LES CENT Gardes

Cent Gardes Conference: HIV Vaccines

Organized by The Mérieux Foundation

Les Pensières Center for Global Health
Veyrier du Lac - France

September 30th to October 2nd, 2019

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

FONDATION MÉRIEUX

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Welcome letter

Dear Participant,

It is our pleasure to welcome you to the symposium:

« Cent Gardes Conferences: HIV Vaccines»

In the Foundation Mérieux's Conference Center ,Les Pensières.
We hope you will enjoy this meeting, which brings together some of the world's foremost experts.

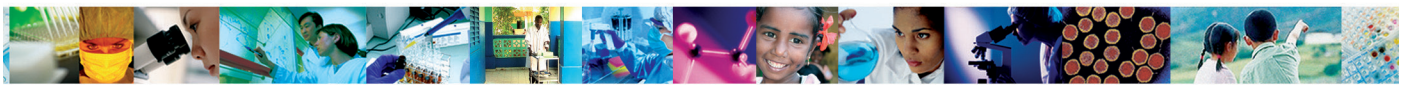
The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Yours sincerely,

Hubert Endtz

Director Scientific
Fondation Mérieux



Scientific programme

Monday, September 30th, 2019

13:30 - 14:00	Registration	
14:00 - 14:30	Welcome addresses	Alain Mérieux François Dabis Roger le-Grand Giuseppe Pantaleo
14:30 - 15:00	Keynote lecture: major global health challenges in the 21st century – what can universities do?	Ole Petter Ottersen
15:00 - 15:30	Keynote lecture: gene editing and the promises of genetic immunotherapy	Anne Galy

Session 1

HIV PREVENTION Chair: Larry Corey (25min presentation + 5min discussion)		
15:30 - 16:00	HIV vaccines at the fork in the road: "Just take it" says that great American philosopher, Yogi Berra	Lawrence Corey
16:00 - 16:30	HIV prevention without a vaccine: where are we now and where are we going?	Myron Cohen
16:30 - 17:00	Update on 702 and 705	Glenda Gray
17:00 - 17:30	Preventing HIV with antibodies: probing effects in the mucosal and lymphoid tissues	Julie Mc Elrath
17:30 - 18:00	General discussion	
19:00	Dinner	

Scientific programme

Tuesday, October 1st, 2019

Session 2

INDUCTION OF bNabs Chairs: Barton Haynes (25 min presentation + 5 min discussion)		
8:30 - 9:00	Induction of bnAbs; how and when will we get there?	Barton Haynes
9:00 - 9:30	Vaccine induction of broadly neutralizing antibodies targeting the HIV-1 fusion peptide	Peter Kwong
09:30 - 10:00	Structural characterization of bnAbs, vaccine candidates, and vaccine-induced antibodies	Ian Wilson
10:00 - 10:30	Induction of neutralizing HIV antibodies by native-like SOSIP trimers	Rogier W. Sanders
10:30 - 11:00	Coffee break	
11:00 - 11:30	Germline-Targeting Vaccine Design for HIV	William Schief
11:30 - 12:00	Long-acting BMS-378806 analogues stabilize the state-1 conformation of the human immunodeficiency virus (HIV-1) envelope glycoproteins	Joseph Sodroski
12:00 - 12:30	Paths to broad neutralization of HIV-1	Alexandra Trkola
12:30 - 13:00	General discussion	
13:00 - 14:30	Group Picture and Lunch	

Scientific programme

Session 3

bNabs UNDER DEVELOPMENT Chair: Michel Nussenzweig (25 min presentation + 5 min discussion)		
14:30 - 15:00	Introduction	Michel Nussenzweig
15:00 - 15:30	Dissecting the in vivo antiviral mechanism(s) of HIV-specific bNAbs	Richard Koup
15:30 - 16:00	Broadly neutralizing antibodies and protection from HIV infection	Dennis Burton
16:00 - 16:30	Coffee break	
16:30 - 17:00	Broadly neutralizing antibody combinations	Dan Barouch
17:00 - 17:30	Discovery and optimization of novel anti-HIV-1 broadly neutralizing antibodies	Craig Fenwick
17:30 - 18:00	Potency of tandem bispecific neutralizing antibody against pathogenic SHIV infection	Zhiwei Chen
18:00 - 18:30	General discussion	
19:30	Dinner	

Scientific programme

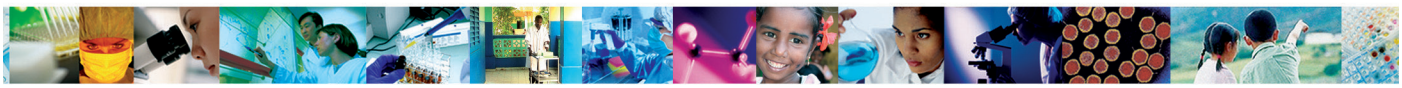
Wednesday, October 2nd, 2019

Session 4

FROM TRANSMISSION TO HOST RESPONSE MODULATION Chair: Robin Shattock (25 min presentation + 5 min discussion)		
8:30 - 9:00	Developing a pipeline to human experimental vaccine studies.	Robin Shattock
9:00 - 09:30	The use of anti-HIV-1 broadly neutralizing antibodies in prevention and treatment experiments	Malcom Martin
09:30 - 10:00	Follicular immune dynamics and development of B cell responses	Constantinos Petrovas
10:00 - 10:30	Coffee break	
10:30 - 11:00	In vivo immune pressure by non-neutralizing antibodies	Mario Roederer
11:00 - 11:30	Modulation of host response to infection and vaccines in preclinical models	Roger Le-Grand
11:30 - 12:00	General discussion	
12:00-13:30	Lunch	

Session 5

HIV CURE Chair: Yves Levy (25 min presentation + 5 min discussion)		
13:30 - 14:00	HIV cure: reality or myth?	Yves Levy
14:00 - 14:30	Role of T follicular helper cells in HIV-1 persistence	Matthieu Perreau
14:30 - 15:00	HIV cure immunotherapy	Steven Deeks
15:00 - 15:30	General discussion	
15:30 - 16:00	Closing remarks	Roger Le Grand Giuseppe Pantaleo



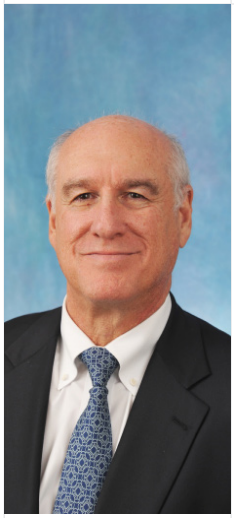
Speakers & Chairs

Dan Barouch, PHD M.D., Ph.D., is Director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center and Professor of Medicine at Harvard Medical School. In addition, he is a key part of the Bill & Melinda Gates Foundation Collaboration for AIDS Vaccine Discovery, the National Institutes of Health Martin Delaney HIV-1 Cure Collaboratory, and the Ragon Institute of MGH, MIT, and Harvard. He received his Ph.D. in immunology from Oxford University and his M.D. summa cum laude from Harvard Medical School. Dr. Barouch's laboratory focuses on studying the immunology and virology of HIV-1 infection and developing novel vaccine and cure strategies. He has also applied his vaccine expertise to other infectious diseases such as Zika virus and tuberculosis. He has advanced novel adenovirus vector-based HIV-1 vaccine candidates from concept and design to preclinical testing, ten phase 1/2a clinical trials, and a large phase 2b efficacy trial with the mosaic Ad26/Env vaccine in sub-Saharan Africa. He has also pioneered the use of broadly neutralizing antibodies for HIV-1 cure strategies, and a series of phase 1 clinical trials are currently underway. Dr. Barouch also led the world's first demonstration of Zika vaccine protection in preclinical studies and has launched a series of phase 1 Zika vaccine clinical trials. Dr. Barouch is board certified in internal medicine and infectious diseases, and he is committed to mentoring students, clinical fellows, research fellows, and junior faculty and to providing clinical care to patients with infectious diseases.

Dennis Burton is the Chair and Professor in the Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla, CA, USA. He was recently awarded the James and Jessie Minor Chair in Immunology. He received his B.A. in Chemistry from Oxford University and his Ph.D from Lund University, Sweden in physical biochemistry. He is the Scientific Director of the International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Consortium and Neutralizing Antibody Center, Director of The Consortium for HIV/AIDS Vaccine Development (CHAVD) at Scripps, and a member of the Ragon Institute of MGH, MIT and Harvard, Boston, USA. He has held many research grants from the NIH and has published more than 400 papers in scientific journals. He has received numerous awards including the Jenner Fellowship of the Lister Institute and a Fellowship in the American Academy of Microbiology. His research is focused on infectious disease, in particular the interplay of antibodies and highly mutable viruses, notably HIV. He is interested in the potential of broadly neutralizing antibodies to inform vaccine design.

Speakers & Chairs

Zhiwei Chen is a tenured professor and the director of AIDS Institute at the University of Hong Kong. He received his Ph.D. from New York University in 1996 based on his research conducted at the Aaron Diamond AIDS Research Center. He has been engaged in studies of HIV origin, molecular mechanisms of HIV/SIV entry, non-human primate models and AIDS vaccine since 1991. His current research focuses on HIV vaccine and functional cure especially by using combined bi-specific neutralizing antibody and PD1-based vaccination, which may potentiate host immunity for prolonged viremia control.



