



# MGTA-456, A First-in-Class Cell Therapy Produced from a Single Cord Blood Unit, Enables a Reduced Intensity Conditioning Regimen and Enhances Speed and Level of Human Microglia Engraftment in the Brains of NSG Mice

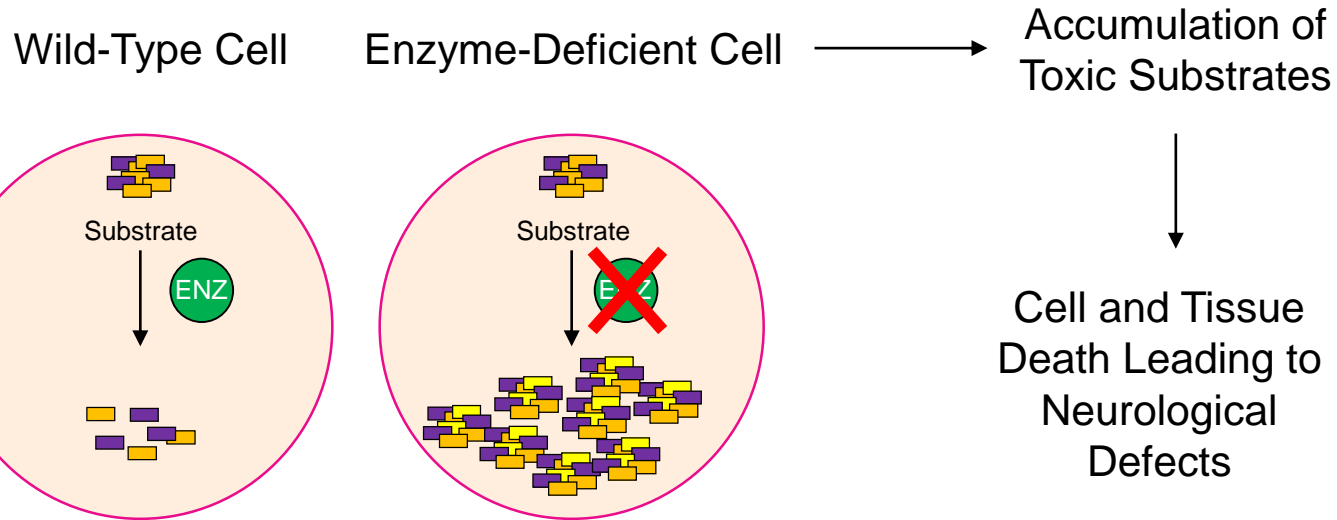
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Magenta Therapeutics  
Cambridge, MA



# Most Inherited Metabolic Disorders (IMDs) Are Characterized by Defective Enzyme Function In Patients

## DEFECTIVE ENZYME FUNCTION IN PATIENTS WITH IMDs



## HEMATOPOIETIC STEM CELL (HSC) TRANSPLANT AS A STANDARD OF CARE FOR SELECTED IMDs

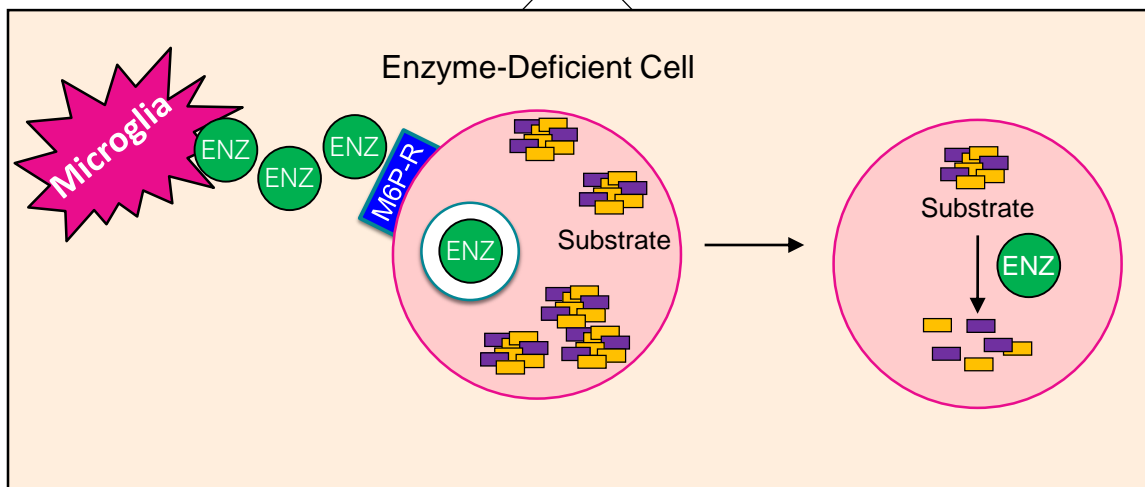
- Mucopolysaccharidosis I, II, IIIA and B, and VI
- Metachromatic Leukodystrophy
- Globoid Cell Leukodystrophy
- Cerebral Adrenoleukodystrophy

Therapeutic Goal  
Restore Functional Enzyme Levels

Cross Correction of Disease

# HSC Transplant Is A Standard Of Care in IMD Indications Where Cross-Correction Can Occur

## CROSS-CORRECTION OF DISEASE BY DONOR-DERIVED MYELOID CELLS IN BRAIN POST-TRANSPLANT



## STRATEGIES TO CROSS-CORRECT

### Allogeneic HSC Transplant

- > 2000 transplants performed since 1980 with documented disease-modifying capabilities
- Cord blood is the preferred source of HSCs
- Cord blood inventory provides rapid access to patients

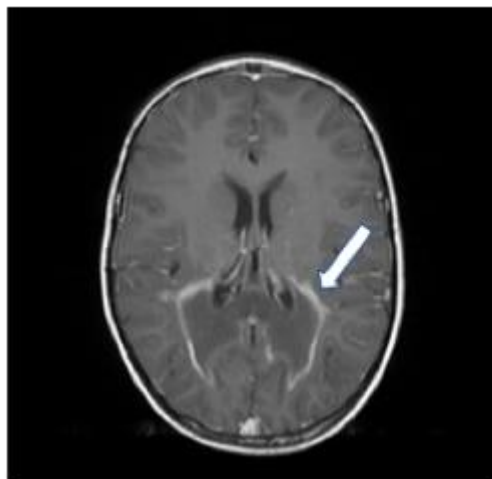
### Autologous Gene Therapy

- Limited by challenging manufacturing processes
- Unknown effects of transduction efficiency and dose

