Single Agent CD45-targeted Antibody Drug Conjugate Enables Full Mismatch Allogeneic Hematopoietic Stem Cell Transplantation in a Murine HSCT Model

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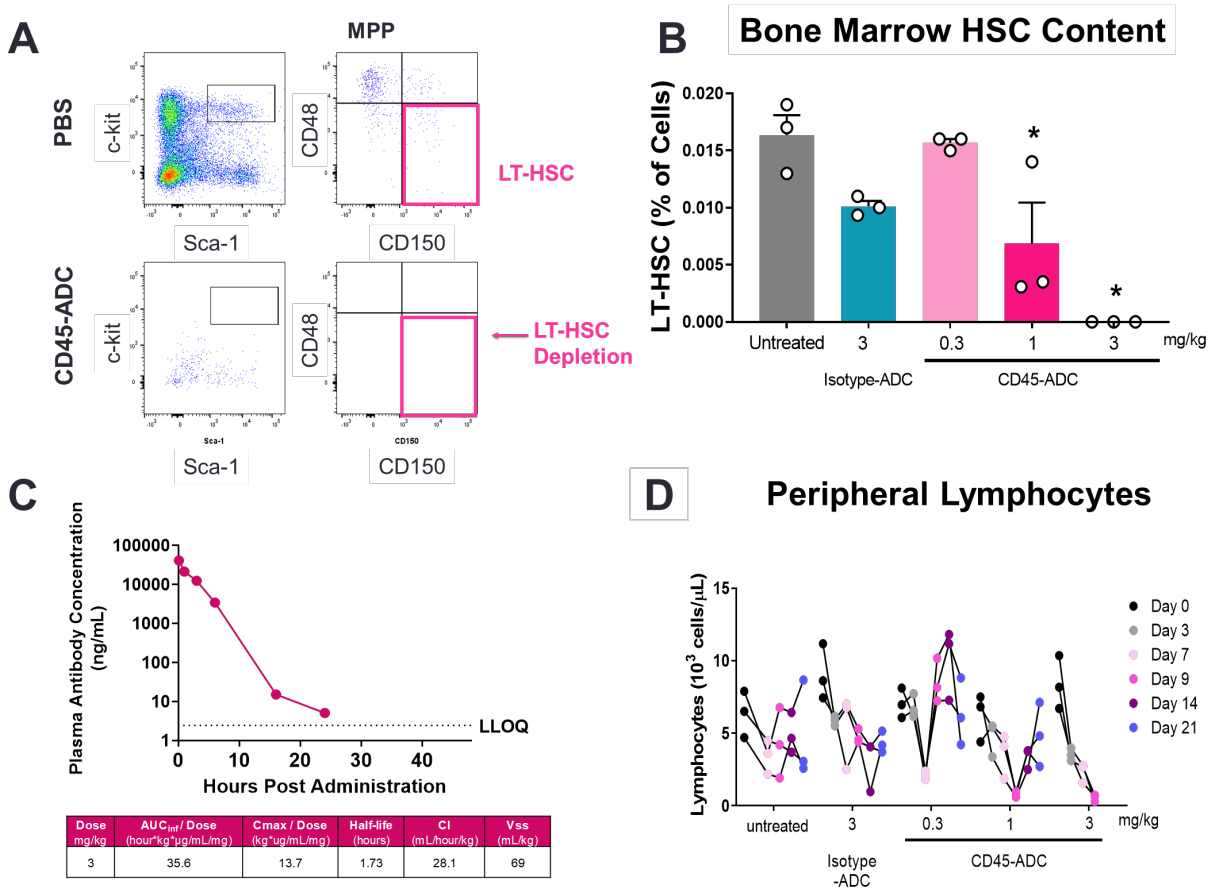
Background

- Hematopoietic stem cell transplant (HSCT) is a potentially curative treatment for malignant and non-malignant disorders (e.g. genetic disorders and autoimmune disease).
- Current regimens for patient preparation, or conditioning, prior to HSCT limit the use of this curative procedure due to regimen-related mortality and morbidities, including risks of organ toxicity, infertility, and secondary malignancies.
- To address these issues, we are developing novel antibody drug conjugates (ADCs) to provide the benefit of full-intensity conditioning to remove disease-causing cells while reducing the severity of conditioning-related adverse events in HSCT.
- We have developed a novel anti-CD45 ADC targeting HSC and immune cells in mice engineered to have rapid clearance. The aim of this study was to determine if it can be used to enable full mismatch allogeneic HSCT in a murine model.

