Eradication of HIV

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Badalona, Barcelona, Catalonia
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• 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 (CD45RO+)
Resting naive CD4T cells
Tissue monocyte-derived cells?
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

**Death of infected cells**

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

Latently infected CD4 T-cells

Macrophages | CD8 T-cells | NK cells

Post-CROI 2015
STRATEGIES TO CURE HIV
BONE MARROW TRANSPLANTATION
The Emerging Race To Cure HIV Infections
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 Martínez-Picado
Observational project, not a clinical trial, to investigate cases of ...

“Allogeneic stem cell transplant in HIV-1-infected individuals”

THE ICISTEM CONSORTIUM

Javier Martinez-Picado (Co-PI, Virologist, AIDS Research Institute IrsiCaixa, Barcelona)
Annemarie Wensing (Co-PI, Clinical Virologist, University Medical Center Utrecht)

Jose L. Diez Martin & Mi Kwon (Hematologists, Hospital Gregorio Marañón, Madrid)
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)
Asier Sáez-Cirión (Immunologist, Pasteur Institute, Paris)
Julian Schulze zur Wiesch (Infectious disease specialist, UMC Hamburg-

JMPicado 20161018
7 patients > 2 years post BM transplantation
Off immunosupresor drugs.
HIV VL undetectable
Mouse VOA negative

<table>
<thead>
<tr>
<th>CCR5</th>
<th>CCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT/WT</td>
<td>Δ32/Δ32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adult Donor</th>
<th>14*</th>
<th>4</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical cord</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

| Total       | 15  | 6  |

*Twp CCR5 Δ32/WT

- Blood
- Apheresis
- Bone Marrow
- CSF
- Ileum biopsies
IMMUNOTHERAPY
Neutralizing Monoclonal Antibodies Discovered since 2009

Cell Membrane

gp41 MPER:
2F5, 4E10
10e8

Trimer (gp120/41)
8ANC195
PGT151
35022

HIV-1 viral spike

CD4 Binding Site:
VRC01, PG04, CH31
SBNC117, 12A12
CH103, VRC07-523

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

N332 Glycan Supersite:
PGT121, PGT128
10-1074

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.
Passive administration of bnAbs (VRC01) prevents HIV-1 transmission in humanized mice, macaques. Transiently reduces plasma viral loads by ~1-3 logs in HIV infected humans.
Results: Viral rebound

- Majority of participants rebounded by week 5
  - 2 participants with delayed rebound at 8, 11 weeks
- Time to rebound not associated with VRC01 level, age, nadir or entry CD4 ct, time on ART

Bar KJ. CROI 2016, Boston, MA. #32LB.
Neutralizing Monoclonal Antibodies Discovered since 2009

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

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

**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.
HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Antibody 10-1074 suppresses viremia in HIV-1-infected individuals

Marina Caskey1,19, Till Schoofs1,19, Henning Gruell2–4,19, Allison Settler1, Theodora Karagounis1, Edward F Kreider5, Ben Murrell6, Nico Pfeifer7, Lilian Nogueira1, Thiago Y Oliveira1, Gerald H Learn5, Yehuda Z Cohen1, Clara Lehmann3,4, Daniel Gillor3, Irina Shimelovich1, Cecilia Unson-O’Brien1, Daniela Weiland2–4, Alexander Robles8, Tim Kümmel3, Christoph Wyen3, Rebeka Levin1, Maggi Witmer-Pack1, Kemal Eren9,10, Caroline Ignacio6, Szilard Kiss11, Anthony P West Jr12, Hugo Mouquet13, Barry S Zingman14,15, Roy M Gulick16, Tibor Keler17, Pamela J Bjorkman12, Michael S Seaman8, Beatrice H Hahn5, Gerd Fätkenheuer3,4, Sarah J Schlesinger1, Michel C Nussenzweig1,18,19 & Florian Klein2–4,19

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 and 12.8 d in individuals with HIV-1 infection. Thirteen individuals with viremia received the highest dose of 30 mg/kg 10-1074. Eleven of these participants were 10-1074-sensitive and showed a rapid decline in viremia by a mean of 1.52 $\log_{10}$ copies/ml. Virological analysis revealed the emergence of multiple independent 10-1074-resistant viruses in the first weeks after infusion. Emerging escape variants were generally resistant to the related V3-specific antibody PGT121, but remained sensitive to antibodies targeting nonoverlapping epitopes, such as the anti-CD4-binding-site antibodies 3BNC117 and VRC01. The 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.

