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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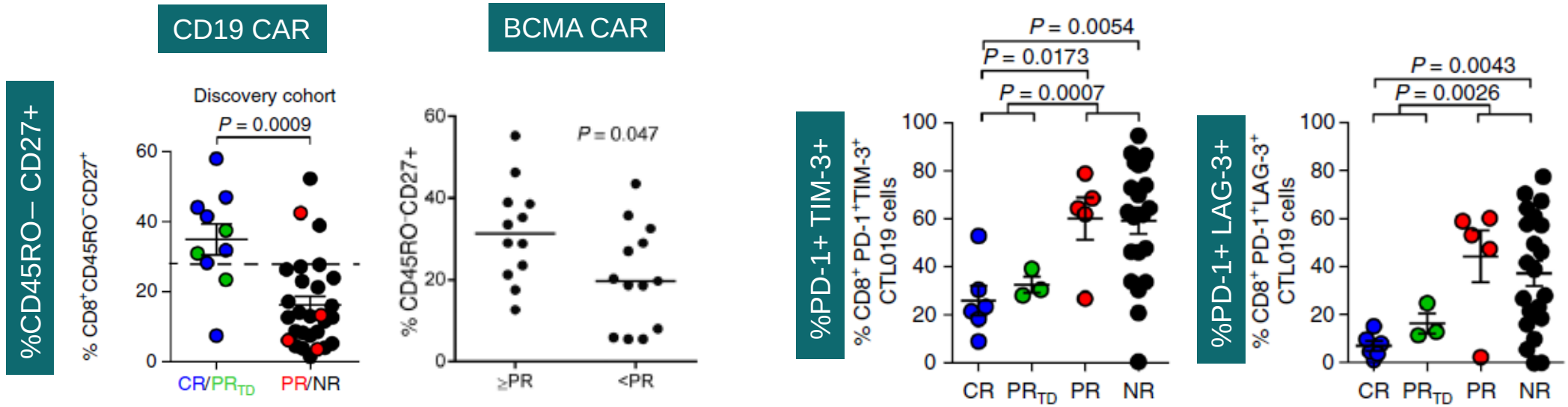
Disclosure

- 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



Fraietta, J. A. et al., *Nat. Med*., **24,** 563-571 (2018)

Cohen, A. D. et al., *J. Clin. Invest*., **129 (6),** 2210-2221 (2019)

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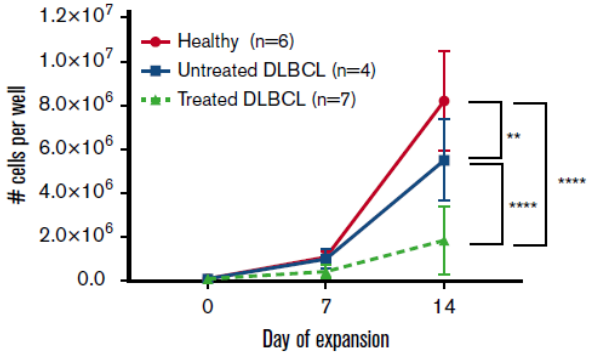
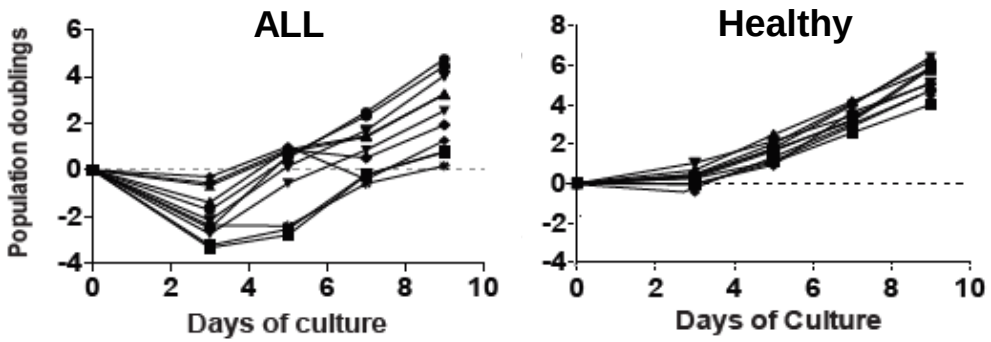
CAR T cells derived from healthy donors show better expansion and efficacy

