mini-Symposium*
Shyam Kottilil, MD, PhD, Institute of Human Virology

A-102 *HCV treatment as prevention*
Kristen Marks, MD, Weill Cornell Medical College

A-103 *Price, Cost-Effectiveness and Affordability of Hepatitis C Drugs: How Did We Get Into This Mess?*
Camilla Graham, MD, Harvard Medical School

A-104 *Comorbidities and Hepatitis C*
Kenneth Sherman, MD, University of Cincinnati

A-105 *The metabolic and cardiovascular complications of HIV*
Barry Peters, MD, Kings College London

A-106 *HIV Infection: What's New Novel and Exciting*
John Bartlett, MD, Johns Hopkins University School of Medicine

A-107 *HIV/HCV coinfection: modern treatment strategies, problems in Eastern Europe*
Alexey Mazus, MD, Head of Moscow Center for HIV/AIDS Prevention and Treatment

A-108 *Viral and cellular biomarkers in HPV-related cancers*
Franco Buonaguro, MD, National Cancer Institute 'Fondazione Pascale'

A-109 *Pathogenesis of anal cancer*
Joel Palefsky, MD, University of California, San Francisco

A-110 *Translational Research to Advance the Prevention and Treatment of HIV-Associated Malignancies*
Corey Casper MD, MPH, Fred Hutchinson Cancer Research Center

A-111 *Controlling the Impact of HIV-related Tuberculosis*
Richard Chaisson, MD, Johns Hopkins Center for Tuberculosis Research and Center for AIDS Research

A-112 *Impact of Antiretroviral Regimen on Renal Transplant Outcomes in HIV-Infected Recipients*
Tracy Sparkes, Pharm.D., University of Maryland School of Pharmacy

B-101 *Unique features of effector to memory transition render CD4+ T cells permissive for latent HIV infection*
Robert Siliciano, MD, PhD, Johns Hopkins University

B-102 *Towards Achieving a State of Reversible HIV-1 Latency in Primary Monocyte-Derived Macrophages (MDM) by M1 Polarization*
Guido Poli, MD, Vita-Salute San Raffaele University

B-103 *Genome-directed antiviral endonuclease therapy: promise and perils*
Keith Jerome, MD, PhD, University of Washington Lab Medicine

B-104 *HIV Cure Research: a status report*
David Margolis, MD, University of North Carolina at Chapel Hill

B-105 *Post Treatment Control: what predicts long-term HIV remission?*
John Frater, MD, PhD, University of Oxford

B-106 *Characterizing the basis for the broad and potent HIV-specific neutralizing antibody response of infants*
Julie Overbaugh, PhD, Fred Hutchinson Cancer Research Center

B-107 *Distinct mechanisms of hormonal control of HIV latency in T-cells and microglial cells*
Jonathan Karn, PhD, Case Western Reserve University

B-108 *Specific HIV integration sites are linked to clonal expansion and persistence of infected cells*
Stephen H. Hughes, PhD, National Cancer Institute

B-109 *HIV Latency and Perinatal Infection*
Deborah Persaud, MD, Johns Hopkins Children's Center

B-110 *The HIV-1 antisense transcript AST promotes latency by recruiting PRC2 to the 5'LTR*
Fabio Romerio, PhD, Institute of Human Virology

B-111 *Sulfotyrosine-Mediated V2-V3 Interaction Stabilizes the HIV-1 Envelope Trimer Facilitating Immune Evasion*
Paolo Lusso, MD, PhD, National Institute of Allergy and Infectious Diseases

C-101 *Vaccines and Mechanisms of Host Defense*
Mark K. Slifka, PhD, Oregon National Primate Research Center at Oregon Health & Science University

C-102 *Dissecting HIV-1 Transmission: Understanding Transmitted Founder Virus Biology*
Beatrice Hahn, MD, Perelman School of Medicine, University of Pennsylvania

C-103 *Genetic Diversity of HIV Reveals the Epidemiological Role of High Risk Groups in Nigeria*
Man Charurat, PhD, Institute of Human Virology

C-104 *A Tumor-Targeting Delivery Platform for p53 Therapy: Translation and Clinical Applications*
Esther H. Chang, PhD, Georgetown University

C-105 *Insulin and IGFBP-3 Associated with Lung Cancer Susceptibility In Current Smokers*
Gloria Yuen Fun Ho, PhD, Albert Einstein College of Medicine

C-106 *The Botswana Combination Prevention Project (BCPP): Addressing the UN 90-90-90 Targets for 2020*
Myron Essex, DVM, PhD, T.H. Chan School of Public Health, Harvard University

C-107 *Stigma and Depression Among Newly Diagnosed HIV Infected MSM in China*
Sten Vermund, MD, PhD, Institute for Global Health, Vanderbilt University Medical Center

C-108 *Recent Cohort Data Suggest Revising US Cervical Cancer Screening Practices in HIV+ Women*
Howard Strickler, MD, Albert Einstein College of Medicine

C-109 *HPV Associated Cervical Cancer in HIV negative African Women*
Clement Adebamowo, BM, ChB, ScD, FWACS, FACS, Institute of Human Virology

C-110 *Human T lymphotropic virus types 1 and 2 (HTLV-1 and -2) and hepatitis C virus (HCV) epidemiology: lessons from studies of blood donors*
Edward L. Murphy, Jr., MD, MPH, University of California, San Francisco

C-111 *Progress toward poliomyelitis eradication - Nigeria, January 2014-July 2015*
John Vertefeuille, PhD, Centers for Disease Control and Prevention

D-101 *HIV-1 neutralizing antibodies induced by native-like envelope trimers*
Rogier Sanders, PhD, Weill Cornell Medical College

D-102 *Presenting native-like HIV-1 envelope trimers on ferritin nanoparticles improves their immunogenicity*
Kwinten Sliepen MSc, University of Amsterdam

D-103 *Studies on native-like SOSIP.664 trimers and other forms of Env*
John Moore, PhD, Weill Cornell Medical College

D-104 *Molecular-level analysis of Env: What's on native trimers and how can we reproduce it in a vaccine?*
Heather Desaire, PhD, University of Kansas

D-105 *Integrin a4b7 expression increases HIV susceptibility in activated cervical CD4+ T cells via an HIV attachment-in dependent mechanism*
Theresa L. Chang PhD , Rutgers University

D-106 *Cellular Immune correlates Analysis of an HIV-1 Pre-exposure Prophylaxis Trial*
Douglas Nixon, MD, PhD, George Washington University

D-107 *Vaccination establishes CXCR5+PD1+CD4+ peripheral blood germinal center T follicular helper cell relatives in humans*
Antje Heit, MD, PhD, Fred Hutchinson Cancer Research Center

D-108 *Special Lecture: Human Antibodies to HIV-1*
Michel Nussenzweig, MD, PhD, The Rockefeller University

D-109 *Special Lecture: Fc Effector functions in the anti-viral response*
Jeffrey Ravetch, MD, PhD, The Rockefeller University

E-101 *Reinhard Kurth Memorial Lecture: Zoonotic Origin of Some Common Human Cancers and Multiple Sclerosis?*
Harald zur Hausen, MD, Nobel Laureate, German Cancer Research Center in the Helmholtz Association

E-102 *Ending the HIV/AIDS Pandemic: The Convergence of Treatment and Prevention*
Anthony Fauci, MD, National Institute of Allergy and Infectious Diseases

E-103 *The Pathway to HIV Vaccine Development*
Barton Haynes, MD, Duke Human Vaccine Institute

E-104 *Can non neutralizing antibodies be the basis for an effective HIV vaccine? Can we determine if RV 144 is "real or Memorex" ?*
Larry Corey, MD, Fred Hutchinson Cancer Research Center

E-105 *Antibodies Against Ebola Virus: Results of the Viral Hemorrhagic Fever Immunotherapeutic Consortium*
Erica Ollmann Saphire, PhD, The Scripps Research Institute

E-106 *Establishment of a Clinical Research Program in the Setting of the Ebola Outbreak in West Africa*
Cliff Lane, MD, National Institute of Allergy and Infectious Diseases

E-107 *Advancing Global Health: Lessons from the response to the HIV epidemic*
Salim Abdool Karim, PhD, Director, Centre for the AIDS Programme of Research in South Africa (CAPRISA)

F-101 *Pharmacologic inhibition of the HIV-1 vif:apobec axis*
Mario Stevenson, PhD, University of Miami

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Kenneth Bagley, PhD, Profectus Biosciences

P-A1 *Does the gut microbiome affect mucosal immune activation and intrarectal susceptibility to SHIV acquisition in naive rhesus macaques?*
Yongjun Sui, PhD, National Cancer Institute, National Institute of health

P-A2 *Towards curtailing HIV latency by combinatorial unblocking viral transcription*
Suresh K Arya, PhD, National Institutes of Health

P-A3 *Identification of proximal biomarkers of PKC agonist activity in HIV-1 latently infected cells*
Sai Vikram Vemula, PhD, Merck

P-A4 *Novel CD4-Based Bi-specific Chimeric Antigen Receptors: Toward a Functional Cure of HIV Infection*
Sara Bolivar-Wagers, BS, NIAID, National Institutes of Health

P-B1 *Prolactinoma in A Transgender Male-To-Female HIV Positive Adult-A Rare Occurrence & A Therapeutic Dilemma*
Waqas Jehangir, MBBS, MD, Raritan Bay Medical Center, Perth Amboy, NJ

P-B2 *Performance of WHO immunological response to predict virological failure in patients with severe versus moderate immunosuppression at antiretroviral therapy initiation*
Martin Herbas Ekat, MD, Ambulatory Treatment Center of Brazzaville

P-B3 *Evaluation of an In-house Molecular HIV-1 Test to Assess Mother-to-Child HIV-1 Transmission in Angola (the APEHC Cohort)*
Francisco N Martin, Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Portugal

P-B4 *Predictors Of Sustained Viral Response To 4-6 Week Duration Therapy With Ledipasvir + Sofosbuvir + Gs-9451 +/- Gs-9669 In Early And Advanced Fibrosis (Nih-Ihv Synergy Trial)*
Sarah Kattakuzhy, MD, IHV

P-B5 *Examining the association of circumcision, sexual behavior and HIV status among men aged 15-59 in Uganda*
Mian B Hossain, PhD, Morgan State University

P-B6 *Development of a Potency Assay for Full Length Single Chain, a subunit vaccine for HIV*
Timothy Fouts, PhD, Profectus BioSciences

P-B7 *Balance of Cellular and Humoral Immunity Determines the Level of Protection by HIV Vaccines in Rhesus Macaque Models of HIV Infection*
Timothy Fouts, PhD, Profectus BioSciences

P-B8 *Software dependent differences in HIV-1 drug resistance determination*
Boyka Baltadjieva, MD, ACL Central Lab at Rosemont, IL

P-B9 *TSCQ Study: A randomized, open-label controlled trial of daily trimethoprim-sulfamethoxazole or weekly chloroquine among adults on antiretroviral therapy in Malawi*
Matthew B Laurens, MD, MPH, Center for Vaccine Development, University of Maryland School of Medicine

P-B10 *Egyptian Healthcare Workers and Hepatitis C Virus Vaccines*
Sayed F Abdelwahab, PhD, Taif University College of Pharmacy

P-B11 *Retreatment of HCV GT-1 in Patients Who Failed Previous Short Course Combination DAA Therapy With 12 Weeks of LDV/SOF is Highly Effective*
Eleanor MP Wilson, MD, MHS, Institute of Human Virology, University of Maryland School of Medicine

P-B12 *Comparison Of Hpv Genotyping Using Roche Linear Array With Spf10-Deia Lipa 25 Version 1 In Nigerian Women Presenting For Cervical Cancer Screening*
Oluranti A Famooto, BSc, Institute of Human Virology, Abuja, Nigeria

P-B13 *Comparison of two HPV detection and genotyping systems in a Nigerian screening population*
Clement Adebamowo, BM, ChB, ScD, Institute of Human Virology, Greenbaum Cancer Center; Division of Cancer Epidemiology, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore

P-B14 *Methylation as a triage marker in a hHPV+ population in Nigeria*
Clement Adebamowo, BM ChB, ScD, Institute of Human Virology, Greenbaum Cancer Center and Division of Cancer Epidemiology, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore

P-B15 *The Burden of Human Papilloma Virus Associated Cancers in Nigeria. 2012-2014*
Elima E Jedy-Agba, MBBCH MSc., Institute of Human Virology Nigeria

P-B16 *The Burden of Human Papilloma Virus Associated Cancers in Nigeria. 2012-2014*
Clement Adebamowo, BM, ChB,. ScD, Institute of Human Virology, Greenbaum Cancer Center; Division of Cancer Epidemiology, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore. Nigerian National System of Cancer Registries Coordinating Center, Abuja, Nigeria

P-B17 *Persistent Human Papillomavirus Infection In A Cohort of Nigerian Women*
Eileen O Dareng, MD, MPH, Department of Strategic Information, Research and Training, Institute of Human Virology, Abuja, Nigeria Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

P-B18 *Prevalence of anal high-risk human papillomavirus infections among HIV-positive and HIV-negative men who have sex with men (MSM) in Nigeria*
Rebecca G Nowak, PhD, Institute of Human Virology, University of Maryland School of Medicine

P-B19 *Colorectal Neoplastic Lesions In Hiv-Infected Patients Compared To Non-Hiv-Infected Patients*
Rebecca G Nowak, PhD, Institute of Human Virology, University of Maryland School of Medicine, Department of Epidemiology and Public Health, Univeristy of Maryland School of Medicine

P-B20 *Evaluation of the feasibility of incorporating HPV DNA-based cervical cancer screening into routine antenatal care in Nigeria: A qualitative study*
Temitope Filade, BNSc, MSc, Institute of Human Virology Nigeria

P-B21 *Validation of HPV genotyping at the African Collaborative Centre of Microbiome and Genomics Research, Institute of Human Virology Nigeria*
Ayotunde Famooto, MSC, African Collaborative Centre of Microbiome and Genomics Research, Institute of Human Virology, Nigeria

P-B22 *Recurrence of Cervical Intraepithelial Lesions after Thermo-coagulation in HIV-positive and HIV-negative Nigerian Women*
Emmanuel A Oga, MD MPH, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD 21201, USA

P-B23 *Prevalence of Ebola viral entry resistance in a diverse population*
Praveen F Cherukuri, PhD, Inova Translational Medicine Institute

P-B24 *Factors Associated With Attrition In a Prospective Cohort Study In Nigeria*
Eileen O Dareng, MD, MPH, Center for Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK Institute of Human Virology, Nigeria

P-B25 *Influence of Spirituality and Modesty on Acceptance of Self Sampling for Cervical Cancer Screening*
Eileen O Dareng, MD, MPH, Center for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom, Institute of Human Virology, Nigeria

P-B26 *Changes in Plasma BLyS Levels in Patients with HCV Mixed Cryoglobulinemic Vasculitis during Treatment with Rituximab*
Emily Comstock, RN, BSN, BA, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD 21201

P-B27 *Targeting the binding interface on a shared receptor subunit of a cytokine family enables the inhibition of multiple member-cytokines with selectable target spectrum*
Yutaka Tagaya, MD PhD, Institute of Human Virology, Unversity of Maryland School of Medicine

P-B28 *Dichotomous Effects of Immune based (Interferon-alpha) and Non-immune based (direct acting antiviral) Therapies on Lipid Biosynthesis*
Lydia Tang, MB ChB, Institute of Human Virology, University of Maryland School of Medicine, Division of Infectious Diseases

P-B29 *Barriers to Cervical Cancer Screening Among Nigerian Women*
Elima E Jedy-Agba, MBBCH, MSc., Institute of Human Virology Nigeria, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK

P-B30 *Association Between Hiv And Persistent Hpv Infections Among Nigerian Women*
Sally N Adebamowo, MD, MSc, ScD, IHVN, NHGRI

P-B31 *Cohort Profile: African Collaborative Center For Microbiome And Genomics Research (ACCME) Study*
Sally N Adebamowo, MD, MSc, ScD, IHVN, NHGRI

P-B32 *cGMP production, characterization, and formulation of IHV01 drug product, the Full Length Single Chain gp120-CD4 (FLSC) chimera formulated in Aluminum Phosphate*
Ilia Prado, MS, MBA, Profectus BioSciences

P-B33 *HPV Persistence and Age-Specific Type Distribution Among Nigerian Women*
Sally N Adebamowo, MD, MSc, ScD, IHVN, NHGRI

P-B34 *Postural tachycardia syndrome (POTS) after Varicella Zoster virus infection (chicken pox): a case report*
Pranith H Kumar, MBBS, MD, University Of Maryland School Of Medicine

P-B35 *Design of a broadly neutralizing human rhinovirus antigen*
Wiggins, T; Lee, W-M; Bushnell, RV; Tobin, JK; Turner, RB; Nara, PN; Tobin, GJ

P-C1 *Full Length Single Chain, A Novel gp120-CD4 Fusion HIV Subunit Vaccine, Does Not Cause a Deleterious Autoimmune CD4 Response in Cynomolgus Macaques*
Jennifer A Schwartz, PhD, Profectus Biosciences

P-C2 *T-cell Based Lentiviral Vaccines*
Shannon R Roff, MS, DVM, University of Florida College of Veterinary Medicine

P-C3 *Targeting the Epitopes in the C1-C2 Region of HIV-1 gp120 for Effective Fc-mediated Effector Function*
Neelakshi Gohain, PhD, University of Maryland

P-C4 *Targeted Sequencing of Broadly Neutralizing Anti-HIV Envelope Antibodies Directly from Plasma*
Mohammad M. Sajadi, Institute of Human Virology

P-D1 *Selection and characterization of neutralizing nanobodies from dromedaries immunized with soluble trimeric HIV-1 Env SOSIP proteins*
Ursula Dietrich, PhD, Georg-Speyer-Haus

P-D2 *Microscopic Detection And Localization Of Hiv Gp120 Epitope Exposures On Cell-Bound Virions*
Meron Mengistu, PhD, Institute of Human Virology of the University of Maryland School of Medicine

P-D3 *Structural Determinants for the Selective Anti-HIV-1 Activity of the All-beta Alternative Conformer of XCL1*
Christina Guzzo, PhD, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Disease (NIAID), NIH, Bethesda, MD

P-D4 *Tyrosine-Sulfated Peptides from the gp120 V2 Domain Block HIV-1 Entry through CCR5 Mimicry*
Qingbo Liu, PhD, National Institute of Allergy and Infectious Diseases, NIH

P-D5 *Two Conserved Tyrosines in the HIV-1 Envelope V2 Loop Play a Critical Role in gp120/gp41 Association*
Peng Zhang, PhD, NIAID,NIH

P-D6 *Effects of influenza vaccination on lymphoid architecture in HIV+ patients on combination antiretroviral therapy (cART)*
Eirini Moysi, PhD, Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL and Immunology Laboratory, Vaccine Research Center, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD

P-D7 *Structural mimicry of the antigen binding modes of rhesus macaque and human anti-gp120 V3 antibodies*
Ruimin Pan, PhD, New York University School of Medicine

P-D8 *Targeting of the catalytic site of host mTOR controls HIV in vivo*
Alonso Heredia, PhD, IHV

P-D9 *A Novel Small Molecule Inhibitor of HIV-1 Entry*
Alonso Heredia, PhD, IHV

P-D10 *Differential Induction of Anti-V3 Crown Antibodies with Cradle and Ladle-Binding Modes in Response to HIV-1 Envelope Vaccination*
Preetha Balasubramanian, MS, NYU Sackler institute

P-D11 *Effect of HIV-1 matrix protein p17 on natural killer cell mediated antibody-dependent cellular cytotoxicity*
Virginia Carroll, PhD, Institute of Human Virology, University of Maryland School of Medicine

P-D12 *Differential Sensitivity of HIV-1 Isolates to Inhibition by Mannose-Binding Lectins Reveals the Heterogeneity of the Virus Envelope Glycosylation*
Muzafar JAN Peer, New York University school of medicine New York, USA

P-D13 *Resistance to N-peptide fusion inhibitors: implications for HIV entry*
Paul W Keller, PhD, Food and Drug Administration

P-D14 *Modulation of SIV and HIV DNA Vaccine Immunity by Fas-FasL Signaling By Jiabin Yan, Juan Carlos Zapata, Charles David Pauza and Maria S. Salvato (presenting)*
Maria S Salvato, PhD, University of Maryland School of Medicine, Institute of Human Virology, Baltimore, MD 21201

P-D15 *Peripheral Blood Lymphocyte HIV DNA Levels Correlate with HIV Associated Neurocognitive Disorders*
Jibreel A Jumare, MBBS, University of Maryland

P-E1 *CD44 and RUNX2: Possible Targets for Prostate Cancer in Bone Microenvironment*
Aditi Gupta, PhD, University of Maryland, Baltimore, Maryland

P-E2 *An Hsc70-binding peptide derived from SV40 Large T antigen is a potent inhibitor of polyoma virus DNA replication*
Neera Sriskandarajah, MSc, Molecular Virology Research Unit, Institut de recherches cliniques de Montréal (IRCM) Division of Experimental Medicine, McGill University

P-E3 *Development of a new humanized mouse model to study anti-HTLV-1 immunity*
Juan C Zapata, PhD, Institute of Human Virology, University of Maryland

P-E4 *HLBT-001- A flavonoid from Tillandsia recurvata shows potent anticancer activity against Aids-Defining and Non-Aids defining cancers*
Ngeh J Toyang, PhD, IHV, University of Maryland School of medicine / Educational & Scientific LLC

A-101

Introduction to Hepatitis C Mini-Symposium

Shyam Kottilil, IHV

Chronic hepatitis C infection affects over 180 million people worldwide and is the major cause of liver cancer and liver transplantation in the Western countries. Recent advances in the therapeutics for HCV has revolutionized the management of patients infected with hepatitis C virus. These new wave of paradigm shift in therapeutics from an injectable interferon based long term treatment with several adverse events with modest efficacy to all oral, simple short duration therapy that can cure almost all treated patients. however, the cost of the medications, lack of awareness of the diagnosis, and insufficient number of providers treating hepatitis C with new agents: all pose challenges in eradicating HCV infection. In this mini symposium, we address the major challenges that we face today in managing HCV infection including health economics, redefining difficult to treat patients and highlight the pathway to move forward.

A-102

HCV treatment as prevention

Kristen Marks, Weill Cornell Medical College

The burden of chronic HCV infection based on NHANES data was estimated at 2.7 million persons in the United States, however a recent study suggests at least 3.5 million when accounting for groups not included in survey such as homeless, incarcerated, etc. This burden of disease makes eradication unrealistic in the near future, even with highly effective treatments. However, elimination, or reduction in the incidence of new infections, through the combination of prevention efforts and treatment remains a worthy goal. Tremendous progress has been made in anti-HCV drug discovery, with multiple classes of antivirals that act directly on the viral life cycle. Well-tolerated direct acting antiviral (DAA) combinations cure the vast majority of people treated. With such effective DAA options available, it is time to evaluate the approach of HCV treatment as prevention. Treatment as prevention requires reaching groups at high risk of transmitting HCV to others such as active drug users and HIV/HCV co-infected MSM with high-risk behaviors. In people who inject drugs, modeling data suggests that scaling up treatment in active drug users in addition to harm reduction interventions such as needle exchange and opiate substitution therapy has potential to dramatically reduce HCV prevalence over time. The impact of treatment on prevention with respect to the epidemic in MSM remains less clear. In the real world, limited data suggests DAA are effective in active drug users and HIV-infected MSM. Reinfection rates remain an important consideration as does the theoretical risk of transmission of DAA-resistant virus strains. Lastly because of cost, those with the most immediate clinical need have been prioritized for DAA treatment, while those at highest risk of transmitting virus are often specifically denied (because of mild disease and/or concern for reinfection). For treatment as prevention to be feasible, linkage to care and access to medications must also improve.

A-103

Price, Cost-Effectiveness and Affordability of Hepatitis C Drugs: How Did We Get Into This Mess?

Camilla Graham, Beth Israel Deaconess Medical Center and Harvard Medical School

The rationing of new treatments for hepatitis C, a devastating yet curable infection, is unprecedented. This presentation will discuss how prices are set for drugs in general with analogies to other high-priced specialty medications in order to understand how prices of direct-acting antiviral (DAA) regimens for hepatitis C treatment may have been determined. Cost-effectiveness studies for hepatitis C (screening and treatment) will be reviewed with a summary of which populations appear cost-effective to treat relative to no treatment and older regimen choices. In general, treatment of hepatitis C is as cost-effective as the treatment of many other diseases in the United States. The role of payers in determining the actual price paid for drugs as well as access to treatment will be discussed. Cost-effectiveness does not equal affordability and the cost of hepatitis C regimens in the short term does pose budget challenges to systems that did not adequately prepare for the demand. Stigma associated with hepatitis C impacts the current reimbursement climate, and physicians and other health providers will need to be advocates for individual patients and on a broader policy level in order to fulfill the promise of these transformative new treatments.

A-104

Comorbidities and Hepatitis C

Kenneth Sherman, University of Cincinnati College of Medicine

While most HCV literature focuses on liver injury and fibrosis progression, a spectrum of systemic disease processes, collectively called C hepatitis-associated systemic manifestations (CHASM), are present in a high proportion of infected persons. These include thyroid disease (Hashimoto's thyroiditis, Grave's disease, and thyroid cancer), cardiovascular disease (atherosclerosis, carotid artery disease, and coronary artery disease), renal disease (MPGN and glomerulosclerosis), eye disease (Mooren's ulcers and sicca syndrome), skin disease (PCT, vasculitis, and lichen planus), lymphomas (NHL and splenic T-cell), and diabetes. Mechanistic understanding of how HCV leads to CHASM processes could lead to development of new interventions. The role of early HCV treatment and cure may result in preventive strategies for a variety of complex disease states. Indeed data strongly supports decreases in all-cause mortality independent of liver disease when HCV cure is achieved. However, some conditions are mediated through autoimmune loop mechanisms and may be less responsive to HCV treatment.

A-105

The metabolic and cardiovascular complications of HIV

Barry Peters, Kings College London

The metabolic and cardiovascular complications of HIV Background: The advent of HAART has markedly reduced mortality and morbidity in HIV. Further reduction will result from applying the findings of the START Study to universal use of HAART, but a greater reduction of mortality & morbidity is likely to result from the management of metabolic/cardiovascular (CV) risk in people with HIV infection. The Challenge: We need to better characterise the key metabolic/CV risks for people with HIV, and manage appropriately. The risks include increased CVR due to HIV itself, individual antiretroviral drugs (ARVs), also risks due to delaying or stopping HAART. There is a marked increase in diabetes in HIV compared to age-matched HIV uninfected, which is increasing over time; in our London Hospital cohort in 2015, 15% of our patients have T2DM (7% in 2005) cf to 6% in general population. There is also greater risk of lipodystrophy, features of metabolic syndrome, and also fragility fractures. These issues are likely to accelerate as our cohorts age. The way forward is to promote good quality studies on metabolic/CV risks in HIV, to educate patients and physicians on the current known risks and to calculate these risks so that management can be given. Lifestyle interventions have variable uptake and adherence but all patients should have access to dietary and exercise advice and smoking cessation support, and where appropriate interventions that might include adjustment to the HAART combination, lipid lowering agents, such as statins, vitamin D and bisphosphonates. It is important that the benefits of managing metabolic/CV issues in people with HIV are available to all individuals in the developing and developed world alike.

A-106

HIV Infection: What's New Novel and Exciting

John Bartlett, Johns Hopkins University School of Medicine

Conflicts of interest: none Presentation goal: Review of topics important to HIV management that are not commonly discussed Rating the evidence: The "when to start" controversy with the United States versus the rest of the world 2012 – 2015. The "START trial" provided a definitive answer with an OR of 1.9 for survival! The Gardner cascade: This highlighted our inept care delivery, but the oft quoted cascade is wrong Immune activation: An important message for all of medicine but we don't know how to measure it, or treat it New ART: The new integrase inhibitors radically changed all guidelines to make ART recommendations before 2015 antiquated. Most exciting new drug might might be cenicriviroc (GSK 744) with a T1/2 of 21-50 days When to start debate: Simply said-" it's never too early" HPTN 065 (P4P4P): The first major P4P4P to lose is now explained. HIV Prevention: ART (?perfect), PrEP, Bridge, on-demand...and why not ABC/3TC HCV: Miracle, Murray and money

A-107

HIV/HCV coinfection: modern treatment strategies, problems in Eastern Europe

Alexey Mazus, Moscow Center for HIV/AIDS Treatment and Prevention

The cohort of patients co-infected with HIV and HCV needs a special approach to monitoring and treatment. The combination of these infectious pathologies negatively effects the prognosis and complicates therapy. At the same time, the majority of patients co-infected with HIV/HCV are injecting drug users, which further complicates their involvement in treatment process. Modern strategies for treatment of HCV by using new classes of antivirals will simplify treatment and increase the frequency of patients with SVR. In Russia, according to official statistics, the number of patients with HIV infection in 2014 was 742,611 people. Of these, 522,611 patients were involved in HIV care of which 221,441 people (42.4%) had chronic hepatitis C. The growing number of patients co-infected with HIV/HCV in recent years corresponds to an increasing number of people involved in care, indicating preservation of a significant number of cases of HIV infection due to injecting drug use. Thus, we can expect that the widespread introduction of modern treatment strategies in Russia will have a positive impact on the pace of development of co-infection and increase the length and quality of life of patients. In general, these data provide an opportunity to assess the situation with co-infection of HIV / HCV in Russian Federation, and are important for public health, the accumulation of necessary resources, the preparation of infrastructure and surveillance.

