

Eradication of Established CD19+ Leukemia using a Single Injection of Chimeric Immunoreceptor Modified Lentiviral Transduced T Cells in a Xenograft NOG Mouse Model

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Disclosure

- The author has no relevant financial disclosures or conflicts of interest.
- This involves no off label use of any medications.

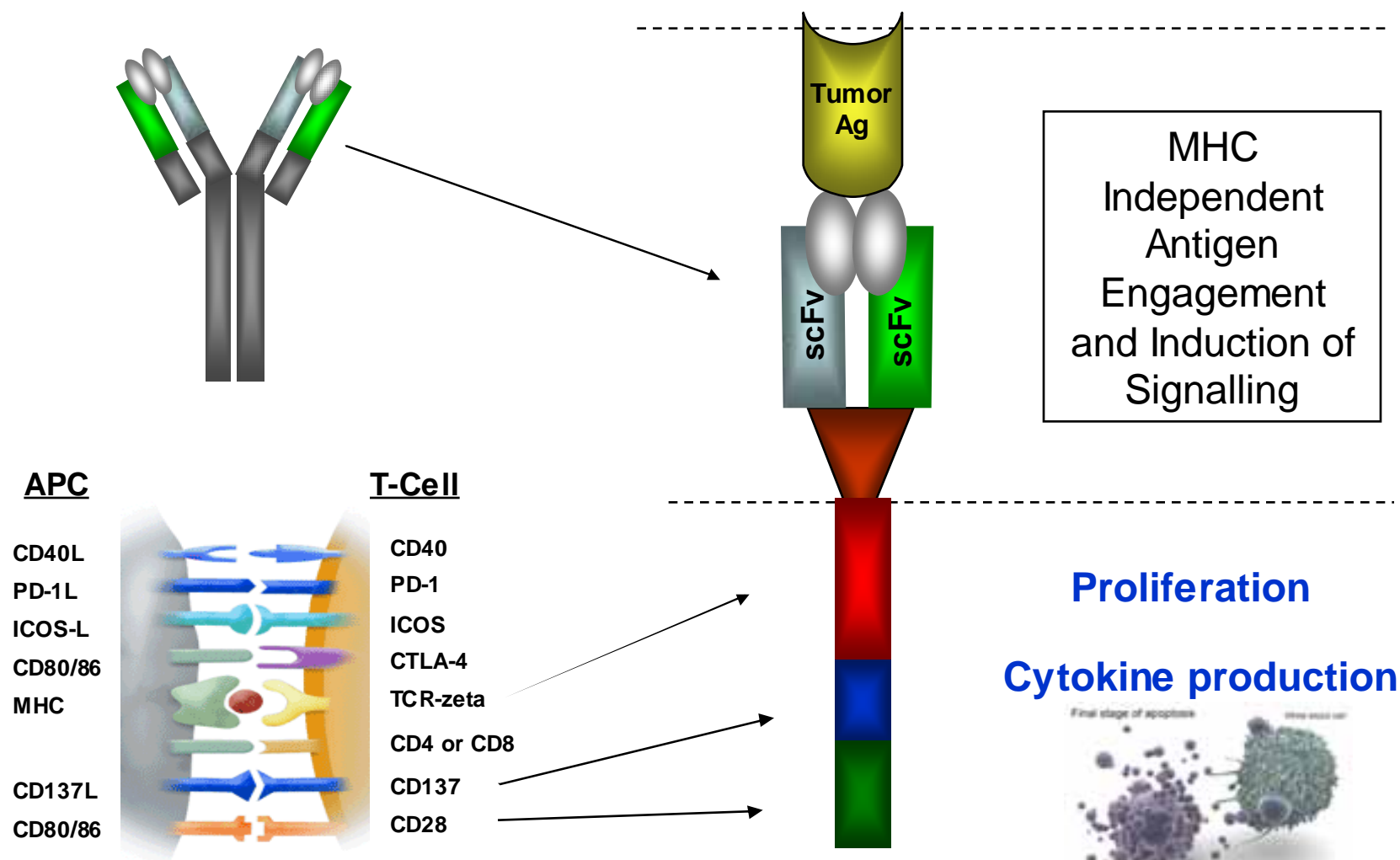


Overview

- Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy, and relapsed ALL is the fifth most common as well as the most common cause of cancer death in children
- Higher doses of chemotherapy for relapsed/refractory disease come with increased toxicity (and not that much more success)
- Donor derived T-cells studied as part of the Graft Versus Leukemia Effect in allogeneic transplant are effective in eradicating hematologic malignancies but at the cost of Graft Versus Host disease
- Chimeric Immunoreceptors are artificial constructs fusing the extracellular antigen-recognition portion of an immunoglobulin with activation and costimulatory domains of T-cell receptors
- Chimeric Immunoreceptors expressed in Autologous T-cells provide the potential for cytotoxic efficacy without Graft Versus Host disease