Healthy donor cells have better and more consistent expansion





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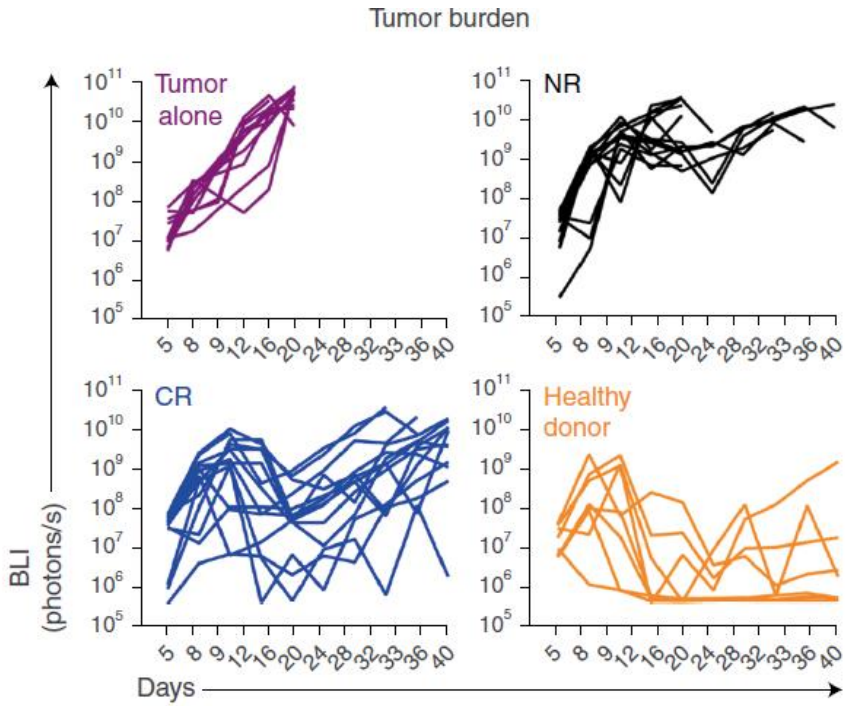
CAR T cells generated from healthy donors show better *in vivo* function in murine model



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Graham, C. E. et al., *Leukemia*., **35,** 3581-3584 (2021)

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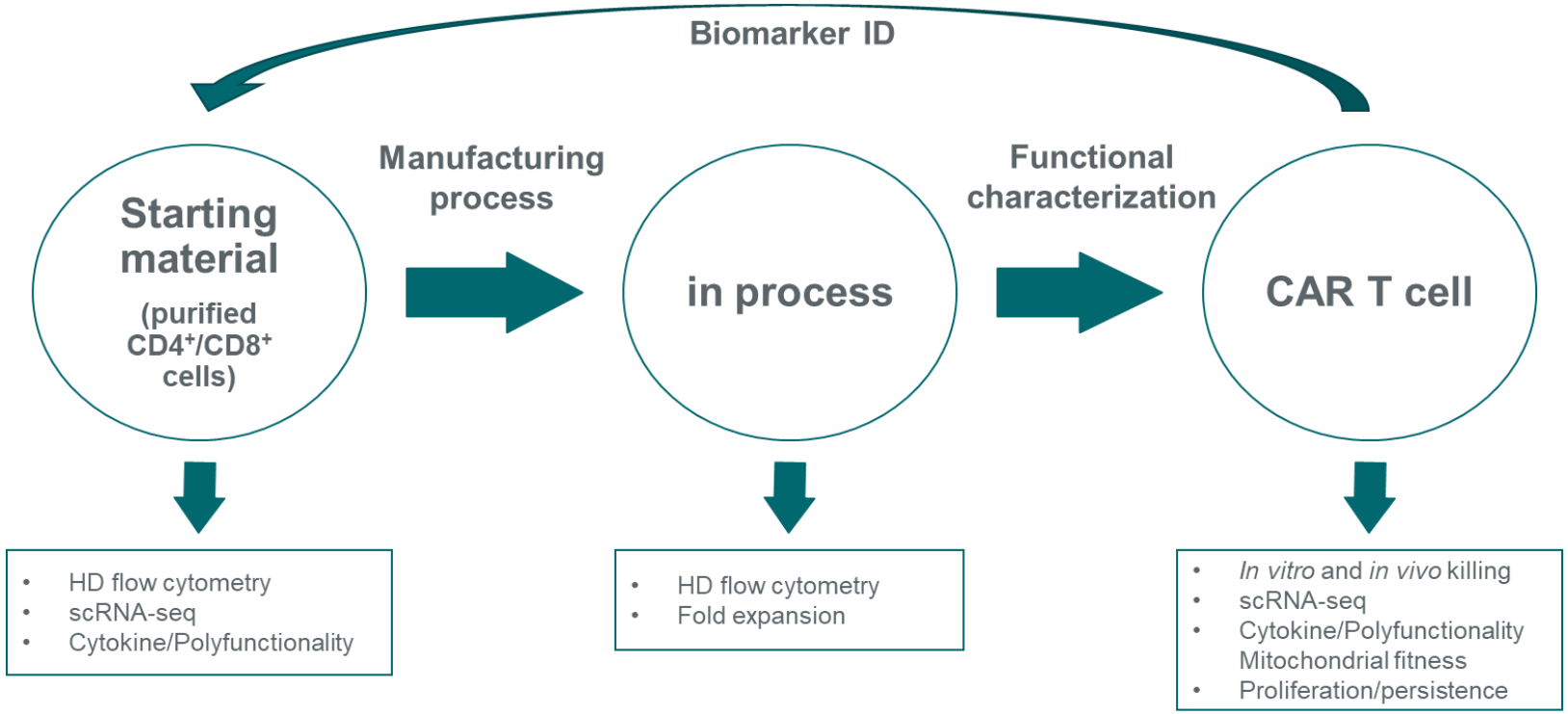
Characterizing T cells from diverse donors to understand factors that affect CAR T cell functionality