A small fraction of individuals with HIV-1 infection develop antibodies that effectively neutralize the majority of existing HIV-1 isolates1–7. Single-cell antibody cloning methods revealed that this serum neutralizing activity is due to one or a combination of monoclonal antibodies that target different nonoverlapping epitopes on the HIV-1 envelope spike3,5,6. These sites of vulnerability include the membrane proximal region8–10, the base of the V3 loop and surrounding glycans11–14, the V1/V2 loops at the apex15,16, the CD4 binding site17–19 and a series of epitopes that span gp120 and gp41 (refs 20,21).

When passively transferred, many of these newly discovered antibodies protect against infection in humanized mice and macaques, even when present at very low concentrations22–29. In addition, combinations of antibodies targeting nonoverlapping epitopes can control active infection in vivo if they are administered intravenously to animals infected with HIV-1, or if they are administered intravenously to mice with HIV-1 infection and the ability of antibodies to engage the host immune system by binding to Fc receptors expressed on a variety of host leukocytes30–33

These preclinical findings were extended to humans in two separate phase I clinical trials. A single intravenous injection of an anti-CD4-binding-site antibody—3BNC117 or VRC01—was generally safe, and it suppressed viremia by 1.3–2.5 $\log_{10}$ in participants infected with a virus that was sensitive to the antibody34–36. Moreover, 3BNC117 infusion was associated with enhanced Fc receptor-dependent clearance

Future: 10-1074 with 3BNC117 and VRC01 could be a very potent combination
Humanized IgG4 mAb. Blocks HIV-1 from entering cells.
- **Binds CCR5 with high affinity, potent inhibition.**
- High barrier to resistance.
- Well tolerated in men, no dose-limiting in animals.
- Designated FDA fast Track drug candidate.
- Single IV or weekly SC injections reduced HIV-1 RNA.

**Phase 2b Study:**
CCR5, CD4 >350, VL <50 with ART.
350 mg once weekly x 12 w.
Those with VL<50 allowed to continue.
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/nature14364

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

Matthew R. Gardner¹, Lisa M. Kattenhorn², Hema R. Kondur³, Markus von Schaewen⁴, Tatyma Dorrman⁵, Jessica J. Chiang⁶, Kevin G. Haworth⁷, Julie M. Decker⁸, Michael D. Alpert⁹, Charles C. Bailey⁹, Ernest S. Neale Jr.¹, Christoph H. Fellinger¹, Vinita R. Joshi¹, Sebastian P. Fuchs³, Jose M. Martinez-Navedo⁴, Brian D. Quinnan¹, Anne H. Yao¹, Hugo Mouquet¹⁰, Jason Gorman¹¹, Baoshan Zhang¹², Pascal Poignard¹, Michel C. Nussenzweig¹³,¹⁴, Dennis R. Burton¹⁵,¹⁶, Peter D. Kwong¹⁷, Michael Platnik Jr.¹⁸, Jeffrey D. Lifson¹⁹, Guangping Gao¹⁹, Ronald C. Desrosiers¹⁹, David T. Evans¹⁶, Beatrice H. Hahn¹⁶, Alexander Plass³, Paula M. Cannon¹, Michael S. Seaman²² & Michael Farzan¹

SHIV-AD8 challenge (pg p27):

Control
- 173-10
- 198-10
- 277-10
- 322-10
rh-eCD4-Ig
- 180-10
- 181-10
- 265-10
- 431-10

Viral RNA (copies ml⁻¹)
Blocking HIV entry

Diagram showing the process of blocking HIV entry:

- **a**: Antibody binding to Envelope protein
- **b**: CD4 binding site
- **c**: CD4-Ig

http://mareaunire.net/2015
Highly potent multifunctional antibody-based molecules against HIV

