MGTA-456 Contains Large Numbers of CD34+CD90+ Hematopoietic Stem Cells Which Contain the NSG Engraftment Activity and Correlate with Time to Neutrophil Recovery Following Transplant into Patients with Hematologic Malignancy

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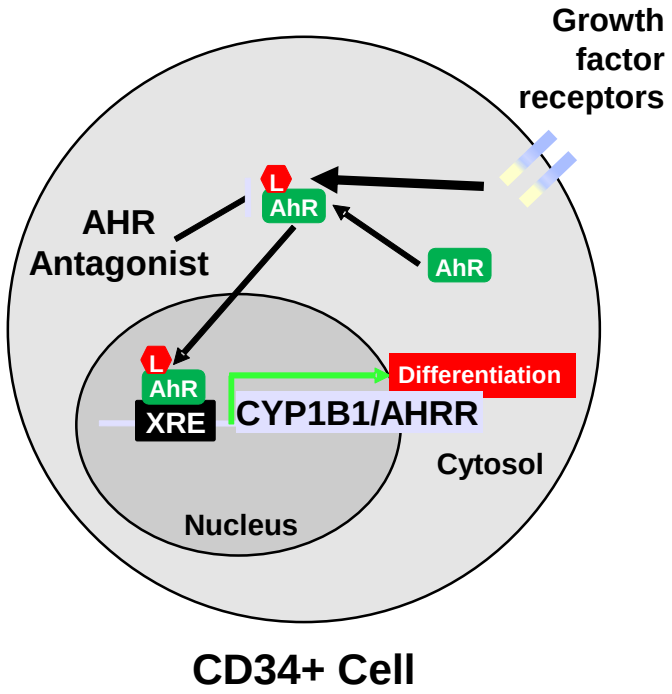
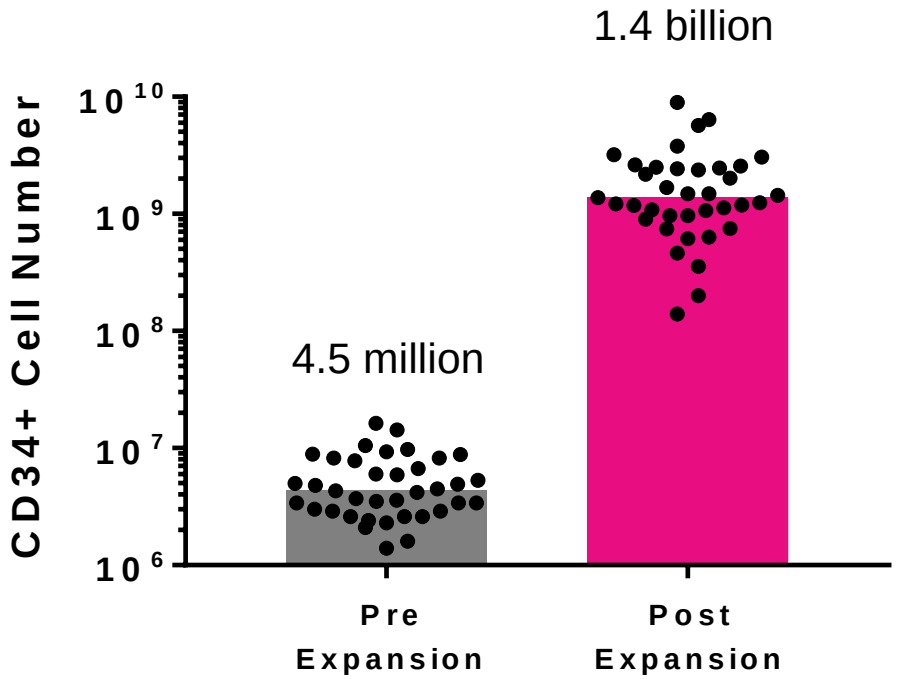
MGTA-456: Aryl Hydrocarbon Receptor (AHR) Antagonism as a Mechanism of HSC Expansion

AHR Antagonist Mediated CD34+ Cell Expansion



Boitano et al., Science 2010

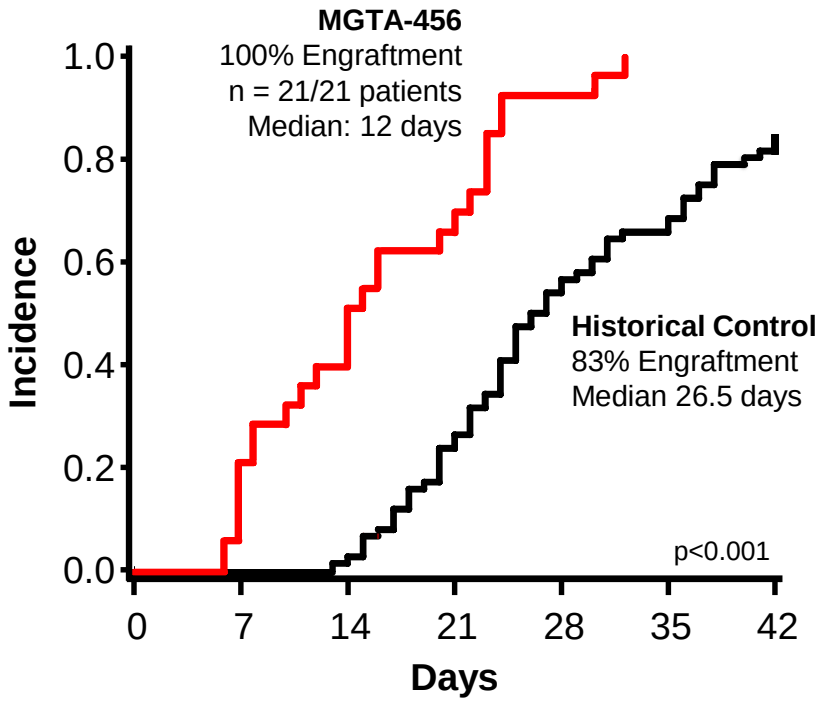
>300-Fold Increase in CD34+ Cell During the Manufacturing Process