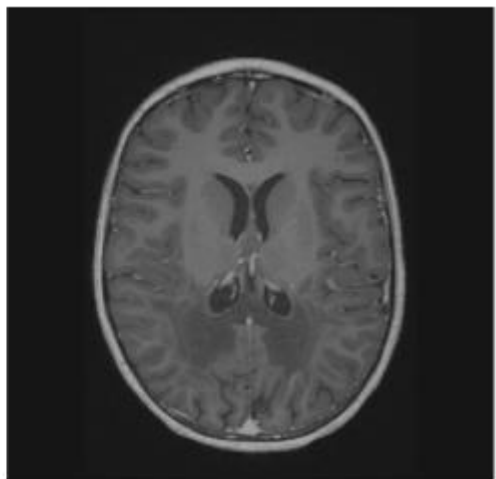
# HSC Transplant is Disease-Modifying, but Graft Failure Remains High

## ENHANCED FOLLOWING TRANSPLANT IN CEREBRAL ADRENOLEUKODYSTROPHY

Pre-Transplant



Post-Transplant (Day 28)



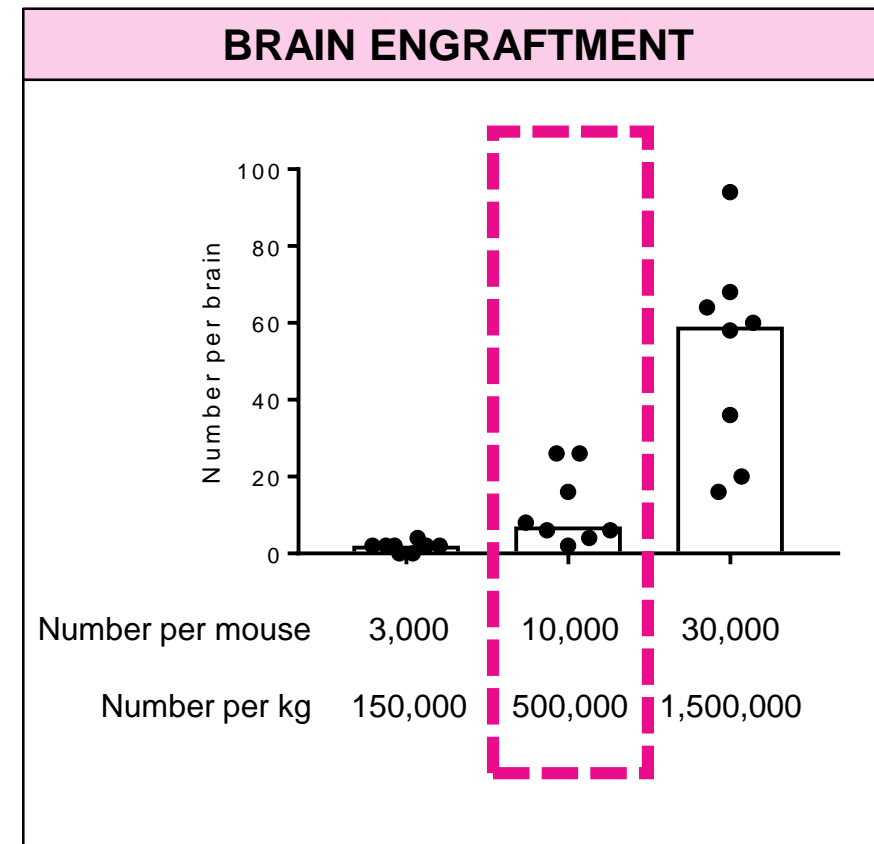
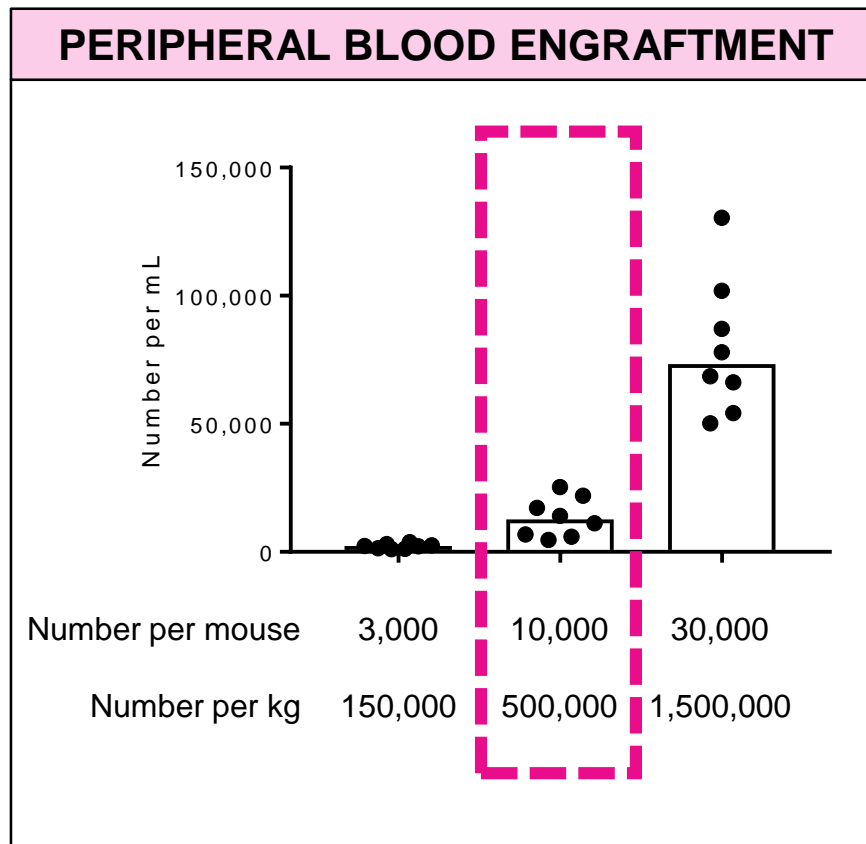
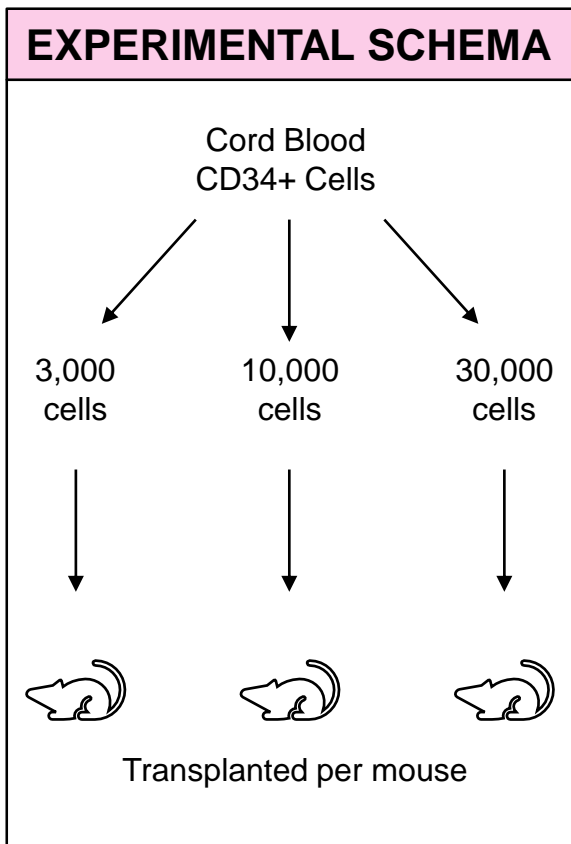
## CIBMTR OUTCOMES IN PATIENTS WITH IMDs

