40 YEARS DISCOVERY OF HIV AT THE INSTITUT PASTEUR

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INSTITUT PASTEUR

40 YEARS OF HIV SCIENCE

NOVEMBER 29TH - DECEMBER 1ST 2023

INSTITUT PASTEUR, PARIS, FRANCE

KEYNOTE SPEAKERS

FRANÇOISE BARRÉ-SINOUSSI
Institut Pasteur, Paris

ANTHONY FAUCI
NIH, USA

SPEAKERS

MARCUS ALTFELD
Leibniz Institute of Virology, Leibniz

MONSEF BENKIRANE
Institut de génétique humaine, Paris

MORGANE BOMSEL
Institut Cochin, Paris

MYRON COHEN
University of North Carolina, Chapel Hill, NC

JOSEPH ERON
University of North Carolina, Chapel Hill, NC

J. VICTOR GARCIA
University of North Carolina, Chapel Hill, NC

GABRIEL GIRARD
SESSTIM Inserm, Marseille

GLENDA GRAY
South African Medical Research Council (SAMRC)

BEATRIZ GRINSTEJN
Fundação Oswaldo Cruz (Fiocruz)

NICOLAS HUOT
Institut Pasteur, Paris

KAMEL KHALILI
Temple University, Philadelphia, PA

JOSEPH LARMARANGE
CEPED, Paris

FLORENCE MARGOTTIN-GOGUET
Institut Cochin, Paris

HUGO MOUQUET
Institut Pasteur, Paris

MIREILLE MPOUDI-ETAME
Military Hospital, Yaoundé

ZAZA NDHLOVU
Harvard University, Cambridge, MA & University of KwaZulu-Natal, Durban

MICHEL C. NUSSENZWEIG
Rockefeller University, New York, NY

WILLIAM SCHIEF
The Scripps Research

LORRAINE SHERR
UCL, London

WESLEY I. SUNDQUIST
University of Utah, Salt Lake City, UT

XU YU
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA

SCIENTIFIC COMMITTEE

CHRISTOPHE D'ENFERT
Institut Pasteur, Paris

FRANCESCA DI NUNZIO
Institut Pasteur, Paris

JAMES DI SANTO
Institut Pasteur , Paris

HUGUES FISCHER
TRT5, Paris

JEAN-MICHEL MOLINA
APHP, Paris

MICHAELA MULLER-TRUTWIN
Institut Pasteur, Paris

ASIER SAEZ-CIRION
Institut Pasteur, Paris

OLIVIER SCHWARTZ
Institut Pasteur, Paris

BRUNO SPIRE,
Sesstim Inserm, Marseille

YAZDAN YAZDANPANAH
Inserm, Paris

CONTACT AND INFORMATION

WWW.40YHIVSCIENCE.CONFERENCES-PASTEUR.ORG
40yhivscience@conferences-pasteur.org

One of the very first photographs of the HIV-1 virus taken on February 4, 1983. Partial view of a cross-section of a T lymphocyte infected by the virus isolated from a patient presenting with generalized lymphadenopathy, which precedes AIDS. Colorized image with the virus shown in blue.

November 29th, 2023

Welcome

29/11/2023
4.30 pm - 6.00 pm

Chairs: Christophe D'enfert, Institut Pasteur, Paris, France
Sharon Lewin, Doherty Institute, Australia

4.30 pm **Opening**
Stewart Cole
President, Institut Pasteur, Paris, France

4.40 pm Yazdan Yazdanpanah
Director of ANRS | EID, INSERM, Paris, France, Paris, France

4.50 pm Anne-Claire Amprou
Ambassadrice de France en charge des questions de santé mondiale

1 **Communities and activists: from confrontation to partnership in research**
5.00 pm Hugues Fischer
TRT5, Pantin, France

2 **Introductory lecture: 40 Years of HIV Science: Much Accomplished, Much To Do**
5.30 pm Anthony S. Fauci
Distinguished University Professor, Georgetown University School of Medicine, Department of Medicine, Bethesda, Maryland, United States

Welcome Cocktail

29/11/2023
6.00 pm

November 30th, 2023

Session 1: Host cell-virus interactions

30/11/2023
9.00 am - 10.20 am

Chairs: Angela Ciuffi, Lausanne University Hospital and University of Lausanne, Switzerland
Frank Kirchhoff, Ulm University, Ulm, Germany

3 **Structure and function of the HIV capsid**
9.00 am Wesley I. Sundquist
University of Utah, Salt Lake City, United States

4 **The Next Frontier: Breakthroughs in HIV Post-Nuclear Entry Research**
9.20 am Francesca Di Nunzio
Institut Pasteur, Paris, France

5 | 9.40 am
Viral fusion and its inhibition
Olivier Schwartz
Institut Pasteur, Paris, France

6 | 10.00 am
Molecular conflict between HIV and host restriction factors
Florence Margottin-Goguet
Institut Cochin, Paris, France

Coffee break

30/11/2023
10.20 am - 10.50 am

Session 2: Host responses to HIV infection

30/11/2023
10.50 am - 12.10 pm

Chairs: Michaela Müller-Trutwin, Institut Pasteur, Paris, France
Guido Silvestri, Emory University, Atlanta, United States

