Broadening The Applicability of Virus specific T cell Therapy From Post BMT To COVID19

Catherine M. Bollard, MD
Disclosures
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Advisory Board: Cellectis, BMS (ad hoc)

Co-Founder: Mana Therapeutics, Catamaran Bio

Board Member: Cabaletta Bio

Stock: Repertoire Immune Medicines, Neximmune
Donor-derived Virus specific T cells are Safe and Effective and Persist in vivo

Bollard and Heslop, Blood 2016, Keller and Bollard, Blood 2020

Prophylaxis/ prevention

Treatment: Overall response

>90%

81 - 94%

Persistence of virus-specific T cells in presence of antigen for at least 12 months

Incl. Cord Blood derived VSTs

(Keller et al, BJH 2019)

(Hanley et al, STM 2013, Abraham et al, Blood Advances 2019)
Can Target up to Six Viruses in Single Product

Novel Antigens Targeted by ex vivo Expanded T-Lymphocytes following Hematopoietic Stem Cell Transplantation (NATS)

Group A
Prophylactic treatment

Group B
Treatment for active CMV/EBV/Ad/HHV6/BK/HPIV3

Dose Level 1:
1 x 10^7 mCTLs/m^2

Dose Level 2:
2 x 10^7 mCTLs/m^2

Dose Level 3:
5 x 10^7 mCTLs/m^2

Additional subjects at MTD (either group)

EBV
CMV
Adenovirus
HHV6
BKV
Parainfluenza 3

PI : Mike Keller
Sponsor : Cath Bollard
What if the donor not available?
Third-party VST treatment

Utilizing a third party VST bank could bypass the need for an available donor, and eliminates the wait for T cell production.
Multivirus VSTs in Third Party Setting

Blood donor

A1, A24; B8, 18; DR1, 15

Trivirus VST

EBV activity – B8, DR1
CMV activity – A24
Adv activity – A1, A24, DR15

A1, 11; B8, 35; DR8
Searched EBV
Also ADV

A2, 24; B7, 27; DR1, 15
Searched CMV
Also ADV, EBV

Adv – A1, 11; B7, 8; DR3, 11
Searched ADV
Also EBV
## Prior Studies of Third-Party VST Support Safety

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>n</th>
<th>Serious adverse events</th>
<th>Clinical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haque, 2007</td>
<td>EBV</td>
<td>33</td>
<td>None</td>
<td>• 52% CR/ PR</td>
</tr>
<tr>
<td>Barker, 2010;</td>
<td>EBV</td>
<td>5</td>
<td>None</td>
<td>• 4 / 5 CR’s</td>
</tr>
<tr>
<td>Doubrovina, 2012</td>
<td>EBV</td>
<td>5</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Leen, 2013</td>
<td>CMV, EBV, Adv</td>
<td>50</td>
<td>8 cases GvHD (2 de novo)</td>
<td>• 74% CR/PR</td>
</tr>
<tr>
<td>Tzannou, 2017</td>
<td>CMV, EBV, Adv, BK, HHV6</td>
<td>38</td>
<td>2 cases of de novo GVHD (gr I)</td>
<td>• 92% CR/PR</td>
</tr>
<tr>
<td>Withers, 2017</td>
<td>CMV, EBV, Adv</td>
<td>30</td>
<td>2 cases of de novo GVHD</td>
<td>• 93% CR/PR</td>
</tr>
<tr>
<td>Prockop, JCI, 2020</td>
<td>EBV post SOT/BMT</td>
<td>46</td>
<td>None</td>
<td>68% CR/PR (BMT) 54% CR/PR (SOT)</td>
</tr>
</tbody>
</table>
Extending Third-party VST therapy

- Antiviral Cellular Therapy for Enhancing T-cell Reconstitution Before or After Hematopoietic Stem Cell Transplantation (ACES)

**Arm A**
Viral infections following Stem Cell Transplantation

**Arm B**
Viral infections in PID patients *before* Transplantation

Banked, partially HLA matched VSTs
Clinical Responses are More Likely with Confirmation of Shared Antiviral HLA Restriction

VST Product Matching and Time to Antiviral Response (CR/PR)

- Confirmed Restriction (n=21)
- No Confirmed Restriction (n=10)
Conclusions - Third Party VSTs

• Low attributable toxicity
• Third party virus specific T cells (VSTs) effective in clearing viral disease (approx 75%)


• T cell expansion seen in approx. 50% of responders
• May require several infusions to sustain benefit – don’t persist long term
• Gene editing opportunities to give in setting of GVHD (Menger et al, Blood 2015)
VSTs Can Target Multiple (?) Any) Viruses/Pathogens after BMT!