A-108

Viral and cellular biomarkers in HPV-related cancers

Franco Buonaguro, Istituto Naz. Tumori - IRCCS “Fondazione Pascale”, Napoli - Italy; **Clorinda Annunziata,** Istituto Naz Tumori - IRCCS “Fondazione Pascale”, Napoli - Italy; **Luigi Buonaguro,** Istituto Naz Tumori - IRCCS “Fondazione Pascale”, Napoli - Italy & Inst of Human Virology, Univ of Maryland, Baltimore, MD - USA;
Maria Lina Tornesello, Istituto Naz Tumori - IRCCS “Fondazione Pascale”, Napoli - Italy

Virtually all cases of cervical cancer are associated with persistent infection with a restricted set of high-risk human papillomaviruses (HPV). The majority of HPV infections induce low grade squamous epithelial lesions that in more than 90% of cases spontaneously regress and in about 10% eventually progress to high grade lesions and even less frequently evolve to invasive cancer. Tumor progression is characterized by (1) increased expression of viral E6 gene and E6-dependent degradation of p53, and increased expression of E7, known to bind and inactivate pRb; (2) integration of viral DNA into host genome with the consequent disruption of E2 viral gene. Molecular markers able to identify viral infections associated with progressing cervical neoplasia are strongly needed for cervical cancer screening and triage. We have recently performed the expression profile analysis of p53-related genes in HPV16-positive carcinomas along with autologous non-tumor tissue, and identified significant differences in the expression levels of genes involved in regulation of apoptosis, cell cycle, proliferation and DNA repair pathways. In particular, BRCA1, CDKN2A (p16), CASP2 and TNFRSF10B genes were significantly up-regulated ($p<0.05$) in cancer lesions. Validation of these candidate biomarkers is currently in progress on a larger number of cases, including different grades of HPV-related neoplastic lesion (CIN1-3 and invasive cervical cancer). Such studies will contribute to the development of new tools for the identification of premalignant lesions at high risk of progession to invasive cervical carcinoma.

A-109

Pathogenesis of anal cancer

Joel Palefsky, University of California, San Francisco

Although the risk of anal cancer is increased among HIV-negative men who have sex with men (MSM) compared with the general population, HIV clearly adds to that risk. Unlike most AIDS-defining malignancies, the incidence of anal cancer has increased since the introduction of antiretroviral therapy (ART), and is estimated to be as high as 131/100,000 among HIV-infected MSM. Anal cancer is now one of the most common non-AIDS defining malignancies (NADM). Anal cancer is very similar biologically to cervical cancer. Like cervical cancer, anal cancer is preceded by high-grade squamous intraepithelial lesions (HSIL) and most cases are associated with HPV 16 infection. Unlike most NADM, anal cancer is potentially preventable through primary prevention (HPV vaccination) and secondary prevention (screening for and treating anal HSIL prior to progression to anal cancer). There are likely to be several mechanisms by which HIV infection contributes to the increased risk of anal cancer including: attenuation of systemic immune response with reduced cell mediated immune response to HPV antigens; local immune response perturbation in the form of chronic HIV-induced low-level tissue inflammation; direct interactions between HIV proteins and HPV within the epithelium including reduction of epithelial tight junction integrity due to tat and gp120, with increased risk of HPV infection due to tat and gp120; and up-regulation of HPV oncogene expression by tat. With evidence for epithelium as a potential reservoir of HIV infection, HIV-HPV interactions may continue despite good HIV control on ART, and may explain in part the lack of impact of ART in reducing the incidence of anal cancer in HIV-infected individuals.

A-110

Translational Research to Advance the Prevention and Treatment of HIV-Associated Malignancies

Corey Casper, Fred Hutchinson Cancer Research Center and the University of Washington

Cancer has emerged as a leading cause of morbidity and mortality among HIV-infected persons worldwide. The incidence of cancer is increased exponentially in HIV-positive individuals, and in the United States it is estimated that nearly 10% of persons living with HIV will develop cancer in their lifetime. Coupled with evolving data which find that persons with HIV who develop cancer have a significantly reduced odds of surviving their cancer, new strategies for cancer prevention and treatment in persons living with HIV are needed. Over the past decade, we have conducted research in HIV-associated malignancies in Seattle and in partnership with the Uganda Cancer Institute in Kampala. In this presentation, data will be discussed from several types of studies: prospective cohort studies to define the natural history of infection with oncogenic viruses in HIV-infected individuals, studies examining the genomics of HIV-associated tumors, epidemiologic investigations of the relationship between HIV and cancer in low-resource settings, translational studies of virus and tumor immunology, and clinical trials of agents for HIV-associated cancer treatment and prevention. Finally, thoughts on how translational research can reduce the burden of HIV-associated cancers in both low- and high-resource settings will be offered.

A-111

Controlling the Impact of HIV-related Tuberculosis

Richard Chaisson, Johns Hopkins University Center for TB Research

Tuberculosis (TB) remains the leading cause of death in people with HIV infection globally. Reducing the burden of morbidity and mortality caused by TB requires a multipronged strategy aimed at reducing transmission, preventing progression of latent TB to active TB, earlier diagnosis of disease and improved therapeutics. In high-burden settings in Africa, the force of TB infection is high and results in continual exposure and re-exposure to infection. Reducing the force of infection requires improved case detection and prompt, effective treatment. Prevention of progression of latent infection is achievable with the combination of antiretroviral therapy and TB preventive therapy. The recent START study demonstrated the efficacy of ART in reducing TB incidence, and the TEMPRANO study confirmed the independent and additive contribution of isoniazid preventive therapy to ART. Prolonged courses of preventive therapy are probably required in high-burden settings, though more sterilizing regimens using rifamycins may be effective. Reducing mortality from TB requires early detection and treatment, as well as improved regimens for multidrug resistant TB. Preventive therapy for HIV-infected contacts of MDR TB cases is an urgent unmet need.

A-112

Impact of Antiretroviral Regimen on Renal Transplant Outcomes in HIV-Infected Recipients

Tracy Sparkes, University of Maryland;
Wana Manitpisitkul, University of Maryland; **Anthony Amoroso**, University of Maryland School of Medicine;
Charles Davis, University of Maryland School of Medicine;
Stephen Bartlett, University of Maryland School of Medicine;
Abdolreza Haririan, University of Maryland School of Medicine

Background: Renal transplantation has become a more common occurrence in HIV-infected individuals. The post-transplant antiretroviral regimen is one of the challenges in this population due to drug interactions with common immunosuppressive agents. Regimens containing protease inhibitors (PI) pose a challenge post-transplant, leading to altered calcineurin inhibitor (CNI) dosing and the potential for increased CNI exposure. This has led to increased utilization of newer agents that lack significant interactions with CNI. The purpose of this study was to examine the impact of PI-based regimens on graft outcomes in HIV-infected renal transplant recipients. Methods: Retrospective study of renal allograft recipients transplanted between 2003-2015 with ≥6 months of follow-up. Maintenance immunosuppressive medications included CNI + mycophenolic acid ± steroids. Results: During this period, our center performed 50 renal transplants in HIV-infected recipients. 26 patients (52%) received a PI based regimen and 24 patients (48%) received a non-PI based regimen. There were no significant differences between groups in terms of age, race, gender, or cause of CKD. The majority of patients in each group received deceased donor renal transplants, and greater than 50% of patients in each group experienced delayed graft function. Significantly more patients in the non-PI group received induction with T-cell depleting agents. The cumulative rejection rate in both groups was 64%. The estimated GFR did not differ between groups at time points evaluated (30 days to 4 years post-transplant). At last follow-up, patient and graft survival was 92% vs. 83% and 81% vs. 58% in the PI and non-PI groups, respectively. Conclusions: HIV-infected renal transplant recipients experienced high rates of rejection regardless of antiretroviral regimen. However, PI-based ARV regimens appear to be associated with better graft survival, suggesting that converting patients to non-PI regimens may not be warranted.

B-101

Unique features of effector to memory transition render CD4+ T cells permissive for latent HIV infection

Robert Siliciano, Johns Hopkins University School of Medicine

Unique features of effector to memory transition render CD4+ T cells permissive for latent HIV infection Kai Deng and Robert Siliciano, Johns Hopkins University School of Medicine The latent reservoir for HIV-1 in resting memory CD4+ T cells is the major barrier to curing HIV-1 infection. Studies of HIV-1 latency have focused on regulation of viral gene expression in cells in which latent infection is established. However, it remains unclear how infection initially becomes latent. In this talk, we discuss recent work demonstrating that a unique set of properties of CD4+ T cells undergoing effector-to-memory transition allow completion of steps in the viral life cycle through integration, but suppress HIV-1 gene transcription, thus allowing the establishment of latency. CD4+ T cells not in this stage are not permissive for latent infection. Establishment of latent HIV-1 infection can be inhibited by viral-specific CD8+ T cells, a result with implications for prevention and elimination of latent HIV-1 infection.

B-102

Towards Achieving a State of Reversible HIV-1 Latency in Primary Monocyte-Derived Macrophages (MDM) by M1 Polarization

Guido Poli, MD, Vita-Salute San Raffaele University; **Francesca Graziano**, San Raffaele Scientific Institute, MIlano, Italy

While the existence of latently infected CD4+ T cells has been demonstrated in infected individuals receiving cART, whether primary myeloid cells are latently infected remains to be firmly established. In this regard, we have previously reported that short-term exposure of primary MDM established from seronegative individuals to pro-inflammatory cytokines (TNF-a plus IFN-g), a modality of cell activation also known as “M1 polarization”, partially prevented productive virus infection in virtue of a downregulation of CD4 from the cell surface couple with an upregulated secretion of CCR5-binding chemokines (E. Cassol et al., J. Immunol 2009). We have further demonstrated that M1-MDM display a post-entry restriction to productive HIV-1 replication in terms of delayed proviral integration and reduced transcription also when cells were infected with a VSV-g pseudotyped virus bypassing CD4 and CCR5 for viral entry (L. Cassetta et al., AIDS 2013). We have recently investigated the potential effect of a second M1 polarization of previously infected M1-MDM (M1x2 protocol) and observed a further reduction of virus production to undetectable levels, at least in terms of RT activity in culture supernatants collected for several days post-stimulation. Recovery of virus replication was however achieved by cocultivation of M1x2-infected MDM with allogeneic PHA-stimulated PBMC, suggesting the existence of a pool of MDM latently infected with replication-competent virus. Additional experiments are ongoing to define the time-dependence and different stimulatory conditions of modulation of this state of potential latent infection in primary MDM.

B-103

Genome-directed antiviral endonuclease therapy: promise and perils

Keith Jerome, Fred Hutchinson Cancer Research Center

A critical challenge for HIV cure is the presence of latently-infected cells, which are only distinguished from normal uninfected cells by the presence of proviral DNA. Targeted endonucleases (zinc finger nucleases, TAL effector nucleases, homing endonucleases, and CRISPR/Cas proteins) offer the ability to specifically disrupt genomic loci of interest, and in principle such loci could include integrated HIV. Our group and others have now demonstrated that these endonucleases can be used to efficiently disrupt or even excise integrated HIV in vitro, confirming the promise of this approach. Nevertheless, several challenges remain before this approach can disrupt a meaningful proportion of the latent HIV reservoir. We recently demonstrated the in vitro emergence of endonuclease-resistant infectious virus, due to a ZFN-induced insertion in the thumb region of reverse transcriptase, producing a virus that could efficiently replicate and yet was resistant to cleavage by the reverse transcriptase-specific ZFN. This suggests that caution should be exercised in the development of antiviral therapies based on a single nuclease. Furthermore, efficient delivery to cells harboring integrated virus in vivo remains an unsolved problem, which must be addressed before these therapies can move into clinical application. We have packaged antiviral endonucleases into adeno-associated virus vectors, which can efficiently deliver them to T cell lines, and are currently evaluating these in the in vivo setting. Our ongoing work focuses on increasing the efficiency of transgene delivery to relevant subsets of T cells, and maximizing the rate of provirus mutagenesis or excision by targeted endonucleases.

B-104

HIV Cure Research: a status report

David Margolis, UNC Chapel Hill

Effective antiretroviral therapy (ART) blunts viremia, enabling HIV-1-infected individuals to control infection and live long, productive lives. However, HIV-1 infection remains incurable owing to the persistence of infected cells harboring integrated provirus within host cellular DNA. This latent infection is unaffected by ART and hidden from the immune system. In the renewed efforts to eradicate persistent infection, spurred in part by the remarkable case of Timothy Brown, initial studies have focused on the development of therapies to disrupt latency. These efforts unmasked residual viral genomes but highlighted the challenge of impacting the diverse viral reservoir in a clinically safe manner, and the need to enable the speedy clearance of latently infected cells. New efforts have begun to use both old and new strategies to enhance the HIV-1-specific immune response, and in a few cases efforts to bring the kick against latency together with the kill of persistently infected cells. Although very substantial challenges remain, the broad and inventive efforts launched to develop eradication therapy inspire hope.

B-105

Post Treatment Control: what predicts long-term HIV remission?

John Frater, University of Oxford

There is growing evidence that early antiretroviral therapy can induce a state of 'post treatment control' in which HIV viraemia remains suppressed when ART is stopped. The possibility that in some individuals HIV viraemia does not return within days after treatment interruption challenges much of our current understanding of HIV persistence. This presentation will review the evidence for PTC, and consider its likely prevalence, mechanism and mode of induction. Data will be presented from studies of individuals given ART in primary infection, and will explore the potential for potential biomarkers that might be used in clinical practice to identify patients who might exhibit PTC. Consideration will be given to the significance of PTC and how it might inform future cure strategies.

B-106

Characterizing the basis for the broad and potent HIV-specific neutralizing antibody response of infants

Julie Overbaugh, Fred Hutchinson Cancer Research Center;
Cassandra Simonich, UW;
Leslie Goo, FredHutch;
Katherine Williams, fredhutch;

In the past few years, many new broad and potent HIV-specific monoclonal antibodies (Mabs) have been isolated from HIV-infected adults. However, because the breadth of these antibodies was acquired over many years, it will be challenging to elicit such Nabs with a vaccine. We found that HIV-infected infants often develop broad and potent HIV-specific Nab responses. Among 28 infants we identified 20 with cross clade Nab responses within the first two years of their infection, including a subset that neutralized Tier 2-3 variants from multiple clades. In some infants, there was evidence of cross clade breadth within the first year of their infection. To characterize these infant antibody responses, we isolated single B cells from sample from an infant with a cross clade Nab response at 336 days PI. We used a combination of sorting for B cells that bound envelope trimer as well as functional screening of cultured B cells for neutralizing activity to identify B cells of interest. Among those B cells identified through functional screening, there are 10 where we have rescued matched VH and VL chains. Six of these Mabs demonstrate some HIV-specific Tier 2 neutralizing activity and one Mab demonstrates potency similar to VRC01 for some viruses tested. In preliminary analysis using a small virus panel, these antibodies show distinct patterns of neutralization and no single Mab isolated to-date recapitulates the full breadth of the original plasma. None of the Mabs share a common VH or VL chain, suggesting that the broad antibody activity in this infant may be due to a polyclonal response.

B-107

Distinct mechanisms of hormonal control of HIV latency in T-cells and microglial cells

Jonathan Karn, Case Western Reserve University; **Biswajit Das**, Case Western Reserve University; **Curtis Dobrowolski**, Case Western Reserve University; **Yoelvis Garcia-Mesa**, Case Western Reserve University; **David Alvarez-Carbonell**, Case Western Reserve University; **Stephanie Milne**, Case Western Reserve University; **Eileen Scully,** Brigham and Women's/Massachusetts General Hospital; **Steven Deeks,** UCSF School of Medicine; **Monica Gandhi,** UCSF School of Medicine; **Rowena Johnston**, amfAR, The Foundation for AIDS Research

Unbiased shRNA library screens identified novel genes and pathways that are required to maintain HIV latency in both T-cells and microglial cells. In T-cells, one of the most prominent and robust "hits" was the estrogen receptor type 1
(ESR-1). Specific antagonists of ESR-1, such as Tamoxifen and Fulvestrant, are weak proviral activators but sensitize latently infected cells to very low doses of the proviral activators TNF-α (NF-κB inducer) and SAHA (HDAC inhibitor). The ESR-1 agonists, propylpyrazoletriol (PPT) diethylstilbestrol, and estrogen had the opposite effect and strongly suppressed both TNF-α and SAHA reactivation. In the HAART treated patient samples there was a modest increase of spliced HIV mRNA when resting memory cells were treated with the ESR antagonists Fulvestrant or Tamoxifen alone. Syngeristic reactivation was observed by combining ESR antagonists and HDACi. β-Estradiol at concentrations in the physiological range led to dramatic reductions in proviral reactivation efficiencies, especially in women, pointing to gender-specific differences in the control of HIV latency. Thus, ESR-1 is a pharmacologically attractive target that can be exploited in the design of therapeutic strategies aimed at inducing proviral clearance from T-cells to eradicate the latent reservoir. In microglial cells ESR-1 does not play a major role in controlling HIV latency, but retinoid X receptor (RXR) plays an analogous role. Treatment of microglial cells with the RXR antagonist Bexarotene blocks HIV transcription and can lead to long-term suppression of proviral reactivation. Thus, our results point to cell type-specific differences in HIV transcriptional control that can be exploited as part of design of Cure strategies.

B-108

Specific HIV integration sites are linked to clonal expansion and persistence of infected cells

Frank Maldarelli, HIV Dynamics and Replication Section, NCI Frederick, Center for Cancer Research at the National Institutes of Health; **Xiaolin Wu**, Leidos Biomedical Research Inc.- Frederick, MD; **Ling Su**, Leidos Biomedical Research Inc.- Frederick, MD; **Francesco Simonetti**, HIV Dynamics and Replication Section, NCI Frederick, and Department of Biomedical and Clinical Sciences, 'L. Sacco' Hospital, University of Milan, Milan, Italy; **David Wells**, Leidos Biomedical Research Inc.- Frederick, MD; **Wei Shao**, Leidos Biomedical Research Inc.- Frederick, MD; **Jonathan Spindler**, HIV Dynamics and Replication Section, NCI Frederick, Center for Cancer Research at the National Institutes of Health; **Andrea Ferris**, HIV Dynamics and Replication Section, NCI Frederick, Center for Cancer Research at the National Institutes of Health; **John Mellors**, Division Infectious Diseases, University of Pittsburgh; **Mary Kearney**, HIV Dynamics and Replication Section, NCI Frederick, Center for Cancer Research at the National Institutes of Health; **John Coffin**, Sackler School of Graduate Biomedical Sciences, Tufts Unviersity; **Stephen Hughes**, HIV Dynamics and Replication Section, NCI Frederick, Center for Cancer Research at the National Institutes of Health

HIV integrates its DNA into many sites in the host genome; thus integration sites can be used as markers to identify clonally expanded cells. We identified the integration sites in PBMCs and CD4+ T cells from patients and used these data to show that there is extensive clonal expansion of infected cells. We have started to determine the sequences of viral DNAs in clonally expanded cells; these sequences are being used to study the structure and expression of the proviruses present in expanded cells.

We have identified >2500 integration sites in PBMCs and CD4+ cells from infected individuals on combination anti-retroviral therapy (cART). About 40% of the integrations were in clonally expanded cells. In one patient, more than 50% of the infected cells were from a single clone; some of the expanded clones persisted for more than 10 years. There were multiple independent integrations in the same orientation as the gene in two introns of the MKL2 and BACH2 genes; many of these integrations were in clonally expanded cells. Both BACH2 and MKL2 are involved in regulating the growth of cells. DNA rearrangements involving these genes have been found in human tumors. There was no evidence for integration in one orientation, or in specific introns, in either of these genes in large libraries prepared by infecting stimulated or unstimulated PBMCs, CD34+ cells, or HeLa cells that were infected in culture. There were, in patients, multiple independent integrations in a number of other growth related genes, some of which were associated with clonal expansion of the infected cells. These data show that HIV integration at certain sites can play a critical role in the expansion and persistence of HIV infected cells.

In one case, we showed that the provirus in an expanded clone was responsible for producing the majority of the virus that was present in the blood of a patient on cART, showing that, in this patient, immune surveillance was not sufficient to prevent clonally expanded cells from producing virions. Additional experiments showed that this virus is replication competent, demonstrating that clonally expanded cells can carry replication competent proviruses that produce infectious virus in patients. Thus, proviruses in clonally expanded cells can be part of the reservoir that gives rise to replicating virus when therapy is interrupted. Our findings have important implications for the development and maintenance of the viral reservoir, for designing and implementing strategies to eliminate persistent HIV infection, for the use of lentiviral vectors for gene therapy in human patients, and, possibly, for the origin of some HIV-related malignancies.

B-109

HIV Latency and Perinatal Infection

Deborah Persaud, Johns Hopkins University School of Medicine

A latent reservoir for HIV in resting memory CD4+ T cells is established early in the course of HIV infection, blocking efforts to eliminate the virus and achieve cure. Within this reservoir, cellular quiescence is the major mechanism maintaining HIV latency. Understanding how this reservoir is established during perinatal infection and maintained through adolescence and young adulthood, despite long-term virologic suppression and in the absence of HIV specific immune responses, will aid in advancing HIV therapeutics aimed at virus eradication. The opportunity to treat HIV infection soon after infection, coupled with the unique properties of the developing neonatal immune system, distinguishes perinatal HIV infection from adult infection. The pathogenesis of HIV persistence in perinatally infected children and adolescents, along with insights into HIV latency during and after HIV remission in the Mississippi child, will be discussed.

B-110

The HIV-1 antisense transcript AST promotes latency by recruiting PRC2 to the 5'LTR

Fabio Romerio, Institute of Human Virology University of Maryland School of Medicine; **Juan Zapata,** Institute of Human Virology Baltimore, MD - USA; **Fatah Kashanchi**, George Mason University Manassas, VA - USA

Although the HIV-1 Tat protein is necessary for viral exit from latency, the prevailing view has been that HIV-1 does not encode for an inducer of latency, and that environmental stimuli indirectly control entry into latency. Histone methytransferases (HMTs) contribute to the establishment of viral latency through precise positioning of the nucleosomes Nuc-0 and Nuc-1 on the 5'LTR. The HMT, EZH2 – a component of the Polycomb Repressor Complex 2 (PRC2) – plays the dominant role in this process. Two very important and possibly related questions are still open. First, how are Nuc-0 and Nuc-1 precisely and invariably positioned at the 5'LTR irrespective of the site and orientation of HIV-1 integration into the host genome? Second, long non-coding RNAs (lncRNAs) are recognized as key participants in this process by tethering PRC2 to the chromatin. What is the lncRNA that recruits PCR2 to the HIV-1 5'LTR? An attractive hypothesis that would answer both questions is that HIV-1 has evolved the ability to encode for its own lncRNA as an autonomous mechanism to recruit PRC2 to the 5'LTR, and to establish latency regardless of the chromatin context, integration site and orientation into the host genome. We demonstrate that an antisense transcript (AST) encoded in the HIV-1 genome and directed from an antisense promoter within the 3'LTR suppresses HIV-1 expression by recruiting PRC2 to the 5'LTR, and promoting epigenetic modifications that lead to the establishment and maintenance of viral latency. These results suggest that HIV-1 encodes for an lncRNA that acts an inducer of viral latency. In addition, they could guide in designing new therapies aimed at reversing or stabilizing latency by interfering or exploiting AST function.

B-111

Sulfotyrosine-Mediated V2-V3 Interaction Stabilizes the HIV-1 Envelope Trimer Facilitating Immune Evasion

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The HIV-1 envelope is a cleverly engineered viral entry machinery featuring a wide array of immune evasion mechanisms. We recently discovered that two conserved tyrosines (Y173, Y177) in the second variable (V2) loop of the gp120 envelope glycoprotein can be post-translationally modified by O-sulfation and functionally mimic the sulfotyrosines present in the N-terminal region of CCR5, interacting with the conserved coreceptor-binding site at the base of V3 (Cimbro et al., Proc. Natl. Acad. Sci. USA 111: 3152, 2014). To get further insights into the functional role of the V2 sulfotyrosines, we examined the effects of tyrosine sulfation modulation and mutagenesis on the neutralization sensitivity of HIV-1. Inhibition of tyrosine sulfation by treatment with sodium chlorate increased HIV-1 sensitivity to soluble CD4 (sCD4) and monoclonal antibodies (mAbs) to CD4-induced (CD4i) or monomer-preferred epitopes; at the same time, neutralization by trimer-specific mAbs was reduced, suggesting that tyrosine sulfation contributes to stabilizing the closed trimer conformation. An even more dramatic effect was observed upon phenylalanine or alanine substitution of the V2 tyrosines, indicating that the tyrosine side-chains play a stabilizing role regardless of their sulfation status. Strikingly, the V2 tyrosine mutants became highly susceptible to neutralization by HIV-1-infected patient sera, including those with low/restricted neutralizing capacity. Altogether, these results document the key role played by the V2 tyrosines, particularly in their sulfated form, as a mechanism of HIV-1 immune evasion.

C-101

Vaccines and Mechanisms of Host Defense

Mark Slifka, Oregon Health & Science University

Vaccines play a vital role in public health and arguably represent the most important advance in modern medicine. Most successful vaccines have been developed empirically but in order to expedite future vaccine development, a better understanding of the tenets of successful vaccine-mediated protection and long-term immunity is needed. The overriding goal of vaccination is to emulate the protection afforded by natural infection but without causing overt disease. This has been established using vaccines that use a) live, attenuated versions of their wild-type counterparts, b) live, attenuated recombinant vaccines, c) inactivated vaccines, or d) subunit vaccines. In nearly all cases, booster vaccination is required. However, in some cases once high-level protective immunity is achieved, the durability of the immune response can be measured in years or even in decades. By learning how to optimize long-term immunity above the protective threshold, we may be able to develop better vaccines that are effective, yet require fewer doses in order to achieve this goal. In this presentation, I will discuss some of our current work on vaccine development in the context of current concepts associated with eliciting protective immunological memory.

C-102

Dissecting HIV-1 Transmission: Understanding Transmitted Founder Virus Biology

Beatrice Hahn, University of Pennsylvania

Mucosal infection with HIV-1 is characterized by the rapid induction of type 1 interferons (IFNs) at the initial sites of entry. However, the extent to which these cytokines control HIV-1 replication during the earliest stages of infection and their contribution to the transmission bottleneck are not understood. We recently found that transmitted founder (TF) viruses that have crossed the mucosa and initiated a productive systemic infection are significantly more resistant to the antiviral effects of type 1 IFNs than viruses that predominate during chronic HIV-1 infection. We also found that this heightened IFN resistance declines rapidly during the first 6 months of infection. To map the responsible viral determinants and IFN-stimulated genes, we have begun to generate infectious molecular clones of TF and matching 6-mo consensus virus pairs and determined their IFN resistance profiles. Most recently, we have characterized HIV-1 transmission pairs, and found that antiviral genes up-regulated by type 1 IFNs during the earliest stages of infection exert significant selective pressure on the transmitted HIV-1 pool, resulting in the establishment of systemic infection by variants that are relatively IFN resistant. It will be important to determine whether these effector mechanisms can be exploited for the design of new prophylactic and therapeutic strategies to combat HIV-1.