Endpoint	Hurler Syndrome	Adrenoleukodystrophy
Neutrophil Engraftment (Day 28)	84% (95% CI: 79-89%)	80% (95% CI: 73-86%)
Graft Failure (1 year)	21% (15-27)%	24% (95% CI: 17-32%)

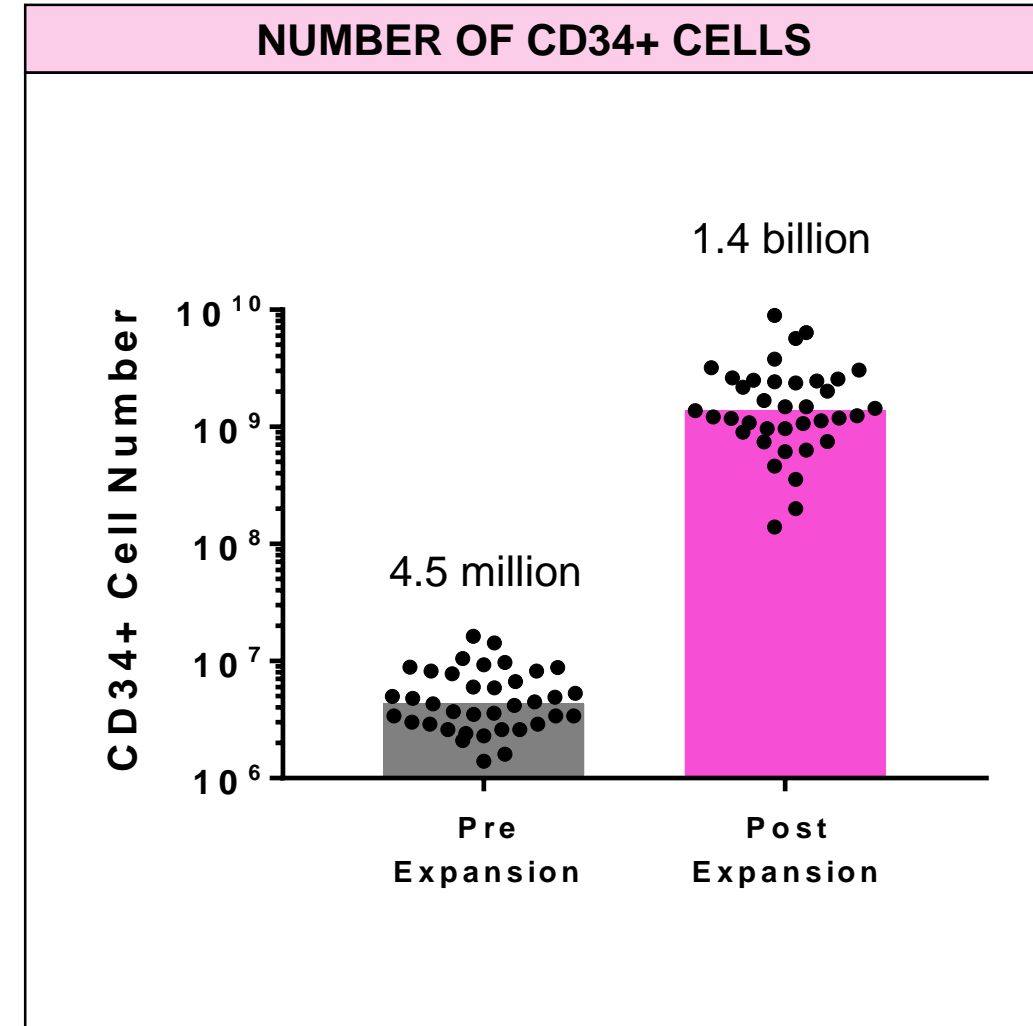
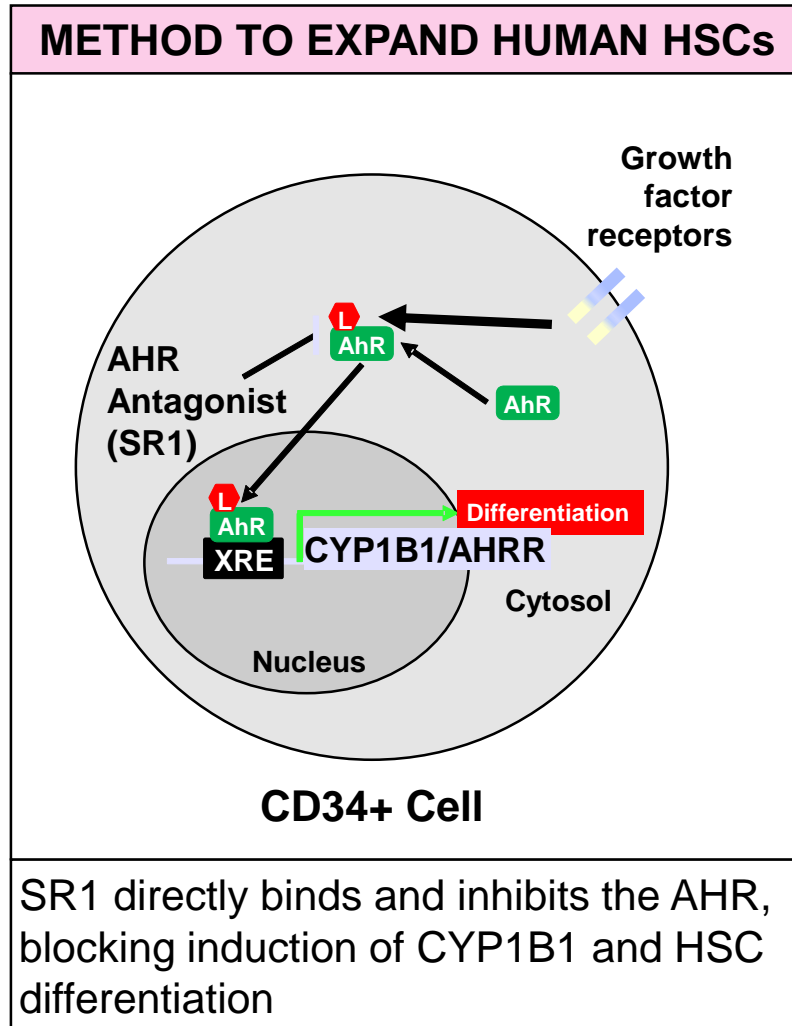
Lund et al. ASH 2018 Abstract #4628

