Engineered Immune-Mobilising Monoclonal T Cell Receptors for HIV Cure

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The HIV Reservoir

- HIV reservoir established early in HIV infection = barrier to a cure
  - Infection, integration → cells transition to a resting state
  - Long half life\(^1\): 73 years to eradicate \(10^6\) cells

- How to eliminate the HIV reservoir?
  - Early ART during PHI: lowers T cell activation & reservoir size\(^2,3\)
  - ‘Kick and Kill’: latency reversal agents + immunotherapeutic

\(^1\)Murray, A. et al., J. Imm. 2016 \(^2\)Ananworanich, J. et al., EBio Medicine 2016 \(^3\)Jain, V. et al., J Infect. Dis. 2013
Immunological response to HIV infection.

- Activated non HIV-specific CD8+ T cell
- Engineered TCR (HIV Gag – SL9; pM)
- Anti-CD3
- CD3
- Destruction of infected cell
- Immune mobilising monoclonal T cell receptors against viruses
- Dead CD4+ T cell
- HIV Gag on HLA class I

Healthy donor/ HIV-naive CD8+ T cell

Exhausted HIV-specific CTL
Aims

• Assess potency of HIV ImmTAV for redirecting CD8+ T cells from patients treated during PHI (SPARTAC cohort)

• Investigate susceptibility of HIV reservoir cells to ImmTAV-mediated killing using an in vitro latency model
ImmTAV redirection of CD8+ T cells from patients treated during PHI
Antiviral efficacy of CD8+ T from PHI patients

• SPARTAC: treated within 6 mo. of seroconversion
• Viral inhibition assay: flow cytometry

= % HIV Gag+ cells

P = 0.003
Conclusions

• ImmTAV redirection improved clearance of HIV+ cells

• Earlier treatment may be required for improved immunologic recovery
  • Comparable effect to chronic HIV patient CD8+ T
  • Impaired antiviral activity compared to healthy donor CD8+ T even with ImmTAV redirection

• Further work to investigate impaired antiviral activity of CD8+ T cells from chronic patients (global)

¹Yang, H. et al., Mol. Therapy 2015
Susceptibility of HIV reservoir cells to ImmTAV-mediated killing
Latency model: resting cell infection

PBMCs

CD4+ Ts

Activated CD4+ Ts

Activated infection (high Gag expression)

Magnetic bead separation

PHA

Resting CD4+ Ts

Resting infection (low Gag expression)

CD8+ T

Activated CD4+ T (CD25/CD69/HLA-DR+)

HIV-infected CD4+ T

HIV

ImmTAV-redirected clearance of Gag+ reservoir cells

- Latency viral inhibition assay:
  - Resting, infected CD4+ T
  - Healthy donor CD8+ (E:T)
  - +/- HIV ImmTAV (m121)

- ImmTAV-redirected clearance of resting, infected T cells
  - Enough Gag visible for detection by ImmTAV without latency reversal
  - Maximum effect at 2:1 E:T

![Graph showing % Elimination vs E:T ratio with ImmTAV (1 nM) and statistical significance levels P < 0.0001, P < 0.0001, P = 0.0003, and P = 0.01.]
‘Kick and kill’: latency reversal agents + ImmTAV

- Addition of LRA to reactivate latent HIV + redirection by ImmTAV
- Bryostatin/romidepsin provided best reactivation
- LRA + latency viral inhibition assay:
  - Increase Gag expression
  - Little effect on ImmTAV-mediated killing

![Graph showing % Change to Untreated (%p24+) and % Elimination with various LRA treatments](image-url)
Impact of ImmTAV-redirection with chronic patient CD8+ T cells

- Latency viral inhibition assay:
  - Healthy donor resting, infected CD4+ T
  - CHI donor CD8+ T (E:T)
  - +/- HIV ImmTAV

- ImmTAV-redirection improves clearance of Gag+ reservoir cells by CHI CD8+ T
  - Low natural CTL response
  - Less than that seen with healthy donors

![Graph showing % Elimination vs. E:T ratio with HIV ImmTAV (1 nM)]
Conclusions

• HIV ImmTAV:
  • Significantly increases ex vivo elimination of HIV+ cells by CD8+ T cells from patients who began ART during PHI
  • Confers HIV-specific killing capacity on CD8+ T cells from healthy donors in a latency model
  • Enhances killing capacity of CD8+ T cells from CHI patients

• Implications:
  • HIV Gag expression in latent reservoir is heterogeneous: a subset may be susceptible to elimination by ImmTAVs without LRAs
  • HIV ImmTAVs have potential as component of eradication strategies (> natural TCR)
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Thank you for listening – questions?