

15TH ANNUAL

INTERNATIONAL MEETING

Institute of Human Virology in partnership with
the Global Virus Network and The Moscow
Center for HIV/AIDS Prevention and Treatment

SEPTEMBER 8 – 12, 2013 | MOSCOW

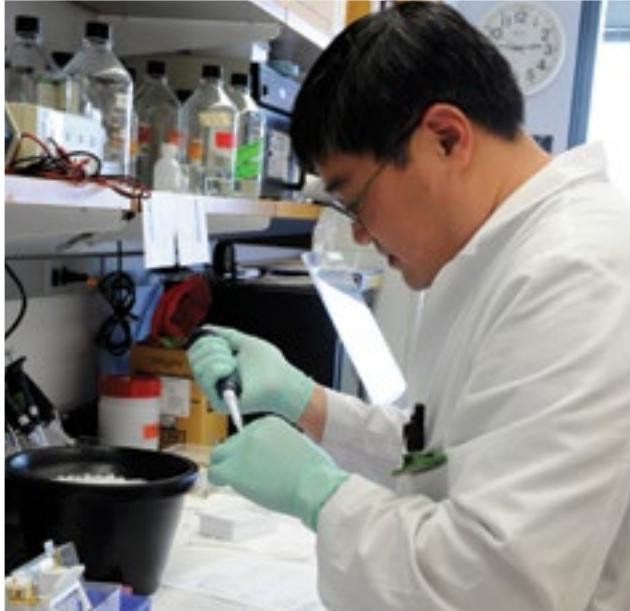


INSTITUTE OF
HUMAN VIROLOGY

IHV is an Institute at the
UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE



GVN
GLOBAL VIRUS NETWORK



INTERNATIONAL MEETING

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Welcome

15th Annual International Meeting of the Institute of Human Virology, in partnership with the Global Virus Network and the Moscow Center for HIV/AIDS Treatment and Prevention

Dear Colleagues and Friends,

The Institute of Human Virology (IHV) at the University of Maryland School of Medicine, the Global Virus Network (GVN), and the Moscow Center for HIV/AIDS Treatment and Prevention welcome you to the Institute's 15th Annual International Meeting. For only the second time in IHV's history, the meeting is convening outside of the Baltimore/Washington DC area. This year we gather in Moscow, a city obviously of deep historical significance and home to stunning architecture, cultural tradition, and the Russian Federation Capitol. Further, uniquely this year, the meeting will include presentations from members of the Global Virus Network, thereby broadening the scope of the meeting. The IHV Annual Meeting has fostered international scientific cooperation since its inception. This year's event recognizes both our commitment to the global fight against HIV/AIDS as well as a focus on several other human viral diseases, and the critical roles played by the scientists, physicians, and public health officials in the Russian Federation. We are pleased to join together for hosting this meeting and believe it will impact the future of research on viral diseases in our countries and throughout our network of collaborating institutions.

This year's open meeting is from Sunday, September 8 through Wednesday, September 12. An outstanding program of Russian and international experts in medical virology will be presented in the Moscow City Meeting Hall. While our major focus continues to be in HIV/AIDS, through the Global Virus Network, we will expand the scope to cover other important human viral diseases including hepatitis, measles, influenza, enterovirus, polio and hemorrhagic fever. For each, we concentrate on the latest developments in antiviral drug treatment or

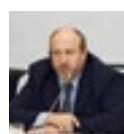
preventive vaccines; we also address the roles for viruses in human cancer, how they cause diseases and how they are spread. Workshops provide practical lessons for managing co-morbidities of HIV/AIDS including hepatitis, cancer, tuberculosis and diabetes. Truly, this meeting combines the best knowledge on diagnosis, treatment and prevention of human viral diseases and will be an important event.

We look forward to you joining us in beautiful Moscow to explore the most recent and important developments in HIV/AIDS research and other viral diseases and to acknowledge the progress and challenges in global health research.

Sincerely,



Robert C. Gallo, MD
Director and Professor
 Institute of Human Virology and
Co-founder & Scientific Director of the
Global Virus Network (GVN)



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



Sharon Hrynkow, PhD
President
 Global Virus Network (GVN)



C. David Pauza, PhD
Associate Director and Professor
 Institute of Human Virology

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HUMAN VIROLOGY**

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UNIVERSITY of MARYLAND
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**GLOBAL VIRUS NETWORK**

Mission Statement

The Institute of Human Virology (IHV) is a world-class center of excellence focusing on chronic viral diseases and virally linked cancers. IHV is dedicated to biomedical research leading to improved treatment and prevention of these diseases.

Our unique structure connects cohesive, multidisciplinary research and clinical programs so that new treatments are streamlined from discovery to patients. IHV is forging local and international programs for research and treatment of human disease.

The IHV is also a Center of Excellence in the Global Virus Network (GVN), and this year's meeting in Moscow will be immediately followed by a shorter GVN meeting. GVN President, Sharon Hrynkow, is the meeting coordinator with Professor Alexey Mazus.

The mission of the Global Virus Network is to strengthen medical research and response to current viral causes of human disease and to prepare against new viral pandemic threats.

The Moscow Center for HIV/AIDS Prevention and Treatment (AIDS Center) of the Moscow Health Department is the main unit of the city service providing HIV prevention and medical treatment services for Moscow citizens living with HIV/AIDS.

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- South African National Institute for Communicable Diseases (NICD), Division of National Health Laboratory Service (NHLs), Janusz Paweska, BVSC, DVSC*, Robert Swanepoel, BVSC, DTVM, PhD

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Moscow Center for HIV/AIDS Prevention and Treatment

The Moscow Center for HIV/AIDS Prevention and Treatment (AIDS Center) of the Moscow Health Department is the main unit of the city service providing HIV prevention and medical treatment services for Moscow citizens living with HIV/AIDS. The center was established based on a department of the Clinical Hospital No. 2 for Infectious Diseases which, since 1985, had started receiving first individuals in the Soviet Union identified as HIV/AIDS positive.

The specialists who provided medical treatment to the first HIV/AIDS positive individuals formed the backbone of the AIDS Center team. Today it employs more than 200 people working in its 7 departments. The AIDS Center receives patients from healthcare institutions who need their HIV-positive diagnosis to be confirmed and be further registered with the Center or those with controversial HIV antibody test results. The Center provides all types of specialist medical treatment to the HIV/AIDS positive people. Patients and their relatives can get consulting, methodological and psychological assistance as well.

The major success of the Center has been the implementation in Moscow medical institutions of a program to reduce the risk of a vertical transmission from an HIV-positive mother to her child during pregnancy and birth. It comes to be of particular relevance today when increasing numbers of HIV-positive women decide to have children. The implementation of special innovative prevention programs has lead to more than a six-fold reduction in the probability of an HIV-positive child birth which is now less than 3 percent.

The Center contributes to scientific research, as well as approves and implements new methods of HIV diagnosis and treatment. The AIDS Center coordinates HIV prevention efforts of all Moscow medical facilities and monitors the quality of HIV laboratory diagnosis in Moscow healthcare institutions.

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The Institute of Human Virology at the University of Maryland School of Medicine is grateful for the assistance provided by our International Organizing Committee

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Communications and Press Policy

To enhance the exchange of information and communication among attendees of the Institute of Human Virology Annual International Meeting, in partnership with the Global Virus Network and Moscow, 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.

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.

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National Institute of Allergy and Infectious Diseases (NIAID)

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Division of AIDS (DAIDS)

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Merck

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Partec

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IHV 2013 Lifetime Achievement Award for Scientific Contributions

Vadim I. Agol, MD, PhD, DSc



Vadim I. Agol is a, if not the, number one polio virologist in the world in terms of the basic science of these viruses. He received an MD diploma cum laude from the 1st Moscow Medical School in 1951 and worked for 5 years at the Karaganda Medical Institute. In 1956 he joined the Institute for Poliomyelitis Research in Moscow (now M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides of the Russian Academy of Medical Sciences) as junior researcher and has been associated with this Institute until now (from 1957 as senior researcher, in 1961-2009 as head of Laboratory of Biochemistry, and now as chief researcher at this lab). He received a PhD in 1954 from the first Moscow Medical School and DSc in 1967 from the USSR Academy of Medical Sciences. In 1963 he participated in the organization of the Department of Virology of the Moscow State University, serving there as Docent and in 1969-2012 as Professor. He also established and continues as head of the Department of Virus/Cell Interactions at the Institute of Physical-Chemical Biology of the same University.

His main scientific interests are focused on diverse aspects of molecular and cellular biology of RNA-containing viruses (primarily picornaviruses) such as non-genetic and genetic interactions (co-discovery of complementation between non-enveloped RNA viruses; first biochemical proof of the

intermolecular recombination between RNA genomes; demonstration of the existence of the non-replicative mechanism of this process), synthesis of viral proteins (first cell-free system for the faithful translation of picornavirus proteins; structural and functional analysis of translational cis-acting element of picornaviral RNAs; discovery and characterization of non-canonical translation initiation factors required for the synthesis of picornaviral proteins; identification of a protease involved in processing of the viral polyprotein; discovery of picornaviral leader proteins; first translational mapping of the flavivirus genome), replication of viral RNA (first evidence for involvement of host proteins in the synthesis of picornavirus RNA; characterization of viral 2C protein involved in the viral replication; functional and structural characterization of replicative cis-elements of the picornavirus genomes), neurovirulence and attenuation of picornaviruses (first mapping of viral phenotypic traits by recombinational analysis; discovery of dependence of attenuation on modulation of viral translation), cellular response to picornaviral infection (discovery of the ability of picornaviruses to trigger and suppress apoptotic response of the cells; discovery of the ability of picornaviruses to permeabilize the nuclear envelope by different mechanisms; demonstration that major picornavirus-induced cellular damages may be caused by interplay between host defense and viral anti-defenses and may be uncoupled from viral reproduction; proposal on the existence of a distinct set of viral proteins, dubbed security proteins, specifically dedicated to the anti-defensive activities), evolution (roles of changes in attenuation determinants, antigenic properties and recombination in the evolution of vaccine polioviruses; molecular epidemiology of poliomyelitis). He actively participated in the world struggle against polio.

Dr. Agol is an (elected) corresponding member of the Russian Academy of Sciences and Russian Academy of Medical Sciences, Honorary Scientist of Russia, recipient of the Triumph prize in biology and medicine, foreign member of the Bulgarian Academy of Sciences, and also received other national and international awards.

Apart from numerous scientific publications, Dr. Agol has published four books of poetry and a book containing an autobiographical novel of his father, well known Soviet geneticist and philosopher Israel Agol, and his own autobiography.

IHV 2013 IHV Lifetime Achievement Award for Public Service

José Esparza, MD, PhD

José Esparza is an internationally recognized expert on HIV/AIDS, vaccine development and global health. His overall mission has been to harness science to address global health problems, focusing on the discovery, development and delivery of vaccines. No one has done more to advance HIV vaccine development.

Since 2004 he has been with the Bill & Melinda Gates Foundation in Seattle, WA first as Senior Advisor on HIV Vaccines and currently as Senior Advisor on Vaccines. In 2012 he was appointed Adjunct Professor of Medicine at the Institute of Human Virology, University of Maryland School of Medicine.

Previously in 1986, he joined the World Health Organization (WHO) in Geneva, Switzerland, to work on viral diseases with epidemic potential. When WHO launched its Global Program on AIDS (GPA) in 1987, Esparza established and led its Biomedical Research Unit. Later he became the Chief of the WHO/GPA Vaccine Development Unit. In 1996 he transitioned to the newly established United Nations Program on HIV/AIDS –UNAIDS (Geneva, Switzerland) as Coordinator of the WHO-UNAIDS HIV Vaccine Initiative. He became a recognized global leader in the field of HIV vaccines.

From 1974 to 1985 he worked in Caracas, Venezuela, at the Venezuelan Institute of Scientific Research – IVIC, at that time, one of the most important research institutions in Latin America. He served as Professor of Virology, Head of the Laboratory of Biology of Viruses and Chairman of the Center of Microbiology and Cell Biology. During this time he published extensively on rotaviruses associated with gastroenteritis.

He is the author of over 175 papers on different aspects of virology, HIV/AIDS and vaccine development. Esparza has served in numerous national and international scientific advisory committees and boards, receiving numerous awards in recognition to his many contributions to global health. He is a member of the National Academy of Medicine of Venezuela and of the Royal Academy of Doctors of Spain.

He received his MD degree in his native country of Venezuela (1968) and a PhD in Virology and Cell Biology from Baylor College of Medicine in Houston, TX (1974).

He currently lives with his wife in Seattle, WA and has a daughter and grandson.



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Previous Recipients of IHV Lifetime Achievement Awards

IHV Lifetime Achievement Award for Scientific Contributions

- 1999 George Klein, Karolinska Institute, Stockholm, Sweden
- 2000 Maurice Hilleman, Merck Research Laboratories, Sumneytown, Pennsylvania
- 2001 Hilary Koprowski, Thomas Jefferson University, Philadelphia, Pennsylvania
- 2002 Alexander Rich, Massachusetts Institute of Technology, Cambridge, Massachusetts
- 2003 Jan Svoboda, Institute of Molecular Genetics, Prague, Czech Republic
- 2004 Paul Zamecnik, Massachusetts General Hospital, Boston, Massachusetts
- 2005 Manfred Eigen, Max Planck Institute, Göttingen, Germany
- 2006 Maxine Singer, National Institutes of Health, Bethesda, Maryland
- 2008 Isaac P. Witz, Tel Aviv University, Tel Aviv, Israel
- 2010 Dr. Rino Rappuoli, Novartis Vaccines in Sienna, Italy
- 2011 Max Essex, Harvard AIDS Institute
- 2012 Thomas A Waldmann, MD, NIH

IHV Lifetime Achievement Award for Public Service

- 2004 Stewart Greenebaum, Greenebaum and Rose Associates, Inc., Baltimore, Maryland
- 2006 Martin Delaney, Project Inform, San Francisco, California
- 2008 John D. Evans, Evans Telecommunication Company and
The Honorable Robert K. Gray, Gray and Company II, Miami, FL
- 2010 Harry Huge, Esq.
- 2011 Bernadine Healy, MD, NIH
- 2011 Yi Zeng, PhD, China CDC

One-Time IHV Lifetime Achievement Award for Excellence in Teaching

- 2010 Michele LaPlaca, Bologna, Italy

IHV Lifetime Achievement Award for Excellence in Medical Education, Clinical Care and Clinical Research

- 2012 John G. Bartlett, MD Johns Hopkins School of Medicine

Program Overview

Sunday, September 8, 2013

9:00 – 10:00	Registration of participants
10:00 – 13:00	Track: Advances in Vaccine Research (I) <i>Conference Hall Sector B+C</i>
13:00 – 14:00	Lunch
14:00 – 17:45	Track: Advances in Vaccine Research (II) <i>Conference Hall Sector B+C</i>