- **EBV+ Lymphoma** *(McLaughlin et al, Blood 2018, Bollard et al, JCO 2018)- 1 clinical trial
- **Pre-clinical targets**
  - **Norovirus** *(Hanajiri et al, JID 2019)- 1 clinical trial
  - **Zika Virus** *(Hanajiri et al, Cytotherapy, 2019)
  - **Mycobacteria** *(Patel et al, Frontiers Immunology, 2019)
  - **Fungal** *(Castillo et al, Molecular Therapy - Methods & Clinical Development. 2018)
  - **HPV** *(McCormack et al Cytotherapy 2018)
Developing T cell therapies for SARS CoV-2

Mike Keller and Team COVID
Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation

Gunjan L. Shah,1,2 Susan DeWolf,1 Yeon Joo Lee,2,3 Roni Tamari,1,2 Parastoo B. Dahi,1,2 Jessica A. Lavery,4 Josel Ruiz,1 Sean M. Devlin,4 Christina Cho,1,2 Jonathan U. Peled,1,2 Ioannis Politikos,1,2 Michael Scordo,1,2 N. Esther Babady,1 Tania Jain,1 Santosh Vardhana,2,8 Anthony Daniyan,2,7 Craig S. Sauter,1,2 Juliet N. Barker,1,2 Sergio A. Giralt,1,2 Cheryl Goss,8 Peter Maslak,9 Tobias M. Hohl,2,3 Mini Kamboj,2,3 Lakshmi Ramanathan,10 Marcel R.M. van den Brink,1,2 Esperanza Papadopoulos,1,2 Genovefa Papanicolaou,2,3 and Miguel-Angel Perales1,2

1Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA. 2Department of Medicine, Weill Cornell Medical College, New York, New York, USA. 3Infectious Disease Service, Department of Medicine; 4Department of Epidemiology and Biostatistics; 5Clinical Microbiology Service, Department of Laboratory Medicine; 6Lymphoma Service and Leukemia Service, Department of Medicine; and 7Transfusion Medicine Service, Cellular Immunology Laboratory, and 8Clinical Chemistry Service, Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA.
Prolonged shedding of viable SARS CoV-2 can be seen post HCT

- > 20 days in three patients
- Longest up to day 61
- Early post HCT/CAR-T (<6 mo)
- No evidence of reinfection
- Secondary cases not assessed

Aydillo, …. Kamboj, NEJM 2020
Deletions in SARS-CoV-2 spike arise during long-term persistent infections in immunosuppressed patients

Can SARS-CoV-2-specific T-cell Therapies be Developed to protect BMT patients?
2003/2004: SARS-CoV Generated Lasting T-cell Responses

T-cell responses 1 year post SARS-CoV Infection

Li et al. J Immuno 2008

T-cell Responses 4 years post SARS-CoV

Fan et al. Arch Virol 2009
Structure & Genome of SARS COV-2
Developing a SARS-CoV-2 T cell Therapeutic from Convalescent Donors

Subject Demographics

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>34.5 (20-69)</td>
</tr>
<tr>
<td>Male gender</td>
<td>21 (46%)</td>
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</tbody>
</table>

**Disease Severity**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mild</td>
<td>38 (83%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>4 (9%)</td>
</tr>
</tbody>
</table>

**Symptoms**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>24 (52%)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>38 (83%)</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>20 (44%)</td>
</tr>
</tbody>
</table>

| Median length of symptoms, days (range) | 12 (0-30) |
| Need for Hospitalization           | 2 (4%)    |

SARS-CoV-2 Antibody Responses (n=46)

Collaboration with Jeff Cohen (NIAID LID), Peter Burbelo (NIDCR)
Keller et al, Blood 2020
Generation of Coronavirus-Specific T-cells Using GMP Compliant Methodologies

PBMC → G-Rex10 → SARS-CoV-2 peptides → IL-4, IL-7 → 10-12 days → Coronavirus-specific T-cells

SARS-CoV-2 Wuhan Hu-1 strain

15mer Overlapping peptide libraries

Keller et al, Blood. 2020 Dec 17;136(25):2905-17
Convalescent Donors Recognize Multiple SARS-CoV-2 Structural Proteins

T-cell Specificity by ELISpot (day 10 post expansion)

Keller et al, Blood. 2020 Dec 17;136(25):2905-17
Similar to Adenovirus, Norovirus, Parainfluenza virus specific T cell Responses – SARS-COV-2 T-cells are Predominantly Th1 CD4⁺

Harris et al. Front Immunol. 2020 Oct 5;11:575977 (Parainfluenza)
Keller et al, Blood. 2020 Dec 17;136(25):2905-17 (SARS-CoV2)
SARS-CoV2 specific T cell clones expanded from Bulk CSTs are also Predominantly CD4+