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



Total 30* donors

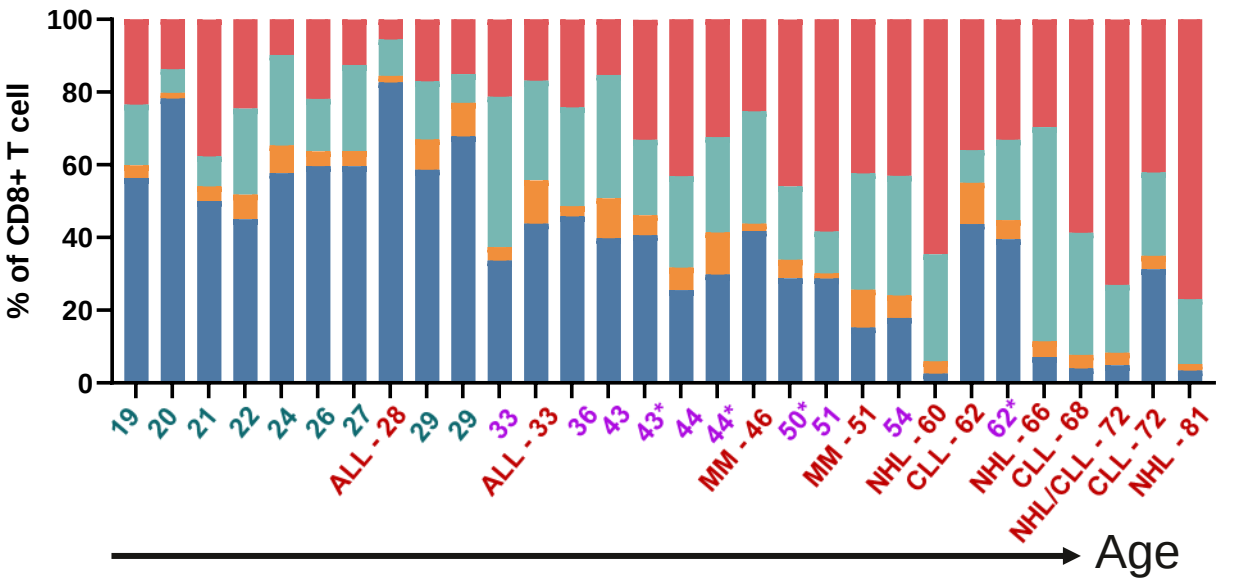
* One donor failed during CAR T manufacturing due to limited proliferation

