Evaluating a Combination of Immune-based Therapies to Achieve Control of HIV Infection

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Overview About Current Strategies for HIV Remission

1. Shock & kill

2. Immune-based therapies

3. Combinations

4. HIVACAR Approach
Strategies for cure

Shock & Kill

Immune-Based Therapies
Shock & Kill strategies

1. cART (intensification, controllers)

2. Latency reversing agents (TLR-3-7-9, HDAC, PKC)

3. Stem cell transplantation

http://www.treatmentactiongroup.org/cure/trials (September 2nd)
Efficacies required for successful latency-reversing agents therapy

Predicting the outcomes of treatment to eradicate the latent reservoir for HIV-1

PNAS 2014: 111: 13475-80
The VISCONTI cohort: the possibility of post-treatment control

Capacity of CD8+ T cells to suppress HIV infection of CD4+ T cells
Determined by log-fold decrease in the level of secreted p24 (CD4 vs CD4:CD8 1:1 cell cultures).

Evolution of cell-associated HIV DNA after treatment interruption in PBMCs from 8 PTCs.

Left: five PTCs experienced a decline in their cell-associated HIV DNA levels
Right: two PTCs maintained stable levels and a positive slope was calculated for OR3

VIRs, viraemic patients; ARTs, treated patients; HICs, HIV controllers; PTCs, post-treatment controllers
post-treatment controller

off cART

LOG10 VL (COPIES/ML)

Months

-150 -100 -50 -10 -5 0 4 8 12

0.0 0.2 0.4 0.6 0.8 1.0

1000000 100000 10000 1000 100 10 1
The graph illustrates the dynamics of viral load (VL), CD4 T cells, CTL responses, and total DNA over time in a post-treatment controller following the discontinuation of cART (off cART). The x-axis represents the months post-treatment, ranging from -150 to 12 months, while the y-axis shows the logarithmic scale for VL (copies/ml) from $10^0$ to $10^6$.

Key observations include:

- **VL (Viral Load)**: The VL is depicted by a red line. There is a notable increase in VL around 0 months post-treatment and a subsequent gradual decrease.

- **CTL responses** (green line): This line shows a sharp increase around 0 months, followed by fluctuations over time.

- **Total DNA**: Indicated by a blue line, it remains relatively stable with minor fluctuations.

- **Integrated DNA**: Represented by a magenta line, it shows a consistent trend with variations.

The shaded area highlights the period around 0 months post-treatment, emphasizing the transient increase in viral load and immune responses. This period is crucial for understanding the natural history of viral rebound and immune response dynamics in the absence of antiretroviral therapy.
Low reservoir is not enough

post-treatment controller

- VL
- CTL responses
- Total DNA
- Integrated DNA

Log_{10} (copies/10^6 CD4 T cells)

VL

Low CTL
Low reservoir
VL rebound

High CTL
Low reservoir
No rebound

SFC/10^6 PBMC
Strategies for cure

Shock & Kill

Immune-Based Therapies
Immune-Based therapies

1. Therapeutic immunization (DC, peptide, protein, DNA, mRNA, viral vectors)

2. Gene therapy to make target cells non-infectable

3. Administration or expression of monoclonal Abs (3BNC117, VRC01, anti-PDL1)

4. Adoptive immunotherapy (CTL)

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Strategies for cure

Shock & Kill

Immune-Based Therapies
PostcART control of HIV

Post-treatment control of HIV infection

Jessica M. Conway\textsuperscript{a,b} and Alan S. Perelson\textsuperscript{b,1}

PNAS 2015: 112: 5467-72
PostcART control of HIV: Combination

**Post-treatment control of HIV infection**

Jessica M. Conway$^{a,b}$ and Alan S. Perelson$^{b,1}$

PNAS 2015: 112: 5467-72
**Combination could not be enough**

1. Host immune environment (inflammatory, Tregs) not able to generate an effective immunity

2. Expansion of pre-existing clones which are exhausted and target escape variants

3. No correct DC antigen presentation

4. B cell follicle sanctuary permits persistent productive virus infection
Combination could not be enough

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   - Adjuvants, antiPDL-1 abs
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• **Beyond antiretroviral therapy**

• HIVACAR is evaluating a combination of immune-based therapies to achieve remission from HIV infection.

• The project aims at changing the current paradigm of HIV treatment by obtaining remission from HIV thanks to effectively targeting residual virus replication and viral reservoirs.
• Improving people’s health, saving resources

• New cost-effective and viable therapeutic strategies are needed for effective control of the HIV epidemic.

