University of Basel

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Universitätsspital Basel

HEMATOPOIETIC STEM CELLS EXPRESSING ENGINEERED CD45 ENABLE A NEAR UNIVERSAL TARGETED THERAPY FOR HEMATOLOGIC DISEASES

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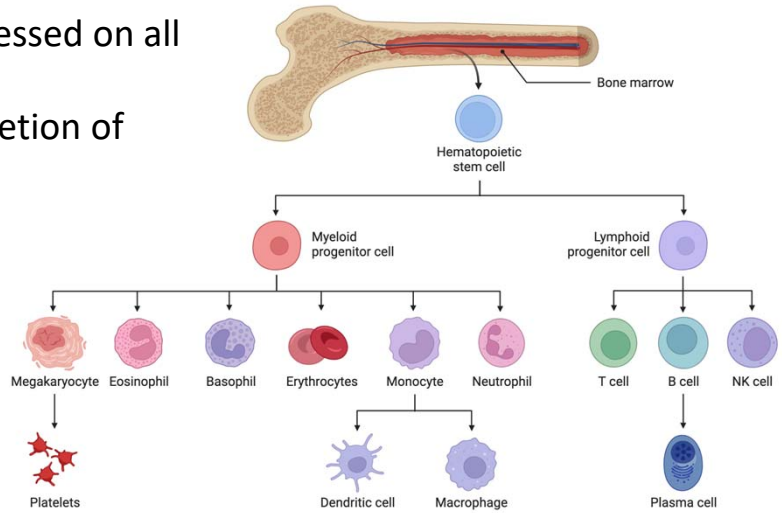
Departement Biomedizin Basel

Background

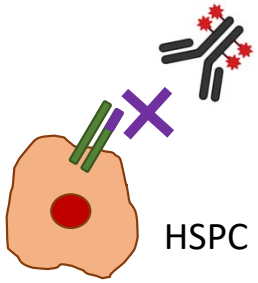
- Untargeted cytotoxic conditioning regimens for hematopoietic stem cell transplantation are associated with transplant related morbidity and mortality.

- The pan-hematopoietic marker CD45 is exclusively expressed on all nucleated hematopoietic cells, could enable targeted depletion of the entire hematopoietic system including HSCs.



Aim

- Identify and characterize CD45 variants that shield from a novel, concurrently developed, highly potent CD45-antibody drug conjugate (CIM053-ADC) while preserving CD45 function.

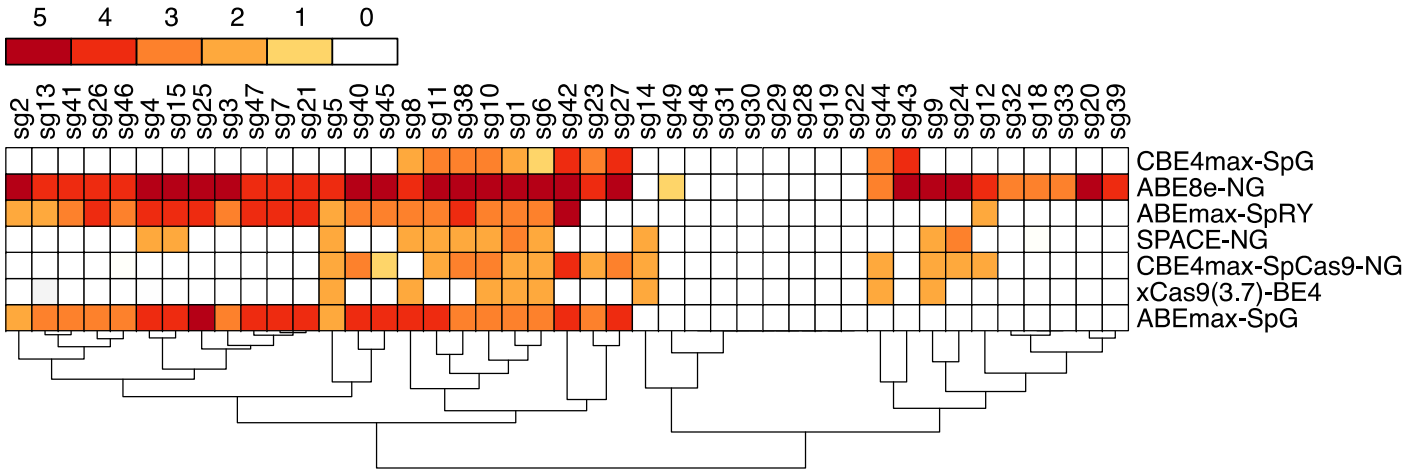


- In vivo selective tumor ablation with preserved hematopoiesis.