Chimeric Immunoreceptor



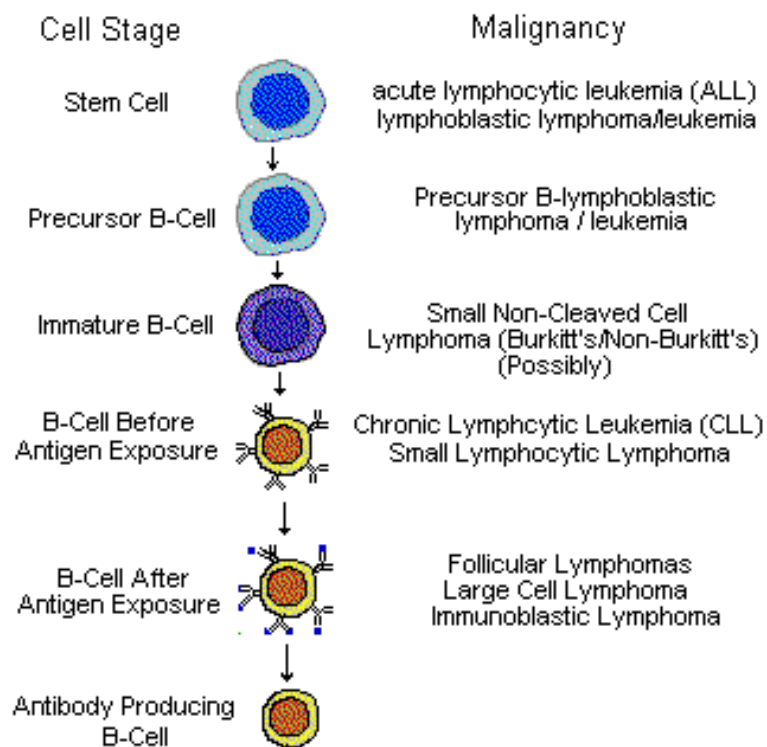
Carreno and Collins. *Annu Rev Immunol.* 2002;20:29.
 Stuart and Racker. *Expert Opin Ther Targets.* 2002;6:275.



CD19 as a tumor target antigen

- CD19 is expressed by the majority of B-cell derived tumors
- Normal CD19 expression is limited to only B-lineage lymphoid cells
- B-cell deficiency is well tolerated given extensive experience with rituximab (anti CD20 antibody), and is treatable with IV immunoglobulin