Myron S. Cohen is the Yeargan-Bate Professor of Medicine, Microbiology and Epidemiology at University of North Carolina at Chapel Hill. He completed his medical training at the University of Michigan and infectious disease training at Yale University. Dr. Cohen is Associate Vice Chancellor and Director of the UNC Institute for Global Health and Infectious Disease, and the co-principal investigator of the NIH HIV Prevention Trials Network (HPTN). He has served on the NIH DAIDS and OAR Advisory and PEFAR Advisory Boards, and the Fogarty International Center Council. Dr. Cohen is a member of the National Academy of Medicine, the American Society of Clinical Investigation and the American Association of Physicians. Dr. Cohen's awards include the Distinguished Career Award from the American Sexually Transmitted Diseases, the Smadel Award and a Special Citation from the Infectious Disease Society of America, The UNC General Alumni Award and O. Max Gardner Award, and the Award for Science from the State of North Carolina. Dr. Cohen led the HPTN 052 trial which demonstrated that antiretroviral treatment of people with HIV infection prevents the sexual transmission, recognized by Science Magazine as the "Breakthrough of the Year" in 2011. This work paved the way for worldwide HIV "treatment as prevention" campaigns. Dr. Cohen is the author of more than 500 publications and two books. Dr. Cohen's four decades of research have focused on the transmission of classical sexually transmitted diseases and HIV, and their prevention.

Speakers & Chairs

Lawrence Corey is a member of Fred Hutchinson Center Research Center, professor of Medicine and Laboratory Medicine at the University of Washington, and past president and director of Fred Hutch. Dr. Corey is also principal investigator of the HIV Vaccine Trials Network, an international collaboration of scientists and institutions dedicated to accelerating the development of HIV vaccines. His honors and awards include election to the National Academy of Medicine, and the American Academy of Arts and Sciences.

François Dabis is a medical doctor, Professor of Epidemiology at the School of Public Health (ISPED) of the University of Bordeaux, France. He has been leading from 2001 to 2016 the Inserm-affiliated "HIV, cancer and global health" research team within ISPED. He is Director of the French National AIDS and Viral Hepatitis Research Agency (ANRS) since March 2017 and Chair of the South West (Nouvelle Aquitaine) Regional Coordination to fight HIV/AIDS and STIs (COREVIH) since June 2017. Dr. Dabis has more than 30 years of experience in research on HIV epidemiology and global health. He has published 750 papers and two leading textbooks in Field Epidemiology. He is the PI of the NIH-funded IeDEA West Africa Collaboration and member of the Scientific Program Committee of the Conference on Retroviruses and Opportunistic Infections (CROI).

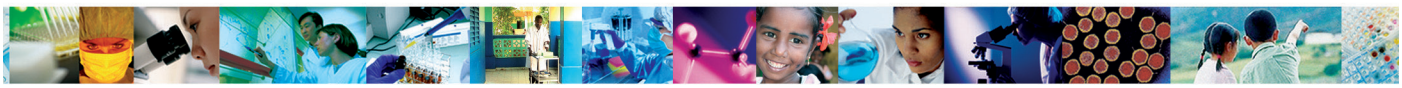
Steven G. Deeks, MD, is a Professor of Medicine in Residence at the University of California, San Francisco (UCSF). He is a recognized expert on HIV-associated immune dysfunction and its impact on HIV persistence (the "reservoir") and has published over 400 peer-review articles on these and related topics. He has been the recipient of several NIH grants, and is one of the principal investigators of DARE (the Delaney AIDS Research Enterprise), which is an NIH-funded international collaboratory aimed at developing therapeutic interventions to cure HIV infection.

Speakers & Chairs

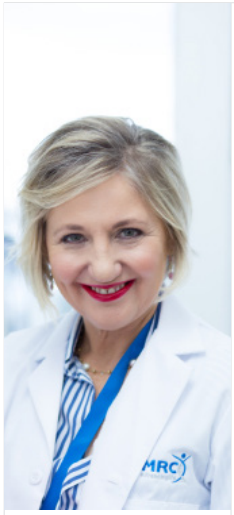
Craig Fenwick

- PhD in Biochemistry at Concordia University in Montreal Canada (1997)
- Postdoctoral Fellow in the Yale University Immunobiology Deptartement, New Haven, Ct, USA, working with Prof. Sankar Ghosh to study the NF-kB signal transduction pathway. (1997-2000)
- Senior Principal Scientist and project leader for 13 years at the Boehringer-Ingelheim Infectious Disease Research & Development, Montreal, Canada. (2000-2013)
  - HIV research in developing novel anti-retroviral agents and HIV latency
  - Biology project leader for the discovery and pre-clinical development of a novel class of non-catalytic site HIV integrase inhibitors. One NCINI, BI 224436, was advanced to Phase 1 clinical trials.
  - Exploratory research in the development of antibodies targeting immune checkpoint inhibitors and immune exhaustion in different infectious diseases including HIV.
- Director of the Clinical Immune Monitoring Platform and Research Scientist in the Immunology and Allergy department at the Lausanne University Hospital (CHUV). Work together with Prof. Giuseppe Pantaleo on multiple projects in immunology research and the development of therapeutic antibodies. (since 2013) These projects include:
  - Identification of a novel class of antagonistic anti-PD-1 antibody that synergizes with classical blocking anti-PD-1 antibody in enhancing tumor suppression in a mouse immunological tumor model. Published in the Journal of Experimental Medicine in 2019.
  - Isolation of novel bNabs from lymph-node derived germinal center B cells of viremic HIV+ donors. Two potent bNabs identified in this screen including the MPER Ab LN01 and the gp120/gp41 interface Ab LN02. A manuscript describing LN01 is accepted for publication in Cell Host & Microbe.

Anne Galy D.Pharm. PhD, is an expert in gene therapy and immunology. Author of more than 115 peer-reviewed articles and part of international networks in clinical gene therapy, Dr. Galy heads the academic research of Genethon in Evry, France where discoveries lead to early phase trials for rare genetic disorders and successful results were obtained in blood/immune disorders. Dr Galy also recently established an Accelerator of Technological Research with Inserm to develop genomic therapy approaches in broad immun-hematological indications. In this new translational research facility, a key project is to reprogram antibody production in B cells to treat cancer or infectious diseases.



Speakers & Chairs

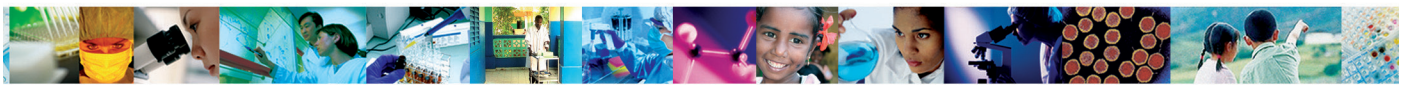


Glenda Gray is an NRF A-rated scientist, CEO and President of the South African Medical Research Council (SAMRC). She is a qualified pediatrician and co-founder of the internationally recognised Perinatal HIV Research Unit in Soweto, South Africa. Prior to her appointment at the SAMRC, she was the Executive Director of the Perinatal HIV Research Unit, an affiliate of Wits University. Glenda's global profile includes a role as Co-PI of the HIV Vaccine Trials Network (HVTN), a transnational collaboration for the development of HIV/AIDS prevention vaccines. She is also Director of International Programmes for HVTN and Chairperson of the Board of the Global Alliance for Chronic Diseases, and a member of the Institute of Medicine of the National Academies, USA. She received South Africa's highest honour - the Order of Mapungubwe - for her pioneering research in PMTCT. Other prestigious accolades include the Nelson Mandela Health and Human Rights Award for her significant contributions in the field of mother-to-child transmission of HIV. Selected as one of Time's 100 Most Influential People in the World, Glenda is a recognised leader in her field. Her qualifications include an MBBCH, FCPaeds (SA), DSc (honoris causa SFU), DSc (honoris causa SUN), LL.D (Rhodes).

Barton F. Haynes, M.D. is Director of the Human Vaccine Institute and Professor of Medicine and Immunology at the Duke University School of Medicine. He is leading a team of investigators in the CHAVI consortium working on a vaccine for HIV/AIDS.

Richard Koup is a Senior Investigator, Chief of the Immunology Laboratory, and Deputy Director of the Vaccine Research Center within the National Institute of Allergy and Infectious Diseases. His research involves the characterization of T cell and antibody factors involved in protective immunity against HIV infection, in order to inform the development of vaccines and treatments. He has published over 300 manuscripts on this and related topics, and has mentored more than 35 graduate and post-graduate students in his career.

Peter Kwong is Chief of the Structural Biology Section at the Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health and Adjunct Professor in the Department of Biochemistry and Molecular Biophysics, Columbia University. He is internationally recognized for his work defining structural aspects of the HIV-1 envelope glycoproteins and their interactions with antibodies. For the last several years, his efforts have focused on applying the atomic-level tools of structural biology to the development of effective vaccines against HIV-1 and other viral pathogens. Further information on Dr. Kwong can be found at https://www.niaid.nih.gov/research/peter-kwong-phd-structural-biology-section

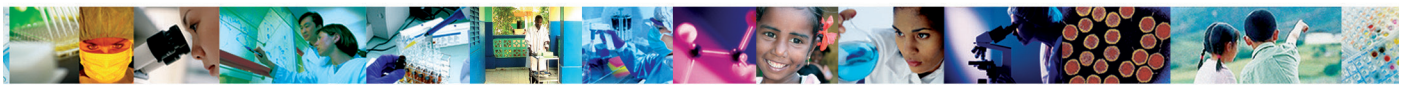


Speakers & Chairs

Roger Le Grand, DVM, PhD, is the head of IDMIT Department, a joint research unit of the CEA, Inserm and Université Paris Saclay, which also host a research infrastructure for non-human primate models of human infectious diseases. His research mainly focuses on host response to human pathogens with the aim to understand basic mechanisms of pathogenesis and develop new prevention strategies. He has a long lasting record on of HIV transmission studies, identification of tissue viral reservoirs and preclinical development of treatment and prevention, with a particular interest in HIV vaccine.