**How Can Patient Outcomes Be Further Improved?**

# Increased Cell Dose Leads to Increased Hematopoietic and Brain Engraftment

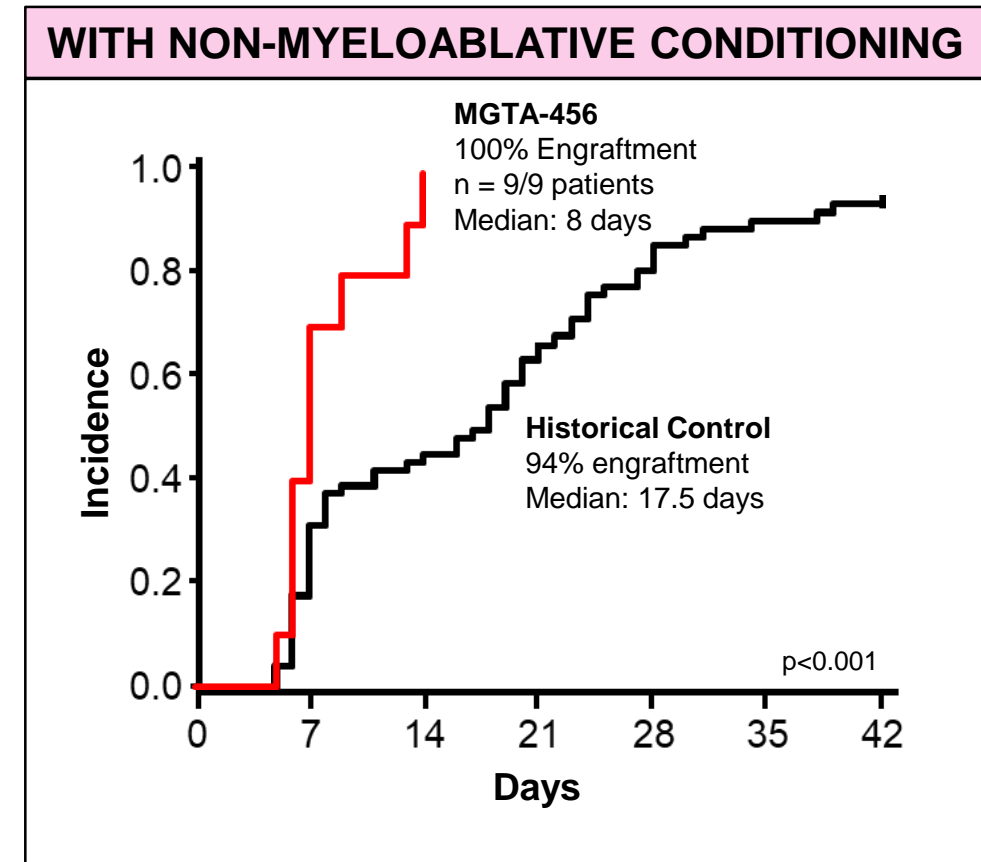
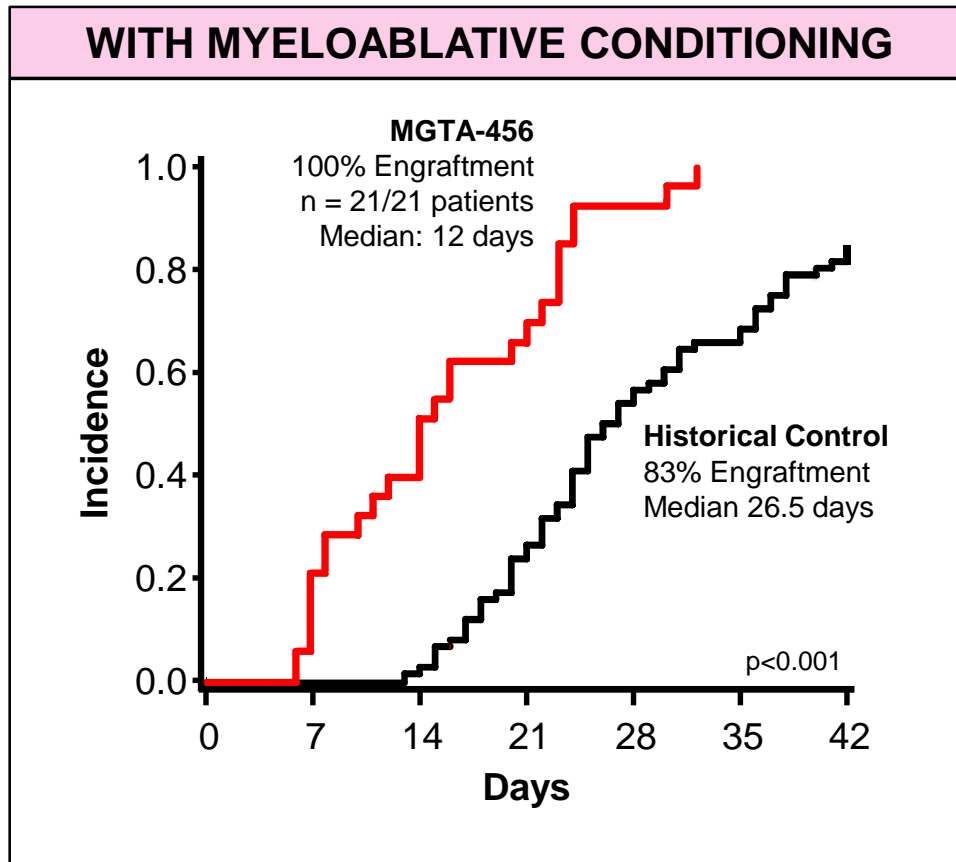