CD45-ADC effectively depletes murine HSCs and lymphocytes



Dose mg/kg	AUC_{inf} / Dose (hour*kg*µg/mL/mg)	Cmax / Dose (kg*ug/mL/mg)	Half-life (hours)	Cl (mL/hour/kg)	Vss (mL/kg)
3	35.6	13.7	1.73	28.1	69

Figure 1: CD45-ADC was dosed on day 0. Bone marrow was collected on day 2 and HSC depletion assessed by flow cytometry. **(A)** Phenotypic long-term HSC (LT-HSC, Lin− cKit+ Sca1+ CD150+ CD48-) depletion 2 days after single dose of CD45-ADC (3 mg/kg) administration. **(B)** % LT-HSC depletion. **(C)** CD45-ADC (3 mg/kg) half-life in C57Bl/6 mice is 1.7 hours. **(D)** Peripheral lymphocytes reach nadir by day 9 post administration of CD45-ADC (3 mg/kg), indicating effective depletion by CD45-ADC. *p <0.05 when comparing CD45-ADC treated mice versus untreated mice.

CD45-ADC enables congenic transplant in murine model

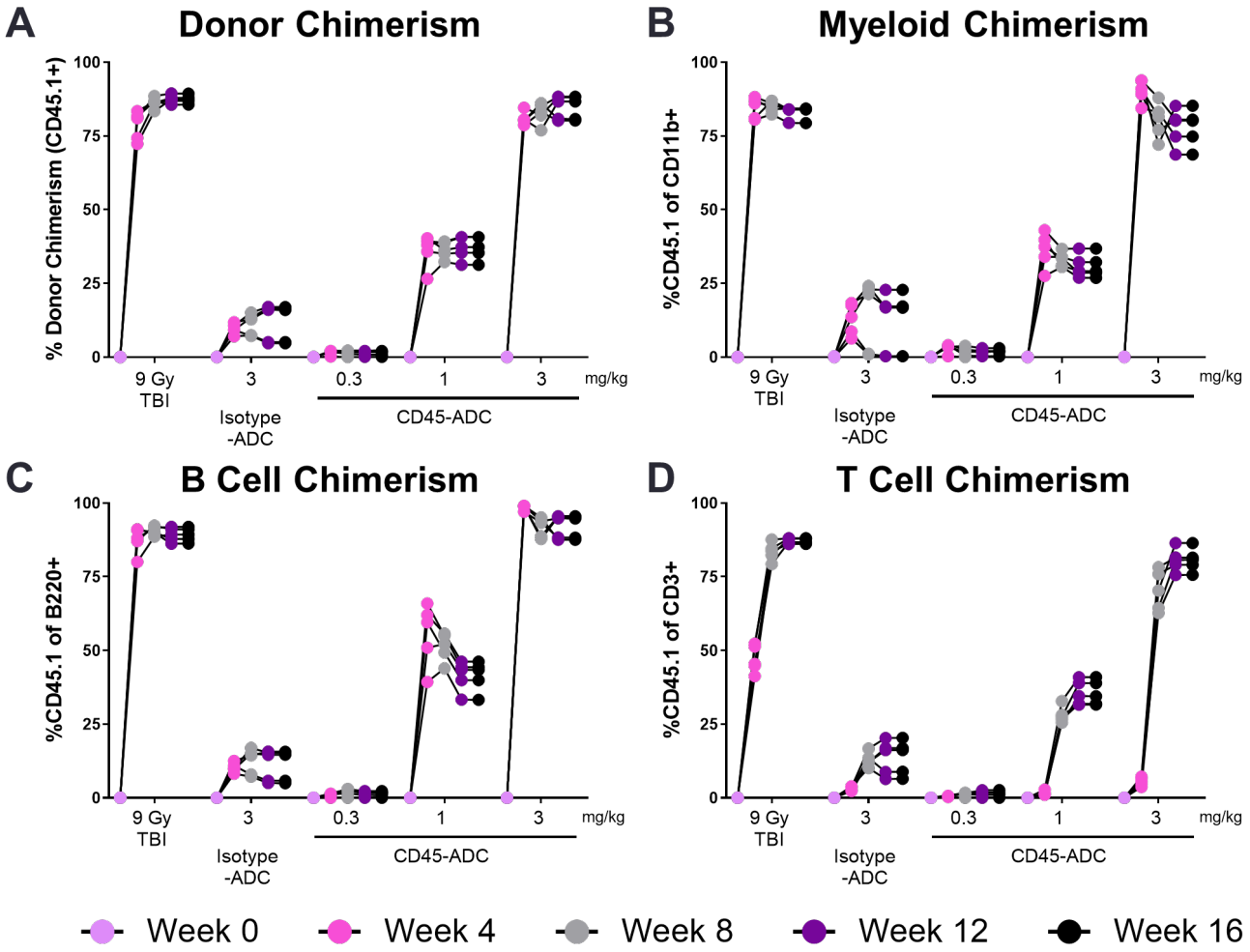


Figure 2: C57Bl/6 mice were conditioned with 9 Gy TBI, Isotype-ADC, or CD45-ADC and transplanted with whole bone marrow from B6.SJL (B6 CD45.1+) mice. **(A)** Peripheral donor chimerism is >85% in mice conditioned with CD45-ADC (3 mg/kg) through 16 weeks post transplant, comparable to mice conditioned with 9 Gy TBI. **(B-D)** Peripheral donor engraftment is multilineage.