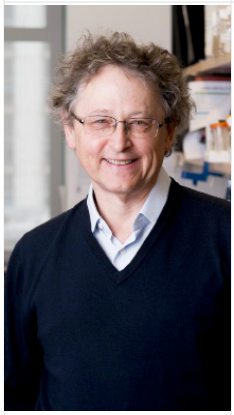
Prof. Yves Lévy, MD, PhD, is the Executive director of the Labex VRI and the coordinator of the European H2020 consortium EHVA (European Alliance for HIV Vaccine). He is the former CEO and Chairman of Inserm, the National Institute of Health and Medical Research (2014-2018). He led also, Aviesan, the French Alliance for Health and Life Sciences (2014-2018). He is Professor of Clinical Immunology at Henri-Mondor Hospital/ Université Paris Est Créteil since 1996. He obtained his MD in 1986 (Créteil University) and his PhD in Immunology in 1991 (Université Paris 7). He has developed a research activity, both in basic science and clinical translational research, in several INSERM units since 1985 and served as the Director of the Inserm Unit 899 in Dallas (Texas, USA) from 2010 to 2012. In 2011, he has created the Labex "Vaccine Research Institute" (VRI), aimed to face the challenges to develop effective vaccines against HIV and (re) emerging infectious diseases. His research activity led to the publication of more than 250 peer-reviewed papers, which led to 10 patents and made Y. Lévy is an internationally renowned key opinion leader in HIV physiopathology, immunotherapeutic and vaccine researches.
At the institutional level, he was Vice Dean of the Medicine Faculty of UPEC until 2012. He served as Special Councelor of the French Minister of Higher Education and Research from 2012 to 2014. He has been appointed member of the UN "Global Health Crises" Task Force by Mr Ban Kimoon (July 2016). In July 2019, he was nominated as "Special envoy" for the fight against Ebola in Central Africa by the French government.

Following graduation from Yale Medical School and Residency Training in Internal Medicine at Strong Memorial Hospital, Rochester NY, Malcolm Martin joined the National Institute of Allergy and Infectious Diseases, NIH where he has investigated both DNA and RNA viruses. His major contributions to the HIV-1 field include: 1) construction of the most widely used full-length infectious molecular clone of HIV-1 (pNL4-3); 2) the first demonstration that no two HIV-1 isolates are genetically identical; 3) initial identification and characterization of the HIV-1 viral infectivity factor (vif) and viral protein U (vpu) genes and their functions; and 4) the demonstration that potent broadly reactive anti-HIV 1 neutralizing antibodies can be used to treat and prevent SIV/HIV chimeric virus infections of rhesus macaques. Dr. Martin was elected to the U.S National Academy of Sciences in 1998 and is currently a Distinguished NIH Senior Investigator.



Speakers & Chairs

Julie McElrath is a Senior Vice President at Fred Hutchinson Cancer Research Center and Director of the Vaccine and Infectious Disease Division. She is a key scientific leader in the development of a clinically effective HIV vaccine and has established a global laboratory platform to elucidate immunity and protective correlates of an effective vaccine as director of the HVTN Laboratory Center. Her research interests focus on a deeper understanding of the components of innate and adaptive immunity that contribute to prevention of infection in humans.



Michel Nussenzweig was born in Sao Paulo Brazil on February 10th 1955. He received a B.S. summa cum laude from New York University in 1976, a Ph.D. degree from the Rockefeller University in 1981 and an M.D. degree from New York University Medical School in 1982. During his PhD with Ralph Steinman he discovered that dendritic cells are antigen presenting cells. After completing a medical internship, and residency, and infectious fellowship at the Massachusetts General Hospital he joined Dr. Philip Leder in the department of genetics at Harvard Medical School for postdoctoral training. He returned to Rockefeller University in 1990 as an assistant professor and Howard Hughes Investigator to head an independent laboratory. He was promoted to professor in 1996 and holds the Zanvil A. Cohn and Ralph M. Steinman Chair of Immunology. He is a member of the American Academy of Arts and Sciences, the US National Academy of Medicine and the US National Academy of Sciences.

Speakers & Chairs

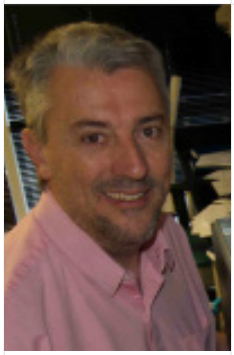
Ole Petter Ottersen took office as President of Karolinska Institutet on August 1, 2017, after having served eight years (2009-2017) as President of the University of Oslo (UiO). From 2002 to 2009 he was Director of the Centre for Molecular Biology and Neuroscience - one of Norway's Centres of Excellence.
He has served as Chief Editor of Neuroscience (2006-2009), the official journal of the International brain research organization (IBRO), and as panel leader in the European research Council (ERC Advanced Grants) from its founding to 2012. He was Founding Chair (2016-2017) of a newly established European university network (the Guild of Research Intensive Universities) and chaired the Lancet Commission that studied the political determinants of global health inequalities (The Lancet-University of Oslo Commission on Global Governance for Health). He has had a strong research interest in the field of neuroscience, with a particular focus on synaptic structure and function and on the molecular mechanisms underlying edema formation and water transport in brain. In recent years he has been engaged in global health, much inspired by his experiences gained as Chair of the Lancet-University of Oslo Commission. He is Honorary Doctor of the University of Kuopio (now University of Eastern Finland) and École Normale Supérieure, Lyon.

Giuseppe Pantaleo M.D., Professor of Medicine, is Chief of the Service of Immunology and Allergy and of the Laboratory of AIDS Immunopathogenesis at the Lausanne University Hospital, University of Lausanne, Switzerland. He is also Executive Director of the Swiss Vaccine Research Institute since 2007. Professor Pantaleo has made seminal contributions in the fields of the immunopathogenesis of HIV infection and antiviral immunity. In particular, he has shown that HIV infection is active and progressive during the clinical latent phase of infection and that lymphoid organs serve as the primary site for HIV infection and replication (Nature
1993; 2nd most cited paper in Science in Year 1993). Furthermore, he has been the first to show in that T follicular helper cells serve as the major CD4 T cell compartment for HIV infection, replication and production (J Exp Med, January 2013). Since 1998 he has been leading a European program in the development of an HIV vaccine platform. Professor Pantaleo is currently leading several international programs supported by the Bill and Melinda Gates Foundation and the European Commission (IDEA Program). Since 2007 has been part of HIV Vaccine Trial Network serving as PI of the Lausanne Clinical Trial Unit and since 2014 as PI of the Lausanne Clinical Research Site.
Professor Pantaleo is author and co-author of more than 300 publications in international scientific journals.

Speakers & Chairs

The first part of Matthieu Perreau career was dedicated to characterize the interactions between HIV vaccine vectors and the host immune system. When he joined the Service of Immunology and Allergy at Lausanne University Hospital, he focused his attention on HIV immunopathogenesis with a particular interest on the HIV reservoirs. His current research projects aims to identify HIV reservoirs in human blood and lymphoid tissues. In this context, they recently showed that T follicular helper cells were enriched in cells containing replication competent virus in treated HIV individuals.

During his Ph.D. at the School of Medicine, National University of Athens, Greece, Constantinos Petrovas, studied the function of anti-phospholipid antibodies in autoimmunity and HIV. He joined the Immunology Laboratory at VRC in 2005 as a staff scientist and since 2015 he is heading the Tissue Analysis Core at VRC, NIAID, NIH. He has extensive experience investigating the human and non-human primate immune system especially in HIV/SIV infection. His previous work focused on the mechanisms mediating the "exhaustion" and particularly the cytokine and survival intrinsic defects of SIV/HIV- specific CD8 T cells. More recently, his research has been focused on the dynamics of CD4 and CD8 T cells at tissue level and particularly in the lymph node follicles in HIV and SIV infection. To this end, he has established cutting-edge imaging assays that are of great importance for these studies.



Mario Roederer's research combines advanced technology development in the setting of single cell analysis (integrating both flow cytometry and transcriptomics), with basic T and B cell immunology. Over the past two decades, he led the effort to develop the state-of-the-art 30+ color flow cytometry. This effort spawned a wide range of technology and assay development efforts, resulting in novel analysis tools, probes, assays, reagents, and applications. Basic research projects include understanding the complete repertoire of T cell functions and antibodies needed to protect against pathogens or cancers, how these functions can be elicited by vaccines, and modulated by host genetics and microbiomes. In addition, his laboratory has extensive experience in developing and applying the nonhuman primate model for research and translation.

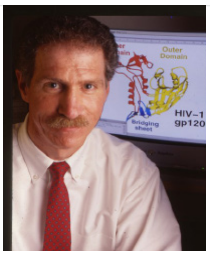
Speakers & Chairs

Rogier W. Sanders studied Medical Biology at the University of Amsterdam and the Rockefeller University in New York. In 2004 he obtained his Ph.D. (cum laude) from the University from Amsterdam. Rogier currently is a Professor of Virology, specializing in Experimental Vaccinology at the Academic Medical Center of the University of Amsterdam and holds an affiliate faculty position at Weill Medical College of Cornell University in New York City where he spends part of his time. His research focuses on HIV-1 envelope glycoprotein vaccines, in particular those based on native-like (SOSIP) trimers, which he co-invented. He has received several prestigious grants such as the Veni, Vidi and Vici grants from the Netherlands Organization for Scientific Research (NWO) and a Starting Investigator grant from the European Research Council (ERC). He participates in various HIV research consortia funded by the EU, NIH/NIAID and the Bill&Melinda Gates Foundation. Rogier has (co-)authored more than 150 articles in scientific journals, including journals such as Nature, Science and Cell. His H-index is 53. In 2011, he received the Dutch Prize for Biochemistry and Molecular Biology.