# MGTA-456: Aryl Hydrocarbon Receptor (AHR) Antagonism as a Mechanism of HSC Expansion



Modified from Wagner et al., Cell Stem Cell 2016

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



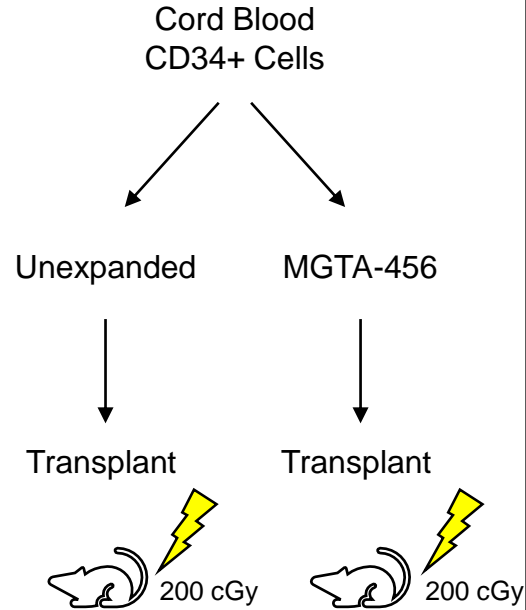
Wagner et al., ASH 2017

## RATIONALE FOR Ph2 CLINICAL TRIAL IN IMDs

- (1) Accelerate engraftment
- (2) Prevent graft failure
- (3) Potentially accelerate and increase donor-derived microglia engraftment?

# MGTA-456 Leads to Enhanced Hematopoietic Engraftment in NSG Mice Compared to Standard of Care

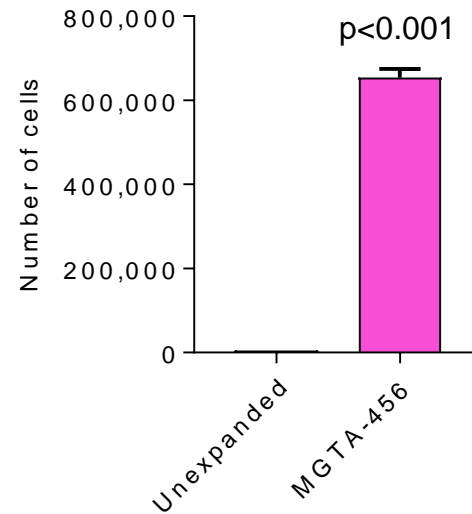
## EXPERIMENTAL SCHEMA



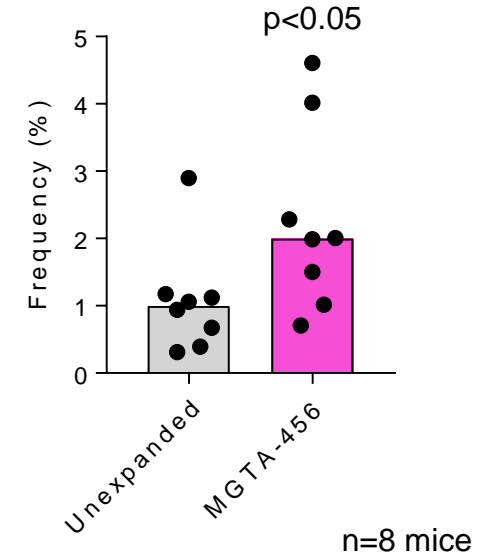
### At 3 Months Post-Transplant:

- hCD45 Frequency in Peripheral Blood
- Microglia in Brain by Flow Cytometry and IHC

## CD34+ FOLD EXPANSION OVER 10 DAYS



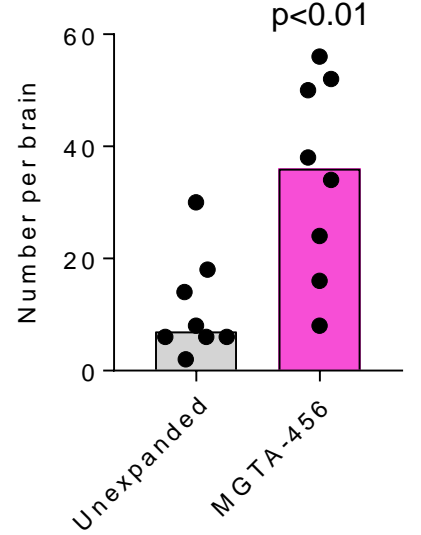
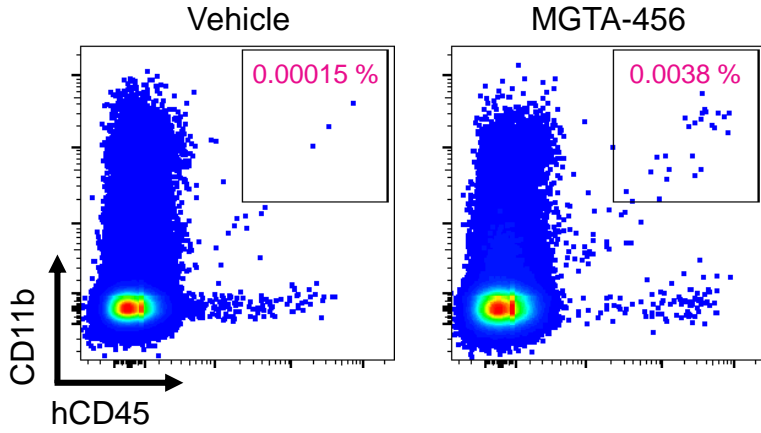
## hCD45 FREQUENCY IN PERIPHERAL BLOOD





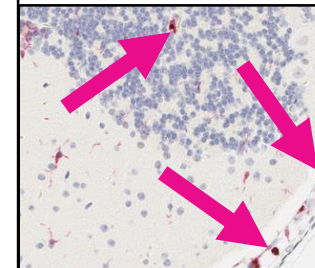
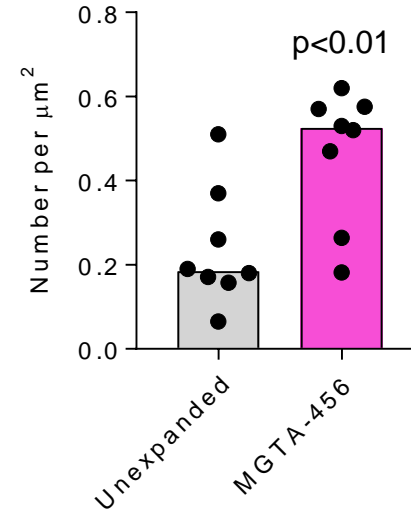
# MGTA-456 Leads to Enhanced Brain Engraftment in NSG Mice Relative to Unexpanded Cells, the Standard-of-Care