B Cell Cancers by Cell Development



Lymphoma Information Network
<http://www.lymphomainfo.net/>

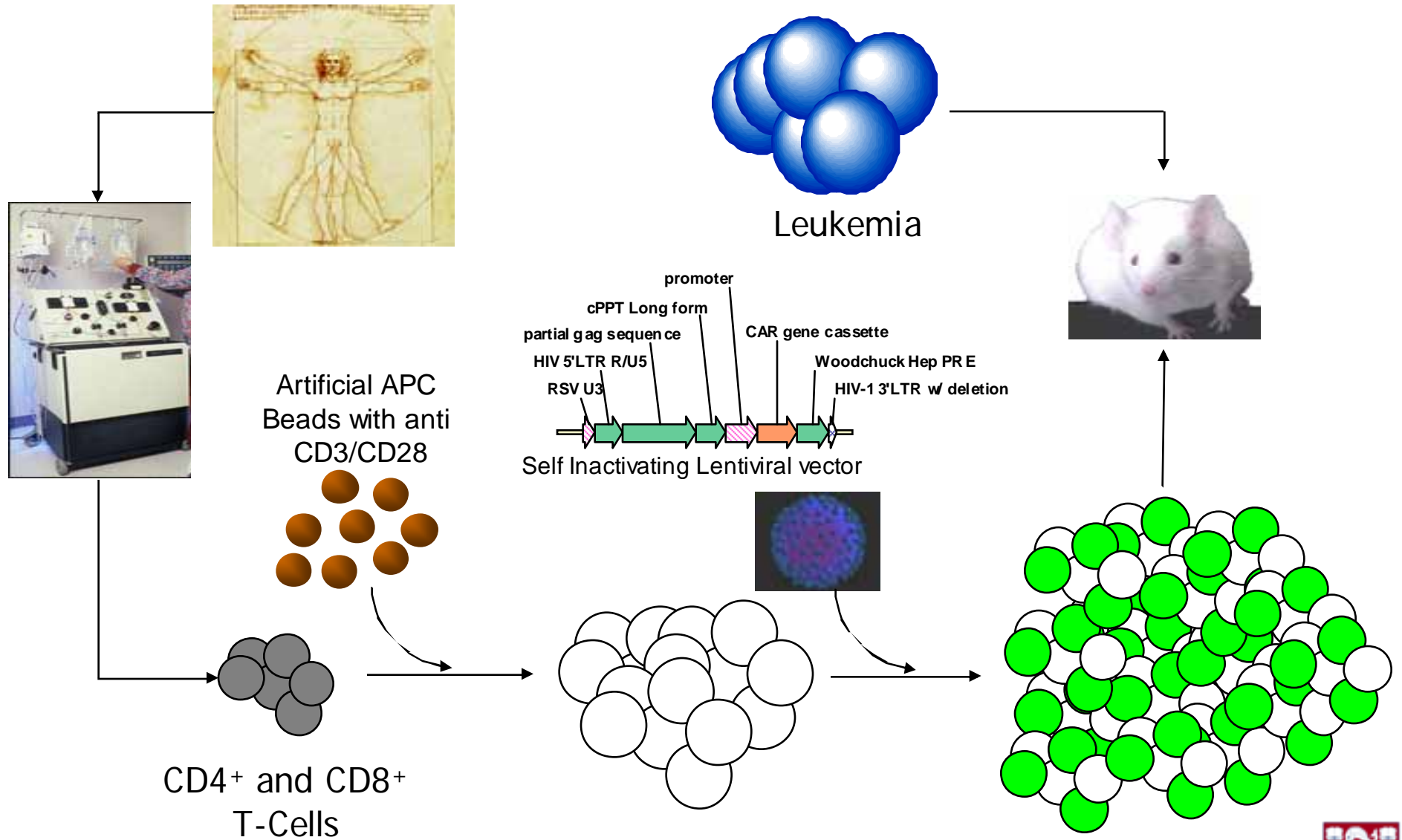


Incorporating co-stimulatory signals

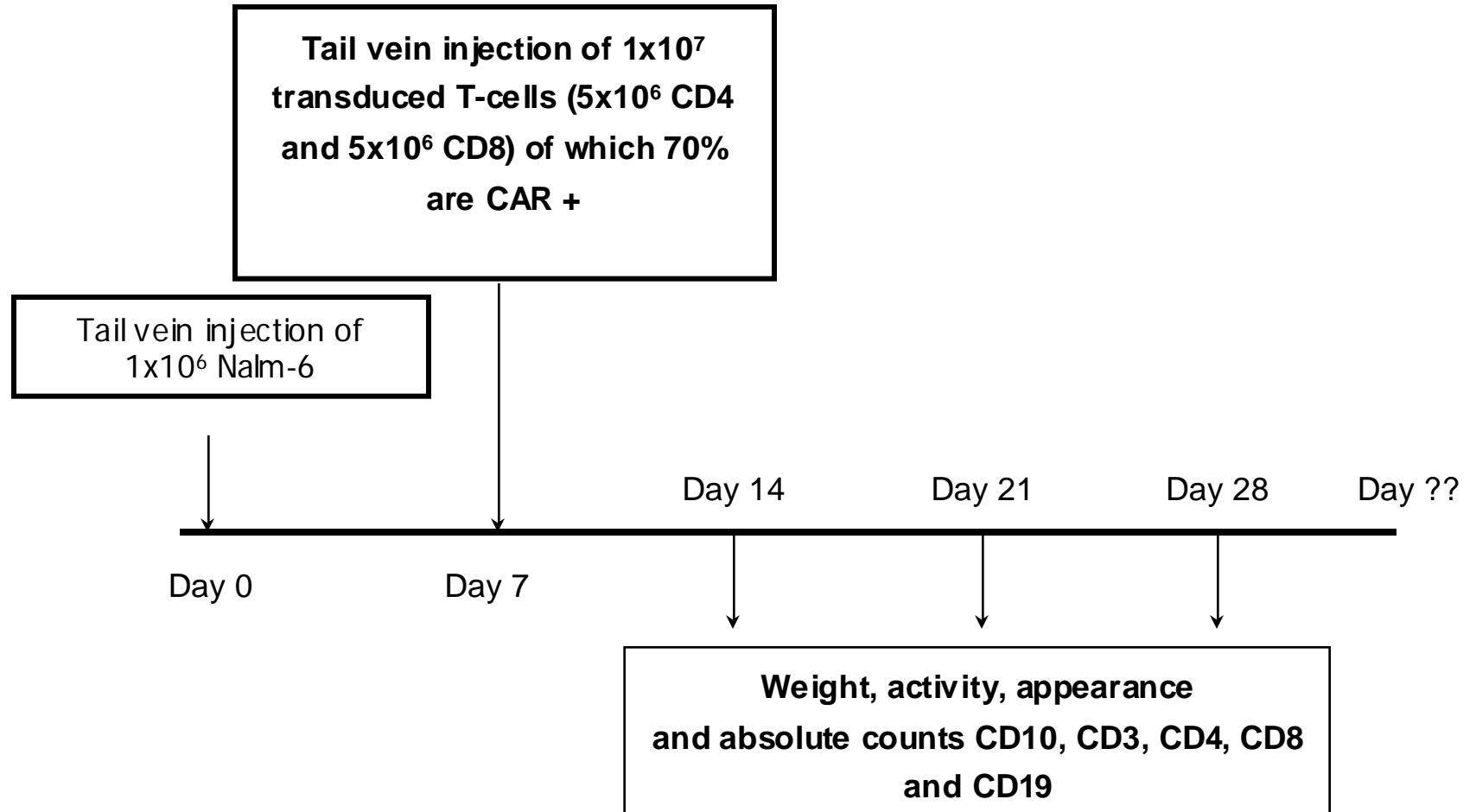
- CD28 provides potent activating signals that enhance CD4 and CD8 T cell:
 - Proliferation
 - Survival
 - Cytokine production
- 4-1BB (CD137) provides signals that:
 - Promote long-term proliferation and survival of CD8 T cells
 - Promote cytokine production
 - enhance CD8+ T cell responses in viral infection and allograft rejection



