Investigación básica y curación del VIH-1

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Covered Sessions

1. Harnessing **Ab** for HIV Prevention and Treatment (PL-15)
2. SIV and HIV **Pathogenesis** (O-1)
3. **Viral Reservoirs** / ART Randomized Clinical Trials (O-2)
4. **Molecular Interplay** from Virus to Host (S-1)
5. Progress in **Gene Therapy** for HIV Cure (PL-78)
6. **Reservoirs**, Relapse, and Remission (O-6)
7. Pushing Frontiers of **Adaptive Immunity** (O-7)
8. Location, Location, Location: The **Lymph Node** (S-7)
9. HIV **Virology**: Putting It All Together (O-11)
10. Natural Born(e) Killers [**NK cells**] (S-10)
Reversing HIV-1 Latency in ART-Treated Patients

TLR-7
Galectin-9

‘Shock’

HIV RNA
HIV proteins

‘Kill’

HIV particles

ART Immune System

Dying infected cell

Deeks Nature 2012 & The Economist 2011
Innate immune detection of microbial nucleic acids

#95LB
Whitney et al.
Transient Plasma Viremia Induced by TLR7 Agonist GS-986 Treatment of Monkeys on ART

Viral reactivation in monkeys treated with 0.3 mg/Kg of GS-986
But peripheral production of IFNα

Post-CROI 2016 J.Martinez-Picado
TLR7 Agonists Induce Transient Plasma Viremia

- Viral reactivation only when using the TLR7 agonists
- No peripheral production of IFNα with GS-9620 (both doses), and minimal production with GS-986 (0.1mg/Kg)

Post-CROI 2016 J.Martinez-Picado
SIV DNA Levels Reduced in Memory CD4+ T cells from TLR7 Agonist Treated Monkeys on ART

👍 More pronounced decreases in viral DNA levels in TLR7 agonist treated animals as compared to placebo
Plasma SIV RNA Rebound after Stopping ART

2 of 9 animals treated with TLR7 agonists have undetectable plasma virus up to 3-4 months off ART, both predicted by *ex vivo* reactivation cultures of PBMCs and inguinal LN.
19 doses of GS-986 or GS-9620 demonstrated...

- induction of transient plasma viremia
- minimal to undetectable plasma IFNα
- decreased viral DNA levels

2 of 9 monkeys treated with TLR7 agonists have remained aviremic for at least 3 months after stopping ART

Phase I clinical studies of GS-9620 in HIV+ ART-treated participants is ongoing (and phase II for HBV)
Human Galectin-9 Is a Potent Mediator of HIV Transcription and Reactivation (#81)

Galectins

- proteins that specifically bind β-galactoside sugars, which frequently glycosylate proteins
- Family of 10-members in humans
- Gal-1 is not essential for HIV infection but helps by accelerating the binding kinetics between gp120 and CD4
- Gal-9 has previously implicated in rheumatoid arthritis

Hypothesis:

- Gal-9 regulates p21, which in turn regulates HIV transcription during ART.
rGal-9 reactivated virus in primary CD4+ T cells from subjects on suppressive ART

Gal-9 plasma levels, in 72 HIV-infected subjects, were associated with levels of CD4+ T CA-HIV RNA (p<0.02)

rGal-9 reactivated virus in J-Lat cells (15.1%) more potently than anti-CD3/CD28 stimulation (4.8%, p<0.0001)

7-fold reduction in the infectivity of reactivated virus through the incorporation APOBEC3
The Lymph Node (#127-130, #82)

Kurosaki et al. Nat Rev Immunol 2015
Stem Cell Transplantation in EpiStem (#366)

A Tale of Two Stem-Cell Transplantations in HIV+ Patients: Clues to Eradicate HIV

The “graft versus HIV-1 reservoir effect” facilitates clearance of the viral reservoir

Patient 1
- Myeloablative Haplo-cord SCT
- CCR5 wt
- 2012
- Chimera 0.2% BM/0.1% PB
- No GvH disease
- +29 month post SCT
- qVOA (IU/PM) 0.034
- Total DNA (cp/10^6 CD4) 25
- Susceptibility (RS and X4 viruses) Susceptible
- Immune supression Effective CD8+ T response
- Activation Markers (HLA-DR+CD38+)
- SCA (HIV-RNA cp/ml) 11.30%
- Ab titers Low levels
- Ileum CD4+ cells N/A
- BM CD3+ cells N/A
- CSF DNA Undetectable

