Eradication of HIV
Bonaventura Clotet
Hospital Universitàri Germans Trias i Pujol
Badalona. Barcelona. Catalonia
• Transparency declaration
• I have served during the past 2 years as a consultant on advisory boards or participated in speakers’ bureaus or conducted clinical trials with Gilead, ViiV and Merck (MSD)
HIV CURE
Life Cycle and Pathogenesis of HIV

Reservoir: Resting Central & Transitional memory CD4 T cells memory (CD45RO+), Resting naive CD4T cells, Tissue monocyte-derived cells?

Viral Rebound After HAART Interruption

HIV-1 Viral Load (Log_{10} RNA Copies/ml) vs. Time Off HAART (Days)

B

HIV DNA (copies/μg PBMC DNA) vs. Time receiving HAART (weeks)

[Diagram and graphs showing the life cycle and pathogenesis of HIV, including reverse transcription of HIV-1 RNA, CD4+ T cell activation, integration of HIV-1 DNA, cell death, and viral rebound after HAART interruption.]
¿Es posible erradicar la infección?
100% Effective HAART Regimen

Plasma HIV-1 RNA (copies/ml)

Time on HAART (years)

Limit of detection (50 copies/ml)

Release from stable reservoirs
Kick and Kill Strategy to Eliminate Reservoirs of Latent HIV

**KICK**
Activate expression of HIV

**KILL**
Kill cells expressing HIV proteins

**Latency Reversal Agents**
- HDACis
- PKC agonists

Latently infected CD4 T-cells

Death of infected cells

**Killing Strategies**
- Therapeutic vaccines
- Anti-Env antibodies
- Anti-PD-L1
- Modified Immunoglobulins
- Het IL15
- TLR-7

Macrophages  CD8 T-cells  NK cells
STRATEGIES TO CURE HIV
BONE MARROW TRANSPLANTATION
The Emerging Race To Cure HIV Infections

Proof negative. The apparent cure of Timothy Ray Brown (left) has given momentum to novel interventions like the gene therapy that Matt Sharp (right) received.
CCR5 Δ32 homozygous cord blood allogeneic transplantation in a patient with HIV: a case report

Rafael F Duarte, María Salgado, Isabel Sánchez-Ortega, Montserrat Arnan, Carmen Canals, Eva Domingo-Domenech, Alberto Fernández-de-Sevilla, Eva González-Barca, Sara Morón-López, Nuria Nogues, Beatriz Patiño, María Carmen Puertas, Bonaventura Clotet, Lawrence D Petz, Sergio Querol, Javier Martinez-Picado

María Salgado

Sara Morón-Lopez  Mª Carmen Puertas
Observational project, not a clinical trial, to investigate cases of ...

“Allogeneic stem cell transplant in HIV-1-infected individuals”
IciStem systematically monitors the patients included for extensive periods of time to better understand the biological clues leading to viral reservoirs reduction and potential cases of HIV-1 eradication/remission among these patients.
Sensitive quantification of the HIV-1 reservoir in ileum-associated lymphoid tissue
**Mouse Viral Outgrowth Assay (mVOA)**

Rational to stop cART in these patients

- **10-50 million CD4+ T cells / mouse**
- **NOD-Scid IL2gR−/−**
- **HIV reactivation**

**HIV Plasma Viremia**

![Graph showing HIV Plasma Viremia with different samples](image)
All in cART

7 patients > 2 years post BM transplantation
Off immunosupresor drugs.
HIV VL undetectable
Mouse VOA negative

**CCR5**

<table>
<thead>
<tr>
<th>Adult Donor</th>
<th>CCR5 Δ32/Δ32</th>
<th>CCR5 WT/WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>16*</td>
<td>4</td>
<td>20</td>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

*Two CCR5 Δ32/WT*
Present and Future

- IciStem has assembled an unprecedented cohort of 12 potential candidates to be the new “Berlin Patients”
- The allo-HSCT is currently the only clinical intervention demonstrating a substantial reduction of the viral reservoir
- Cellular/humoral immune responses are under investigation
- Design of a future Analytical Treatment Interruption protocol is in our agenda
  - Viral persistence (lower level or sanctuary sites)?
  - Differences in those HSCT with CCR5Δ32?
  - Role of GvHIV reactivity?
THE ICISTEM CONSORTIUM