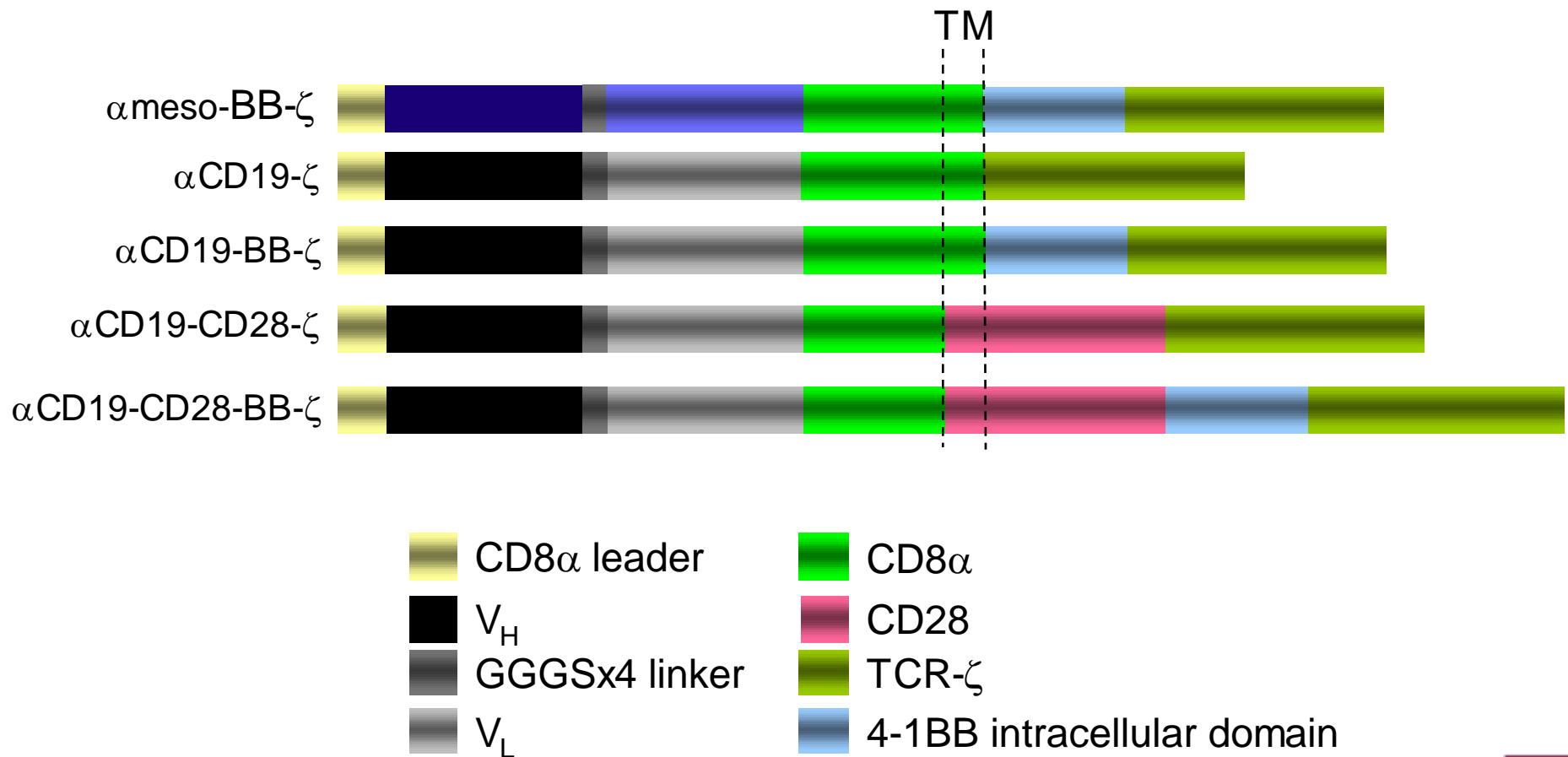
Pre-clinical Experimental Model



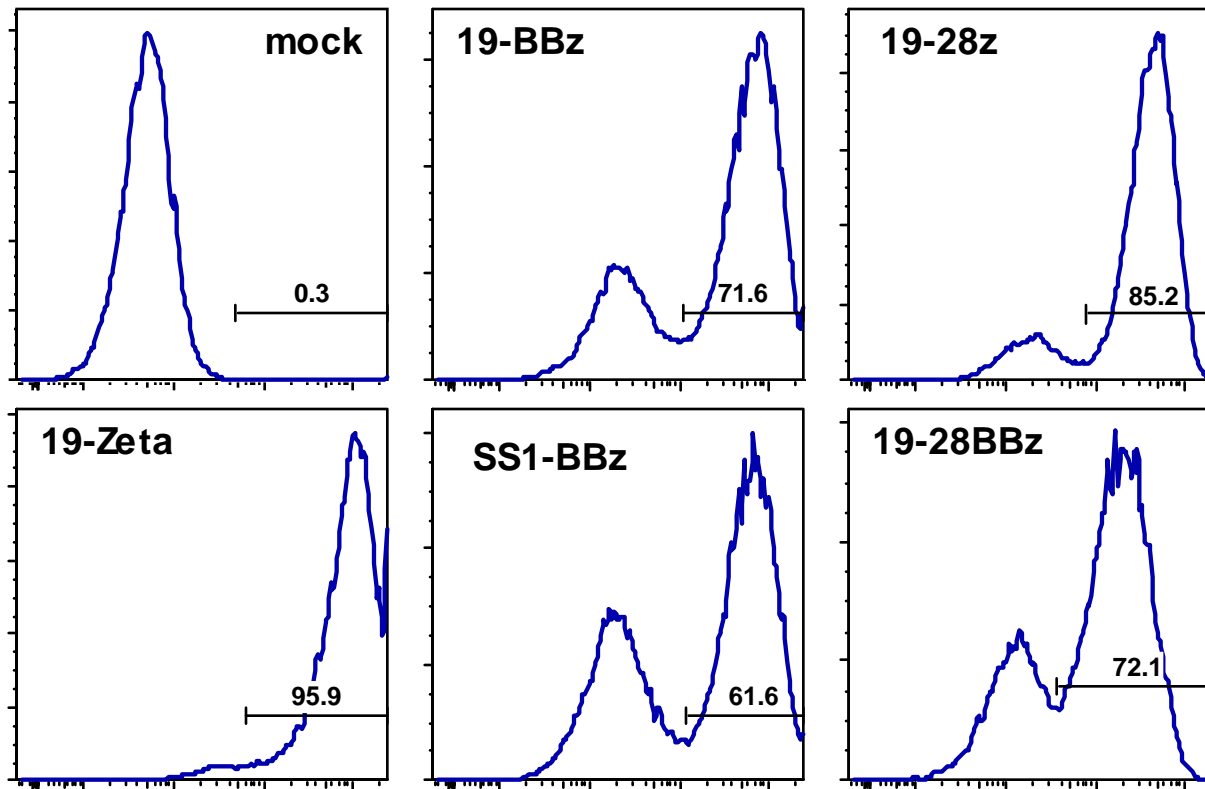
