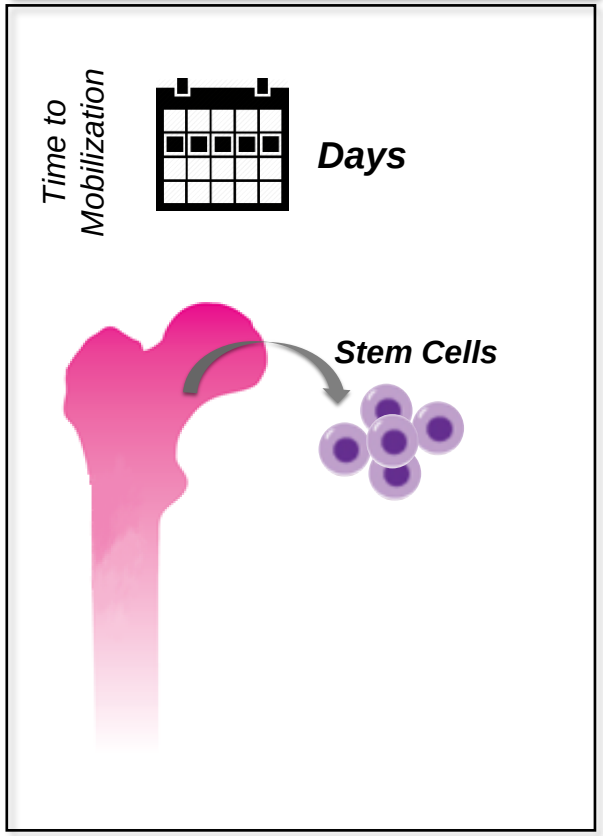
MGTA-145, in Combination with Plerixafor, Rapidly Mobilizes Large Numbers of HSCs in Humans That Can Be Gene Edited with CRISPR/Cas9 and Mediate Superior Engraftment to Standard-of-Care

Kevin A. Goncalves, PhD
Magenta Therapeutics

MGTA-145 + Plerixafor Enables Rapid and Robust Mobilization of Hematopoietic Stem Cells (HSCs)

G-CSF Induced Mobilization



65,000 transplants annually
70% use mobilized peripheral blood

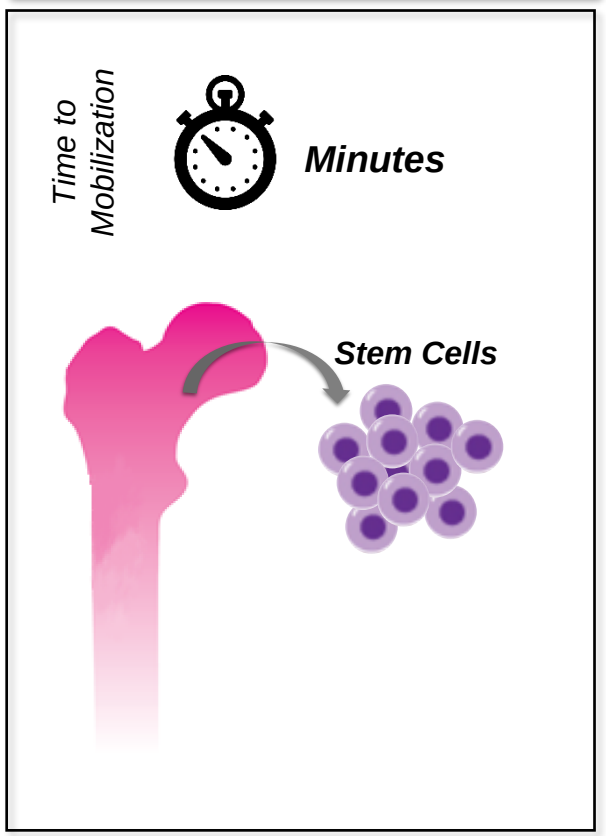
Limitations to Current Mobilization Standard of Care:

- Requires 5+ days
- Variable yields
- Adverse events, some for the duration of mobilization
- Contraindicated/precautions in certain diseases

Benefits of Novel Mobilization:

- Shorten mobilization phase
- Fewer/shorter duration of adverse events
- On demand mobilization enables more flexible scheduling