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

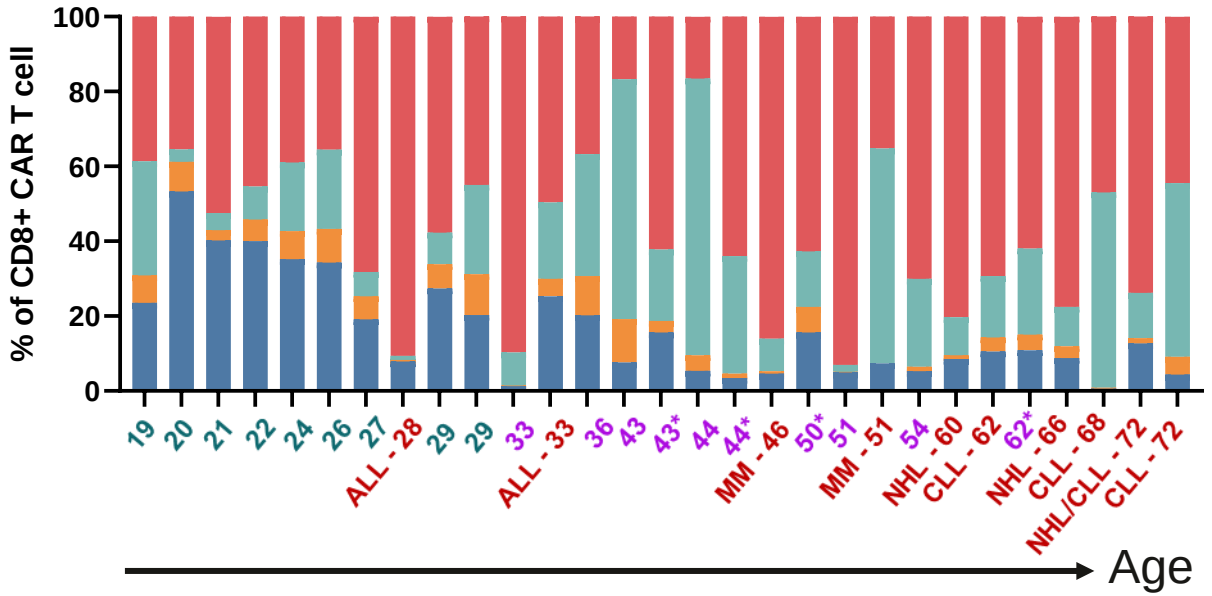
CAR construct: ALLO-715 (anti-BCMA)

Younger donors have higher frequency of T cells that express markers associated with Stem/Central memory T cells

Starting material phenotype



End of manufacturing phenotype



- T_{EMRA} ($CCR7^{-}$ $CD45RA^{+}$)
- T_{EM} ($CCR7^{-}$ $CD45RA^{-}$)
- T_{CM} ($CCR7^{+}$ $CD45RA^{-}$)
- T_N/T_{SCM} ($CCR7^{+}$ $CD45RA^{+}$)

