T cell therapy for viruses

Ann Leen

Viral infections post-transplant

• 40% deaths after alternative donor transplant due to viral infections

• Antiviral drugs
  – Costly
  – Significant side effects
  – Often ineffective

• Alternative - Adoptive T cell transfer
Immunotherapy for viral infections

- Virus-specific T cells as prophylaxis and treatment
  - EBV
  - Adv/EBV (bivirus)
  - Adv/EBV/CMV (trivirus)
Generation of trivirus-specific T cell lines using Ad5f35 vectors

PBMCs → B95-8 EBV virus → EBV LCL → Ad5f35pp65 transduced EBV LCLs → Restimulation

Clinical Outcome Summary – Donor-specific setting

- In vitro expanded donor-derived virus-specific T cells targeting Adv, EBV, CMV
  - Safe
  - Reconstituted antiviral immunity for EBV, CMV and Adv
  - Effective in clearing disease
  - Considerable expansion in vivo

Leen et al, Nat Med. 2006
Leen et al, Blood. 2009
Limitations

- Cost
- Complexity
- Limited viral range
Cost

PBMCs → EBV LCL → Ad5f35pp65 transduced EBV LCLs

Reduce cost: Replace virus/vector with peptides

EBV LCL → 15mer pepmixes

Ad5f35pp65

Target antigens
- EBV- EBNA1, LMP2, BZLF1
- CMV- IE1, pp65
- Adv- Hexon, Penton
Specificity

Reduce cost – peptides

Complexity

day 0 – VST initiation 2.4 x 10^7

day 9 - restim 2 x 10^7

day 12 – IL2 feed 6 x 10^7

day 16-harvest and reseed 6 x 10^7

day 20 – split + IL2 feed

day 23 – harvest and reseed 1.2 x 10^8

day 27 – split + IL2 feed

Day 30 - harvest/freeze 3.6 x 10^8
Reduce complexity:
Simplifying Production using G-Rex devices

- Gas permeable membrane allows CO₂/O₂ exchange
- Supports cell growth with large volumes of media
- Reduces feeding frequency and manipulation
- No rocking or stirring

Manufacturing limitations

Reduce cost – peptides ✔
Gerdemann et al, Mol Ther, 2012

Reduce complexity – G-Rex ✔
Vera et al, JIT, 2010

Extend target viruses - HHV6+ BK ✔
Gerdemann et al, Blood, 2013

Clinical trial – PACT application
**ARMS - Rapidly generated T cell lines targeting 5 viruses**

AdV– Hexon, Penton  
EBV– EBNA1, LMP2, BZLF1  
CMV– IE1, pp65  
BKV– LT, VP1  
HHV6– U11, U14, U90

**PACT - 0053**

T cell stimulation/ expansion  
10 days

*Papadopoulou et al, Sci Trans Med, 2014*

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**Patients infused**

- 11 pts infused on study:  
  - 4 pts: 5x10^6/m^2 (DL1)  
  - 4 pts: 1x10^7/m^2 (DL2)  
  - 3 pts: 2x10^7/m^2 (DL3)

- No dose limiting toxicity  
  - 1 Grade II skin GvHD (improved with topical steroids)

- 3 infused prophylactically  
  - All remained infection-free for at least 3 months

- 8 pts had active infections
8 pts treated for infections

<table>
<thead>
<tr>
<th>Patient with</th>
<th>AdV</th>
<th>CMV</th>
<th>EBV</th>
<th>BKV</th>
<th>HHV6</th>
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<tr>
<td>1 virus</td>
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<td>x</td>
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</table>

Clinical response - Pt with AdV

Viral load
mVSTs
AdV T cells

Graph showing viral load, mVSTs, and AdV T cells over time.
Clinical response - Pt with EBV-PTLD

Pre mVSTs

Post mVSTs

EBV copies/μg DNA

EBV T cells

mVSTs

Viral load

wk-2 wk-1 Infusion wk1 wk2 wk3 wk4 wk5 wk6 wk8 wk12

Clinical response - Pt with CMV

Antigenemia (CMV)

CMV T cells

mVSTs

Viral load

Pre wk3 wk5 wk6 wk8 wk12
Clinical response - Pt with BKV

Clinical response - Pt with HHV6
Outcomes

- **Complete response: (V)***
  - viral load to the normal range
  - resolution of clinical signs/symptoms

- **Partial response: (PR)**
  - >50% reduction in viral load

8 pts treated for infections

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<td>PR</td>
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Old vs New

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<thead>
<tr>
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<th>Conventional</th>
<th>Rapid</th>
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<tbody>
<tr>
<td>Specificity</td>
<td>AdV, EBV, CMV</td>
<td>AdV, EBV, CMV, BK, HHV6</td>
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<tr>
<td>Blood vol.</td>
<td>60ml</td>
<td>20ml</td>
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<tr>
<td>Cells</td>
<td>LCL, VSTs</td>
<td>VSTs</td>
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<tr>
<td>Time</td>
<td>56-84 days</td>
<td>10 days</td>
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<tr>
<td>Cell #</td>
<td>200x10^6</td>
<td>390x10^6</td>
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Summary

• Feasible to generate broad spectrum VST products

• Manufacturing simple and robust

• VST therapy safe

• VST therapy effective
## Thanks

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