• Combined antiretroviral therapy (cART) has proven to be highly effective to prevent clinical progression and death, but on its own is unable to eradicate HIV infection, and is therefore needed lifelong.

• Its significant cost constitutes important limitations for widespread use in developing countries, but also in the developed world.

• A safe, affordable and scalable therapeutic alternative for HIV infection could address both the individual and public health limitations associated with lifelong cART
• Investigating clinical, economic, and psychosocial aspects

• **Immune based therapies**
  
  A combination of immune-based therapies with latency reversing agents will be investigated to understand if it helps eliminate viral reservoirs and induce new and effective HIV immune responses that can contain viral rebound after cART cessation. To do this, an innovative phase I/IIa, multinational, multi-centre, randomised, open-label, controlled clinical trial will be conducted. Results are expected in 2021.

• **Psychosocial and economic research**
  
  Any innovative therapeutic approach in HIV infection has ethical, economic, and psychosocial consequences. A detailed study about these aspects is conducted, involving both participants in the HIVACAR clinical trial and the greater community of people living with HIV. Results will be disseminated to people living with HIV, policy makers and the general public in Europe to better inform their future decisions.
**Intranodal** vaccination of HIV-1 infected patients with mRNA encoding **TriMix** and **HIVACAT**

**Activation signals: TriMix**

1. CD40L mRNA
   - CD40
   - CD40L
   - induction of DC maturation

2. TLR4 mRNA
   - CD8+ CTL
   - support activated T cell survival and proliferation

3. CD70 mRNA
   - CD70
   - CD27
   - LPS

**Antigen: HIVACAT or HIVACAR**

- Gag
- Pol
- Vif
- Nef

**IN mRNA**

**In situ DC modification**

- HIV-1 specific T-cell responses
WP1. SCIENTIFIC COORDINATION AND PROJECT MANAGEMENT
   Leader: IDIBAPS
   Timing: M1-M60

WP2. DESIGN AND MANUFACTURING OF A PERSONALIZED mRNA VACCINE
   Leader: IRSICAIXA
   Timing: M14-M33

WP3. CLINICAL TRIAL PREPARATION AND MONITORING
   Leader: ECRIN-ERIC
   Timing: M1-M45

WP4. CLINICAL TRIAL PHASE I/IIa IMPLEMENTATION
   Leader: IDIBAPS
   Timing: M15-M60

WP5. IMMUNE MONITORING AND CLINICAL DATA ANALYSIS
   Leader: AARHUS
   Timing: M5-M60

WP6. SOCIO-ECONOMIC AND PSYCHO-SOCIAL IMPACT AND PATIENT ENGAGEMENTS
   Leader: EATG and UCM
   Timing: M1-M60

WP7. DISSEMINATION AND EXPLOITATION
   Leader: IDIBAPS and eTheRNA
   Timing: M1-M60
• **International and interdisciplinary**

• Organisations from different European countries and from the USA joined their strength to build up the HIVACAR consortium.

- Consorci Institut d’Investigacions Biomèdiques August Pi i Sunyer, SP
- eTheRNA immunotherapies NV, BE
- Fundació Privada Institut de Recerca de La Sida-Caixa, SP
- Aarhus University Hospital Skejby, Denmark Institute of Clinical Medicine, Aarhus University, DK
- Vrije Universiteit Brussel, BE
- Laboratory of Molecular Immunology, The Rockefeller University, US
- Centro Nacional de Biotecnología, CSIC, SP
- Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia Centre for Excellence in HIV/AIDS, CND
- European AIDS Treatment Group, DE
- Facultad de Ciencias Económicas y Empresariales. Universidad Complutense de Madrid, SP
- European Clinical Research Infrastructure Network- European Clinical Research Consortium, FR
- Asphalion, S.L., SP
- Assistance Publique Hôpitaux de Paris, FR
- Zabala Innovation Consulting S.A, SP
Get in touch with HIVACAR

Europe as a centre for excellence
Both the clinical trial and the study on economic and psychosocial aspects will be conducted in Belgium, Denmark, France and Spain.

The clinical trial will recruit at:
Hospital Clínic de Barcelona, Barcelona – Spain
Hospital Germans Trias i Pujol, Badalona – Spain
Aarhus University Hospital Skejby, Aarhus – Denmark
Assistance Publique Hôpitaux de Paris, Paris – France
Vrije Universiteit Brussel, Brussels – Belgium

Learn more about HIVACAR on our website:
www.hivacar.org
Or send an email to EATG:
projects@eatg.org