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

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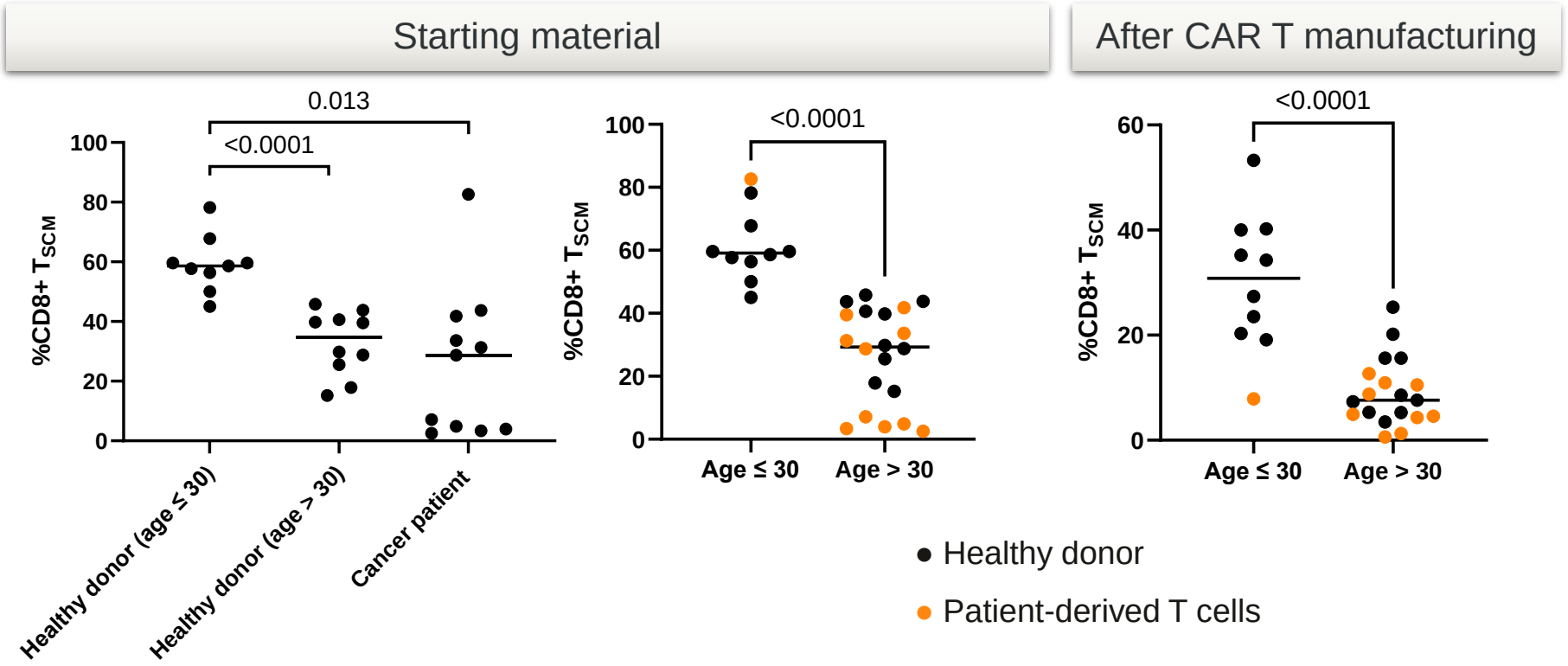
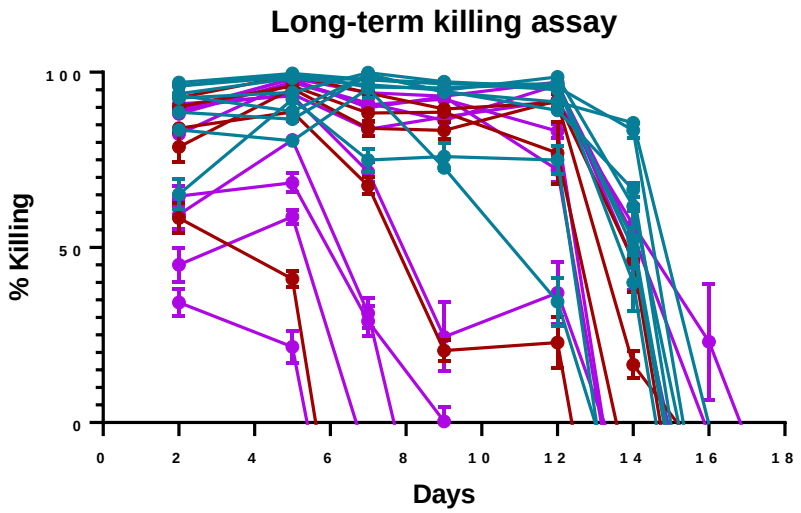
Both donor age and disease state are associated with lower $\%T_{SCM}$ and the difference increases during CAR T manufacturing