Methods



Chimeric Immunoreceptors



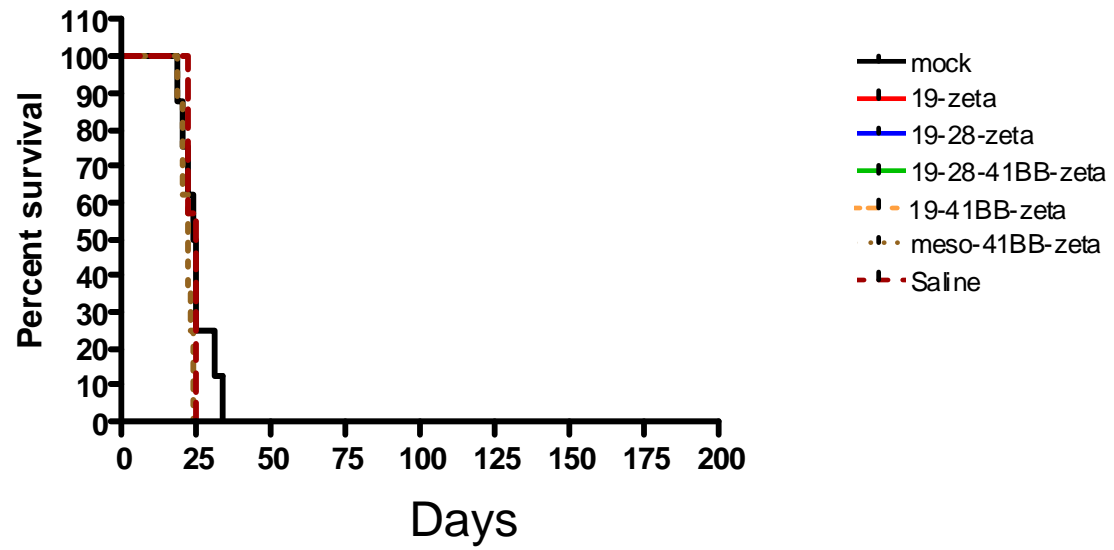
ND150 CAR Positive T cells Day of Injection