7 | 10.50 am
Sex differences in HIV-1 pathogenesis
Marcus Altfeld
Leibniz Institute of Virology, Leibniz, Germany

8 | 11.10 am
Using Spatial Biology and Multi-Omics approaches to understand HIV Persistence in tissues
Zaza Ndhlovu
Harvard University, Cambridge, MA & University of KwaZulu-Natal, Durban, South Africa

9 | 11.30 am
Exploring Broadly Neutralizing Antibodies for HIV-1 Therapy
Michel C. Nussenzweig
Rockefeller University, New York, United States

10 | 11.50 am
NK cell differentation and viral control in SIV infection models
Nicolas Huot
Institut Pasteur, Paris, France

Lunch

30/11/2023
12.10 pm - 2.00 pm

Session 3: Social / implementation Sciences

30/11/2023
2.00 pm - 3.20 pm

Chair: Meg Doherty, World Health Organization, Geneva, Switzerland

11 | 2.00 pm
Don't pass me by - the person at the centre of HIV... (Zoom TBC)
Lorraine Sherr
University College London, United Kingdom

12 | 2.20 pm
Clinical implementation of HIV discoveries
Beatriz Grinstejn
Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro, Brazil

13 2.40 pm **Undoing Risk? Sociological Perspectives on HIV Prevention**
Gabriel Girard
SESSTIM Inserm, Marseille, France

14 3.00 pm **Transforming effective innovations into efficient interventions: contributions from social and implementation sciences**
Joseph Larmarange
CEPED, Paris, France

Coffee break

30/11/2023
3.20 pm - 3.50 pm

Session 4: Viral Persistence and Viral control

30/11/2023
3.50 pm - 5.50 pm

Chairs: Christine Rouzioux, University of Paris Descartes, Paris, France
Danny Douek, National Institute of Allergy and Infectious Diseases National Institutes of Health, Bethesda, United States

15 3.50 pm **HIV-1 Cure informed by Elite Controllers**
Xu Yu
Ragon Institute of MGH, MIT and Harvard, Cambridge, United States

16 4.10 pm **New insights into viral control**
Asier Saez-Cirion
Institut Pasteur, Paris, France

17 4.30 pm **Resident microbiota is a major driver of the acquisition and pathogenesis of HIV and EBV**
J. Victor Garcia
The University of Alabama at Birmingham, Birmingham, United States

18 4.50 pm **Non-T cell tissue niches for HIV reservoirs in human macrophages and megakaryocytes and their cross talk**
Morgane Bomsel
Institut Cochin, Paris, France

19 5.10 pm **The journey of HIV-1 DNA: From its synthesis to integration into the host genome**
Monsef Benkirane
Institut génétique humaine, Montpellier, France

20 5.30 pm **Human broadly neutralizing antibodies to HIV-1 and beyond**
Hugo Mouquet
Institut Pasteur, Paris, France

December 1st, 2023

Session 5: HIV Prevention

01/12/2023
9.00 am - 10.30 am

Chairs: Roger Le Grand, IDMIT, CEA, Fontenay-Aux-Roses, France
Daniela Rojas-Castro, Coalition Plus, Pantin, France

21 9.00 am
Treatment of HIV for Prevention: Reaching Full Potential
Myron Cohen
University of North Carolina, Chapel Hill, United States

22 9.20 am
Past, Present and Future of PrEP
Jean-Michel Molina
Infectious Diseases Saint-Louis Hospital, CHU Saint Louis, Paris, France

23 9.50 am
Vaccine design to induce broadly neutralizing antibodies against HIV
William Schief
Scripps research, La Jolla, United States

24 10.10 am
Vaccine Evaluation and Development in Africa : COVID-19 Pandemic Lessons for HIV Vaccine R&D
Glenda Elisabeth Gray
WHC Perinatal HIV Research Council, Johannesburg, South Africa

Coffee break

01/12/2023
10.30 am - 11.00 am

Session 6: New therapeutic strategy against HIV

01/12/2023
11.00 am - 12.00 pm

Chairs: Alexandra Calmy, Hopitaux universitaires de Genève, Geneva, Switzerland
Aahidjo Ayouba, Institut de Recherche pour le Développement, Montpellier, France

25 11.00 am
Novel antiretroviral therapies for people with HIV and why we need them
Joseph Eron
University of Chapel Hill, North Carolina, United States

26 11.20 am
Therapeutic strategies in Africa: Could one size fit all?
Mireille Mpoudi-Etame
ANRS | EID, Yaounde, Cameroon

27 11.40 am
CRISPR for the elimination of HIV-1
Kamel Khalili
Temple University, Philadelphia, United States

Closing address

01/12/2023
12.00 pm - 12.55 pm

12.00 pm **Introduction**

Jean-François Delfraissy
President of the French National Consultative Ethics Committee,

28 **HIV 40 years later, where are we going?**

12.10 pm Françoise Barré-Sinoussi
Prix Nobel de physiologie ou médecine (2008), Institut Pasteur, Paris, France