William Schief has a B.S. in Applied Mathematics from Yale University and a Ph.D. in Physics from the University of Washington. He is a Professor in the Immunology and Microbiology Department at The Scripps Research Institute, Director of Vaccine Design at the International AIDS Vaccine Initiative Neutralizing Antibody Center at TSRI, and an Associate Member of the Ragon Institute of MGH, MIT and Harvard. Dr. Schief's work focuses on computation-guided and structure-based design of immunogens and immunization regimens, with the goal of inducing broadly neutralizing antibodies against HIV and other pathogens that have frustrated traditional vaccine design strategies.

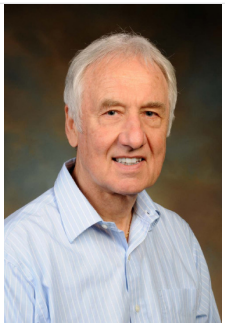
Robin Shattock leads the Section of Immunology and Infection within the Department of Infectious Diseases at Imperial College London. The main focus of his research is the investigation of the mechanisms of mucosal infection and development of novel vaccine and biotherapeutic strategies. He has secured funding from the MRC-UK, European Commission, EPSRC, CEPI, and Bill and Melinda Gates Foundation. He is the scientific director of the European AIDS Vaccine Initiative (EAVI2020) and Director of the Imperial EPSRC Future Manufacturing Research Hub (FVMR). He leads the RapidVac project funded by CEPI, creating vaccines against emerging infections.

Speakers & Chairs

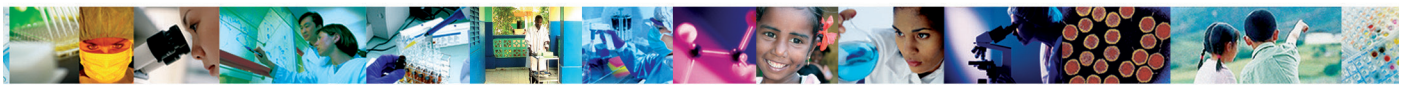


Joseph Sodroski, M.D. is a Professor in the Department of Microbiology at Harvard Medical School and the Dana-Farber Cancer Institute. The Sodroski laboratory studies the entry of human immunodeficiency virus (HIV-1) into cells. The conformational transitions of the HIV-1 envelope glycoproteins that contribute to virus entry are being characterized. Small-molecule inhibitors that interrupt HIV-1 entry are being developed.

Alexandra Trkola's main research focus is on HIV-1 entry and the neutralizing antibody response to HIV-1. She acquired her PhD in 1993 at the University of Agriculture, Vienna, Austria based on her work on neutralizing antibodies to HIV-1. For her post doctoral training she joined John Moore's group at the Aaron Diamond AIDS Research Center, New York in 1994 continuing to work on neutralizing antibodies and the then newly discovered coreceptors of HIV-1. In 2000 she started as independent group leader at the Division of Infectious Diseases at the University Hospital Zurich, Switzerland. In 2004 she was appointed assistant professor at the University of Zurich. Since March 2008 she is full professor for Medical Virology at the University of Zurich and since September 2008 director of the same institute (https://www.virology.uzh.ch/de/research/gtrkolad.html). The main interest of her research is focussed on deciphering the neutralizing antibody response to HIV-1. Current work in the Tkola lab focusses on unravelling factors that steer broadly neutralizing antibody development, the design of bnAb inducing immunogens and novel broadly neutralizing inhibitors of HIV-1 entry.



Ian. A. Wilson received his B.Sc. in Biochemistry from Edinburgh University, a D. Phil. and D.Sc. in Molecular Biophysics from Oxford University, did postdoctoral research at Harvard University, and joined The Scripps Research Institute in 1982, where he is Hansen Professor of Structural Biology and Chair of the Dept. of Integrative Structural and Computational Biology. His laboratory focuses on the structural basis of immune recognition including antibodies (>300), MHC class I and II, and T cell, cytokine and Toll-like receptors. His current research is on how HIV-1, influenza virus, HCV and
P. falciparum are recognized by broadly neutralizing antibodies to inform on design of novel vaccines and therapeutics. From 2000–2016, Dr. Wilson directed the Joint Center for Structural Genomics (JCSG) that pioneered high-throughput structural methods and led to 1,600 novel structures.
Dr. Wilson is a Fellow of the Royal Society, Fellow of the Royal Society of Edinburgh, Member of the American Academy of Arts and Sciences, Foreign Associate of the National Academy of Sciences, on the Statistical Board of Reviewing Editors for Science and Cell Editorial Board, and authored 790 papers.



Major global health challenges in the 21st century – what can universities do?

Ole Petter Ottersen
Karolinska Institute, Sweden

Human activity is pushing the world towards its very planetary boundaries, requiring us all to view health in a broader context than ever before. Successfully combatting the major global health challenges of the 21st century will require a new, interdisciplinary approach grounded in a common commitment to achieving better health for all. Universities must be more responsive to these global challenges and prepare to shoulder greater responsibility for identifying solutions and leading change. The higher education sector is uniquely positioned to prepare coming generations to think and act "horizontally" – beyond traditional barriers and silos – in research, innovation, education, and public outreach.

Nearly all of the United Nations' Agenda 2030 goals reflect the close interrelationship between achieving both global health and a more sustainable world. Success in achieving these goals will require greater interdisciplinarity and cross-sectoral governance in science, education, and even policy-making. It will also require that we make systemic changes to our institutions of higher education so that our research and education more accurately reflect the inextricable relationship between health, poverty, justice, social sustainability, climate, and the economy. In order to seek inspiration and solutions from other fields, we must teach our students and young researchers to think and act knowledgeably, critically, and ethically across disciplines and sectors. This will in fact require that we dare to rethink the very nature of our often highly specialized higher education programmes.

Historically, universities have brought about landmark innovations that have expanded economies, generated new energy sources, improved health, extended lives, and answered eternal questions of the natural world. But some of these innovations have also contributed to the perilous, unsustainable world in which we find ourselves today. Universities have not only a responsibility to lead, teach, and innovate, but should also be accountable for harnessing their strengths to move the world towards a more equitable and sustainable state.

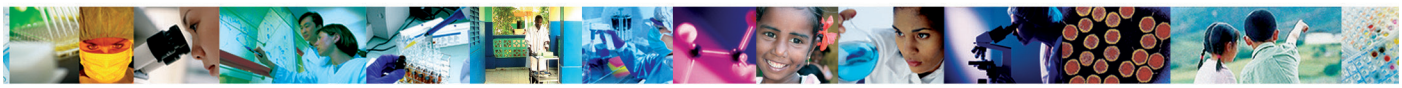
Gene editing and the promises of genetic immunotherapy

Anne Galy
Inserm and Genethon, France

The fields of gene therapy and of immunotherapy are progressing rapidly and have merged successfully by giving rise to the first CAR T cell medicines, opening the door to novel forms of genetic immunotherapy. Technological advances have always had a great impact in this domain. Indeed, gene editing is a technological breakthrough that provides unprecendented possibilities for precise genomic modifications, in practical and clinically-applicable ways. Remarkable recent results have shown that immunoglobulin gene loci can be gene-edited to reprogram the antibody specificies in B cells. It now becomes possible to envision novel forms of vaccination based on the use of gene-modified B cells. However, many hurdles will remain along the way to obtain safe and efficient approaches and to turn this concept into a widely applicable strategey. Yet, efforts are ongoing and new avenues will be discussed.

Session 1

HIV prevention



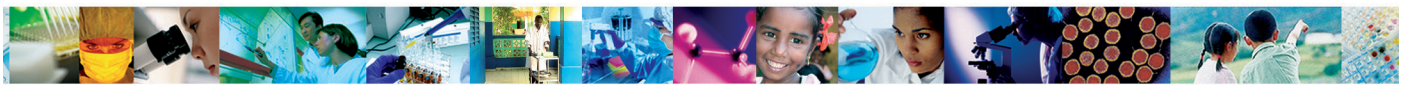
HIV vaccines at the fork in the road: "Just take it" says that great American philosopher, Yogi Berra

Lawrence Corey
HIV Vaccine Trials Network/Fred Hutchinson Cancer Research Center, United States

The HIV vaccine field has 4 efficacy trials in the field; 3 fully enrolled and 1 (HVTN 706) starting October of 2019. HVTN 702, 705 & 706 define whether vector prime, recombinant protein boost induces functionally effective non-neutralizing binding antibodies. The genesis of these regimens differs; HVTN 705, and 706 utilize mosaic Ad26/gp140 boost regimen which demonstrated envelope binding antibodies, ADCP, and ELISPOT were correlates of reduced acquisition from low dose mucosal challenge studies of NHP. In humans, the mosaic Ad26/gp140 regimen induces a greater antigenic breadth, some CD8+ T cell responses, and greater durability than the regimen used in HVTN 702. The ALVAC gp120 regimen used in HVTN 702 was developed as a clade C enhancing extension of the ALVAC gp120 regimen used in RV144.The HVTN 702 regimen exhibits better gp120 binding, but somewhat less V2 breadth and magnitude than the RV144regimen; likely related to the inherent properties of the gp120 strains used for the recombinant proteins. Efficacy at a level of >40% in association with some reasonable correlate of protection will propel the continued development of non-neutralizing regimens; either alone or in association with neutralizing antibody immunogens. Lack of efficacy is likely to make continued development of such approaches difficult until better pre-clinical models of HIV efficacy are developed.