## hCD45+CD11b+ NUMBER IN BRAIN



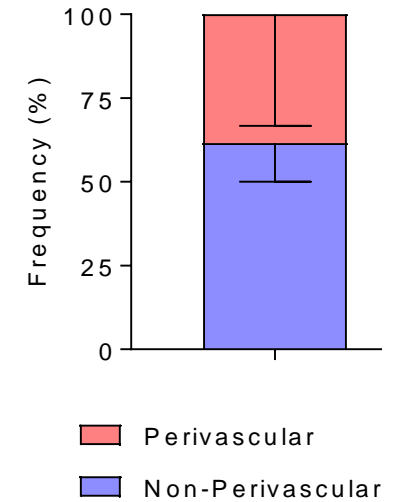
n=8 mice

## Ku80+lba-1+ NUMBER BY IHC

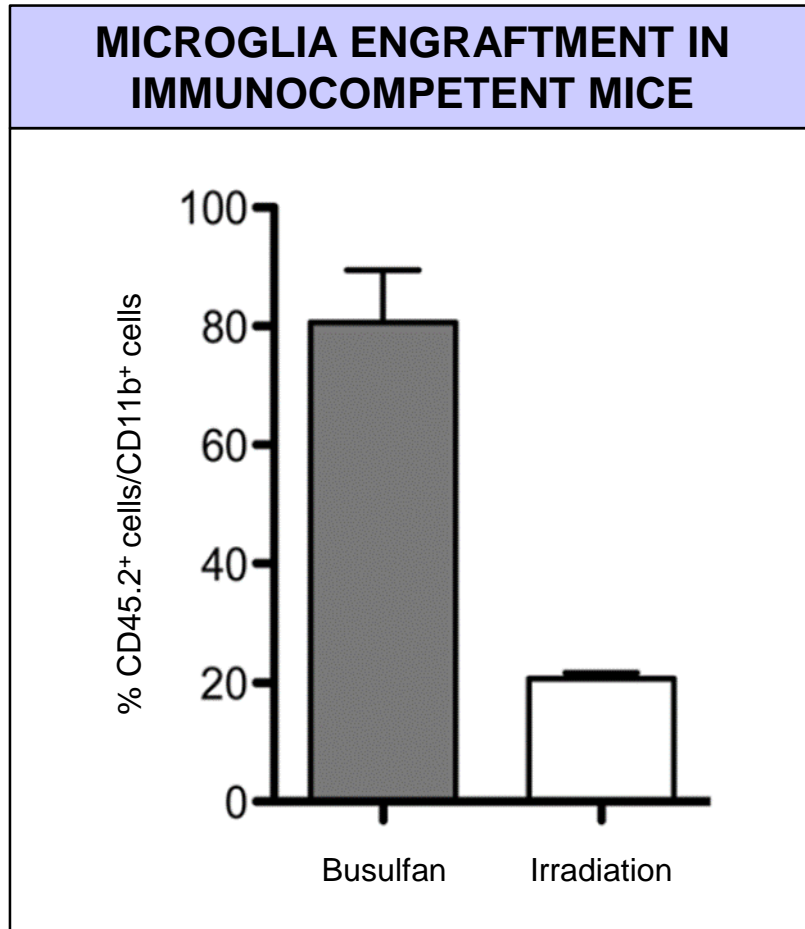


Ku80+lba-1+  
microglia  
indicated by  
magenta  
arrows

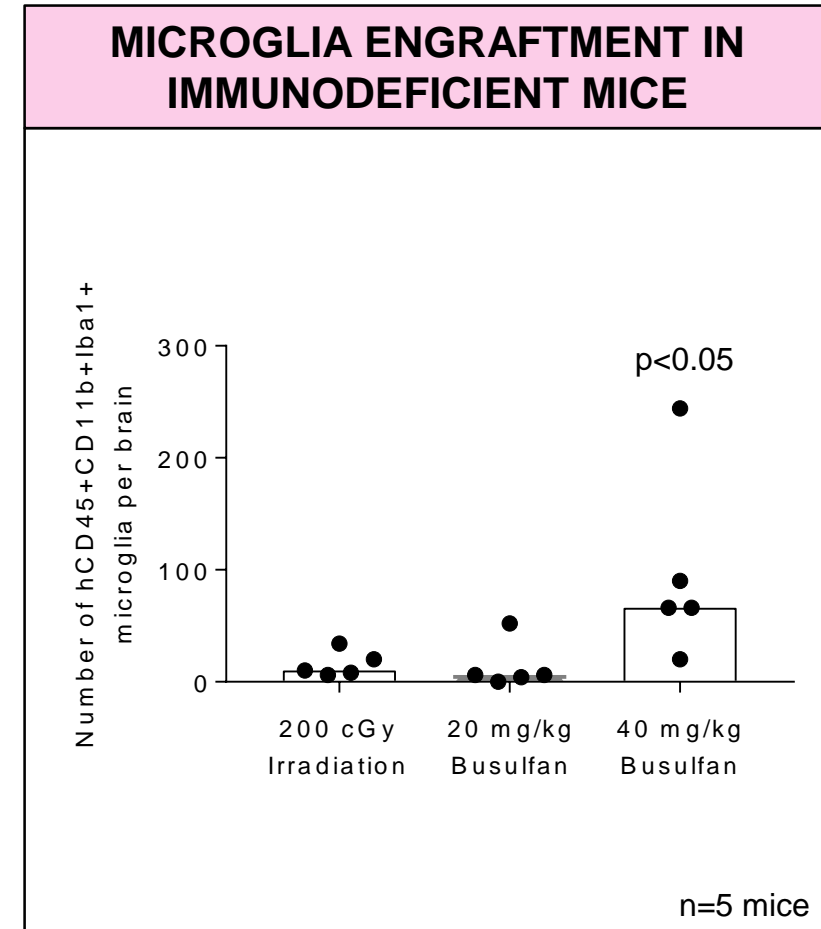
## LOCALIZATION OF Ku80+lba-1+ MICROGLIA