Modified from Wagner et al., Cell Stem Cell 2016

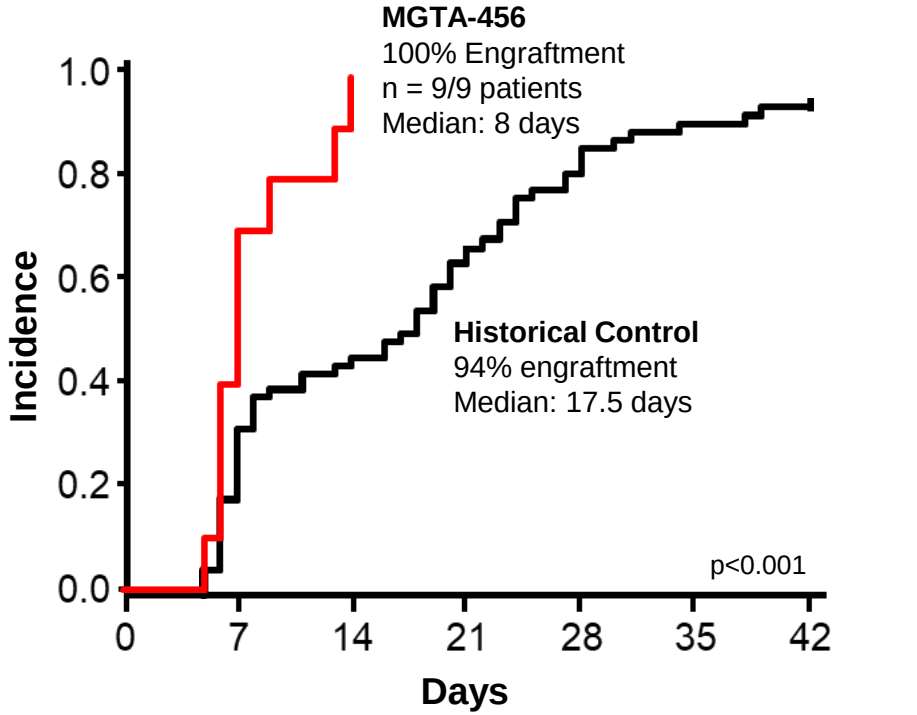
MGTA-456 Has Been Clinically-Validated in Hem/Onc Patients