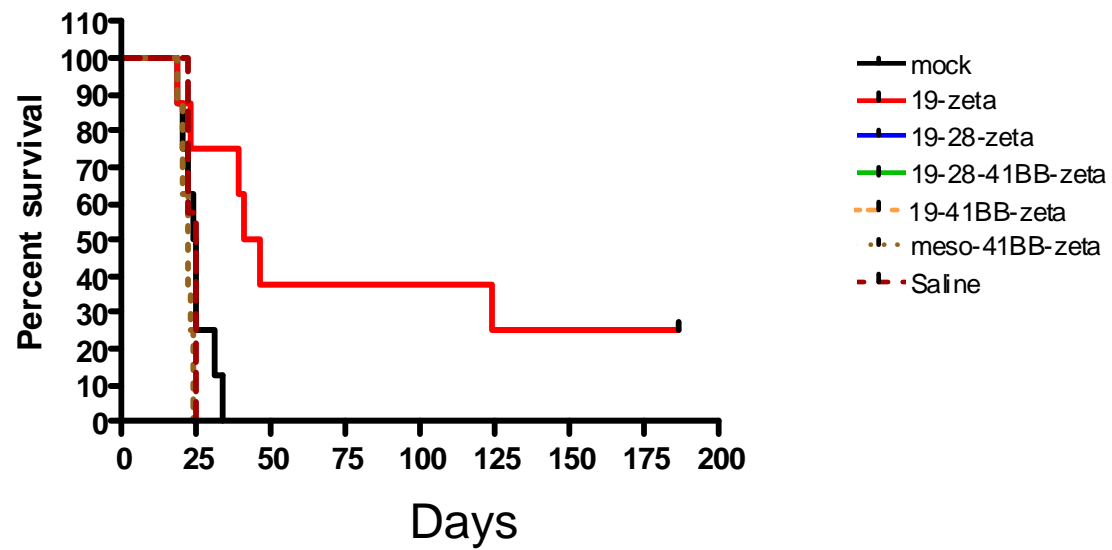
scFv expression



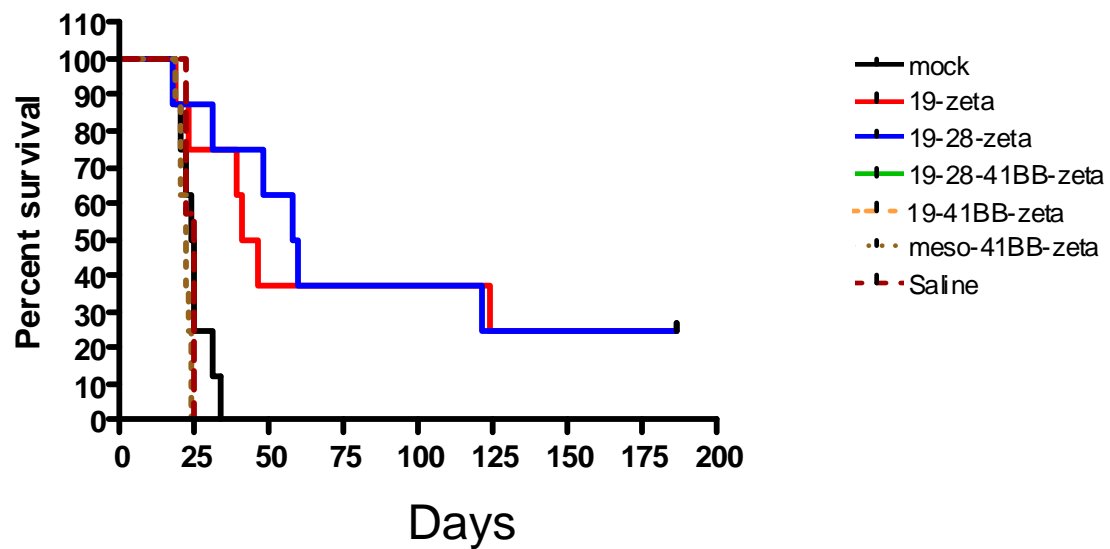
Overall Survival



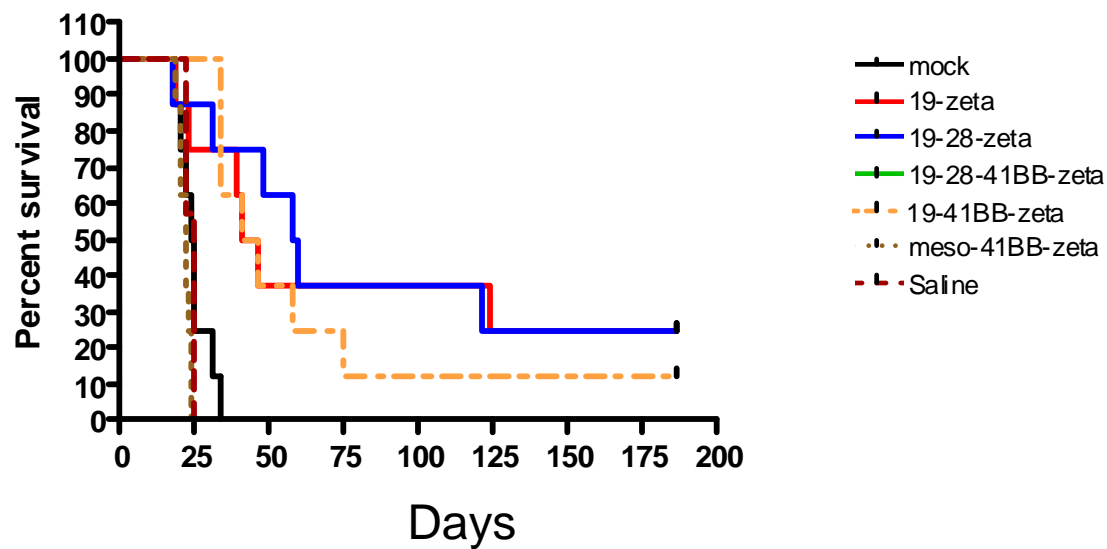
Overall Survival



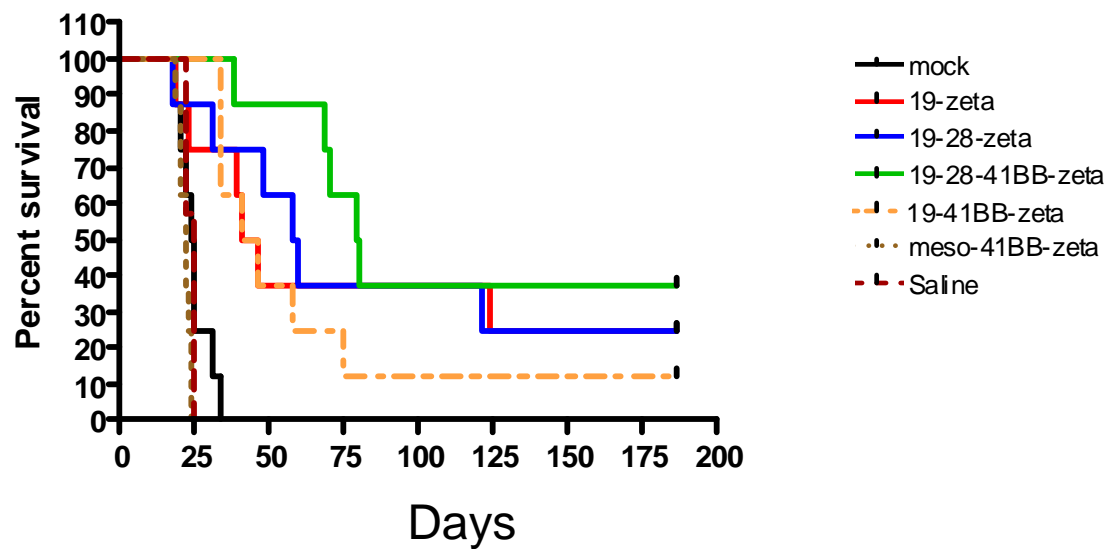
Overall Survival



Overall Survival

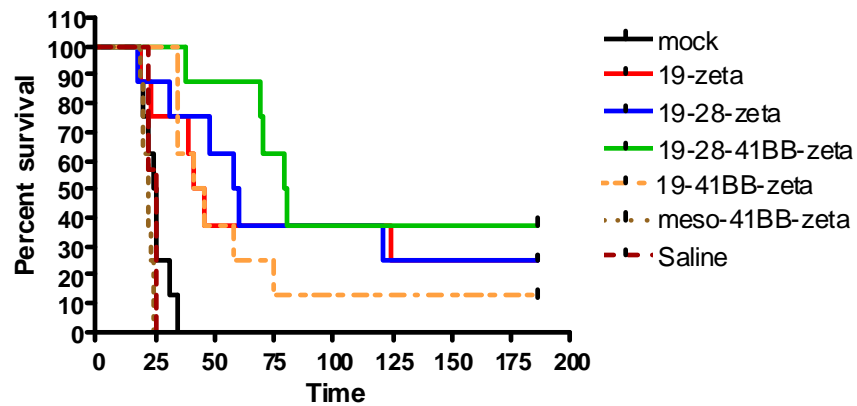


Overall Survival