12.40 pm **Sylvie RETAILLEAU, ministre de l'Enseignement supérieur et de la Recherche**

End of meeting

01/12/2023
12.55 pm

ORAL COMMUNICATIONS

November 29th - December 1st, 2023

Institut Pasteur - HAll of CIS

Communities and activists: from confrontation to partnership in research

H. Fischer
TRT5, Pantin, France

This presentation will review 40 years of aids activism in France in 3 parts. First, the reasons of a mobilisation, the constitution of several groups and organizations, from gay community to aids fighting organisations, from people support to political mobilisation, from hopelessness to angry. Second, the emergence and structuring of a coalition for a better efficiency and for a pooling of skills building and expertise: the TRT-5 group. It has gradually become the place for building a partnership with researchers while also remaining a more political place of mobilization. Partnership with the ANRS, place of lobbying for legislative advances toward health democracy, vigilance towards the pharmaceutical industry, construction of international exchanges, widening the scope of action including hepatitis, STIs and prevention, has been in the agenda of the group. Third, our place today. As a partner for research programs and gradually research actor himself, however, the group also continues to defend the interests of individuals, PLWHIV as well as the most vulnerable communities.

Introductory lecture: 40 Years of HIV Science: Much Accomplished, Much To Do

A.S. Fauci
Distinguished University Professor, Georgetown University School of Medicine, Department of Medicine, Bethesda, Maryland, United States

Since the discovery of HIV in 1983, many major advances have been made in HIV natural history, virology, pathogenesis, host responses, antiretroviral drug development, prevention, vaccinology, and efforts toward a cure, as well as the prevention and treatment of HIV-related conditions such as opportunistic infections and malignancies. Some of the highlights from this extraordinary scientific journey as will efforts to implement HIV countermeasures through programs such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) will be presented through the lens of an American-physician scientist who helped lead the U.S. HIV/AIDS research effort. However, many scientific and implementation challenges remain as the global community works to defeat the HIV pandemic by developing new interventions, bringing them to scale, and delivering them to the communities who need them most. Promising new approaches to HIV treatment and prevention will be discussed—including long-acting antiretrovirals and monoclonal antibodies, novel HIV immunogens for vaccines that induce broadly neutralizing antibodies.

Structure and function of the HIV capsid

W.I. Sundquist
University of Utah, Salt Lake City, United States

The HIV capsid organizes the viral replication complex, protects the viral nucleic acids from innate immune surveillance, and targets the virus to the nucleus for integration. The capsid is also the target for Gilead's very potent and long-lasting anti-HIV drug, Lenacapavir/Sunlenca®. I will review the advances in our understanding of viral capsid structures and functions, and how this understanding is being leveraged to create new therapeutic opportunities.

The Next Frontier: Breakthroughs in HIV Post-Nuclear Entry Research

F. Di Nunzio
Institut Pasteur, Paris, France

HIV integration takes place at chromatin sites that facilitate the release of a high level of viral progeny. Alternatively, the virus can also exist discreetly within the host. To integrate into the host cell's genome, HIV must reverse transcribe its genetic material from RNA to DNA. Notably, the viral genome is enclosed within the capsid shell, which recent research has shown to persist after viral fusion with the cellular membrane. This capsid shell acts as a shuttle to assist the virus in navigating into the host cell.

Traditionally, textbooks have indicated that the uncoating (loss of the viral capsid) and the reverse transcription processes occur exclusively within the host cytoplasm. However, recent discoveries, including our own, have revealed that these steps take place within the nuclear compartment of the infected cell. This post-nuclear entry step is associated with the remodeling of the nuclear landscape. Intriguingly, HIV-1 exploits a recently discovered biological phenomenon called liquid-liquid phase separation (LLPS) to efficiently undergo nuclear reverse transcription and integrate into neighboring active chromatin. Further details on this phenomenon will be discussed.

Viral fusion and its inhibition

O. Schwartz
Institut Pasteur, Paris, France

Cell-cell fusion, also known as syncytia formation, is a biological process where two or more individual cells merge their membranes, resulting in the formation of a multinucleated cell known as a syncytium. During viral infection, fusogenic viral proteins trigger the fusion of infected cells with neighboring uninfected cells. This process is observed with many enveloped viruses such as human immunodeficiency virus (HIV), SARS-CoV-2 and paramyxoviruses. Enveloped viruses likely exploit this mechanism to spread within their hosts, to trigger inflammation and to partly avoid immune responses. However, the immune system, through the action of antibodies and of innate components may control syncytia formation and viral spread.

I will discuss various aspects of virus induced cell-cell fusion. I will also present results about how syncytia formation can be monitored in cell culture. We have developed a technique combining label-free holo-tomographic microscopy with Artificial Intelligence to visualize and quantify the subcellular changes triggered by SARS-CoV-2. This method will be applied to other viruses including HIV. It will help understanding the causes and consequences of virus-induced cell-cell fusion.