MYELOABLATIVE CONDITIONING
Flu / Cy / TBI 1320



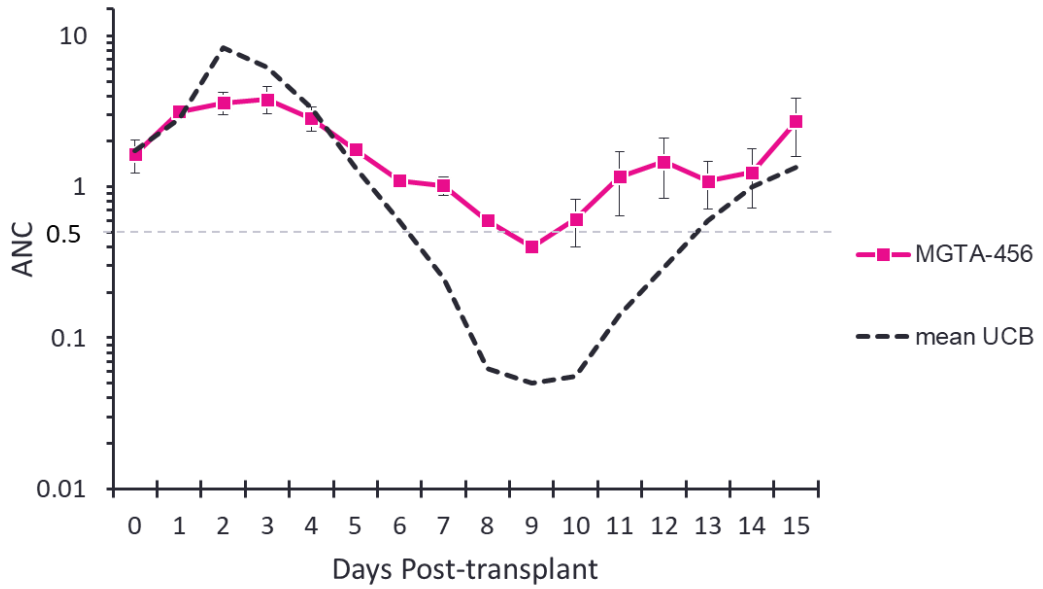
Wagner et al., ASH 2017

NON-MYELOABLATIVE CONDITIONING
Flu / Cy / TBI 200

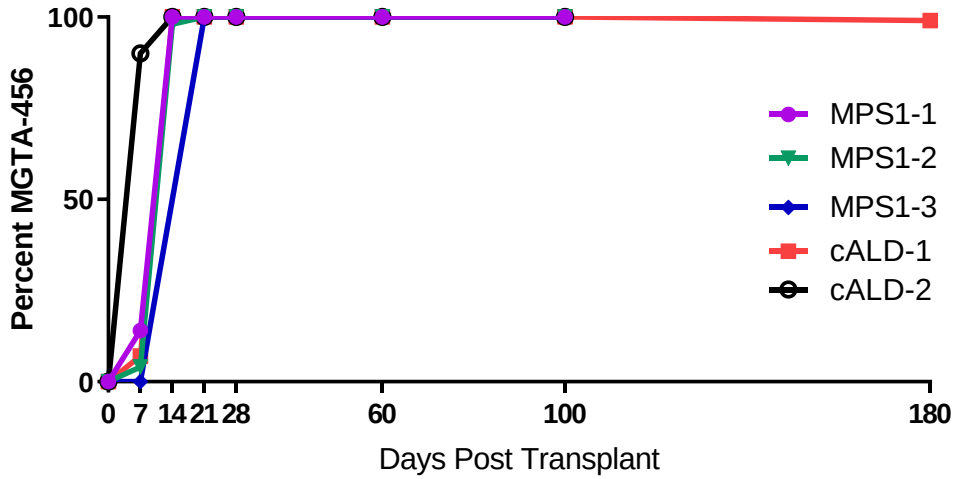


Ongoing MGTA-456 Phase II Trial In Inherited Metabolic Diseases

Neutrophil Recovery



Myeloid Chimerims



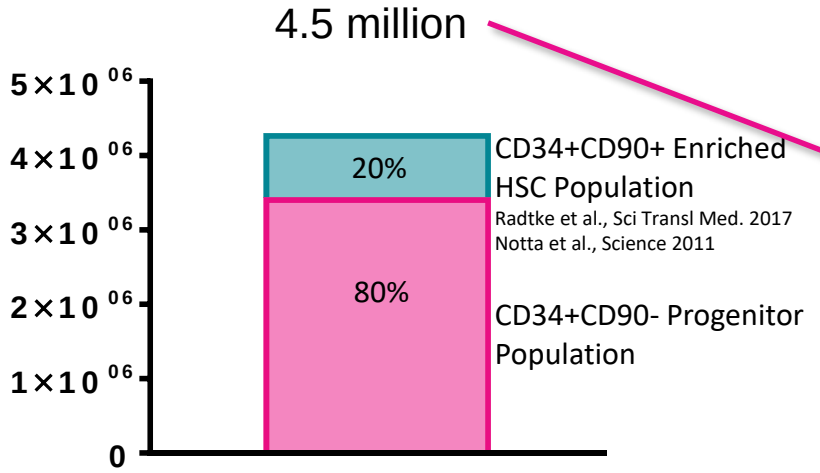
Also see: Paul Orchard, Abstract 122

What Cells In MGTA-456 Are Responsible for Rapid Engraftment

(1) Characterized the cellular composition of MGTA-456
(2) Identify the cells with engraftment activity in mice
(3) Correlate cell doses with neutrophil recovery in humans