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• Gero Hütter (Hematologist, Cellex Dresden)
• Jürgen Kuball (Hematologist, University Medical Center Utrecht)
• Monique Nijhuis (Virologist, University Medical Center Utrecht)
• Vanderson Rocha (Hematologist Cord Blood Bank Specialist Oxford University)
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Koen van Besien, Jan van Lunzen

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IMMUNOTHERAPY
Clinical Use of Antibodies

Prevention and Treatment are Different

**Prevention**
- Prevent acquisition of infection
  - Block Transmission event

**Treatment**
- Have to deal with greater viral diversity
- mAbs complementary to ARV
- Different mechanism of action?
- Potential to impact the cell-associated viral reservoir

- Block viral entry
  - CD4 T-cell
- Cell killing
  - NK cell killing of infected cells
Neutralizing Monoclonal Antibodies Discovered since 2009

gp41 MPER:
2F5, 4E10
10e8

Trimer (gp120/41)
8ANC195
PGT151
35022

HIV-1 viral spike

CD4 Binding Site:
VRC01, PG04, CH31
3BNC117, 12A12
CH103, VRC07-523

N332 Glycan Supersite:
PGT121, PGT128
10-1074

V1V2 Apex:
PG6, PG16, CH01-04
PGT141-45, PGDM1400
CAP256-VRC26

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

Mascola JR. CROI 2016, Boston MA. #15.
Antibody 10-1074 suppresses viremia in HIV-1-infected individuals

Monoclonal antibody 10-1074 targets the V3 glycan supersite on the HIV-1 envelope (Env) protein. It is among the most potent anti-HIV-1 neutralizing antibodies isolated so far. Here we report on its safety and activity in 33 individuals who received a single intravenous infusion of the antibody. 10-1074 was well tolerated and had a half-life of 24.0 d in participants without HIV-1 infection. Escape variants to 10-1074 remained sensitive to Abs targeting nonoverlapping epitopes to antibody targeting nonoverlapping epitopes even the anti-CD4 binding site 3BNC117 and VRC01. These results demonstrate the safety and activity of 10-1074 in humans and support the idea that antibodies targeting the V3 glycan supersite might be useful for the treatment and prevention of HIV-1 infection.

Future: Combination of 10-1074 with anti-CD4 binding site 3BNC117 and VRC01 could be a very potent combination
New trispecific Ab format from Sanofi

A Pegu. CROI 2018. Boston, US. #113LB.

Amenable for Long Acting formulation similar to parental bnAbs
Neutralizing Monoclonal Antibodies Discovered since 2009

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

Mascola JR. CROI 2016, Boston MA. #15.
Broadly Neutralizing Antibodies Against HIV-1

- Breadth
- Potency (IC$_{80}$ at g/ml)

A Pegu. CROI 2018. Boston, US. #113LB.
Trispecific and bnAb sensitivity of SHIVs

<table>
<thead>
<tr>
<th>Antibody</th>
<th>SHIV BaLP4</th>
<th>SHIV 325C</th>
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</thead>
<tbody>
<tr>
<td>VRC01</td>
<td>0.067</td>
<td>&gt;50</td>
</tr>
<tr>
<td>PGDM1400</td>
<td>&gt;50</td>
<td>0.015</td>
</tr>
<tr>
<td>10E8</td>
<td>0.475</td>
<td>12.8</td>
</tr>
<tr>
<td>VRC01/PGDM1400-10E8v4</td>
<td>0.055</td>
<td>0.168</td>
</tr>
</tbody>
</table>

Combination of SHIV BaL and SHIV325c was selected for in vivo challenge study

N=24 macaques challenged intrarectally with both SHIV viruses simultaneously.

5 mg/kg IV

A Pegu. CROI 2018. Boston, US. #113LB.
Plasma Viremia

Trispecific antibody provided complete protection compared to partial protection by the single bnAbs

*Fisher exact test, p = 0.0058
Highly potent multifunctional antibody-based molecules against Human Immunodeficiency Virus.