Molecular conflict between HIV and host restriction factors

F. Margottin-Goguet
Institut Cochin, University of Paris Cité, INSERM U1016, CNRS UMR8104, Paris, France

Sequencing of the genomes of HIV-1 and HIV-2 following their identification as causative agents of human AIDS revealed an unsuspected genetic complexity. In addition to the *gag*, *pol* and *env* genes, which represent the prototypical retroviral genes, the HIV genomes encode two critical regulatory proteins, tat and rev, as well as a set of « accessory » or « auxiliary » proteins. The latter were soon found dispensable for viral replication, at least in certain *in vitro* cellular systems. However, the emergence of these auxiliary proteins, which have no counterparts in other retroviral groups, strongly suggested that they fulfill specific needs of HIVs in the context of natural infection. Accordingly, they have stimulated intense investigation for 40 years. The current view strikingly illustrates the ever-lasting molecular conflict between viruses and their host cells. Indeed, HIV auxiliary proteins principal function is to rid the virus of host factors that compromise its replication: the so-called restriction factors. These host factors are not passive barriers but rather intrinsic antiviral cell defenses acquired during evolution. Here we will focus on one viral auxiliary protein, namely Vpx, which is specific for the HIV-2/SIVsm lineage. We will show how the study of Vpx led to the discovery of prominent host restriction factors, SAMHD1, a dNTP hydrolase, and HUSH, a repressor of HIV gene expression that could contribute to HIV latency. Inactivation of HUSH by Vpx strengthens the idea of HIV latency as a cellular defense mechanism protecting genomic and proteomic integrity.

Sex differences in HIV-1 pathogenesis

M. Altfeld
Leibniz Institute of Virology, Leibniz, Germany

Immune responses differ between females and males, with consequences for infectious diseases and autoimmune diseases. In my presentation, I will review sex differences in HIV-1 pathogenesis, and present novel data on the role of genes encoded by the X chromosome and steroid hormones in mediating sex differences in immune responses against HIV-1

Using Spatial Biology and Multi-Omics approaches to understand HIV Persistence in tissues

Z. Ndhlovu
Harvard University, Cambridge, MA & University of KwaZulu-Natal, Durban, South Africa

My research seeks to address the major obstacle to HIV cure by identifying means of enhancing immune responses in secondary lymphoid organs (SLO) where HIV hides to evade detection and elimination by the immune system. My presentation will focus on the spatial transcriptomic analysis of HIV infected lymph nodes to better understand molecular mechanisms that contribute to follicular reservoir persistence within SLOs in the face of suppressive antiretroviral therapy. This work will guide the development of new approaches to overcome barriers to HIV eradication in tissues.

Exploring Broadly Neutralizing Antibodies for HIV-1 Therapy

M.C. Nussenzweig
Rockefeller University, New York, United States

The 40 years since Professors Barre-Sinoussi and Montagnier discovered HIV-1 have seen enormous progress in HIV-1 prevention and therapy. What was once a death sentence is now a chronic disease. However, there is still no cure and no vaccine. Nevertheless, a small number of infected individuals develop antibodies that can neutralize the diverse collections of viruses. Early in the pandemic it was recognized that sera containing this activity might prevent infection. The Nussenzweig laboratory developed methods to identify and molecularly clone these broadly neutralizing antibodies from infected individuals. Testing in animal models indicated that the human monoclonals can prevent disease, clear infected cells and treat infection. Human trials are underway with the aim of determining whether antibodies therapies can be used in combination with traditional ART and whether antibodies can impact anti-HIV-1 immunity, or the size and composition of the HIV-1 reservoir.

NK cell differentation and viral control in SIV infection models

N. Huot*[1], B. Jacquelin[1], V. Contreras[2], M. Lazzerini[1], C. Petitdemange[1], E. Beaumont[1], R.K. Reeves[3], R. Le Grand[2], M. Müller-Trutwin[1]

[1]Institut Pasteur, Université Paris-Cité, Unité HIV, Inflammation et Persistance, Paris, France [2]CEA-Université Paris Sud-Inserm, U1184, IDMIT Department, IBFJ, Fontenay-Aux-Roses, France [3]Duke University School of Medicine, Division of Innate and Comparative Immunology, Center for Human Systems Immunology, Durham, United States

Natural killer (NK) cells play a vital role in immediate immune responses against stressed, transformed, or infected cells. Their activity is regulated through a complex interplay of inhibitory and activating receptors, which contribute to their diverse phenotype and functionality. This diversity is influenced by genetic and environmental factors, including cytokines, previous infections, vaccinations, age, and lifestyle choices. Recent discoveries have highlighted NK cells' adaptability and their potential to transform into long-lasting memory cells, offering new avenues for therapeutic applications.

HIV-1 infection often impairs NK cell functions, alters their tissue distribution, and diminishes their ability to control viral reservoirs. Despite their critical role, studies on NK cell function in tissues during HIV infection are however limited. Our previous studies raised the hypothesis of a perturbation of NK cell differentiation leading to impaired anti-viral control in lymph nodes. Recent studies have unveiled the natural presence of NK cell precursors (NKP) in various tissues outside the bone marrow, like the thymus, lymph nodes, and liver. Despite this knowledge, the mechanisms governing NK cell maturation, the emergence of adaptive NK cells, and their interactions within the immune system remain unclear. Additionally, the impact of chronic viral infections on NKP and their ability to combat pathogens is not well understood.