Magenta Mobilization



MGTA-145, In Combination with Plerixafor, Rapidly Mobilizes HSCs

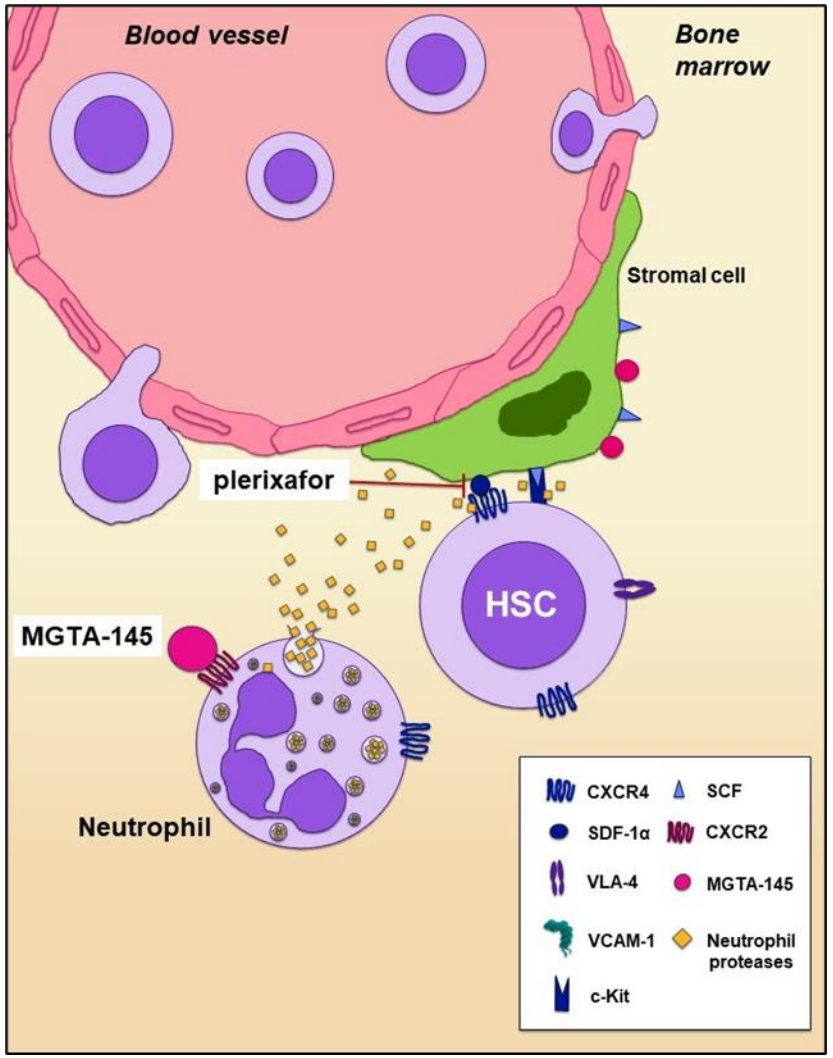
NOVEL MOBILIZATION AGENT

MGTA-145 (GroβT) + **plerixafor** (AMD3100)

CXCR2 agonist *CXCR4 antagonist*

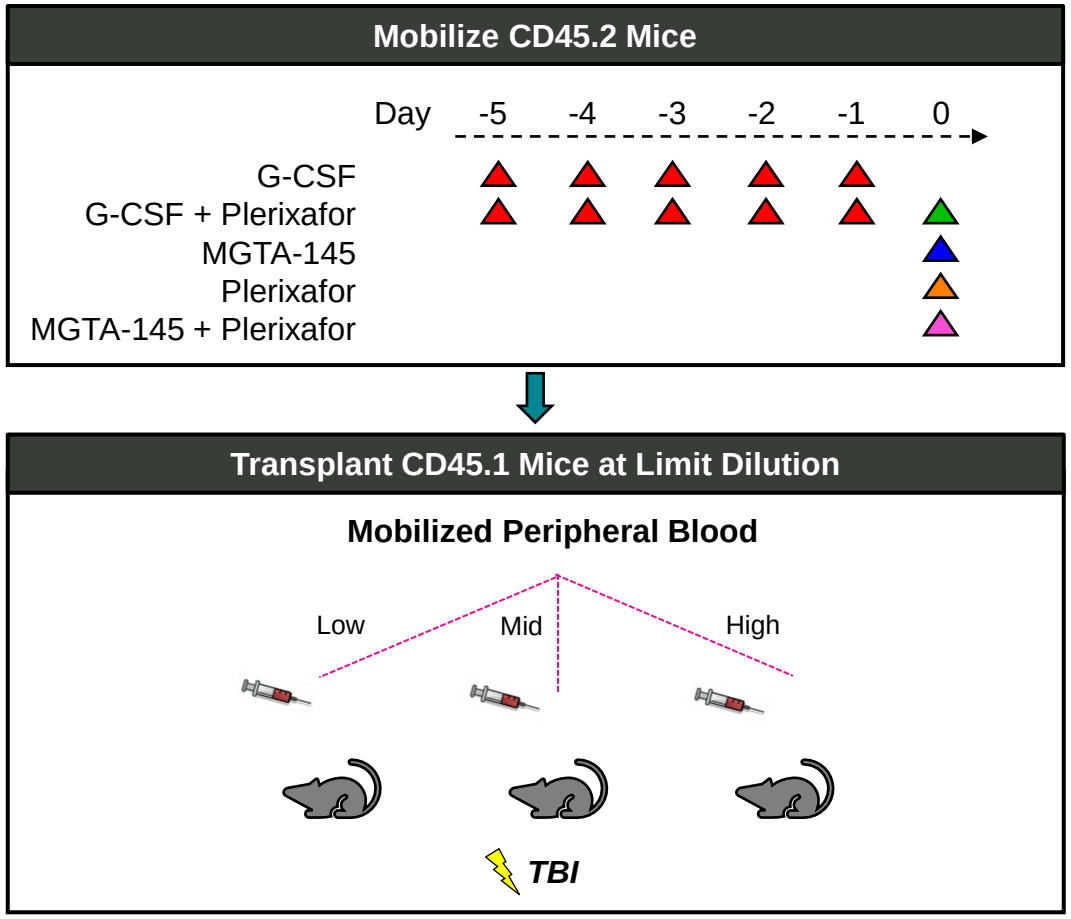
KEY FEATURES

- Rapid & robust mobilization of HSCs in mice and non-human primates
  [Hoggatt et al, *Cell* 2018; Goncalves et al, *Blood* 2018; Karpova et al, *JCI* 2019]
- Single-day dosing and collection
- Well-tolerated
- Mimics physiological response

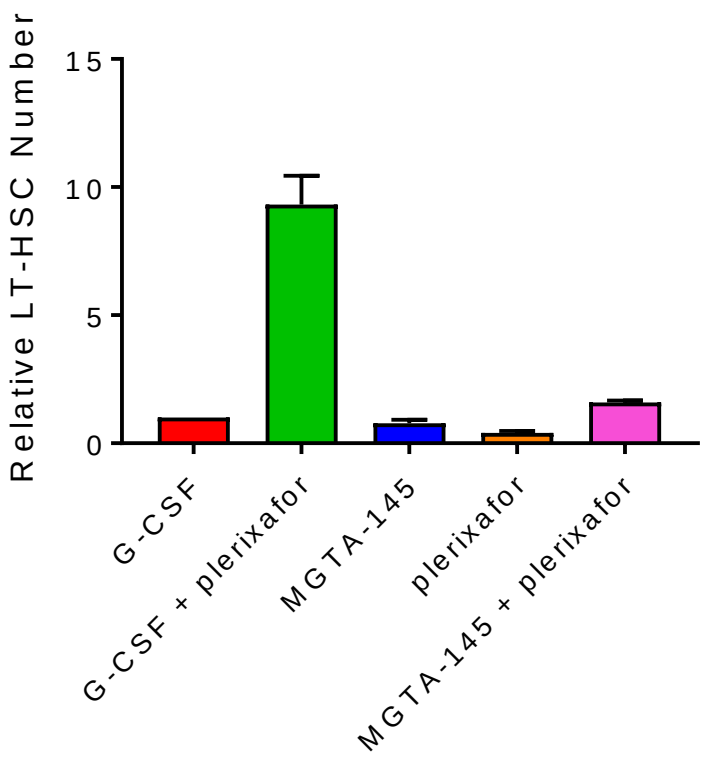


MGTA-145 + Plerixafor Mobilizes Higher Numbers of Mouse HSCs Relative to Standard-of-Care