Julià Blanco, Jorge Carrillo, Bonaventura Clotet
Highly potent multifunctional antibody-based molecules against HIV

Recombinant antibodies with enhanced antiviral activity: The eCD4-Ig molecule

LETTER

doi:10.1038/nature24564

AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges

Matthew R. Gardner¹, Lisa M. Kattenhorn², Hans R. Kondur³, Markus von Schaewen⁴, Tatyana Dorfman⁵, Jessica J. Chiang⁶, Kevin G. Haworth⁷, Julie M. Decker⁸, Michael D. Alpert⁹, Charles C. Bailey⁹, Ernest S. Neale Jr.⁹, Christoph H. Fellinger⁹, Vinata R. Joshi⁹, Sebastian P. Fuchs⁹, Jose M. Martinez-Navedo⁶, Brian D. Quinlan⁵, Annie Y. Yao⁶, Hugo Mouquet⁹, Jason Gorman¹⁰, Barshik Zhang¹, Pascal Poignard¹, Michel C. Nussenzweig¹, Dennis R. Burton¹, Peter D. Kwong³, Michael Platan Jr¹¹, Jeffrey D. Lifson⁵, Guangping Guo⁵, Ronald C. Desrosiers⁵, David T. Evans⁵, Beatrice H. Hahn⁵, Alexander Ploss⁵, Paula M. Cannon⁵, Michael S. Seaman⁵ & Michael Farzan³

![Diagram of CD4-Ig molecule with CCR5 and eCD4-Ig sequences]

![Graph showing SHIV-AD8 challenge with viral RNA levels over weeks after AAV inoculation]

SHIV-AD8 challenge (pg pg)(p27):

Control
- 173-10
- 198-10
- 277-10
- 322-10

rh-eCD4-Ig
- 180-10
- 181-10
- 265-10
- 431-10

AAV-expressed eCD4-Ig
- 400-10
- 400-10
- 400-10
- 400-10
Highly potent multifunctional antibody-based molecules against HIV

Recombinant antibodies: IrsiCaixa molecules

1) Antiviral activity

<table>
<thead>
<tr>
<th>MOLECULE</th>
<th>IC50 (ng/ml)</th>
<th>NL43</th>
<th>BAL</th>
<th>AC10</th>
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<tbody>
<tr>
<td>MOLECULE-0</td>
<td>10,820</td>
<td>27,390</td>
<td>&gt;100</td>
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<tr>
<td>MOLECULE-1</td>
<td>0.108</td>
<td>0.050</td>
<td>&gt;100</td>
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<tr>
<td>MOLECULE-5</td>
<td>0.037</td>
<td>0.007</td>
<td>0.375</td>
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<tr>
<td>MOLECULE-7</td>
<td>0.029</td>
<td>0.004</td>
<td>0.189</td>
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<tr>
<td>MOLECULE-8</td>
<td>0.035</td>
<td>0.028</td>
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<tr>
<td>MOLECULE-10</td>
<td>0.793</td>
<td>2.924</td>
<td>&gt;100</td>
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<td>MOLECULE-11</td>
<td>0.110</td>
<td>0.026</td>
<td>1.454</td>
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RATIO

<table>
<thead>
<tr>
<th>MOLECULE-7</th>
<th>MOLECULE-1</th>
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<tbody>
<tr>
<td>x5</td>
<td>x12</td>
</tr>
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Description:

- 1st Generation
- REFERENCE (Farzan’s)
- AlbaJuna molecules 5 & 7 (bispecific Ab) with high ADCC

Graphs showing the antiviral activity of different molecules against HIV.
THERAPEUTIC VACCINE
Target non-escaped epitopes

Immunogenicity data from >1,000 infected individuals screens for T cell responses to the entire HIV proteome yielded 26 regions identified as “beneficial” (PR>1) in HIV-1 Gag, Pol, Vif and Nef proteins that were:

i) preferentially targeted by individuals with low viral loads,
ii) turned out to be more conserved and
iii) elicited responses of higher functional avidity and broader cross-reactivity

Mothe B et al, JTM 2012
Currently in Phase I in HIV Infected people
Innate immune detection of microbial nucleic acids TLR-7

TLR: Toll-like Receptor agonists
Reactivates the HIV

Gürtler & Bowie Trends Microbiol. 2013
LRAs IN COMBINATION WITH THERAPEUTIC VACCINE or BNabs
Ad26/MVA Therapeutic Vaccination with TLR7 Stimulation in SIV-Infected Rhesus Monkeys