C-103

Genetic Diversity of HIV Reveals the Epidemiological Role of High Risk Groups in Nigeria

Erik Volz, Imperial College London; **Rebecca Nowak**, Institute of Human Virology, University of Maryland School of Medicine; **Nicaise Ndembi**, Institute of Human Virology Nigeria; **Gustavo Kijak**, US Military HIV Research Program and Henry M. Jackson Foundation; **Stefan Baral**, Johns Hopkins Bloomberg School of Public Health; **William Blattner**, Institute of Human Virology, University of Maryland School of Medicine; **Manhattan Charurat**, Institute of Human Virology

Introduction: Pathogen genetic diversity is shaped by host-species population structure and contact patterns, and much can be learned about host population structure by analysis of random samples of pathogen genetic sequences. We demonstrate that by combining realistic infectious disease models with a population genetic model, it is possible to estimate transmission rates between groups with different risk behaviour. We apply the new methods to HIV sequence data from Abuja, Nigeria. The epidemiological role of small key populations in sub Sahara Africa is poorly understood, and targeted interventions focused on key populations promise to have increased efficacy at reducing population-level AIDS-related morbidity and mortality. Methods: We analysed 151 HIV-1 sequences from a cohort of men who have sex with men (MSM) in Abuja, Nigeria between 2012 and January 2015, and these data were combined with 158 HIV-1 sequences from the general population of Abuja over the same period. We developed a series of compartmental models which account for population structure by sex, clinical stage of infection, and risk group. The models account for secular trends in risk behaviour and trends in diagnosis and treatment. This was combined with a structured coalescent genealogical model which was fitted to time-scaled HIV phylogenies. Models were extended to predict effectiveness of interventions targeted at MSM. Results: Incidence of infection in MSM is estimated 12.5% (95%CI: 9.0-17.6) in 2014, which is consistent with previous estimates based on longitudinal cohorts. We estimate the population attributable fraction (PAF) of transmissions from MSM, and find it is increasing in recent years. More infections are prevented per unit cost using targetted interventions. Discussion: While recent incidence of infection has fallen in Nigeria, incidence and PAF has grown in MSM, highlighting the need to target high risk groups to achieve control of HIV even in generalised epidemics.

C-104

A Tumor-Targeting Delivery Platform for p53 Therapy: Translation and Clinical Applications

Esther H. Chang, Georgetown University; **Kathleen Pirollo**, Georgetown University

A nanodelivery system has been developed comprising a self-assembled, biodegradable, cationic liposomal nanoparticle, which bears a targeting moiety that homes to receptors expressed on the surface of many tumor types. When systemically administered, this platform nanocomplex can efficiently and selectively deliver gene medicines, including plasmid DNA, si/miRNAs, and ODNs as well as small molecule therapeutic agents, cytotoxic chemotherapeutic agents and imaging contract agents not only to primary tumors, but also to metastases. The nanocomplex targets cancer stem cells and crosses the blood-brain barrier. An inherited p53 mutation is the primary genetic abnormality in Li-Fraumeni Cancer Syndrome, and p53 is altered in many tumors. Various treatment strategies have focused on targeting p53. We have demonstrated that tumor-specific nanodelivery of the wtp53 gene (product termed SGT-53) sensitizes many tumors to standard chemotherapies and to radiotherapy by enhancing apoptotic cell death. SGT-53 has completed Phase Ia and Ib clinical trials in patients with advanced solid tumors and was well tolerated. Even as a single agent, >70% of patients demonstrated stable disease or better. Furthermore, analyses of metastatic tumor biopsies from patients treated with escalating doses of SGT-53 revealed a dose-dependent accumulation of the transgene in the tumors, but not in the normal skin tissue of the patients. In Phase 1b, anti-tumor effects have been observed with the combination therapy. Two Phase II trials assessing the efficacy of SGT-53 in combination with standard therapies in pancreatic cancer and glioblastoma patients are ongoing. Active tumor-targeting delivery of cancer therapies markedly enhances their effectiveness.

C-105

Insulin and IGFBP-3 Associated with Lung Cancer Susceptibility In Current Smokers

Gloria Ho, Albert Einstein College of Medicine

Only 10-20% of tobacco smokers develop lung cancer. Identifying biomarkers associated with susceptibility to lung cancer in ever-smokers may help to identify high-risk individuals for lung cancer screening. The epidermal growth factor receptor (EGFR) signaling network is involved in lung carcinogenesis. This study examined whether six ligands that activate or suppress these signaling pathways were associated with lung cancer in ever-smokers. A nested case-control study within the Women's Health Initiative cohort of postmenopausal women assessed baseline plasma levels of insulin, insulin-like growth factor (IGF)-1, insulin-like growth factor binding protein (IGFBP)-3, interleukin (IL)-6, hepatocyte growth factor (HGF), and nerve growth factor (NGF) in 1,143 ever-smoking lung cancer cases and 1,143 controls. Baseline level of leptin was also measured as an adiposity biomarker. Similar to BMI, leptin level was inversely associated with lung cancer risk (odds ratio [OR] per Ln [pg/mL] = 0.85, 95% confidence interval [CI] = 0.74-0.98). After adjusting for adiposity and other lung cancer risk factors, high insulin levels were associated with increased lung cancer risk (OR for 4th quartile vs. others [ORq4] = 2.06, 95% CI = 1.30-3.26), whereas IGFBP-3 had a linear inverse association (OR per µg/mL = 0.64, 95% CI = 0.41-0.98), in current smokers, but not former smokers. The insulin association was consistent across subgroups defined by BMI and histological type, but the IGFBP-3 association was specific for small cell lung cancer. There was a modest, positive association between IGF-1 and lung cancer risk in current smokers (ORq4 = 1.44, 95% CI = 0.90-2.29). Null associations were found for IL-6, HGF, and NGF. High insulin levels, but reduced levels of IGFBP-3, were associated with increased lung cancer risk in current smokers. Involvement of insulin in lung cancer was independent of obesity.

C-106

The Botswana Combination Prevention Project (BCPP): Addressing the UN 90-90-90 Targets for 2020

M. Essex, Harvard T.H. Chan School of Public Health

The BCPP is one of several large trials in Africa designed to test the value of antiretroviral (ARV) drugs to prevent transmission of HIV. Based in Botswana, the trial involves about 100,000 adults aged 16–64. It is a pair-matched, community-randomized design covering 30 villages with an average population of 6,000. The primary goal is reduction of 36-month cumulative incidence for the 15 villages that receive the prevention interventions, which include 3-drug ARV to all adults with viral load (VL) ≥ 10,000 and/or CD4 ≤ 500. A baseline household survey (BHS) is conducted in 20% of randomly selected households in all 30 villages to establish a cohort to monitor incidence. Viral genetic linkage (VGL) was used to refine the analysis of incident infections to estimate the fraction that likely originated within each intervention village, as TasP can only prevent infections that originate in the site where it is used. We have developed procedures using VGL with full-length genomes and different sampling densities to estimate clustering according to village of origin in BCPP. BHS sampling also revealed that Botswana has a very effective national ART program. In response to UNAIDS 90–90–90 goals, the first is the fraction of HIV-positive people who already know they are positive. For Botswana, the best estimate for this is 81%. Using the same BHS data, about 86% of people who know they are positive are already on treatment, and 96% of those on treatment were in complete viral suppression. This results in a score of 67%, already close to the 2020 goal of 73%.

C-107

Stigma and Depression Among Newly Diagnosed HIV Infected MSM in China

Jun Tao, Vanderbilt Institute for Global Health; **Lijuan Wang**, Chaoyang CDC; **Aaron Kipp**, Vanderbilt Institute for Global Health; **Han-zhu Qian,** Vanderbilt Institute for Global Health; **Lu Yin**, Vanderbilt Institute for Global Health; **Yuhua Ruan**, State Key Laboratory for Infectious Disease Prevention & Control; National Center for AIDS/STD Control & Prevention, Chinese Center for Disease Control & Prevention; **Yiming Shao**, State Key Laboratory for Infectious Disease Prevention & Control; National Center for AIDS/STD Control & Prevention, Chinese Center for Disease Control & Prevention; **Hongyan Lu**, Beijing CDC; **Sten Vermund**, Vanderbilt Institute for Global Health, Vanderbilt University School of Medicine

HIV-related stigma is a risk factor for depression among persons living with HIV, but this has not been studied in persons who are newly diagnosed. Men who have sex with men (MSM) are vulnerable to depression and/or anxiety due to their identity as members of a discriminated minority group, potential social isolation, and, frequently, high risk of HIV acquisition. We evaluated the stigma-depression association among newly diagnosed HIV-infected Chinese MSM in Beijing. Methods: We recruited 366 MSM who were newly diagnosed in the baseline survey of a randomized clinical trial. HIV-related stigma was measured by a scale constructed with sensitivities towards Asian culture. Exploratory factor analysis helped validate the scale. Depression was assessed from the Hospital Anxiety and Depression scale (HADS). Depression was categorized as normal, borderline, and suspicious. Multivariable ordered logistic regression was used to assess the association between continuous stigma scores and depression. Results: The HADS classified 30% of participants as depressed. The HIV-related stigma scale proved valid, and 4 subscales were replicated in the exploratory factor analysis. Median scores for enacted, felt, vicarious, and internalized stigmas were 0, 17, 2, and 5, respectively. One point increase of stigma scores was associated with a 3-9% increase in the odds of being depressed, with internalized stigma (shame, guilt, contact avoidance) having the strongest association (aOR=1.09, 95%CI: 1.07, 1.12). Conclusion: HIV-related stigma was a risk factor for depression among newly diagnosed HIV-infected MSM. Interventions for coping with internalized stigma following HIV diagnosis may reduce depression and improve downstream indications of the care continuum: linkage to care, retention, and adherence to antiretroviral therapy.

C-108

Recent Cohort Data Suggest Revising US Cervical Cancer Screening Practices in HIV+ Women

Howard Strickler, Albert Einstein College of Medicine

HIV+ women have several fold increased risk of invasive cervical cancer and precancerous cervical lesions, relative to the general population, as well as increased prevalence, incidence, and persistence of oncogenic human papillomavirus (oncHPV), the viral cause of cervical cancer. Each of these risks increases with diminishing CD4+. According to data from the Women's Interagency HIV Study (WIHS), the largest prospective US cohort of HIV+ and at-risk HIV- women, a quarter of HIV+ women at each clinic visit have abnormal Pap tests (i.e., atypical squamous cells of undetermined significance or more severe [ASC-US+]). Most of these abnormal Pap tests do not, however, reflect clinically relevant disease; i.e., cervical intraepithelial neoplasia grade 2 or more severe (CIN-2+) by histology. USPHS guidelines currently recommend aggressive screening of HIV+ women: 2 Pap tests at 6 month intervals in the first year following diagnosis of HIV and, if normal, then on an annual basis. However, WIHS data have shown that HIV+ women with normal Pap tests who additionally co-test oncHPV- have a similar low 5-year risk of CIN-2+ and CIN-3+ as those who are HIV-. Conversely, HIV+ women who tested oncHPV+ despite a normal Pap had a 5-year cumulative risk of CIN-3+ of 4%. In multivariable Cox models, testing positive for non16-oncHPV was associated with a 3-fold increased risk of CIN-3+ relative to oncHPV-, whereas it was 13-fold for HPV16+, and 9-fold for those with LSIL by Pap (a benchmark for immediate colposcopy). Overall, HIV+ women with a normal Pap who test oncHPV- may not require screening for several years, whereas those who are HPV16+ may warrant immediate colposcopy, and those positive for other oncHPV have intermediate risk.

C-109

HPV Associated Cervical Cancer in HIV negative African Women

Clement Adebamowo, University of Maryland School of Medicine

Cervical cancer is the second commonest cancer in Africa where it accounts for an estimated 92,340 new cases, an ASR of 33.4 per 100,000 and mortality rate of 21.5 per 100,000 in 2012. Persistent infection by high risk Human Papilloma Virus infection is a necessary but not sufficient cause of the disease and other factors e.g. HIV infection and smoking play a role in cervical carcinogenesis. Studies from developed countries have identified HPV types 16 and 18 in more than 70% of all cervical cancer cases but probably accounts for less in African population. HPV infection is ubiquitous and some 80% of women are infected at some point in their lives. Nevertheless infection persists only in about 10% and leads to carcinogenesis in a minority of these. The limited data available from studies of HIV negative African women suggests that there is marked heterogeneity and high prevalence of multiple hrHPV types' infections in these populations. The proportional contribution of each of these hrHPV types, their likelihood of persistence and the aggregate contribution of multiple infections to cervical carcinogenesis in this population is not well characterized. While there is evidence for genetic predisposition to HPV infection, there has been no Genome-Wide Association Study (GWAS) of the genetic predispositions to persistent hrHPV infection to date. Recent developments in genomics and microbiomics also suggest a role for the vaginal microenvironment – the vaginal microbiome and cervical cytokines – in persistent infection but there are few studies of these. Despite these gaps in knowledge, developed countries have reduced incidence of cervical cancer by over 65% in the past 4 decades using a Pap smear, liquid cytology and most recently HPV DNA based testing. However these technologies have not translated well to developed countries where the incidence and mortality of cervical cancer is still similar to what it was in developed countries 50 years ago

C-110

Human T lymphotropic virus types 1 and 2 (HTLV-1 and -2) and hepatitis C virus (HCV) epidemiology: lessons from studies of blood donors

Edward Murphy, Univ. of California San Francisco

HTLV-1, HTLV-2 and HCV cause chronic infections of humans, are transmitted parenterally and cause serious outcomes after long latencies. It is interesting to compare and contrast the characteristics of these viruses in several domains. Both HTLV-2 and HCV are highly prevalent among injection drug users (IDUs) in the United States and Europe and show age and sex prevalences consistent with a birth cohort effect due to epidemics of IDU in the 1960s and 1970s. HCV is broadly prevalent at 1% to 2% in many countries, with foci of hyper-endemicity due to presumed iatrogeneic transmission. In contrast, HTLV-1 is also globally prevalent but with a more spotty distribution linked to human migrations. HTLV-1 and HTLV-2 are clearly transmitted sexually whereas HCV is not. All three viruses have long periods of viral latency. In the case of HTLV-1 and HTLV-2, there is integration of pro-virus into the host genome and clonal expansion of CD4+ and CD8+ lymphocytes, respectively, but little production of cell free viral RNA. For HCV, 20% – 50% of those infected resolve the infection with maintenance of antibody but resolution of plasma viremia while the remainder has chronic viremia. HTLV-1 infection leads to adult T-cell leukemia/lymphoma (ATL) in 2% – 4% of those infected after 40 – 50 years of latency and acquisition of infection during infancy carries greater risk. Both HTLV-1 and HTLV-2 cause a myelopathy in 4% and 1% of those infected, respectively, again after long latency except for rare cases of with acute onset following transfusion acquired HTLV infection. HCV causes cirrhosis and hepatocellular carcinoma but again in only a small fraction of those infected and better prognostic indicators are needed for HCV.

C-111

Progress toward poliomyelitis eradication - Nigeria, January 2014-July 2015

Andrew Etsano, National Primary Health Care Development Agency, Federal Republic of Nigeria; **Rajni Gunnala**, Global Immunization Division, Center for Global Health, US Centers for Disease Control and Prevention; **Faisal Shuaib**, Federal Ministry of Health, Federal Republic of Nigeria; **Eunice Damisa**, National Primary Health Care Development Agency, Federal Republic of Nigeria; **Pascal Mkanda**, World Health Organization, Nigeria Office; **Johnson Ticha**, World Health Organization, Nigeria Office; **Richard Banda**, World Health Organization, Nigeria Office; **Charles Korir**, World Health Organization, Nigeria Office; **Ana Chevez**, World Health Organization, Nigeria Office; **Ogu Enemaku**, United Nations Children's Fund, Nigeria Office; **Melissa Corkum**, United Nations Children's Fund, Nigeria Office; **Lora Davis**, Global Immunization Division, Center for Global Health, US Centers for Disease Control and Prevention; **Gatei wa Nganda**, Global Immunization Division, Center for Global Health, US Centers for Disease Control and Prevention; **Cara Burns**, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, US Centers for Disease Control and Prevention; **Steve Wassilak**, Global Immunization Division, Center for Global Health, US Centers for Disease Control and Prevention; **John Vertefeuille**, Centers for Disease Control and Prevention

Since the 1988 launch of global polio eradication efforts, four of the six World Health Organization regions have been certified polio-free. In the remaining regions (African & Eastern Mediterranean), only Nigeria, Afghanistan, and Pakistan have never interrupted wild poliovirus (WPV) transmission. During 2003-2013, Nigeria was a reservoir for WPV reintroduction into 26 previously polio-free countries. In 2012 a national emergency plan was launched to intensify polio eradication efforts in Nigeria. This report summarizes Nigeria's polio status during January 2014-July 2015. During this period, 13 polio vaccination campaigns were implemented. No WPV cases have been reported in 2015 (versus six during the same 2014 period). Onset of the last reported WPV type 1 case was July 24, 2014 in Kano. One case of circulating vaccine-derived poliovirus type 2 (cVDPV2) has been reported in 2015, compared with 30 cases reported in 2014. With 12.8 non-polio acute flaccid paralysis cases per 100,000 nationally, polio surveillance exceeds the international standard of ≥2 but subnational gaps remain. Of eight WPV genetic clusters detected in Nigeria in 2012, four persisted in 2013 and two in 2014. Environmental surveillance at 38 sites identified no WPV and one cVDPV2 positive sample in 2015 linked to a 2005 emergent strain from Nigeria. Pending laboratory testing of specimens collected through July 23, Africa is poised to be certified polio-free as early as 2017. This will require maintaining political support and program funding in the absence of WPV transmission, ensuring high levels of population immunity, including in children in the security compromised northeast, and strengthening surveillance in poor-reporting districts.

D-101

HIV-1 neutralizing antibodies induced by native-like envelope trimers

Rogier Sanders, Academic Medical Center of the University of Amsterdam and Weill Medical College of Cornell University

A challenge for HIV-1 immunogen design is the difficulty of inducing neutralizing antibodies (NAbs) against neutralization-resistant (tier 2) viruses that dominate human transmissions.We show that a soluble recombinant HIV-1 envelope glycoprotein trimer that adopts a native conformation, BG505 SOSIP.664, induced NAbs potently against the sequence-matched tier 2 virus in rabbits and similar but weaker responses in macaques. The trimer also consistently induced cross-reactive NAbs against more sensitive (tier 1) viruses. Tier 2 NAbs recognized conformational epitopes that differed between animals and in some cases overlapped with those recognized by broadly neutralizing antibodies (bNAbs), whereas tier 1 responses targeted linear V3 epitopes. A second trimer, B41 SOSIP.664, also induced a strong autologous tier 2 NAb response in rabbits. Thus, native-like trimers represent a promising starting point for the development of HIV-1 vaccines aimed at inducing bNAbs.

D-102

Presenting native-like HIV-1 envelope trimers on ferritin nanoparticles improves their immunogenicity

Kwinten Sliepen, Academic Medical Center of the University of Amsterdam; **Gabriel Ozorowski,** The Scripps Research Institute; **Judith Burger**, Academic Medical Center of the University of Amsterdam; **Thijs van Montfort**, Academic Medical Center of the University of Amsterdam; **Melissa Stunnenberg**, Academic Medical Center of the University of Amsterdam; **Ilja Bontjer**, Academic Medical Center of the University of Amsterdam; **Celia LaBranche**, Duke University Medical Center; **David Montefiori**, Duke University Medical Center; **John Moore**, Weill Medical College of Cornell University; **Andrew Ward**, The Scripps Research Institute; **Rogier Sanders**, Academic Medical Center of the University of Amsterdam Weill Medical College of Cornell University

Presenting vaccine antigens in particulate form can improve their immunogenicity by enhancing B cell receptor cross-linking and B cell activation. We describe ferritin-based protein nanoparticles that display multiple copies of native-like HIV-1 envelope glycoprotein trimers (BG505 SOSIP.664) to improve upon the promising neutralizing antibody responses obtained with BG505 SOSIP.664 alone. With the aim of increasing neutralization breadth we also generated SOSIP.664-ferritin nanoparticles from different viral strains from subtypes A, B and C. Trimer-bearing nanoparticles were significantly more immunogenic than trimers in both mice and rabbits. Furthermore, rabbits immunized with the trimer-bearing nanoparticles induced significantly higher neutralizing antibody responses than when the same trimers were delivered as soluble proteins. Thus, nanoparticle-displayed native-like trimers might be valuable in the quest for an HIV-1 vaccine aimed at inducing broadly neutralizing antibodies.

D-103

Studies on native-like SOSIP.664 trimers and other forms of Env

John Moore, Weill Cornell Medical College

On behalf of a team of researchers at WMCM, the AMC (Amsterdam) and the Scripps Research Institute, I will discuss in vitro and animal immunization studies involving native-like SOSIP.664 trimers. In some cases, the properties and performance of these proteins will be compared and contrasted with other, non-native forms of Env. The ultimate goal of the SOSIP. trimer program is to induce broadly neutralizing antibodies, which has not yet been achieved. Strategies towards this goal will be discussed.

D-104

Molecular-level analysis of Env: What's on native trimers and how can we reproduce it in a vaccine?

Heather Desaire, University of Kansas

Numerous HIV vaccine design strategies that have advanced towards early clinical trials include boosting immune response with a recombinant, truncated form of Env, the trimeric surface antigen on the HIV-1 virus. Production of this protein in quantities large enough to support clinical trials is a challenge, and vaccine development efforts now predominantly favor generation of the soluble, monomeric gp120 component of this protein. Thus far, the protein has not been effective at eliciting neutralizing antibodies in humans, and we hypothesized that a contributing cause for this lackluster performance was that the recombinant, truncated preparations of gp120 are not effective mimics of native Env. We have conducted glycosylation and disulfide bonding analyses of many gp120 and gp140 vaccine candidates destined for clinical trials and compared their molecular profiles to trimeric, native-like Env of multiple sequence types. The results show that a conserved "native" glycosylation profile exists among native-like Env trimers, but gp120 and uncleaved gp140s typically do not adopt this glycosylation profile. Furthermore, unless the truncated Env is expressed as a gp140 and engineered to stabilize the gp120/gp140 interface, such as by using the SOSIP modifications, its disulfide bonding profile is typically highly heterogenous, with the majority of the disulfide bonds matching a non-native profile. Taken together these results emphasize that many vaccine design and production efforts need reconsideration, if developers intend to deliver recombinant Env in a native conformation as part of their vaccine strategy.

D-105

Integrin a4b7 expression increases HIV susceptibility in activated cervical CD4+ T cells via an HIV attachment-independent mechanism

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Background: CD4+ T cells, the principal target in acute SIV and HIV infection, are crucial for the establishment and dissemination of HIV infection in mucosal tissues. Studies indicate that α4β7 CD4+ T cells are preferentially infected by HIV in vitro and during acute SIV infection. The integrin α4β7 is thought to promote HIV capture by target cells; however, the role of integrin α4β7 in HIV transmission remains controversial. In this study, we characterized immune phenotypes of human cervical T cells and examined HIV preference in integrin α4β7+ CD4+ T cells. In vitro all-trans retinoic acid differentiated peripheral CD4+ T cells (at-RA differentiated cells) were included as a comparison. Results:In both peripheral and cervical cells, the majority of HIV p24+ cells were activated CD4+ T cells expressing integrin α4β7. Among infected at-RA differentiated cells, the frequency of CCR5 expression was higher in HIV p24+ cells than in HIV p24- cells; no such difference was observed in cervical cells. Neither the cyclic hexapeptide CWLDVC nor a monoclonal antibody against integrin α4β7 blocked HIV attachment or gp120 binding to target cells regardless of the presence of CD4, indicating that integrin α4β7 did not facilitate HIV capture by target cells. Conclusion: Integrin α4β7 expression increases HIV susceptibility, but the mechanism is not through promoting HIV binding to target cells.

D-106

Cellular Immune correlates Analysis of an HIV-1 Pre-exposure Prophylaxis Trial

Peter Kuebler, University of California San Francisco; **Megha Mehrotra**, Gladstone Institute; **Jeff McConnell**, Gladstone Institute; **Sara Holditch**, Gladstone Institute; **Brian Shaw**, Gladstone Institute; **Leandro Tarosso**, University of Sao Paulo; **Kaitlyn Leadabrand**, University of California, San Francisco; **Jeffrey Milush**, University of California, San Francisco; **Vanessa York**, University of California San Francisco; **Rui Andre Saraiva Raposo**, The George Washington University; **Rex Cheng**, University of California San Francisco; **Emily Eriksson**, University of California San Francisco; **Vanessa McMahan**, Gladstone Institute; **David Glidden**, University of California San Francisco; **Stephen Shiboski,** University of California San Francisco; **Robert Grant**, Gladstone Institute; **Esper Kallas**, University of Sao Paulo; **Douglas Nixon**, The George Washington University

The majority of HIV exposures do not result in an established systemic infection. Preexposure Prophylaxis (PrEP) trials provide the right subjects with sufficient numbers to investigate mechanisms of resistance. We leveraged the global iPrEx PrEP trial to query T cell mediated mechanisms of resistance. We compared those who remained HIV-1 seronegative (HESN) to those who became infected during the trial with the variables of HIV-specific IFN-γ T cell responses, frequency and phenotypes of activated T cells and HLA MHC Class I genotypes. HIV-specific IFN-γ responses were more frequent in HESN when compared to matched pre-infection samples from those who became infected. Logistic regression analyses suggested a reduced infection risk was associated with a Vif-specific response Hazard Ratio = 0.36, 95% CI [0.19 - 0.66]. In pilot analyses of T cell activation, the frequency of CD38+HLA-DR+ CD8+ T cells was greater in those who seroconverted relative to those that remained uninfected (1.30% vs. 0.82%, respectively, p=0.005). HLA-B15 showed the strongest association with infection outcomes among all others. HLA-B15 allele frequency in HESN was 0.0392 in HESN and 0.1961 in those who became infected. HLA-B15 and was also associated with lower T cell response frequency. PrEP studies provide the naturalistic setting to assess the immune fingerprint of HIV resistance in HESN, providing the right control group, sufficient subject numbers and clinical outcomes to associate infection risk. We found Vif-specific T cell responses and lower T cell activation was associated with reduced infection risk while Protease responses, greater frequencies of activated T cells, and having the HLA-B15 Class I MHC allele was associated with increased HIV infection risk.

D-107

Vaccination establishes CXCR5+PD1+CD4+ peripheral blood germinal center T follicular helper cell relatives in humans

Frank Schmitz, Center for Infectious Disease Research, Seattle, WA; **Sarah Gerdts**, Fred Hutchinson Cancer Research Center, Seattle, WA; **Britta Flach**, Fred Hutchinson Cancer Research Center, Seattle, WA; **Miranda Moore**, Fred Hutchinson Cancer Research Center, Seattle, WA; **Jonathan Perkins**, University of Washington, Seattle, WA; **Harlan Robins**, Adaptive Biotechnologies Corporation, Seattle, WA; **Alan Aderem**, Center for Infectious Disease Research, Seattle WA; **Paul Spearman**, Emory University and Children's Healthcare of Atlanta, GA; **Georgia Tomaras**, Duke University, Durham, NC; **Stephen De Rosa**, Fred Hutchinson Cancer Research Center, Seattle, WA; M. **Juliana McElrath**, Fred Hutchinson Cancer Research Center, Seattle, WA; **Antje Heit,** Fred Hutchinson Cancer Research Center

Protective vaccines against microbial pathogens are designed to elicit long-lasting antigen-specific T- and B-cell responses. CD4+ T follicular helper cells (Tfh) are specialized in supporting and selecting higher affinity B cells during the germinal center (GC) reaction in lymph nodes. Thus, the identification of a circulating Tfh relative with a potential role in this process is an area of intense interest, particularly if their properties provide insight into how the antibody response is shaped. Recently, functional counterparts of GCTfh cells were identified within the pool of circulating CXCR5+ CD4 memory T cells. To understand whether such cells are induced following vaccination we used additional markers for GCTfh, PD1 and ICOS, to stratify circulating CXCR5+ Tfh subsets into three distinct subsets and followed them longitudinally upon vaccination to investigate their diversity, kinetics, and ontogeny. Analysis of the T-cell receptor clonal repertoire revealed a clonal relationship between circulating, PD1-expressing subsets and tonsillar GCTfh cells. Furthermore, a vaccine-specific PD1+ICOS+ subset clonally expanded one week after vaccine boost, correlated with vaccine-specific IgG serum antibodies, phenotypically resembled GCTfh cells and showed a clonal relationship to persistent PD1+ICOS- memory cells. Thus, vaccination establishes Tfh relatives in circulation that expand upon antigen reencounter with the potential to serve as early, cellular marker for GC activity upon vaccination.

D-108

Special Lecture: Human Antibodies to HIV-1

Michel Nussenzweig, The Rockefeller University

Abstract not available.