Preclinical studies indicate that passive administration of bnAbs or induction of high titers of neutralizing antibodies by native trimeric immunogens are capable of protecting NHP from experimental challenge. Neutralization titers required in both instances seem relatively similar - about 1:400 to achieve 60-70% and 1:600 to achieve 90% protection. The AMP studies (HVTN 703/704) are a collaboration between the HVTN/HPTN and VRC, utilizing a single monoclonal to define the level of neutralization associated with protection in humans. Minor escape variants are common in the initial swarm of infecting viruses, with little loss in replication fitness. Similar to ART, the bnAb field will require mixtures of bnAb combinations with markedly extended half-life's, and enhanced tissue concentration are entering clinical development. Lastly, trimeric antigens and germline binding immunogens have entered clinical trials. Whether the titers and breadth of such responses can approach the levels needed remains to be determined. We are hopeful that our NHP colleagues will explore the combination of non-neutralizing and neutralizing regimens to see if some additive efficacy can be established.

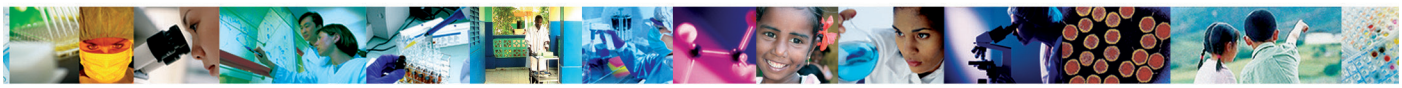
The AMP, HVTN 702 and HVTN 705 studies are under continuous monitoring by their DSMB's and we await the next 12 months to see if there are emerging data to guide the field.



HIV prevention without a vaccine: Where are we now and where are we going?

Myron Cohen
The University of North Carolina at Chapel Hill, United States

The earliest HIV prevention efforts were focused on safer sex and the treatment of STDs, but only modest benefits were realized. Antiretroviral treatment (ART) which suppresses viral replication greatly reduces vertical (mother to baby) HIV transmission and virtually eliminates the sexual transmission of HIV. Broader and earlier ART is directly linked to falling HIV incidence in most sub-Saharan countries, but recent population based studies demonstrate the limits of "treatment as prevention". Antiviral agents can also be used as pre- and post-exposure prophylaxis. Oral tenofovir-FTC (Truvada, and more recently Descovy) has demonstrated reliable prevention of HIV acquisition. Topical antiretroviral agents (tenofivir and dapivirine) offer modest protection from HIV infection. To date, all daily HIV prevention agents have been compromised by variable adherence. Accordingly, long acting agents are in development. Clinical trials (HPTN 083 and 084) are exploring the potential for an every eight-week injectable agent-cabotegravir- for pre-exposure prophylaxis (PrEP). ART (tenofovir alefenamide or caabotegravir) can also be used in long-acting implants or other devices. Additional new drugs with the potential for HIV prevention include MK8591 and several HIV capsid inhibitors. Combining ART with a contraceptive agent (i.e. a multipurpose technology) may make PrEP more attractive to women of childbearing age, and increase adherence. Broad neutralizing antibodies (bnAbs) also offer potential as PrEP, and combination bnAb trials are anticipated. As the HIV pandemic recedes more localized epidemic and endemic spread of HIV can be seen in defined "at risk" populations, and especially vulnerable young men and women. Precision prevention packages directed at these populations will be required.



Update on 702 and 705

Glenda Gray
SAMRC, South Africa

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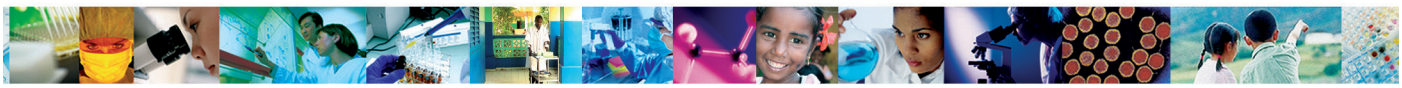


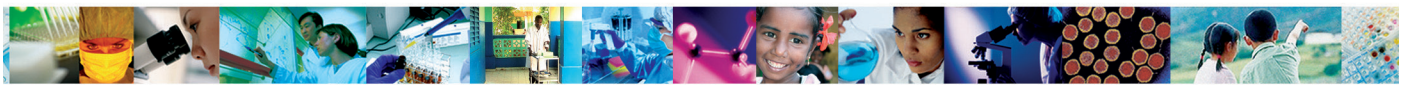
Preventing HIV with antibodies: probing effects in the mucosal and lymphoid tissues

Julie Mc Elrath
Fred Hutchinson Cancer Research Center, United States

Potent, broad neutralizing antibodies against HIV likely play a major role in protection against HIV infection. Extensive efforts are underway to evaluate the feasibility of their induction by vaccination or administration as monoclonal antibodies (mAbs) by passive immune prophylaxis in clinical trials. We have initiated two approaches to optimize the evaluation of the antibody responses in lymphoid and mucosal tissues. We incorporated fine needle aspiration of draining lymph node cells post-immunization, which permit tracking of antigen-specific B and Tfh cells associated with immunization and may reveal early germinal center events that support vaccine-induced affinity maturation pathways and enhanced potency. In addition, we have examined vaginal, cervical and rectal tissues and secretions in persons receiving the HIV broad neutralizing mAbs VRC01 or VRC01LS intravenously. Our findings indicate that the mAbs localize in these mucosal sites and retain anti-HIV functional activities ex vivo in mucosal biopsy explants against sensitive viral strains. Findings to date will be highlighted and serve as a framework to address key antibody activities in future analyses.

Session 2

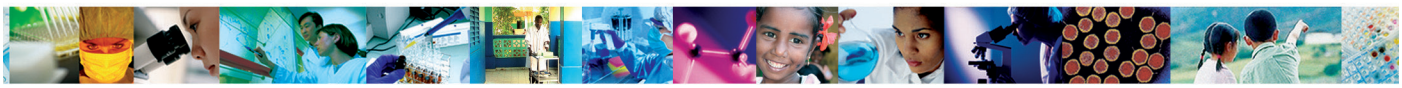
Induction of bNabs



Induction of bnAbs; how and when will we get there?

Barton Haynes
Duke University, United States

Design of vaccines to induce broadly neutralizing antibodies (bnAbs) is a major goal of HIV vaccine development. However, induction of bnAbs by Env immunogens is disfavored by both host controls and Env structural constraints. The field is focused on design of immunogens that can target bnAb precursors, coupled with selection of sequential immunogens to guide bnAb B cell lineages to full affinity maturation. Success in developing such a complex vaccine will require cooperation and collaboration by the field. A path forward for bnAb vaccine development will be discussed.



Vaccine induction of broadly neutralizing antibodies targeting the HIV-1 fusion peptide

Peter Kwong
Vaccine Research Center, NIAID/NIH, United States

The vaccine induction of antibodies, capable of neutralizing diverse strains of HIV-1 has been a long-sought goal. Recently, we found that focusing the immune response to exposed N-terminal residues of the fusion peptide (FP) coupled to boosting with Env trimer could induce cross-clade neutralizing responses in mice, guinea pigs and rhesus macaques (1-3). We are now working to boost the breadth, potency and consistency of FP-directed responses. With 32 macaques, we tested 7 different vaccination regimens, each with a boosting module comprising 5 immunizations of FP-carrier conjugate and envelope (Env)-trimer. Comparison of vaccine regimens, enabled by use of a common boosting module, revealed FP-carrier priming to imprint cross-reactive FP-directed HIV-neutralizing responses. A cocktail of FP-carrier and Env-trimer elicited the earliest broad responses. We identified a signature – appearing as early as week six and involving the frequency of B cells recognizing both FP-conjugate and Env-trimer– that was predictive of the vaccine-elicited breadth roughly a year later. Identification of FP-carrier imprinting, cocktail approach, and early signature should accelerate vaccine efforts to improve FP-directed neutralizing responses – and we are now working to manufacture and to test FP-based immunizations in clinic.

1. Kong R, et al. (2016) Fusion peptide of HIV-1 as a site of vulnerability to neutralizing antibody. Science 352, 828-833.
2. Xu K, et al. (2018) Epitope-based vaccine design yields fusion peptide-directed antibodies that neutralize diverse strains of HIV-1. Nat Med. 24, 857-867.
3. Kong R, et al. (2019) Antibody Lineages with Vaccine-Induced Antigen-Binding Hotspots Develop Broad HIV Neutralization. Cell 178, 567-584.