Our research focuses on NK cell differentiation, functional specialization, and lineage relationships in tissues during simian immunodeficiency virus (SIV) infections in animal models of pathogenic (macaque) and non-pathogenic (African Green Monkey, AGM) infection. We delve into the intricate journey of NK cells, tracing their development from hematopoietic stem cells to lineage-committed NK precursor cells (NKP). By longitudinally analyzing tissue samples from animals infected with SIV, we identified distinct NK cell differentiation patterns between non-pathogenic and pathogenic infections, especially in cytokine profiles during different phases of the host response to infection. This comprehensive analysis enhances our understanding of NK cell generation with potent antiviral activity and lays the foundation for identifying new targets for immunotherapies, promising advancements in antiviral treatments.

Don't pass me by - the person at the centre of HIV...

L. Sherr
University College London, United Kingdom

The arrival of HIV signified a dramatic turn in the approach to care, prevention, inclusion and human understanding. As the intricacies of the HIV virus were explored, as testing and treatments came on board, as humanity recorded transmission pathways, the biomedical phenomenon of HIV opened up the burning need for holistic approaches and shone a light on the importance of social science to understand every step of the pathway. This talk will track the use of evidence based social science to understand both the impact of HIV and possible solution pathways in the management and response. The focus will concentrate on women and children as an example of groups who are often overlooked, misunderstood and underserved.

Clinical implementation of HIV discoveries

B. Grinstejn
Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro, Brazil

From the earliest elucidation of the HIV replication cycle leading to the identification of targets for therapeutic intervention, the number of ARV drugs has expanded, and effective treatment was simplified and can be as simple as one pill once a day or two injections every 2 months. Anti-retroviral therapy not only restores life expectancy to near normal, but also eliminates the risk of HIV transmission when consistently used. For those under vulnerability to HIV infection, either daily/on demand oral tenofovir/emtricitabine or an injection of cabotegravir every 2 months can serve as effective pre-exposure prophylaxis. Although there is an urgent need to continue to pursue innovation science toward an HIV vaccine, an ART-free remission, and a cure, there remains a major challenge in the optimal implementation in low- and middle-income countries (LMICs) of the advances that we already have in the areas of HIV prevention, diagnosis, treatment, and care. These approaches must be adapted for each at-risk population to address racial and ethnic, gender, cultural, socioeconomic, and geographic parameters within each of these groups. Successful implementation of HIV prevention and treatment strategies in LMICs need to take into consideration the numerous challenges that must be overcome, including structural, legal, and societal barriers such as stigma, discrimination, criminalization, lack of access to health care, food insecurity, and homelessness, among others. Community engagement plays a crucial role in the successful implementation of HIV discoveries. Involving community members in the design, planning, and execution of HIV-related studies helps ensuring that research objectives align with the priorities and needs of the community.

Undoing Risk? Sociological Perspectives on HIV Prevention

G. Girard
SESSTIM Inserm, Marseille, France

For the past 40 years, risk has been at the heart of debates, studies and practices surrounding the AIDS epidemic: whether on an intimate, community, medial or political level. But the paradigms of HIV risk have shifted dramatically in recent decades, with TasP, PrEP, normalization and chronicization... This talk proposes to put into perspective how risk is still a driver and an unthought in social relations, public policy and research. The intervention will be based on a critical reading of some key social science works in the field of prevention and risk perception.

Transforming effective innovations into efficient interventions: contributions from social and implementation sciences

J. Larmarange
CEPED, Paris, France

The history of the fight against AIDS has been marked by the development of major scientific and biomedical innovations: antiretroviral treatments, rapid screening tests, pre-exposure prophylaxis... However, these innovations have often been insufficient on their own to curve the epidemics. It has also been essential to innovate in terms of funding, organisation of services and care, advanced "out-of-hospital" strategies, human rights, taking account of the specific characteristics of the most vulnerable populations, etc.

Effective innovation will be ineffective if it is not adapted to the social, cultural, and legal constraints faced by populations and to the structural, organisational, and economic constraints of healthcare systems. Hence the need for a genuine science of implementation that is necessarily interdisciplinary and intersectoral.

HIV-1 Cure informed by Elite Controllers

X. Yu
Ragon Institute of MGH, MIT and Harvard, Cambridge, United States

HIV-1 elite controllers arguably represent the closest possible approximation to a cure of HIV-1 infection. Two possible types of an HIV-1 cure have been recognized thus far: a virological cure with the elimination of all HIV-infected cells that encode for replication-competent HIV, and a functional cure, characterized by enrichment of intact proviruses within heterochromatin positions associated with deep latency. Both forms of a cure may result from immune-mediated clearance of HIV-1 reservoir cells harboring intact proviruses in accessible chromatin locations. Effective immune responses in people living with HIV-1 may, after extended periods of antiretroviral therapy, also be able to induce viral reservoir profiles dominated by intact proviruses in heterochromatin locations; such an atypical reservoir profile, might, in rare cases, contribute to drug-free control of HIV after treatment interruption. Identifying immune mechanisms that can drive selection of intact proviruses in deep latency will represent an important research priority for future studies.

