Deploying a CD45-Antibody Drug Conjugate for Allogeneic Hematopoietic Stem Cell Transplant in Non-Human Primates

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BACKGROUND

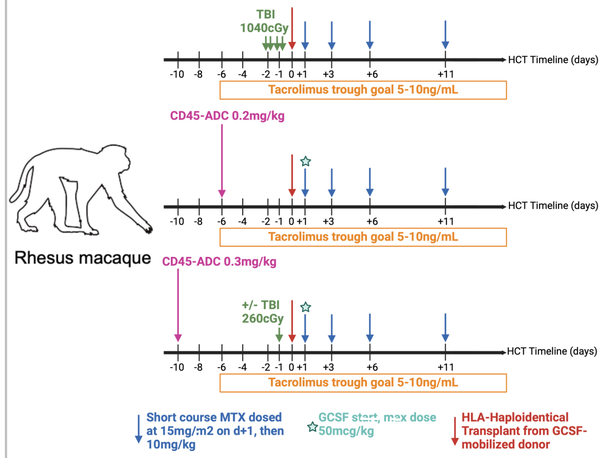
- Conventional allogeneic hematopoietic cell transplantation (HCT) requires high doses of chemotherapy +/- total body irradiation (TBI) for successful engraftment.
- However, chemotherapy and/or TBI cause multiple off-target toxicities, limiting the number of patients eligible and willing to proceed to HCT.
- Targeted conditioning, including antibody-drug conjugates (ADCs) are being developed.
- ADCs targeting CD45, a transmembrane receptor found on hematopoietic stem and progenitor cells (HSPCs) and mature leukocytes, have been developed and evaluated for allogeneic HCT in mice. In mouse models, CD45-ADCs show efficacy in depletion of HSPCs, successful donor engraftment across MHC barriers, and a favourable toxicity profile.
- ADC-based conditioning studies in allogeneic-HCT in large animal models, which are likely necessary for clinical translation, are lacking.

OBJECTIVES

- Compare the HSPC depletion following CD45-ADC to myeloablative (1040cGy) TBI.
- Evaluate the kinetics and durability of donor chimerism following CD45-ADC compared to myeloablative TBI.
- Characterize the safety profile of CD45-ADC.

METHODS

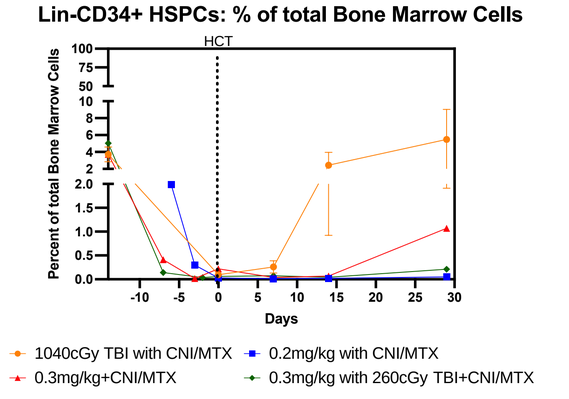
- Four pilot experiments were completed: **(i)** myeloablative TBI (1040cGy) controls (n=3), **(ii)** 0.2mg/kg CD45-ADC on day-6 (n=1), **(iii)** 0.3mg/kg CD45-ADC on day-10 (n=1), **(iv)** 0.3mg/kg CD45-ADC + nonmyeloablative 260cGy TBI on day -1 (n=1).

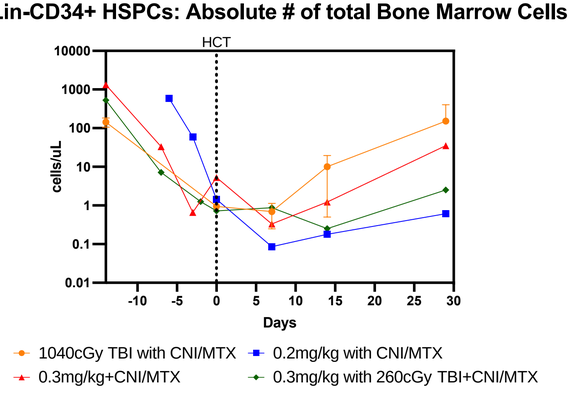


RESULTS

CD45-ADC dosed at 0.2mg/kg or 0.3mg/kg depletes HSPCs similarly to myeloablative TBI

Comparing the depletion of bone marrow lineage-negative CD34+ (Lin-CD34+) hematopoietic stem and progenitor cells across cohorts. i-iv. Percentage (top) and absolute numbers in cells/uL (bottom) depletion of the bone marrow Lin-CD34+ HSPC population at the nadir after conditioning