A single dose of CD45-ADC enables minor mismatch allogeneic transplant of Balb/c CD45.1 donor cells into DBA/2 recipients

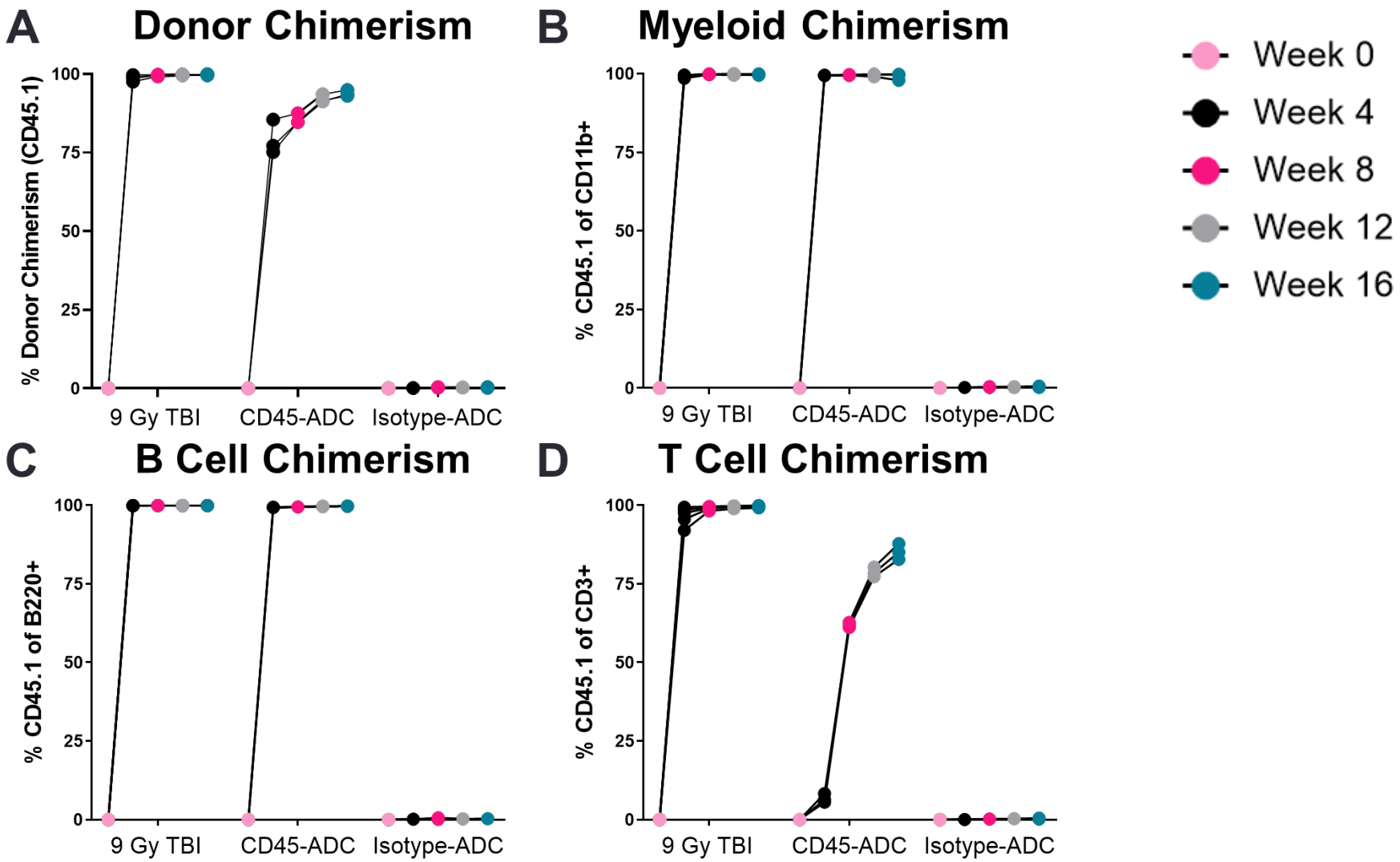


Figure 3: C57BL/6 mice were conditioned with 3 mg/kg Isotype-ADC or CD45-ADC. CD45-ADC enables ≥ 95% donor chimerism **(A)** and peripheral donor engraftment through 16 weeks is multilineage **(B-D).**

A single dose of 5 mg/kg CD45-ADC enables allogeneic transplant of Balb/c CD45.1 donor cells into C57BL/6 recipients