Recombinant antibodies: IrsiCaixa molecules

1) Antiviral activity

**IC50 (ng/ml)**

<table>
<thead>
<tr>
<th>MOLECULE</th>
<th>NL43</th>
<th>BAL</th>
<th>AC10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOLECULE-0</td>
<td>10,820</td>
<td>27,390</td>
<td>&gt;100</td>
</tr>
<tr>
<td>MOLECULE-1</td>
<td>0,108</td>
<td>0,050</td>
<td>&gt;100</td>
</tr>
<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>
</tr>
<tr>
<td>MOLECULE-8</td>
<td>0,035</td>
<td>0,028</td>
<td>1,327</td>
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<tr>
<td>MOLECULE-10</td>
<td>0,793</td>
<td>2,924</td>
<td>&gt;100</td>
</tr>
<tr>
<td>MOLECULE-11</td>
<td>0,110</td>
<td>0,026</td>
<td>1,454</td>
</tr>
</tbody>
</table>

**Description**

- MOLECULE-0: 1st Generation
- MOLECULE-1: REFERENCE (Farzan’s)
- MOLECULE-5: AlbaJuna molecules

**RATIO**

| MOLECULE-7/MOLECULE-1 | x5   | x12  | >100 |

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Highly potent multifunctional antibody-based molecules against HIV

Recombinant antibodies: IrsiCaixa molecules

2) Antibody Dependent Cellular Cytotoxicity (ADCC)

![Graph showing relative ADCC activity (%)]
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
HIVACAT T-cell Immunogen design (HTI)

# of HIV suproteins (n=8) with IFNg response

- 2x pDNA
- 3x pDNA
- 3x pDNA

## MVA boost increases responses broadly after 3 pDNA vaccinations

### 3x pDNA

### 3x pDNA + 1 MVA

- IFNg SFC/10^6 splenocytes
  - Gag-p17
  - Gag-p24
  - Gag-p15
  - Pol-Prot
  - Pol-RT
  - Pol-Int
  - Vif
  - Nef

- Mean and SD is shown

- 6 out of 6 mice

- pDNA: 100µg IM / dose
- MVA: 10^6pfu IM / dose
HIVACAT T-cell Immunogen design (HTI)

Interestingly, MVA-HTI vaccine was able to boost responses (both in breadth and magnitude,) in the two groups analyzed, with significantly increased magnitudes of responses in the group that obtained 3 doses of pDNA-HTI

MVA-HIVACAT vaccine Elicits CD8 effector memory response which has been associated with HIV control in Elite Controllers and in the animal model (Picker et al. Nature 2011)
Activating latent HIV
### Activating latent HIV: in vitro

- **Cytokines**
  - IL-7\(^1,2\)
  - IL-15\(^3\)
  - IFNa 2b

- **Histone deacetylase (HDAC) inhibitors\(^4,5\)**
  - Valproic Acid
  - Vorinostat (SAHA)
  - Romidepsin
  - Panobinostat

- **Anti-alcohol agent**
  - Disulfiram\(^6\)

- **Methylation inhibitors**
  - 5-aza-dC\(^7\)

- **Immune modulation**
  - Anti PD1

- **NF-kB activators**
  - Prostratin, PMA, TNFα\(^4\)

- **Akt/HEXIM-1 modulators**
  - HMBA\(^8\)

- **Histone Methyltransferase inhibitors (HMTI)\(^9\)**
  - Chaetocin, BIX-01294

- **Other**
  - Quinolines\(^10\)

- **Combination enhances potency\(^4,9,11\)**

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1. Wang, J Clin Invest 2005
2. Saleh, Retrovirol 2011
3. Chomont, 6th IAS Rome 2011
10. Xing, J Antimicrob Chemother 2012
VIRAL CONTROL INDUCED BY HIVconv VACCINES & ROMIDEPSIN IN EARLY TREATED INDIVIDUALS

Beatriz Mothe
IrskiCaixa AIDS Research Institute
Badalona, Spain
BCN 02 Study Design

BCN 01  
n=24  

BCN 02  
n=15

MVA.HIVconsv 2x10^8 pfu (im)  
Romidepsin 5mg/m² (iv) - HDACi

Mothe B. et al, BCN 02  
CROI 2017  

10Borthwick, 2014; 11Mutua, 2016; 12Mothe, CROI 2016, PO 320  
13Sogaard, 2015; 14Leth, 2016
### Study Participants