Subject 4, 1 month
- Spike pool
  - CD4
    - 99.7
    - 0.008
  - CD8
    - 99.6
    - 0.004
- Spike pool
  - CD4
    - 98.9
    - 0.009
  - CD8
    - 98.7
    - 0.003

Subject 5, 1 month
- Membrane pool
  - CD4
    - 98.5
    - 0.64
  - CD8
    - 99.7
    - 0.008
- Membrane pool
  - CD4
    - 97.8
    - 0.85
  - CD8
    - 98.9
    - 0.0078

Clone 1
- Spike pool
  - TNF-α
    - 0.005
  - IFN-γ
    - 64.9

Clone 2
- Spike pool
  - TNF-α
    - 0.033
  - IFN-γ
    - 74.6

Clone 3
- Membrane pool
  - IFN-γ
    - 0.18
  - TNF-α
    - 22.3

Clone 4
- Membrane pool
  - IFN-γ
    - 0.20
  - TNF-α
    - 49.0

Clone 5
- Membrane pool
  - IFN-γ
    - 0.083
  - TNF-α
    - 99.0

Brad Jones,
Eva Stephenson
Cornell University
Most but not all convalescent patients have Antibodies to Spike and Nucleocapsid

Collaboration with Jeff Cohen NIAID
Keller et al, Blood. 2020 Dec 17;136(25):2905-17
Seropositive Virus Exposed Donors Recognize a Broader Range of Viral Proteins Compared with Seronegative Exposed Donors

Keller et al, Blood. 2020 Dec 17;136(25):2905-17
Multiple Donors Recognize Epitopes Predominantly within a Conserved Region of Membrane Protein

Membrane Epitopes

Keller et al, Blood. 2020 Dec 17;136(25):2905-17
Less Donors Recognize Epitopes within Spike and Nucleocapsid

Keller et al, Blood. 2020 Dec 17;136(25):2905-17
SARS-CoV-2 Epitopes Cross-React with Described Variants But not Seasonal CoV

Keller et al, Blood. 2020 Dec 17;136(25):2905-17
Moving SARS-CoV2 T cell Therapies to the Clinic
Improving Product Potency - IL15 Appears to Enhance CST Specificity

Chris Lazarski
Jessica Durkee Shock
Mariah Jensen Wachspress
IL15+7 Optimized Cytokine Cocktail Over IL4+7 Especially for CD8+ CSTs

IL 15+7: Mean 3.2x
IL4+7: Mean 1.9x
Can Vaccinated, SARS-Cov2 Unexposed Donors be used to Manufacture SARS-CoV2-specific T cells and are they Cross Reactive?
Vaccinated Donors Elicit
Spike specific T cell responses in addition to
Spike specific Ab Responses

Paper available as PrePrint in:
https://www.researchsquare.com/article/rs-403449/v1
Vaccinated Donor-Derived T cells exhibit cross-reactivity against B.1.1.7 and B.1.351 variants

Paper available as PrePrint in:
https://www.researchsquare.com/article/rs-403449/v1
Immunotherapy for COVID-19

• Reports to date:
  • Gladstone D *et al.* *Annals IM*:
    • 2 patients with ARDS treated with cord blood derived T-regulatory cells

<table>
<thead>
<tr>
<th>Table 1. Laboratory Values: Patient 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>CB Treg infusion</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
</tr>
<tr>
<td>IL-12, pg/mL</td>
</tr>
<tr>
<td>IFN-γ, pg/mL</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
</tr>
<tr>
<td>MCP-1, pg/mL</td>
</tr>
<tr>
<td>MCP-4, pg/mL</td>
</tr>
<tr>
<td>TNFα, pg/mL</td>
</tr>
</tbody>
</table>

• Phase I studies:
  • Regulatory T-cell therapy for COVID-19: 1 developing study
  • SARS-CoV-2 T-cell therapy: 1 recruiting, 1 closed, 2 developing studies
  • MSCs for COVID-19: 2 recruiting, 2 developing studies
  • NK cell therapy for COVID-19: 2 recruiting studies
Conclusions

• Multiple CD4-restricted (and rarer CD8-restricted) epitopes are recognized by convalescent donors
  - Responses are predominantly membrane specific
  - Seroconversion seems to correlate with the breadth of T cell responses

• It is possible to expand SARS-CoV-2 specific T-cells from recovered and vaccinated donors, which may have clinical applicability for the treatment of BMT patients

• Clinical data using SARS-CoV2 specific T cells pending
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Eva Stevenson

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Peter Burbelo

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