Identification of base editable CD45 extracellular domain regions to achieve shielding from targeted therapies

CD45

Domain 1 and 2



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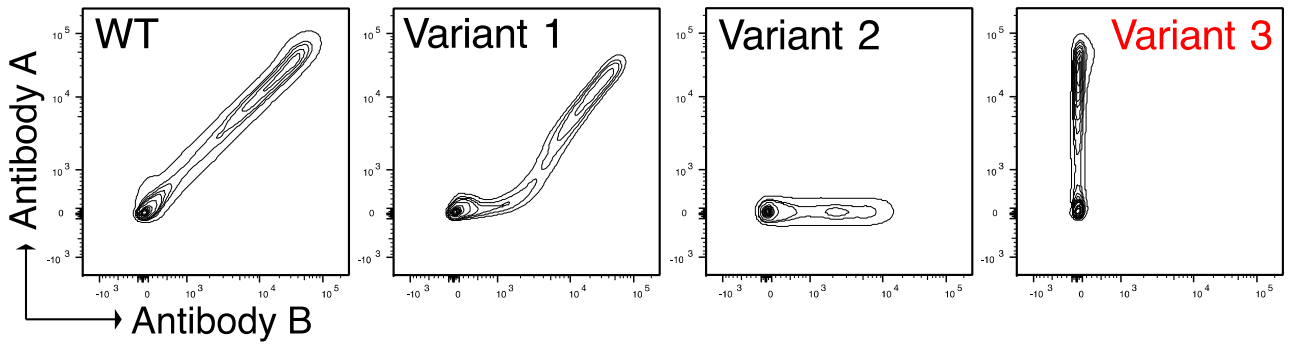
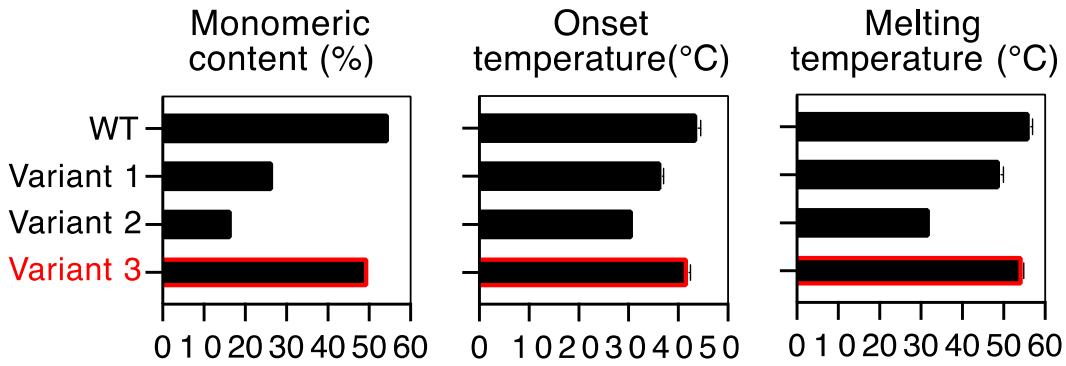
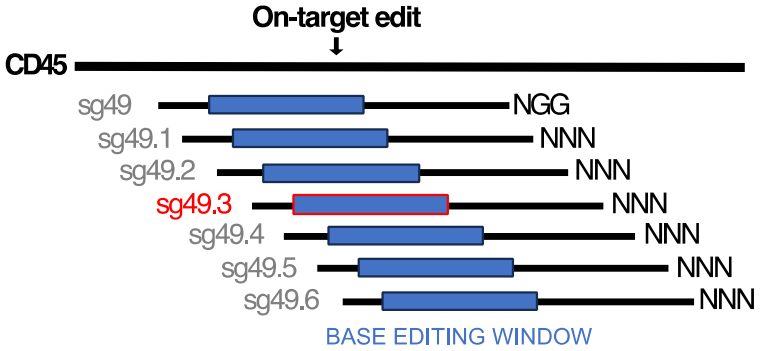
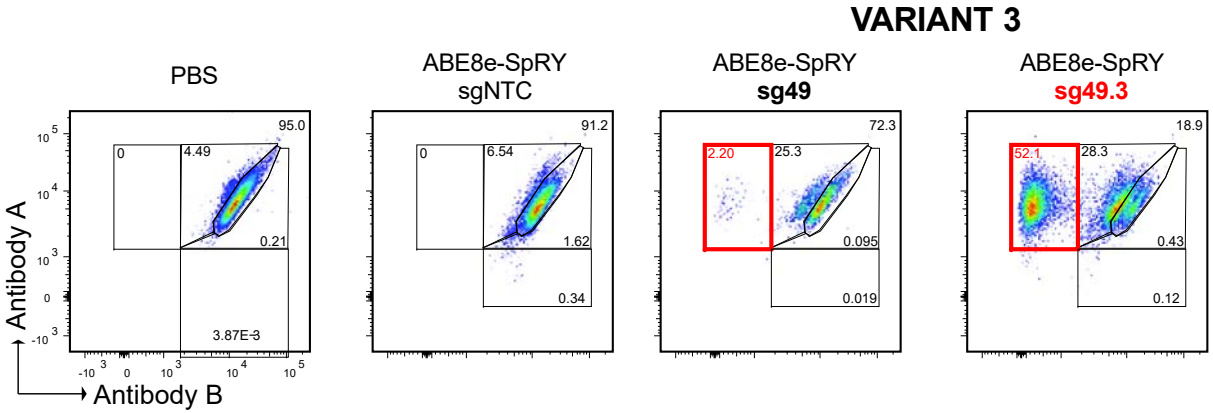