EXPERIMENTAL SCHEMA

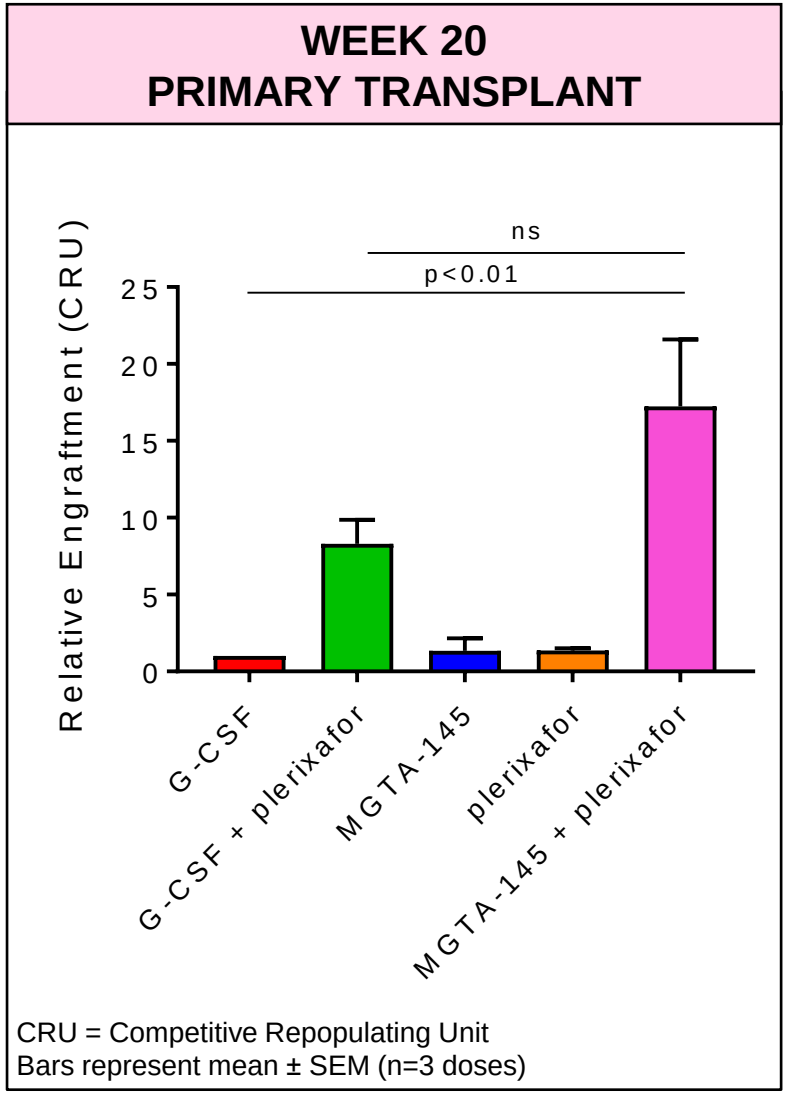


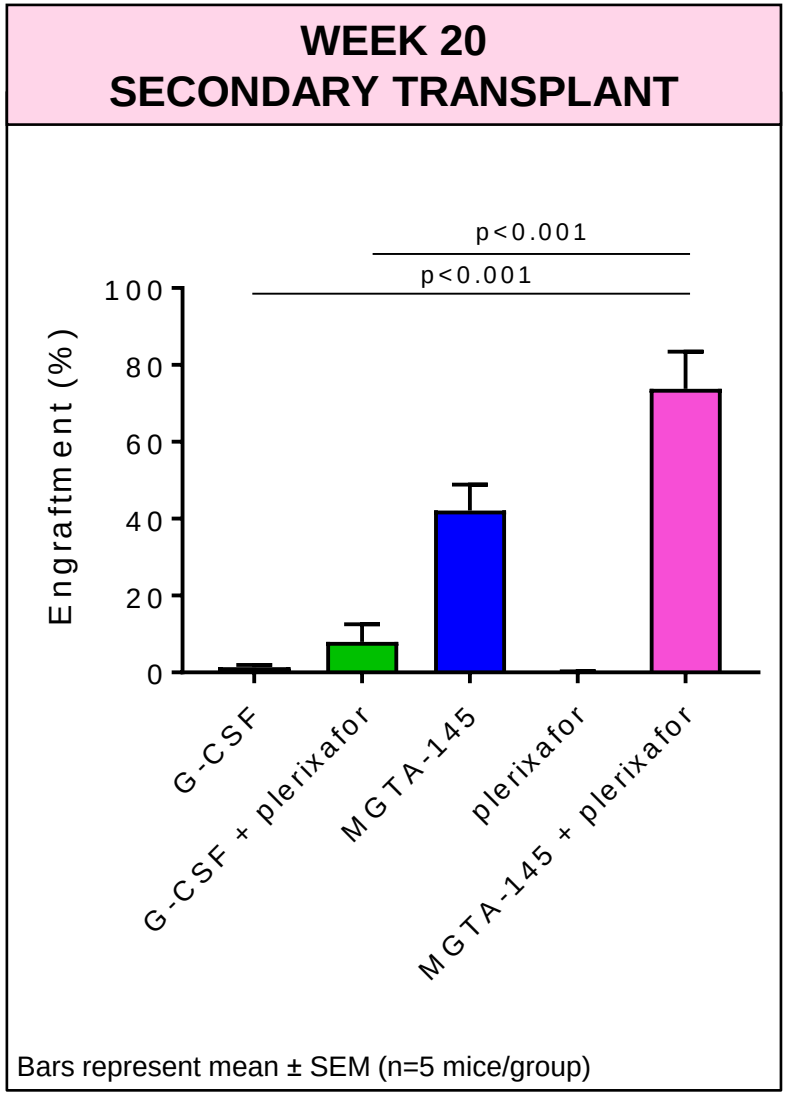
LONG-TERM (LT)-HSC MOBILIZATION



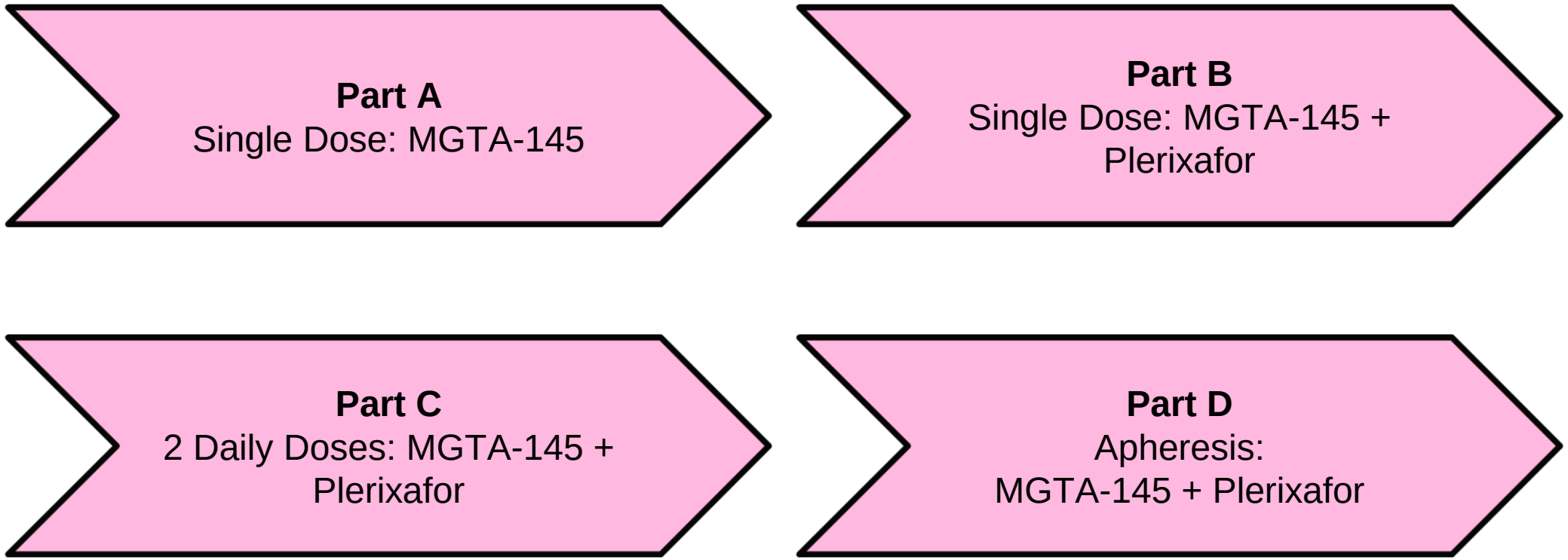
LT-HSCs defined as Lin$^-$c-Kit$^+$Sca1$^+$CD150$^+$CD48$^-$
Bars represent mean ± SEM (n=2 independent experiments)

MGTA-145 + Plerixafor Mobilizes Higher Numbers of HSCs with Durable Primary and Secondary Engraftment in Mice Relative to Other Mobilization Regimens





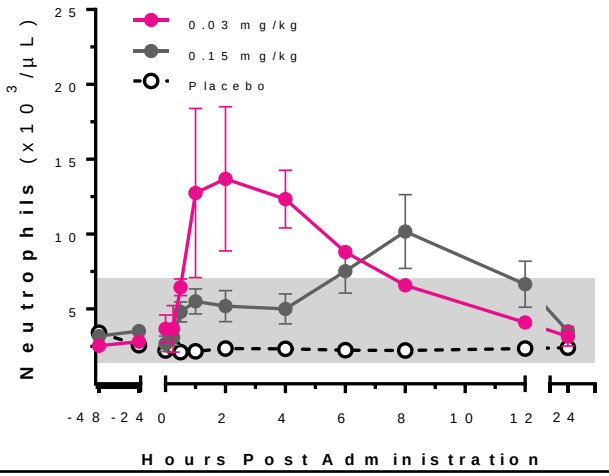
MGTA-145-101 Healthy Volunteer Study Schema



