Cellular Mechanisms Affecting Allogeneic CAR T Cell Expansion and Rejection in Large B-Cell Lymphoma

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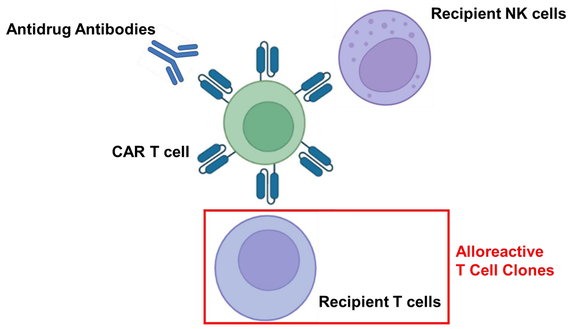
Background

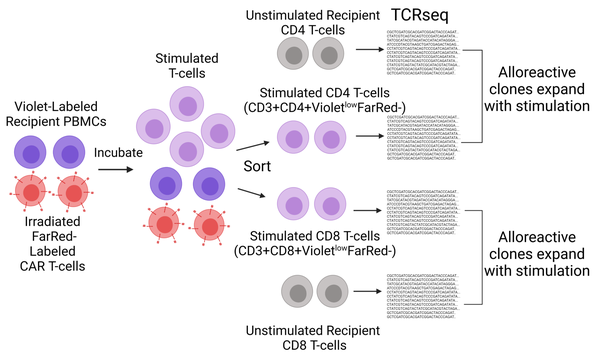
- Expansion and persistence remain challenges in clinical implementation of allogeneic CAR T cell therapy
- Despite the use of products derived from the same donor, patient responses are heterogeneous
- Detailed understanding of the immune response to allogeneic CAR T cell therapy is lacking



Hypothesis

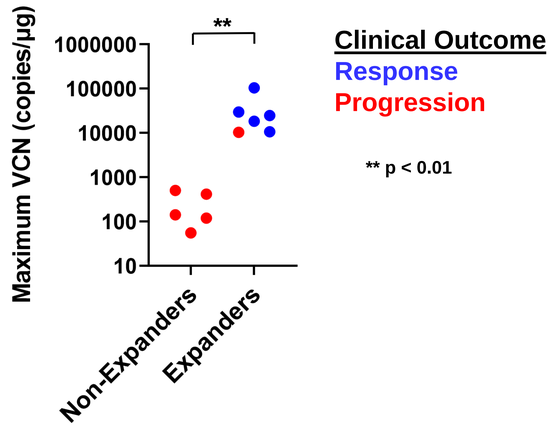
- Recipient-derived alloreactive T cells limit allogeneic CAR T cell expansion and clinical efficacy

Methods



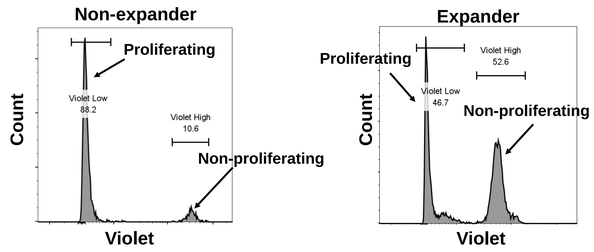
- 11 patients with relapsed/refractory large B-cell lymphoma treated on the ALPHA-2 phase 1/2 trial (NCT004416984) with the same lot of ALLO-501A were selected
- ALLO-501A is a healthy donor-derived anti-CD19 CAR T cell product with T cell receptor knockout
- Pre-lymphodepletion peripheral blood mononuclear cells (PBMCs) were used for alloreactive T cell identification

CAR T Cell Expansion

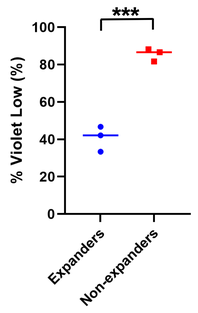


- 6 patients had robust CAR T cell expansion (expanders)
- 5 patients had poor CAR T cell expansion (non-expanders)
- Expanders had longer CAR T cell persistence and a higher frequency of clinical responses than non-expanders
- 6 patients (3 expanders and 3 non-expanders) were selected for alloreactive T cell identification and tracking