Monday, September 9, 2013

9:00 – 9:30	Registration of participants
10:00 – 12:00	Track: Advances in Antiviral Drug Discovery (I) <i>Grand Conference-Hall</i>
12:00 – 13:00	Lunch
13:00 – 14:00	Official Opening Ceremony of the Conference <i>Grand Conference-Hall</i>
14:00 – 15:00	Public Lecture by Dr. Robert C. Gallo <i>Grand Conference-Hall</i>
15:00 – 16:30	Track: Advances in Antiviral Drug Discovery (II) <i>Grand Conference-Hall</i>
16:30 – 17:00	Presentation of IHV Lifetime Achievement Awards to Vadim I. Agol and José Esparza <i>Grand Conference-Hall</i>
17:00 – 17:30	Lecture in Honor of the Recipients of the IHV Lifetime Achievement Award <i>Grand Conference-Hall</i>
19:30 – 21:00	Awards Gala Banquet <i>Yar Restaurant</i>

Program Overview

Tuesday, September 10, 2013

9:00 – 12:15	Track: Mechanisms of Viral Pathogenesis <i>Conference Hall Sector B+C</i>
12:15 – 13:30	Lunch
13:30 – 17:00	Track: Mechanisms for Virus Transmission <i>Conference Hall Sector B+C</i>
14:00 – 16:00	Public Lectures by John G. Bartlett and Robert R. Redfield <i>Moscow State University of Medicine and Dentistry named after A.I.Evdokimov</i>
16:00 – 17:30	Public Lectures by G. Steven Burrill and Robert C. Gallo <i>I.M. Sechenov First Moscow State Medical University</i>
18:00	Adjourn

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Wednesday, September 11, 2013

9:00 – 12:00

Track: Viruses and Cancer
Conference Hall Sector B+C

12:00 – 14:00

Lunch

14:00 – 18:00

**Track: Clinical Management of Co-Morbidities
in HIV/AIDS**
Conference Hall Sector B+C

19:00 – 21:00

Opening Dinner of the Global Virus Network
Keynote Speaker: G. Steven Burrill
Chairman, Global Virus Network
Russian Academy of Medical Sciences

By Invitation Only:

14:30 – 18:30

GVN Meeting, Conference Hall, Sector T

19:30

Welcome Dinner of the GVN
Keynote Speaker: G. Steven Burrill
Chairman, Global Virus Network
Russian Academy of Medical Sciences

Thursday, September 12, 2013

GVN Meeting (closed) and Moscow International Virology Week Sessions

Speaker Schedule

Sunday, September 8, 2013
Conference-Hall Sector B+C

9:00 - 10:00 Registration

10:00 - 13:00 Advances in Vaccine Research (I)

*Chairs: R.M.Khaitov, member of the Russian Academy of Sciences and Russian Academy of Medical Sciences, M.D., Professor, Director of the National Research Centre Institute of Immunology, Federal Medical and Biological Agency of Russia,
N.A.Malyshev, M.D., Professor, Chief Physician of Clinical Hospital for Infectious Diseases No.1 of the Moscow Health Department, Russia*

KEYNOTE PRESENTATION:

E.V.Karamov, R.M.Khaitov

National Research Centre Institute of Immunology, FMBA of Russia

101 - Biomedical Prevention of HIV/AIDS in Russia (30 min.)

G.O. Gudima

National Research Centre Institute of Immunology, FMBA of Russia

102 - HIV/AIDS Vaccines in Russia: Clinical Trials and Estimation of Acceptance in Population (20 min.)

I.A.Kofiadi

National Research Centre Institute of Immunology, FMBA of Russia

103 - Genetic Factors Defining Resistance and Susceptibility to HIV/AIDS (20 min.)

A.V.Filatov, D.V.Mazurov

National Research Centre Institute of Immunology, FMBA of Russia

104 - Cell-to-cell Transmission of HIV-1: Role of Virological Synapse (15 min.)

11:25 - 11:40 Break

I.A.Nikolaeva

National Research Centre Institute of Immunology, FMBA of Russia

105 - Rationale for HIV/AIDS Vaccines Design (20 min.)

R.I.Attaullakhanov

National Research Centre Institute of Immunology, FMBA of Russia

106 - Enhance Expression of Transgene in Adenovirus (15 min.)

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S.V.Korobova

National Research Centre Institute of Immunology, FMBA of Russia
107 - The Modern Methods of HIV/AIDS Vaccine Evaluation (15 min.)

M.M.Shmarov

Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation
108 - Development of Universal Vaccines against Flu (15 min.)

A.V.Tkachuk

Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation
109 - Genetically Engineered Tuberculosis Subunit Vaccine (15 min.)

13:00 - 14:00 Lunch

14:00 - 17:30 Advances in Vaccine Research (II)

Chairs: A.L.Ginzburg, Vice President of the Russian Academy of Medical Sciences, M.D., Professor, Director of Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation,

A.P.Kozlov, Doctor of Biological Sciences, Professor, Director of the Biomedical Centre (St.Petersburg, Russia)

Antonio Lanzavecchia, MD

Director of the Institute for Research in Biomedicine (Switzerland)

110 - Keynote presentation: Broadly Neutralizing Antibodies for Serotherapy and Vaccine Design (30 min.)

Alexander Schmidt, MD

Director, Clinical Research and Translational Science, GlaxoSmithKline Biologicals (US)

111 - Update on Dengue Vaccines (20 min.)

Li Xiuling

National Vaccine and Serum Institute (China)

112 - Development of Enterovirus 71 Vaccine (20 min.)

Shen Shuo, PhD

Wuhan Institute of Biological Product (China)

113 - Epidemics of Acute Gastroenteritis Caused by Viruses and Vaccine Development in China (20 min.)

Luigi Buonaguro, MD

Ist. Naz.Tumori "Fond. G. Pascale" (Italy)

114 - Virus-Like Particles and Particle Vaccines (20 min.)

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15:50 - 16:10 Break

Dan Barouch, MD, PhD

Director of the Centre for Virology and Vaccine Research in the Department of Medicine at Beth Israel Deaconess Medical Center (US)

115 - Novel HIV Vaccine Strategies (20 min.)

Jay A. Berzofsky, MD, PhD

Chief, Vaccine Branch, Center for Cancer Research, National Cancer Institute (US)

116 - Strategies and Mechanisms for Induction of Mucosal T Cell Immunity (20 min.)

HONORARY LECTURE:

José Esparza, MD, PhD

Senior Advisor on HIV Vaccines of the Bill and Melinda Gates Foundation (US)

117 - 30 Years of HIV Vaccine Research (40 min.)

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Monday, September 9, 2013
Grand Conference-Hall

9:30 - 12:00 Advances in Antiviral Drug Discovery (I)

Chairs: A.I. Mazus, M.D., Professor, Head of the Moscow City Centre for AIDS Prevention and Treatment (Russia)  GVN, GLOBAL VIRUS NETWORK

Robert R. Redfield, M.D., Associate Director of the Institute of Human Virology, University of Maryland School of Medicine (US)  GVN, GLOBAL VIRUS NETWORK

PLENARY LECTURE:

Jan Balzarini, MD, PhD

Laboratory of Virology and Chemotherapy, Rega Institute (Belgium)

118 - The Dense Glycan Shield on the HIV Envelope: the Achilles Heel of the Virus? (30 min.)

John G. Bartlett, MD

Director, HIV Care Program, The Johns Hopkins Hospital (US)

119 - The Anti-HIV Drug Pipeline (20 min.)

S.N.Kochetkov

Laboratory of Enzymology of Transcription, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences

120 - Development of New HIV Inhibitors (20 min.)

Fujie Zhang, MD  GVN, GLOBAL VIRUS NETWORK

National Centre for AIDS/STD Control and Prevention (China)

121- Progress, Achievements and Challenges: a Review of China's Free Antiretroviral Therapy Program (20 min.)

Anders Vahlne, MD  GVN, GLOBAL VIRUS NETWORK

Karolinska Institute (Sweden)

122 - Peptide Inhibitors of HIV (20 min.)

James Rooney, MD

Vice President of Medical Affairs, Gilead Sciences, Inc. (US)

123 - New Antiretroviral Therapies (20 min.)

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Leonid Margolis, PhD  GVN

Head, Section of Intercellular Interactions, Eunice Kennedy Shriver National Institute of Child Health and Human Development (US)

124 - HIV Transmission and Pathogenesis in ex vivo Tissues (20 min.)

12:00 - 13:00 Lunch

13:00 - 14:00 Official Opening Ceremony of the Conference
Welcoming Remarks

14:00 - 14:45 Special Opening Lecture

A.I. Mazus, M.D., PhD, Head, Moscow Center for HIV/AIDS Treatment and Prevention, welcoming Ram Petrov, MD, PhD, Head, Immunology Section, Institute of Bioorganic Chemistry, Russian Academy of Sciences who will introduce Robert C. Gallo, M.D., Director and Professor Institute of Human Virology, University of Maryland School of Medicine, Member, United States National Academy of Sciences and Co-Founder of the Global Virus Network

Robert C. Gallo, MD  GVN

Institute of Human Virology, University of Maryland School of Medicine (US)

A personal journey with human retroviruses

14:45 - 15:00 Break

15:00 - 17:00 Advances in Antiviral Drug Discovery (II)

Chairs: C. David Pauza, Ph.D., Associate Director of the Institute of Human Virology, University of Maryland School of Medicine (US)  GVN,

Leonid Margolis, Doctor of Biological Sciences, Professor, Chief of the Section of Intercellular Interactions (National Institutes of Health)(US)  GVN

Alain Lefeuvre, MD  GVN

Progress toward a HIV cure

125 - Department of Infectious Diseases, Toulon General Hospital (France) (20 min.)

Luis Menéndez-Arias, PhD  GVN

Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM) (Spain)

126 - Questions and challenges in HIV drug resistance: A molecular perspective (20 min.)

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Vadim Bichko, MD

Viriom Ltd. (Russia)

127 - Safety, pharmokinetics and efficacy of VM-1500, a novel reverse transcriptase inhibitor, In healthy volunteers and HIV-infected patients (20 min.)

Ulrike Protzer, MD

Institute of Virology TU Munich (Germany)

128 - Cure of HBV infection: can APOBEC3 deaminases mediate it? (20 min.)

A.I. Mazus, MD

Director, Moscow Center for HIV/AIDS Treatment and Prevention (Russia)

Summary remarks (10 min.)

16:30 - 16:45 IHV Lifetime Achievement Award for Scientific Research to Vadim Agol, MD, PhD., DSc
Introduction by Leonid Margolis, PhD

16:45 - 17:00 IHV Lifetime Achievement Award for Public Health to Jose Esparza, MD, PhD.
Introduction by Robert C. Gallo, MD

17:00 - 17:45 Special Lecture Honoring the IHV Lifetime Achievement Award Winners

Konstantin Chumakov, PhD

Chief of the Laboratory of Method Development, Division of Viral Products in the Food and Drug Administration (US)

129 - Polio Vaccines: The Past, Present and the Future

17:45 Adjourn

19:30 IHV Gala Awards Banquet
Yar Restaurant

Speaker Schedule

Tuesday, September 10, 2013
Conference-Hall Sector B+C

9:00 - 12:15 Mechanisms of Viral Pathogenesis

Chairs: Peter Horal, Ph.D., University of Gothenburg (Sweden) 

B.S. Naroditsky, Ph.D., Prof., Assistant Director, Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation

REINHARD KURTH HONORARY LECTURE – Introduction by Robert C. Gallo, MD

William Hall, MD 

University College, Dublin (Ireland)

130 - HTLV-I and Adult T Cell Leukemia/Lymphoma (ATLL) : Cellular and Molecular Basis of Transformation (30 min.)

Stephan Becker, PhD 

Institute of Virology at the University of Marburg (Germany)

131 - Replication and Assembly of Filoviruses (20 min.)

Guido Poli, MD 

Head, AIDS Immunopathogenesis Unit, San Raffaele Scientific Institute (Italy)

132 - A Novel Pathway of Proviral HIV-1 Latency Regulated by Aminoacid Starvation and HDAC-4 (20 min.)

Erica Ollmann Saphire, PhD 

Department of Immunology and Microbial Science of the Scripps Research Institute (US)

133 - Ebola virus matrix: structural transformation begets multiple structures in the virus life cycle (20 min.)

Massimo Palmarini, DVM, PhD, FRSE 

Chair of Virology, University of Glasgow Centre for Virus Research (UK)

134 - Host Restriction of Schmallenberg Virus (20 min.)

10:50 - 11:00 Break

C. David Pauza, PhD 

Institute of Human Virology, University of Maryland School of Medicine (US)

135 - HIV-associated immunodeficiency despite potent antiretroviral therapy with CD4 T cell reconstitution (20 min.)

Michael Bukrinsky, MD, PhD

Department of Microbiology, Immunology and Tropical Medicine at the George Washington University (US)
136 - HIV-1 Nef regulates activity of endoplasmic reticulum chaperone calnexin (20 min.)

HONORARY LECTURE**V.I.A gol, MD, PhD, DSc**

M.P.Chumakov Institute of Poliomyelitis and Viral Encephalitis, Russian Academy of Medical Sciences (Russia)
137 - Interplay Between Host Defenses and Viral Anti-defenses: A Major Factor of Cytopathogenicity of Picornaviruses (35 min.)

12:15 - 13:30 Lunch

13:30 - 17:00 Mechanisms for Virus Transmission

Chairs: Salim Abdo ol Karim, M.D., Ph.D., President of South African Medical Research Council (South African Republic)  GVN GLOBAL VIRUS NETWORK, Saulius Chaplinskas, M.D., Ph.D., Director, Center for Communicable Diseases and AIDS, Vilnius, Lithuania

PLENARY LECTURE:**Diane Griffin MD, PhD  GVN GLOBAL VIRUS NETWORK**

Alfred and Jill Sommer Professor, Chair of the Department of Molecular Microbiology and Immunology, the Johns Hopkins Bloomberg School of Public Health (US)

138 - Understanding protective immunity: Lessons from measles (30 min.)

Barry J. Beaty, PhD  GVN GLOBAL VIRUS NETWORK

University Distinguished Professor, Department of Microbiology, Immunology and Pathology, Colorado State University (US)

139 - Dengue Vector Control: Critical Needs and Opportunities for Helping to Control the Dengue Pandemic (20 min.)

Myron Essex, DVM, PhD

Mary Woodard Lasker Professor of Health Sciences Harvard School of Public Health, Harvard University (US)
140 - Reversing the Epidemic of HIV-1C in Southern Africa with Treatment as Prevention (20 min.)

Steven O'Brien

St. Petersburg State University (Russia)

141 - Gene Discovery and Data Sharing in Genome Wide Association Analyses: lessons from AIDS genetic restriction genes (20 min.)

15:00 - 15:10 Break

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M.P. Chumakov Institute of Poliomyelitis and Viral Encephalitis, Russian Academy of Medical Sciences (Russia)
142 - Sochi Virus as a Highly Pathogenic and Life-threatening Agent (20 min.)

Janusz T. Paweska, DVSc, dr hab, Prof Vet Sci

Head, Centre for Emerging and Zoonotic Diseases, National Institute for Communicable Diseases National Health Laboratory Service (South African Republic)

143 - Rift Valley Fever Virus: a Virus with Potential for Global Emergence (20 min.)

E.I.Korenberg

Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation

144 - Viral-Bacterial Mixed Infections Transmitted by Ticks: Diagnosis and Prevention in Russia (20 min.)

Guodong Liang, MD

National Institute for Viral disease Control and Prevention, China CDC (China)

145 - Arbovirus and Related Infectious Diseases in China (20 min.)

Xiaoping Dong, PhD

National Institute for Viral Disease Control and Prevention, China CDC (China)

146 - Understanding the Pathogenesis of Prion and Surveillance for Human Prion Diseases in China (20 min.)