D-109

Special Lecture: Fc Effector functions in the anti-viral response

Jeffrey Ravetch, The Rockefeller University

Antibodies produced in response to a foreign antigen are characterized by polyclonality, not only in the diverse epitopes to which their variable domains bind but also in the various effector molecules to which their constant regions (Fc domains) engage. Thus, while Fab-antigen interactions are crucial to the specificity of the antibody response, there is a crucial role for the Fc domain in mediating the diverse effector properties triggered by antigen recognition, even for processes traditionally attributed solely to recognition by the Fab, such as neutralization of toxins and viruses. Specific interactions of the IgG Fc domain with distinct receptors expressed by diverse immune cell types result in the pleiotropic effector functions for IgG, including the clearance of pathogens and toxins, lysis and removal of infected or malignant cells, modulation of the innate and adaptive branches of immunity to shape an immune response, and initiation of anti-inflammatory pathways that actively suppress immunity. The Fc domain mediates these diverse effector activities by engaging two distinct classes of Fc receptors (type I and type II) on the basis of the distinct conformational states that the Fc domain may adopt. These conformational states are regulated by the differences among antibody subclasses in their amino acid sequence and by the complex, biantennary Fc-associated N-linked glycan. I will discuss the diverse downstream proinflammatory, anti-inflammatory and immunomodulatory consequences of the engagement of type I and type II Fc receptors in the context of infectious diseases.

E-101

Reinhard Kurth Memorial Lecture: Zoonotic Origin of Some Common Human Cancers and Multiple Sclerosis?

Harald zur Hausen, Deutsches Krebsforschungszentrum

Red meat consumption has been considered in a large number of prospective epidemiological studies as a major risk for colon cancer. Only recently attempts have been published to identify specific types and factors in red meat contributing to this risk (1, 2). The available data point to a specific risk after long-time consumption of meat from Eurasian dairy cattle, particularly based on data from India, Mongolia, Japan and Korea. In the first two of these countries the colon cancer risk is very low, in India almost no beef is being consumed (Hindu population), in Mongolia red meat consumption is very high, but as far as beef is concerned, it mainly originates from Zebu-derived cattle and yaks. In Japan and Koreas beef consumption increased dramatically after World War II and after the Korean War. A substantial increase in colon cancer incidence occurred ~15-20 years after these wars. Breast cancer incidence is high in most countries with high incidence of colon cancer. Yet, in some regions remarkable differences exist: in Japan and Korea breast cancer occurs less frequently than colon cancer, in India breast cancer exceeds the rate of colon cancer. In additional countries (China and Bolivia) breast cancer incidence is low, corresponding to a low consumption of cow milk. There appears to exist a correlation between dairy cattle milk consumption and breast cancer incidence (2). Our laboratory isolated a larger number of small novel single-stranded circular DNA molecules, presumably of viral origin. In cattle sera we found 10 specific DNAs, belonging into three different groups. From cow milk six different isolates have been obtained, all belonging into one of these groups. Human sera were negative for these agents. Autopsy material from two patients with multiple sclerosis, however, contained milk-related isolates. The available data do not provide definite evidence for a role of these agents in human diseases, although transfection of their DNAs into human cells leads to active transcription of messenger RNA from these genomes (Eilebrecht et al., unpublished).

E-102

Ending the HIV/AIDS Pandemic: The Convergence of Treatment and Prevention

Anthony Fauci, National Institute of Allergy and Infectious Diseases, NIH

The common goal for all who work in the field of HIV/AIDS research is to control and ultimately end the HIV/AIDS pandemic. In this regard, significant progress has been made in combating HIV/AIDS worldwide. Yet, we must build further on these successes. Inherent in this endeavor is the task of driving down of HIV incidence globally. In order to accomplish this, a combination of non-vaccine and vaccine prevention approaches will be needed. For example, with regard to non-vaccine prevention, recent evidence has highlighted the potential impact of scaling up various iterations of "treatment as prevention" and the selective application of pre-exposure prophylaxis with antiretroviral drugs. Vaccine prevention holds new promise, with efforts to improve upon the modest success of the RV144 trial. On a parallel track to optimizing the RV144 results is the intensive effort to design immunogens that might induce broadly neutralizing antibodies. Furthermore, passive transfer of broadly neutralizing antibodies is being studied as a means to prevent and/or treat HIV infection. While non-vaccine and vaccine-based prevention approaches have the potential to drive HIV incidence toward zero, a significant "implementation gap" remains between the development of interventions and their delivery to people who need them, a gap that must be closed if we are to realize the end of the HIV/AIDS pandemic.

E-103

The Pathway to HIV Vaccine Development

Barton Haynes, Duke Human Vaccine Institute at Duke University School of Medicine,

Over the past 10 years the HIV vaccine field has worked to define the roadblocks preventing the development of an HIV vaccine. and has worked to develop strategies to overcome them. Recent success in isolation of potent broadly neutralizing antibodies (bnAbs), in discovery of pathways and mechanisms of bnAb induction, in defining novel modes of bnAb regulation and in discovery of atypical mechanisms of CD8 T cell killing of HIV-infected CD4+ T cells have opened new avenues for strategies for HIV vaccine design. Work now is ongoing to move new vaccine concepts into proof-of-concept experimental medicine Phase I clinical trials, and to test the effect of new immunization strategies on the human immune system. In addition, efforts are also ongoing to improve the design of the pox prime/pox + Env boost strategy that resulted in an estimated 31% efficacy in the RV144 trial. Progress made to date in overcoming vaccine roadblocks will be discussed, and the remaining path forward for HIV vaccine development will be outlined.

E-104

Can non neutralizing antibodies be the basis for an effective HIV vaccine? Can we determine if RV 144 is "real or Memorex" ?

Larry Corey, Fred Hutchinson Cancer Research Center

Abstract not available.

E-105

Antibodies Against Ebola Virus: Results of the Viral Hemorrhagic Fever Immunotherapeutic Consortium

John Dye, USAMRIID; **Kartik Chandran**, Albert Einstein College of Medicine; **Gary Kobinger**, PHAC; **Yoshihiro Kawaoka**, University of Wisconsin; **Larry Zeitlin**, Mapp Biopharmaceutical; **Andrew Ward**, The Scripps Research Institute; **Cory Nykiforuk**, Emergent Biosciences; **Javad Aman**, Integrated Biotherapeutics; **Jonathan Lai**, Albert Einstein College of Medicine; **Erica Saphire**, The Scripps Research Institute

The Viral Hemorrhagic Fever Immunotherapeutic Consortium is a field-wide, global collaboration that aims to understand which antibodies are effective against filoviruses and arenaviruses and why, and how maximally effective therapeutic cocktails could be assembled. In 2007, it was found that a potent neutralizing mAb was unable to control the course of Ebola virus infection. In 2012, however, it was determined that cocktails of mAbs, including non-neutralizing antibodies, could provide lifesaving postexposure protection against Ebola virus. After these results, the questions in the field were: Is a cocktail of mAbs (vs. a single mAb) necessary? Which combinations offer additive or synergistic functions? Which compete? Which are best? And why? Does in vitro neutralization correlate with in vivo protection? If not, why not? The likely requirement of more than one antibody to mitigate escape, the rarity of the most effective antibodies, and the number of unknowns in terms of the best correlates of protection suggested a large scale, multidisciplinary approach as the best way forward. Over 25 laboratories across 10 countries organized to analyze their assembled pool of mAbs using structural, biochemical, cellular and in vivo analysis. One key facet of this consortium is that all the mAbs are de-identified, for impartial analysis. A second key facet is its scale: antibodies from multiple labs are being compared side-by-side under the same assay condtiions ("apples to apples"), expediting selection, and allowing cocktails to be assembled using rare antbodies from around the globe. The results from the first year will be presented including structures, epitope mapping, and functional analysis. We find that only some potential antibody epitopes consistently lead to in vitro neutralization; others offer protection in the absence of in vitro neutralization.

E-106

Establishment of a Clinical Research Program in the Setting of the Ebola Outbreak in West Africa

Clifford Lane, National Institutes of Health

In August, 2014, then Liberian Minister of Health Gwenigale sent a letter to HHS Secretary Burwell asking for help from the US in establishing a clinical research program to evaluate experimental approaches to the treatment and prevention of Ebola virus disease. In the subsequent months scientists from the two countries worked together to form the Liberian-US Clinical Research Program. The individual elements of clinical research ranging from basic lab support to site monitoring were identified and a Liberian and a US representative assigned to each area. Three protocols have been initiated under this partnership. The first, a randomized, phase II, placebo-controlled trial of the rVSV and ChAd3 vaccine candidates was initiated in February, 2015 and completed enrollment of 1500 subjects in May, 2015. The second, a randomized, controlled, adaptive trial to sequentially test therapeutic candidates was initiated in March and has thus far enrolled approximately 60 subjects in Liberia the US, Sierra Leone and Guinea. The third, an observational study of survivors of Ebola virus disease was initiated in June, 2015 and thus far has enrolled approximately 400 individuals. As part of this work a substantial effort has gone into building both healthcare and clinical research infrastructure with the goal of establishing a sustainable clinical research program in West Africa that will be remain active beyond the current outbreak.

E-107

Advancing Global Health: Lessons from the response to the HIV epidemic

Salim Abdool Karim, Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal

Enormous gains have been made in controlling the HIV epidemic over the past decade, saving millions of people from infection and AIDS-related illness and death. In 2013, the number of new HIV infections had decreased by 38% since 2001 to 21 million, and the number of AIDS-related deaths decreased by 35% since 2005 to 15 million. In some parts of the world, mother-to-child transmission of HIV has been virtually eliminated. Continued scientific discovery and activism, along with resource mobilisation, political commitment, and implementation has created this favourable trajectory. Scientific breakthroughs and innovation in all facets of the response, and the generation and use of evidence and data have been and will continue to be essential to the success of the AIDS response. This presentation draws upon the UNAIDS-Lancet Commission on “Defeating AIDS – Advancing Global Health” to describe some of the lessons from the AIDS response that could inform the global health. For example, health-system adaptations (eg, standardising first-line regimens, fixed-dose combinations) and innovations (eg, point of care or home-based HIV testing, peer support for treatment, task-shifting, community mobilisation) have provided important lessons on how health services can sustainably reach ever increasing numbers of patients in need of treatment. Indeed, these lessons are being used by the health services in chronic disease care (eg, diabetes and hypertension). The AIDS response has also pioneered rigorous monitoring of a broad set of indicators. This kind of tracking has been a crucial way to hold leaders, institutions, and governments accountable and to adjust AIDS responses. The future of Global Health could be profoundly impacted by drawing up the efforts by UN agencies to end AIDS as a public health threat by 2030.

F-101

Pharmacologic inhibition of the HIV-1 vif:apobec axis

Mario Stevenson, University of Miami Miller Medical School; **Tariq Rana**, UC San Diego.

Apobec 3G is a cellular cytidine deaminase that potently antagonizes infection by primate lentiviruses including HIV-1 and SIV. The antiviral activity of Apobec 3G involves the induction of extensive G to A deamination of nascent viral cDNA, rendering it biologically inactive. To counteract the antiviral activity of Apobec proteins, lentiviruses have evolved the vif protein that ubiquitylates and targets apobec 3G for proteasomal degradation. Despite the potent antiviral activity of these cellular restrictions, they have yet to be exploited for therapeutic management of HIV-1 infection. We previously identified a lead compound (RN18) that inhibits viral replication only in the presence of the apobec 3G protein. Structure Activity Relationship (SAR) studies have identified potent RN18 analogs (IC50 <100nm) that also exhibit antiviral activity only in the presence of apobec 3G. While resistance to the lead molecule, RN18 is governed by mutations in RT, resistance to RN18 analogs is governed by an amino acid substitution in a region of vif that mediates binding to the ubiquitylation apparatus. Mutations in RT were found to markedly increase viral fitness over wild-type viruses but only in the presence of apobec 3G. This suggests that Apobec 3G exhibits pressure on HIV-1 even in the presence of a fully competent vif protein. We further demonstrate that virions made in the presence of these agents are non-infectious. Therefore, vif antagonists may have utility in limiting the spread of virions from long-lived reservoirs in infected individuals on suppressive therapy. Preclinical studies indicate that these agents have very low toxicity in vivo. Studies to assess efficacy in the SIV/macaque model are underway.

F-102

HIV-1 matrix protein p17 promotes lymphangiogenesis by autophagy-mediated unconventional proteins secretion

Arnaldo Caruso, University of Brescia

AIDS-related lymphomas (ARL) account for a large proportion of malignancies in HIV-1-infected individuals and differ from other lymphomas for their high-grade and aggressive metastatic nature. Lymphangiogenesis is important in supporting proliferation and survival of lymphomas, and plays a key role in tumor dissemination. HIV-1 is not inserted within malignant cells, suggesting an indirect role for HIV in ARL incidence, which may involve HIV-1 proteins expressed in lymphatic tissue. The HIV-1 matrix protein p17 (p17) accumulates and persists in the lymph nodes of patients even under highly active antiretroviral therapy and exerts pro-angiogenic activity by binding to the chemokine receptors CXCR1 and CXCR2 expressed on endothelial cells. In light of this finding, the aim of the present study was to determine the effect of p17 on lymphangiogenesis and to elucidate the mechanism underlaying p17 effects. HIV-1 p17 promoted lymphangiogenesis of lymph node-derived lymphatic endothelial cells (LN-LECs) following nutrient starvation, after binding to CXCR1 and CXCR2 and by activating the Akt and ERK signaling pathways. Lymphangiogenesis did not occur when p17 was added to cells treated with 3-methyladenine or silenced for beclin-1, GRASP55 or Rab8a expression, thus suggesting that p17 increases autophagy-mediated unconventional proteins secretion. Indeed, we found that p17 lymphangiogenic activity was mostly mediated by autophagosome-mediated endothelin-1 secretion. Our data suggest that p17 may produce a microenvironment in the lymph node that may foster lymphoma development, progression and metastasis. Therapies targeting p17-mediated autophagy alterations may decrease lymphangiogenesis and offer new opportunities to combat ARLs.

F-103

A conformational switch that turns on the B cell growth-promoting activity of the HIV-1 matrix protein p17

Wangxiao He, Center for Translational Medicine, Xi'an Jiaotong University School of Life Science and Technology, China; **Federica Campilongo**, Department of Molecular and Translational Medicine, University of Brescia Medical School, Italy; **Francesca Caccuri**, Department of Molecular and Translational Medicine, University of Brescia Medical School, Italy; **Weirong Yuan**, Institute of Human Virology, University of Maryland School of Medicine, USA; **Kristen Varney**, Department of Biochemistry and Molecular Biology, University of Maryland School of Medicine, USA; **Arnaldo Caruso**, Department of Molecular and Translational Medicine, University of Brescia Medical School, Italy; **Robert Gallo**, Institute of Human Virology, University of Maryland School of Medicine, USA; **Wuyuan Lu**, Institute of Human Virology, University of Maryland School of Medicine, USA

Background: The HIV-1 matrix protein p17 of 132 amino acid residues is a structural protein essential for viral assembly and maturation. Recent studies suggest that p17 and certain variants in particular are functionally associated with non-Hodgkin's lymphoma (NHL) in HIV-1 infected individuals as they promote the growth of transformed B cells and induce angiogenesis and lymphangiogenesis of vascular and lymphatic endothelial cells in vitro and in vivo; these growth-promoting effects are mediated by the chemokine receptors CXCR1 and/or CXCR2. Despite these findings, the structural basis of how p17 promotes lymphoma development remains unknown. Results: By analyzing folding and stability of various p17 variants using a battery of biophysical techniques, we found that their B cell growth-promoting activity is strongly correlated with protein destabilization and/or unfolding. Thus, we hypothesize that a mutation-induced conformational change endows p17 with an acquired or enhanced ability to promote receptor-mediated lymphomagenesis. To test this hypothesis, we forced two highly conserved Cys residues, 10 Å away in the native structure of an inactive p17 from HIV-1 clade B isolate BH10, to form an intra-molecular disulfide bond. This disulfide-constrained p17 protein in a non-native conformation was, as expected, significantly destabilized and less structured, but fully active in promoting clonogenic growth of transformed B cells. Conclusion: We have identified disulfide bonding as a conformational switch in p17 that turns on its lymphomagenic activity. Since HIV-1 associated NHL strongly correlates with viral replication and p17 is prone to mutate and persists in the germinal centers of lymph nodes long after HAART suppression of HIV, this conformational and functional switch, controlled by mutation-induced protein destabilization in an oxidizing environment, may underlie critical molecular events leading ultimately to the development of NHL in HIV/AIDS patients.

F-104

Hepatitis virus associated liver cancer: pathogenesis and immunotherapeutic strategies

Franco Buonaguro, Istituto Naz. Tumori - IRCCS "Fondazione Pascale", Napoli - Italy; Clorinda Annunziata, Istituto Naz Tumori - IRCCS "Fondazione Pascale", Napoli - Italy; **Luigi Buonaguro**, Istituto Naz Tumori - IRCCS "Fondazione Pascale", Napoli - Italy & Inst of Human Virology, Univ of Maryland, Baltimore, MD - USA; **Maria Lina Tornesello**, Istituto Naz Tumori - IRCCS "Fondazione Pascale", Napoli - Italy

Abstract not available

F-105

Site-Specific Metastasis Revisited

Isaac Witz, Tel Aviv University, IHV, University of Maryland School of Medicine

The fact that metastasis is site specific is known for almost 150 years but ignored by many cancer researchers and clinicians. The interactions between cancer cells and the microenvironment of future metastatic sites are significant players in the metastatic cascade but many cellular and molecular determinants leading to site-specific metastasis await discovery. Elucidating the mechanisms underlying organ specificity of metastasis is of prime importance not only in basic cancer research but mainly in precision (personalized) medicine. Circulating tumor cells disseminate to future metastatic sites. Interactions with the microenvi]ronent of these sites may lead to the formation of dormant micrometastasis. The micrometastases remain in a state of dormancy until ‘‘awakened’’ to progress towards overt metastases. The mechanisms that maintain dormancy of disseminated tumor cells in a certain metastatic microenvironment and those that awaken the dormant micrometastases, driving their progression towards frank metastasis, are still obscure. It is clear, however, that the metastatic microenvironment plays a major role in these events. Three topics will be discussed in this presentation: 1. Indications that the same type of microenvironmental cells in different organs may display a different molecular profile and that metastases originating from a single tumor that develop in different organ microenvironments may express different characteristics. 2.Cancer cells hijack physiological mechanisms operating in a particular organ to form and sustain metastasis in that organ.3. Interactions between metastatic cells with the metastatic microenvironment may be bidirectional i.e. promote or antagonize metastasis formation. Here we will report on a novel microenvironment-derived anti metastasis factor.

F-106

Transition State Gp120 Structures as HIV Vaccines

Anthony DeVico, PhD, Institute of Human Virology; **Timothy Fouts**, Profectus Biosciences, Inc., Baltimore, MD 21224; **Jennifer Schwartz**, Profectus Biosciences, Inc., Baltimore, MD 21224; **Bruce Gilliam**, Institute of Human Virology, University of Maryland School of Medicine, University of Maryland, Baltimore, Baltimore, Maryland, 21201; **Robert Redfield**, Institute of Human Virology, University of Maryland School of Medicine, University of Maryland, Baltimore, Baltimore, Maryland, 21201; **Robert Gallo**, Institute of Human Virology, University of Maryland School of Medicine, University of Maryland, Baltimore, Baltimore, Maryland, 21201; **George Lewis,** Institute of Human Virology, University of Maryland School of Medicine, University of Maryland, Baltimore, Baltimore, Maryland, 21201 Protective efficacy from an HIV vaccine will heavily depend on anti-envelope antibodies that block the entry and spread of diverse viral strains. Thus, an HIV vaccine will have to generate humoral responses that selectively recognize highly conserved and functional epitopes. Accordingly, we have been developing HIV vaccine strategies based on observations that very highly conserved epitopes are presented on HIV gp120 as it transitions through different structural states during viral entry. Here we will cover the virological basis for this approach; describe an immunogen (FLSC) designed to mimic transition state gp120 structures; discuss how the immunogenicity of FLSC is linked with humoral effector functions, protective efficacy and virion recognition; describe our progress in the clinical manufacture of FLSC; and outline immediate plans for Phase I clinical testing.

F-107

Adjuvant dependant RAS activation and mucosal envelope antibody to V2 correlate with reduced risk of Sivmac251 acquisition

Genoveffa Franchini, National Cancer Institute, Bethesda

A Canarypox/gp120/alum vaccine decreased the risk of HIV acquisition in humans. We demonstrate here the efficacy of this vaccine regimen in the SIVmac251 macaque model when we used alum but not MF59 adjuvant. We analyzed innate and adaptive cells responses, antibody Fc profiles and glycoforms and found that alum elicited envelope-dependent mucosal NKp44+ Innate Lymphoid Cells producing IL-17, and V2 peptide-specific IgG antibodies, associated with vaccine efficacy. In contrast, MF59 induced mucosal V2 peptide-specific IgG that associated with increased risk of infection. Alum modulated the expression of 12 genes, seven of which are part of the RAS pathway, which correlated with vaccine efficacy, and in turn that were associated with innate responses and adaptive mucosal antibody responses to V2. Thus, activation of the RAS pathway, preservation of mucosal integrity and mucosal antibody to V2, in concert, reduce the risk of SIVmac251 acquisition.

F-108

The role of a dual pre- and post- entry innate and adaptive immune mechanism in protection against HIV-1 infection

Yufei Wang, King's College London; **Trevor Whittal,** King's College London; Stuart Neil, King's College London; **Gary Britton**, King's College London; **Durdana Rahman**, King's College London; **Mukesh Mistry,** King's College London; **Supachai Rerks-Ngarm**, Department of Disease control, Nonthaburi, Thailand.; **Punnee Pitisuttithum**, Mahidol University, Thailand; **Jaranit Kaewkungwal**, Mahidol University, Thailand; **Sorachai Nitayaphan,** Armed Forces Research Unit, Thailand; **Nelson Michael,** Walter Reed Army Institute of Research, Maryland, USA; **Merlin Robb**, US Military Research Programme, USA; **Jerome Kim**, Walter Reed Army Institute of Research, Maryland, USA; **Thomas Lehner,** Kings College London

The aim of this study was to examine the paradigm that a dual innate pre- and post-entry inhibition of HIV-1 may have been involved in the protective mechanism of the systemic Thai RV144, as observed in the London mucosal HIV-1 vaccine trial. In the Thai trial plasma MIP-1β was significantly upregulated within 2 weeks after the last immunization, followed by a decrease in CCR5 coreceptors of HIV-1, which inhibits entry of the virus into CD4+ T cells. APOBEC3G (A3G) and Tetherin mRNA in PBMC and A3G protein in CD4 CD45RO+ memory T cells were also upregulated. It is likely that these molecules were elicited by cellular stress of the RV144 vaccine, demonstrated by having induced HSP70, whilst the mucosal vaccine consists of an HIV-HSP70 conjugate. In both trials the mechanism involved pre-entry inhibition of transmission of the virus by the decreased availability of CCR5. Replication of any virus which gained entry into CD4+ T cells will have been inhibited by an increase in intracellular HIV-1 restriction factors. Importantly, the 3 CC chemokines showed significant direct correlation with the A3G restriction factor. In the Thai trial there was also a significant direct correlation between the vaccine induced innate CCR5 and the adaptive CD4+ T cell proliferative responses to HSP70. Furthermore, the dual innate immune mechanism was also found in alloimmunized women and in long-term non-progressors, suggesting that it may constitute a general protective mechanism against HIV-1 infection. This innate mechanism of pre-and post-entry inhibition of HIV-1 may contribute to the critical eclipse period and to subsequent adaptive immunity, which maintains H!V-1 inhibition.

F-109

Antigenicity of the Human Immunodeficiency Virus Envelope on Virions in Solution by Fluorescence Correlation Spectroscopy

Krishanu Ray, University of Maryland School of Medicine; **Meron Mengistu,** Institute of Human Virology, University of Maryland School of Medicine; **Joseph Lakowicz**, University of Maryland School of Medicine; **George Lewis,** Institute of Human Virology, University of Maryland School of Medicine; **Anthony DeVico**, Institute of Human Virology, University of Maryland School of Medicine, 725 West Lombard St, Baltimore, MD 21201

The envelope glycoproteins on HIV particles are structurally heterogeneous, making it difficult to equate antigenicity with neutralization sensitivity. Efforts to address this question typically employ immobilized reagents and indirect measures of antibody interactions, which can produce inexact antigenicity profiles. Towards this, we applied a single molecule based approach using fluorescence correlation spectroscopy (FCS) that uses fluctuations in fluorescent signals to measure diffusion and reaction kinetics of fluorescently-labeled anti-envelope monoclonal antibodies (MAbs) as they attach to virions. Our method allows monitoring antibody-virion binding interaction with all reactants continuously in solution. FCS binding profiles of anti-envelope antibodies were determined using different virus types. Anti-gp120 MAbs against the 2G12 or b12 epitopes marking functional envelope structures potently neutralized CCR5-tropic JRFL and BaL pseudotyped viruses and exhibited efficient virion binding in solution. MAbs against various CD4-induced (CD4i) epitopes considered hidden on functional envelope structures exhibited limited binding to these pseudoviruses and were not neutralizing. Anti-gp41 MAb 2F5 neutralized both pseudoviruses despite limited virion binding. Overall our experimental data suggest that virion antigenicity in solution is not the only factor that might determine neutralization sensitivity. A variety of mechanisms may converge to produce the overall neutralizing profile of a given HIV variant, depending on variables such as envelope genotype, coreceptor tropism, and virus production method.

G-101

Special Lecture: The T cell receptor is a mechanosensor

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The abTCR was recently revealed to function as a mechanoreceptor. That is, it leverages mechanical energy generated during immune surveillance and at the immunological synapse to drive biochemical signaling following ligation by a specific foreign peptide-MHC complex (pMHC). I shall review the specialized structural adaptations that optimize this transmembrane receptor for mechanotransduction including 1) the CbFG loop region positioned between Vb and Cb domains that allosterically gates both dynamic TCR-pMHC bond formation and lifetime; 2) the rigid super b-sheet amalgams of heterodimeric CD3eg as well as CD3ed ectodomain components of the αβTCR complex; 3) the abTCR subunit connecting peptides (CP) linking the extracellular and transmembrane (TM) segments, particularly the oxidized CxxC motif in each CD3 heterodimeric subunit that facilitates force transfer through the TM segments and surrounding lipid, impacting cytoplasmic tail conformation; and 4) quaternary changes in the abTCR complex that accompany pMHC ligation under load. How bioforces foster specific abTCR-based pMHC discrimination and why dynamic bond formation is a primary basis for kinetic proofreading are discussed with emphasis on pathogen and tumor recognition. Finally, I will review data showing that the preTCR complex employs a similar mechanobiology to that of the abTCR to interact with self-pMHC ligands, impacting early thymic repertoire selection prior to the CD4+CD8+ double positive thymocyte stage of development.

G-102

Modulating Env conformation: a new approach to eliminate HIV-1-infected cells

Andrés Finzi, Université de Montréal / CRCHUM

Prevention of HIV-1 transmission and progression likely requires approaches that can specifically eliminate HIV-1-infected cells. There is increasing evidence supporting a role of Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) in controlling HIV-1 transmission and disease progression. However, Env epitopes targeted by antibodies effective at mediating ADCC are poorly exposed on the unliganded HIV-1 envelope glycoprotein (Env) trimer. Indeed, HIV-1 has evolved a sophisticated mechanism to avoid exposure of ADCC-mediating Env epitopes by downregulating CD4 and by limiting the amount of Env at the cell surface. We observed that interaction of Env with the CD4 receptor was required for efficient exposure of ADCC-mediating Env epitopes. In that context, HIV-1-infected cells presenting HIV-1 Env in the CD4-bound conformation on their surface were found to be preferentially targeted by ADCC-mediating antibodies present in sera of HIV-1-infected individuals. We therefore tested the capacity of rationally-designed CD4-mimetic compounds (CD4mc) to promote the CD4-bound conformation of Env and thereby sensitize HIV-1-infected cells to ADCC. We observed that certain CD4mc induce the CD4-bound conformation of Env and thereby sensitize cells infected with primary HIV-1 isolates to ADCC mediated by easy-to-elicit antibodies present in sera from early converters and chronically-infected individuals. Importantly, CD4mc also enhanced recognition and ADCC-mediated elimination of HIV-1-infected cells by antibodies present in breast milk and cervico-vaginal lavages of HIV-1-infected women. Finally, we identified one CD4mc with the capacity to sensitize endogenously-infected ex-vivo-amplified primary CD4 T cells to ADCC mediated by autologous sera and effector cells. By pushing Env into the CD4-bound conformation, CD4mc might represent an alternative and/or complementary approach to currently-available drugs for preventing viral transmission and might be helpful for eradication strategies.