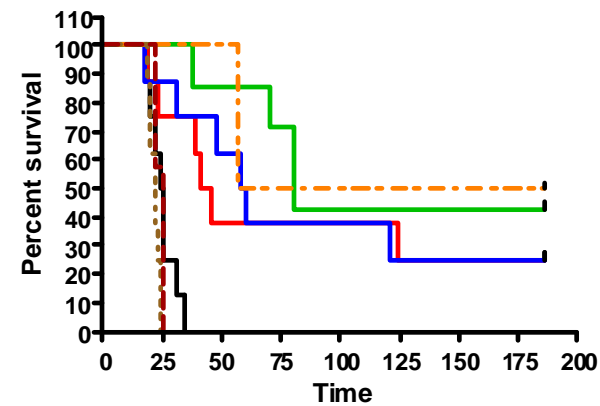


Influence of Xenogeneic Graft Versus Host Disease

Overall Survival



Overall Survival – GVHD Excluded

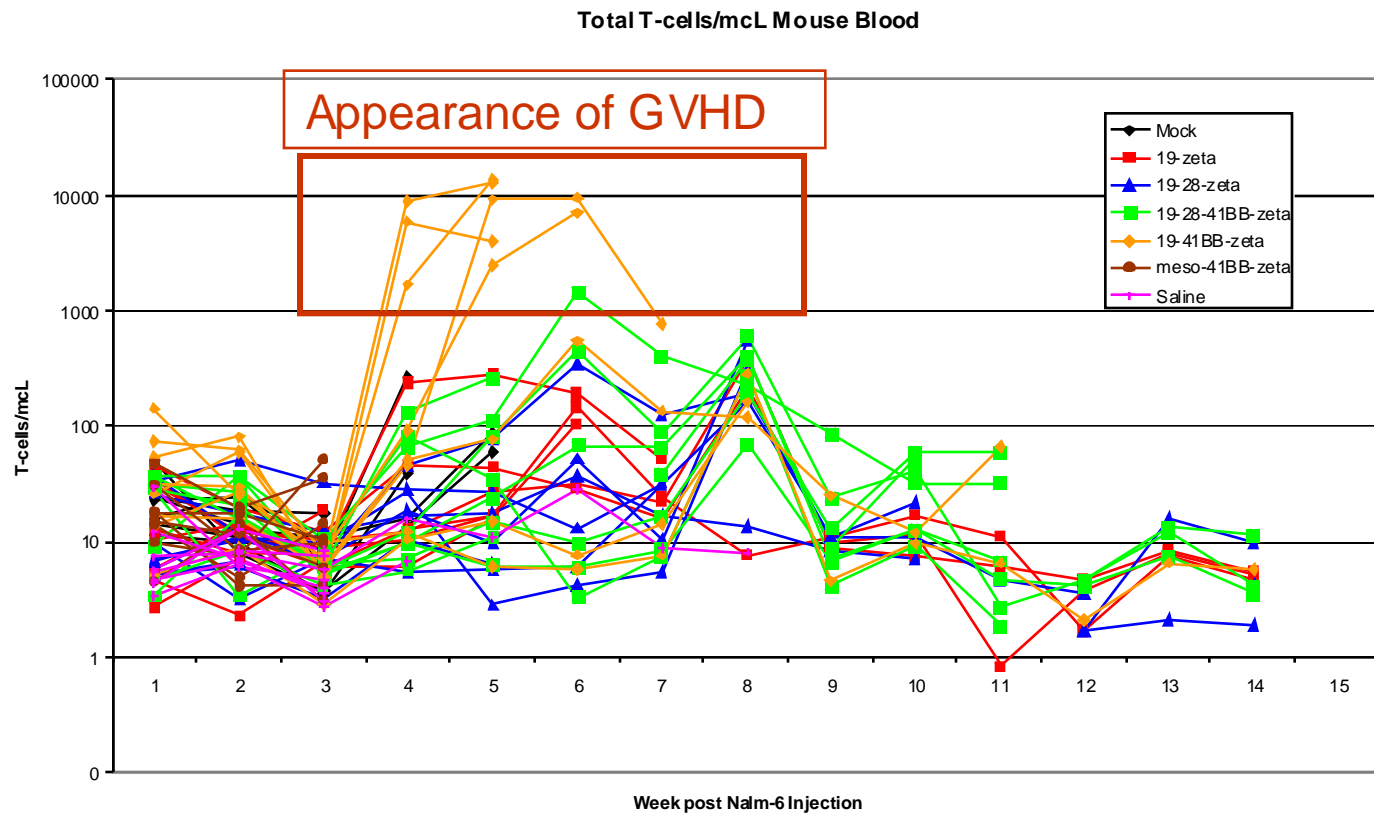


Group	Median OS	Median OS (GVHD excluded)
Saline	25	25
Mock	24	24
Meso-41BB-zeta	22	22
19-zeta	41*	41*
19-28-zeta	58*	58*
19-41BB-zeta	41*	57
19-28-41BB-zeta	79*	80*