New insights into viral control

A. Saez-Cirion
Institut Pasteur, Paris, France

Antiretroviral treatment cannot eliminate HIV reservoir cells that cause viral rebound if treatment is interrupted, requiring lifelong treatment. However, some people, post-treatment controllers (PTC), are able to stably control viremia after treatment interruption, achieving a status of durable HIV remission. We are studying the parameters associated with post-treatment control in 30 PTC from the VISCONTI study and in animals from the p(rimate)-VISCONTI study, which aims to explore, in a macaque model of SIV infection, the influence of early ART initiation in post-treatment control. Our results show that initiation of antiretroviral treatment during primary infection, promotes the durable maintenance of viral control after the interruption of treatment. We have found that early treatment may favor the maturation of the memory response against the virus, allowing a more efficient secondary response after treatment interruption. In addition, we have identified genetic fingerprints and NK cell signatures that suggest an important role of NK cells in post-treatment control. A better understanding of the mechanisms of post-treatment control may lead to the development of new immunotherapies to achieve HIV remission.

Resident microbiota is a major driver of the acquisition and pathogenesis of HIV and EBV

J.V. Garcia
University of North Carolina, Chapel Hill, United States

Germ free (GF) mice are the gold standard for exploring microbiota's role in health and disease. However, many human pathogens do not replicate in mice. We developed GF humanized mice that are systemically reconstituted with human immune cells. Using GF-BLT mice and conventional (CV)-BLT mice colonized with resident microbes, we evaluated microbiota's role in EBV and HIV (two human-specific pathogens) acquisition, replication, and pathogenesis. Resident microbiota enhanced the establishment of EBV infection and EBV-induced tumorigenesis. Resident microbiota increased mucosal HIV acquisition and replication. Oral and rectal HIV acquisition were 300% and 200% higher in CV-BLT mice, respectively. HIV-RNA levels were up to 34-fold higher in plasma and over 1,000-fold higher in tissues of CV-BLT mice. Thus, resident microbiota are a major driver of the acquisition and pathogenesis of two clinically relevant human-specific pathogens.

Non-T cell tissue niches for HIV reservoirs in human macrophages and megakaryocytes and their cross talk

M. Bomsel

Laboratory of Mucosal Entry of HIV and Mucosal Immunity, Institut Cochin, University of Paris Cité, CNRS, UMR8104, Inserm, U1016, Paris, France

Despite efficient combined antiretroviral therapy (cART), HIV-1 eradication is hampered by viral persistence in cell reservoirs. Genetic analyses of the virus rebounding upon cART interruption showed that HIV reservoirs not only establish in circulatory CD4+ T-cells but also in non T-cells in tissues. The nature of these tissue reservoirs and mechanisms of persistence remained unclear, although likely candidates were tissue macrophages and megakaryocytes that are both infected by the virus upon early infection.

Challenging the paradigm of a CD4+ T-cell only reservoir, we established that in individual under suppressive cART, resident mucosal macrophages harbor viral DNA, RNA and viral particles stored in a virus containing compartments (VCCs) characteristic of myeloid cells. Moreover, these persistently infected macrophages form a replication competent reservoir from which viral latency could be reversed upon TLR4 activation. We next evaluated the implication of macrophage immunometabolic pathways in HIV-1 persistence. We demonstrated that this transcriptionally active reservoir resides in M4-polarized macrophages with and inflammatory IL-1R+ S100A8+ MMP7+ phenotype prone to glycolysis. The alarmin S100A8, an endogenous TLR4-ligand produced by M4-macrophages and implicated in " sterile" inflammation reactivated infectious virus production and release from these macrophage reservoirs *in vitro* in a process that metabolically depends on glycolysis.

We next revealed that bone marrow megakaryocytes, at least in cART-suppressed patients with sustain low CD4+T cells counts, formed an additional reservoir with integrated viral DNA. In these patients, megakaryocyte reservoirs produced platelets sheltering infectious HIV-1. *In vitro,* patient platelets harboring HIV propagated the virus to macrophages, in a process that could be prevented with the drug abciximab, an anti–integrin aIIb/b3 Fab.

Altogether, inflammatory M4-macrophages constitute a major tissue reservoir of replication-competent HIV-1, which reactivate viral production upon S100A8-mediated autocrine/paracrine glycolytic stimulation. Furthermore, our study suggests that platelets may be transient carriers of HIV-1 and may provide an alternative pathway for HIV-1 dissemination in HIV-1-infected individuals on cART with viral suppression. Finally, platelets are known to be the major carrier of platelet factor 4 (PF4), the cytokine polarizing macrophages to the M4-subtype and to contain the alarmin S100A8, which is synthesized by megakaryocytes in addition to myeloid cells. We therefore suggest that HIV infected platelets establishes a cross talk between the two reservoirs in megakaryocyte and macrophages. Capture of infected platelets with tissue macrophages together with local release of platelet PF4 and the alarmin S100A8 may contribute to M4-polarization, and sustain the long lasting reservoir in macrophages. These HIV-1 persistence pathways needs to be targeted in future HIV eradication strategies.