Base editing in CD34+ hematopoietic stem and progenitor cells (HSPCs) in vitro





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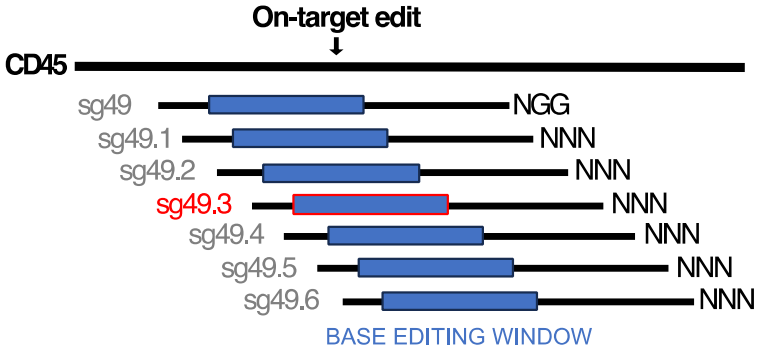

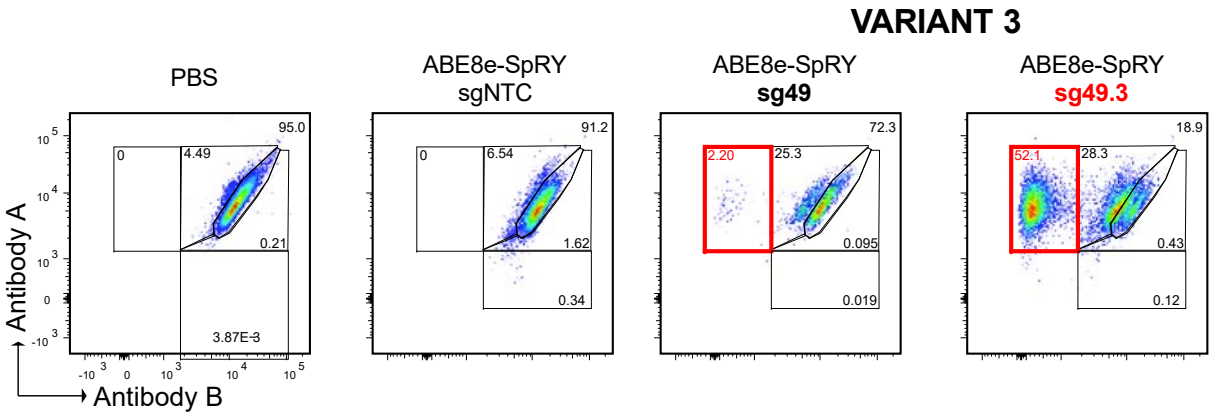

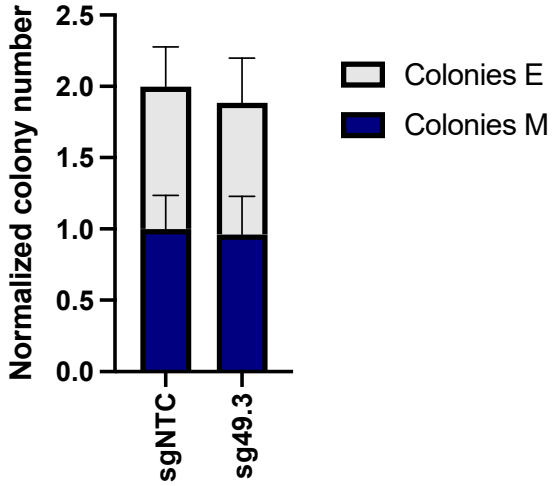