Cellular Composition of MGTA-456 Pre and Post Expansion

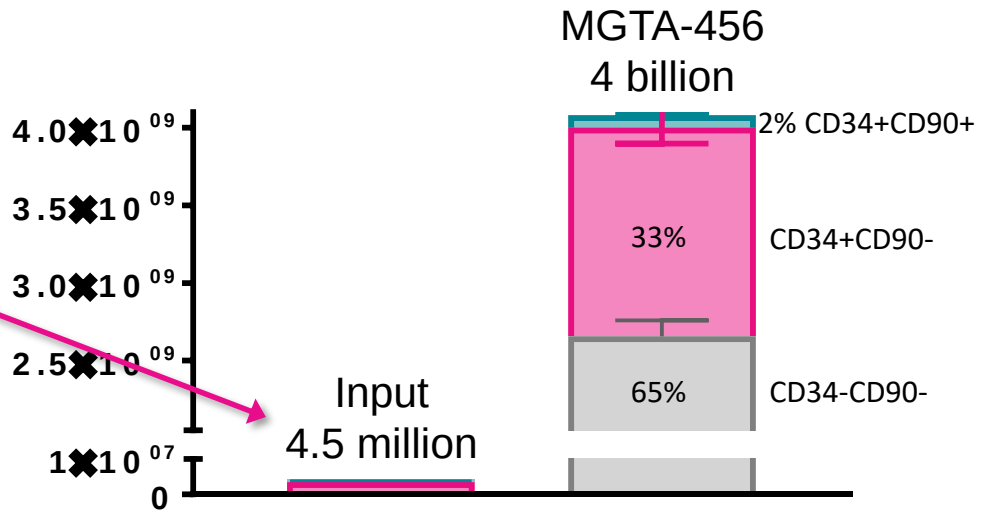
Cellular Composition Pre-Expansion



Population	*Cells/Kg (x 10^5)
CD34+CD90-	0.51
CD34+CD90+	0.13

*Doses based on 70 kg patient

Cellular Composition Post-Expansion

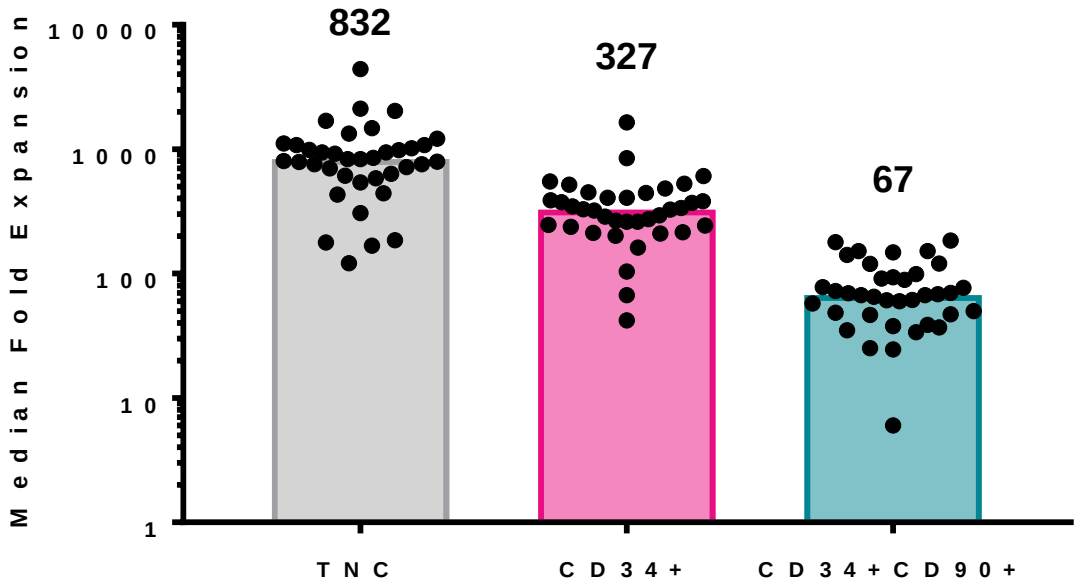


Population	*Cells/Kg (x 10^5)
CD34-CD90-	371.0
CD34+CD90-	189.0
CD34+CD90+	11.4

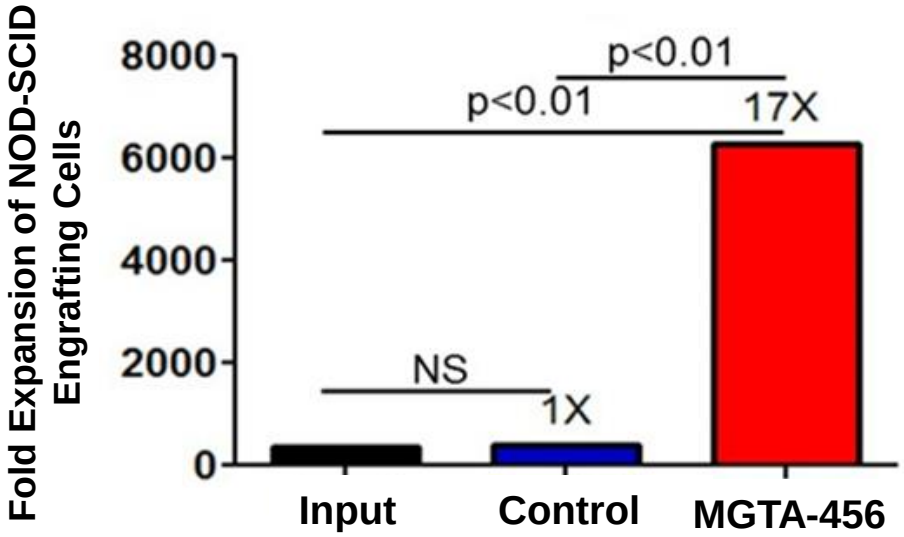
*Doses based on 70 kg patient

Fold Expansion of Cell Populations Within MGTA-456

Fold Expansion From 41 Clinical Productions



Fold Expansion of NOD-SCID Engrafting Cells