The journey of HIV-1 DNA: From its synthesis to integration into the host genome

M. Benkirane
Human Genetics Institute, Montpellier, France

During retroviral infection, viral genomic RNA is used to synthesize a histone-free, viral DNA copy. vDNA will ultimately integrate into the host genome to ensure its maintenance and expression. This course of the viral genome is undermined by traps set up by the host cell. We will discuss the role of viral proteins present in virions and host factors associated with neosynthesized viral DNA in the escape from intracellular immunity.

Human broadly neutralizing antibodies to HIV-1 and beyond

H. Mouquet
Institut Pasteur, Paris, France

HIV-1 broadly neutralizing antibodies (bNAbs) develop in rare infected individuals called Elite neutralizers, and target distinct regions of the viral envelope glycoprotein. bNAbs can neutralize a wide spectrum of heterologous viral strains, protect non-human primates from infection and confer long-term viral suppression in people living with HIV-1 following treatment interruption. Hence, bNAbs hold great promises for HIV-1 treatment and prevention, and may help achieving a functional HIV-1 cure. We will present our latest findings on the identification and in-depth characterization of novel HIV-1 bNAbs isolated from viremic and post-treatment controllers.

Treatment of HIV for Prevention: Reaching Full Potential

M. Cohen
University of North Carolina, Chapel Hill, United States

The development of ever better antiretroviral drugs for the treatment of HIV infection is heralded as one of the most important accomplishments of the 20th and 21st centuries, saving countless lives. But observational and randomized controlled trials demonstrated that successful suppression of HIV replication also eliminates viral transmission. Accordingly, treatment as prevention (TaSP) has become a critical biological strategy to prevent HIV infections. At an individual level, activists launched the U=U campaign (undetectable viral load equals an uninfectious person) designed to inspire commitment to treatment, reduction of stigma, and improve the lives of people living with HIV. Most recently, an extensive review of the literature demonstrates that viral suppression below 1000 copies/ml plasma is sufficient to prevent HIV transmission. At a population level UNAIDS launched the 95-95-95 campaign: find 95% of infected people, link 95% of them to care, and suppress viremia 95% of the time. This campaign has been widely embraced and subjected to evaluation through cross-sectional surveys (Population-based HIV Impact Assessment, PHIAs). In every country studied longitudinally, HIV incidence has fallen as the “95-95-95” goal has been approached. In Eswatini and Bostwana HIV incidence near zero have been reported. However, TaSP is “leaky” because it fails to deal with hard to reach and marginalized populations at risk for HIV acquisition: sex workers and their clients, MSM, people who inject drugs, transgender people., young people, and mobile populations. And no strategy leads to immediate treatment of people with acute HIV infection who cannot be readily detected but are held responsible for as many as a third of new infections in some studies. TaSP is among the most important tools for HIV prevention, but methods and strategies to meet well-defined challenges must be developed for TaSP to reach maximal and sustained benefit.

Past, Present and Future of PrEP

J. Molina
University of Paris Cité, INSERM U944 and Department of Infectious Diseases, St-Louis and lariboisièr Hospitals, APHP, Paris, France

A sustained focus on HIV prevention is required to reach the WHO/UNAIDS Goals of less than 200,000 new HIV-infections by 2030. Pre-exposure prophylaxis (PrEP) is a key element of the combination prevention strategy for HIV, along with anti-retroviral therapy (ART), HIV testing, and condom provision.

First evidence on the efficacy and safety of daily oral pre-exposure prophylaxis (PrEP) with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) for the prevention of HIV infection was published more than a decade ago, but it was only in 2015 following the results of two European studies that the full potential of PrEP was appreciated and led to broad approval by the World Health Organization (WHO). PrEP was gradually scaled up with near 4 million PrEP users in 2023, but PrEP remains largely underused.

There are substantial inequalities and regional variability in its availability and implementation. As a result, overall coverage for people who are at the highest risk is still deficient. In France, a recent study estimated that only 28% of MSM reported the use of PrEP for their last condomless anal intercourse with a casual partner.

The key determinant of PrEP efficacy is medication adherence, which is particularly challenging in daily dosing regimens for some of the most at-risk populations, such as cis and transgender women, young individuals, racial and ethnic minorities, and injecting drug users.

Long-acting agents and extended-release formulations are very promising novel PrEP candidates. Long-acting injectable cabotegravir (CAB-LA) is the first injectable ART approved for HIV PrEP in the USA. CAB-LA has demonstrated safety and superior effectiveness for preventing HIV infection than daily TDF-FTC among MSM, transgender women, and cisgender women when administered as a single 600-mg intramuscular injection every 2 months. Lenacapavir is another long-acting antiretroviral drug, from the new class of HIV capsid inhibitor, which is also being assessed as an injectable PrEP agent, in phase III PrEP trials. LEN-LA can be self-administered in the subcutaneous tissue once every 6 month and has a great potential for PrEP if trials demonstrate effectiveness.