G-103

Use of bnAbs and bnAb-based bispecific antibodies to target HIV-expressing cells in vivo

Richard Koup, Vaccine Research Center, NIAID, NIH

T follicular helper (Tfh) CD4 T cells are located within the germinal centers (GC) of lymph nodes (LN), are a source of residual viral replication during antiretroviral therapy and contribute to the latent reservoir. Broadly neutralizing antibodies (bnAbs) can target HIV-expressing Tfh cells to purge the latent reservoir either alone or as bispecific antibodies that also target CD8 T cells. We tested multiple bnAbs for their ability to detect HIV-infected cells. We also characterized the localization, frequency, and function of CD8 T cells in GCs. In vitro infected CD4 T cells and Tfh from HIV-infected subjects were surface stained with multiple different bnAbs. We analyzed the phenotype, localization and function of CD8 T cells in tonsils and LNs from non-infected and HIV-infected viremic individuals. Polychromatic flow cytometry was used for phenotypic analysis and confocal imaging for spacial localization. In vitro cytolytic activity of sorted CD8 T cell populations was tested in a killing assay using an anti-HIV Env/anti-CD3 bispecific-antibody. CD4bs and glycan V1/2 and V3 directed bnAbs very efficiently stained in vitro infected CD4 T cells and Tfh from HIV-infected subjects. Phenotypic analysis of tonsillar cells revealed a memory population of CD8 T cells expressing a CCR7lowCXCR5high profile compatible with follicular localization, and confocal imaging confirmed the presence of a small population of CD8 T cells within the GC. These GC CD8 T cells were expanded in HIV-infected LNs, and they produced perforin and GzB. GC localized CD8 T cells had the greatest ability to mediate killing of HIV-infected target cells after cross-linking with an anti-HIV Env/anti-CD3 bispecific antibody. BnAbs can detect surface expression of HIV envelope on Tfh in vivo. HIV infection is characterized by accumulation of CD8 T cells within LN follicles. These CD8 T cells are functionally capable of mediating bispecific antibody-mediated killing of HIV-infected CD4 T cells.

G-104

Breaking the species barrier: IgG subclasses in man and macaques

Ying Chan, Dartmouth; **Austin Boesch**, Dartmouth; **Nana Osei-Owusu**, Dartmouth; **Sarah Cocklin,** BIDMC; **Joern Schmitz**, BIDMC; **Margaret Ackerman**, Dartmouth

Antibodies raised in Rhesus Macaques (Macaca mulatta, MM) in many preclinical vaccine studies are often evaluated in vitro for titer, antigen-recognition breadth, and neutralization potency or effector function, and in vivo for potential associations with protection. However, despite reliance on this key animal model in translation of promising candidates for evaluation in first in man studies, little is known about the properties of MM IgG subclasses and how they may compare to human IgG subclasses. We evaluated the binding of MM IgG1, IgG2, IgG3, and IgG4 to human FcγR and their ability to elicit the effector functions of human FcγR-bearing cells, and unlike in humans, find a notable absence of subclasses with relatively silent Fc regions. As inter- and intra-species differences in IgG sequence and function pose potential caveats to the translation of findings in these key animal models, understanding antibody immunobiology in primates may provide value in the design and evaluation of future vaccine candidates.

G-105

Defining protective antibody profiles against HIV utilizing systems serology

Galit Alter, Harvard Medical School

While antibody titers and neutralization are considered the gold-standards for the selection of a successful vaccine, these parameters are often inadequate predictors of protective immunity. Instead, antibodies mediate an array of additional extra-neutralizing Fc-mediated activities. Thus, when neutralization fails to predict protection, additional features of the humoral immune response, including Fc-mediated antibody activity, may participate in protective immunity, necessitating the use of more complex antibody profiling tools for the identification of unanticipated immunological correlates and/or for the downselection of protective vaccine antibody profiles. Thus a comprehensive, multivariate computational approach was developed that profiles relationships between humoral markers, termed Systems Serology, to profile individual vaccine trials. Each vaccine regimen induced a unique humoral “fingerprint”, clustering based on immunogen type/regimen, but also by protective/non-protective outcomes. Deeper interactome analyses, additionally, highlighted mechanistically critical antibody Fc-profiles and relationships that may mark “protective” humoral immune signatures. Moreover, application of this multivariate approach to case-control sample data from the RV144 HIV vaccine trial identified unexpected relationships between correlates of risk, and raises potential mechanistic insights into immune complex composition that may underlie protective immunity to HIV. Collectively, multi-dimensional relational comparisons of humoral fingerprints offers a unique method for the evaluation and design of novel vaccines against pathogens for which the correlates of protection remain elusive.

G-106

The pro- and anti-inflammatory effector functions of IgG

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Immunoglobulin G (IgG) antibodies play an important role in the defense against pathogenic microorganisms but are also responsible for tissue destruction and inflammation during autoimmune diseases such as rheumatoid arthritis and SLE. Paradoxically pooled IgG preparations from thousands of donors (IVIg) are also an efficient treatment to suppress several autoimmune diseases and chronic inflammation. Research over the last years has highlighted the role of the sugar domain attached to the IgG Fc-fragment as a molecular switch, which can enhance or block the pro- and anti-inflammatory effector functions of the antibody molecule. Of note, altered IgG glycosylation patterns, containing low levels of terminal galactose and sialic acid residues, have been associated with active autoimmune disease in RA, SLE, and Crohns disease, for example. As sialylated IgG glycovariants have been suggested to be responsible for the anti-inflammatory activity of IVIg, one possible mechanism of IVIg therapy may be to replenish this active anti-inflammatory and immunomodulatory IgG glycovariant, thereby re-establishing immune homeostasis. The aim of this presentation is to summarize our current knowledge about the molecular and cellular mechanisms involved in the pro- and anti-inflammatory activities of IgG and how we can use novel humanized mouse models to translate the findings obtained in inbred mouse models to the human immune system.

G-107

Enzymatic manipulation of antibody Fc-mediated effector functions

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In order to evade host immune mechanisms, many bacteria secrete immunomodulatory enzymes. Streptococcus pyogenes, one of the most common human pathogens, secretes a large endoglycosidase, EndoS, which removes carbohydrates in a highly specific manner from IgG antibodies. This renders antibodies incapable of eliciting host effector functions through either complement or Fc g receptors, providing the bacteria with a survival advantage. On account of this antibody-specific modifying activity, EndoS is currently being developed as a promising injectable therapeutic for autoimmune diseases that rely on autoantibodies. Additionally, EndoS is a key enzyme used in the chemoenzymatic synthesis of homogenously glycosylated antibodies with tailored Fc g receptor-mediated effector functions. Despite the tremendous utility of this enzyme, the molecular basis of EndoS specificity for, and processing of, IgG antibodies has remained poorly understood. We have recently determined the X-ray crystal structure of EndoS. Based on this structure, we rationally designed chimeric endoglycosidases in which we exchanged the glycosidase domain of EndoS with that of EndoF1 in order to create unique enzymes for customized glycan remodeling on IgG antibodies. This novel glycoprotein engineering strategy for constructing chimeric endoglycosidases that are able to manipulate the glycan composition on IgG antibodies provides new opportunities to engineer antibodies with unique glycan compositions for therapeutic applications.

G-108

Some HIV-1 virions are more equal than others: Mosaics of Envs on individual HIV virions as evaluated with flow virometry

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The ability of HIV to infect cells depends on the “functional” conformation of envelope spike glycoproteins (Env). However, other non-functional Env conformations are also displayed on virions. Determination of whether functional and non-functional forms of Env are co-displayed requires analysis of individual virions. We have applied a recently developed “flow virometry” to probe the conformation of Envs on single virions. Individual HIV virions were captured with 15-nm magnetic nanoparticles (MNPs) decorated with anti-Env antibodies that recognize different epitopes of either the “functional” or non-functional Envs (monomeric, uncleaved gp160, or “stumps”). The MNP-virions complexes were isolated in a magnetic field. Our technology distinguished virions that were homogenous or mosaic with respect to functional and non-functional forms of Env. The majority of virions were not mosaic: if an HIV-1 virion has at least one functional spike, there is a low probability that this virion also carries defective spikes or gp41 stumps. A small fraction of virions was highly mosaic and carried various combinations of Env monomers, uncleaved gp160, stumps, and trimeric Envs. These virions do not contribute to the infection of human lymphoid tissue ex vivo, thus confirming the results of flow virometry. Flow virometry demonstrated that on the majority of virions in an HIV preparation there are either exclusively functional trimeric Envs or predominantly defective Envs. Only a relatively small fraction of virions were mosaic with respect to carrying both functional and nonfunctional Envs. The contribution of this fraction to HIV infection of human tissue is small. This all-or-nothing viral strategy is likely to facilitate HIV evasion of the immune response subverting the focus of humoral responses into the generation of non-neutralizing antibodies at no cost to infectious virions. In general, flow virometry provides new insight in the structure of HIV virions that may be important for the development of anti-HIV-1 vaccines.

G-109

TBK1/IKKε, the non-canonical IκB kinases, promote survival and proliferation of HTLV-1-transformed T cells by maintaining Stat3 activity

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Persistent activation of NF-κB is a prerequisite for development of adult T cell leukemia-lymphoma (ATL) caused by human T cell leukemia virus type 1 (HTLV-1). Tax, the HTLV-1 genome-encoded viral transforming protein, constitutively activates the canonical IκB kinases (IKK). However, the role of the non-canonical IκB kinases, TBK1 and IKKε, in the pathogenesis of HTLV-1-associated leukemia remains unknown. We here show that TBK1/IKKε are crucial pro-survival molecules by maintaining persistent activity of Stat3, while TBK1 also plays an important role in facilitating a full-scale activation of NF-κB. Consistent with this finding, silencing Stat3 by the specific shRNA or by the chemical inhibitor ruxolitinib results in drastic impediment of leukemia cell growth. We further find that in HTLV-1-transformed T cells expressing Tax, TBK1 co-localizes with the canonical IκB kinases in the lipid raft microdomains. The wild type Tax, but not M22, the Tax mutant defective in activating the canonical IKK, promotes the lipid raft translocation of TBK1. This phenomenon correlates with Tax activation of both NF-κB and Stat3. Tax does not interact directly with TBK1/IKKε, and it rather engages a crosstalk between the canonical IKKs and TBK1/IKKε. Our data, therefore, demonstrate a key role of TBK1/IKKε in the survival and proliferation of HTLV-1-transformed T cells and implicate a potential therapy targeting TBK1/IKKε and Stat3 in controlling HTLV-1-mediated oncogenesis.

G-110

Live attenuated rubella vectors stably express SIV Gag and HIV Env proteins in a highly immunogenic vaccine platform

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Live attenuated viruses are among our most potent and durable vaccines. We have adapted the rubella vaccine strain RA27/3 as a live vector to express vaccine inserts such as HIV env, SIV gag, and other viral proteins. The vector combines the antigenicity of HIV with the safety, potency, and durability of Rubella vaccine, which have been demonstrated in millions of children: one dose protects for life against rubella infection. We have greatly expanded the size and range of vaccine inserts that can be accommodated by the vector. Initially, we inked together 2 to 4 discrete gag T cell epitopes in tandem.. Recently, we have expressed the entire SIV Gag P27. Initially, we expressed Env determinants such as the MPER sequence. Currently, we can express the engineered outer domain of gp120 (from Bill Schief) or gp120 core structures (from Leo Stamatatos). These antigens range from 180 to 360 amino acids and are stably expressed for at least 6 passages, after which most inserts are stable. Vector growth and the Immunogenicity of gag inserts was tested in rhesus macaques. Anti-Gag titers increased steadily for 6 weeks after a single dose, and were comparable to SIV infection.. The antibodies persisted for >6 months and declined at the same rate as anti-rubella antibodies, which protect for lilfe. Re-exposure to the vector boosted antibody titers strongly. The T cell response (measured with Barbara Felber) depended on priming with DNA vaccine, followed by a vector boost. This reached levels comparable to the best adeno vectors. Immunogenicity testing is pending for gp120 core structures. Binding antibodies will be teseted by ELISA, and neutralizing activity will be tested agaisnt the same or different HIV isolates. Rhesus macaques are readily infected by rubella vectors, and they are the animal model of choice for SHIV challenge. If the animals develop neutralizing antibodies to Env, they will be tested by SHIV challenge. Rubella vectors can infect monkeys or man. Any signs of protective immunity could be readily translated into human vaccine design.

G-111

DNA prime/subunit boost using SIVE660 based rhFLSC yields 75% efficacy against cross clade SIVmac251 intrarectal challenge

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An effective vaccine for HIV still remains elusive. Our previous studies showed that a protein-based FLSC (a genetic fusion of gp120 and CD4) protected macaques against repeat rectal challenges with SHIV162P3 but efficacy was low. We hypothesized that DNA would provide a superior prime to a subunit boost than subunit alone and that the adjuvants IL-12 and/or LTA1 would improve priming. FLSC delivery regimens were evaluated in a challenge model using SIVsmE543 antigens and a cross clade challenge with SIVmac251. Eight macaques/group were immunized with DNA expressing a gag/pol fusion and FLSC with/without LTA1, IL-12 or LTA1+IL-12 by electroporation on weeks 0, 4 and 8. Booster immunizations of 300 ug of FLSCsmCG7V/alum were given at week 42. Two weeks later, animals were weekly challenged rectally 10 times with SIVmac251. Immune measures were compared using T tests (parametric) or Mann-Whitney Rank Sum Tests (non-parametric). Infection rates were compared using Log Rank tests. The DNA/IL-12 prime regimen provided 75% efficacy compared to the same regimen without IL-12. Efficacy did not correlate with antibody binding or neutralizing titers to Tier 1 SIVmac251 whereas ADCC titers and antibody binding ratios of FcgR3/ FcgR1 correlated with protection, provided T cell responses were low. The DNA/LTA1/IL-12 regimen generated substantially superior CMI responses, but showed no protection. These results suggest that vaccines generating ADCC capable antibodies with high FcgR3/ FcgR1 ratios that evoke minimal T cell responses may be the most protective.

P-A1

Does the gut microbiome affect mucosal immune activation and intrarectal susceptibility to SHIV acquisition in naïve rhesus macaques?

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The role of commensal bacteria in modulating immune activation in the gastrointestinal (GI) tract is largely unknown. As the risk of HIV-acquisition is increased by gut immune activation, we indeed observed that two cohorts of naïve Indian rhesus macaques from two separate sources, which had different rectal immune activation, demonstrated significantly different challenge outcomes in our recent repeated low-dose intrarectal simian-human immunodeficiency virus (SHIV) challenge study. The rectal mucosal immune activation correlated inversely with the number of intrarectal exposures needed for viral infection. To assess whether microbial communities account for this non-pathogen-associated GI immune activation and the susceptibility to SHIV exposure, we examined the gut microbiome by 16S rRNA MiSeq using the fecal samples collected one week before the serial challenges. The preliminary principal component analysis of the gut taxa showed that these two cohorts had different microbial compositions even after more than 5 months of co-housing. A compositional look at gut taxa revealed down-regulation of the ratio of bacteroides to prevotella in the more susceptible cohort, similar to that previously observed in HIV-infected patients. Furthermore, local immune activation might be influenced by specific gut bacteria, such as firmicutes, which were found more abundantly in the resistant cohort, and inversely correlated with the frequency of Ki67+CCR5+CD4+T cells (SHIV target cells) in the rectal mucosa. Detailed analysis and potential confirmatory studies are underway. This study can provide novel insights into the microbiome-host interactions, and thus pave the way for potential strategies to reduce susceptibility to HIV-1 transmission.

P-A2

Towards curtailing HIV latency by combinatorial unblocking viral transcription

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The idea that it may be possible to 'cure' AIDS is beginning to be accepted. Whether that is realistic or a pipe dream remains to be seen. The impediment is HIV latency. Thinking is that (i) if we could wake up the virus and (ii) kill it without allowing it to infect naïve cells, the battle would be won. To our knowledge no sure-fire way of doing either currently exists. Not surprising, different drugs activate silent virus differentially in cell cultures or in patients. HIV latency essentially is transcriptional block – resulting from block of transcriptional initiation due to limiting transcriptional factors (e.g., NFkB); suppression of transcriptional elongation due insufficiency of Tat; epigenetic modification of the viral genome by promoter methylation; or chromatin remodeling by histone acetylation. It makes sense then to target multiple blocks by a combinatorial approach. We have tested this idea in a cell culture model of latency where provirus carries reporter GFP gene and its activation is scored by GFP flow cytometry. We have used (i) prostratin to activate NFkB, (ii) Tat to promote transcript elongation, (iii) Aza CdR to demethylate the viral promoter, and (iv) HDAC inhibitor SAHA to uncondense the chromatin. The results confirm that combination of agents is more effective than single agents. For example, prostratin alone and prostratin plus Tat increased GFP expression by 20 and 100 folds, respectively. Tat alone only minimally activated. Tat being an elongation factor, unless transcription has been initiated, there is nothing to elongate.
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P-A3

Identification of proximal biomarkers of PKC agonist activity in HIV-1 latently infected cells

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A small population of resting memory CD4+ T cells harboring transcriptionally silent, but replication competent human immunodeficiency-1 (HIV-1) proviruses is considered to be the major obstacle for HIV eradication in patients on anti-retroviral therapy (ART). Latent virus reactivation using protein kinase C (PKC) agonists is one approach the field is leveraging to flush HIV from latent reservoirs. Thus, increased understanding of the molecular mechanisms of action of this approach is necessary to inform of biological signaling as well as potential off-target effects associated with PKC agonists. We used an RNA-Seq-based approach to identify genes and pathways modulated following treatment of CD4+ T cells with PKC agonists. Primary human CD4+ T cells were treated with either PMA, Prostatin or Ingenol-3-Angelate for various time periods. At 3h and 24h post-treatment, cells were harvested and RNA-Seq was performed. Treatment with the three PKC agonists induced a time-dependent alteration in host cell gene expression pattern. Bioinformatic analysis revealed high similarity in the genes and pathways altered, with at least 42% of genes showing similar changes in expression between controls and the three compounds tested. Immune response pathways strongly associate with the gene expression changes observed at 3 h post-treatment, while pathways associated with mitochondrial dysfunction and oxidative phosphorylation predominated at 24 h. Quantitative reverse transcriptase PCR (qRT-PCR) validation of a subset of the RNA Seq data confirmed modulation of genes with higher expression levels across the three PKC agonists in HIV-1 latently infected Jurkat cells. Overall, our results could offer new insights into the mechanism of action of PKC agonists in latently infected cells, and therefore inform on eradication strategies for latent HIV.

P-A4

Novel CD4-Based Bi-specific Chimeric Antigen Receptors: Toward a Functional Cure of HIV Infection

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Introduction: Durable control of HIV after cessation of antiretroviral therapy is a much sought-after goal toward a 'functional cure' of infection. We are developing a strategy based on targeted killing of HIV-infected cells by genetically modified T cells; when adoptively transferred back to the infected person, these cells will potentially provide the long-term control of infection needed for a functional cure. Experimental Approach: We designed chimeric antigen receptors (CARs) with extremely high potency and breadth, and devoid of potential undesired activities. The CARs contain novel bi-specific extracellular targeting domains composed of sequences from invariant human proteins, and directed against distinct highly conserved determinants on the HIV Env glycoprotein. The targeting domains consist of human CD4 (extracellular domains 1 and 2) linked to the carbohydrate recognition domain (CRD) of a human C-type lectin, which specifically recognizes the high-mannose glycans on gp120. To test activity, T cells expressing experimental and control CARs were mixed with HIV-infected autologous PMBC; HIV suppression was assessed by measuring p24. Compared to a monospecific CD4 CAR, the bi-specific CD4-CRD CARs exhibited extraordinary potency; very similar patterns were observed with genetically diverse HIV-1 isolates. Importantly, the CRD moiety prevented the CD4 component from acting as an entry receptor and rendering transduced CD8+ T cells susceptible to HIV-1 infection. Conclusion: The minimal immunogenicity predicted for invariant all-human sequences, coupled with likely limits on virus escape imposed by targeting two highly conserved Env determinants, highlight the potential of these CARs toward an HIV functional cure.

P-B1

Prolactinoma in A Transgender Male-To-Female HIV Positive Adult-A Rare Occurrence & A Therapeutic Dilemma

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Pituitary adenoma has been reported in patients treated with estrogen or transsexual male-to-female gender. Estrogen directly stimulates the cells of the lactotroph & this can lead to lactotroph hyperplasia & even prolactinoma. HIV is associated with an increase risk of adenomas such as prolactinoma. A 22-year old HIV transsexual male-to-female presented with breast tenderness & galactorhea. Previously, patient underwent a transgender procedure including breast & buttocks estrogen pellet implant. She took estrogen injections for 2 years. She was taking once a day regime of rilpivirine-emtricitabine-tenofovir. Breast exam revealed milk discharge from the right nipple with bilateral breast tenderness. Serum Prolactin was 1147ng/ml. An MRI of the brain showed 2.5x2.2x2.3cm suprasellar mass. Patient was diagnosed with Pituitary Macroadenoma & was treated with Cabergoline. 3 months later her serum Prolactin level decreased to 96ng/ml. When prolactinoma is diagnosed in a patient with HIV infection & a transgender male-to-female, the question arises is prolactinoma an association of HIV or is secondary to estrogen exposure. Another challenge is when it comes to management of such patient as there have been significant interactions between antiretroviral & prolactinoma treatment drugs. Although there has not been a documented interaction between Cabergoline or & Rilpivirine. Rilpivirine like most other non nucleoside reverse transcriptase inhibitors such as Efavienz is metabolized through CYP isoenzyme system & may increase levels of Cabergoline by decreasing its metabolism leading to toxicity. In patients who have high viral load, it is better to start such patients on Efavienz-based regimens to suppress viral load before switching to Rilpivirine-based regime. In such patients using dopamine agonist can be a real challenge due to drug interactions.

P-B2

Performance of WHO immunological response to predict virological failure in patients with severe versus moderate immunosuppression at antiretroviral therapy initiation

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Objectives: To evaluate sensitivity and specificity of WHO-immunological criteria (CI) to predict virological failure (EV) among patients with severe (who have high incidence of opportunistic infections) versus moderate immunosuppression at ART initiation.Methods: HIV-positive patients naive to ART follow-up between January 2004 and December 2011, at Ambulatory Treatment Center of Brazzaville(CTA), Congo, and Age ≥18years on ART since ≥12month with combination of 2NRTIs plus 1INNTI; Were divided into two groups: G1=severe (CD4 50% drop from CD4 count peak and CD4 cell count lower than baseline. Sensitivity of CI to predict EV was analyzed across level of viral load ≥1000copies/mlResults: We included 329 patients in G1 and 216 in G2. The median values at baseline were: Age: 44years (Inter Quartile Range (IQR):3-50) versus 43years (IQR:37-51), p=0.99; CD4: 104cells/mm3 (IQR: 53-162) versus 264cells/mm3 (IQR 230-303), p< 0.00, prior AIDS illness: 72.9% versus 64.4%, p=0.02. Over the eight-year study period, in 12-month follow-up incidence rate of opportunistic infections was 3 versus 1.2 per 100person-years, p<0.001 and 16.9% versus 16%, p=0.49, 10.3% versus 9%, p=0.42 patients respectively had confirmed virological and immunological failure in G1 and G2 respectively, only 7(2.13%) versus 3patients (1.38%) met both the IC and EV. Performance of CI was: sensitivity: 27.9%(95%CI: 17-40) versus 48%(95%CI:34-67), specificity :88.5%(95%CI:84-92) versus 83.5%(95%CI: 77-89), PPV :38.8%(95%CI:25-54) versus 47%(95%CI:33-62), NPV :82.4 %(95%CI: 78-87) value 84%(95%CI: 78-89) respectively in G1 and G2.Conclusion: Severe immunosuppression at initiation of ART is not associated with the low sensitivity of WHO-immunological criteria. Viral load, reference tools for the diagnosis of failure should be available in resource-constrained settings.

P-B3

Evaluation of an In-house Molecular HIV-1 Test to Assess Mother-to-Child HIV-1 Transmission in Angola (the APEHC Cohort)

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HIV-1 mother-to-child transmission (MTCT) rate in Angola was 25% in 2013. Only 17% of the HIV-1-exposed infants received virological testing within two months of birth. Our aim was to develop and validate a cost-effective and sensitive molecular test for early infant diagnosis (EID) of HIV-1 infection using dried blood spots (DBS) in Angola. The assay is a qualitative nested PCR based on primers targeting the conserved integrase region of HIV-1 subtypes prevailing in Angola (A, C-J) and B subtype. Analytical sensitivity was determined using DBS spiked with serious dilutions of: 1) reference plasmids containing the integrase gene of subtypes A-J in HIV-1 seronegative blood; 2) ACH-2 cells which contain a single copy of HIV-1B provirus per cell. The clinical sensitivity and specificity was evaluated using 100 HIV-1 positive DBS samples and 50 HIV-seronegative DBS samples from healthy volunteers. Overall, 154 DBS samples from HIV-1-exposed infants enrolled in the Angolan PErinatal HIV Cohort (APEHC) from a municipal Hospital in Luanda (HDP) were screened in triplicate, using chelex-based DNA extraction. HIV-1 serology results at 18 months were used as diagnostic reference. The limit of detection of the assay was 3 HIV-1 proviral copies using ACH-2 cells and 2-10 copies, depending on subtype, using reference plasmids. Clinical sensitivity was 95.7%, 14% of the positive results being obtained from patients with HIV-1 RNA less than 20 copies/mL. HIV-1 MTCT rate in the APEHC was 1.9% in 2013 (3 infants infected). HIV-1 infection in infants was detected as early as one month after birth. The cost per test was less than 10€ which compares to 30€ of commercial assays. The high analytical and clinical sensitivities of our test have enabled accurate EID of HIV-1 infection in infants of the APEHC. The low vertical transmission rate within the cohort is consistent with the current high standard of pediatric care provided. The simplicity and cost effectiveness of the assay recommends it for implementation in Angola and other low income countries.

P-B4

Predictors Of Sustained Viral Response To 4-6 Week Duration Therapy With Ledipasvir + Sofosbuvir + Gs-9451 +/- Gs-9669 In Early And Advanced Fibrosis (Nih-Ihv Synergy Trial)

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BACKGROUND: Directly-acting antivirals (DAA) have streamlined the treatment of hepatitis C, however, limited data exists to define minimum duration of therapy. The aim of this study is to further elucidate treatment length and predictive factors of response in early and advanced fibrosis patients treated with combination DAA therapy. METHODS: In this single-center, open label, phase 2a trial, 100 HCV monoinfected participants were sequentially enrolled into three treatment arms. Treatment naive (TN) patients with F0-F2 fibrosis received LDV/SOF+GS-9451 (n=25) or LDV/SOF+GS-9451+GS-9669 (n=25) for 4 weeks. Patients with F3-F4 fibrosis received LDV/SOF+GS-9451 for 6 weeks (n=25 TN & n=25 IFN-Treatment Experienced (TE)). HCV RNA was measured using Roche COBAS Taqman v2.0 assay with a LLOQ of 25 IU/ml. Primary endpoint was sustained virologic response defined as HCV RNA BLLOQ 12 weeks post-treatment (SVR12). Pretreatment serum samples were analyzed for resistance-associated variants (RAV) using the Illumina deep sequencing platform. RESULTS: In the early fibrosis cohort, 10/25 (40%) patients receiving LDV/SOF+GS-9451 achieved SVR12, and 5/25 (20%) receiving LDV/SOF+GS-9451+GS-9669 achieved SVR12, with one patient lost to follow up. Baseline HCV VL >6 million was a predictor of relapse in univariate analysis and no patient with RAVs conferring >20 fold resistance achieved SVR. In the advanced fibrosis cohort, 37/50 (74%) achieved SVR, with no correlates of response on univariate analysis. TN (68%) and TE (80%) patients had no significant difference in response rate. In the TN cohort, two patients were lost to follow up. CONCLUSIONS: In this cohort study, combination DAA treatment resulted in moderate rates of SVR when given for six weeks, but was not effective for four weeks. Patients with high baseline VL and resistance mutants are likely to relapse with 4 week therapy. Larger studies are required to further characterize the biologic correlates in the unique group of responders to short duration therapy.

P-B5

Examining the association of circumcision, sexual behavior and HIV status among men aged 15-59 in Uganda

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Introduction: After a series of studies that revealed the protective effect of male circumcision against HIV infection, WHO/UNAIDS in 2007 recommended the adoption of safe male circumcision as one of the effective strategies in reducing heterosexually acquired HIV. To this effect, in 2010 the Ministry of Health in Uganda developed a circumcision policy, and circumcision was added to the strategy to protect against AIDS. Objective: This research examines the associations among circumcision status, risky sexual behaviors and HIV serostatus among men. Data and methods: This research uses data from the 2011 Uganda AIDS Indicator Survey, focusing on a subsample of 7,969 weighted cases of men age 15-59 who have ever had sex and who have received their HIV test results. Several weighted crude and adjusted logistic regression models were estimated in order to examine the association between circumcision and HIV status among men. Results and discussion: At the multivariate level, the research establishes the independent relationships between circumcision status and risky sexual behaviors, and HIV serostatus. Results show that 28% of men in Uganda have been circumcised. Results from the logistic regression models show that circumcised men are more likely to engage in risky sexual behaviors, while age at circumcision is not significantly associated with these behaviors. Results also show that circumcised men are significantly ($p<0.010$) less likely to be HIV-positive. Because male circumcision does not provide complete protection against HIV infection, WHO, and UNAIDS recommend that the procedure be offered as part of a comprehensive package of HIV prevention services. Although it is not known whether male circumcision reduces transmission of HIV from men to women, male circumcision provides indirect protection for women by reducing their exposure to men who are infected with the virus.