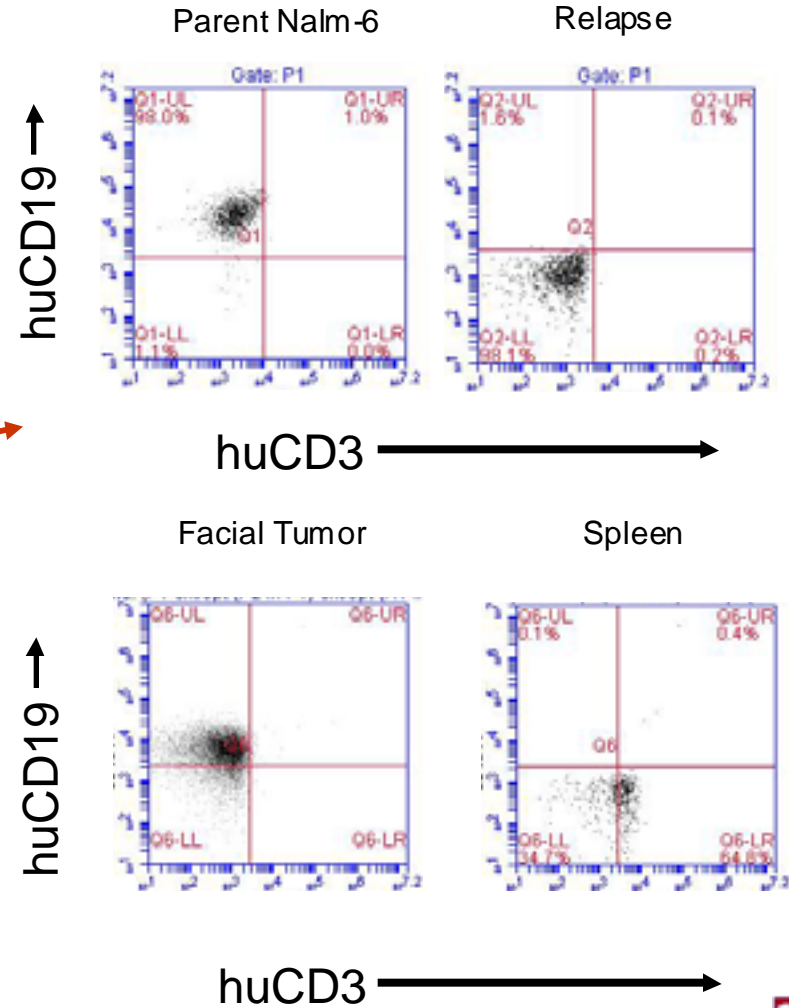
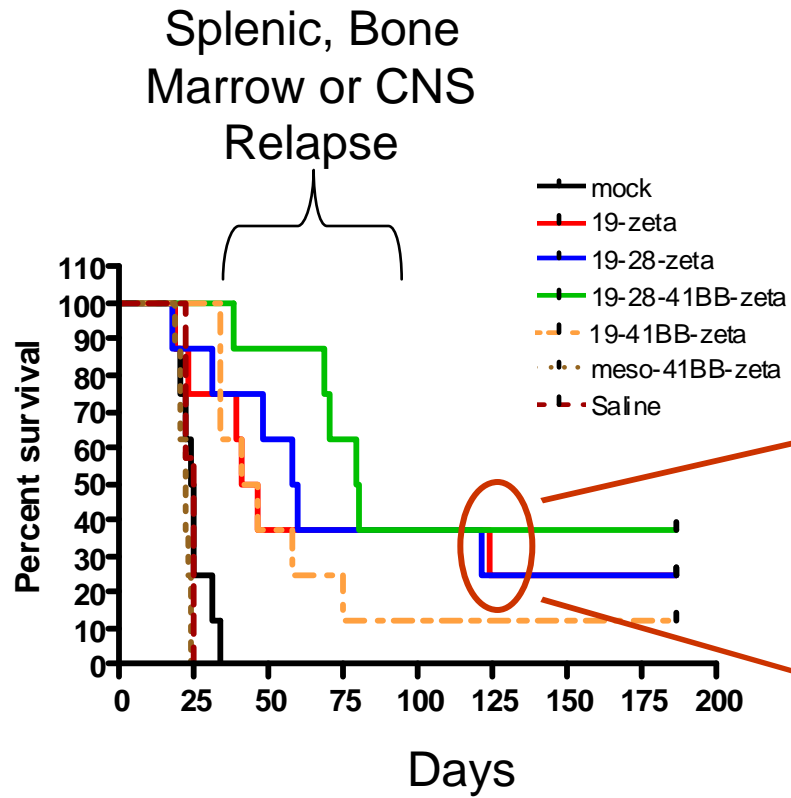
*p<0.001 (mock)



Total Peripheral Blood T Cells correlate with onset of GVHD



Disease Progression or Relapse



Summary

- Immunoreceptor modified T cells generated by lentiviral transfection of *ex vivo* expanded T cells can effectively eradicate human leukemia in a xenograft NOG mouse model with only a single injection of 1×10^7 T cells.
- Slight survival advantage over other constructs is observed with the 19-28-41BB- ζ CAR
 - Including apparent eradication of disease (survival >100 days post disappearance of circulating T cells, >60 days since any relapse in any other group)
- High total circulating T cells correlates with xenogeneic GVHD mortality in the absence of detectable leukemia



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