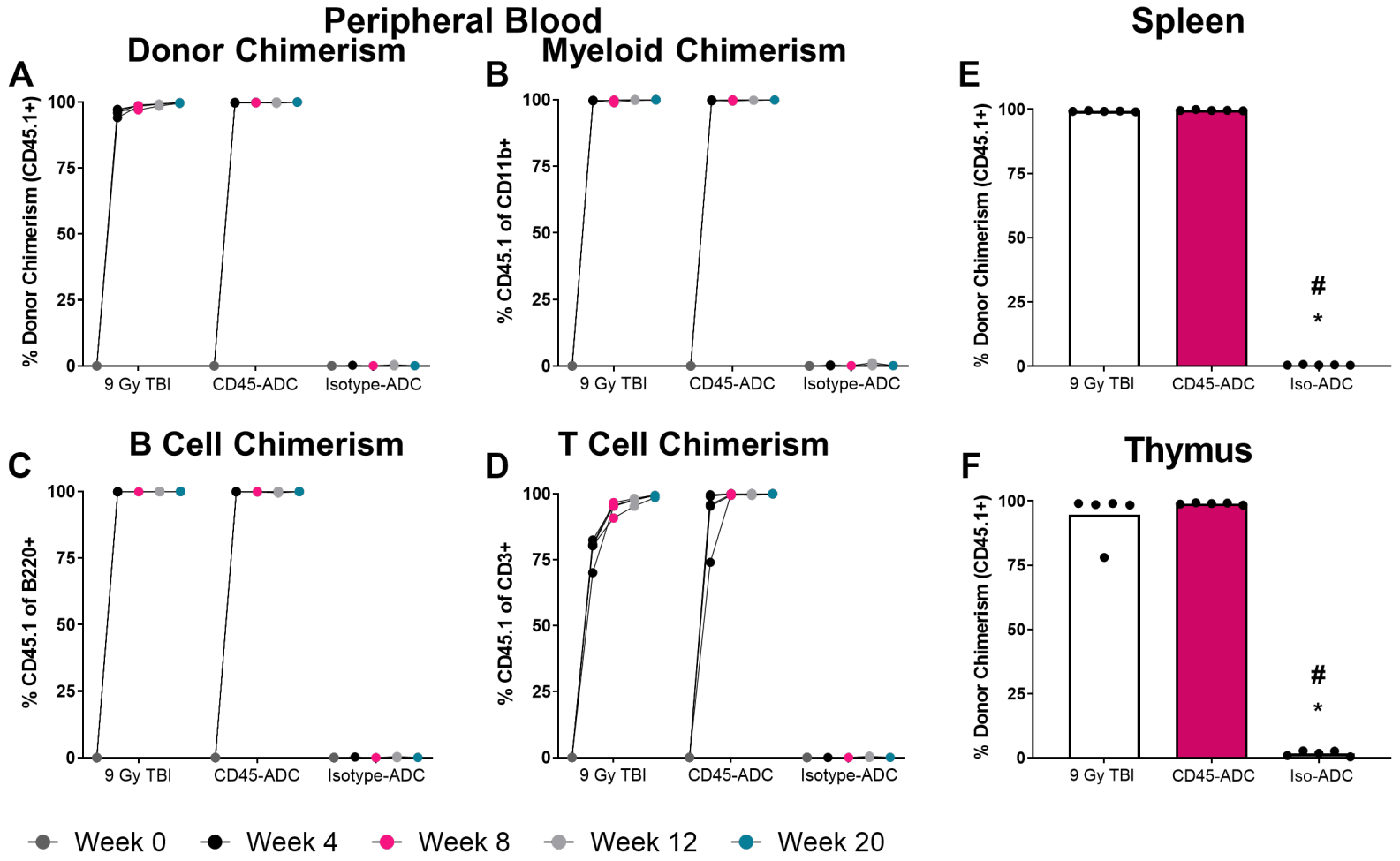


Figure 4: C57BL/6 mice were conditioned with 5 mg/kg Isotype-ADC or CD45-ADC. CD45-ADC enables ≥ 95% donor chimerism **(A)** and peripheral donor engraftment is multilineage **(B-D)**. Terminal splenic (E) and thymic (F) chimerism in CD45-ADC conditioned mice were similar to TBI. *p<0.05 versus TBI; #p<0.05 versus CD45-ADC; ANOVA with post hoc Tukey's multiple comparisons test.

Conclusions

- A single dose of the tool CD45-ADC is fully myeloablative and enables complete chimerism in a full mismatch allogeneic HSCT model without the need for additional conditioning agents.
- This targeted approach for safer conditioning could improve the risk-benefit profile for allogeneic and haploidentical HSCT and may extend the curative potential of this modality.

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