Structural characterization of bnAbs, vaccine candidates, and vaccine-induced antibodies

Ian Wilson
The Scripps Research Institute, United states

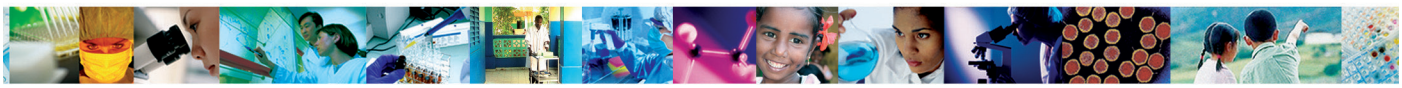
My laboratory has determined atomic structures of the envelope protein (Env) of HIV-1 and complexes with many potent, broadly neutralizing antibodies. We are continuing to add to our knowledge of how the human immune system can respond to infection by HIV-1. Our current work is focussed on x-ray structures of bnAbs from natural infection and vaccine-induced antibodies in complex with various strains and subtypes of HIV-1 and designed immunogens. This structural information is being used in structure-assisted vaccine design for HIV-1.

IAW is supported by NIH grants UM1 AI144462 (CHAVD), P01 AI110657 (HIVRAD), and BMGF OPP1196345 (IAVI NAC CAVD).

Induction of neutralizing HIV antibodies by native-like SOSIP trimers

Rogier W. Sanders
Laboratory of Experimental Virology, Dept. Medical Microbiology, Academic Medical Center of the University of Amsterdam, The Netherlands

Inducing HIV-1 neutralizing antibodies against neutralization-resistant (Tier-2) virus strains has been a challenge. While native-like (SOSIP) envelope trimers based on various HIV-1 strains can induce neutralizing antibodies against the autologous (Tier-2) viruses, the induction of broadly neutralizing antibodies (bNAbs) is much more challenging. A critical step in this process is the activation of naïve B cells expressing germline antibody precursors that have the potential to evolve into bNAbs. We have reengineered the BG505 SOSIP trimer to engage germline precursors of bNAbs that target the trimer apex or the CD4 binding site. The resulting GT1, GT1.1 and GT1.2 trimers (GT for germline targeting) bind multiple bNAb germline precursors in vitro. Crystal structures of GT1 and GT1.2 reveal a native-like conformation and the successful incorporation of design features associated with binding of multiple bNAb germline precursors. Immunization experiments in a knock-in mouse models expressing VRC01-class germline precursors show that these trimers activate germline precursor B cells in vivo, resulting in the secretion of specific antibodies into the sera. The Ab response in VRC01-class precursor knock-in mice can be further 'shaped' by the design and selection of next-step 'shaping' immunogens and 'polishing' immunogens. Sequence analysis of the B cell receptors of memory B cells in these mice after receiving a regimen of germline-targeting, 'shaping' and 'polishing' immunogens reveals that such a regimen selects for VRC01-class somatic mutations as well as rare insertions and deletions that are found in VRC01-class bNAbs. VRC01-class MAbs isolated from these mice have the capacity to neutralize heterologous wild-type HIV-1 isolates. Thus, SOSIP trimers are a suitable platform for immunization regimens aimed at inducing bNAbs.



Germline-targeting vaccine design for HIV

William Schief
The Scripps Research Institute
International AIDS Vaccine Initiative
Ragon Institute of MGH, MIT and Harvard, United States

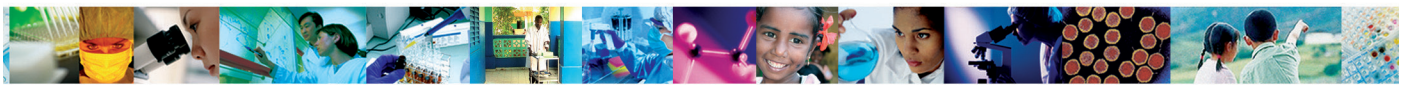
Vaccine induction of broadly neutralizing antibodies (bnAbs) will likely be crucial to solving the global health challenge posed by HIV. The HIV envelope trimer, the target of both bnAbs and strain-specific neutralizing antibodies, is heavily glycosylated and has an antigenic surface that varies significantly among different HIV isolates. Therefore, vaccine elicitation of bnAbs using stable trimer immunogens that mimic native spikes presents major challenges. Potent HIV bnAbs are typically highly mutated and their germline-reverted forms typically show little or no reactivity to wild-type HIV antigens. Thus, key barriers to bnAb elicitation include activating bnAb precursor B cells and guiding bnAb maturation. We will discuss different strategies for bnAb induction that are advancing to clinical trials. We will focus our attention primarily on criteria for effective bnAb precursor priming, where the quest to induce bnAbs begins.

Long-acting BMS-378806 analogues stabilize the state-1 conformation of the human immunodeficiency virus (HIV-1) envelope glycoproteins

Shitao Zou[1,2], Shijian Zhang[1], Althea Gaffney[3], Maolin Lu[4], Haitao Ding[5], Mark Farrell[3], Hanh T. Nguyen[1], Connie Zhao[1], Saumya Anang[1,] Cameron Abrams[6], Navid Madani[1], John C. Kappes[5,7], Walther Mothes[4,] Amos B. Smith III[3] and Joseph Sodroski[1,8]

[1]Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Department of Microbiology, Harvard Medical School, Boston, MA 02215, USA; [2]Suzhou Cancer Center Core Laboratory, Nanjing Medical University Affiliated Suzhou Hospital, Suzhou, Jiangsu, China; [3]Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, USA; [4]Department of Microbial Pathogenesis, Yale University School of Medicine, New Haven, CT 06536, USA; [5]Department of Medicine, University of Alabama at Birmingham, AL 35294, USA; [6]Department of Chemical and Biological Engineering, Drexel University, Philadelphia, PA 19104, USA; [7]Birmingham Veterans Affairs Medical Center, Research Service, Birmingham, AL 35294, USA; [8]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

During human immunodeficiency virus (HIV-1) entry into cells, the viral envelope glycoprotein (Env) trimer ((gp120/gp41)3) binds receptors, CD4 and CCR5, and fuses the viral and cell membranes. CD4 binding changes Env from a metastable pre-triggered (State-1) conformation to a default intermediate (State-2) conformation and then to the full CD4-bound (State-3) conformation. Most broadly neutralizing antibodies are able to recognize the State-1 conformation of Env. However, most soluble, well-characterized HIV-1 Env trimers are in a State-2-like conformation. Presentation of a State-1 Env immunogen could hypothetically increase the efficiency with which broadly neutralizing antibodies are elicited. To identify potential sources of State-1 Envs, we have studied HIV-1 membrane Envs on cell surfaces and virus-like particles in the presence of entry inhibitors. One class of entry inhibitors that includes BMS-378806 blocks CD4-induced conformational changes in Env important for entry and is hypothesized to stabilize a State-1-like Env conformation. We found that BMS-378806 strengthened the labile, non-covalent interaction of gp120 with the Env trimer, enhanced the binding of some broadly neutralizing antibodies and decreased the binding of poorly neutralizing antibodies. We identified novel BMS-378806 analogues that stabilized Env conformation for several weeks after a single application. These long-acting BMS-378806 analogues may facilitate enrichment of the metastable State-1 Env conformation for structural characterization and presentation to the immune system.

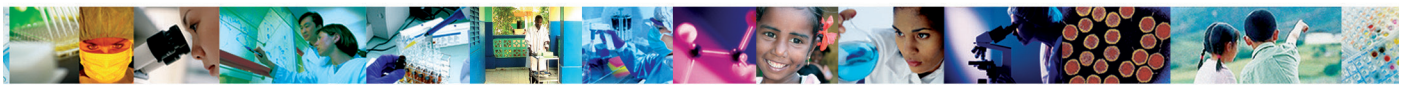


Paths to broad neutralization of HIV-1

Alexandra Trkola
Institute of Medical Virology, University of Zurich, Switzerland

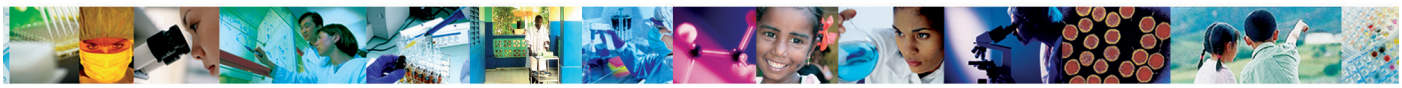
Understanding pathways that promote HIV-1 bnAb induction is crucial to advance bnAb-based vaccines. We recently conducted the Swiss 4.5K Study, a large screen for neutralization breadth in 4'484 individuals with chronic HIV-1infection. Here we report on the XbnAb cohort that emerged from this work. The XbnAb cohort comprises 304 HIV-1 infected individuals with bnAb activity and 304 demographically matched controls without neutralization activity. Analysis of the XbnAb cohort corroborates bnAb linked parameters previously identified in the Swiss 4.5K study underlining the enormous potential of the XbnAb cohort in unravelling key factors of bnAb evolution such as immune correlates, host genetic factors and decisive Env signatures.

Further to the definition of bnAb imprinting Env immunogens we explore Env sub-domains that are relevant for bnAb induction and activity using novel broadly neutralizing inhibitors we selected from Designed Ankyrin Repeat Protein (DARPin) libraries. Here we report on broadly neutralizing DARPins (bnDs) that neutralize with exceptional breadth (80-100%). All bnDs identified thus far target Env differently than bnAbs revealing additional sites or approach angels for broad neutralization. Most interestingly, the highly conformation dependent binding of bnDs allows an indirect structure definition of Env antigens. Although binding modes differ, DARPins proved to have the same preferences and difficulties in recognizing Env antigen as antibodies, namely a reduced capacity to engage the closed trimer and a strong preference towards binding known immunodominant regions such as the V3. This capacity to recapitulate key features of the humoral immune response suggests DARPins as a novel and effective tool to assess candidate immunogens prior to extensive animal testing.