Patient 3
- Burkitt NHL HIV-1+ RS tropic
- Cord Blood (5/6)
- CD34+ HLA-mismatched donor
- Peripheral Blood Progenitor Cells SCT
- CCR5 wt
- 2013
- Full Chimera (30 days)
- GvH disease
- +20 month post SCT
- - no cART interruption
- - qVOA (IU/PM) Undetectable
- - Total DNA (cp/10^6 CD4) Undetectable
- - Susceptibility (RS and X4 viruses) Susceptible
- - Immune supression Non Effective CD8+ T response 1.41%
- - Activation Markers (HLA-DR+CD38+)
- - SCA (HIV-RNA cp/ml) 5
- - Ab titers Undetectable
- - Ileum CD4+ cells DNA Undetectable
- - BM CD3+ cells DNA Undetectable
- - CSF RNA Undetectable
Restriction factors and IFN

Viral capsid core

Uncoating

SAMHD1

APOBEC3

Vpx

Viral genomic RNA

Reverse transcription

DNA

Integration

Nucleus

Proivirus

mRNA

Translation

Vpu

Env

Nef

Vpx

APOBEC3

Gag

Vif

Gag, Pol

Tetherin

Packaging

Release

Vpx

APOBEC3

Simon et al. Nat Immunol 2015
SERINC-3/5: novel restriction factors

- Plasma membrane proteins that are incorporated into progeny virions in the absence of Nef and inhibit HIV-1 infectivity.

#57 Pizzato; #136 Wu et al.; Figure from C Aiken, Nature 2015
SERINC-3/5 proteins impair viral delivery

- SERINC3/5 are highly expressed in primary human HIV-1 target cells
- No regulated by IFNα
- Preventing their downregulation by Nef is a potential anti-HIV strategy

Infectivity of Nef− HIV produced in CRISPR-Cas9 mediated SERINC KO

Relative infectivity

- Ctrl
- SERINC3−/−
- SERINC5−/−
- SERINC3/5−/−

JurkatTAg-derived virus producer cells

#136 Wu et al.
The type I IFNs: first line of defense

- Mucosally transmitted founder HIV are more resistant to the antiviral effects of type 1 IFNs than HIV-1 strains that predominate during chronic infection (#133)

- Relative expression, antiviral properties and effector mechanisms utilized by the 12 IFNα subtypes against HIV-1 infection of mucosal tissues remain unknown (#134)
  - IFNα8, IFNα6 and IFNα14 had the greatest antiviral activity
  - IFNα2, the clinically approved subtype, and IFNα1 were both highly expressed but exhibited relatively weak antiviral activity
CD8$^+$ T cells, DCs, and ...
CD8 T Cells Are Required to Suppress Viremia in SIV-Infected ART Treated RM (#22)

Reconstitution with CD8 (but not NK) is associated with viral resuppression
Identification of a Highly Functional DC Subset in EC by Single-Cell RNA-Seq (#19)

PBMCs from EC

Media

+ HIV-1

Single-cell Sorting of CD14-CD11cHi HLADR cells at 24/48h culture

Single-cell RNA-Seq analysis (24+48h)

Total 85 cells with HIV virus and 54 cells with media alone
Subset of cDC: CD64\textsuperscript{high}PD-L1\textsuperscript{high}

- Upregulation of IFN-stimulated genes and remarkably effective functional antigen-presenting properties, including proliferation of both CD4 and CD8 T cells

- How to induce such subset?

HIVneg DC + 100 Nt Gag ssDNA or 100 Nt Gag dsDNA + TLR3L = PDL1Hi CD64Hi DC
Early History of the North American HIV/AIDS Epidemic (#140)

Molecular biology, phylogenetics, and historical analysis to investigate the timing and geography of the emergence of HIV-1 group M subtype B in the U.S.

8 samples + Patient “0”

And the Band Played On
1987 by Randy Shilts
Early History of the North American HIV/AIDS Epidemic (#140)

By 1978-79 the HIV-1 epidemic in the U.S. already exhibited extensive genetic diversity – particularly in NYC – having emerged around 1970 from a founder virus drawn from an older and more diverse subtype B epidemic in the Caribbean.

No evidence for patient “0” being really “Zero”
Thanks

- Fundació Lluita contra la SIDA
- Gilead