Erica N. Borducchi, Crystal Cabral, Kathryn E. Stephenson, Jinyan Liu, Peter Abbink, David Ng'ang'a, Joseph P. Nikolola, Amanda L. Brinkman, Lauren Peter, Benjamin C. Lee, Jessica Jimenez, David Jetton, Jade Mondesir, Shanell Mojja, Abishek Chandrashekhar, Katherine Molloy, Galtt Alter, Jeff M. Geroki, Alison L. Hill, Mark G. Lewis, Maria G. Pan, Hanneke Schuitemaker, Joseph Hesselgesser, Roman Galazun, Jerome H. Kim, Merlin L. Robb, Nelson L. Michael and Dan H. Barouch.

Borducchi et al, 2016, Nature Epub Ahead of Print
The combination of Ad26/MVA vaccination and GS-986 resulted in a significant 1.74 log reduction in median setpoint viral loads and a 2.5-fold delay in the time to viral rebound following ART discontinuation as compared with sham controls.

Moreover, 3 of 9 animals demonstrated virologic control to undetectable levels in the absence of ART. These 3 animals had high cellular immune magnitude and breadth and negative viral DNA prior to ART discontinuation.

These data demonstrate the proof-of-concept that the combination of therapeutic vaccination and innate immune stimulation can impact viral rebound following ART discontinuation.
PGT121 (bNAb) Combined with GS-9620 (TLR7 agonist) Delays Viral Rebound in SHIV-Infected Rhesus Monkeys

Aim: To assess anti-reservoir activity of bNAbbs (beyond ARV activity)

- 44 rhesus monkeys infected IR with SHIV-SF162P3. ART (TDF/FTC/DTG) initiated at week 1 (day 7)
- Prolonged ART suppression x 96 weeks.
- TLR7 agonist: 10 x GS-9620 by oral gavage at weeks 96, 98, 100, 102, 104, 106, 108, 110, 112, 114
- PGT121: 5 x PGT121 infusions at weeks 106, 108, 110, 112, 114
- ART discontinued at week 130 (16 weeks after last PGT121/TLR7)

Dan H Barouch. CROI 2018. Boston, MA. #73LB
Neutralizing Monoclonal Antibodies Discovered since 2009

**gp41 MPER:**
- 2F5, 4E10
- 10e8

**Trimer (gp120/41):**
- 8ANC195
- PGT151
- 35022

**CD4 Binding Site:**
- VRC01, PG04, CH31
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**V1V2 Apex:**
- PG6, PG16, CH01-04
- PGT141-45, PGDM1400
- CAP256-VRC26

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups.

Mascola JR. CROI 2016, Boston MA. #15.
No PGT121 PK levels in Lymph Nodes and Colorectal Biopsies for 8-10 Weeks before ART Discontinuation (Week 120)

- No PGT121 plasmal LN or colorectal biopsies levels for 8-10 Weeks before ART D/C
- No/Minimal SHIV-Specific CD8 T Cell Responses in PBMC or Lymph Nodes
- GS-9620 Administration Activates CD4 T Cells
- PGT121 + GS-9620 Reduces Viral DNA in PBMCs and Lymph Nodes to undetectable
SHIV RNA Following ART Discontinuation

**Sham**
- 11/11 Rebound (100%)

**PGT121**
- 9/11 Rebound (82%)

**PtG121+TLR7**
- 10/11 Rebound (91%)
- 6/11 Rebound (55%)

Dan H Barouch. CROI 2018. Boston, MA. #73LB
PGT121 + GS-9620 Delays Time to Viral Rebound Following ART Discontinuation

- Residual PGT121 cannot explain the delay in rebound; levels <1 mg/ml (rebound threshold) for >2 months prior to ART withdrawal

- Mechanism may involve activation of infected CD4+ T cells by GS-9620 followed by enhanced binding and clearance by PGT121; no evidence of a bNAb induced “vaccinal effect”

- These data suggest that bNAbs combined with an innate immune stimulant may effectively target the viral reservoir

Dan H Barouch. CROI 2018. Boston, MA. #73LB
THANK YOU VERY MUCH

Special thanks to Javier Martinez-Picado & Julià Blanco for providing me some of these slides.