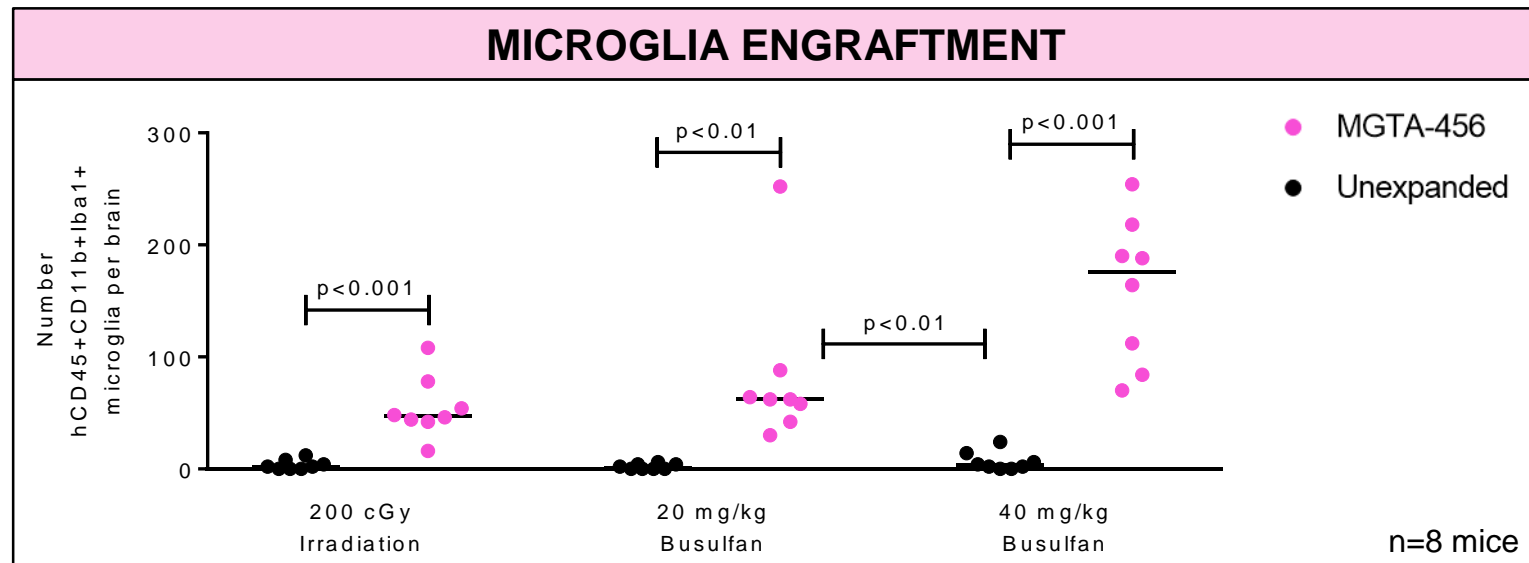
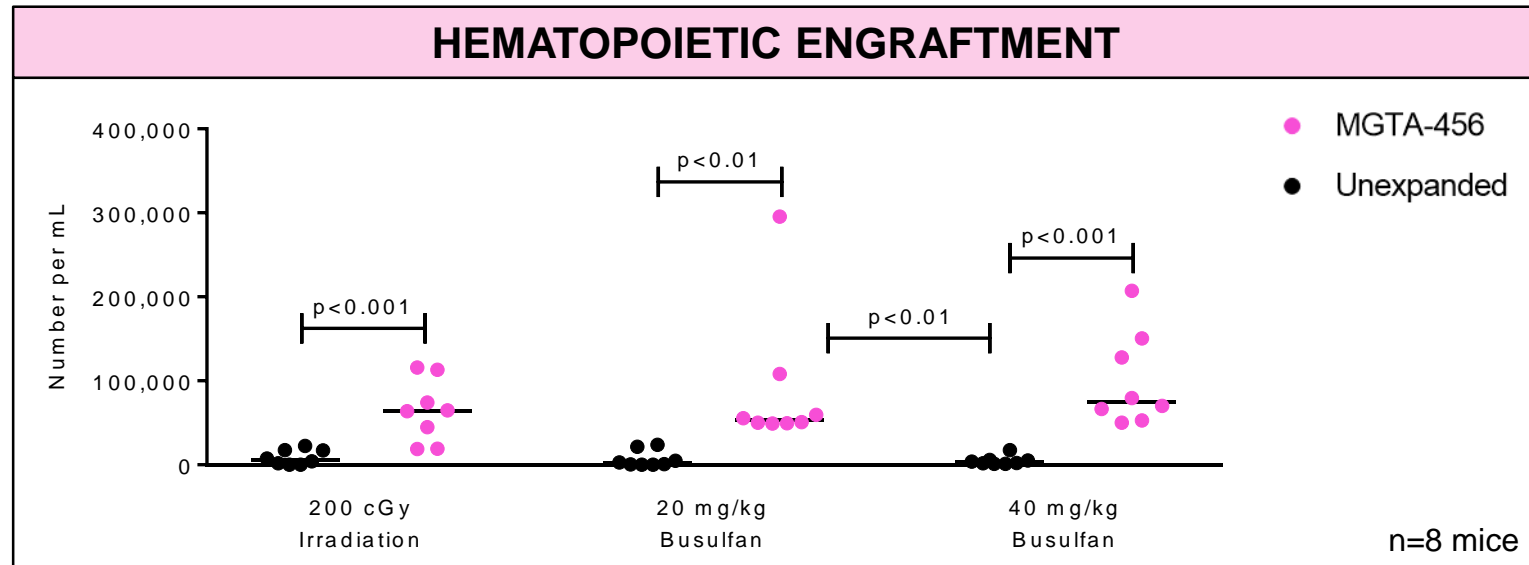
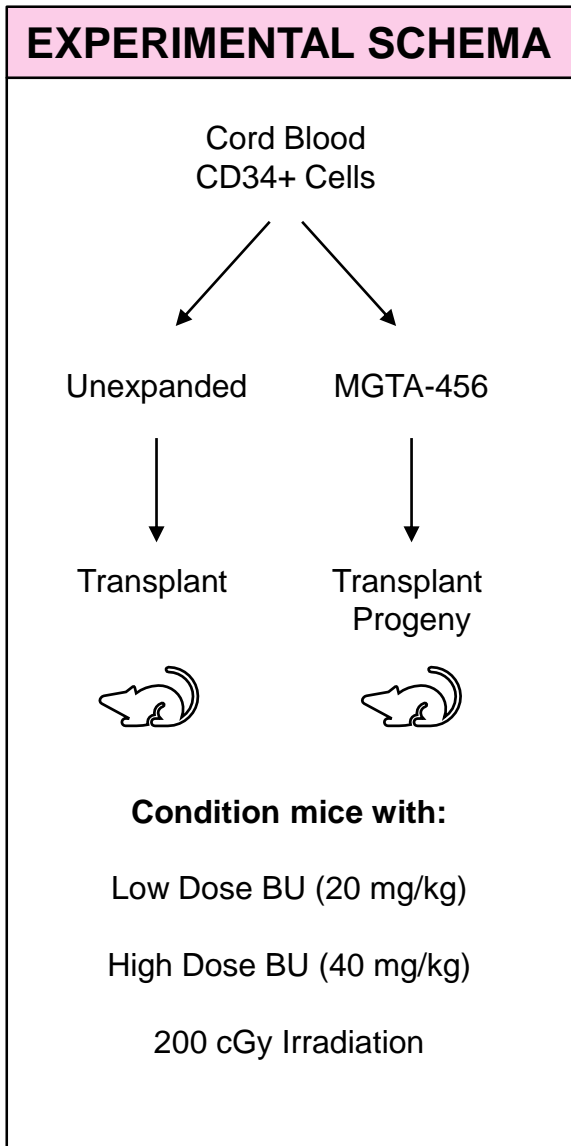
# Busulfan Dosing Enables Enhanced Brain Engraftment Compared To Irradiation