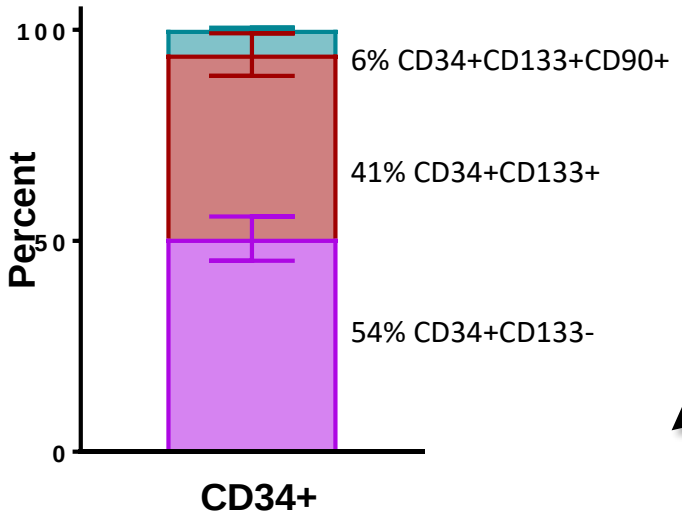


Boitano et al., Science 2010

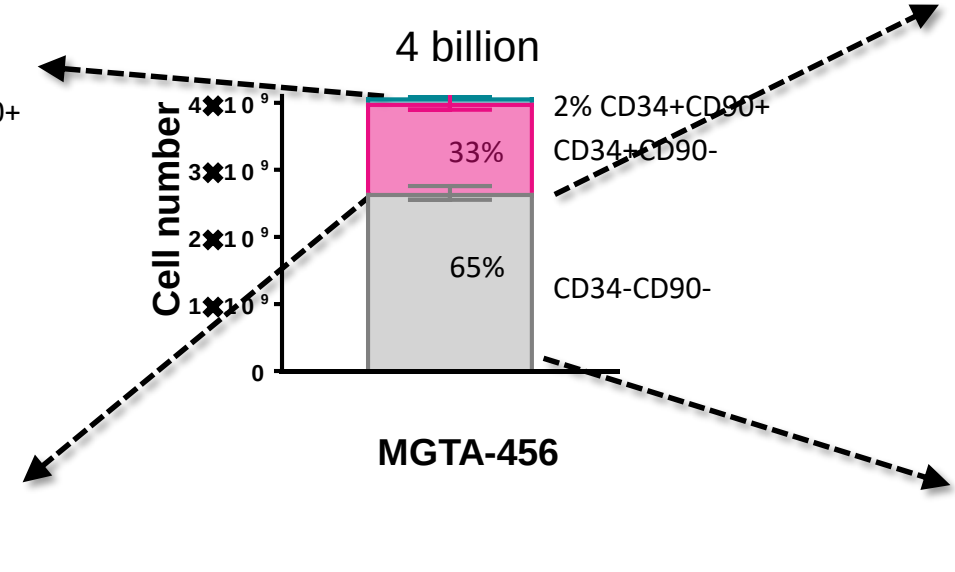
What cell types are present within the CD34+ and CD34- compartment of MGTA-456

MGTA-456 Contains Multiple Hematopoietic Lineages

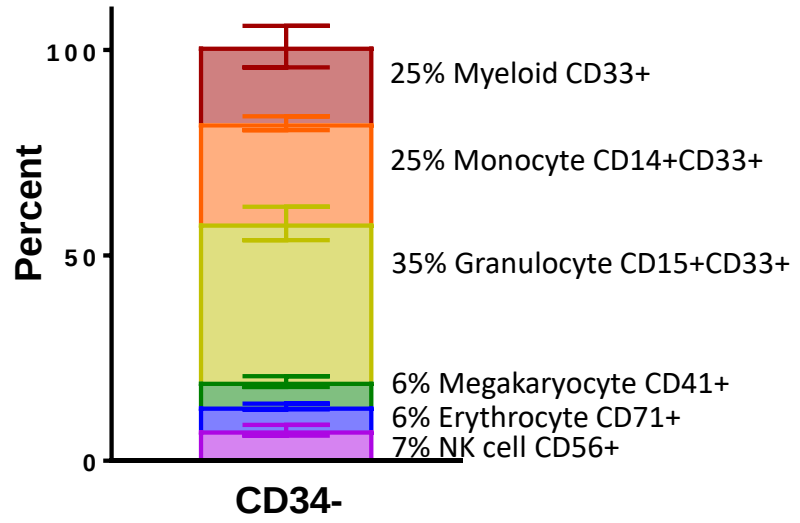
Subpopulations of the CD34+ Cells of MGTA-456



MGTA-456 Cellular Composition Post-Expansion



Subpopulations of the CD34- Cells of MGTA-456



- CD3, CD8, CD4, CD19, CD10, CD235a, CD86, FceR1 and CD16+ cells are not present in MGTA-456

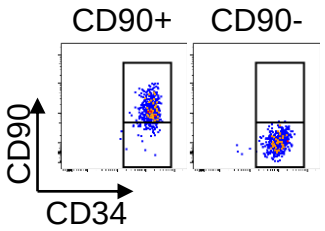
What cell population are responsible for engraftment?