Saulius Chaplinskas, MD, PhD

Director, Center for Communicable Diseases and AIDS (Lithuania)

147 - Globalization and New Challenges Caused of Communicable Diseases (20 min.)

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Wednesday, September 11, 2013
Conference-Hall Sector B+C

9:00 - 12:00 Viruses and Cancer

Chairs: Volker Erfle, Helmholtz Centre (Germany)  GVN, A.D.Kaprin, M.D., Professor, Director of P.Herzen Moscow Research Oncology Institute of the Health Ministry of Russia

OPENING COMMENT:

Robert C. Gallo, MD  GVN

Institute of Human Virology, University of Maryland School of Medicine (US) (10 min.)

Silvia Franceschi, MD

Special Advisor, Head, Infections and Cancer Epidemiology Group, International Agency for Research on Cancer (IARC) (France)

148 - HPV, HIV, and Cancer: A Global Challenge (20 min.)

Anna Linda Zignego, MD, PhD

Director, Interdepartmental Center MaSVE, Department of Experimental and Clinical Medicine, University of Florence (Italy)

149 - HCV and Lymphoma (20 min.)

Franco M. Buonaguro, MD  GVN

Director, Molecular Biology and Viral Oncogenesis Unit, National Cancer Institute "Fondazione G. Pascale" (Italy)

150 - Carcinogenesis of HPV (20 min.)

Patrick Moore, MD, MPH  GVN

Professor, Department of Microbiology and Molecular Genetics, School of Medicine and Department of Infectious Diseases and Microbiology, University of Pittsburgh (US)

151 - Tumorigenic Polyoma Viruses (20 min.)

10:20 - 10:40 Break

Luigi Chieco-Bianchi, MD  GVN

Immunology and Molecular Oncology, Veneto Institute of Oncology, Dept of Surgery, Oncology & Gastroenterology, University of Padua (Italy)

152 - Insights into the pathogenesis of HHV8-driven body cavity lymphomas (20 min.)

Masao Matsuoka, MD, PhD*Institute for Virus Research, Kyoto University (Japan)*

153 - Molecular Pathogenesis by HTLV-1 bZIP Factor (20 min.)

William A. Blattner, MD*Professor and Associate Director, Institute of Human Virology, University of Maryland School of Medicine (US)*

154 - HIV and Cancer in Africa (20 min.)

A.P.Kozlov*Professor and Director, Biomedical Center (Russia)*

155 - Evolution by Tumor Neofunctionalization and Phenomenon of Tumor Specifically Expressed, Evolutionarily Novel (TSEEN) Genes (20 min.)

14:00 - 18:00 Clinical Management of Co-Morbidities in HIV/AIDS

Chairs: John G. Bartlett, M.D., Director of the HIV Care Program, the Johns Hopkins Hospital (US), A.I. Mazus, M.D., Professor, Head of the Moscow City Centre for HIV/AIDS Prevention and Control (Russia)  GVN, Robert R. Redfield, M.D., Assistant Director of the Institute of Human Virology, University of Maryland School of Medicine (US)

Barry Peters, MB BS, DFFP, MD, FRCP*King's College London (UK)*

156 - HIV and metabolic disease: Clues to control of HIV infection from the immune and virological response to high dose Vitamin D challenge (25 min.)

Riccardo Dolcetti, MD*Head, Cancer Bio-Immunotherapy Unit, IRCCS – National Cancer Institute (Italy)*

157 - Pathogenesis of Epstein-Barr Virus-driven Lymphomas of HIV+ Patients: new insights of potential clinical relevance (25 min.)

Shyam Kotttilil, MD, PhD*National Institute of Allergy and Infectious Diseases (US)*

158 - Hepatitis C Treatment Update: Current Status and Future Directions (25 min.)

Rohit Talwani, MD  GVN*Institute of Human Virology, University of Maryland School of Medicine (US)*

159 - Hepatitis B Treatment Update: Current Status and Future Directions (25 min.)

15:40 - 15:55 Break**Bruce Gilliam, MD  GVN***Institute of Human Virology, University of Maryland School of Medicine (US)*

160 - Treatment Strategies to Minimize the Impact of Antiretroviral Drug Toxicities (25 min.)

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E.M.Bogorodskaya, MD, PhD

Moscow City Research and Practical Centre for Tuberculosis Control (Russia)

161 - Anti-tuberculosis Treatment for HIV-positive Patients in Moscow (20 min.)

Abubakar Mussa Maghimbì, MD, MMed

Institute of Human Virology (Tanzania)

162 - Confronting Tuberculosis in an African Population with HIV (20 min.)

Patrick Mallon, MD, PhD

Associate Dean for Research and Innovation, UCD School of Medicine and Medical Science (Ireland)

163 - HIV and kidney function with a focus on traditional risk factors and role of TDF, PI and other medication (25 min.)

Closing remarks: A.I.Mazus  , Robert R. Redfield  (10 min.)

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 John G. Bartlett, MD
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 Anders Vahlne, MD 
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 Leonid Margolis, PhD 
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 Alain Lafeuillade, MD 
 Department of Infectious Diseases, Toulon General Hospital (France)
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 Luis Menéndez-Arias, PhD 
 Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM) , Madrid (Spain)
- 127 *Safety, pharmokinetics and efficacy of VM-1500, a novel reverse transcriptase inhibitor,
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 Vadim Bichko, M.D.
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- 128 *Cure of HBV infection: can APOBEC3 deaminases mediate it?*
 Ulrike Protzer, MD 
 Institute of Virology, TU Munich (Germany)

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 University College, Dublin (Ireland)
- 131** *Replication and Assembly of Filoviruses*
Stephan Becker, PhD 
 Institute of Virology at the University of Marburg (Frankfurt, Germany)
- 132** *A Novel Pathway of Proviral HIV-1 Latency Regulated by Aminoacid Starvation and HDAC-4*
Guide Poli, MD 
 Head, AIDS Immunopathogenesis Unit, San Raffaele Scientific Institute (Italy)
- 133** *Ebola virus matrix: structural transformation begets multiple structures in the virus life cycle*
Erica Ollmann Saphire, PhD 
 Department of Immunology and Microbial Science of the Scripps Research Institute (US)
- 134** *Host Restriction of Schmallenberg Virus*
Massimo Palmarini, DVM, Ph.D., FRSE 
 Chair of Virology, University of Glasgow Centre for Virus Research (UK)
- 135** *HIV-associated immunodeficiency despite potent antiretroviral therapy with CD4 T cell reconstitution*
C. David Pauza, PhD 
 Institute of Human Virology, University of Maryland School of Medicine (US)
- 136** *HIV-1 Nef regulates activity of endoplasmic reticulum chaperone calnexin*
Michael Bukrinsky, MD, PhD
 Department of Microbiology, Immunology and Tropical Medicine at the George Washington University (US)

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V.I.A gol, MD, PhD, DSc
M.P.Chumakov Institute of Poliomyelitis and Viral Encephalitis, Russian Academy of Medical Sciences (Russia)
- 138** *Understanding protective immunity: Lessons from measles*
Diane Griffin MD, PhD 
Alfred and Jill Sommer Professor, Chair of the Department of Molecular Microbiology and Immunology, the Johns Hopkins Bloomberg School of Public Health (US)
- 139** *Dengue Vector Control: Critical Needs and Opportunities for Helping to Control the Dengue Pandemic*
Barry J. Beaty, PhD 
University Distinguished Professor, Department of Microbiology, Immunology and Pathology, Colorado State University (US)
- 140** *Reversing the Epidemic of HIV-1C in Southern Africa with Treatment as Prevention*
Myron Essex, DVM, PhD
Mary Woodard Lasker Professor of Health Sciences Harvard School of Public Health, Harvard University (US)
- 141** *Gene Discovery and Data Sharing in Genome Wide Association Analyses: lessons from AIDS genetic restriction genes*
Steven O'Brien
St. Petersburg State University (Russia)
- 142** *Sochi Virus as a Highly Pathogenic and Life-threatening Agent*
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M.P. Chumakov Institute of Poliomyelitis and Viral Encephalitis, Russian Academy of Medical Sciences (Russia)
- 143** *Rift Valley Fever Virus: a Virus with Potential for Global Emergence*
Janusz T. Paweska, DVSc, dr hab., Prof Vet. Sci. 
Head, Centre for Emerging and Zoonotic Diseases, National Institute for Communicable Diseases National Health Laboratory Service (South African Republic)
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E. I. Korenberg
Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation

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Guodong Liang, MD 
 National Institute for Viral disease Control and Prevention, China CDC (China)
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Biomedical Prevention of HIV/AIDS in Russia

E.V. Karamov and R.M. Khaitov

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and Biological Agency, RU

The epidemic of HIV/AIDS in Russia is currently in its concentrated phase characterized by concomitant coinfections (hepatitis B and C and tuberculosis). Although subtype A1 is dominant, subtype B and CRF 03 (A/B recombinant) are also present. Recent subepidemic eruptions of HIV infection in Siberia/Urals and the Far East have involved A/G recombinant and subtype C, respectively. Approaches to biomedical prevention of HIV/AIDS in Russia include vaccine and microbicide development.

Candidate HIV vaccines have been developed independently by three Russian research centers. In one of them, the conjugated protein–polymer vaccine VICHREPOL, use is made of an original domestic immunoadjuvant polyoxydonium. This candidate, developed in the Institute of Immunology, is currently undergoing a phase II clinical trial.

A broad-coverage screening of natural and synthetic compounds for anti-HIV activity is currently underway in Russia, aiming at identification of chemicals appropriate for pre-exposure prophylaxis and use as microbicides. Unique compositions of antivirals have been developed, as well as nanotechnology-based means of their delivery, the combinations thereof showing significant promise as microbicide preparations.

The presentation will highlight the present state of research on biomedical prevention of HIV/AIDS in Russia.

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HIV/AIDS vaccines in Russia: clinical trials and estimation of acceptance in population

**¹Gudima G., ¹Sidorovich I., ¹Karamov E.,
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HIV/AIDS vaccines and also PrEP are considered as the most perspective approaches to control HIV/AIDS epidemic. Candidate conjugated polymer-subunit HIV vaccine VICHREPOL, developed in Moscow Institute of Immunology, successfully passed phase I clinical trials and now is at the start of phase II trials. Two other candidate vaccines (DNA-based and viral vector-based) are also passed phase I trials. Positive effect of vaccination depends of the coverage of population and this coverage depends of vaccine uptake. Estimation of possible uptake of HIV vaccine is very important to provide its further effective application. Pilot investigation of readiness for HIV vaccination in Russia (Moscow region) was performed (416 persons, 254 (61%) – men, 162 (39%) – women, age of 16–55). 60% of respondents were ready for HIV vaccination. 79% of respondents with risk of HIV infection, agreed to be vaccinated vs 48% of those disclaimed the risk of HIV infection. Readiness for HIV vaccination is 20% lower in respondents with children vs childless. In case of 30% vaccine efficacy readiness for vaccination was 3.5 points of 10; in case of 50% efficacy – 5.2 points of 10; 8.8 points of 10 – in case of 90–95% efficacy. Readiness for vaccination also depends from its duration, number of doses in course, possible adverse side effects, mode of vaccination. 20% of respondents agreed only for free vaccination, 45% – for paid vaccination. Readiness for HIV vaccination is lower in general population (60% vs 78%) and in HIV infection risk groups (79% vs 95–97%) in Russia vs some other countries [Suraratdecha et al., 2005]. It is necessary to improve education programs aimed to inform on HIV vaccines development, its safety and application.

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Genetic factors defining resistance and susceptibility to HIV/AIDS**Kofiadi IA, Alexeev LP, Khaitov RM****FSBI "NRC Institute of Immunology" FMBA of Russia, RU**

One of the priorities for fundamental biomedical science is the discovery of the molecular-genetic basis of HIV pathogenesis. The progress in this area widens the possibilities for further improvement of HIV/AIDS prevention and therapy approaches. In this framework we have studied the population distribution of CCR5 rs333, CCR2 rs1799864, SDF1 rs1801157, HCP5 rs2395029, HLA-C rs9264942 and HLA-B*5701 genetic polymorphisms associated with susceptibility to HIV and AIDS and antiviral drugs intolerance among 1120 seronegative individuals comprising 12 ethnically distinct groups inhabiting Russia, Belarus, Ukraine, Kazakhstan, Kyrgyzstan and Moldova (Pomors, Russians (Vologda and Pskov region), Belarus, Ukrainians, Gagauz, Udmurts, Tatars, Chechens, Kazakhs, Kyrgyz, Tuvinians). The rs333 variant is represented at most in the population of Pomors. The homozygotes who have significantly lower risk of HIV infection comprising 3% of the population. The least frequency of CCR5 polymorphism was described for Chechens, Kazakhs, Kyrgyz, Tuvinians: 6, 6, 5 and 2% correspondingly. The highest incidence of CCR2 polymorphism was described for Chechens, Kazakhs and Kyrgyz. The other alleles under study did not reveal significant differences in distribution. The protective effect of the studied polymorphisms in CCR5, CCR2, SDF1 genes is characterized as cumulative. Based on the frequencies of three-loci genotypes we have established the values of relative hazard of AIDS onset and relative hazard of AIDS-caused death for the populations under study. The risks fall in range 0.79-0.94 and 0.76-0.93, correspondingly. We have found that interpopulation genetic variability confers for statistically relevant differences in the hazards estimated.

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Cell-to-cell transmission of HIV: role of virological synapse**Mazurov DV, Filatov AV****Institute of Immunology, RU**

HIV-1 infects CD4+ T-lymphocyte by cell free viral particles released from the surface of effector cells or after the formation of intercellular contact between infected cell and healthy lymphocyte. The last way of infection was designated as cell-to-cell viral transmission. The current studies suggest that cell-to-cell transmission of HIV occurs in peripheral lymph nodes at the early stage of infection and is more efficient pathway of virus dissemination than cell-free infection. One of the most accepted models of HIV transmission is the formation of virological synapse (VS); tight intercellular adhesion junction sharing structural similarity with immunological synapse. VS forms after HIV surface protein gp120 expressed on the plasma membrane of infected cells in prefusogenic conformation recognizes CD4 receptor on target cell. Viruses transmitted across VS undergo endocytosis by target cells, so that viral entry occurs via endocytic compartments and not via cell surface. This feature of cell-to-cell transmission accounts for the resistance of HIV to the neutralizing antibodies. Although the different stages of HIV cell-to-cell transmission have been extensively studied, the levels of correlation between virus transmission and targets infection were not accurately quantified. To fill up the gap in our understanding of cell-mediated viral infection, we have developed a new methods and improved vectors to quantify the levels of VS formation, cell-to-cell infection, and macromolecular transport across the cell-cell contact. New T cell lines stably producing recombinant virus like particles and reporter RNA, as well as modified target cells were generated.