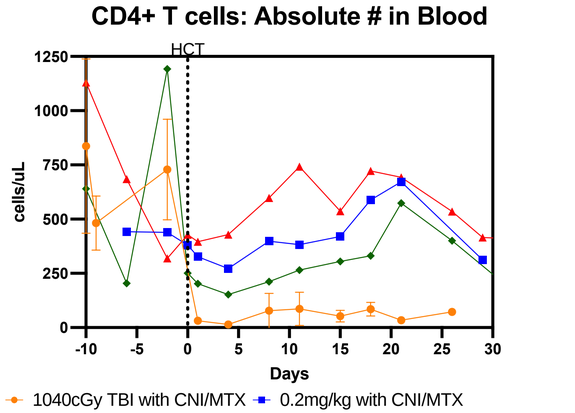


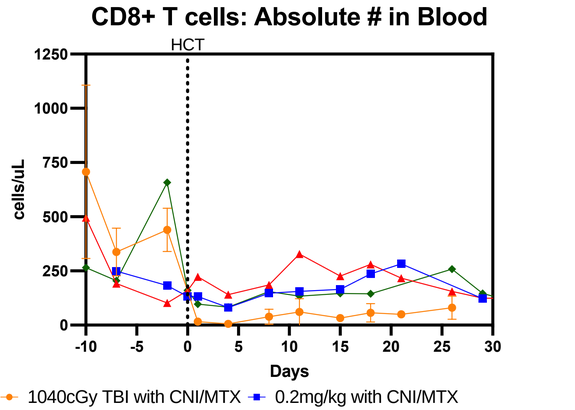
- Myeloablative TBI led to a 99.4% depletion of CD34+Lin- HSPCs compared to 99.8% in cohort ii, 99.6% in cohort iii, and 99.9% depletion in cohorts iv.

RESULTS

CD45-ADC led to less T-cell depletion compared to myeloablative TBI

Comparing the depletion of CD4+ and CD8+ T-cells across cohorts. i-iv. depletion of CD4+ T-cells (top) and CD8+ T-cells (bottom) in cells/uL.



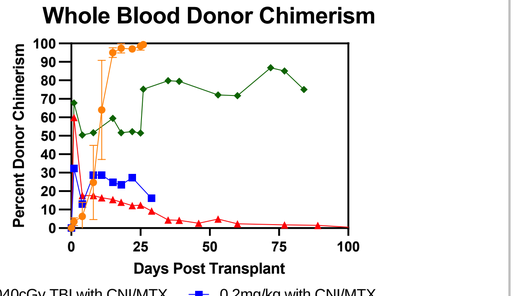


- Myeloablative TBI led to a 94.9% depletion of CD4+ T-cells compared to 26% in cohort ii, 65%, and 68.4% in cohort iv.
- Myeloablative TBI led to a 96.4% depletion of CD8+ T-cells compared to 46.9% in cohort ii, 55.2% in cohort iii and 63.5% in cohort iv.

RESULTS

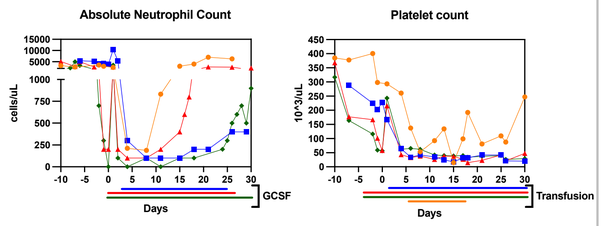
CD45-ADC with 260cGy TBI leads to durable donor chimerism after haploidentical HCT

Comparison of whole blood chimerism assessed by microsatellite analysis through the first 100 days post-transplant in cohorts i-iv.



- Myeloablative TBI leads to 100% donor chimerism by d+30 post-transplant.
- Likely due to less T-cell depletion compared to myeloablative TBI, cohorts ii and iii demonstrated mixed chimerism, and eventual transplant rejection.
- To increase T-cell depletion, a single non-myeloablative dose of 260cGy TBI was added to CD45-ADC (cohort iv). **This led to durable whole blood donor chimerism through the length of analysis (75% on d+84, animal sent to necropsy for GVHD).**

Neutrophil and platelet reconstitution



- Neutrophil and platelet engraftment appear delayed following CD45-ADC compared to myeloablative TBI

CONCLUSIONS

- CD45-ADC resulted in significant HSPC depletion, comparable to myeloablative-TBI.
- The combination of CD45-ADC with a single non-myeloablative 260cGy dose of TBI led to stable donor chimerism.
- These pilot results suggest that CD45-ADC may be a successful addition to HCT conditioning, even across major MHC barriers.