- 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



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

Cells assayed at the end of process

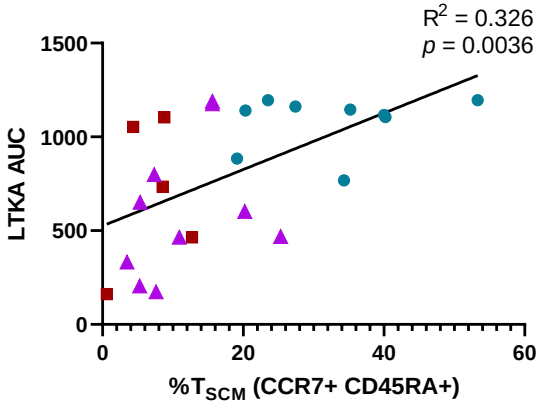
Effector to target ratio = 1:1

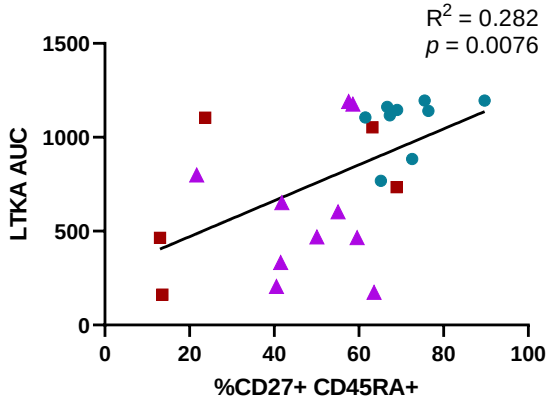
Target cell: MM1s

CAR: ALLO-715 (anti-BCMA)

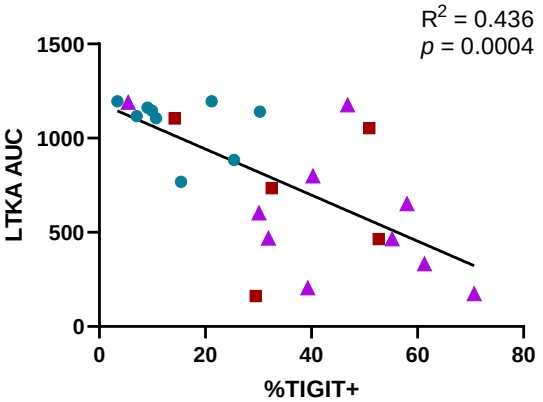
All percentages based on CAR$^+$ CD8$^+$ T cells

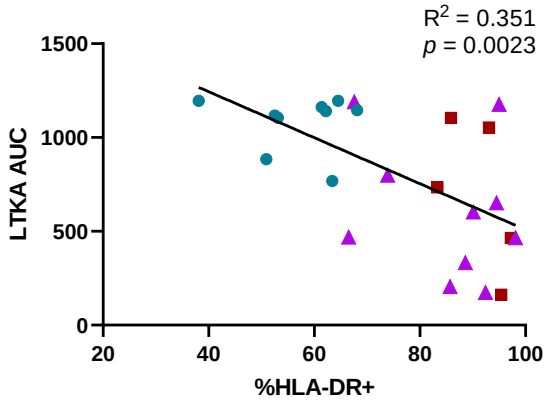
Less differentiated T cell phenotype positively trends with *in vitro* anti-tumor activity