Session 3

bNabs under development



Introduction

Michel Nussenzweig
Rockefeller University and HHMI, United States

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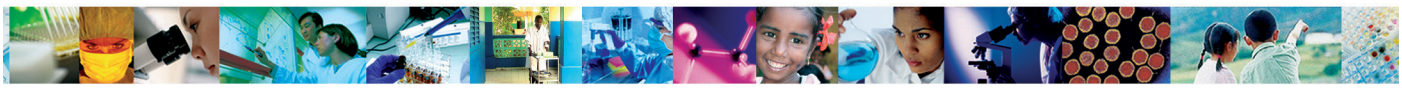


Dissecting the in vivo antiviral mechanism(s) of HIV-specific bNAbs

Richard Koup
Vaccine Research Center, NIAID, NIH, United States

Treatment of HIV infection with either antiretroviral therapy (ART) or neutralizing monoclonal antibodies (NAbs) leads to a reduction in HIV plasma virus. Both ART and NAbs prevent new rounds of viral infection but NAbs may have the additional capacity to accelerate the loss of virus-infected cells through Fc R-mediated effector functions, which should affect the kinetics of plasma virus decline. Here we formally test the role of effector function in vivo by comparing the rate and timing of plasma virus clearance in response to a single dose treatment with either unmodified NAb or those with either reduced or augmented Fc function. When infused into viremic SHIV-infected rhesus macaques, there was a 21% difference in slope of plasma virus decline between wt NAb and NAb with reduced Fc function. NAb engineered to increase Fc RIII binding and improve ADCC in vitro resulted in arming of effector cells in vivo yet led to viral decay kinetics similar to NAbs with reduced Fc function. These studies show that the predominant mechanism of antiviral activity of HIV NAbs is through inhibition of viral entry, but that Fc function can contribute to the overall antiviral activity, making them distinct from standard ART.

Broadly neutralizing antibodies and protection from HIV infection

Dennis Burton
Scripps Research, USA; Ragon Institute, United States

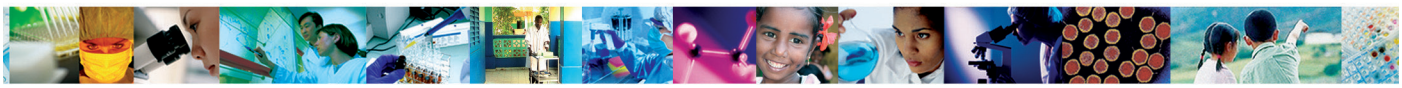
Protection from viral infection by neutralizing antibodies will be discussed generally and focused particularly on the role of antibody effector function in protection by broadly neutralizing antibody PGT121 against SHIV infection in macaques.

Broadly neutralizing antibody combinations

Dan Barouch

Center for Virology and Vaccine Research,
Beth Israel Deaconess Medical Center,
Ragon Institute of MGH, MIT, and Harvard, United States

We reported last year that administration of the broadly neutralizing antibody PGT121 with a TLR7 agonist led to delayed or prevented viral rebound in SHIV-SF162P3-infected rhesus monkeys that initiated ART during acute infection. For both HIV-1 prevention and therapy, combinations of broadly neutralizing antibodies will likely be required. I will describe new data related to the development of antibody combinations in vitro, in preclinical studies, and in clinical trials.



Discovery and optimization of novel anti-HIV-1 broadly neutralizing antibodies

Craig Fenwick
Lausanne University Hospical (CHUV), Switzerland

Broadly neutralizing antibodies (bNabs) targeting HIV Envelope have considerable potential for their use as prophylactic and therapeutic agents against HIV-1 infection. However, as with antiretroviral drugs, antibody monotherapy targeting the virus inevitably leads to the emergence of viral variants with antibody resistance. As such, combinations of bNabs targeting different viral epitopes on Env are needed to strongly suppress infectious virus, inhibit a wide breadth of viral strains in the general population and prevent viral escape. In an effort to identify novel bNabs with a complementary neutralization profiles to advanced bNabs in the clinic, our group adopted the strategy of isolating neutralizing antibodies from lymph-node derived germinal center B cells of HIV-1 viremic donors and elite controllers. This approach allowed for the identification of two novel bNabs, one binding to the highly conserved MPER region of gp41 and the other to the gp120/gp41 interface region. The broad anti-MPER neutralizing antibody LN01, neutralizes 92% of a multi clade panel of 118 viral strains and exhibits functional activity in the killing of HIV infected cells. Structural analysis revealed that LN01 recognizes the helical MPER-TM epitope in a unique orientation and membrane via two specific lipid-binding sites of the antibody paratope. The anti-gp120/gp41 interface antibody LN02, has the highest neutralization breadth in its class at 74% and exhibits a potent neutralizing activity. Through site directed mutagenesis in the CDR variable regions and the use of a high throughput antibody production platform, >350 LN02 mutations were screened leading to the identification of a variant with a 10-fold improved potency and a neutralization breadth of 82% against a 106-strain viral panel. This optimization was achieved without the loss of antibody production yield, biophysical properties or increased signs of polyreactivity. Overall, these two novel bNabs represent promising new candidate for the prevention and treatment in HIV infection that could complement the neutralization profiles of other advanced bNabs in strongly suppressing the vast diversity of global circulating viruses.

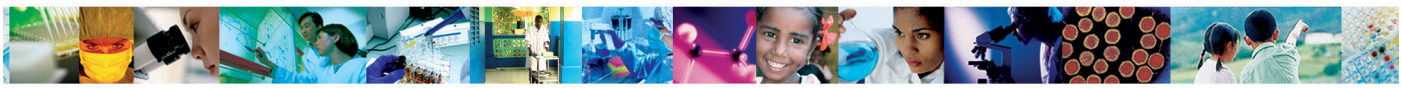
Potency of tandem bispecific neutralizing antibody against pathogenic SHIV infection

Zhiwei Chen
The University of Hong Kong, Hong Kong

Passive immunization of potent and broadly neutralizing antibodies (bNAbs) is a promising strategy in the fight against HIV/AIDS. Our previous study has demonstrated that a tandem bi-specific bNAbs, namely BiIA-SG, is effective for HIV-1 protection in humanized mice. However, its potential for clinical development remains unknown. We, therefore, sought to investigate the prophylactic and therapeutic potential of BiIA-SG against pathogenic simian-human immunodeficiency virus (SHIV) challenge in Chinese-origin rhesus macaques (CRM). In this study, we established a CRM/SHIVSF162P3 model using CRM-adapted SHIVSF162P3. By a high dose of intravenous challenge with SHIVSF162P3 (5000TCID50), majority of CRMs developed persistent viremia, diarrhea, body weight loss, rapid disease progression, and death within 2 years. Meantime, we tested BiIA-SG through administered intramuscularly 1 day before challenge for prophylaxis, and either 1 day or 3 days after challenge for early therapeutic interventions. We found that the average half-life of BiIA-SG is around 2.3 days in CRMs. A single intramuscular injection of BiIA-SG one day before SHIVSF162P3 infection conferred full protection in all macaques tested as determined by lack of viremia, T cell responses and seroconversion. Moreover, with a single intramuscular injection of BiIA-SG after 1 day or 3 days of SHIVSF162P3 challenge, the peak viremia was significantly postponed, followed by undetectable setpoint viral loads from 2 months post infection onwards, and importantly, prevented the rapid progression to AIDS in all animals. Mechanistically, BiIA-SG targeted mainly at SHIVSF162P3 but not the CD4 molecule for viral entry and promoted the induction of CD8+ T cells for durable viral suppression because a rapid viral rebound was induced in animals treated with the T-cell-depleting anti-CD8β antibody. This study demonstrates the efficacy of BiIA-SG in controlling pathogenic SHIV infection in CRMs. Our findings may warrant further investigation of BiIA-SG for HIV-1 immunotherapy in patients.

Session 4

From transmission to host response modulation



Developing a pipeline to human experimental vaccine studies.

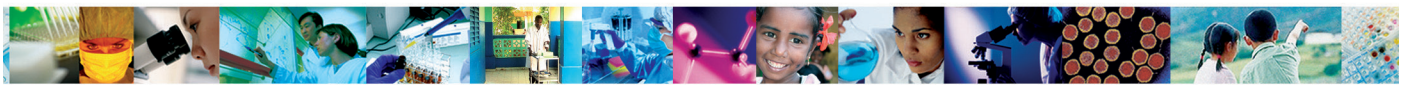
Robin Shattock
Imperial College, United Kingdom

The development of a preventative HIV-1 is likely dependent up the design of immunogens able to drive the naïve B cell repertoire to towards the induction of broadly neutralising antibodies (bNAb). Such approaches, by their very nature can only by fully evaluated in human trials and may ultimately require the assessment of a large number of immunogens and strategies to iterate the pathways needed to drive B cell responses towards the induction of rare bNAb. However, the testing of immunogens in human trials remains a substantial bottleneck to the pace of discovery. Using examples from the European AIDS Vaccine Initiative 2020 (EVI2020), this presentation will explore new pathways for translation of novel immunogens into early clinical programs. Focusing on a human centric approach to HIV-1 vaccine development the presentation will ask what next steps might be needed to accelerate HIV-1 vaccine discovery and reduce the risk of late stage failure in larger efficacy trials.