P-B6

Development of a Potency Assay for Full Length Single Chain, a subunit vaccine for HIV

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Antibodies that recognize highly conserved domains on envelope could inhibit HIV infection by direct neutralization or by Fc receptor-dependent effector mechanisms including ADCC. The Full Length Single Chain (FLSC) is a gp120-CD4 D1D2 fusion that stably expresses a highly conserved transition state structure that is exposed on gp120 after it engages CD4, and is antigenically distinct from free gp120 or the trimeric envelope. This transitional structure can be defined by monoclonal antibodies such as N12-i2 that recognize CD4 induced epitopes. We exploited this aspect to develop a potency assay based on the binding of N12-i2 to the FLSC subunit that could be used for in process and release testing during cGMP manufacture as well as to assess long term stability of drug substance and drug product. Antibody responses that competed with N12-i2 correlated with protection in 'proof-of-concept' studies in rhesus macaques that used both the single high dose and multiple low dose SHIV challenge models. Competitive titers to N12-i2 correlated with the dose of FLSC administered in two separate rabbit studies. The first used increasing doses of FLSC formulated in Alum. The second, used varying ratios of FLSC/gp120 also formulated in Alum. In both cases, the competitive titers to N12-i2 also correlated with antibody titers to FLSC but not gp120. Additional experiments were performed to determine the specificity, linearity, LLOQ, reproducibility, etc in order to qualify the assay. Based on these results, binding of CD4i antibody N12-i2 to FLSC was selected to be the principle measure of potency for the FLSC vaccine.

P-B7

Balance of Cellular and Humoral Immunity Determines the Level of Protection by HIV Vaccines in Rhesus Macaque Models of HIV Infection

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A guiding principle for HIV vaccine design has been that cellular and humoral immunity work together to provide the strongest degree of efficacy. However, three efficacy trials of Ad5-vectored HIV vaccines showed no protection. Transmission was increased in two of the trials, suggesting that this vaccine strategy elicited CD4+ T cell responses that provide more targets for infection, attenuating protection or increasing transmission. The degree to which this problem extends to other HIV vaccine candidates is not known. Here, we show that a gp120-CD4 chimeric subunit protein vaccine (full-length single chain (FLSC)) elicits heterologous protection against SHIV or SIV acquisition in three independent rhesus macaque repeated low-dose rectal challenge studies with SHIV162P3 or SIVmac251. Protection against acquisition was observed with multiple formulations and challenges. In each study, protection correlated with antibody dependent cellular cytotoxicity (ADCC) specific for CD4-induced epitopes (CD4i) provided that the concurrent anti-vaccine T cell responses were minimal. Protection was lost in instances where T cell responses were high or when the requisite antibody titers had declined. Our studies suggest that balance between a protective antibody response and antigen-specific T cell activation is the critical element to vaccine-mediated protection against HIV. Achieving and sustaining such a balance, while enhancing antibody durability, is the major challenge for HIV vaccine development, regardless of the immunogen or vaccine formulation.

P-B8

Software dependent differences in HIV-1 drug resistance determination.

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Introduction Software for HIV-1 genotypic drug resistance testing is routinely used to generate clinical drug resistance interpretations. In this study we compare and quantify the differences found in the results obtained with distinct software. Methods A HIV sequencing data of forty five (45) clinical samples belonging to a cohort of treatment-experienced patients was generated and analysed by using ViroSeq (VS) Genotyping Software v3.0.0.32. All (VS) results were compared to the FDA-registered DPM product and to the RUO ViroScore-HIV® system from Advanced Biological Laboratories which include several knowledge databases i.e. Stanford HIVdb v7.0.1 (SD) or the virtual-phenotypic-based interpretative system from Geno2Pheno v3.3 (G2P). Results Overall, G2P was the algorithm which showed fewer interpretations classified as “Resistant” (8.9%, compared to 9.4% with SD and 9.2% with VS) and VS was the one which showed the highest percentage of “Susceptible” interpretations (86.1%, compared to 75.3% with SD and 78.3% with G2P). For 41 of the samples we were able to retrieve resistance interpretations for 19 drugs with all three algorithms, allowing us to compare 779 drug resistance results between algorithms. In 34.1% of the samples, VS reported different resistance interpretations for at least one drug when compared to SD, all of them involving a 1-level lower resistance value (from Resistant [R] to Intermediate [I] or from I to Susceptible [S]). When considering only the interpretations where SD was in agreement with G2P (714), VS reported 1-level lower resistance values for at least one drug in 12.2% of the samples. Of the 26 different results obtained by VS when compared with SD, Etravirine, Rilpivirine and Ritonavir-boosted Saquinavir jointly account for 53.8% of the cases (19.2%, 15.4% and 11.5%, respectively). Conclusions Laboratories performing DR testing should be aware of alternative interpretive systems which could be used to supplement their existing DR reports.

P-B9

TSCQ Study: A randomized, open-label controlled trial of daily trimethoprim-sulfamethoxazole or weekly chloroquine among adults on antiretroviral therapy in Malawi

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Before antiretroviral therapy (ART) became widely available in sub-Saharan Africa, several studies demonstrated that daily trimethoprim-sulfamethoxazole (TS) prophylaxis reduced morbidity and mortality among HIV-infected adults by preventing malaria, respiratory infections and diarrhea. However, the applicability of results to individuals already on ART in sub-Saharan Africa and the relative benefits of malaria prevention compared to antibacterial prophylaxis in terms of long-term outcomes have not been definitively evaluated. In 2012, a randomized controlled, open label, phase III trial of continuing TS prophylaxis compared to discontinuing TS prophylaxis and starting weekly chloroquine (CQ) prophylaxis or simply discontinuing TS prophylaxis was initiated. This study aims to determine if TS continues to benefit HIV-infected Malawian adults after good response to ART. Comparing the use of TS, which prevents both malaria and bacterial infection to CQ, which prevents only malaria, will distinguish the relative impact of each regimen vis-à-vis health outcomes and virological control among adults on ART. The study will recruit a total 1400 HIV-infected adults with nondetectable viral load and CD4 count >250/mm3 from two antiretroviral therapy clinics in Malawi and will follow them until 2018. To date, the cohort has been extremely healthy with a cumulative rate of 6.0 WHO clinical stage 3 and 4 events and deaths per 100 person-years of follow up. The study will have >80% power to detect a 35% reduction in these primary endpoint events in the TS or CQ arms compared to those receiving no prophylaxis. The results of this study will inform HIV management in all malaria-endemic countries.

P-B10

Egyptian Healthcare Workers and Hepatitis C Virus Vaccines

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To date, there is no licensed Hepatitis C Virus (HCV) vaccine and what constitutes a protective immune response or correlate of protection against HCV infection is still vague. The Egyptian case of HCV is unique with a prevalence of ~15% among the general population and ~90 of the isolates belonging to genotype 4. This constitutes a great risk for Egyptian healthcare workers (HCW). The National Liver Institute (NLI) is a teaching hospital that focuses its clinical practice and research on liver diseases with ~1500 employees. The NLI receives ~125,000 outpatient visits and admits ~15,000 patients/year. Over 85 % of the adult patients attending the facility have anti-HCV antibodies, and 65–75% of them are also viremic. HCV spontaneous clearance occurs in 15-50% of infected subjects indicating that natural resistance to chronic infection exists. The mechanisms behind successful HCV clearance suggest the coordination of multiple arms of the immune system, with cell-mediated immunity (CMI) playing a crucial role in this process. We reported an anti-HCV prevalence of 16.6% among the NLI HCW and 72.1% of them were viremic. HCV incidence was 2.04/1000 person-years and incidence was high (4.8%) among needle-stick injury subjects. Interestingly, >25% of these HCW demonstrated strong HCV multi-specific CMI without viremia or seroconversion, suggesting clearance of low HCV infection(s). IL28B. rs12979860 predicted the outcome of HCV infection among these HCW (p0.05). In conclusion, the Egyptian HCW could be ideal subjects for HCV vaccine trials and correlates of protection could be closely monitored among them.

P-B11

Retreatment of HCV GT-1 in Patients Who Failed Previous Short Course Combination DAA Therapy With 12 Weeks of LDV/SOF is Highly Effective

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Introduction: Directly-acting antivirals (DAAs) revolutionized HCV therapy, but retreatment options for patients failing combination DAA therapy remain unstudied. Our aim is to determine if HCV genotype-1 patients who failed short course therapy with 3 or 4 DAAs, including LDV/SOF, can be retreated with 12 weeks of LDV/SOF. Methods: In this single-center, open-label, phase 2a trial, patients with HCV gt-1, early stage (F0-F2) liver fibrosis and previous exposure to combination DAA therapy (LDV/SOF with GS-9451 ± GS-9669) were eligible for treatment with 12 weeks of LDV/SOF. HCV RNA was measured by the Abbott assay, lower level of quantitation (LLOQ) 12 IU/ml. The primary endpoint was HCV viral load (VL) less than LLOQ 12 weeks after end of therapy (SVR12). Deep sequencing of NS5B and NS5A regions was performed at baseline by Illumina next generation sequencing technology. Results: The study enrolled 34 persons; 32 (94%) completed 12 weeks of LDV/SOF. Two patients withdrew consent after Day 0. Participants were predominantly male (82%) and black (82%), mean age 58.9 years, and BMI 27.3 kg/m2. Baseline HCV VL was 1.3 x 106 IU/mL (IQR 5.8x105 – 3.9x106), 76.5% (26/34) were infected with HCV gt 1a, and median Metavir fibrosis stage was 1. Time from relapse to retreatment was 22 weeks (± 8 weeks). SVR12 rates were 91% (31/34; ITT). At baseline, 29/34 patients (85%) had resistance-associated variants (RAVs) consistent with greater than 25 fold resistance in NS5A. Of all patients completing therapy, 1 patient with NS5A RAVs relapsed. Conclusions: For the first time, we demonstrate a high SVR rate following retreatment with DAAs in patients who have previously failed DAA-only therapy.

P-B12

Comparison Of Hpv Genotyping Using Roche Linear Array With Spf10-Deia Lipa 25 Version 1 In Nigerian Women Presenting For Cervical Cancer Screening

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Background: There is need for accurate genotyping of Human Papillomavirus (HPV) infections because persistent infection with High-Risk HPV (hrHPV) is a necessary cause for CIN2+. It is essential therefore to evaluate various genotyping assays that have been developed for this very important endeavor within the context of epidemiological studies of HPV infections in different parts of the world. In this study, we compare HPV genotyping using the SPF10 DEIA LiPA25 version 1 with Roche Linear Array HPV genotyping assays in Nigerian women attending cervical cancer screening program. Methods: One hundred and five women were tested for HPV infection using Roche Linear array HPV genotyping test, a PCR amplification technique on target DNA followed by hybridization using reverse line blot system and SPF10 DEIA genotyping system followed by LiPA25 version 1 genotyping, a 28 oligonucleotide probes that recognize 25 different types tailed with poly (dT) and immobilized as parallel lines onto membrane strips. Results: HPV genotypes were detected in 36% (38/105) of the samples using SPF10 and 23% (24/105) of the samples using linear array. Some 65% (68/105) samples showed absolute agreement between the assays (concordant), 27% (28/105) samples were discordant while 9% (9/105) samples showed correspondence for some but not all genotypes detected on both strips (compatible). Conclusions: There was 65% absolute agreement between the two assays and the SPF10/LiPA assay detected more HPV infections than the linear array.

P-B13

Comparison of two HPV detection and genotyping systems in a Nigerian screening population

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Objectives: To compare the SPF10 system to the GP5+/6+ system for high risk HPV (hrHPV) screening on cervicovaginal samples in Nigeria. Methods: In Karu, a suburban district of Abuja, Nigeria, 400 women were randomized for a self- or hospital-collection after flyer recruitment. A volume of 250ul was used for DNA isolation with the MagNA Pure and 750ul was used for nucliSENS easyMAG isolation. MagNA Pure isolates were tested with the SPF10-PCR-DEIA-LiPA25, version 1 system, a test often used in epidemiological studies. GP5+/6+-PCR-EIA, a clinically validated cervical cancer screening method, followed by Luminex genotyping was performed on the nucliSENS easyMAG isolate. qPCR was done (RNaseP) to assess the level of human DNA. Results: Samples of 298 women (74.5% response), with a mean age of 41.1 (SD 7.8, Range 30-62) years were included. The SPF10 showed 23.8% hrHPV+ versus 10.4% with the GP5+/6+. The SPF10 found 9 (3%) samples positive for HPV genotype 16 or 18 versus 4 (1%) by GP5+/6+. Comparing HPV genotypes identified by both systems, 22/29 (75.9%) had concordant genotypes, with the SPF10 system finding additional (low risk) genotypes. Conclusions: Cervical cancer screening by hrHPV testing seems feasible in Nigeria. Corresponding with previous studies (Hesselink et al., 2008), the level of hrHPV+ found by SPF10 was higher compared to GP5+/6+. HrHPV genotyping with both systems showed good agreement. To assess the clinical relevance of any hrHPV+ result, a follow-up study collecting a colposcopy directed biopsy and a repeat hrHPV test is being performed. Results are expected by September 2015.

P-B14

Methylation as a triage marker in a hHPV+ population in Nigeria

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Objectives: To assess the feasibility of the Precursor-M methylation test as a triage marker on self-collected and hospital-collected samples amongst a hrHPV+ population in a resource limited setting. Methods: A total of 400 women were invited to participate through flyer recruitment in Abuja, Nigeria. After randomization, 200 were asked to self-collect and deposit cervical samples at designated collection points and 200 were invited to the hospital for a hospital-collected sample (HCS). A dry flocked swab was used in both groups. DNA was isolated with the nucliSENS easyMAG, tested with the GP5+/6+-PCR-EIA. A qPCR (RNaseP) to assess the level of DNA was performed. EIA+ samples with a Cq<28 (human genomic DNA concentration >1ng/ul) were tested with the Precursor-M methylation kit. Cut-offs for positivity were applied as described by the test manufacturer. Results: Samples from all 298 responding women (74.5% response) were included. The mean age of the women was 41.1 (sd 7.8, range 30-62). A total of 29 samples were found hrHPV+ by GP5+/6+; 28 (96.6%) contained enough DNA for Precursor-M testing (11 HCS, 17 self-samplers). 28.6% (8/28), including 3 HCS and 5 self-samplers, were methylation positive. Conclusions: The percentage of 28.6% methylation positive samples corresponds with previous findings (De Strooper et al., 2014). In order to assess the feasibility of methylation testing as a triage marker in the detection of high grade CIN lesions in an all-molecular screening setting, a follow-up study collecting a colposcopy directed biopsy will be performed. Results are expected by September 2015.

P-B16

The Burden of Human Papilloma Virus Associated Cancers in Nigeria. 2012-2014

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Background: The Human Papilloma Virus (HPV) is a necessary cause of cervical cancer and is associated with other cancers including vulval, vaginal, anal, penile and oropharyngeal cancers. In this study, we evaluate the burden of HPV associated cancers using data from population based cancer registries (PBCR) in Nigeria. Methods: We obtained data on cancers that are considered to be associated with HPV based on the IARC monograph 100b including cancers of the Cervix (C.53), Vulva (C.51), Vagina (C.52), Anus (C.21), Penis (C.60) and Oropharynx (C.01,C.09,C.10) from PBCR in Abuja (Central Nigeria), Enugu (Eastern Nigeria) and Calabar (South Eastern Nigeria). Previous literature using prevalence data and relative risks suggest that the Population Attributable Fractions (PAFs) for HPV associated cancers in developing countries were Cervical (100%) Vulval and Vaginal (40%), Anal (90%), Oropharynx (12%) in women and, Penile (40%) Anal (90%) Oropharynx (12%) in men Results: Among women, the 3 PBCR reported a total of 2,986 cases of cancer between 2012 and 2014 with 493 HPV associated cancers contributing 16.5% of the total cancers. Of the 493 HPV associated cancers, 430 were cervical cancers, 27 vulva cancers, 20 anal cancers, 8 vaginal cancers and 8 oropharyngeal cancers. Of these 463 (94%) were attributable to HPV infection. The PBCR reported 1,875 cancers in men between 2012 and 2014. Of these, 40 were HPV associated cancers including 22 anal cancers, 16 oropharyngeal cancers and 2 penile cancers constituting (2%) of all cancers in men. Some 23 (57.5%) of the 40 HPV associated cancers were attributable to HPV infection. Conclusion: Cervical and vulva cancers were the most common HPV associated cancers among Nigerian women and anal cancers was the commonest HPV associated cancer in Nigerian men. Our findings suggest that approximately 57.5% of all HPV associated cancers in men and over 90% of all HPV associated cancers in women can be prevented if HPV infection is eliminated.

P-B17

Persistent Human Papillomavirus Infection In A Cohort of Nigerian Women

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Objectives: Persistent infection with high risk HPV is associated with increased risk of cervical cancer. Therefore understanding the predictors of persistence may provide some insights in characterizing infections that may have clinical significance. Methods: From August 2012 to December 2013, we recruited women at our cervical cancer screening clinics in Abuja. Nurses collected ecto-cervical samples for HPV determination which was performed using Roche® Linear Array (for 278 baseline samples) and SPF10 DEIA, LiPA25 version 1 for all other samples. Relative risks were estimated using Poisson regression models with robust error variance. Results: Of the 1020 women enrolled, (aged 18 - 61 years), 727 (71.1%) returned for follow up after mean (SD) 8.6 (4.0) months. Some 42.4% (432/1020) of the participants were HIV positive. Baseline prevalence of any HPV infection was 41.2% (401/973) and of these, 256 women returned for follow-up. Some 62.1% (159/256) remained persistently positive for any HPV. The RR (95%CI, p-value) for an association with prevalent any HPV were 0.99 (0.98 – 0.99, 0.02) for age, 1.23 (1.12 – 1.35, <0.001) for HIV infection, 1.26 (0.97 – 1.63, 0.08) for presence of other STIs, and 1.59 (1.28 – 1.99, <0.001) for abnormal VIA results. The RR (95%CI, p-value) for persistent infection with any HPV were 1.67 (1.39 – 2.01, <0.001) for HIV infection and 2.26 (1.64 – 3.11, <0.001) for abnormal baseline VIA. Conclusions: This preliminary data suggest a high level of persistence of any HPV infection among women with prevalent any HPV infection. Significant predictors of persistence included HIV infection and an abnormal VIA result at baseline. Updated analysis, by HPV genotype, will be available in September.

P-B18

Prevalence of anal high-risk human papillomavirus infections among HIV-positive and HIV-negative men who have sex with men (MSM) in Nigeria.

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Introduction: Prevalence estimates of anal high-risk human papillomavirus (HR-HPV) are needed in sub-Saharan Africa where HIV is endemic. This study evaluated anal HR-HPV in Nigeria among HIV-positive and HIV-negative men who have sex with men (MSM) for future immunization recommendations. Methods: We conducted a cross-sectional study to compare the prevalence of anal HR-HPV infections between 64 HIV-negative and 90 HIV-positive MSM. Multivariate Poisson regression analyses were used to examine demographic and behavioral risk factors associated with any HR-HPV infections. Results: The median age of the 154 participants was 25 years (interquartile range [IQR]: 22-28, range: 16-38) and the median age at initiation of anal sex with another man was 16 years (IQR: 13-18, range: 7-29). The prevalence of anal HR-HPV was higher among HIV-positive than HIV-negative MSM (91.1% vs. 40.6%, p<0.001). In the multivariate analysis, HIV infection (adjusted prevalence ratio [aPR]: 2.02, 95% CI: 1.49-2.72), ten years or more since anal sexual debut (aPR: 1.26, 95% CI: 1.07-1.49), and concurrent relationships with men (aPR: 1.31, 95% CI: 1.04-1.67) were associated with increased anal HR-HPV prevalence. Conclusions: Anal HR-HPV infection is high for young Nigerian MSM and rates are amplified in those co-infected with HIV. Providing universal coverage as well as catch-up immunization for young men may be a more effective prevention strategy in Nigeria.

P-B19

Colorectal Neoplastic Lesions In Hiv-Infected Patients Compared To Non-Hiv-Infected Patients

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Introduction: Non-AIDS defining cancers are the second leading cause of death in HIV-infected individuals, and colorectal cancer is the fourth leading cancer among HIV-infected individuals. The optimal approach to colorectal cancer screening in HIV-infected individuals is yet to be defined. Methods: We collected clinical data and colonoscopy results on 263 HIV-infected patients matched with 657 non-HIV-infected patients on age, race, and sex to compare the prevalence, type, and location of colorectal neoplastic lesions. Frequency distributions and descriptive statistics were used to characterize the study population. The primary exposure was HIV infection, and the primary outcome was any adenoma or adenocarcinoma. Logistic regression models were used to estimate odds ratios with 95% confidence intervals (CI). Results: HIV-infected patients were less likely to have any adenoma (22% vs. 27.9%, p=.04), tubular adenomas >10 mm (0.4% vs. 2.9%, p=.02), and serrated adenomas (0.0% vs.2.6%, p=<.01). There was no difference in the prevalence of adenocarcinoma in HIV-infected patients compared to non-HIV-infected individuals (1.5% vs. 0.8%, p=0.29). The lower risk of any adenoma remained after controlling for age, sex, smoking status, body mass index (BMI), and diabetes mellitus [adjusted odds ratio (aOR), 0.61; 95% (CI), 0.43-0.88]. When stratified by diabetes mellitus, HIV-infected patients without diabetes mellitus had the lowest risk (aOR, 0.47; CI, 0.31-0.71). Conclusions: HIV-infected patients had a lower prevalence of colorectal neoplastic lesions, including high risk adenomas, than non-HIV-infected patients. Earlier screening for colorectal cancer is not indicated in this population.

P-B20

Evaluation of the feasibility of incorporating HPV DNA-based cervical cancer screening into routine antenatal care in Nigeria: A qualitative study

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Introduction: Persistent high-risk HPV infection is a necessary cause of cervical cancer. HPV DNA testing is now the primary WHO recommended approach to cervical cancer screening. Cervical cancer screening uptake remains abysmally low in Nigeria and in other low and middle income countries (LMIC). Antenatal care-based HPV DNA testing is a largely unexplored strategy to increase uptake of cervical cancer screening in LMIC. Up to 70% of women in Africa attend ANC at least once during their pregnancy and many attend at least twice. We evaluated the acceptability of HPV DNA testing as part of routine antenatal care among pregnant women and healthcare workers in Nigeria. Methodology: We conducted focus group discussions (FGD) among pregnant women and Key Informant Interviews among healthcare providers at a hospital facility in Abuja, Nigeria. A total of 24 muslim and christian pregnant women were invited for the focus groups and each group comprised of 6-10 participants. Obstetric/Gynaecologists (O&G) and ANC nurses were interviewed. We used content analysis method for data analysis. Coding sheets were developed to summarize findings. Results: Our study showed fair level of knowledge and awareness of cervical cancer and cervical cancer screening among the pregnant women, however, practice was poor, as none of the women had ever been screened for cervical cancer. Lack of awareness about cervical cancer screening, costs, and fear of screening outcome were commonly cited as barriers to uptake. The nurses interviewed expressed reservations about the willingness of pregnant women to participate in screening but there was a high level of willingness among the pregnant women to be screened during the ANC period. Their religion and parity played no role in determining the acceptance of HPV DNA testing in ANC. The O&G specialists expressed full support for integrating HPV DNA testing into routine ANC services. Conclusion: Our results show the need to explore more innovative public health interventions to reduce cervical cancer burden in LMIC.

P-B21

Validation of HPV genotyping at the African Collaborative Centre of Microbiome and Genomics Research, Institute of Human Virology Nigeria

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Establishment of molecular diagnostics for research requires high quality laboratory practices and validation of research methods by established laboratories. Amongst the objectives of the NIH funded H3Africa project at the African Collaborative Center for Microbiome and Genomics Research (ACCME), IHVN, Nigeria is molecular epidemiology of HPV infection. Methods: Staff from ACCME-IHVN were trained in HPV genotyping technology using the SPF10 PCR-DEIA-LiPA25, version 1 at the DDL Diagnostic Laboratory, Netherlands after which participants enrolled in the ACCME study of persistent HPV infection and cervical cancer in Nigeria were tested. Accuracy of results was ensured by sharing with collaborators at DDL for review before certification. A quality control panel of 18 positive samples and 10 negative samples were selected from a pool of 90 samples tested in Abuja were sent to DDL for re-testing.Results: The kappa statistic for agreement between detection of HPV genotypes by SPF10 DEiA in both laboratories was 0.85, (p <0.001), 95% CI (0.66, 1.05). All HPV negative sample results were concordant between both laboratories. Of the 18 samples used in the HPV Positive QC panel, 16 (88.8%) showed concordance of HPV genotypes, 1 (5.6%) showed compatibility for some but not all genotypes and 1 (5.6%) sample had discordant genotypes in both laboratories. Two of the 18 HPV positive samples in Nigeria tested negative at DDL. Of these 2, one was found positive for HPV 66 while the second sample had multiple HPV 45,53,70. Neither sample was genotyped for HPV at DDL. Of the 16 concordant HPV positive samples on DEIA, one sample was genotyped as type 52 in Nigeria but HPV X in Netherlands, while a second sample was genotyped as 40 in Nigeria but 40 and 58 in the Netherlands. Significance:The capacity of African scientists to conduct high throughput scientific research can be enhanced through training but also requires long term mentoring by international collaborating laboratories.

P-B22

Recurrence of Cervical Intraepithelial Lesions after Thermo-coagulation in HIV-positive and HIV-negative Nigerian Women

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Background The burden of cervical cancer remains huge globally, more so in sub-Saharan Africa. Effectiveness of screening, rates of recurrence following treatment and factors driving these in Africans have not been sufficiently studied. The purpose of this study therefore was to investigate factors associated with recurrence of cervical intraepithelial lesions following Thermo-coagulation in HIV-positive and HIV-negative Nigerian women using Visual Inspection with Acetic Acid (VIA) or Lugol's Iodine (VILI) for diagnosis. Methods A retrospective cohort study was conducted, recruiting participants from the cervical cancer "see and treat" program of IHVN. Data from 6 sites collected over a 4-year period was used. Inclusion criteria were: age ≥18years, baseline HIV status known, VIA or VILI positive and thermo-coagulation done. Logistic regression was performed to examine the proportion of women who returned for their scheduled follow-up, those with recurrence and factors associated with recurrence. Student's t-test was used to compare continuous variables between HIV-positive and HIV-negative women while Fisher's exact test was performed for categorical variables. Results Out of 177 women included in study, 67.8% (120/177) were HIV-positive and 32.2% (57/177) were HIV-negative. Recurrence occurred in 16.4% (29/177) of participants; this was 18.3% (22/120) in HIV-positive women compared to 12.3% (7/57) in HIV-negative women but this difference was not statistically significant (p-value 0.31). Women aged ≥30 years were much less likely to develop recurrence, adjusted OR = 0.34 (95% CI = 0.13, 0.92). Among HIV-positive women, CD4 count <200cells/mm3 was associated with recurrence, adjusted OR = 5.47 (95%CI = 1.24, 24.18). Conclusion Recurrence of VIA or VILI positive lesions after Thermo-coagulation occurs in a significant proportion of women. HIV-positive women with low CD4 counts are at increased risk of recurrent lesions and may be related to immunosuppression.