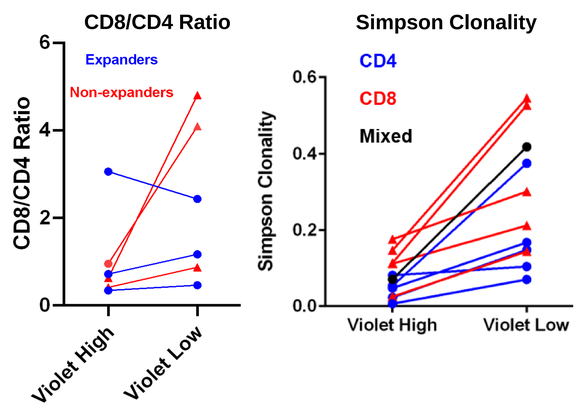
In Vitro Recipient T Cell Proliferation



- Non-expanders had more robust *in vitro* recipient T cell proliferation after exposure to ALLO-501A (85.5% vs. 40.7% proliferating, p < 0.001)

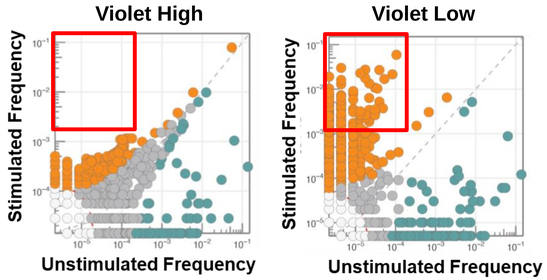


Proliferating T Cell Characteristics

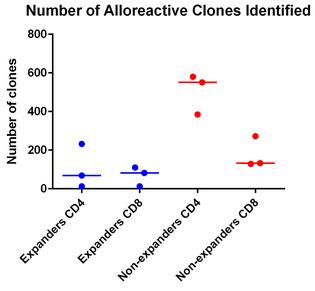


- Proliferating T cells had higher CD8⁺ fractions and increased clonality compared to non-proliferating T cells

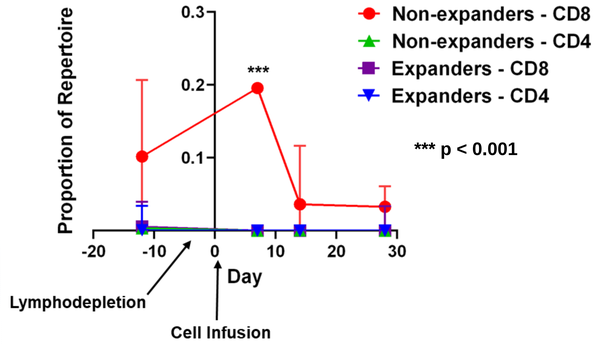
Alloreactive T Cell Identification



- Alloreactive T cell clones were identified as those enriched in the stimulated sample compared to the unstimulated sample by Fisher's test with p-value threshold $1x10^{-5}$
- More alloreactive clones were identified in non-expanders (median 551 CD4⁺, 133 CD8⁺ clones) than expanders (median 69 CD4⁺, 82 CD8⁺ clones)



Alloreactive T Cell Tracking



- Non-expanders had higher alloreactive CD8⁺ T cell frequencies than expanders at day 7 (median sum of alloreactive CD8⁺ clone frequencies 0.2 vs. 0, p < 0.001)
- A similar pattern was not observed for alloreactive CD4⁺ T cell frequencies

Conclusions

- We have successfully developed an assay to identify alloreactive CD4⁺ and CD8⁺ T cell clones in clinical samples
- Non-expanders had more robust *in vitro* T-cell proliferation upon exposure to ALLO-501A
  - Suggests that assay may recapitulate some aspects of expander vs. non-expander phenomenon
- Non-expanders had higher frequencies of alloreactive CD8⁺ clones following treatment
  - Similar pattern not apparent for CD4⁺ clones
  - Suggests that alloreactive CD8⁺ clones may be involved in early rejection of allogeneic CAR T-cells

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