105**Rationale for HIV vaccines design****Irina A.Nikolaeva, Igor G.Sidorovich****National Research Center – The Institute of Immunology of the Federal Medical-Biological Agency, RU**

Development of an effective and safe HIV vaccine presents unique challenges. Despite the progress in understanding the biology of HIV-1 and its recognition by the human immune system, we have not yet developed an efficacious HIV-1 vaccine. During the last years, the results were obtained that has given hope that vaccination may prevent HIV-1 acquisition. The results of post-RV144 correlates and sieve analyses suggest that vaccine worked probably involving an immunological mechanism in the second variable loop (V2). A high resolution structure of the envelope trimer was solved, and this information is being used for the design of new generations of vaccines aimed at inducing protective antibodies. New techniques have facilitated the discovery of new human broadly neutralizing antibodies (BrNabs) that target and delineate diverse conserved epitopes on the envelope glycoprotein spike. The epitopes of these BrNabs can serve as templates for immunogen design aimed to induce similar antibodies. A separate goal of HIV vaccine research is to identify the best strategy for immunization and delivery agents. Several vectors and adjuvants have been developed. Significant advances have been made towards the development of tools to assess preclinical efficacy and understanding the correlates of protection in non human primate models. We observe the preventive potential of microbicides, PrEP, and earlier antiretroviral treatment of infected individuals has been demonstrated. All of these interventions may have a significant impact in reducing the incidence of HIV infections. However a safe and efficacious vaccine will be the most efficient way to control global HIV-1 pandemic, and scientific opportunities look promising.

106**Enhance expression of transgene in adenovirus****Ataullakhanova, RU**

No abstract provided.

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The modern methods for HIV/AIDS vaccine evaluation

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The spread of HIV/AIDS increases worldwide, a safe and efficacious vaccine remains the cornerstone for a prevention strategy to stop HIV-1 epidemic. Both humoral (neutralizing antibodies) and cellular (CTL) responses are able to control HIV infection. Non-neutralizing HIV-specific antibodies could play an important role in preventing or controlling HIV infection. These antibodies can bind to infected cells and recruit innate immune effector cells, such as natural killer (NK) cells, to lyse infected cells through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cell-mediated virus inhibition (ADCVI). The measurement of immune responses directed specifically against the HIV is critical for understanding the interplay between the virus and the host immune system. By characterizing the immunological correlates of protection against HIV infection, such measurements will aid in the development of efficacious prophylactic vaccine. To improve vaccine antigens and adjuvant, it is also necessary to assess a similarity of vaccine – and virus – induced immune responses. The evaluation of antigen-specific humoral response includes measurement amount and specificity of vaccine-induced antibodies (in ELISA or WB), their neutralizing activity and ADCC or ADCVI. ELISPOT, intracellular cytokine flow cytometry assays and Luminex are the most common assays to determine CTL response. They all determine immune response by the detection of the cytokines (IFN-gamma, TNF-alpha, IL2) secreted by cells upon antigen-stimulation. MHC tetramer binding assay measures the absolute number of cells that recognize a particular epitope without providing any information regarding the functionality of the cells.

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Development of universal vaccines against flu: reality and prospects

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Two surface glycoproteins hemagglutinin and neuraminidase are the main antigens for obtaining traditional flu vaccines due to their high immunogenicity and ability to induce generation of neutralizing antibodies. High genetically instability of influenza virus provides antigenic diversity of these glycoproteins between strains. Subunit vaccines based on one of these surface antigens are characterized by narrow specificity. Modern vaccines should provide protection against several or all subtypes of influenza A viruses. In addition sporadic influenza outbreaks of newly emerged influenza A viruses may cause the next pandemic.

Today there are no flu vaccines of a wide range of action, so-called "universal" vaccines. Several flu vaccines with a broad cross-protectivity are tested in different phases of clinical trials.

In this report the analysis of the modern researches directed on creation of flu "universal" vaccines including data obtained by researchers of Gamaleya institute of epidemiology and microbiology is carried out.

Genetic immunization technology is used for development of "universal" vaccine. Recombinant pseudoadenoviral particles coding of influenza virus conservative antigens were used as a vector for gene delivery. Polypeptide, containing hemagglutinin conservative epitopes, was used in addition to traditional influenza conservative antigens M1, M2 and NP. Animal experiments demonstrated that developed vaccines were very efficient against different influenza subtypes (80%-100% survivability).

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109**Problems and prospects of development of the subunit TB vaccine**

Tkachuk A.B., Lunin V.G., Karyagina A.S., Gintsburg A.L. Gamaleya Research Institute for Epidemiology and Microbiology, RU

Tuberculosis (TB) causes about 1.4 million deaths each year. Currently the only licensed anti-tuberculosis vaccine is Bacille Calmette-Guérin (BCG). This live attenuated vaccine has been in use for over 80 years and has displayed up to 80% efficacy against serious forms of the disease, e.g., meningitis, in children. However, efficacy in adults against pulmonary tuberculosis ranges from 0 to 80% in different trials. The protective immunity generated by BCG decreases with time, and almost disappears after 20-25 years, resulting in a vulnerability of the adult population to primary infection and reactivation of latent TB. Thus, development of an effective preventive vaccine and new "post-infection" vaccine are still important aims of vaccinology.

In this study we report the development of novel subunit protein-based vaccine against tuberculosis. Our vaccine consists of two recombinant mycobacterium proteins - Ag85A and fusion protein ESAT6-CFP10. These antigens are strongly recognized by T cells and they have demonstrated protective efficacy in animal models. However, because the protein component of the subunit vaccine is poorly immunogenic, the recombinant protein vaccine was adjuvanted with novel, three-component adjuvant system composed of the dextran, cationic DEAE-dextran and oligodeoxynucleotide CpG. This adjuvant was chosen on the basis of its ability to induce strong protective immunity in animal models of *M. tuberculosis* infection, by delivering a TLR9 ligand into the endosomal pathway. Recombinant vaccine proteins possess dextran-binding domain, which helps create «depot» effect and provide prolonged interaction of vaccine antigen with T-cells.

We investigated immunogenicity and protection properties of our vaccine on mice and guinea pigs models of tuberculosis, and also performed toxicity studies. We demonstrated that our subunit vaccine stimulates th1 immune response and is protective against tuberculosis with the same efficacy as BCG. Furthermore, our vaccine showed good result in toxicity studies in mice, guinea pigs and rabbits.

110**Broadly neutralizing antibodies for serotherapy and vaccine design**

Antonio Lanzavecchia

Institute for Research in Biomedicine, Bellinzona and Institute of Microbiology, DE

Memory B lymphocytes and long-lived plasma cells represent a repository of the antigenic experience of an individual. By analyzing the specificity and function of these cells we can gain insights into the human immune response to pathogens and vaccines, identify correlates of protection, and isolate neutralizing antibodies and protective T cells. To interrogate human memory B cell and plasma cell repertoires we developed two culture-based high-throughput methods that are used to isolate, with high efficiency, human monoclonal antibodies of distinctive specificities. Unusually potent neutralizing antibodies against human cytomegalovirus were isolated from infected donors and used to identify the viral ligands and to design an experimental vaccine. We also isolated antibodies of exceptional breadth, such as a pan-influenza A neutralizing antibody and an antibody that neutralizes both respiratory syncytial virus and metapneumovirus. By targeting conserved structures, these broadly neutralizing antibodies are less prone to select escape mutants and are therefore promising candidates for prophylaxis and therapy of infections as well as tools for the design of improved subunit vaccines.

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Update on dengue vaccines

Alexander C. Schmidt

GlaxoSmithKline Biologicals, US

Forty percent of the world's population is at risk for dengue, and 100 million apparent infections are estimated to occur annually. In a minority of cases, dengue fever progresses to severe disease at the time of defervescence, inducing a capillary leak syndrome accompanied by thrombocytopenia that can result in shock and organ failure. Thus the medical need for a dengue vaccine is obvious. The four dengue virus serotypes are transmitted by Aedes mosquitoes, and protective immunity against the infecting serotype (homotypic immunity) is long lived and thought to be conferred by virus-neutralizing antibodies and some T cell help. However, antibodies induced by one serotype often cross-react with the other serotypes. If antibodies fail to neutralize and instead opsonize, they can enable the virus to infect IgG receptor-bearing cells. This phenomenon, termed antibody-dependent enhancement, is thought to play a role in the pathogenesis of severe dengue, and is of concern to vaccine developers. Several investigational dengue vaccines are currently in clinical development, and many different vaccination approaches are being explored. These span from live-attenuated dengue viruses to chimera between yellow fever and dengue viruses, to subunit, DNA, and whole virus inactivated vaccines. A recent Phase 2b study of the vaccine most advanced in development did not show statistically significant protection against disease due to any serotype, adding much uncertainty to the entire field. Our understanding of the contributions of humoral and cell mediated responses to protection and to pathogenesis is clearly less than perfect, and selection, presentation and adjuvantation of antigens need thought and attention.

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The Development of Enterovirus 71 Vaccine

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Enterovirus 71 (EV71) is a major cause of epidemic outbreaks of hand-foot-and-mouth disease (HFMD) worldwide. The virus belongs to the family Picornaviridae, genus Enterovirus. 3 genotypes—A, B, and C and more than 10 sub-genotypes have been identified. After the initial identification of this virus in 1969, some large outbreaks of HFMD have been reported worldwide.

EV71-induced HFMD is usually characterized by the formation of maculopapular or vesicular lesions on the skin and oral mucosa, especially on the palms, soles, and mouth.. There were a greater number of fatal cases with brainstem encephalitis, pulmonary edema and/or hemorrhage, and cardiopulmonary collapse.

Developing effective vaccines is considered a top choice among all control measures. We evaluated the ability of inactivated virus vaccine to elicit neutralizing antibody and to provide protection against lethal infection of EV71 in suckling mice. The purity of EV71 vaccine was up to 96.8% by HPLC identification. The purified EV71 vaccine induced high levels of neutralizing antibodies, these antibodies were shown to be protective against lethal infection when passively transferred to susceptible newborn mice. With a challenge dose of 50LD₅₀ virus/mouse, suckling mice born to dams immunized with inactivated virus showed 100% survival. In preliminary animal trial, no side effects were detected when monkeys were immunized with purified EV71 vaccine either at normal or large doses.

The vaccine was approved for the clinical evaluation in 2009. The phase 1/2/3 clinical trial was completed in March, 2013. The data suggested that the inactivated EV71 vaccine had a clinically acceptable safety profile and good immunogenicity in healthy children and infants. Our data indicated that inactivated EV71 vaccine is the choice of vaccine preparation capable of fulfilling the demand for effective control.

113**Epidemics of Acute Gastroenteritis Caused by Viruses and Vaccine Development in China****Shen Shuo****Wuhan Institute of Biological Product, China
National Biotec Group (CNBG), CN**

The leading etiological agents of viral gastroenteritis are group A rotaviruses, noroviruses, adenoviruses (type 40, 41) and astroviruses in China in the last 20 years. The prevailing serotypes of rotaviruses are G type 1, 2, 3, 4 and 9, while G8 has been emerged recently in China. Accordingly, trivalent and hexavalent vaccines are under development by the two Institutes under CNBG. The trivalent oral vaccines are reassortants of VP4 and VP7 genes of human strains and other backbone genes of Lanzhou lamb rotavirus (LLR). The safety of lamb rotavirus vaccine strain has been proved since licensing in 2000 in China. The phase 3 clinical trials of the trivalent vaccines are in the progress in Henan province, China. The hexavalent oral vaccines are reassortants of VP7 genes of human strains and the other genes of UK strain, developed by and collaborated with NIH, USA, and PATH. The preclinical studies at Wuhan Institute of Biological Product have been completed and the hexavalent vaccine is ready for phase 1 clinical study. The novoviruses are increasingly detected in epidemics of acute viral gastroenteritis and spontaneous cases of people of all ages in China, including the rapid spreading of the newly emerged pandemic GII.4 variant (Sydney strain 2012) to China. The new Sydney strains were isolated in different areas and analysis of complete sequence demonstrated the rapid evolution. The surveillances and epidemic studies of these emerging viruses support the development of vaccines against the infections caused by noroviruses. The new variant co-circulated with other genotypes of GI and GII genogroups in human and multiple valent vaccines may needed to be developed..

114**VLPs and particle vaccines****Luigi Buonaguro, MD****Ist. Naz.Tumori "Fond. G. Pascale," IT**

VLPs represent a powerful tool for vaccine development, representing the closest strategy to the native viruses for displaying and delivering conformational epitopes, with improved induction of antibodies and immune response in its whole. Moreover, the lack of genetic material makes VLPs the “safer counterpart” of live attenuated or killed viral vaccines which, indeed, may induce limited but possible undesired effects.

VLP-based vaccines have been developed from both enveloped and non-enveloped viruses to target infectious and non-infectious diseases and are in various stages of development spanning preclinical evaluation to market. In particular, the only two preventive cancer vaccines licensed are based on VLP approach (HBV and HPV vaccines).

Overall, pre-clinical and clinical trials with different VLP-based vaccines have shown they are well tolerated and can be administered by a number of routes, including intramuscular, subcutaneous, oral or intranasal. VLP vaccines have also been demonstrated to be highly immunogenic and capable of stimulating protective immunity in a number of instances when administered with or without adjuvants. Their potent immunogenicity is a result of several factors, including the ability to incorporate key immunogenic properties of viruses into a single entity and to hit the cells relevant for initiate an effective adaptive immune response.

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Immune Correlates of Protection in Rhesus Monkeys

Dan Barouch

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MA, US

We have previously reported the protective efficacy of Ad26/MVA vector regimens expressing SIVsmE543 Env/Gag/Pol antigens against SIVmac251 challenge. Here we assess the potential utility of adding a protein trimer boost to adenovirus based vaccine regimens. We produced stable SIV and HIV Env gp140 trimers and assessed the immunogenicity and protective efficacy of Ad prime, Env gp140 trimer boost regimens against SIVmac251 and SHIV-SF162P3 challenges in rhesus monkeys. Vector prime, protein boost vaccine regimens induced higher titer binding and neutralizing antibodies compared with protein only regimens. Clinical studies to evaluate Ad26/MVA and Ad26/ protein vaccine regimens are planned.

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Strategies and mechanisms for vaccine induction of mucosal T cell immunity

Jay A. Berzofsky

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National Cancer Institute, NIH, US

Most HIV transmission is through mucosal surfaces. We previously found in mice that CD8 T cells must be in the local mucosa to prevent mucosal viral transmission. Intrarectal delivery was most effective, but not so practical. We devised a strategy to mimic intrarectal delivery through the oral route by encapsulating antigens in nanoparticles enclosed in microparticles that protected against stomach acid and enzymes and released the nanoparticles in the large intestine for uptake by dendritic cells. Different formulations resulted in selective release in the small or large intestine and T cell immunity in those sites, revealing a heretofore unknown subcompartmentalization between the small and large intestinal mucosal immune system. Delivery to the colon mimicked intrarectal delivery for protection of mice against intrarectal vaccinia virus challenge. We translated this to macaques, showing similar selective delivery and some preliminary evidence of efficacy in a SHIV intrarectal challenge model. The subcompartmentalization also implies that the homing receptors for T cells to traffic to the small and large intestine must differ. We found that indeed, small intestinal DCs induce T cells to home to the small intestine, whereas colonic DCs induce homing to the colon. This difference appears to correlate with different levels of retinoic acid production and differential induction of homing integrins and chemokine receptors. Besides the ability to mimic the benchmark intrarectal immunization by a more acceptable route, such subcompartmentalization may be useful for selective immunization, and understanding the mechanisms involved in homing may allow selective targeting of T cells to the right compartment.