The use of anti-HIV-1 broadly neutralizing antibodies in prevention and treatment experiments

Malcom Martin
National Institute of Allergy and Infectious Diseases, United States

We have used the R5 tropic SIV/HIV chimeric virus (SHIV), SHIVAD8-EO, which produces sustained levels of plasma viremia in inoculated macaques, exhibits a Tier 2 neutralization sensitivity phenotype, produces neutralization or drug resistant variants in bNAb and ART treated animals, respectively, causes irreversible depletions of CD4+ T cells in infected monkeys, and induces symptomatic and fatal immunodeficiency untreated monkeys to investigate treatment and prevention questions in non-human primate models of HIV/AIDS. In prevention studies, utilizing a repeated-low dose intrarectal challenge regimen in combination with native and modified anti-HIV-1 broadly acting neutralizing antibodies (bNAbs), a single intravenous infusion of 10-1074-LS mAb markedly delayed SHIVAD8-EO acquisition for 18 to 37 weeks (median = 27 weeks). In treatment experiments, we previously reported that the administration of a single 2-week course of two potent bNAbs (3BNC117 and 10-1074), beginning 3 days following SHIVAD8-EO inoculation of rhesus macaques, led to control of virus replication in 6 of 13 animals during a 2-year observation period. Infusion of T cell depleting anti-CD8 mAbs into the 6 controller monkeys led to a transient decline in levels of CD8+ T cells and rapid reappearance of plasma viremia. This wave of virus replication was subsequently suppressed with the re-emergence of CD8+ T cells. Plasma viremia has since remained at low/undetectable levels in these elite controllers for nearly 5 years. The control of an established SHIVAD8-EO infection by combination bNAb therapy has now been extended to the more clinically relevant immunotherapy initiation time of 2 weeks post infection (PI). Whether administered alone, or in combination with anti-retroviral drugs, bNAb administration at week 2 PI has resulted in control of plasma viremia to undetectable levels in 6 of 12 animals within 1 to 2 years of beginning treatment.



Follicular immune dynamics and development of B cell responses

Constantinos Petrovas
VRC, NIAID, NIH ; United States

The generation of antigen-specific B cell responses in specialized follicular areas called germinal centers (GCs) requires the orchestrated function of highly differentiated cells like follicular helper CD4 T (Tfh) and GC B cells. LN areas are characterized by the compartmentalization of immune and stromal cell populations and the presence of a complex network of soluble factors and chemokines governing the intra-tissue trafficking of naïve and effector cell populations as well as their local interactions. The cellular and molecular mechanisms mediating the development of broadly neutralizing antibodies in some HIV infected individuals are not well understood. Recent data showing the tissue heterogeneity of relevant populations, as well as the lymph node immune dynamics in HIV and SIV infection will be discussed. Novel platforms for the comprehensive understanding of the tissue microenvironment (positioning, molecular signatures of particular immune cell targets, local milieu) that could further promote the development of new antiviral treatments and vaccination strategies will be also discussed.

In vivo immune pressure by non-neutralizing antibodies

Mario Roederer
Vaccine Research Center, National Institute of Allergy and Infectious Diseases , NIH, Bethesda, MD ; United States

The NHP model for antibody interventions has been limited by the availability of primate mAb reagents against pathogenic viruses such as mac239 or smE660. Over the past four years, we used targeted isolation strategies to isolate a broad range of NHP mAbs (against CD4bs, V1, V2, V3, MPER, HMP, CD4i, etc.), which have a wide range in activities such as ADCC and neutralization. We are using these reagents to model mAb interventions in clinical trials, including passive immunization, AAV-vectored administration, bi-specifics, and CAR T cells, in both prevention and therapeutic settings. Recently, we explored the role of 4 7 binding in SIV pathogenesis. Byrareddey et al reported that treatment of SIV-infected NHP during ART with primatized ACT-1 (pACT1), a mAb agonist of 4 7, resulted in remarkable long term virologic control. We used mAbs ITS09 and ITS12 against SIV Env V2 that also block binding to 4 7; neither neutralizes mac239. We also used the fully neutralizing CD4bs mAb ITS103.

Animals treated with ITS103 had ~2 week delayed virus rebound, concomitant with rapid viral escape with mutations near the CD4bs like those arising in clinical trials of VRC01. Unexpectedly, 8/8 highly viremic animals in the pACT1 and anti-V2 treated groups showed Env mutations, comprising a large deletion in V4. 4/4 animals in these groups that controlled viremia below 104/ml (post ART) remained wild type in V4.

This study demonstrates in vivo immune pressure from non-neutralizing mAbs. Our data also support an important, but not essential, in vivo role of SIV Env binding to 4 7 integrin. We conclude that the effects of blocking 4 7 on virus pathogenesis are mediated solely by blocking Env binding, and not cellular redistribution in vivo. Finally, we find evidence for mutational "escape" at sites distal to the epitope, suggesting that sieving analyses should not necessarily be restricted to the relevant mAb binding footprints.

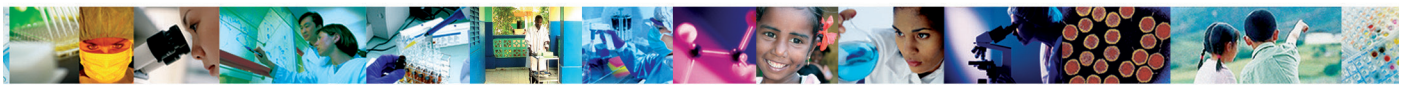
Modulation of host response to infection and vaccines in preclinical models

Roger Le-Grand
CEA-INSERM-Université Paris Saclay, France

The objective of the work is to characterize molecular and cellular interactions occurring at different stages of response to vaccines and infections with the aim to identify new approaches for improving efficacy of vaccines immune-therapies. The dynamics of innate and adaptive responses occurring following immunization of NHP have been analysed using a variety of approaches combining in vivo imaging, microscopy, transcriptomic and flow and mass cytometry. Comparison of routes of injection, combination of adjuvants and prime-boost strategies have been used to inform the design of immunization strategies based HIV envelope trimers and/or the vaccine antigen targeting to appropriated dendritic cells. The presented work is the results of the collaborative efforts of EAVI2020 and the EHVA European projects, and programs of the ANRS and the Vaccine Research Institute.

Session 5

HIV cure

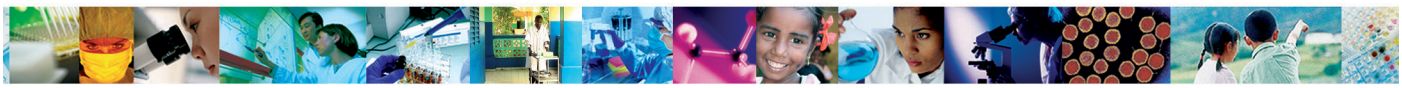


HIV cure: reality or myth?

Yves Levy
Vaccine Research Institute, France

Despite being associated with a dramatic reduction in morbidity and mortality, combined antiretroviral therapies (c-ART) are not able to eradicate HIV. The HIV viral reservoir is present even in virologically suppressed individuals and its elimination is regarded as one of the main obstacles to achieving a cure. Strengthened by recent scientific advances the field is focused on development of strategies able to improve the immune control of HIV replication aimed to prolong the period of remission leading to improvement of quality of life, decrease in morbidity and sparing costs.

I will discuss during my talk these recent advances and whether HIV cure might be reality or myth.



Role of T follicular helper cells in HIV-1 persistence

Matthieu Perreau
Lausanne University Hospital, Lausanne, Switzerland

Increasing number of evidences indicate that B-cell follicles might be anatomical sanctuaries for active and persistent transcription in both HIV/SIV viremic controllers and in ART treated aviremic HIV-infected individuals and have underscored the importance of the delineation of mechanisms allowing viral persistence in lymph nodes (LNs) to ultimately eradicate or functionally cure HIV.

While multiple mechanisms may be involved in the regulation of HIV transcription, recent studies suggest that immune checkpoint (IC) molecule expression may contribute to control HIV-1 transcription and therefore maintain HIV-1 latency in HIV-infected memory CD4 T cells. We therefore hypothesized that IC/IC-ligand (IC-L) interactions may contribute to modulate HIV latency/virus reactivation in LN microenvironment.

In the present study, we demonstrate that PD-1 and TIGIT, the two major ICs expressed on T follicular helper (Tfh) cells ex vivo, are functionally active and regulate TCR-mediated HIV-1 transcription and production in vitro. However, PD-L1 (PD-1-ligand) and CD155 (TIGIT-ligand), predominantly co-expressed on LN migratory dendritic cells (DCs), preponderantly locate in extra-follicular areas of ART treated subjects, suggesting that IC/IC-L interactions might be selectively reduced in germinal centers (GCs) of ART-treated subjects. Interestingly, we show that LN migratory DCs could modulate TCR-mediated HIV-1 production from LN PD-1+/Tfh cells of ART treated HIV-infected individuals by a mechanism involving PD-L1-2/PD-1 interactions.

These results indicate that LN migratory DCs expressing IC-Ls may more efficiently restrict HIV-1 transcription in the extra-follicular areas versus GCs and explain the persistent HIV transcription in PD-1+/Tfh cells after prolonged ART.

HIV cure immunotherapy

Steven Deeks
University of California, San Francisco, United States

Despite the fact that 60% of people living with HIV currently receive antiretroviral therapy (ART), recent gains in controlling the epidemic may be threatened: key incidence rates are declining only modestly, and the sustainability of current programs remains unknown. Given the complexities and expenses associated with life-long medication, developing an effective curative intervention is now a global priority. Based on (1) studies of elite and post-treatment control, (2) advances in cancer immunotherapy and (3) recent successes in achieving SIV/SHIV cures/remissions in non-human primates a series of early-stage clinical studies have been implemented, many using approaches developed initially to prevent HIV acquisition. Recent data from these studies and how they are being used to design the first generation of proof-of-concept combination studies will be reviewed.

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