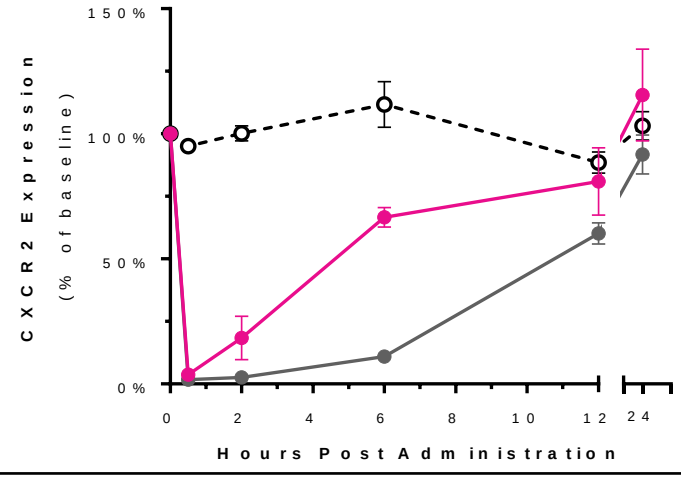
DiPersio et al. TCT 2020

MGTA-145 has Rapid On-Target Neutrophil PD with Minimal Activation

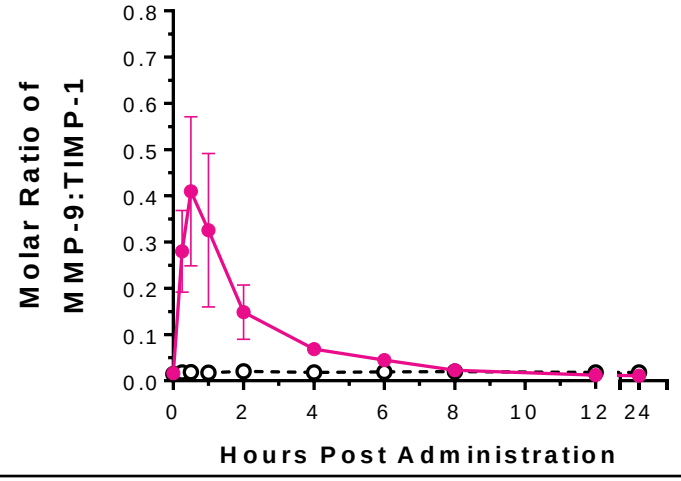
NEUTROPHIL MOBILIZATION



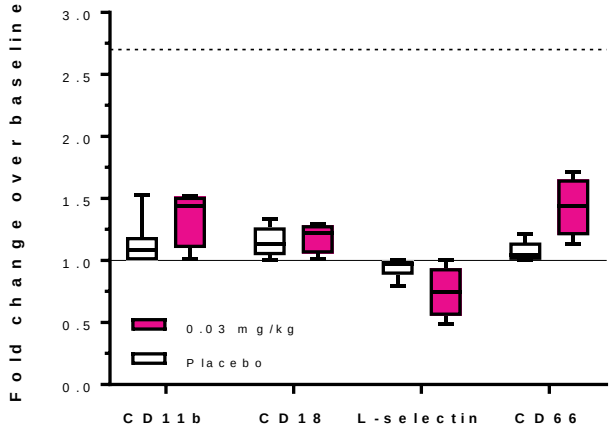
CXCR2 TARGET DOWN-MODULATION



MMP-9 RELEASE



MINIMAL NEUTROPHIL ACTIVATION



Dotted line represents the anticipated effect of 5 days of G-CSF [Falanga *et al*., *Blood*. 1999]

MGTA-145 Enables Reliable Collection of >2x10^6 CD34$^+$ Cells in One Day

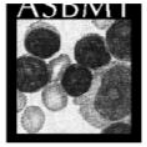
Part B: Mobilization at 0.015 versus 0.03 mg/kg, 2h stagger

Mobilization Regimen	**MGTA-145 dose** (mg/kg)	**Subjects** (n)	**Peak CD34$^+$** (#/µL) Median (range)	**% ≥ 20** / µL	**% ≥ 40** / µL
MGTA-145 + Plerixafor	0.015	6	**35** (17-78)	**83%** (5/6)	**33%** (2/6)
	0.03	6	**40** (18-63)	**83%** (5/6)	**50%** (3/6)
Plerixafor	0	14	**26** (13-78)	**64%** (9/14)	**21%** (3/14)

Part D: Apheresis Collection at 0.015 versus 0.03 mg/kg dose, 2h stagger

MGTA-145 dose (mg/kg)	**Subjects** (n)	**Total CD34$^+$ Yield** (x10^6) Median (range)	**CD34$^+$ / kg** (x10^6)		
			Mean	Median	Range
0.015	4	310 (118-525)	4.0	3.7	1.5 - 7.0
0.03	4	321 (239-500)	4.1	4.3	2.7 – 5.3

CD34+ CD90+ Cells Contain HSCs Responsible for Robust Engraftment in Humans and Non-human Primates



Transplantation of Highly Purified CD34+Thy-1+ Hematopoi… Breast Can…

Robert S.
Wendy W…
Irving L.
William …

ELSEVIER

Experimental Hematology 28 (2000) 858–870

EXPERIMENTAL HEMATOLOGY

Transplantation with selected autologous peripheral blood CD34+Thy1+ hematopoietic stem cells (HSCs) in multiple myeloma: Impact of HSC dose on engraftment, safety, and immune reconstitution

Maur…
Catherine …
Philippe Maz…
Gilbert Fine[c], Kerry A…

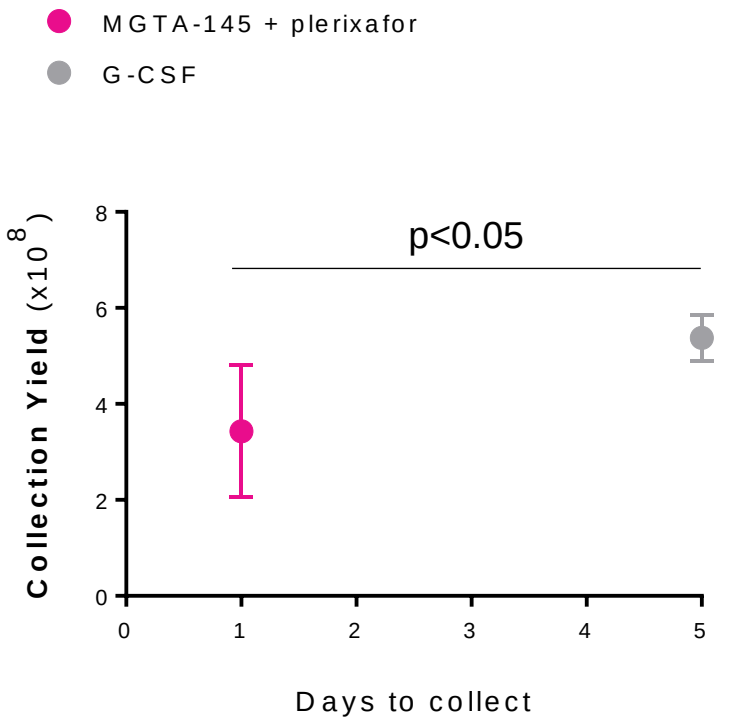
Sci Transl Med. 2017 November 01; 9(414): . doi:10.1126/scitranslmed.aan1145.