117**30 Years of HIV Vaccine Research****José Esparza****Bill and Melinda Gates Foundation, Seattle, WA, US**

Soon after HIV was discovered as the cause of AIDS in 1983–1984, there was an expectation that a preventive vaccine would be rapidly developed. The first HIV vaccine paradigm was aimed at inducing neutralizing antibodies, with numerous recombinant envelope proteins tested in clinical trials. It came to an end in 2003, with the negative results from the VaxGen trials in North America and Thailand.

The second paradigm aimed at inducing CD8+ T-cell responses, and it led to the development of DNA vaccines and of live-recombinant viral vectors, especially poxviruses and adenoviruses (Ad). The concept was tested in the STEP and Phambili trials, using an Ad5 vector. The trials were stopped in 2007, after an interim review of STEP showed that the vaccine failed to prevent HIV infection or to decrease virus load in vaccinated volunteers who became infected, and even enhanced HIV acquisition in a subpopulation of vaccinated individuals.

The current wave of vaccine development is attempting to induce more complex immune responses and exploring novel approaches. The RV 144 trial in Thailand, which assessed the protective efficacy of a prime-boost protocol using a canarypox vector followed by gp120 boosts, showed 31.2% efficacy in preventing HIV acquisition and presumptive immune correlates have been identified. The field is now exploring new leads that include the rational design of novel immunogens based on epitopes recognized by broadly neutralizing antibodies, live replication-competent vectors and the role of potentially protective non-neutralizing antibodies.

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118**The dense glycan shield on the HIV envelope: the Achilles heel of the virus?****Jan Balzarini**

Rega Institute for Medical Research, BE

The envelope gp120 of HIV contains an unusual high amount of N-glycans that serves as a dense shield to hide immunogenic epitopes on gp120 against the immune system. There exists a wide variety of glycan-binding agents with different specificities to recognize carbohydrate moieties present on the HIV envelope. Several of the carbohydrate-binding agents (CBA) are potent inhibitors of at least four different pathways of HIV to infect virus-susceptible cells and to be transmitted to virus-exposed individuals. These CBAs have been demonstrated (i) to inhibit cell-free virus infection of CD4+ T-lymphocytes and macrophages, (ii) to block syncytia formation between persistently HIV-infected (gp120-expressing) cells and uninfected cells, (iii) to prevent virus capture by DC-SIGN-expressing cells and (iv) to block transmission of DC-SIGN-captured virus particles to uninfected CD4+ T-lymphocytes. CBAs represent the only agents reported to be able to concomitantly interact with these four processes, which can be advantageous from a microbicide perspective. Interestingly, CBA drug pressure in cell culture forces the virus to select for mutant variants that have multiple N-glycan deletions in their envelope, and thus, to uncover immunogenic epitopes on gp120. Accumulation of such envelope mutations compromises the infectivity of the virus. Several gp120 antibodies show a markedly increased activity against such mutant viruses. CBAs may, therefore, represent an entirely novel therapeutic concept in that they inhibit virus entry into its susceptible cells, and prevent DC-SIGN-directed virus transmission, but in addition, they may trigger the host immune system as soon as drug-related (N-glycan) mutations appear in the viral envelope.

119**The Anti-HIV Drug Pipeline****John G. Bartlett**

Johns Hopkins University School of Medicine, US

New Drugs by Class

NRTI: Tenofovir alafenamide fumarate (TAF) is the pro-drug of tenofovir with advantages of slight increase activity and reduced renal/bone toxicity. The phase 2 trial (Zolopa A. 2012 CROI, Abstr 99LB) compared TAF vs. another TDF prodrug (TFV, each with EFV, COBI/FTC in 170 treatment naïve patients. At 24 weeks both groups achieved VL <50 c/mL; TAF showed better renal and bone safety.

InSTI: Dolutegravir (DTG) – New once daily DTG/2NRTIs that shows potency with good activity vs. RAL-resistant strains.

- S/GSK 1265-744 ("744"): This is a next generation InSTI with a T1/2 of 21-50d!

NNRTI: MK1439 – This new potent NNRTI showed exceptional potency with 25 mg monotherapy once daily (Anderson M, 2013 CROI;Abstr. 100).

- RPV-LA: A novel nanosuspension of RPV with steady state release after 600 mg given SC or IM every 3 months.

Entry Inhibitors: Cenicriviroc (CVC) antagonizes CCR5 receptor, but also CCR-2 receptors to possibly reduce immune activation. ART activity is comparable to EFV.

- BMS 663068 (or BMS 068): This is a prodrug of BMS-529 that binds gp125 to prevent HIV binding to CD4 cells. A small trial showed 42 of 48 treatment-naïve patients responded; the 6 exceptions had a genetic factor that accounted for nonresponse.

Pharmacoenhancer: Cobicistat (COBI) is a potential substitute for RTV to boost ARVs and is already FDA-approved in combination as EVG/COBI/TDF/FTC.

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Development of New HIV Inhibitors

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No abstract provided.

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Progress, achievements and challenges: a review of China's free antiretroviral therapy program

Fujie Zhang

National Center for AIDS/STD Control and
Prevention, CN

In order to respond to the rapid emergence of a large number of AIDS cases and subsequent peak of death in the early 2000's, Chinese government launched its National Free ART Program in 2002. The initial stage of this program mainly focused on former plasma donors at six provinces in central China under the China Comprehensive AIDS Response Program. Since the release of "Four Free and One Care" policy in late 2003, the ART program was quickly scaled up to the whole country and had covered 64% of individuals known to have AIDS by the end of 2006. As more resources became available, second line drugs, free viral load and free resistance tests became parts of routine services successively between 2007 and 2010, which represented the standardization of China's ART program. Due to the encouraging findings of ART's both survival and prevention benefits, China's ART program stepped into a phase of fast expanding. The sum of newly treated patients in 2011 and 2012 almost equal the accumulative sum of the previous nine years. By the end of 2015, this program aims to treat 358,600 HIV/AIDS patients in China. With the fast expansion of the program, China successfully decreased the overall mortality of HIV from 39.3 per 100 person-years in 2002 to 14.2 per 100 person-years in 2009. Progress indicators also suggested improvement at implementation. However, there are many challenges remain, which in long run may threaten the sustainability and effectiveness of the program. More attention should be paid to the groundwork of the program and more efforts should be made to improve the overall capacity of the program and its related systems.

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Peptide Inhibitors of HIV

Anders Vahlne, MD

Karolinska Institute, SE

No abstract provided.

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New HIV Therapies

James F Rooney, Michael Miller, Andrew Cheng
Gilead Sciences, US

The advent of triple drug highly active antiretroviral therapy in 1996 was a turning point in the battle to control HIV disease. For the first time, HIV replication could be effectively limited resulting in marked improvements in morbidity and mortality from HIV infection. However, the treatment regimens were complex with patients having to take many pills at different times during the day, and the regimens were associated with significant long term side effects. Subsequent treatment strategies have focused on simplification of dosing to facilitate adherence and better tolerated regimens. Various combination pills were developed beginning with Combivir (zidovudine/ lamivudine) given twice daily and then Truvada (tenofovir DF/emtricitabine) given once daily in combination with a third or fourth drug. This led to the development of single tablet regimens (STR), a single pill that provided complete therapy for treatment of HIV infection. The first STR was Trizivir (zidovudine/ lamivudine/abacavir) given twice daily, which was followed by the once daily STRs Atripla (tenofovir DF/emtricitabine/efavirenz), Complera (tenofovir DF/emtricitabine/rilpivirine), and Stribild (tenofovir DF, emtricitabine, cobicistat, elvitegravir), which are now the most commonly used medications for the initial treatment of HIV infection. New drugs are in development, including the tenofovir prodrug TAF (tenofovir alafenamide fumarate) and the integrase inhibitor dolutegravir, which may offer advantages in safety, efficacy, and simplicity of dosing, and could be included in future STRs.

124**Male-to-Female HIV-1 Transmission: Lessons from Ex Vivo****Leonid Margolis****National Institute of Child Health and Human Development, NIH, US**

The mechanisms of male-to-female HIV-1 transmission mediated by semen are not well-understood. To decipher these mechanisms, we developed a system of cervico-vaginal tissue ex vivo to which HIV-1 is transmitted from semen under controlled laboratory conditions. Semen samples obtained from HIV-1-infected and control men were analyzed for the presence of 21 cytokines, and HIV-1 transmission was simulated ex vivo by deposition on cervico-vaginal explants of virus suspended in semen or in PBS enriched with particular cytokines. In HIV-1-infected men, the cytokine spectrum was significantly changed, resulting in the establishment of new correlations and the strengthening of pre-existing correlations between different cytokines: HIV-1 infection increases the number of such correlations from 21 to 72. These changes in semen were local and different from ones in blood from the same individuals. One of the most upregulated seminal cytokines was IL-7, which enhanced replication of HIV-1 in cervico-vaginal tissue. This enhancement was associated with the suppression of apoptosis as evaluated from the expression of apoptotic markers, a decrease in the depletion of infected cells as evaluated from flow cytometry, and an increase in cell cycling as evaluated from Ki67 staining.

In conclusion, HIV-1 establishes new strong correlations between various cytokines, thus imposing a high rigidity on their network that may contribute to the impaired capacity of the immune system to respond to microbial challenges. Seminal cytokines, in particular IL-7, may be key determinants of HIV-1 transmission from men to their uninfected female partners through vaginal intercourse and may become a new target for preventive and therapeutic strategies.

125**Progress Toward A Cure for HIV****Alain Lefeuvre****General Hospital, Toulon, FR**

Combined antiretroviral therapy (cART) has dramatically increased life expectancy during HIV infection but must be taken life-long. Consequently, it carries problems of compliance, resistance, toxicity and cost. Finding a cure against HIV would resolve these issues. In theory, it could be either a "functional" or a "sterilizing" cure, but its main goal would be to keep HIV replication at bay without continuing cART. A couple of situations already exist where this has been achieved:

- The Berlin patient who is free of cART more than 5 years following an allogenic bone marrow transplant from a donor with the delta 32 mutation on the CCR5 gene;
- The "Mississippi child" who received cART within 31 hours after birth;
- The "VISCONTI" patients who received cART at acute HIV infection and remained aviremic when this therapy was stopped a few years later;
- Two patients who received allogenic stem cell transplantation for lymphomas and have no trace of HIV, although cART is still continued.

Developing therapeutic strategies toward a HIV cure needs a deep understanding of the mechanisms that allow HIV persistence in reservoirs despite cART. Using current knowledge, approaches trying to purge the HIV reservoir have reached clinical trials using vorinostat. These trials showed the need of more potent activators combined with an immunologic intervention to eliminate cells where latent HIV has been activated. However, as the HIV reservoir is probably more complex than initially thought, other strategies than reactivation have to be pursued, including gene therapy.

126**Questions and challenges in HIV drug resistance: A molecular perspective****Luis Menéndez-Arias**

Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), ES

The introduction of potent combination therapies in the mid-90s had a tremendous impact on AIDS mortality. However, drug resistance has been a major factor contributing to antiretroviral therapy failure. At present, reverse transcriptase (RT) inhibitors constitute the backbone of successful antiretroviral therapies. The HIV-1 RT is a heterodimer composed of subunits of 560 and 440 amino acids. Mutations in the RT-coding region selected during treatment with nucleoside RT inhibitors (NRTIs) confer resistance by altering discrimination between NRTIs and natural substrates (dNTPs), or by conferring a phosphorolytic activity (dependent on pyrophosphate or ATP) that unblocks the chain-terminating inhibitor from the 3' end of the DNA that is being synthesized. The most relevant mutations conferring resistance to RT inhibitors map within the DNA polymerase domain of the RT (first 260 residues), and this region is subjected to genotypic analysis in order to select the proper antiretroviral treatment.

Despite the reasonable knowledge of the correlates between HIV genotype and the virological response to current therapies, our knowledge is still incomplete. The effects of antagonistic mutations and amino acid substitutions outside the DNA polymerase domain of the RT have been poorly characterized and examples will be given to illustrate the complexities of mutational patterns involved in resistance. In addition, I will provide examples of epistatic effects of HIV-1 protease and RT mutations that could affect viral fitness. Finally, an overview of mutational pathways and mechanisms of resistance to novel antiretroviral drugs (e.g. raltegravir, elvitegravir, etravirine, rilpivirine and maraviroc) will be briefly presented.

127**Safety, pharmokinetics and efficacy of VM-1500, a novel reverse transcriptase inhibitor, In healthy volunteers and HIV-infected patients****Vadim Bichko, M.D.**

Viriom Ltd. (Russia)

No abstract provided.

128**Cure of HBV infection: can APOBEC3 deaminases mediate it?****Ulrike Protzer**

Technische Universität München / Helmholtz Zentrum München, DE

Current antivirals cannot efficiently control but not eliminate hepatitis B virus (HBV) in the 300 million carriers at risk to develop liver diseases and cancer, because HBV establishes a stable nuclear cccDNA in infected hepatocytes. Interferon can clear HBV but therapeutic dosing is limited by side effects. We found a mechanism by which nuclear viral DNA can specifically be degraded. In HBV-infected cells and primary human hepatocytes, human liver-needle biopsies and in vivo mouse models, interferon and even at much lower doses lymphotoxin- $\alpha\beta$ -receptor activation up-regulated nuclear APOBEC3 family deaminases. Cytidine-deamination resulted in apurinic/apyrimidinic site formation and finally cccDNA degradation. No deamination was detected in genomic DNA since HBV-core protein targeted the APOBEC3 protein to cccDNA. Inducing nuclear APOBEC3 deaminases e.g. by triggering the lymphotoxin- $\alpha\beta$ -receptor pathway will be of high interest for the development of new therapeutics. The combination with existing antivirals shows great promise to eliminate the virus in chronic hepatitis B.

129**Polio Vaccines: The Past, Present and the Future****Konstantin Chumakov**

FDA Office of Vaccines Research and Review, US

Inactivated Polio Vaccine (IPV) and live Oral Polio Vaccine (OPV) are among the most successful and widely used vaccines in the history of medicine. The history of their development and subsequent evolution in response to changing epidemiological and socio-economic circumstances will be reviewed along with new efforts to develop a new generation of polio vaccines. OPV was responsible for virtual elimination of the disease, and its worldwide eradication may be achieved in few years. Paradoxically, this monumental accomplishment demands introduction of a new generation of vaccines specifically designed for the new polio-free world to ensure the lasting success of the eradication campaign. Both current vaccines have their strengths and weaknesses: OPV is inexpensive and easy to administer, but its virus can revert to virulence and cause paralytic disease. IPV is highly efficient and safe but is more expensive, requires several intramuscular injections, and does not induce fully adequate mucosal immunity. New vaccines must combine the best characteristics of both. Lower cost of IPV and broader immune response could be achieved by using adjuvants, alternative routes of administration, and increasing production yield. Production of IPV is associated with biosecurity concerns because it is made from highly virulent strains. Novel approaches to reduce virulence of strains used for IPV manufacture will be discussed. Development of a more genetically stable OPV is underway by attempting to reduce rates of mutations and recombination. Polio vaccines were a paradigm for many other vaccines, and lessons learned from their evolution could help develop other prophylactic products.