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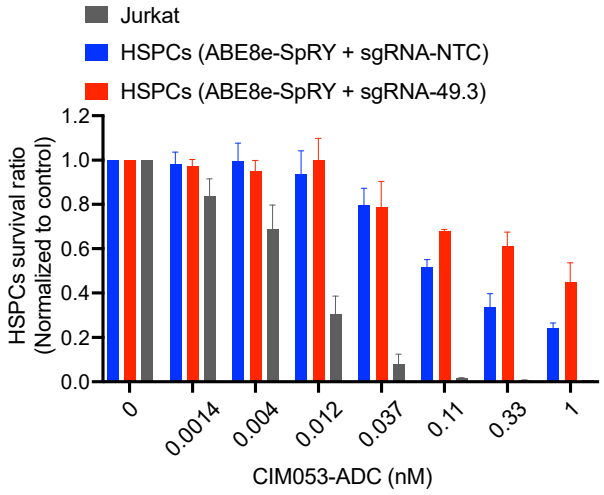
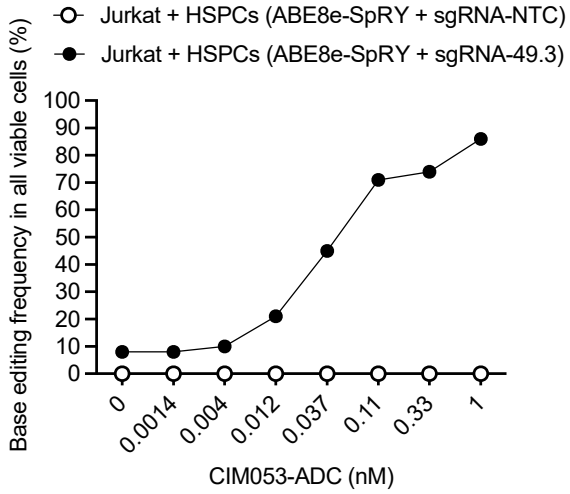
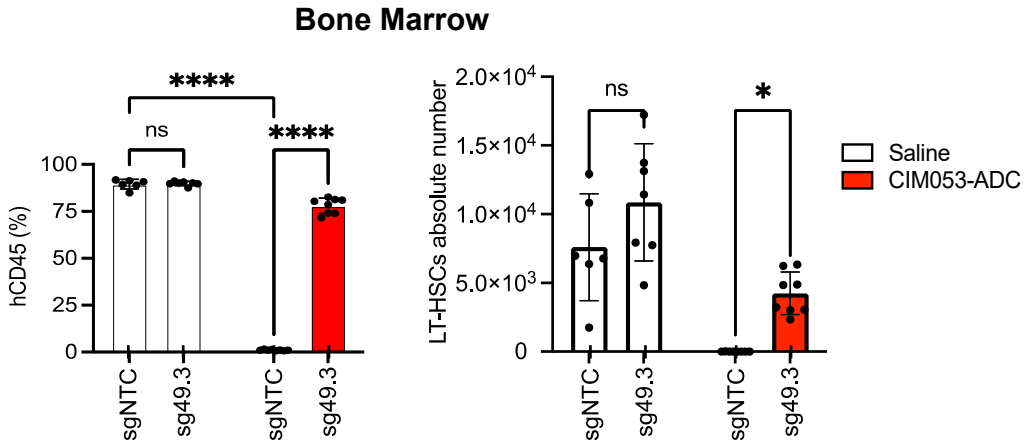
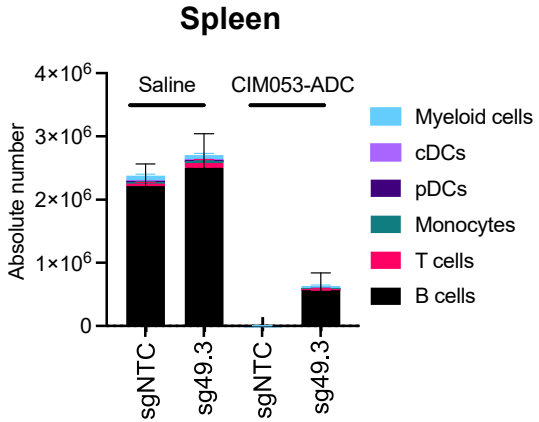
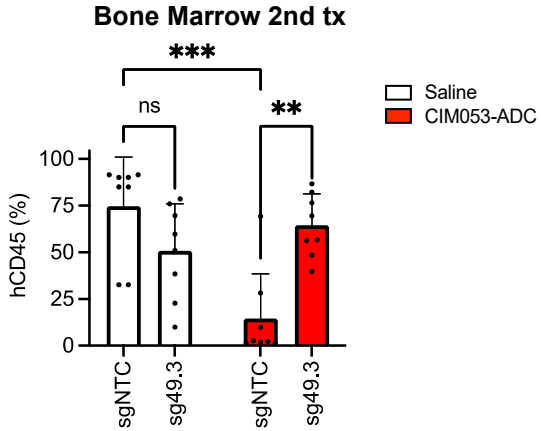