A distinct hematopoietic stem cell population for rapid multilineage engraftment in nonhuman primates

Stefan Radtke[#1,2], Jennifer E. Adair[#1,3], Morgan A. Giese[1], Yan-Yi Chan[1], Zachary K. Norgaard[1], Mark Enstrom[1], Kevin G. Haworth[1], Lauren E. Schefter[1], and Hans-Peter Kiem[1,3,4,*]

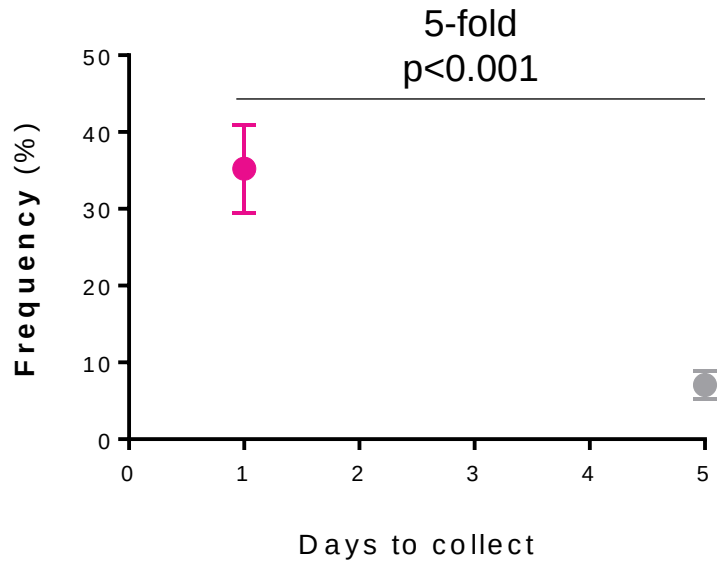
MGTA-145 + Plerixafor Enables Greater Collection of HSCs after Apheresis in a Phase 1 Healthy Volunteer Study

CD34+ NUMBER

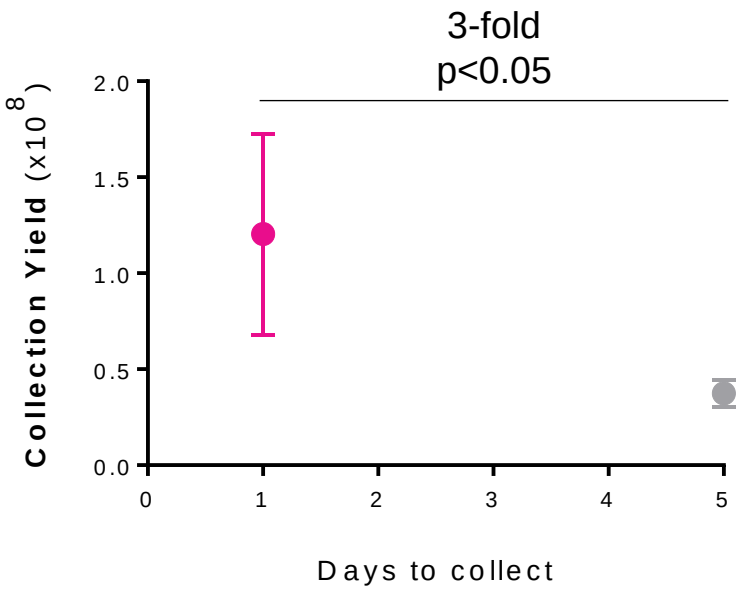


MGTA-145 + plerixafor: n=7 donors (mobilized with 0.015 or 0.03 mg/kg MGTA-145)
G-CSF: n=3 donors

CD34+CD90+CD45RA- FREQUENCY



CD34+CD90+CD45RA- NUMBER



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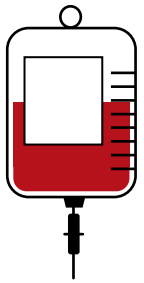
MGTA-145 + Plerixafor CD34+ Cells from Phase 1 Healthy Volunteer Study Show Higher Multilineage Engraftment Compared to G-CSF Mobilized CD34+ Cells in NSG Mice

EXPERIMENTAL SCHEMA

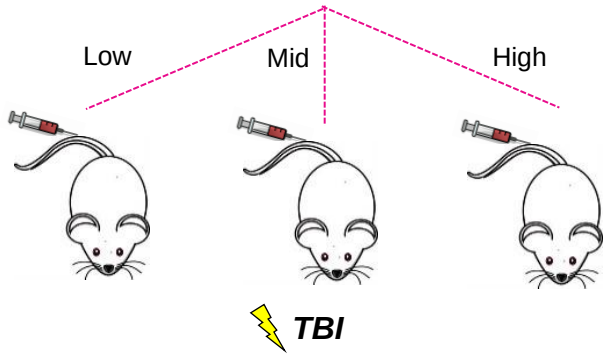
Collect mobilized CD34⁺ cells



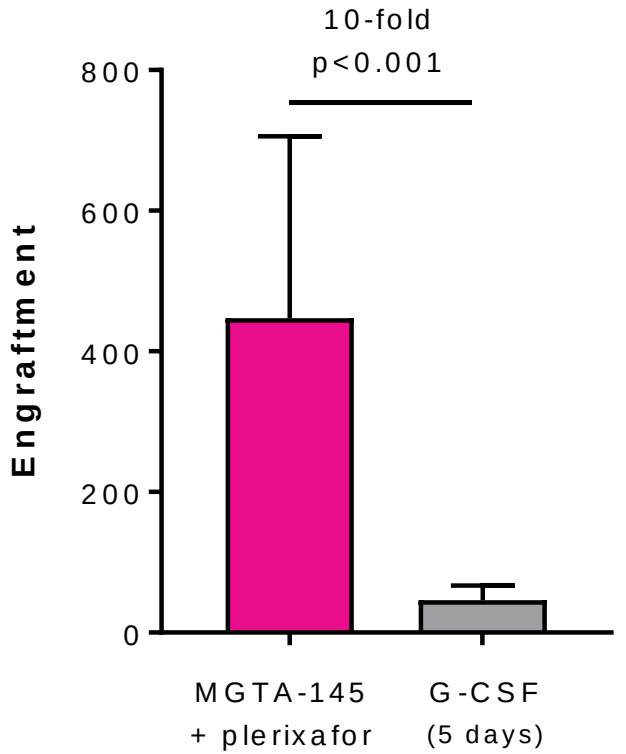
MGTA-145 + plerixafor Apheresis product
(Part D)
vs.
G-CSF-mobilized peripheral blood