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Reinhard Kurth Honorary Lecture
**HTLV-I and Adult T Cell Leukemia/
 Lymphoma (ATLL) : Cellular and Molecular
 Basis of Transformation**

William W Hall, Hirofumi Sawa and Hideki Hasegawa
 University College, Dublin, IE; Hokkaido University,
 Sapporo, JP; National Institute of Infectious Diseases,
 Tokyo, JP

HTLV-I infection is endemic in a number of well defined geographical regions and is associated with the development of ATLL, an aggressive T cell malignancy. While the pathogenesis of ATLL is incompletely understood, the viral regulatory and oncoprotein Tax is considered to play a central role. To better understand the role of Tax and to develop animal models of disease we have generated transgenic mouse models which have remarkably reproduced the clinical, pathological, hematological and molecular features of human disease. Studies on the latter have highlighted the important role of chemokines in the infiltrative and migratory properties of malignant cells, allowed the identification of specific cellular signalling pathways involved and the employment of specific inhibitors as treatment modalities. Treatment responses however have been limited and this can be attributed to the presence of cancer stem cells (CLCs). We will describe the identification and characteristics of the CLCs and demonstrate their important role in disease progression. In addition we will summarise studies employing proteomic approaches to identify unique CLC protein expression profiles which may serve as important targets towards eradicating the CLC population and which might serve as key therapeutics.

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Replication and assembly of filoviruses
 Larissa Kolesnikova, Gordian Schudt, Olga Dolnik,
 and Stephan Becker
 Institut für Virologie, Philipps-Universität
 Marburg, DE

The family of *Filoviridae* comprises Marburg and Ebola virus which both cause severe life-threatening diseases characterized by high fever, rash, thrombocytopenia and hemorrhagic diathesis. The pathogenesis of the syndrome is not completely understood; probably the dynamic replication of filoviruses in the infected host leads to an uncoordinated immune response. Detailed understanding of the basic mechanisms of filoviral assembly and interaction with host cells is key to identify targets of antiviral intervention. The first sign of filovirus replication that can be detected microscopically in the infected cell is the formation of inclusions in the perinuclear region. Inclusions contain all filoviral nucleocapsid proteins (NP, VP35, VP30, VP24, and L) but also the matrix protein VP40 and a number of cellular proteins. Viral nucleocapsids are formed within the inclusions by specific interactions among the viral proteins. Mature nucleocapsids are transported across the cytoplasm to the plasma membrane with the help of the actin cytoskeleton. In the cell periphery nucleocapsids are associated with the matrix protein and channeled into filopodia, the site of filoviral release. Nucleocapsids inside filopodia are cotransported together with the unconventional motor protein myosin 10. Transport of nucleocapsids and release of viral particles is supported by the cellular ESCRT machinery.

132**A Novel Pathway of Proviral HIV-1 Latency Regulated by Aminoacid Starvation and HDAC4**

Guido Poli, Elisa Vicenzi, Maria Vittoria Schiaffino and Carine Van Lint
Vita-Salute San Raffaele University and Scientific Institute, IT

An intrinsic property of all retroviruses is their capacity to establish a state of latent infection in addition to active viral replication. Both genetic and epigenetic factors contribute to silence the integrated provirus and are nowadays targets of experimental approaches aiming at reactivating virus expression in order to kill the infected cells either by immune-mediated mechanisms (such as CTL) or by pharmacological agents. We have recently uncovered an unsuspected pathway triggered by essential aminoacid starvation and involving the downregulation of HDAC4, a class II HDAC, leading to a significant uprising of latent HIV-1 infection in chronically infected cell lines, such as ACH-2 cells, expressing this enzyme, but not in similar cell lines, such as U1, negative for HDAC4 expression. Both pharmacological targeting of HDAC4 and siRNA-mediated downregulation of its expression gave the same result. A similar phenomenon was observed for heterologous transgenes, driven by different promoters, introduced for gene therapy purposes, but not for their endogenous counterparts. This observation suggests that the mTOR-independent pathway triggered by aminoacid starvation and involving HDAC4 modulation represents or contributes to an intracellular response to foreign nucleic acids (I. Palmisano et al., PNASPlus 2012). More recent results with a broader variety of HIV-1 latency models will be discussed.

133**Structural basis for ebolavirus matrix assembly and budding; protein plasticity allows multiple functions**

Zachary Bornholdt, Takeshi Noda, Dafna Abelson, Peter Halfmann, Malcolm Wood, Yoshihiro Kawaoa, Erica Ollmann Saphire
The Scripps Research Institute, California, US

Proteins, particularly viral proteins, can be multifunctional, but the mechanism(s) behind this trait are not fully understood. Here, we illustrate through multiple crystal structures, biochemistry and cellular microscopy that the Ebola virus VP40 protein rearranges into different structures, each with a distinct and essential function required for the ebolavirus life cycle. A butterfly-shaped VP40 dimer trafficks to the cellular membrane. There, electrostatic interactions trigger rearrangement of the polypeptide into a linear hexamer. These hexamers construct a multi-layered, filamentous matrix structure that is critical for budding and resembles tomograms of authentic virions. A third structure of VP40, formed by a different rearrangement, is not involved in virus assembly, but instead uniquely binds RNA to regulate viral transcription inside infected cells. These results provide a functional model for ebolavirus matrix assembly and the other roles of VP40 in the virus life cycle, and demonstrate how a single, wild-type, unmodified polypeptide can assemble into different structures for different functions.

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A cellular restriction factor blocking replication of an emerging bunyavirus in human cells: clues for cross-species barriers?

Mariana Varela, Ilaria Piras, Angela McLees, Catrina Mullan, Frederick Arnaud, Xiaohong Shi, Esther Schnettler, Alain Kohl, Richard Elliott and Massimo Palmarini

MRC-University of Glasgow Centre for Virus Research, UK

Schmallenberg virus (SBV) is a novel orthobunyavirus of ruminants that emerged in Europe in the summer of 2011. Although mild clinical signs are observed in infected adult animals, transplacental infection has been associated with the development of congenital malformations, stillbirths and abortions. SBV has spread dramatically across north-western Europe reaching 100% prevalence in some herds. Despite antibodies against SBV being found in a variety of animal species neither human cases nor positive serology in highly exposed humans have been detected.

We have recently developed molecular and serological tools, and an experimental *in vivo* model as a platform to study SBV pathogenesis, tropism and virus-host cell interactions. Specifically we developed a reverse genetics system that aided us in unraveling determinants of virulence.

Here, we report identification of a cellular factor that restricts SBV replication. While the human orthologue restricts SBV replication under different experimental conditions, no restriction is observed by the ovine counterparts. We show that the restriction is specific since SBV replication is restored under the presence of a known viral restriction factor antagonist. We also show that this viral restriction factor and SBV nucleocapsid co-localize at the cell membrane and in the perinuclear region and we partially unravel the mechanism of restriction. Based on these results we hypothesize that the lack of positive human serology to SBV is related to the ability of this cellular factor to restrict SBV replication and we are currently exploring if these findings can be extended to other bunyaviruses.

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HIV-associated immunodeficiency despite potent antiretroviral therapy with CD4 T cell reconstitution

Bhawna Poonia, Suchita Chaudry, Haishan Li, Cristiana Cairo and C. David Pauza

Institute of Human Virology, University of Maryland School of Medicine, US

CD4 T cell reconstitution in patients with HIV is associated with increased responses to conventional vaccines and improved resistance to opportunistic infections. However, prolonged therapy fails to replenish a capacity for immune control over HIV and patients who interrupt therapy inevitably rebound to pre-treatment viral burden in plasma. Only elite patients, termed NVS or natural virus suppressors (1), control viremia to undetectable levels in the absence of therapy. Our earlier studies on NVS patients showed that this group was distinguished from all other HIV patients by the presence of normal levels of CD56+ V 2V 2 T cells in blood (2) reflecting reconstitution of the T cell receptor repertoire through new cell synthesis (3). The CD56 marker identifies cytotoxic effector lymphocytes including NK, CD8, T and NKT subsets, but its function remains unknown. We have now shown persistent depression of CD56 expression on CD8 T cells from HIV+ individuals except for NVS patients where the levels approach those found in normal controls. The CD56+ CD8 T cell subset is highly responsive to stimulus, expresses high levels of perforin/granzyme and the small population remaining in HIV patients on therapy, also express the immune exhaustion marker TIM-3, indicating cells may be lost through an apoptosis mechanism. The persisting defect in CD56 expression for two T cells subsets is consistent with a lack of cytolytic effector function and is present in patients with complete virus suppression for many years due to treatment, long after the T cell population is refreshed by new cell synthesis. The block to lytic effector function may explain why treated patients fail to eradicate viral reservoirs; this mechanism is a key target for new therapies designed to cure HIV disease.

1. M. M. Sajadi, A. Heredia, N. Le, N. T. Constantine, R. R. Redfield, HIV-1 natural viral suppressors: control of viral replication in the absence of therapy. *AIDS* **21**, 517 (2007).
2. D. J. Riedel et al., Natural viral suppressors of HIV-1 have a unique capacity to maintain gamma delta T cells. *AIDS* **23**, 1955 (2009).
3. S. Chaudry, C. Cairo, V. Venturi, C. D. Pauza, The gamma delta T cell receptor repertoire is reconstituted in HIV patients after prolonged antiretroviral therapy. *AIDS* **epub ahead of print**, (2013).

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HIV-1 Nef regulates activity of endoplasmic reticulum chaperone calnexin

Lucas Jennelle¹, Ruth Hunegnaw¹, Larisa Dubrovsky¹, Tatiana Pushkarsky¹, Michael L. Fitzgerald², Dmitri Sviridov³, and Michael Bukrinsky^{1*}

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HIV-1 Nef promotes viral replication by downmodulating a number of cell surface transmembrane proteins, such as CD4, MHC-I and MHC-II, which are targeted by Nef to various degradation pathways. Nef is also responsible for downregulation of cellular cholesterol transporter ABCA1, and this effect contributes to development of atherosclerosis in HIV infected patients. Surprisingly, in contrast to CD4 and MHC I, to which Nef has to bind to exert downregulation, binding to ABCA1 turned out to be unnecessary for inactivation of ABCA1 by Nef. Here, we identified a novel mechanism by which Nef influences activity of host cell and viral proteins. We show that Nef interacts with an endoplasmic reticulum chaperone calnexin, which is essential for folding and maturation of glycosylated proteins. Nef disrupts calnexin interaction with ABCA1, thus impairing functionality of this protein, but increases affinity and enhances interaction of calnexin with gp160, promoting maturation and functionality of viral Env proteins. Knock-down of calnexin lead to reduced fusion activity of HIV-1 envelope and reduced virion infectivity, as well as to defective cholesterol efflux, which is mediated by ABCA1. However, gp160 and ABCA1 interacted with calnexin differently: while gp160 binding to calnexin was dependent on glycosylation, interaction of ABCA1 with calnexin was glycosylation-independent. Therefore, Nef binds to calnexin and stimulates interaction between calnexin and gp160 at the expense of ABCA1 and probably other ER proteins. These results provide a mechanistic explanation for previously unexplained effect of Nef on functionality of ABCA1, and suggest a mechanism for upregulation of HIV infectivity by Nef through stimulation of Env maturation.

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Interplay between host defenses and viral anti-defenses as a major factor of viral cytopathogenicity

Vadim I. Agol

M.P.Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences and A.N.Belozerky Institute of Physical-Chemical Biology, Moscow State University, RU

The prevailing paradigm posits that virus-induced cellular injuries (cytopathic effect, CPE) are caused by hijacking of cellular substrates, energy, and infrastructure by the pathogens for the needs of their reproduction. However, this appears to be not the sole, and even not the most important, mechanism of cellular pathology triggered by viral infections. There is ground to believe that the most severe harm may come not from viral reproduction as such but rather from (miscalculated) host defenses as well as from viral anti-defensive activities. The experiments to be presented strongly support this notion. By using as a model system HeLa cells infected with mengovirus (a strain of encephalomyocarditis virus, a lytic picornavirus), we show that the major signs of CPE caused by this virus can be uncoupled from its reproduction. This can be achieved by partial mutual disarmament of the virus (by mutational inactivation of one of its anti-defensive "security" proteins, the leader protein) and the host (by chemical inhibition of one of its defensive innate immunity mechanisms, apoptosis). Under such conditions, the appearance of major cellular injuries is postponed until well after the completion of the viral reproduction. Remarkably, a more profound disarmament of the virus (by additional deletion of its second security protein, 2A) accompanied with a marked suppression of the viral reproduction leads to a faster death of the infected apoptosis-deficient cells due primarily to their defensive suicidal programmed necrosis. Thus, efficient strategies to ameliorate virus-induced injuries may include measures aimed at suppression of not only viral reproduction or viral anti-host functions but also of host defenses

138**Understanding protective immunity:
Lessons from measles**Wen-Hsuan Lin and Diane E. Griffin

Johns Hopkins Bloomberg School of Public Health, US

Measles is the poster child for establishment of life long immunity to re-infection. This is associated with a prolonged persistence of measles virus (MeV) RNA in blood and lymphoid tissue. The live attenuated vaccine is also effective, but the immune responses are less robust and of somewhat shorter duration than after natural infection. Through study of a variety of experimental DNA and virus-vectored vaccines in rhesus macaques followed by wild type MeV challenge, we have identified 4 levels of protective immunity: 1) protection from both rash and viremia; 2) protection from rash, but not viremia; 3) protection from rash and viremia, but not infection; 4) no protection with possibility of enhanced disease. Protection from rash requires high levels of high avidity MeV neutralizing antibody, but this is not sufficient to protect from viremia. MeV-specific T cells alone do not protect from rash or viremia, but lead to more rapid clearance of MeV RNA from blood. Antibody and T cell responses to the hemagglutinin (H) and fusion (F) surface glycoproteins protect from rash and viremia, but not infection leading to late appearance of viral RNA in blood. Parenteral or deep lung respiratory delivery of the live virus vaccine protects against rash, viremia and infection. Further studies are needed to determine if experimental vaccines require additional antigens or induction of a different type of immune response to recapitulate the protection provided by the live attenuated vaccine virus and natural infection.

139**Dengue vector control: critical needs and opportunities for helping to control the dengue pandemic**Barry Beaty

Department of Microbiology, Immunology, and Pathology, Colorado State University, US

Aedes aegypti mosquito control is currently the only option for controlling and preventing epidemic dengue and dengue hemorrhagic fever. However, current approaches for vector control are not stemming the rising tide of dengue disease throughout the tropical world. In the absence of a vaccine, new and effective approaches are needed to improve vector control. Novel approaches to prevent dengue virus transmission will be described and discussed, including 1) the Casa Segura approach to prevent dengue transmission in the home, 2) development of a new generation of molecular mosquitocides to address the rise of resistance to existing insecticides, and 3) engineering dengue virus resistant mosquitoes. There is a public health imperative to increase the armamentarium for vector control.

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[CONTENTS](#)[EVENTS SCHEDULE](#)[SPEAKER SCHEDULE](#)[ABSTRACTS INDEX](#)**Abstracts****140****Reversing the Epidemic of HIV-1C in Southern Africa with Treatment as Prevention****M. Essex****Harvard School of Public Health, US**

The epidemic of HIV-1C in southern Africa is characterized by a sustained prevalence that is substantially higher than for other epidemics of HIV/AIDS. Perhaps the best correlate of transmission is high viral load (HVL), which we target to prevent spread of HIV in a community randomization trial based on antiretroviral treatment (ART) as prevention (TasP). Designed for over 100,000 adults in 30 randomized villages in Botswana, this trial also utilizes other prevention interventions such as HIV testing, male circumcision, clinical linkage and ART chemoprophylaxis during pregnancy. Viral phylogenetics is used to estimate the proportion of incident infections originating in test villages, and thus the relative contribution of TasP for preventing transmissions. Analysis of results through modeling includes estimating cost effectiveness and estimations of contributions for different prevention interventions.