CD34+CD90+ Cells Contain the NSG Engraftment Activity in Uncultured cells

Cord Blood
CD34+ Cells

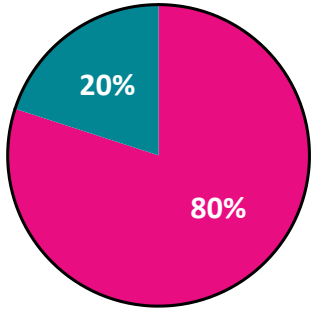
Uncultured

Sort Cells:



Transplant

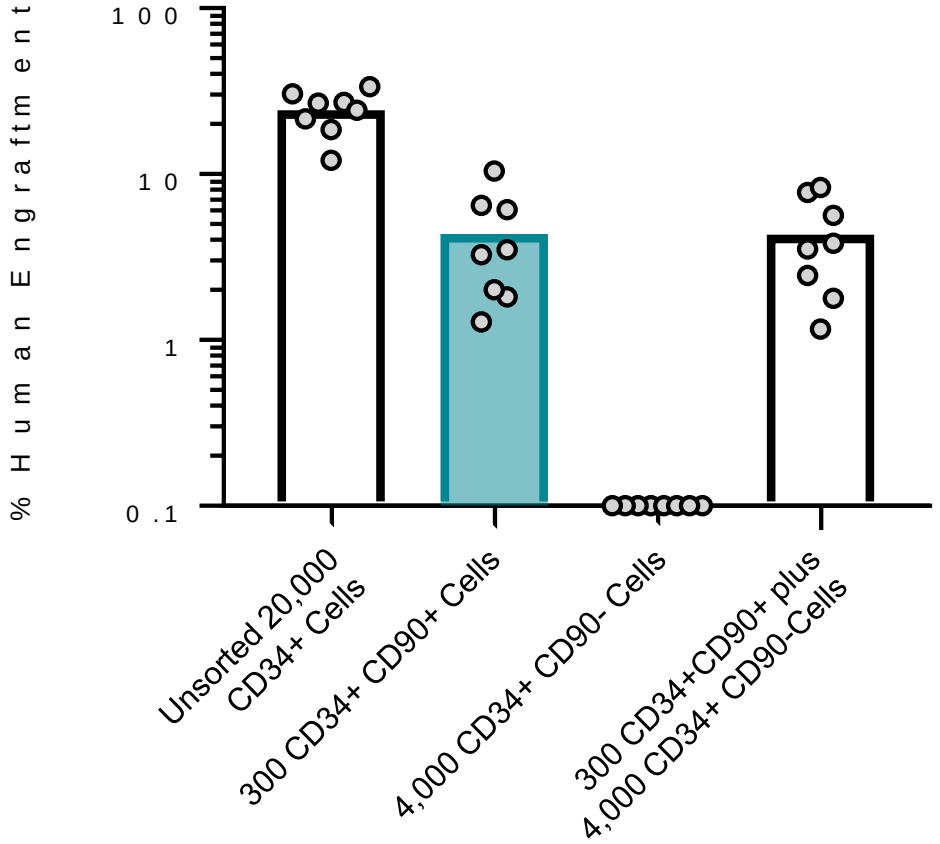
Uncultured
20,000 cells/mouse



300
CD34+CD90+
cells/mouse

4000
CD34+CD90-
cells/mouse

Human engraftment in the bone marrow at 13 weeks

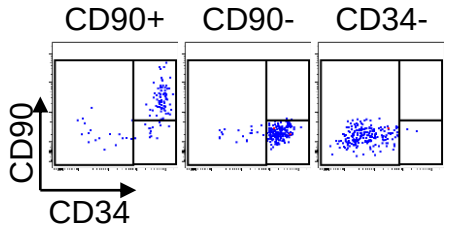


CD34+CD90+ Cells Contain the NSG Engraftment Activity in MGTA-456

Cord Blood
CD34+ Cells

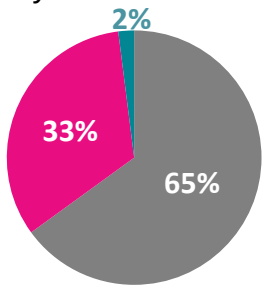
MGTA-456

Sort Cells:



Transplant

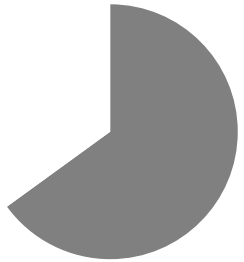
2x10^6 cells/mouse
(Progeny of 4500 CD34+ cells)