P-B23

Prevalence of Ebola viral entry resistance in a diverse population

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Whole-genome sequencing (WGS) is fast evolving into a population genetics tool to estimate effect of sequence variants on human health and fitness. However, predicting the role of variants that confer protection remains challenging. Given this, we hypothesized that use of large population datasets and integrative-omics data could be used to delineate the role of protective variants in specific genes involved in Ebola viral pathogenesis. As a pilot study we performed trio-based WGS on 3,060 ethnically diverse individuals derived from a study in which infants (and both parents) undergo WGS, as well as other 'omic analyses, at birth, and are then followed prospectively. Variants in genes (e.g. NPC1, CTSB, VPS11, VPS33A, etc.) known to play key roles in Ebola viral entry into human cells were evaluated for overall variant burden and loss-of-function via protein truncation. An additional gene (NPC2) with overlapping biochemical role but no clear role in Ebola viral entry pathway was used as control. Additionally, RNASeq was performed on a subset of individuals. We screened WGS data for variants with predicted large functional effects in the gene set. We identified 69 novel variants (not in dbSNP v.144), of which 7 were missense and 4 protein truncating in NPC1 in heterozygous state, compared to 3 rare missense variants in control gene NPC2. Furthermore, we identified heterozygous protein truncating mutations in genes within the Ebola viral entry pathway (eg. CTSB=7; VPS11=3; VPS41=3) compared to only 1 heterozygous variant in NPC1. Based on NPC1 variation spectrum in our cohort, and corresponding to results from previous biological models, we predicted that 0.11- 0.37 % of our diverse population would have resistance to Ebola virus. RNASeq analysis of heterozygous NPC1 truncation variants showed skew in the allelic-distribution. We conclude that whole genome and transcriptome data can serve as a tool for predictive analysis of viral susceptibility and resistance.

P-B24

Factors Associated With Attrition In a Prospective Cohort Study In Nigeria

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Prospective studies with a high proportion of attrition can suffer from selection bias. It is important to assess factors associated with attrition and reasons for study drop out, as results may help in study design. We designed a prospective cohort study to evaluate epidemiological, host and HPV-viral factors associated with cervical pre-cancer. We recruited 1020 women in Nigeria and followed them over a median period of 14.4 months with scheduled clinic visits at 6 and 12 months. Women with at least 2 visits during the study period were considered responders. We conducted exit phone interviews for non-responders and compared demographic, lifestyle, reproductive and sexual characteristics of responders and non-responders using logistic regression and explored the reasons for attrition. Of the 1020 women enrolled, 717 (70%) returned for at least one follow up visit. Of the sociodemographic characteristics evaluated (age, marital status, length of time at residence, educational level, religion and socioeconomic status), only age was significantly associated with attrition, with older women being less likely to drop out than younger women (OR: 0.96, CI: 0.94-0.98, p <0.001). Of the lifestyle risk factors evaluated (smoking, alcohol consumption, exercise frequency, presence of other chronic ailments, personal perception of health status and HIV status), HIV infection was statistically associated with attrition, with HIV positive women being less likely to drop out than HIV negative women (OR: 0.46, CI: 0.34, 0.62, p <0.001). The main reasons for study drop out were inability to be reached (39%, 118/303) appointment no show (34%, 103/303), ineligibility during study period (16%, 47/303) and voluntary withdrawal (11%, 33/303). Inability to reach participants was the commonest reason for study drop out. Future prospective cohort study designs in a developing country like Nigeria, need to account for this in sample size considerations and plan to reduce this by collecting adequate tracking information at recruitment.

P-B25

Influence of Spirituality and Modesty on Acceptance of Self Sampling for Cervical Cancer Screening

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Introduction: Whereas systematic screening programs have reduced the incidence of cervical cancer in developed countries, the incidence remains high in developing countries. Among several barriers to uptake of cervical cancer screening, the roles of religious and cultural factors such as modesty have been poorly studied. Knowledge about these factors is important because of the potential to overcome them using strategies such as self-collection of cervico-vaginal samples. In this study we evaluate the influence of spirituality and modesty on the acceptance of self-sampling for cervical cancer screening. Methodology: We enrolled 600 participants in Nigeria between August and October 2014 and collected information on spirituality and modesty using two scales. We used principal component analysis to extract scores for spirituality and modesty and logistic regression models to evaluate the association between spirituality, modesty and preference for self-sampling. All analyses were performed using STATA 12 (). Results: Some 581 (97%) women had complete data for analysis. Most (69%) were married, 50% were Christian and 44% were from the south western part of Nigeria. Overall, 19% (110/581) of the women preferred self-sampling to being sampled by a health care provider. Adjusting for age and socioeconomic status, spirituality, religious affiliation and geographic location were significantly associated with preference for self-sampling, while modesty was not significantly associated. The multivariable OR (95% CI, p-value) for association with self-sampling were 0.88 (0.78 – 0.99, 0.03) for spirituality, 1.69 (1.09 – 2.64, 0.02) for religious affiliation and 0.96 (0.86 – 1.08, 0.51) for modesty. Conclusion: Our results show the importance of taking cultural and religious beliefs and practices into consideration in planning health interventions like cervical cancer screening. To succeed, public health interventions and the education to promote it must be related to the target population and its preferences.

P-B26

Changes in Plasma BLyS Levels in Patients with HCV Mixed Cryoglobulinemic Vasculitis during Treatment with Rituximab

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Background: Mixed Cryoglobulinemic Vasculitis (MC) is a known complication of chronic hepatitis C virus (HCV) infection, characterized by monoclonal expansion of IgM secreting B cells. B-lymphocyte Stimulator (BLyS), a member of the tumor-necrosis-factor super family of ligands, is an essential in vivo regulator of B cell homeostasis. High levels of BLyS have been observed in several autoimmune B cell mediated diseases. In this study, we evaluated plasma BLyS levels in patients with HCV-MC before, during, and after treatment with rituximab (RTX) compared with normal volunteers (NV). Methods: We treated patients with HCV-MC with 4 cycles of IV RTX (375mg/m2) and followed for response for an additional year. Plasma samples were tested for the levels of BLyS using ELISA from patients with HCV-MC (N=14) before (day 0), during RTX treatment (month 1, 4), during full recovery (month 8), and from normal volunteers (NV) (N=8). ANOVA was used for statistical comparisons on the levels of BLyS between the different groups. Result: Plasma BLyS levels were elevated among patients with HCV-MC (Mean 1.12 ± 0.4 ng/mL) when compared with NV (Mean 0.67 ± 0.1 ng/mL). Among patients with HCV-MC, plasma BLyS levels increased at one month post treatment with RTX (Mean 3.6 ± 0.6 ng/ml, p=0.03). In patients with HCV-MC, BLyS levels were inversely correlated with B cell counts (r=-0.81, p2ng/mL at month 8 in 4/6 patients who either had a relapse or did not achieve remission. Conclusion: BLyS levels are elevated in patients with B cell autoimmunity, such as HCV-MC. In patients with HCV-MC, persistently high levels of BLyS were observed in those who relapsed following RTX, thus suggesting a pathogenic role for BLyS in HCV-MC. These results provide a rationale for targeting BLyS, along with B cell depletion therapies, as a novel approach for the management of HCV-MC.

P-B27

Targeting the binding interface on a shared receptor subunit of a cytokine family enables the inhibition of multiple member-cytokines with selectable target spectrum

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The common gamma molecule (γc) is a shared signaling receptor subunit used by six γc-cytokines. These cytokines play crucial roles in the differentiation of mature immune system and are involved in many human diseases. Moreover, recent studies suggest that multiple γc-cytokines (IL-2, -4, -7, -9. -15, and -21) are pathogenically involved in a single disease, thus making the shared γc-molecule as a logical target for therapeutic intervention. However, the current therapeutic strategies seem to lack options to treat such cases, partly because of the lack of appropriate neutralizing antibodies recognizing the γc, and more importantly because of the inherent and practical limitations in the use of monoclonal antibodies. For example, combinatorial use of monoclonal antibodies (mAb) for clinical use becomes prohibitingly expensive. Moreover, a mixture of cytokines would be only marginally inhibitable by mAb against one of the mixtures (the experimenal demonstration will be shown in the presentation) so such inhibition targeting only one of the factors by mAb may generate a misleading conclusion that the relevant factor is not causing the disease. By targeting the binding interface of the γc and cytokines, we successfully designed peptides that can not only inhibit multiple γc-cytokines but with selectable target spectrum. Notably, the lead-peptide inhibited three γc-cytokines (IL-2, 15, and -9) without affecting other cytokines. Structural and mutational analyses of our peptide provide new insights to the current understanding on the binding geometry of γc-cytokines the γc-molecule. Furthermore, our peptide, when conjugated to polyethylene glycol to gain stability in vivo, efficiently block the action of IL-2 and IL-15 in multiple animal models. Collectively, our technology can be expandable to target various combinations of γc-cytokines and thereby provide a novel strategy to improve current anti-cytokine therapies against necrotizing diseases, including HAM/TSP, an HTLV-1 caused myelopathy as the primary target.

P-B28

Dichotomous Effects of Immune based (Interferon-alpha) and Non-immune based (direct acting antiviral) Therapies on Lipid Biosynthesis

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Chronic hepatitis C (HCV) infection is associated with dyslipidemia. Neither the underlying mechanisms nor the impact of treatment are understood. HCV is now treated with interferon (IFN)-free, direct acting antiviral (DAA)-only therapy. Here, we delineate the effects of IFN-based and IFN-free DAA therapy on lipid profiles in chronic HCV patients. Veterans cured with IFN-containing therapy between 2011 and 2013 at the Baltimore VA Medical Center were identified. Baseline, end of treatment (EOT), and 1-year post-EOT total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) values were analyzed. Baseline, 8 weeks post EOT and 1 year post EOT lipids were also evaluated among patients cured with DAA-only therapy (6 weeks of ledipasvir/sofosbuvir+GS9451 or GS9669). Changes in mean were analyzed with the paired t-test. Lipids for 29 veterans were analyzed. Mean LDL decreased on treatment by 10.7% (baseline 110.4 to EOT 98.6 mg/dl, p=0.089), followed by a significant 18% increase from EOT to 1 year (116.4 mg/dl, p=0.0058). Mean HDL did not change from baseline to EOT; however, from EOT to 1 year it increased significantly (36.4 to 41.7 mg/dl, 14.6%, p=0.032) to a level not different from baseline (p=0.1). In contrast, among those treated with DAA-only therapy (28 patients) LDL increased significantly from baseline to 8 weeks post-EOT (85.9 to 102.1 mg/dl, 19%, p=0.018), decreasing by 1 year (92.7 mg/dl, P=0.076) to a level not significantly different from baseline (P=0.34). Pre and post treatment lipids differed between patients treated with IFN and those treated without. These findings suggest that direct interruption of viral replication with DAA therapy is associated with an increase in LDL and the decrease in LDL with IFN-based therapy is IFN-related. In both scenarios, treatment-associated changes do not appear to be sustained long term.

P-B29

Barriers to Cervical Cancer Screening Among Nigerian Women

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Introduction: Uptake into cervical cancer screening programs in developing countries is poor. We explored prevailing beliefs and attitudes towards cervical cancer among two religious groups in Nigeria. Methods: We conducted four focus group discussions (FGDs) among Muslim and Christian women. Discussions were conducted in 2 hospitals, one in the South West and the other in the North Central region of Nigeria. Data analysis was done using a combination of deductive and inductive processes using Atlas.ti version 7.5. Results were obtained using the query tools and Boolean operators to interrogate the codes. Results: Most participants in the FGDs had heard about cervical cancer except Muslim women in the South Western Nigeria focus group who had never heard about cervical cancer. Participants believed that wizardry, multiple sexual partners and inserting herbs into the vagina cause cervical cancer. Only one participant knew about the Human Papillomavirus. Among the Christian women, majority of respondents had heard about cervical cancer screening and believed that it could be used to prevent cervical cancer. Participants mentioned religious and cultural obligations of modesty, gender of healthcare providers, fear of disclosure of results, fear of nosocomial infections, lack of awareness, discrimination at hospitals and need for spousal approval as barriers to uptake of screening. These barriers varied by religion across the geographical regions. Conclusions: Barriers to cervical cancer screening vary by religious affiliations. Interventions to increase cervical cancer awareness and screening uptake in multi-cultural and multi-religious communities need to take into consideration the varying cultural and religious beliefs in order to design and implement effective intervention programs.

P-B30

Association Between Hiv And Persistent Hpv Infections Among Nigerian Women

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Background: Cervical cancer incidence has remained stable in HIV+ women but the prevalence, persistence and multiplicity of HPV infection appears different comparing HIV+ to HIV- women. We examined the association between HIV, prevalent and persistent HPV infections among women in a prospective cohort in Nigeria. Methods: Women were recruited from cervical cancer screening programs in Abuja, Nigeria between 2012 and 2014, data on demographic characteristics, risk factors of HPV infection and samples of cervical exfoliated cells were collected at baseline, 6 and 12 months follow-up visits. DNA enzyme immunoassay (DEIA) and Roche Linear Array HPV Genotyping Test® were used to characterize HPV. Persistent HPV infection was defined as positive results on 2 consecutive DEIA tests. Logistic regression models were used to estimate the association between HIV and the risk of HPV infections. Results: Among the 1020 women enrolled, the mean age (±SD) was 37(8), 44% and 56% were HIV+ and HIV-, respectively. The prevalence of any HPV infection was 53% (58% among HIV+; 42% among HIV-, p-value <0.001); the prevalence of persistent HPV infection was 17% (78% among HIV+; 22% among HIV-, p-value <0.001). The multivariate relative risk and 95% confidence interval (95 % CI) was 3.22 (95% CI: 2.40 - 4.32, p-value <0.001) for any HPV infection and 5.52 (95% CI: 3.61 - 8.44, p-value <0.001) for persistent HPV infection, comparing HIV+ to HIV- women, adjusted for variables that reached statistical significance in univariate analyses: age, age at sexual initiation, number of lifetime sexual partners, marital status and level of education. Conclusions: HIV infection is associated with increased risk of any HPV and persistent HPV infections. Previously, we reported that the most prevalent high risk HPV types were HPV35 (8.7%) and HPV56 (7.4%) among HIV+ women, and HPV52 and HPV68 (2.8%, each) among HIV- women, from a subset of this population. We will present the results of the specific HPV types in the entire study population, at the forthcoming conference.

P-B31

Cohort Profile: African Collaborative Center For Microbiome And Genomics Research (ACCME) Study

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Background: Cervical cancer is the second commonest cancer in Africa. Much remains unknown about the prevalence and pathogenicity of human papilloma virus (HPV) types, mechanism of disease and there is a need for new biomarkers for screening programs. Methods: ACCME is a multicenter prospective cohort study of host germline, somatic and HPV genomics and epigenomics, and vaginal microenvironment; and their association with cervical cancer in 10,000 HIV negative women in Nigeria. Data on demography, lifestyle, medical history, serum, germline DNA, HPV genotype and vaginal pH are collected at baseline and during follow-up visits every 6 months. Samples of exfoliated cervical cells are analyzed for high-risk HPV with Roche LINEAR ARRAY® and vaginal bacterial composition and abundance are characterized by deep sequencing of barcoded 16S rRNA gene fragments (V4) on Illumina MiSeq platform. Colposcopy and biopsy are conducted on participants with clinical lesions and those with persistent high risk HPV infections Results: By July 2015, ~8500 participants had been enrolled unto the cohort. The mean (SD) age of the study participants at baseline was 40 (10) years. Most of the participants were married (76%), attended university (44%) and had professional jobs (37%). All the study participants have had vaginal sex, 17% have had oral sex and only 2% have ever had anal sex. We found 30% of the study participants were HPV positive and 70% were HPV negative. The mean (SD) vaginal pH in the study population was 5.2 (0.5). Further analyses to characterize high-risk HPV types and determine persistence are ongoing. Also, characterization of cervical cytokines and vaginal microbiome are underway. Conclusions: ACCME is a paradigm for translational research in biomarker discovery that addresses high impact public health challenges affecting women's health in Africa and the rest of the world.

P-B32

cGMP production, characterization, and formulation of IHV01 drug product, the Full Length Single Chain gp120-CD4 (FLSC) chimera formulated in Aluminum Phosphate

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The FLSC vaccine is fusion protein consisting of a modified full length gp120 protein, derived from HIVBaL, and the first two domains (D1D2) of human CD4, genetically fused via a 20 amino acid linker. Experiments in Rhesus macaques demonstrated protection using HEK 293 cell produced rhesus FLSC. A master cell bank expressing human FLSC was prepared from G293H, a derivative of HEK-293 cell that grows in suspension, using the GPEx® retrovector transduction system. Tumorgenicity studies performed in athymic nude mice demonstrated that the FLSC MCB generated tumors at the same rate as the HEK-293 cell line available from ATCC. Bioreactor production rates were consistent from the 2L to the 200L scale, yielding approximately 1 gms/liter after downstream purification. Drug substance was predominately monomeric, and expressed the expected CD4 induced structure. A drug product formulation with aluminum phosphate was developed. Potency studies demonstrated a significant relationship between the dose of the FLSC/Alum (IHV01) and the induction of the desired CD4i directed immune response. Immunogenicity studies performed in rhesus macaques showed that the FLSC/Alum formulation induced antibodies directed to CD4i epitopes and mediated ADCC activity while T cell responses were modest. A repeat-dose (N+1) toxicity study in rabbits demonstrated that the majority of the effects observed were attributed to general inflammation occurring with intramuscular vaccine administration and/or an active immune response towards the antigen. An immunotoxicity study in cynomolgus monkeys showed no deleterious autoimmune effects directed to CD4. A phase 1 clinical trial with IHV01 is anticipated to start in September, 2015.

P-B33

HPV Persistence and Age-Specific Type Distribution Among Nigerian Women

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Background: Different trends have been reported on the age prevalence of HPV in Africa. The results of some studies showed there was a high peak of HPV prevalence among younger women, which decreased with age, but among older women the prevalence either decreased, reached a plateau or increased. There is scare data on the relation between persistent HPV infection and age. Methods: Women presenting at cervical cancer screening programs in Abuja, Nigeria between 2012 and 2014 were enrolled, data on demographic characteristics, risk factors of HPV infection and samples of cervical exfoliated cells were collected at baseline, 6 and 12 months follow-up visits. DNA enzyme immunoassay (DEIA) and Roche Linear Array HPV Genotyping Test® were used to characterize HPV. Persistent HPV infection was defined as positive results on 2 consecutive DEIA tests. We used logistic regression models to estimate the association between HIV and the risk of HPV infections. Results: We enrolled 1020 women, their mean(SD) age was 37(8), the prevalence of any HPV and persistent HPV was 53% and 17%, respectively. The women were dichotomized into age groups, young: 18 – 35 (42%) and older: > 35 years (58%). The prevalence of any HPV infection was 47% among the young women and 53% among the older women, p-value = 0.004. The prevalence of persistent HPV infection was 44% among the young women and 56% among the older women, p-value = 0.67. The multivariate odds ratio (OR) and 95% confidence interval (95 % CI) among the young women was 1.30 (95% CI: 0.85 - 1.16, p-value 0.06) for any HPV infection and 0.84 (95% CI: 0.58 - 1.21, p-value 0.35) for persistent HPV infection, compared to older women. Conclusion: These results suggest that the pattern of HPV persistence among young and older women is not different. We will present the results on type specific HPV infection stratified by age, at the upcoming meeting.

P-B34

Postural tachycardia syndrome (POTS) after Varicella Zoster virus infection (chicken pox): a case report

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Introduction Postural tachycardia syndrome (POTS) is one of the most common manifestations of orthostatic intolerance (1). The current criteria for diagnosing POTS is an increase in heart rate of 30 beats/min or more within 10 mins. of standing or head up tilt test in the absence of orthostatic hypotension, the heart rate is usually 120 beats/min or higher (2). There are symptoms of associated sympathetic hyperactivity and cerebral hypoperfusion. The symptoms include light headedness, blurred vision, cognitive difficulties, generalized weakness, palpitations, chest pain and tremulousness. To the best of our knowledge this is the first reported case of POTS occurring after an episode of chicken pox Case presentation A 26 year old Indian man complained of history of fall during micturition – 2 episodes within a span of 2 weeks. The episodes occurred at night. There was no history of loss of consciousness associated with these episodes. Prior to the fall patient had history of extreme fatigue, mental confusion and difficulty in concentration. Patient also had complaints of palpitations and tremulousness. He had no history of headache. History of any sweating disturbances was absent. There was no history of smoking or history of alcohol intake. History of exercise intolerance was also present. He also complains of discomfort on exposure to cold. There was no significant history of similar complaints in the family. The patient was apparently normal before these symptoms began shortly after an episode of chicken pox for which the patient was hospitalized. The patient received treatment for a day and was later discharged. He received oral antivirals. Since then the patient started noticing that the symptoms were gradually progressing. Patient had experienced the first episode of fall recently. Patient also has a past history of tuberculosis detected after lympahadenopathy. He has received complete course of anti tubercular treatment commonly referred to as DOTS regimen in India. Conclusion Look for recent viral infections in POTS

P-B35

Design of a broadly neutralizing human rhinovirus antigen

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The 150+ serotypes of Human rhinoviruses (HRV) cause the majority of the common colds. Although the disease is relatively mild for most of those infected, infection with HRV can exacerbate asthma and COPD and result in hospitalizations or death. Infection with one serotype stimulates serotype-restricted humoral immunity that is thought to protect from re-infection at neutralization titers as low as 1:2. However, little, if any, cross-serotype immunity is developed and the individual is open to infection by any of the other serotypes.
Using a multi-pronged approach that included analysis of escape mutants, evolution in experimentally infected humans, studies of divergent sequences, and analysis of structural data, we designed a series of antigenic variants using our Immune Refocusing Technology (IRT). Five IRT mutants, each having amino acid substitutions in one epitope only, were reverse engineered into recombinant HRV16 and into baculovirus-expressed HRV39 VLPs. As expected, rabbits immunized with unmodified HRV16 or HRV39 antigens developed neutralizing antibodies restricted to the parental antigen. However, sera from rabbits immunized with the IRT antigens cross-neutralized numerous serotypes. The leading candidate, 39M5, stimulated antibodies that neutralized 40 of the 61 serotypes tested. The data demonstrate the power of the Immune Refocusing Technology in the design of broadly protective antigens and encourage the further development of HRV IRT antigens as vaccine candidates.

P-C1

Full Length Single Chain, A Novel gp120-CD4 Fusion HIV Subunit Vaccine, Does Not Cause a Deleterious Autoimmune CD4 Response in Cynomolgus Macaques

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Full length single chain (FLSC) is a novel HIV vaccine that presents conserved CD4i epitopes on HIV envelope. The constrained structure is achieved with single chain complexes of gp120 and CD4 fragments. FLSC elicits cross-reactive antibodies and heterologous protection against SHIV/SIV in three independent low-dose rectal challenge studies in rhesus macaques and is being developed as a subunit vaccine for clinical evaluation. We performed preclinical immunotoxicology studies to assess potential safety issues specifically derived from a deleterious autoimmune response to CD4. Two studies were performed in cynomolgus macaques. The presence of deleterious antibody responses to CD4 were assessed by ELISA, CD4+ cell staining, as well as impact to a mixed lymphocyte reaction (MLR). CD4+ T cell loss and impact to the immune response to KLH were also assessed. In study 1, we verified that depletion of CD4+ cells impacted the induction of primary and secondary KLH-specific IgG and IgM antibody responses, justifying the use of the antibody response to KLH as an indicator of an autoimmune response to CD4. In study 2, immunization with multiple high doses of FLSC did not induce an autoimmune response to CD4 that had any deleterious effects in any assays that were employed. Little to no impact was seen on CD4 binding/function by flow cytometry and MLRs. Therefore, FLSC did not induce any deleterious autoimmune responses to CD4 and continues to be a promising vaccine candidate for evaluation in a Phase I clinical trial.
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P-C2

T-cell Based Lentiviral Vaccines

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The failure to elicit high (>80%) protective immunity in recent human and animal trials may be due to the inclusion of vaccine epitopes that enhance lentiviral infection. Therefore, 3 unique approaches were utilized in the selection and delivery of T-cell based vaccine epitopes. First, cytotoxic T lymphocyte (CTL)-associated epitopes conserved among lentiviruses: FIV, HIV-1 and SIV were analyzed for T-cell proliferation, cytokine and CTL-associated cytotoxin production, and viral enhancement. Second, selected epitopes from p24, MA, RT and Env were evaluated for reactivity to human (HLA) and feline (FLA) leukocyte antigen supertypes common in the general population of both humans and cats. Evaluation of FLA binding pockets in the cat model have demonstrated considerable similarity to those of HLA supertypes A3, B27, B44, A24, B7, A2, and A1 (EpiVax Inc). Third, lentivirally-conserved (LC) epitopes identified from p24 and RT peptides were constructed into multi-antigenic peptides (MAPs), and tested in the FIV-cat model. In a pilot vaccine study, MAP constructs of 4 FIV epitopes (2-p24, 2-RT) conferred complete protection in 1 cat with delayed infection in 2 cats (vaccine group, n=4), whereas all 4 challenge-control cats were unprotected. Notably, the non-LC epitope and its MAP construct enhanced FIV infection, whereas the MAP consisting of overlapping epitopes had an overall inhibitory activity. Selected LC epitopes from p24, MA, RT and Env induced robust CTL and polyfunctional T-cell activity in humans and cats. An expanded study including 9 LC epitopes is ongoing (n=18). Current results underscore the need for careful selection of protective epitopes and targeted exclusion of enhancing epitopes for any vaccine design.

P-C3

Targeting the Epitopes in the C1-C2 Region of HIV-1 gp120 for Effective Fc-mediated Effector Function

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Accumulating evidence indicates a role for Fc receptor (FcR)-mediated effector functions of antibodies, including antibody-dependent cell-mediated cytotoxicity (ADCC), in prevention of HIV-1 acquisition and in post-infection control of viremia. Consequently, an understanding of the molecular basis for Env epitopes that constitute effective ADCC targets is of fundamental interest for humoral anti-HIV-1 immunity and for HIV-1 vaccine design. A substantial portion of FcR-effector function of potentially protective anti-HIV-1 antibodies is directed toward non-neutralizing, transitional, CD4-induceable (CD4i) epitopes associated with the gp41 reactive region of gp120 (Cluster A epitopes). Our previous studies defined two highly conserved epitope sub-groups within the Cluster A region; the A32-like epitope which maps to the mobile layers 1 and 2 within C1-C2 regions of gp120 and a hybrid A32-C11-like epitope which maps to elements of both the A32-like sub-region and the 7 layered β-sheet of the gp41-interactive region of gp120. Here we elucidate the structural basis for antigen engagement into an effective immune-complex that leads to potent ADCC function to the Cluster A region. We also present the structure based design of an independent inner domain molecule, ID, an immunogen candidate stably expressing the Cluster A epitopes involved in potent FcR-effector function to HIV-1 within a minimal structural unit of gp120.

P-C4

Targeted Sequencing of Broadly Neutralizing Anti-HIV Envelope Antibodies Directly from Plasma

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Current methods to study broadly neutralizing anti-HIV envelope monoclonal antibodies are based on methods that isolate and screen B cells ex-vivo based on antiviral function or antigen binding. Although antibodies recovered in this manner are obviously valuable, whether they contribute to the circulating plasma neutralizing activity in the source subject must be inferred by indirect methods. Importantly, it is unclear if such antibodies would exist and function in a milieu of poorly neutralizing and/or non-neutralizing anti-envelope antibodies of various specificities; the type of diversity that might arise during HIV infection or vaccination. Existing antibody isolation methods have limited capacity to address such issues, in part because there is discordance between circulating anti-envelope antibody specificities and the memory B cell pool. To address these issues, we focused on chronically HIV-infected subjects we previously reported to have concurrent poorly neutralizing and very broadly neutralizing (> 75% Tier 2 tested) plasma antibodies. To identify the broadly neutralizing moiety, we developed a novel methodology based on affinity purification and isoelectric focusing to purify anti-gp120 antibodies; amino acid sequencing of the recovered immunoglobulin; and the generation of a subject-matched genetic database of immunoglobulin sequences from memory B cells and/or plasma cells. Using a targeted algorithm, gaps in amino acid sequences are reconciled with genetic information in order to create constructs that produce whole immunoglobulin. In this manner, we have uniquely recapitulated a series of potent anti-gp120 antibodies directly representing the broadly neutralizing activity circulating in the plasma of an HIV-infected person. Characterizations of antibody specificity are ongoing.

P-D1

Selection and characterization of neutralizing nanobodies from dromedaries immunized with soluble trimeric HIV-1 Env SOSIP proteins

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Selection and characterization of neutralizing nanobodies from dromedaries immunized with soluble trimeric HIV-1 Env SOSIP proteins Kathrin Koch1, U. Wernery2, K. Khazanehdari2, W. Danquah3, F. Koch-Nolte3, Ursula Dietrich1 1Georg-Speyer-Haus, Frankfurt, Germany; 2Central Veterinary Research Laboratory, Dubai, UAE; 3University Clinics Hamburg-Eppendorf, Germany Besides conventional IgGs, camelids produce antibodies devoid of light chains and the CH1 domain. Generally, these VHH or nanobodies show high affinity and specificity for their target antigen. Their small size (15 kDa) and extended CDR3 loops allow penetration into cavities not accessible by conventional Abs. These properties make nanobodies suitable tools for therapeutic and preventive applications. Soluble gp140 SOSIPs from a subtype C consensus Env were generated from the gp160 clones provided by the NIH AIDS Reagent Program. Antigenic integrity was confirmed by Blue Native PAGE, SDS-PAGE and ELISA. Purification of trimeric Env was achieved by size exclusion followed by anion exchange chromatography. Dromedaries were immunized with the subtype C SOSIPs. VHH phage immune libraries were generated and panned against the same antigens. Selected clones were tested in ELISA and neutralization experiments. Sera from immunized dromedaries showed high serum antibody responses by ELISA and neutralized the autologous pseudoviruses in the TZM-bl assay. About 1,000 clones from the biopannings with the VHH phage immune libraries on subtype C SOSIPs were tested by ELISA. Sequence analyses identified 25 distinct VHH families among the positive clones. Eight VHH neutralized the autologous subtype C pseudovirus and 7 of these also neutralized Tier 2 strains from heterologous subtypes. Immunization of dromedaries with subtype C Env constructs resulted in the elicitation of broadly neutralizing VHH nanobodies. The breadth and potency of these antibodies will be further examined with respect to their epitope specificity and neutralization capacities.