141**Gene Discovery and Data Sharing in Genome Wide Association Analyses: lessons from AIDS genetic restriction genes**

Stephen J O'Brien, Anton Svitin, Sergey Malov, Nikolay Cherkazov Pavel Dobrynin, Paul Geerts, Jennifer Troyer, Sher Hendrickson-Lambert, Efe Sezgin, Holli Hutcheson, Theodosius Dobzhansky Center for Genome Bioinformatics, St. Petersburg State University (RU)

As genome wide association studies plus whole genome sequence analyses for complex human disease determinants are expanding, it seems useful to develop strategies to facilitate large data sharing, rapid replication and validation of provocative statistical associations that straddle the threshold for genome wide significance. At this conference, we shall announce GWATCH, (Genome Wide Association Tracks Chromosome Highway) a web based data release platform that can freely display and inspect unabridged genome tracked association data without compromising privacy or Informed Consent constrictions, allowing for rapid discovery and replication opportunities. We illustrate the utility with HIV-AIDS resistance genes screened in combined large multicenter cohort studies GWAS (MACS, HGDS, MHGS, ALLIVE , LSOCA HOMER) developed and studied over the last decades.

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142**Sochi virus as a highly pathogenic and life-threatening agent****E.Tkachenko, T.Dzagurova, B.Klempa, D.Kruger****Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, RU; Institute of Virology, DE**

A new genotype of Dobrava-Belgrade virus (DOBV), Sochi virus, was found in the Black Sea field mouse, *Apodemus ponticus*. This mouse is naturally occurring in the Southern European Russia and transcaucasian countries between the Black and the Caspian Sea. Recently, cell culture isolates of Sochi virus have been generated from *A. ponticus* and an HFRS patient with fatal outcome.

At the present state of knowledge, Sochi virus seems to be the most dangerous representative of DOBV. Virus diagnostics in patients was accomplished by immunofluorescence assay, serotyping of neutralizing antibodies, and RT-PCR amplification of viral genome segments. In phylogenetic analyses we found a spatial clustering of the viral nucleotide sequences derived from patients and mice trapped at different localities of the Russian Black Sea coast region demonstrating Sochi virus as the causal pathogenic agent in humans. We currently oversee in detail the clinical courses of 51 patients with confirmed Sochi virus infection. The case fatality rate was determined to be as high as 14%. Nearly 60% of clinical courses were defined as severe (including deaths) and nearly 40% as moderate. Four times more males than females were affected. Quite unusual for hantavirus disease, also young people became ill due to Sochi virus infection; 10% of patients were found between 7 and 15 years old and the age average of all patients was not much higher than 30 years.

There is an urgent need to monitor the epidemiology of the new virus - not only because of its health-threatening character in this particular geographical area but also because of its potential ability to overcome host species barriers. Colonization of nearly related host species, as *A. flavicollis* or *A. sylvaticus*, by the virus could dramatically increase its geographical spread and consequently further enhance the danger for the human population.

143**Rift Valley fever virus: A virus with potential for global emergence****Janusz T. Paweska****Center for Emerging and Zoonotic Diseases,
National Institute for Communicable Diseases of the National Health Laboratory Service, ZA**

The capacity of Rift Valley fever virus (RVFV) to spread into new territories by crossing significant natural geographic barriers, re-emerge in endemic regions after long periods of silence to cause large outbreaks in human and animal populations constitute a formidable challenge for public and veterinary health authorities as well as for scientific communities worldwide. In spite of recent advances in research on RVFV pathogenesis, molecular epidemiology, outbreak prediction, development of new diagnostic tools and vaccines, some fundamental aspects of the epidemiology and ecology of the virus remain elusive. Large outbreaks of RVF are associated with anomalous high rainfalls leading to massive flooding and the resultant swarms of competent mosquito vectors transmitting the virus to a wide range of susceptible vertebrate species. However, the exact mechanism of RVFV natural transmission during interepizootic periods remains largely unknown, including the postulated long-term virus persistence in transovarially infected eggs of floodwater *Aedes* mosquito species, and the role of wild mammals as reservoirs. The presence of competent mosquito vectors in countries free of RVF, the wide range of mammals susceptible to the virus, the global changes in climate, and increased animal trade and travel are some of the factors which might contribute to international spread. This presentation provides the background to the major outbreaks, molecular biology and epidemiology of RVFV, and overviews aspects of ecology, host and vector range which make the virus a potential global emerging threat.

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Viral/bacterial mixed infections transmitted by ticks: Diagnosis and prevention in Russia

Korenberg, E. I.

Gamaleya Scientific Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation, RU

No abstract provided.

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Arbovirus and related infection disease in China

Guodong Liang

National Institute for Viral Disease Control and Prevention, China CDC

Arboviruses (arthropod-borne viruses) are maintained in nature in cycles involving hematophagous arthropod vectors such as mosquitoes, midges, ticks and susceptible vertebrate hosts human or animals. At present, more than 550 arboviruses have been identified, among which are more than 130 virus species that can cause disease in susceptible vertebrate hosts. Today, Dengue fever, West Nile virus disease, and Rift valley fever etc. still outbreak in the worldwide. Study of arboviruses not only becomes the important topics of virology, but also appears to be a social problem directly related with the public health.

Japanese Encephalitis Virus (JEV), Dengue Virus (DENV), Crimean-Congo Hemorrhagic Fever Virus (CCHFV) (also known as Xinjiang Hemorrhagic Fever Virus in Chinese, XHFV), and Tick-Borne Encephalitis Virus (TBEV) are the four principal arboviruses of public health importance in mainland China at present.

There is a growing body of evidence indicating that other arboviruses are present and causing human infections and disease in China. Over the past years, an investigation of arbovirus has been carried out in China, across the country, to learn more about arboviruses, or viruses spread by insects. The various specimens with a total number of 897, 369 have been collected from 29 provinces of mainland China, including 841, 576 mosquitoes, 16, 315 ticks, 5, 968 sandflies, 960 midges, 436 bats, 2, 309 animal specimens, 18, 579 clinical specimens from patients with fever and viral encephalitis and 13, 380 serum specimens from healthy populations. Total 512 arbovirues strains, belonging to 23 species in 10 genuses of 7 families, were isolated from various specimens, including Flavivirus, Alphavirus, Bunyavirus, dsRNA virus and DNA virus have been identified.

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Understanding the pathogenesis of prion and surveillance for human prion diseases in China

Xiao-Ping Dong

National Institute for Viral Disease Control and Prevention, China CDC

Through human prion disease cases, infectious animal models, cell models and prion proteins, the neuropathological and pathogenic characteristics of prion diseases, the cytotoxicity of pathological prion, the conversion and replication of prion and the infectivity of prion strains were comprehensively evaluated. With the established specimen bank of human and experimental prion diseases, several potential methodologies for diagnosis have been set up. Recently, high sensitive tools, e.g. PMCA and RT-QuIC, have been established. Since 2006, a national CJD surveillance has been conducted, covering 12 provinces in mainland China. The epidemiological, clinical and laboratory features of Chinese CJD were firstly described. Dozens of Chinese genetic prion diseases have been firstly identified.

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Globalization and New Challenges Caused of Communicable Diseases

Saulius Chaplinskas, MD, PhD

Center for Communicable Diseases and AIDS, LT

No abstract provided.

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148**HPV, HIV, and Cancer: A Global Challenge**Silvia Franceschi

The seminal discovery that human papillomavirus (HPV) infection causes cervical cancer provides an opportunity for prevention by vaccination and new screening approaches. Approximately 600,000 new cancer cases per year are attributable to HPV worldwide of which about half million in less developed countries (de Martel et al, Lancet Oncology, 2012). These cancers include all cervical cancers, the vast majority of anal cancers and approximately half of cancers of the vulva, vagina, and penis. In the head and neck, HPV is clearly involved in a fraction of cancer of the oropharynx that varies between 10% and 70% by geographic area and the burden of cancer caused by tobacco use. Most HPV infection is harmless and clears spontaneously but persistent infection with high risk HPV (notably type 16) is one of the most powerful human carcinogens. HPV disrupts normal cell cycle control promoting uncontrolled cell division and the accumulation of genetic damage. Two effective prophylactic vaccines composed of HPV-16/18 and HPV-16/18/6/11 virus like particles have been introduced in many developed countries as a primary prevention strategy. HPV testing is clinically valuable for secondary prevention in triaging low grade cytology and as a test of cure following treatment. More sensitive than cytology, primary screening by HPV testing could allow screening intervals to be extended. If these prevention strategies can be implemented in developing countries, many thousands of lives could be saved. HIV-positive individuals are at increased risk of HPV infection and cancer sites associated with HPV. cART and cervical screening may avoid an increase in cervical cancer in sub-Saharan cancer.

149**HCV AND lymphoma: Genetic and epigenetic factors**Zignego AL, Gragnani L, Fognani E, Piluso A

Center for Systemic Manifestation of Hepatitis Viruses- University of Florence, IT

Over 180 million people worldwide are chronically infected with the hepatitis C virus (HCV). HCV infection is a major cause for hepatocellular carcinoma (HCC), moreover the association with B-cell lymphoproliferative disorders (LPDs) like mixed cryoglobulinemia (MC) or B-cell non-Hodgkin lymphoma (B-NHL) is undisputed. The mechanisms by which HCV contributes to LPD development are still poorly understood. Available data suggest that the viral infection may induce LPDs through a multifactorial and multistep process that involves the sustained activation of B cells, the abnormal and prolonged B cell survival, and genetic and/or epigenetic factors.

Concerning genetic factors, different authors reported an association between specific HLA clusters or B-cell activating factor promoter genotype and a higher risk of developing MC and lymphoma. In addition, the results of a large, ongoing genome wide association study (GWAS) will probably allow the identification of specific genetic profile of HCV patients with LPDs.

Furthermore, microRNAs (miRNAs) can give a major contribution to the pathogenesis of several neoplastic, lymphoproliferative diseases and it is conceivable their involvement in the pathogenesis of HCV-related LPDs. We recently showed that specific miRNAs were differently modulated in PBMCs from HCV patients who developed MC and/or NHL. In addition, HCV patients who developed HCC, showed a differential miRNAs regulation.

In conclusion, available data suggest that the genetic/epigenetic analysis of HCV-related cancerogenesis is of great usefulness in both the pathogenetic and clinical/translational areas possibly allowing the definition of diagnostic/prognostic markers for early detection of lymphatic or hepatic cancer.

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Carcinogenesis of HPV

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Human papillomavirus are oncogenic DNA virus able to transform cutaneous and mucosal epithelial cells. The most relevant transforming mechanisms is the down-regulation of two oncosuppressor genes: p53 and pRb. For their frequency of detection in invasive lesions some genotypes have been defined "high risk" and their carcinogenicity has been referred to (a) their capacity to induce persistent infections, for the efficacy to escape the host immune system, (b) the binding affinity of their E6/E7 oncoprotein to the respective oncosuppressors, and (c) their efficacy to induce genomic instability. In vivo risk of cancer progression, in particular transition from pre-invasive to invasive cancer lesions, and the subsequent frequency of developing metastatic lesions as well as responsivity to anticancer treatment, is due to specific virus-host interactions and genomic damages. As paradigm the better prognosis and higher responsivity to treatment of HPV-positive oropharyngeal cancers in comparison to HPV-negative cancers. Mutations in genes of the apoptotic pathway, particularly the TP53 gene, have been analyzed in cervical cancers. A significant higher mutation frequency of TP53 gene in the CAC adenocarcinoma (32 of 241; 13.3%) compared to SCC squamous cell carcinoma (39 of 657; 5.9%; P=0.0003, (2) test) has been identified. Three codons (175, 248 and 273) were the most commonly mutated in both, codon 249 mainly in SCC, codon 282 only in CAC. The G to A and C to T transitions were the prevalent type of mutations in both SCC and CAC (48.7% and 53.5% of all mutations, respectively). The frequency of C to A transversion was relatively high only in CAC (25%), while the mirror mutation G to T was comparatively frequent in SCC (14.6%).

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Using genomics to search for new viral causes and treatments for human cancer

**Patrick S. Moore, Yuan Chang
American Cancer Society Professor, Cancer Virology Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA, US**

Although animal polyomaviruses, such as SV40, have been critical models in cancer research for over one-half century, polyomaviruses have not--until recently--been linked to human cancer. Using digital transcriptome subtraction, Merkel cell polyomavirus (MCV) was discovered in 2008 to infect most Merkel cell carcinomas, the most severe form of skin cancer. Normally, MCV is a common and asymptomatic infection of the human skin. In Merkel cell tumors, however, the virus integrates and undergoes mutations that eliminate viral replication but allow continued expression of viral oncogenes. MCV and MCC reveal a new model for carcinogenesis in which a rare combination of xenomutations to healthy skin flora initiate a deadly cancer. Using new sequencing technologies, the causes previously-unsuspected viral cancers can be uncovered and clues for new rational drug therapies can be designed.

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152**Insights into the pathogenesis of HHV8-driven body cavity-based lymphoma**

Maria Luisa Calabro¹, Laura Lignitto¹, Adriana Mattiolo¹, Elena Negri¹, Luca Persano², Lisa Ganesello¹,

Luigi Chieco-Bianchi³

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Human herpesvirus 8 is associated with the development of primary effusion lymphoma (PEL), an aggressive non-Hodgkin's lymphoma characterized by the proliferation of the malignant lymphocytes almost exclusively in large serous cavities. The mechanisms involved in the preferential tropism for serous cavities and in the aggressive course of PEL remain to be fully clarified. To study the role of host microenvironment in PEL progression, we previously compared the antineoplastic activity of a murine interferon- \diamond -expressing lentiviral vector (mIFN- \diamond -LV) to that of a human IFN- \diamond -LV in a murine model of peritoneal PEL. We demonstrated that in vivo targeting of the murine microenvironment showed an antineoplastic activity comparable to that observed with the hIFN- \diamond -LV. These findings highlighted the relevant role of body cavity environment in PEL growth and indicated that modulation of microenvironment may impair PEL growth in vivo. By using cocultures of PEL cell lines with human mesothelial cells (HMC), we mimicked the interactions existing in body cavities to analyze the mechanisms involved in PEL progression. PEL cells induced a myofibroblastic morphology in HMC, paralleled by an expression profile indicative of the occurrence of epithelial-mesenchymal transition (EMT). Moreover, HMC increased proliferation and resistance to apoptosis of PEL cells. These data indicate that PEL cells induce EMT in HMC and fibrosis of serous membranes. In turn, HMC modulate PEL cell turnover, thus providing a milieu favorable to PEL progression. These findings open new perspectives into the mechanisms involved in PEL progression and may indicate new targets for PEL treatment.