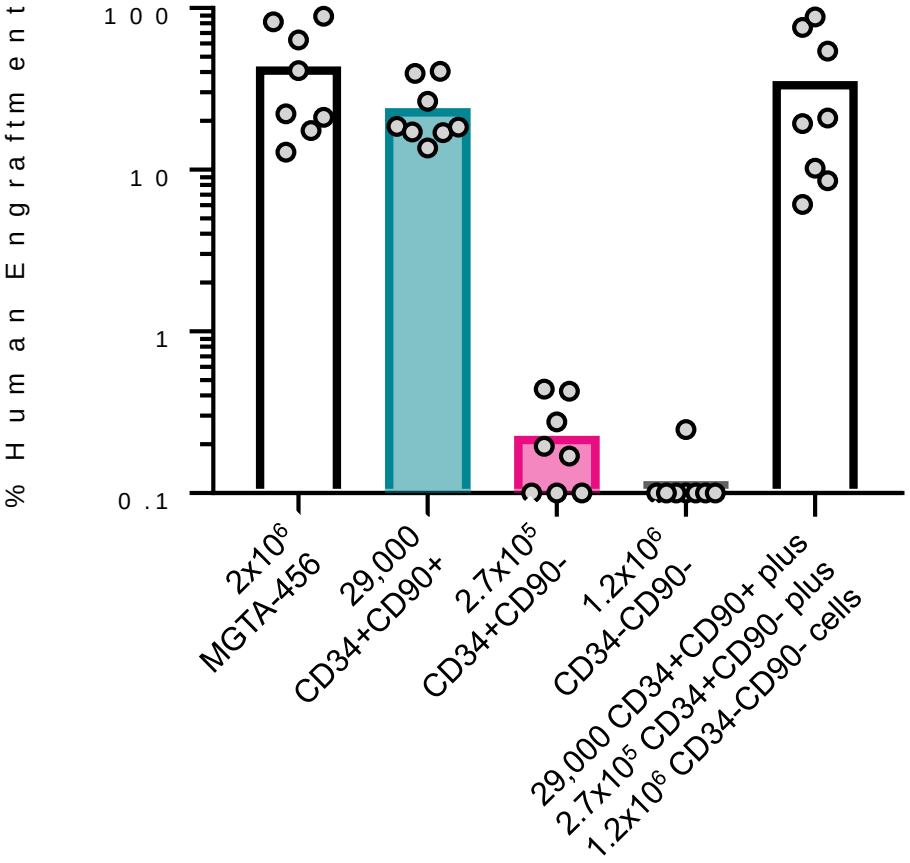
29,000
CD34+CD90+
cells/mouse

2.7x10^5
CD34+CD90-
cells/mouse

1.2x10^6
CD34-CD90-
cells/mouse



Human engraftment in the bone marrow at 13 weeks



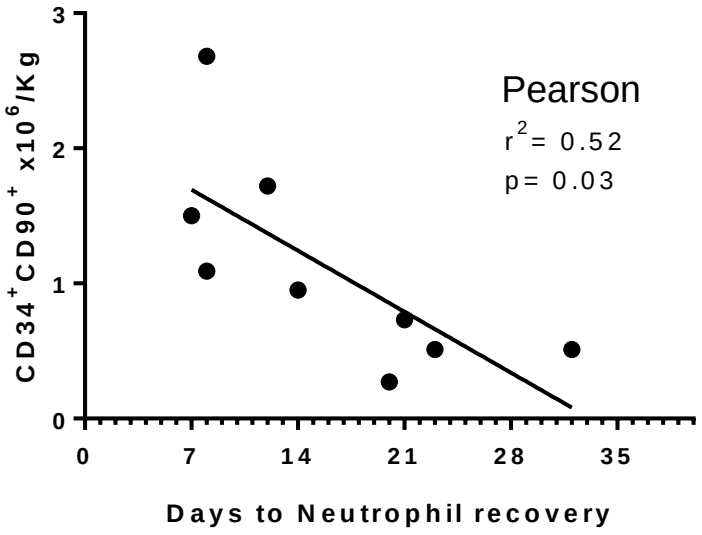
MGTA-456 As a Stand-Alone Graft After Myeloablative Conditioning in Patients With Hematologic Malignancy

Factors		MGTA-456	Historical Control	P value
Number		9	151	
Age (yrs)	Median (range)	25 (15-53)	27 (2-54)	0.13
Weight (kg)	Median (range)	93.8 (41-107)	66.7 (11-136)	0.04
Disease	Acute Leuk MDS CML/CLL NHL/HD	78% 11% 0 11%	85% 3% 3% 9%	0.63
Status	High	11%	17%	0.67
CMV sero	Positive	89%	55%	0.08
Karnofsky	90-100	89%	95%	0.75

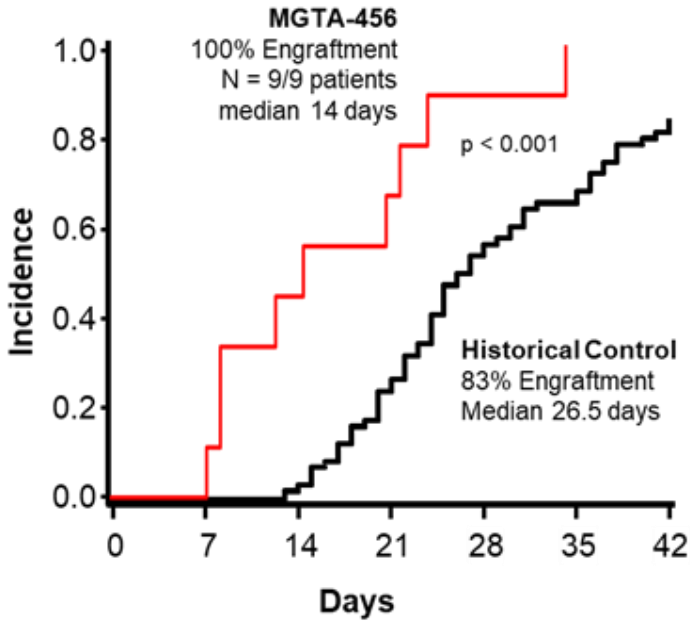
The Dose of CD34+CD90+ cells/kg Had the Strongest Correlation with Time to Neutrophil Recovery