The use of long-acting broadly neutralizing antibodies (bNAbs) is another promising approach to preventing HIV acquisition. Topical agents or microbicides are other alternatives. In 2021, the WHO recommended a monthly dapivirine intravaginal ring for HIV prevention in cis-gender women, based on the results of two phase-III randomized placebo-controlled clinial trials showing a 27% and 35% relative reduction of HIV incidence.

Finally, innovative alternatives for PrEP include new drug delivery systems such as subdermal implants and transdermal devices that could provide continuous protection from HIV over time, and multipurpose prevention technologies, which could deliver prevention for HIV and other STIs, with or without contraception.

Despite the progress made in scaling up PrEP, this prevention strategy has not yet reached its full potential in curtailing the HIV epidemic. At each step of the PrEP care continuum, several barriers persist. A more ambitious and holistic approach is still required to address individual, structural, social, and political barriers. To achieve this goal, specific attention must be given to PrEP awareness and education.

Vaccine Evaluation and Development in Africa : COVID-19 Pandemic Lessons for HIV Vaccine R&D

G. Gray
South African Medical Research Council (SAMRC), Cape Town, South Africa

The lack of regional investment in vaccine research and development was a major contributor to the delayed and limited access to COVID-19 vaccines in Africa during the pandemic. Despite a high need for vaccines, given the high burden of infectious disease, only1% of all vaccines are locally manufactured with a rarity of institutions on the continent being WHO prequalified for vaccine manufacturing. In terms of vaccine development, Africa only contributed 5 of the almost 300 COVID-19 vaccine candidates under investigation demonstrating the paucity of vaccine discovery and development capabilities on the continent. In terms of clinical development, the majority of clinical trials were conducted in South Africa, where most of the continental clinical and laboratory infrastructure and expertise lie, largely attributed to the sustained international and national investment in HIV and TB research. South Africa has a robust and responsive regulator with seasoned ethics committees necessary for appropriate oversight to support the quality of the data required for licensure. Experienced teams were able to evalaute a variety of vaccine candidates from early phase clinical development to late stage efficacy trials, contributing over 50 000 participants, including People Living with HIV (PLWH). In addition, 500 000 health care workers were enrolled in a phase 3B implementation study contributing to global knowledge on safety and real world effectiveness of the Ad26 SARS.CoV.2 vaccine. In an attempt to redress the lack of vaccine R&D on the continent, many initiatives are in play to develop local capacity including the establishment of multiple mRNA technology platforms which has the potential to support vaccine discovery on the continent. Building on the international investment of the NIH, a recent USAID co-operative agreement awarded to the BRILLIANT consortium of scientists from 8 African countries is the first international award enabling African scientists and advocates to be involved in HIV vaccine discovery and development. An investment in vaccine immunogen discovery and platform design, preclinical and clinical development will support the meaningful participation of African scientists in the quest to find a HIV vaccine.

Novel antiretroviral therapies for people with HIV and why we need them

J. Eron
University of Chapel Hill, North Carolina, United States

Current antiretroviral therapy for people with HIV (PWN) is remarkably effective and reliably safe. Most PWH can be managed with one combination pill each day and even PWH with resistant virus can maintain HIV RNA suppression with once daily therapy. These treatments are not successful in all PWH. Some have highly resistant virus and require new agents that work by new mechanisms. Others struggle to manage oral therapy or are hardly reached by our traditional medical approaches. Alternative antiretroviral that work by novel mechanisms or have characteristic or delivery systems that allow infrequent dosing will help us reach all people with HIV benefiting individual and public health. This talk with explore these new antiretroviral agents, long acting strategies and novel combinations that have entered clinical care or clinical trials.

CRISPR for the elimination of HIV-1

K. Khalili
Temple University, Philadelphia, United States

The application of the CRISPR gene editing approach to animal models results in the removal of the designated integrated proviral DNA from host DNA with no adverse effects on the health of the treated animal. Inactivation of HIV-1 in humanized mice by CRISPR along with editing of CCR5, a co-receptor for HIV-1, in the host genome results in suppression of viral rebound in more than 50% of experimental animals. These observations support the notion that HIV-1 cure by CRISPR is possible.

HIV 40 years later, where are we going?

F. Barré-Sinoussi
Nobel Prize in Physiology or Medicine (2008), Institut Pasteur, Paris, France

Much progress has been made in the development of tools to prevent, diagnose and treat HIV infection. However, we still do not have a vaccine and antiretroviral treatments are not curative as HIV persists in many compartments of the body. Implementation of these tools at large scale worldwide remains a critical challenge as well as the sustainability of life-long therapies. Development of an effective vaccine and of novel HIV therapeutic strategies, which both required more basic and translational science, are an absolute necessity to end the HIV epidemic. The past four decades of HIV/AIDS science are a good example of a broad comprehensive and collective response to an emerging human threat in the spirit of Louis Pasteur. This must even be developed further by extending transdisciplinary partnerships for enhancing the global response to HIV and emerging pandemics.