153**Molecular pathogenesis by HTLV-1 bZIP factor**

Masao Matsuoka

Institute for Virus Research, Kyoto University, JP

Human T-cell leukemia virus type 1 (HTLV-1) mainly transmits by cell-to-cell contact. Therefore, this virus induces proliferation of infected cells to facilitate transmission. In HTLV-1 infected individuals, infected cells proliferate in vivo. This proliferation of infected cells leads to the development of adult T-cell leukemia (ATL) and inflammatory diseases including HTLV-1 associated myelopathy (HAM). HTLV-1 bZIP factor (HBZ) is consistently expressed in ATL cells and HTLV-1 infected cells, and plays a critical role in their proliferation. Transgenic expression of HBZ causes T-cell lymphoma and inflammatory diseases, indicating that HBZ is critical for the pathogenesis of HTLV-1.

We analyzed the function of HBZ and found that it possessed opposite functions to Tax in many pathways. We found that Tax could activate the classical Wnt pathway while HBZ inhibited it by interacting with TCF1/LEF1. The canonical Wnt pathway is activated in the thymus, and its transcription factors, TCF1/LEF1, suppressed the viral gene transcription by Tax. Conversely, the canonical Wnt pathway is suppressed in the peripheral T cells in which the non-canonical Wnt pathway is activated. HBZ enhanced the expression of Wnt5a, which is a ligand in non-canonical Wnt signaling. Knockdown of Wnt5a suppressed the proliferation and migration of ATL cells. Thus, activation of the non-canonical Wnt pathway by HBZ is linked with proliferation of ATL cells.

These findings suggest that HTLV-1 is adapted to, not thymic T cells, but peripheral T cells. HBZ modulates the intracellular environment suitable for HTLV-1 replication and proliferation of infected cells.

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Responding to the challenge of AIDS Associated Cancers in Nigeria**Dr. William Blattner and Clement Adebamowo**

The stabilization of the HIV epidemic in Africa has uncovered new epidemic of HIV associated comorbidities including cancers which the poorly developed health care system, poor infrastructure and lack of personnel is unable to cope with. In November 2012, international leaders in Cancer Research and Policy from 15 countries met at the NIH, Bethesda and made recommendations about the interventions needed to respond to the global cancer challenge in the world. These include (a) Creation of reliable, population-based registries that define the incidence, mortality, and survival rates of different types of cancers (b) Implementation of prevention measures to mitigate factors now known to promote cancer—tobacco, certain infectious agents, ultraviolet radiation, alcohol, obesity, lack of exercise, and diet, (c) Screening individuals for certain cancers (of the cervix, breast, prostate, and colorectum, in particular) and (d) Optimal cancer treatment. In this presentation, I will highlight how the Institute of Human Virology, University of Maryland (IHV) and the Institute of Human Virology Nigeria (IHVN) working with partners in Nigeria and internationally have implemented these recommendations and present data illustrating the outcome of our interventions. For example, Since 2010, 21 cancer registries have been developed or re-strengthened in Nigeria and 3 of these have met the WHO criteria for population based cancer registration (PBCR). These registries are now able to contribute data to the global cancer incidence database after more than 30 years during which there was no data from Nigeria. With mainstreaming of an additional 3 PBCR this year, we would have increased the proportion of Africa covered by PBCR from 11% to 32%. Our results also correct distortions in the estimates of cancer incidence and mortality in Nigeria which was previously based on projections derived from data from cancer registries of other African countries that had been used in the past.

Cervical cancer is the commonest female cancer in Africa and in women living with HIV/AIDS. Implementation of screening programs has reduced incidence in developed countries by 80% in recent decades but incidence in developing countries remain stable or has been increasing. IHV implements an innovative “screen and treat” with immediate treatment with cold coagulation, digital cervicography for QA/QC and web based consultation for second opinion for early detection of cervical cancer. In collaboration with the Nigerian authorities and other partners, this program plans to reach 1,000,000 Nigerian women with at least 1 lifetime screening event over the next 10 years.

This screening project laid the foundation for the NIH funded African Collaborative Center for Microbiome and Genomics Research (ACCME), part of the Wellcome Trust and NIH funded H3Africa initiative, which we set up at the IHVN and is currently engaged in integrative epidemiology of cervical cancer that is exploring the host and viral genomics and epigenomics, somatic cervical cancer genomics as part of NIH led Cancer Genome Atlas mapping project (TCGA), vaginal microenvironment – innate immunity and vaginal microbiota, as well as detailed risk factor characterization of prevalent and persistent HPV infection. Preliminary results from early studies conducted at this Center will be presented.

Because of dearth of systematic information about the epidemiology of AIDS Associated Cancers in Africa, we have created a matched prospective cohort of persons living with HIV/AIDS and healthy volunteers who are being followed up every 2 years with detailed clinical evaluation and collection of data and biological samples in order to improve knowledge of the epidemiology of HIV Associated Comorbidities and provide high quality biological samples for molecular and omics studies. In my presentation, I will also mention some of the trainings that we have conducted, research into other cancer risk factors and the work we are doing to map the infrastructural needs for oncology treatment in Nigeria.

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Evolution by Tumor Neofunctionalization and Phenomenon of Tumor Specifically Expressed, Evolutionarily Novel (TSEEN) genes**Andrei P. Kozlov, PhD****The Biomedical Center, St. Petersburg (RU)**

Earlier I formulated the hypothesis of the possible evolutionary role of tumors. This hypothesis suggests that tumors supply evolving multicellular organisms with extra cell masses for the expression of newly evolving genes. After expression of novel genes in tumor cells, tumors differentiate in new directions and give rise to new cell types, tissues and organs.

In the presentation, the bulk of data supporting the positive evolutionary role of tumors will be reviewed, obtained both in the lab of the author and from the literature sources.

The following issues will be addressed: the widespread occurrence of tumors in multicellular organisms; features of tumors that could be used in evolution; the relationship of tumors to evo-devo; examples of recapitulation of some tumor features in recently evolved organs; the types of tumors that might play the role in evolution; examples of tumors that have played the role in evolution.

The discussion of experimental confirmation of nontrivial predictions of the hypothesis will include the analysis of evolutionary novelty of tumor-specifically expressed EST sequences; ELFNI – AS1, a human gene with possible microRNA function expressed predominantly in tumors and originated in primates; PBOV1, a human gene of the recent de novo origin with predicted highly tumor-specific expression profile; and the evolutionary novelty of human cancer/testis antigen genes.

The conclusion is made that expression of protogenes, evolutionarily young and/or novel genes in tumors might be a new biological phenomenon, a phenomenon of TSEEN (**T**umor **S**pecifically **E**xpressed, **E**volutionarily **N**ew) genes, predicted by the hypothesis of evolution by tumor neofunctionalization.

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HIV and metabolic disease: Clues to control of HIV infection from the immune and virological response to high dose Vitamin D challenge

Barry Peters

Kings College London, UK

Effective use of HAART markedly reduces morbidity and mortality due to classical HIV disease. The 4 key emerging diseases in people with HIV that are amenable to prevention & therapy are Coronary Heart Disease, Renal Disease, Fragility Fractures, Diabetes.

These constitute an increasing burden of morbidity and mortality in HIV uninfected people due to an aging population and are becoming even more prevalent in people with chronic HIV.

The issue is exemplified by fragility fractures, a major cause of mortality in the elderly, and emerging as a manifestation occurring earlier in people with HIV, and increasing in incidence.

The Probono Study from Kings College London demonstrated among 222 patients with matched controls that reported fractures at any site during adulthood occurred more frequently in HIV than controls, 45 (20.3%) vs. 16 (7.2%) (OR=3.27; p=0.0001). Osteoporosis was more prevalent in HIV (17.6% vs. 3.6%, p<0.0001). In HIV, use of highly active antiretroviral therapy (HAART), low body mass and serum PTH were significantly related to low BMD in multivariate analysis.

The changing patterns of morbidity and mortality in HIV, driven by the metabolic consequences of HIV infection itself, and the HAART therapy requires development of an appropriate screening and management response.

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Pathogenesis of Epstein-Barr Virus-driven lymphomas of HIV+ patients: new insights of potential clinical relevance

Riccardo Dolcetti

C.R.O. – IRCCS, National Cancer Institute, IT

Human Immunodeficiency Virus (HIV)+ patients have an increased risk to develop lymphomas, including a significant fraction of histotypes associated with Epstein-Barr Virus (EBV) infection. Although restoration of EBV-specific T-cell function induced by HAART has led to a decreased incidence of the more immunogenic EBV-associated lymphomas, such as immunoblastic and primary central nervous system lymphomas, other EBV+ histotypes are still prevalent in the HAART era, particularly Hodgkin's lymphoma. Therefore, factors other than HIV-induced immune suppression are probably required for the development of EBV-related lymphomas in this setting. Particular attention is being given to the identification of microenvironmental stimuli able to up-regulate critical EBV latency proteins or to induce/enhance EBV replication. In fact, recent evidence indicates that, although latency programs predominate in EBV-driven tumors, lytic EBV replication may also be of pathogenic relevance, at least in the early phases of cell transformation. This is particularly relevant for HIV-related lymphomagenesis since the underlying impairment of immune responses may favour uncontrolled activation of EBV lytic replication in latently-infected B lymphocytes. Available data indicate that local expression of distinct cytokines, including IL-4 and IL-13, may up-regulate the expression of the LMP-1 oncoprotein in B cells, thus favoring lymphomagenesis. In the search of microenvironmental factors that may promote the development of EBV-driven lymphomas in HIV+ patients, we obtained evidence supporting a pathogenic role for HIV matrix protein p17, which accumulates in lymphoid tissues of HIV+ individuals, even during HAART. Our findings support a direct contribution of HIV p17 to the development of EBV-driven lymphomagenesis and may provide the rationale for new strategies of clinical intervention in this setting.

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Hepatitis C Treatment Update: Current Status and Future Directions**Shyam Kottilil****National Institute of Allergy and Infectious Diseases,
NIH, US**

Hepatitis C virus infection is a major cause of liver disease, with 170 million persons infected worldwide. Hepatitis C virus is a ssRNA virus that preferentially infects human hepatocytes. Approximately 80% of HCV infections progress to chronicity, with development of hepatic fibrosis over time with 20% developing cirrhosis within 25 years, and 20% of these developing hepatocellular carcinoma. HCV remains the primary cause of liver transplantation worldwide. Of the 1 million people infected with HIV in the United States, about a third are co-infected with HCV. While cART has dramatically decreased the number of AIDS-related opportunistic infections, HCV-related liver disease has become leading cause of death in this population. HIV/HCV coinfecting individuals have an accelerated progression of liver disease and lower therapeutic response rates when compared to their HCV mono-infected counterparts. In light of the higher rates of adverse events observed with current treatment in HIV/HCV coinfecting patients, there remains a need for therapies with improved response rates, convenient dosing schedules, and safety profiles. Currently, the field of HCV therapeutics is evolving to rapidly develop strategies that are highly safe and efficacious for the eradication of HCV without the use of interferon formulations. Directly acting antivirals that target various stages of the HCV life cycle are being developed and will likely revolutionize the management of HCV by simplifying treatment, improving tolerability of regimens, and decreasing duration of therapy while maintaining or increasing rates of SVR. This presentation will discuss the newer therapeutics that are being developed for treating hepatitis C in HIV-infected subjects.

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Hepatitis B Treatment Update: Current Status and Future Directions**Rohit Talwani****Institute of Human Virology, US**

The current standard of care for chronic hepatitis B infections entails use of nucleoside/nucleotide analogue reverse transcriptase inhibitors or pegylated interferon. The presentation will:

- Provide an overview of the current standard of care for treatment of chronic HBV in patients with and without HIV co-infection including a review of treatment endpoints in chronic HBV infection
- Explore future directions of HBV treatment including an evaluation of strategies geared toward attaining a functional cure of chronic HBV infection

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Treatment Strategies to Minimize the Impact of Antiretroviral Drug Toxicities

Bruce Gilliam**Institute of Human Virology, US**

Treatment success with antiretroviral drug regimens continues to improve. However, as HIV infected patients live longer, the clinician and patient are challenged with managing the complications of numerous co-morbidities and drug toxicities. While some of these problems may not be able to be prevented, the availability of multiple new antiretroviral agents now gives the clinician and patient multiple options to achieve virologic suppression. This raises the question of which combinations of antiretroviral agents have optimal safety and toxicity profiles for the individual patient. The potential implications of the choice and usage of certain antiretroviral agents and regimens and their known and potential advantages and disadvantages/toxicities will be reviewed and the avenues for further investigation will be highlighted. The complexities of managing an HIV infected patient today, including co-morbidities and antiretroviral drug toxicities, suggest that newer treatment strategies which reevaluate the factors and considerations that influence how antiretroviral agents and regimens are chosen may well move away from the currently recommended regimens in the future to attain the goal of minimization of long-term antiretroviral toxicities.

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Anti-tuberculosis Treatment for HIV-positive Patients in Moscow

E.M.Bogorodskaya**Moscow City Research and Practical Centre for Tuberculosis Control**

No abstract provided.

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Challenges Fueling the Complexities of TB Diagnosis & TB/HIV Comorbidity in Tanzania- IHV experience

**Abubakar Maghimbji, MD, Mtebe Majigo, MD,
Vincent Mashinji, MD, George Loy, MD, Sekela
Mwakyusa MD**

Institute of Human Virology, University of Maryland
School of Medicine (TZ)

Background: Tanzania with a population of 44.9 million is classified as one of the 22 high burden countries for tuberculosis (TB). The country houses 5,972 health facilities; the majority in urban areas while rural areas have limited access to TB diagnostic services. The TB notification rate for all cases in 2011 was 153/100,000 people with 59/100,000 being smear positive. Nevertheless, the 2013 National TB prevalence survey revealed prevalence of bacteriological confirmed TB was 354/100,000 with the rural areas more affected. The findings signify more TB than reported. TB continues to major driver of mortality in HIV patients, as reported by facilities supported by IHV, with the highest mortality in our HIV project. 20% died while on TB treatment and 73% died with symptoms of TB. **Challenges:** IHV's program reports a low rate of TB among HIV patients. By June 2013, 20 districts treated 35,502 HIV patients, with only 1% diagnosed with TB; almost half being from 4 districts with the TB intervention project. The result is likely due to insufficient diagnostic services. In some areas, patients travel 100km to access services. More refined diagnostic techniques to increase sensitivity like LED Microscopy, molecular technology, and sputum culture are insufficient which poses particular challenges for HIV/AIDS patients. TB detection activities have primarily remained health facility based endeavors with minimal community involvement. These circumstances do not provide for an optimal environment for increased TB case detection and hence hinders TB control efforts. **Interventions:** IHV implements a WHO funded TB program in Tanzania to support active intensified case management which has led to finding more TB cases, with 38% of all forms of TB, and 36% Smear and/or bacteriological positive. Our challenge was the inadequacy of sensitive diagnostic facilities, and hence installed one GeneXpert machine which registered an increase of 6.6% TB cases that were missed by fluorescent microscopy. Building on experience gained and lessons learned, IHV plans to impact case detection through the installation of 4 more GeneXpert machines at high prevalence sites which have limited access to diagnosis.

Conclusion and Recommendation: Health systems strengthening for laboratory diagnosis and empowering community case identification can result in a marked increase in TB case finding. With the multidrug-resistant *Mycobacterium tuberculosis* emerging at an alarming rate, support is required to identify and detect suspected cases, improve diagnostic capacity with efficient technology, and improve linkage between diagnostic centers and treatment facilities.

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HIV and kidney function with a focus on traditional risk factors and role of TDF, PI and other medication

Patrick Mallon

UCD School of Medicine and Medical Science, IE

No abstract provided.