Transplant NSG Mice at Limit Dilution

CD34⁺ cell doses

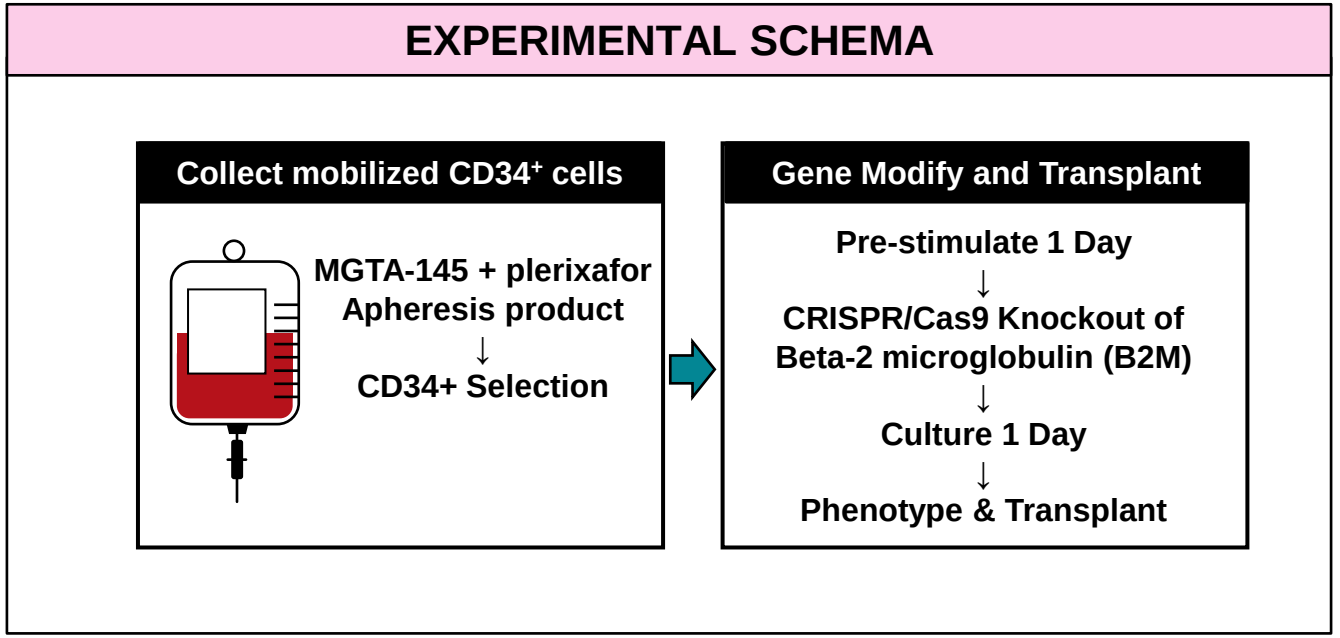


WEEK 12 NSG ENGRAFTMENT



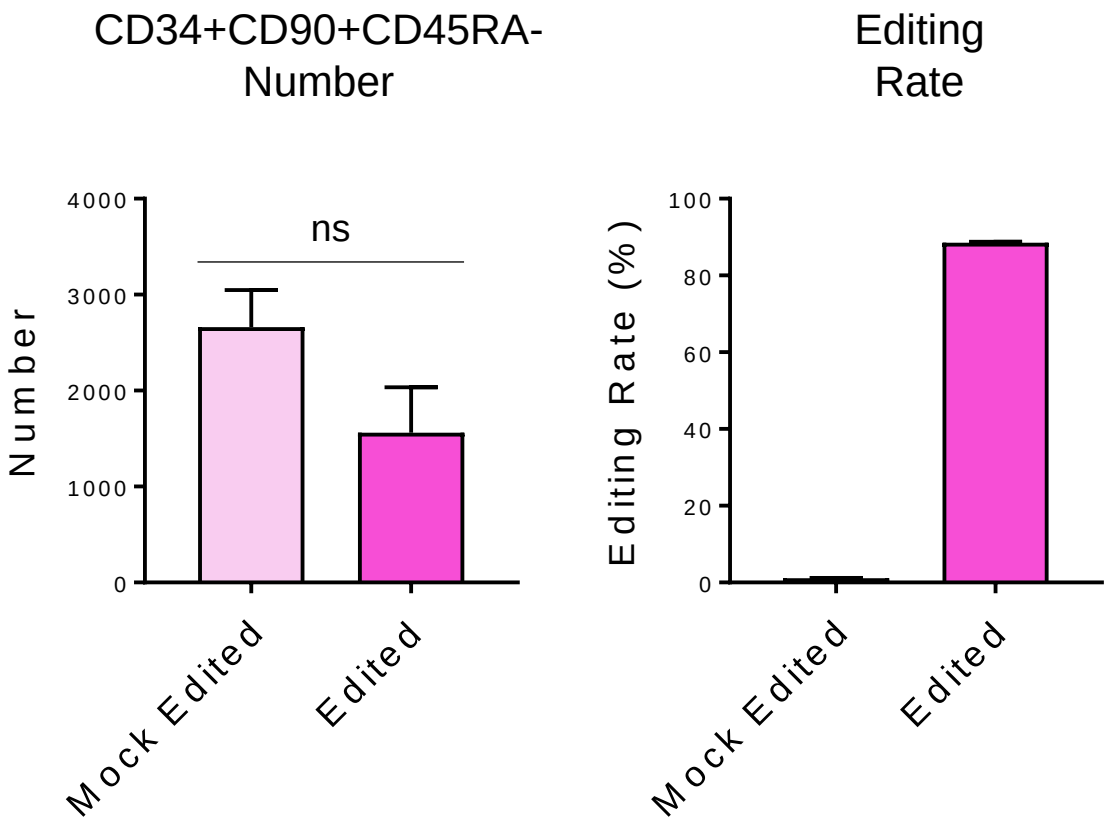
SRC per 1x10⁶ cells ± 95% CI
MGTA-145 + plerixafor: n=2 donors (at 0.03 mg/kg dose level)
G-CSF: n=3 donors
n=7-8 mice per cell dose

Can MGTA-145 + Plerixafor CD34+ Be Gene Modified?