$n=15$

<table>
<thead>
<tr>
<th></th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at study entry, median (range)</strong></td>
<td>43 (33 - 51) y.o.</td>
</tr>
<tr>
<td><strong>Days since HIV to cART, median (range)</strong></td>
<td>92 (28 - 164) days</td>
</tr>
<tr>
<td><strong>Pre cART $\log_{10}$ HIV-1 RNA copies/ml, median (range)</strong></td>
<td>4.9 (3.2 - 5.8) $\log_{10}$ cp/ml</td>
</tr>
<tr>
<td><strong>Years on cART median (range)</strong></td>
<td>3.23 (3.03 – 3.77) years</td>
</tr>
<tr>
<td><strong>cART, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC/RAL</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>ABC/3TC/RAL</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>2 (13%)</td>
</tr>
<tr>
<td><strong>CD4+ T-cell counts at study entry, median (range)</strong></td>
<td>728 (416 – 1,408) cells/mm³</td>
</tr>
<tr>
<td><strong>Ratio CD4/CD8 at study entry, median (range)</strong></td>
<td>1.37 (0.97 – 1.93)</td>
</tr>
</tbody>
</table>
HIVconv responses were effectively boosted after >2 years from 1st CM

Change in CTL immunodominance pattern towards conserved regions
Viral Reactivation

- Detectable viremia in 14 / 15 during RMD infusions at least once (pVL>20cp/ml)
- Detectable viremia in 60% of patients after 1st MVA.HIVconsv vaccination.

Mothe B. et al, BCN 02
CROI 2017 – 119LB
Monitored Antiretroviral Pause (MAP)

- 13 participants have interrupted cART to date.

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Mothe B. et al, BCN 02
CROI 2017 – 119LB
Innate immune detection of microbial nucleic acids

TLR: Toll-like Receptor agonists

Reactivates the HIV

Gürtler & Bowie Trends Microbiol. 2013

#122
#123
#124
#125
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 were 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.
COMBINATION OF STRATEGIES TO ACHIEVE THE CURE OF HIV
Multiple strategies for eradication

Vaccine (HTI)

Infected cell destruction

Infected cell

Cytotoxic T lymphocyte (CTL)

HIV-1 infected patient

HIV-1 free individual
Multiple strategies for eradication

Vaccine (HTI)
- CTL
- CTL
- DC (SIGLEC-1)
- Delivered HDAC Inhibitors, TLR-7; het-L15, RIG-I

Anti-PD1 boosting?

Infected cell destruction

Vaccine (HTI)

HIV-1 infected patient

HIV-1 free individual
Multiple strategies for eradication

- Virus Neutralization by AJ-Mabs
- New infections protection
- Infected cell destruction
- Infected cell

Vaccine (HTI)

Anti-PD1 boosting?

Vaccine (HTI)

IgGs AlbaJunaMabs (AJ-Mabs) (IgG+CCR5+CD4+FX)

HIV-1 infected patient

HIV-1 free individual
Multiple strategies for eradication

IgGs AlbaJunaMabs (AJ-Mabs) (IgG+CCR5+CD4+FX)

Vaccine (HTI)

Virus inactivation
Neutralization by AJ-Mabs

New infections protection

Infected cell destruction

Vaccine (HTI)

Anti-PD1 boosting?

HIV-1 infected patient

HIV-1 free individual
Multiple strategies for eradication

Vaccine (HTI)
- Therapeutic Vaccine (HTI)
- HDACs inhibitors delivered through Siglec-1 mechanism; TLR7; Heterodimeric IL-15,RIG-I
- Anti-PD-1 as CD8 and vaccine boosters?
- Recombinant proteins (AlbaMab/JunaMab)
- Microbiome increased diversity??

Inactivated virus

Neutralization by AJ-Mabs

New infections protection

Infected cell destruction

Anti-PD1 boosting?

Infection

Vaccine (HTI)

HIV-1 infected patient

HIV-1 free individual

IgGs
AlbaJunaMabs (AJ-Mabs)
(IgG+CCR5+CD4+FX)

DC (SIGLEC-1) Delivered HDAC Inhibitors TLR-7, hetIL-15, RIG-I

AJ-Mabs

X

Free virus

Infected cell

CTL

NK

Vaccine (HTI)
THANK YOU VERY MUCH

Special thanks to Javier Martinez-Picado for providing me some of these slides