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





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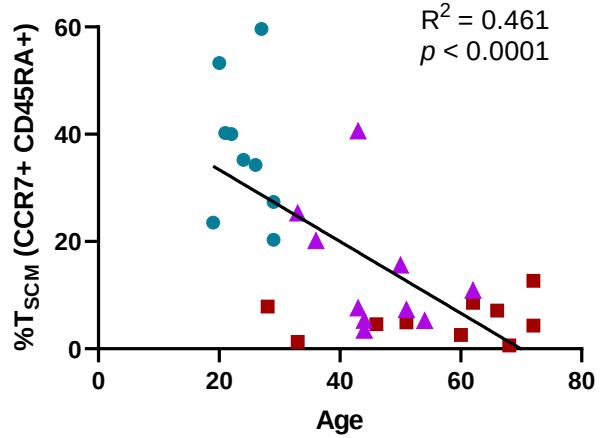
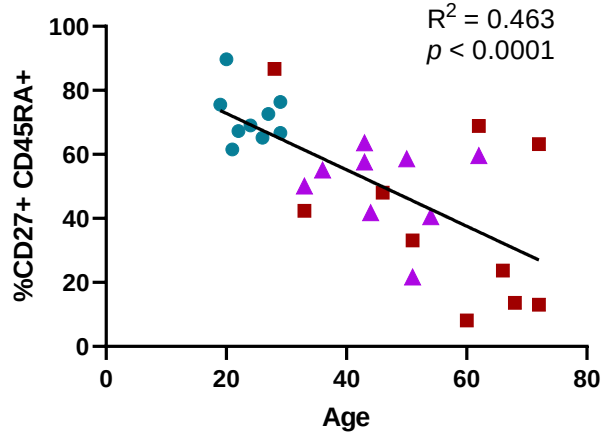
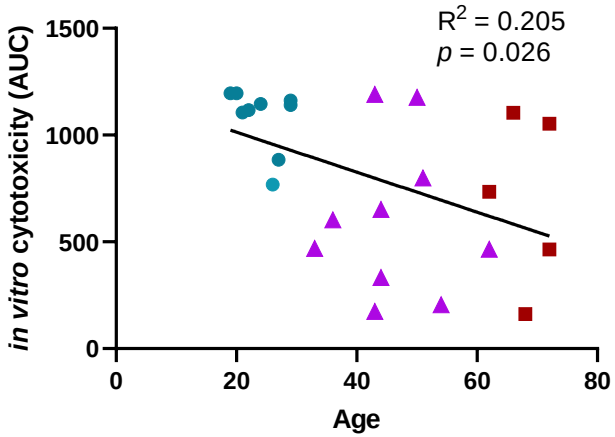
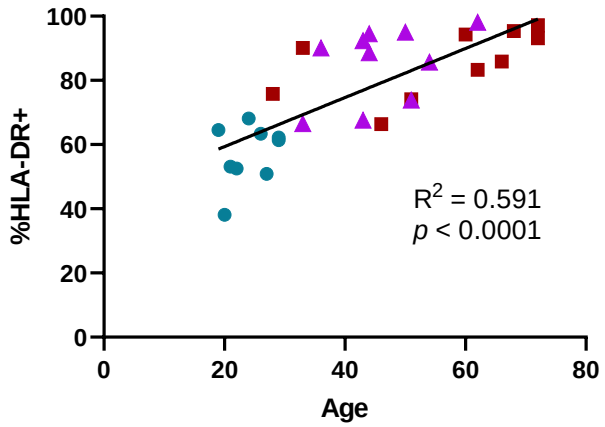
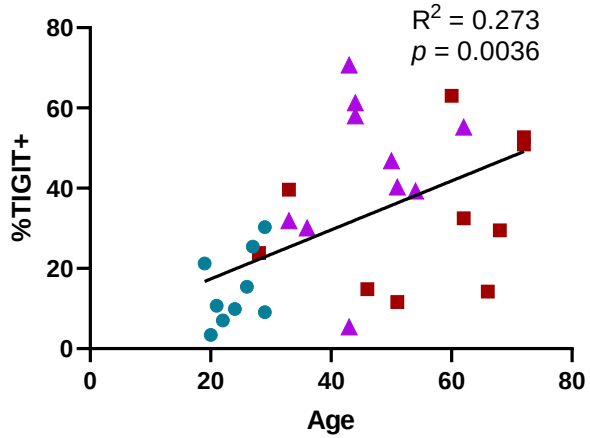
T cells from younger donors have less-differentiated phenotype, better *in vitro* cytotoxicity and lower expression of exhaustion markers

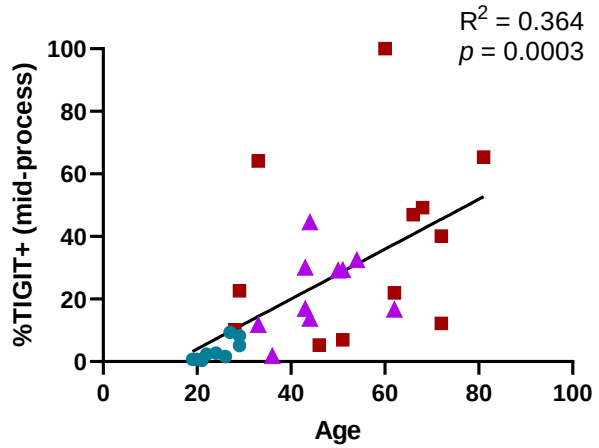












● **Healthy donor (age ≤ 30)**
▲ **Healthy donor (age > 30)**
■ **Cancer patient**

Cells assayed at the end of process

Effector to target ratio = 1:1

All percentages based on CAR^+ $CD8^+$ T cells

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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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Thanks to:

The Allogene team

*Collaborators at Cellectis

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