Allogeneic CAR T Cells Derived From Younger Donor T Cells Have More Desirable T Cell Phenotype And Better *in vitro* Functionality

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Disclosure

• Full-time employee of Allogene Therapeutics
• Equity interest in Allogene Therapeutics
Biomarkers that predict efficacy in autologous CAR T cell therapy

Less differentiated T cell phenotype, expression of PD-1, TIM-3 and LAG-3 on T cells correlate with patient response


CAR T cells derived from healthy donors show better expansion and efficacy

Healthy donor cells have better and more consistent expansion

CAR T cells generated from healthy donors show better *in vivo* function in murine model


Graham, C. E. et al., *Leukemia.*, 35, 3581-3584 (2021)
Characterizing T cells from diverse donors to understand factors that affect CAR T cell functionality

Total 30* donors

* One donor failed during CAR T manufacturing due to limited proliferation

6 out of 11 patient-derived T cells had limited expansion and were excluded from functional assay evaluation

CAR construct: ALLO-715 (anti-BCMA)

Healthy donors (age ≤ 30)  
(n = 9)  
Age: 19 – 29  
BMI: 18.9 – 27.4

Healthy donors (age > 30)  
(n = 10)  
Age: 33 – 62  
BMI: 21.8 – 51.7

Cancer patients  
(n = 11*)  
Age: 28 – 81  
BMI: N/A  
Disease: ALL, CLL, NHL, MM

Starting material  
(purified CD4+/CD8+ cells)

Manufacturing process

Functional characterization

CAR T cell

Biomarker ID

- HD flow cytometry
- scRNA-seq
- Cytokine/Polyfunctionality

- HD flow cytometry
- Fold expansion

- In vitro and in vivo killing
- scRNA-seq
- Cytokine/Polyfunctionality
- Mitochondrial fitness
- Proliferation/persistence
Younger donors have higher frequency of T cells that express markers associated with Stem/Central memory T cells.

Healthy donor (age < 30)
Healthy donor (age ≥ 30)
Cancer patient

*: Healthy donor with BMI > 30
ALL = acute lymphocytic leukemia, MM = multiple myeloma, CLL = chronic lymphocytic leukemia, NHL = non-Hodgkins lymphoma
Both donor age and disease state are associated with lower $\%T_{SCM}$ and the difference increases during CAR T manufacturing.

- Donor age and disease state both contribute to the lower percentage of $T_{SCM}$ in starting material and final CAR T cells.
- Patient-derived T cells tend to have lower $\%T_{SCM}$ at the end of manufacturing despite similar $\%T_{SCM}$ in starting material.
T cell subset, activation, and exhaustion marker expression correlate with *in vitro* anti-tumor activity

**Long-term killing assay reveals different *in vitro* anti-tumor activity between donors**

**Less differentiated T cell phenotype positively trends with *in vitro* anti-tumor activity**

**Exhaustion and activation markers negatively trend with *in vitro* anti-tumor activity**

- Healthy donor (age ≤ 30)
- Healthy donor (age > 30)
- Cancer patient

Cells assayed at the end of process

Effector to target ratio = 1:1

Target cell: MM1s

CAR: ALLO-715 (anti-BCMA)

All percentages based on CAR⁺ CD8⁺ T cells

![Graphs showing Long-term killing assay](image)

![Graphs showing correlation between marker expression and anti-tumor activity](image)
T cells from younger donors have less-differentiated phenotype, better \textit{in vitro} cytotoxicity and lower expression of exhaustion markers.
Summary

• Characteristics and performance of CAR T cells produced from healthy donors from ages 19 - 62 were compared to CAR T cells derived from cancer patient samples

• Cells from younger donors had improved characteristics compared to older donors
  – Less differentiated T cell phenotype negatively associated with donor age
  – Expression of specific exhaustion and activation markers positively correlated with increased donor age
  – *In vitro* anti-tumor activity negatively trends with increased donor age

• Cells from cancer patients performed less well than those from healthy donors
  – Production of CAR T from patient samples showed a higher failure rate
  – Less differentiated T cell phenotype negatively associated with disease state

• This study outlines the opportunity of using young healthy donor materials for allogeneic CAR T products
  – Potential to eliminate manufacturing failures
  – Ability to improve product characteristics and potency
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Leading Today, Defining Tomorrow

Thanks to:
The Allogene team
*Collaborators at Cellectis

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