P-D2

Microscopic Detection And Localization Of Hiv Gp120 Epitope Exposures On Cell-Bound Virions

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The pathways of protein domain exposure on the HIV surface delimit relationships between infection and humoral immunity and provide an important framework for developing approaches to treat or prevent HIV infection. The gp120 and gp41 components of HIV envelope trimers have been intensely studied in the context of free virions and it is understood how these proteins must experience multiple structural rearrangements during the course of host cell receptor engagement. However, the impact of such changes on the structural features of an intact virion bound to a host cell remains an ongoing, critical question. Previous predictions held that conserved envelope domains operating within cell contact zones encounter a variety of spatial constraints that occlude their exposure and/or immunoreactivity. Although transition state gp120 domains absent on free virions but induced by CD4 binding (CD4i) are predicted to be profoundly occluded on cell-bound HIV, cognate anti-CD4i antibodies reproducibly mediate ADCC against target cells presenting attached virions. Prompted by such discrepancies, we applied confocal and superresolution microscopic techniques to interrogate virions bound to target cells. Surprisingly, these analyses showed that CD4i epitopes on gp120 are visibly exposed and reactive with whole cognate antibodies on bound virion surfaces for a period of hours. These exposure patterns resemble what is observed for constitutively expressed neutralizing epitopes on cell-bound virions. Further, three-dimensional direct STORM showed that CD4i epitopes were unexpectedly exposed distal to the HIV- cell contact interface in a manner readily accessible to circulating antibodies. Such distal exposures of certain CD4i epitopes was abrogated on mutant virions with aberrant matrix structures. Collectively these observations suggest that previously unsuspected structural dynamics emerge on HIV during host cell attachment. Such processes may provide new windows of vulnerability to antiviral countermeasures.

P-D3

Structural Determinants for the Selective Anti-HIV-1 Activity of the All-beta Alternative Conformer of XCL1

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We recently reported that the C-chemokine XCL1/lymphotactin is a conformation-dependent broad-spectrum inhibitor of HIV-1 infection, acting at the level of viral entry via an unconventional mechanism that is mediated by direct interaction with the external envelope glycoprotein, gp120. HIV-1 inhibition by XCL1 requires access to the alternative all-beta conformation, which interacts with glycosaminoglycans (GAG) but not with the specific XCL1 receptor, XCR1. To investigate the structural determinants of the HIV-inhibitory function of XCL1, we performed a detailed structure-function analysis of a stabilized all-beta variant, XCL1 W55D. Individual alanine substitutions of two basic residues within the 40s' loop, K42 and R43, abrogated the ability of XCL1 to bind to the viral envelope and block HIV-1 infection; moreover, a loss of HIV-inhibitory function, albeit less marked, was seen upon individual mutation of three additional basic residues, R18, R35 and K46. In contrast, mutation of K42 to arginine did not cause any loss of function, indicating that the interaction with gp120 is primarily electrostatic in nature. Strikingly, four of these five residues cluster to form a large (~350Å2) positively-charged surface in the all-beta XCL1 conformation, while they are dissociated in the classic chemokine fold, which is inactive against HIV-1, providing a structural basis for the selective antiviral activity of the alternatively-folded XCL1. Furthermore, we observed that changes to the N-terminal domain, which is proximal to the cluster of putative HIV-1 gp120-interacting residues, also affect the antiviral activity of XCL1. Interestingly, the complement of residues involved in HIV-1 blockade is partially overlapping, but distinct from those involved in the GAG-binding function of XCL1. These data identify key structural determinants of anti-HIV activity in XCL1, and may be useful in guiding the rational design of new inhibitors of HIV-1 entry.

P-D4

Tyrosine-Sulfated Peptides from the gp120 V2 Domain Block HIV-1 Entry through CCR5 Mimicry

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We recently identified two sulfated tyrosines, Tys173 and Tys177, in the second variable (V2) region of HIV-1 gp120 and shown that they play a role in stabilizing the pre-fusion conformation of the envelope trimer. The sulfated region of V2 has a high similarity with the N-terminal domain of CCR5, which also contains sulfated tyrosines and interacts with V3-loop base of gp120, suggesting a potential intramolecular interaction mode between V2 and V3. Here, we employed a tyrosine-sulfated V2-derived peptide, pV2alpha-Tys, to investigate binding to gp120 and its functional consequences. A direct interaction was observed between peptide pV2alpha-Tys and the base of V3, with Tys177 playing a dominant role. Surface plasmon resonance showed that binding of the pV2alpha-Tys is enhanced by CD4-induced conformational changes in gp120, and the effect is even more significant with a soluble trimer. Functionally, pV2alpha-Tys inhibits HIV-1 entry and fusion by preventing CCR5 utilization, with a potency comparable to that of a sulfated CCR5 N-terminal peptide, pCCR5-Tys. These studies characterize the structural and functional features of the V2-V3 intramolecular interaction, providing new leads for the design of therapeutic and vaccine strategies for the control of HIV/AIDS.

P-D5

Two Conserved Tyrosines in the HIV-1 Envelope V2 Loop Play a Critical Role in gp120/gp41 Association

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The second variable (V2) loop of the major HIV-1 envelope glycoprotein, gp120, contains two conserved tyrosines (Y173, Y177) that can be post-translationally modified by O-sulfation and mediate intramolecular interaction with the base of the V3 loop, thereby stabilizing the closed, antibody-protected conformation of the envelope trimer (Cimbro et al., Proc. Natl. Acad. Sci. USA 111: 3152, 2014). To further dissect the functional role of the V2 tyrosines, we introduced single or double phenylalanine and alanine substitutions in a prototypic R5 envelope (BaL) and examined the impact of such mutations on HIV-1 infectivity using a pseudotype assay. All the mutants exhibited a loss of infectivity although to varying extent, ranging from a minimal reduction with the single phenylalanine mutant Y173F to an almost complete functional abrogation with the double alanine mutant Y173A/Y177A. Since the V2 tyrosines are involved in stabilizing the intramolecular V2-V3 complex, we hypothesized that the loss of infectious function could be related to decreased trimer stability. Indeed, we found that the functional impairment of the mutants correlated with a reduced stability of gp120/gp41 association, as documented by increased levels of both spontaneous and sCD4-induced gp120 shedding into the supernatants of 293T cells expressing the wild-type or mutated envelopes on their surface membrane. In parallel, as detailed in an accompanying Abstract by Guzzo et al., the V2 mutated envelopes exhibited increasing degrees of neutralization sensitivity, associated with a more open trimer configuration. Likewise, prolonged incubation of the pseudovirus stocks at 4˚C caused a significant further reduction in infectivity, which was correlated with the initial degree of functional impairment of the mutants. These results demonstrate that the V2 tyrosines play an important role in stabilizing the native HIV-1 envelope trimer.

P-D6

Effects of influenza vaccination on lymphoid architecture in HIV+ patients on combination antiretroviral therapy (cART)

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Introduction: Persons with HIV/AIDS have significant morbidity/mortality due to influenza virus and are thus targeted for prevention through immunization. However, despite numerous reports on post-immunization antibody titers, the effects of vaccination on the lymphoid tissue architecture of patients on cART and local virus reactivation have not yet been explored. Methods/Results: Lymph node (LN) -derived cells and tissues from healthy controls and virologically suppressed HIV+ subjects were obtained pre- and post- vaccination and analyzed by polychromatic flow cytometry, multicolour confocal imaging and histocytometry. The effect of influenza vaccination on viral dynamics was determined in sorted LN-CD4 T cell populations by quantifying the de-novo synthesis of early HIV transcripts. Influenza -specific antibody titers were measured by hemagglutination inhibition assay. Tissue structure and follicular organization was notably different between healthy and HIV+ individuals. Flu vaccination differentially affects the lymphoid architecture as well as the frequency of follicular CD4 T cells in these two groups, which may explain previous observations of variable B cell responses to immunization in HIV- infected individuals. Furthermore, vaccination exerted an impact on the actively transcribed virus in follicular CD4 T cell populations. Conclusion: Chronic HIV-infection establishes a fingerprint of lymphoid changes that is irreversible by cART. Our study shows that these changes further perturb the antigenic response towards an important immunogen and set the stage for further mechanistic studies that could elucidate ways to enhance immunogenicity in such high-risk populations.

P-D7

Structural mimicry of the antigen binding modes of rhesus macaque and human anti-gp120 V3 antibodies

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Background: Nonhuman primates (NHPs), such as rhesus macaques, are currently the best preclinical models for studying HIV vaccines. The details of how NHP Abs can mimic human Abs will be useful in evaluating NHP Ab responses to HIV vaccine candidates. The extensive knowledge of the antigen binding modes of anti-V3 Abs allows a structural comparison of NHP and human Ab binding modes. Methods: We have crystallized and determined the epitope complex structures of rhesus macaque anti-V3 monoclonal Abs (mAbs) 2.10A (encoded by a VH5 family gene and derived from an animal infected with SHIV SF162P4) and P2A10 and P2E3 (encoded by VH3 family genes and from an animal infected with SHIV SF162P3N). These structures were compared to the Ab-epitope interactions of human anti-V3 mAbs encoded by the equivalent human genes. Results: Human anti-V3 mAbs preferentially use VH5, VH1 and VH3 family genes with the antigen binding sites resembling either a cradle or ladle, respectively, as previously described. Similarly, rhesus macaque mAb 2.10A utilizes the cradle-binding mode while mAbs P2A10 and P2E3 use the ladle-binding mode. Additionally, the amino acids encoded by both human and macaque VH3 and VH5 family germline genes are critical for shaping the antigen binding sites. Thus, key elements in the antigen-Ab interactions are preserved between human and rhesus macaque mAbs. Conclusion: The antigen binding modes of human and rhesus macaque mAbs targeting HIV-1 gp120 V3 epitopes were found to be structurally extremely similar at the atomic level.

P-D8

Targeting of the catalytic site of host mTOR controls HIV in vivo

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HIV necessitates host factors for successful completion of its life cycle. Mammalian target of rapamycin (mTOR) is a conserved serine/threonine kinase that forms two complexes, mTORC1 and mTORC2. Rapamycin is an allosteric inhibitor of mTOR that selectively inhibits mTORC1. Rapamycin interferes with viral entry of CCR5 (R5)-tropic HIV and with basal transcription of the HIV LTR, potently inhibiting replication of R5 HIV but not CXCR4 (X4)-tropic HIV in primary cells. The newly developed ATP-competitive mTOR kinase inhibitors (TOR-KIs) inhibit both mTORC1 and mTORC2. Using INK128 as a prototype TOR-KI, we demonstrate potent inhibition of both R5 and X4 HIV in primary lymphocytes (EC50 2 log10 units and partially restored CD4/CD8 cell ratios. Targeting of cellular mTOR with INK128 (and perhaps others TOR-KIs) provides a potential strategy to inhibit HIV, especially in patients with drug resistant HIV strains.

P-D9

A Novel Small Molecule Inhibitor of HIV-1 Entry

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Background Anti-retroviral therapy has transformed HIV-1 infection into a managed condition with near normal life expectancy. However, a significant number of patients remain with limited therapeutic options due to HIV-1 resistance, side effects or drug costs. Further, it is likely that current drugs will not retain efficacy, due to risks of side-effects and transmitted resistance. Results We describe compound 5660386 (3-ethyl-2-[3-(1,3,3-trimethyl-1,3-dihydro-2H-indol-2-ylidene)-1-propen-1-yl]-1,3-benzothiazol-3-ium) as a novel inhibitor of HIV-1 entry. Compound 5660386 inhibits HIV-1 entry in cell lines and primary cells, binds to HIV-1 envelope protein and inhibits the interaction of GP120 to CD4. Further, compound 5660386 showed a unique and broad range activity against primary HIV-1 isolates from different subtypes and geographical areas. Conclusions Development of small molecule entry inhibitors of HIV-1 such as 5660386 may lead to novel classes of anti-HIV-1 therapeutics. These inhibitors may be particularly effective against viruses resistant to current anti-retroviral drugs and could have potential applications in both treatment and prevention.

P-D10

Differential Induction of Anti-V3 Crown Antibodies with Cradle and Ladle-Binding Modes in Response to HIV-1 Envelope Vaccination.

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The V3 loop in the HIV-1 envelope glycoprotein gp120 is one of the key targets for neutralizing antibodies (Abs). The V3 crown in particular has conserved structural elements that are targeted by neutralizing Abs. Two Ab-V3 binding modes, designated cradle and ladle, have been identified based on many X-ray crystal structures of human anti-V3 mAbs from HIV-infected patients. Anti-V3 Abs with the cradle-binding mode use mainly the VH5-51 genes, while those with the ladle-binding mode use various VH1-VH4 family genes. However, very little is known about the types of anti-V3 Abs induced by vaccination. In this study, first we examined the V3 Abs induced in human vaccinees in the VAX003 (B/E) and VAX004 (B/B) trials who received bivalent recombinant gp120 protein vaccines. Our data show that the titers of anti-V3 Abs with either cradle or ladle binding modes were relatively low in the sera of these vaccinees, but a higher percentage of responders were observed in VAX004 than VAX003. In both trials, a higher percentage of responders generated Abs using the cradle-binding mode than Abs with the ladle-binding mode. When we compared with other species, like macaques and rabbits, the percentage of animals that produced Abs with the V3 cradle mode were again higher compared to those producing the V3 ladle-mode Abs,regardless of the envelope subtypes used in vaccine. In contrast, BALB/c mice immunized with HIV envelope proteins generated V3 Abs of only the ladle-binding mode and not of cradle binding mode. We further showed that most, but not all, V3 Abs of cradle-binding mode produced in humans, macaques and rabbits mediated virus neutralization. V3 ladle-binding Abs from mice also mediated virus neutralization. Hence, both V3 cradle-binding and ladle-binding Abs can mediate virus neutralization. Altogether, our data demonstrate differences in the fine specificity of V3 Abs generated in humans and animal models upon immunization of HIV envelope.

P-D11

Effect of HIV-1 matrix protein p17 on natural killer cell mediated antibody-dependent cellular cytotoxicity

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HIV-1 matrix protein, p17, can persist in tissues of HIV-infected patients despite effective antiviral therapy. In addition to its role in the virus life cycle, extracellular p17 modulates diverse functions in vitro, including the enhancement of lymphocyte proliferation and cytokine production, chemotaxis of monocytes and B cells, angiogenesis and lymphangiogenesis, suggesting it plays a role in development of HIV-associated malignancies, i.e. lymphoma and Kaposi's sarcoma. Multiple cellular binding partners of p17 have been reported, i.e. heparin sulfate proteoglycans, CXCR1, and CXCR2. In this study, we characterized CXCR1/2 expression and p17-binding ability of human PBMC by flow cytometry to confirm these results and identify other cellular targets of p17. As expected, monocytes expressed CXCR1/2 and bound AlexaFluor430-labeled p17. CXCR1/2 were not detected on B cells cultured under normal conditions, yet the majority of B cells bound labeled p17. In contrast, CXCR1 and CXCR2 were readily detected on CD56+CD3- natural killer (NK) cells, yet only a minority of NK cells bound labeled p17. Stimulation of PBMC with various cytokines did not modify CXCR1/2 expression patterns, with the exception of NK cells. In particular, CXCR2 expression on NK cells was sensitive to IL-4, IL-13, and TNFα. Given that the PI3-kinase signaling pathway downstream of CXCR1/2 overlaps with that of CD16/FcγRIIIA, we hypothesize that p17 can modulate NK cell antibody-dependent cellular cytotoxicity (ADCC). In support, preliminary results suggest that p17 inhibits PI3K/Akt signaling in primary NK cells and inhibits NK cell mediated ADCC. Thus, persistent HIV-1 p17 may contribute to the chronic NK cell dysfunction observed in infected patients.

P-D12

Differential Sensitivity of HIV-1 Isolates to Inhibition by Mannose-Binding Lectins Reveals the Heterogeneity of the Virus Envelope Glycosylation

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HIV envelope is densely coated with 18-33 potential N-linked glycans sites (PNGS), each differing in occupancy and composition affecting immunogenic and antigenic properties of the virus. Little is known about the heterogeneity in composition of these PNGS among different viruses. Using lectins with different oligosaccharide specificities, we studied the heterogeneity of the N-linked glycosylation present on HIV-1 Env. We studied 4 HIV-1 viruses SF162, BaL, JRFL, REJO with PNGS ranging from 25-29. The viruses showed distinct sensitivity to GNA and HHA with median IC50 values ranking as, SF162<BAL<JRFL<REJO implying that these viruses display glycans with different levels/types of mannose residues. When JRFL and REJO viruses were produced in the presence of glycosylation inhibitors kifunensine, swainsonine and 293S GnTI-/- cells, to produce homogenous N-glycans with mainly Man9-, Man9-5 + hybrid, and Man5- core, respectively, both viruses became similarly sensitive to GNA and HHA. To further delineate the mannose composition of these viruses, we used lectins which bind to different branches of Man5-9GlcNAc2 core present on the HIV Env: a) GRFT binds to the terminal manα1-2man arms, b) SV-N binds to the D3 arm, and c) CV-N requires the D1 arm. In comparison to REJO, JRFL was highly sensitive to these lectins, with GRFT being most sensitive followed by CV-N and SV-N. However, viruses produced in the presence of glycosidase inhibitors were similarly sensitive to these lectins. None of the viruses were inhibited by PHA-E and LCA lectins which recognize only galactosylated glycans confirming that HIV has mostly high mannose type glycans. Overall, our data demonstrates that HIV-1 isolates display different sensitivity to lectins due in part to the microheterogeneity of N-linked glycans expressed on the Env of these isolates.

P-D13

Resistance to N-peptide fusion inhibitors: implications for HIV entry

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HIV-1 envelope (Env) mediates both receptor binding and membrane fusion between the virus and host cell. This occurs through a series of conformational changes to both gp120 and gp41 subunits upon receptor binding which sequentially prime the virus for coreceptor interaction, expose and insert the fusion peptide into the target membrane, and drive formation of the 6-helix bundle (6HB) from the N-(HR1) and C-terminal (HR2) gp41 heptad repeats. Peptides corresponding to either heptad repeat region interrupt this process, stalling entry/fusion at an intermediate state. Resistance to N-terminal peptides consistently evolves along two genetic pathways we previously identified, corresponding to a founder mutation in either HR1 or HR2, respectively. Both pathways also include distinct sets of mutations in gp120, suggesting multiple routes of crosstalk between gp41 and gp120. We used structure-based modeling combined with our genetic data to guide site directed mutagenesis of gp120 and gp41 in order to define potential sites of interaction. Mutations were designed to conformationally fix Env and potentially reveal traditionally difficult to isolate fusion intermediates. Mutants are being analyzed for function, biochemical properties, receptor interactions, and antigenic profile as a means to define the conformational state(s) of stabilized Env, and their potential roles within the fusion pathway. The implications of these findings on the mechanism of envelope mediated fusion will be discussed.

P-D14

Modulation of SIV and HIV DNA Vaccine Immunity by Fas-FasL Signaling By Jiabin Yan, Juan Carlos Zapata, Charles David Pauza and Maria S. Salvato (presenting)

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We tested whether modulating the Fas-apoptotic pathway can enhance immune responses to DNA vaccination or lymphocytic choriomeningitis virus (LCMV) infection. Mice were electroporated with plasmids expressing a variety of pro- or anti-apoptotic molecules related to Fas signaling and then either LCMV-infected or injected with plasmid DNA expressing SIV or HIV antigens. Whereas Fas or FasL knockout mice had improved CMI, down-regulation of Fas or FasL by shRNA or antibody failed to improve CMI and was accompanied by increases in regulatory T cells (Treg). Two “adjuvant” plasmids were discovered that significantly enhanced plasmid immunizations. The adjuvant effects of Fas-associated death domain (FADD) and of cellular FLICE-inhibitory protein (cFLIP) were consistently accompanied by increased effector memory T lymphocytes and increased T cell proliferation. This adjuvant effect was also observed when comparing murine infections with LCMV-Armstrong and its persisting variant LCMV-Clone 13. LCMV-Armstrong was cleared in 100% of mice nine days after infection, while LCMV-Clone 13 persisted in all mice. However, half of the mice pre-electroporated with FADD or cFLIP plasmids were able to clear LCMV-Clone 13 by day nine, and, in the case of cFLIP, increased viral clearance was accompanied by higher CMI. Our studies imply that molecules in the Fas pathway affect the apoptosis of cells involved in immunity. (Published in The Viruses, March 2015)

P-D15

Peripheral Blood Lymphocyte HIV DNA Levels Correlate with HIV Associated Neurocognitive Disorders

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Introduction Mononuclear cells play a key role in facilitating the pathogenic mechanisms leading to HIV associated neurocognitive disorders (HAND). We examined the association between levels of HIV DNA within monocytes and lymphocytes and HAND. Method Blood samples were obtained from 40 antiretroviral naïve participants in Nigeria. CD14+ cells and T&B lymphocytes were isolated from peripheral blood mononuclear cells by bead separation (84-98% purity for CD14+ cells). Total HIV DNA was quantified using real-time PCR assay targeting HIV LTR-gag and cell input numbers determined by the number of CCR5 copies/sample. Utilizing a 7-domain neuropsychological test battery and activities of daily living assessment, participants were classified as either unimpaired, having asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), or HIV associated dementia (HAD) in line with the Frascati criteria. Results The mean log10 HIV DNA copies/106 cells were higher for T & B lymphocytes than for CD14+ monocytes (P-value: 0.0002). In a multivariable linear regression adjusting for CD4 count, viral load and lymphocyte count, compared to unimpaired individuals, the mean copy numbers for T & B lymphocytes were higher among those with HAND (P-value: 0.01) and for those with MND (P-value: 0.02 [Tukey adjusted: 0.07]). In a multivariable logistic regression adjusting for same variables, the odds of cognitive impairment was 6.7 times greater per log increase in HIV DNA within T & B lymphocytes (P-value: 0.02). There was no significant association between cognitive impairment and HIV DNA within CD14+ monocytes. Conclusion In this cohort we found a strong association between levels of cell-associated HIV DNA within the lymphocyte subset and HAND. Further studies looking at similar association among patients with suppressed viremia are required for inference on integrated DNA.

P-E1

CD44 and RUNX2: Possible Targets for Prostate Cancer in Bone Microenvironment

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Aditi Gupta and Chellaiah MA Background: Pathological skeletal fractures develop in prostate cancer patients as a result of bone loss induced by androgen deprivation therapy and bone metastases. In this regard, there is a critical need for novel pharmacotherapeutic approaches to control this debilitating disease. The objective of our study is to inhibit the expression and function of RANKL in metastatic prostate cancer cells. Results: We found a significant increase in the expression of CD44, a cell surface receptor in prostate cancer cells derived from human bone metastases (PC3). We find that RUNX2 and Smad 5 are involved in the regulation of expression of RANKL. CD44 and αvβ3 signaling pathways support RANKL expression by phosphorylation of RUNX2 and Smad 5, respectively. RUNX2-Smad 5 complex formation and intranuclear targeting of RUNX2 are functionally required for this process. An inhibitor to integrin alpha v and SiRNA to CD44 attenuated the expression of RANKL in PC3 cells. Small molecular weight peptides to CD44 and RUNX2 have the potential to block localization of RUNX2 in nuclei and RANKL expression/secretion.Conclusions/Future Perspectives: We found that CD44 and RUNX2 peptides have the potential to block RANKL expression and osteoclast differentiation in vitro. A large number of genes are thought to play a role in lymphopoiesis. CD44 and RUNX2 have been implicated in lymphopoiesis through MSCs/T-cells interaction. CD44 is considered a marker for MSCs. There are observations also show that MSCs can promote tumor growth through the release of tumor and vascular growth factors by releasing immunosuppressive reagents. CD44 and RUNX2 might contribute to immune modulation Therefore, finding the immune suppressor/regulatory cells are a vital feature in autoimmune/ cancer metastasis research field. Also, it will be a great breakthrough to identify a potential therapeutic target that plays a key role in the immunomodulation of proteins at tumor microenvironment (Supported by NIH-NIAMS 5 R01 AR066044-02).

P-E2

An Hsc70-binding peptide derived from SV40 Large T antigen is a potent inhibitor of polyomavirus DNA replication

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The Large T Antigen (TAg) of polyomaviruses (PyVs) is a helicase required for viral DNA replication and an oncoprotein that stimulates quiescent cells to reenter a proliferative state conducive to viral DNA synthesis. In doing so, TAg engages in multiple protein-protein interactions with host DNA replication and cell-cycle control machineries. To identify which viral-host interaction might be susceptible to competition by a peptidic inhibitor, we scanned the TAg protein with 50-60 amino acid long overlapping peptides for functional dominant-negative inhibitors in our cell-based assay of SV40 DNA replication. This method identified a potent inhibitory peptide derived from the first exon of TAg which bears high sequence homology with the J-domain of the Hsp40/DNAJ co-chaperone family, and is required for viral DNA replication. Studies have found that the J-domain interacts with Hsc70 and stimulates its ATPase/chaperone activity, to release E2F from pRb-containing complexes bound to TAg to promote viral DNA replication and transformation. Characterization of our J-domain inhibitory peptide (aa 2-64) confirmed that it interacts with Hsc70. Mutagenesis of the HPD motif conserved in all known DnaJ homologues, abolished the interaction of the peptide with Hsc70 and its ability to inhibit SV40 DNA replication. Notably, the overexpression of this J-domain peptide could also inhibit viral DNA replication for the clinically relevant human PyVs JCV, BKV and MCV, whose reactivation in immunocompromised patients is associated with the development of progressive multifocal leukencephalopathy, BK-induced nephropathy, and Merkel Cell Carcinoma respectively. Collectively, these results suggest that the J-domain peptide inhibits viral DNA replication by competing with full length TAg for Hsc70 binding. As such, this peptide represents a promising tool to study the function of Hsc70 in PyV DNA replication and to develop therapies for the treatment of PyV-associated diseases including Merkel Cell Carcinoma caused by MCPyV.

P-E3

Development of a new humanized mouse model to study anti-HTLV-1 immunity

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HTLV-1 is the only known human virus that causes leukemia (adult-T cell leukemia, ATL) , which is a fatal disorder without established treatment at the moment. Thus, the development of a new treatment represents an unmet medical need. In collaboration with the stem-cell transplant group of the Cancer Center of the University of Maryland, we have conducted a longitudinal study of ATL patients who have received allogeneic stem-cell transplant (AlloSCT) and observed that the restoration of competent anti-HTLV-1 T-cell immunity coincided with the suppression of ATL relapse in these patients. On the other hands, the ATL patients in their acute leukemic phase showed almost negligibleanti-HTLV-1 immunity, whereas HTLV-1 infected individuals in their asymptomatic latency phase show detectable immunity against this virus. These observation prompted us to hypothesize that the diminished T-cell immunity against HTLV-1 may underlie the transition from asymptomatic latency to acute leukemic phase. In particular, we observed that the anti-HTLV-1 CD8 T cells in acute ATL patients show signs of severe T-cell exhaustion. So we set a goal to test if reversion of T-cell exhaustion may help restore effective anti-HTLV-1 immunity and thereby allow to control the malignant expansion of HTLV-1+ CD4 cells in vivo. To test this hypothesis, we transferred the leukemic T-cells and non-leukemic lymphocytes from a few patients into severely immune compromised NSG (NOD-SCID/gc knockout) mice and observed the successful expansion of ATL leukemia and non-leukemic T and B cells from patients in these mice. Preliminary results suggest that anti-PD1 intervention augmented the homeostatic expansion of anti-HTLV-1 CD8 T cells in mice and contributed to suppressed proliferation of HTLV-1+ CD4 T cells in these mice. These results collectively suggest that we can develop a new anti-ATL strategy involving the anti-T-cell exhaustion to stop disease progression at the chronic phase, before the fatal acute expansion starts.