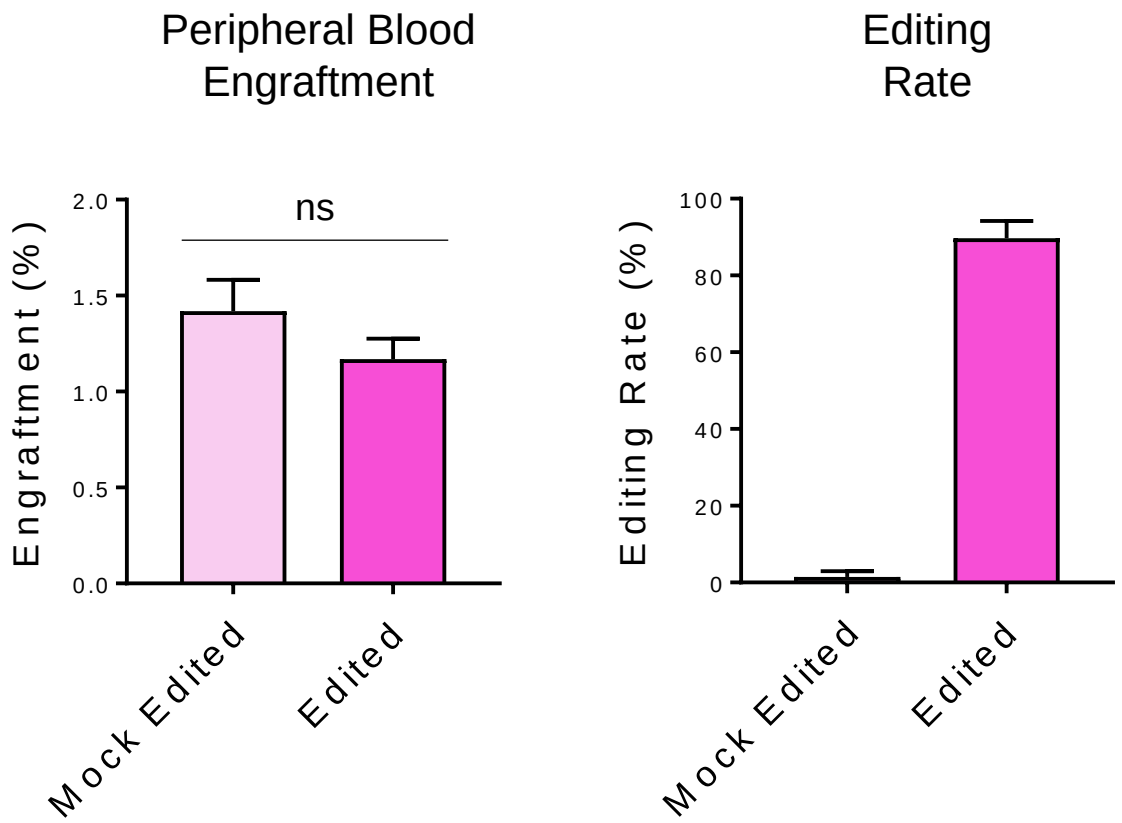
MGTA-145 + Plerixafor CD34+ Cells from Phase 1 Healthy Volunteer Study Can Be Efficiently Gene Modified and Engraft in NSG Mice

IN VITRO GENE EDITING



Mean ± SD (n=2)

WEEK 12 NSG ENGRAFTMENT



n=7-8 mice

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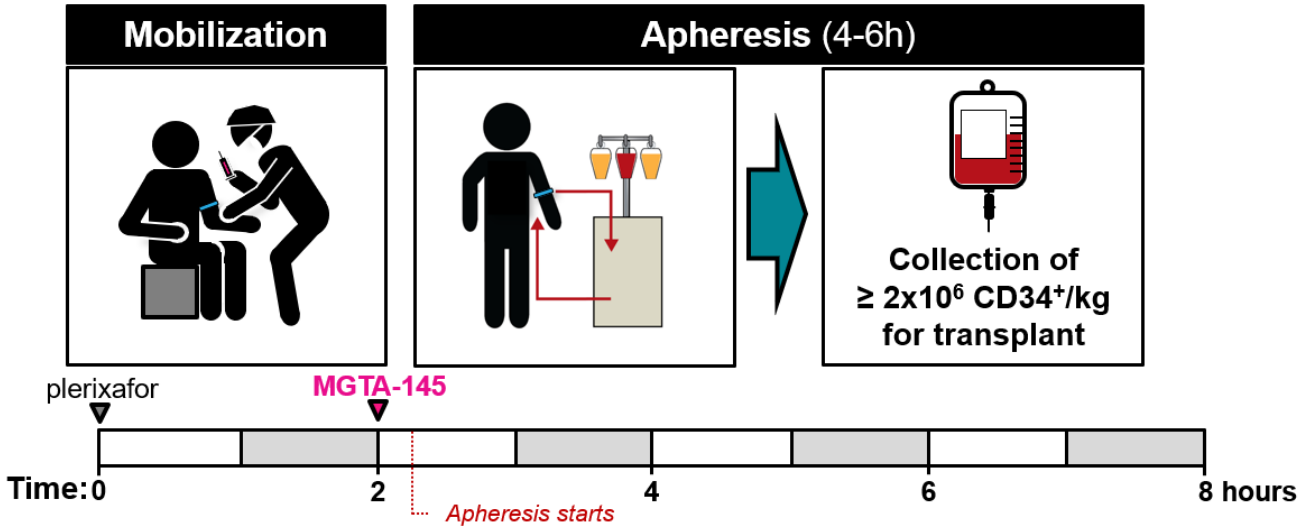
MGTA-145 + Plerixafor Mobilizes High Numbers of Functional HSCs

- MGTA-145 engages CXCR2 on neutrophils to mobilize CD34$^+$ cells into peripheral blood with limited neutrophil activation.
- MGTA-145 in combination with plerixafor reliably mobilizes sufficient HSCs for a transplant.
- MGTA-145 + plerixafor enables collection of high numbers of CD34$^+$ CD90$^+$ cells capable of robust engraftment in NSG mice.
- MGTA-145 + plerixafor CD34+ cells can be efficiently gene-modified and engraft in NSG mice.
- The number of functional stem cells mobilized by MGTA-145 + plerixafor provides a strong rationale for conducting mobilization studies of allogeneic and autologous transplant in autoimmune diseases, hematologic malignancies, and hematopoietic gene therapy.



Acknowledgments

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