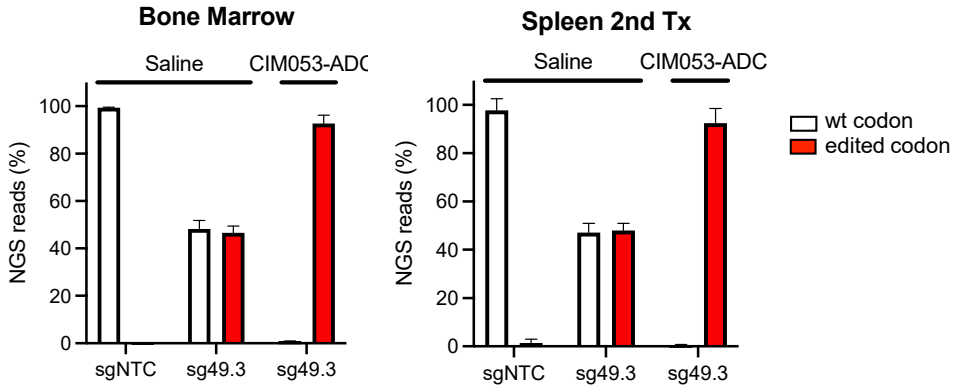


Variant 3 shields hematopoietic cells from CIM053-ADC killing in vivo

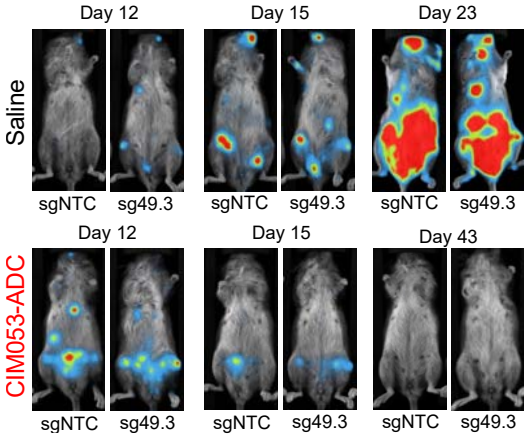


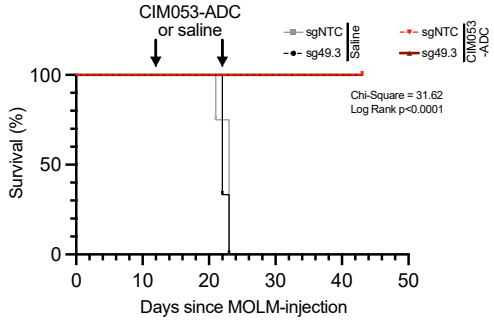


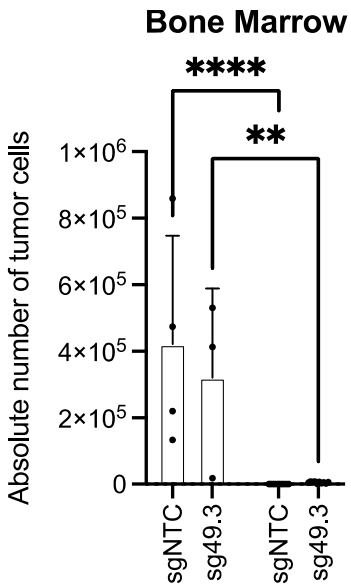


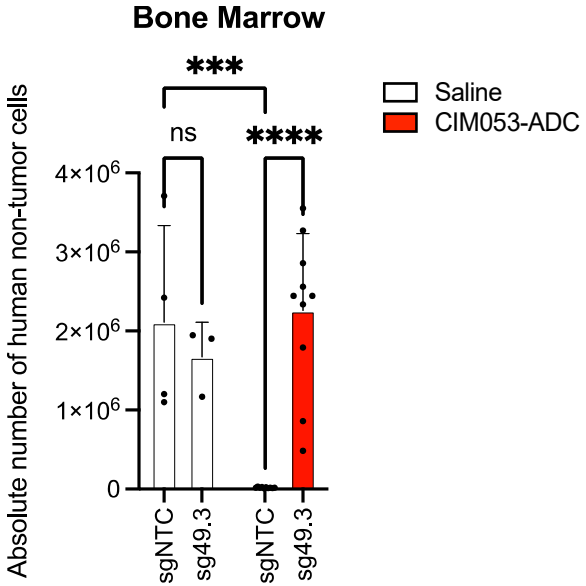


In vivo CIM053-ADC mediated selective tumor eradication with preserved hematopoiesis









Conclusions

- Identified CD45 variants with favorable biophysical properties.
- Generation of a novel, potent anti-CD45 antibody drug conjugate (CIM053-ADC) which depletes tumor cells and HSPCs. CD45 variant 3-expressing HSPCs are shielded from CIM053-ADC while maintaining intact protein properties.
- Edited HSPCs engraft, differentiate in vivo and are shielded from CIM053-ADC.
- Selective tumor and unedited human cell depletion in vivo with preservation of edited human hematopoietic cells.
- We envision that CIM053-ADC can be used for a targeted and less toxic conditioning protocols for HSC transplantation. Furthermore, CD45 shielded HSPCs could enable higher, longer and/or repetitive antibody dosing, potentially allowing for post-transplant adjustment of donor chimerism and targeted treatment of minimal residual disease in $CD45^{+}$ malignancies.

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➡ **Poster #**