- MGTA-456 as a stand-alone graft after myeloablative conditioning in patients with hematologic malignancy
- Transplant outcomes were compared to identically-treated historical cohorts transplanted with unmodified UCB (n=151)

Correlation of CD34+CD90+ cell dose with speed of neutrophil recovery

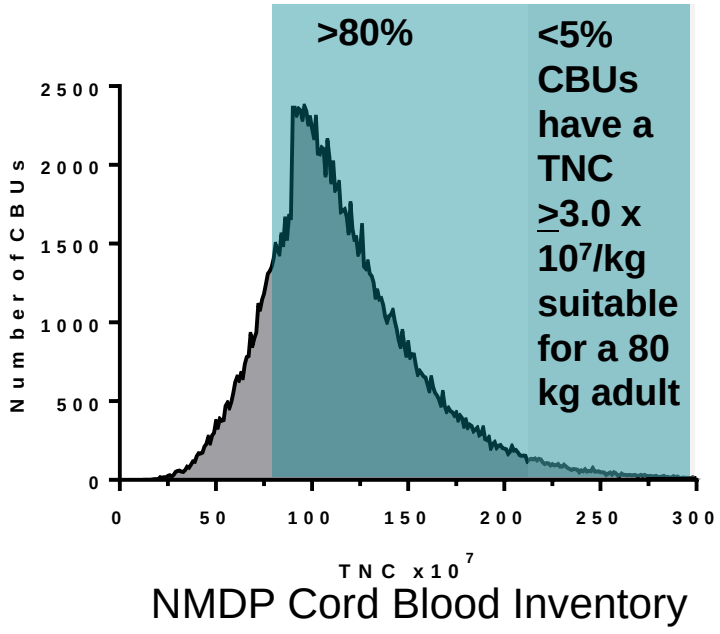


Median time to neutrophil recovery



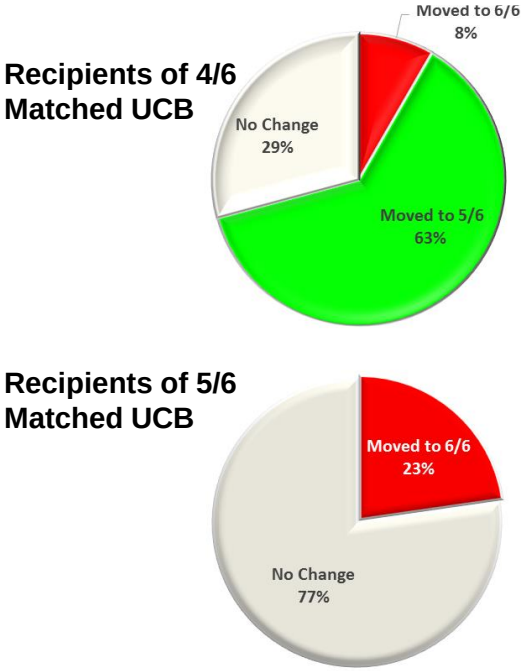
MGTA-456 Enables a New Cell Dose Threshold of 1.0 x 10^7 TNC/kg and the Use of Better HLA Matched Units

Cord blood unit availability for Adults



NMDP Cord Blood Inventory

University of Minnesota cord blood transplants (n=47)



Result

51% of patients treated today could find a better HLA matched cord blood unit with MGTA-456

Summary

- The expanded CD34+ cell fraction of MGTA-456 contains large doses of CD34+CD90+ HSC and progenitors
- The expanded CD34+CD90+ population of MGTA-456 is responsible for engraftment in NSG mice
- Consistent with the NSG results, the dose of CD34+CD90+ cells/kg had the strongest correlation with time to neutrophil recovery in patients
- 100% engraftment at a median time of 14 days with 67% overall survival at 2 years was observed with MGTA-456 as a stand alone graft
- 51% of patients treated today could find a better HLA matched cord blood unit with MGTA-456

Next Steps for MGTA-456

- Phase 2 investigator-initiated study of MGTA-456 in patients with hematologic malignancies is ongoing
  - This study will explore using smaller better HLA-matched cord blood units and increase the number of patients with blood cancers treated with MGTA-456 utilizing myeloablative conditioning
  - NCT03674411

- Phase 2 Magenta sponsored trial to investigate MGTA-456 in patients with inherited metabolic disorders undergoing hematopoietic stem cell transplantation
  - NCT03406962

- Additional TCT abstracts on MGTA-456:
  - Paul Orchard, Abstract 122
  - Kevin A. Goncalves, Abstract 124

Acknowledgments

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