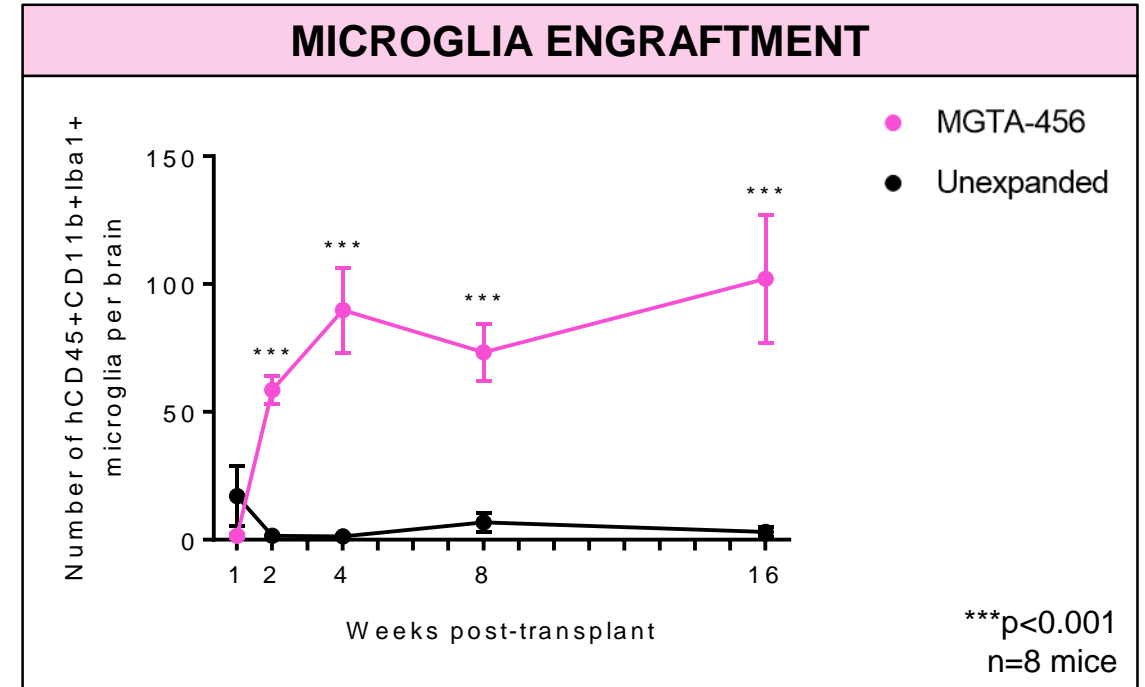
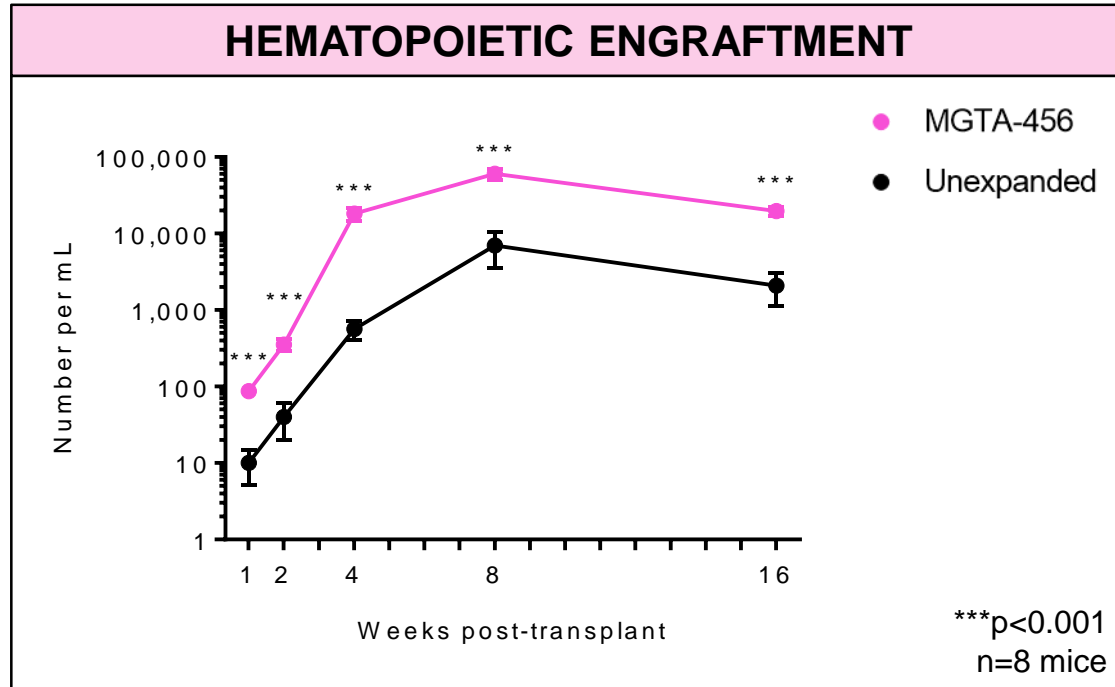
Modified from Capotondo et al. Sci Adv 2017



# MGTA-456 Enables A Reduced Intensity Conditioning Regimen and Enhances Level of Human Microglia Engraftment in the Brains of NSG Mice Relative to Standard-of-Care

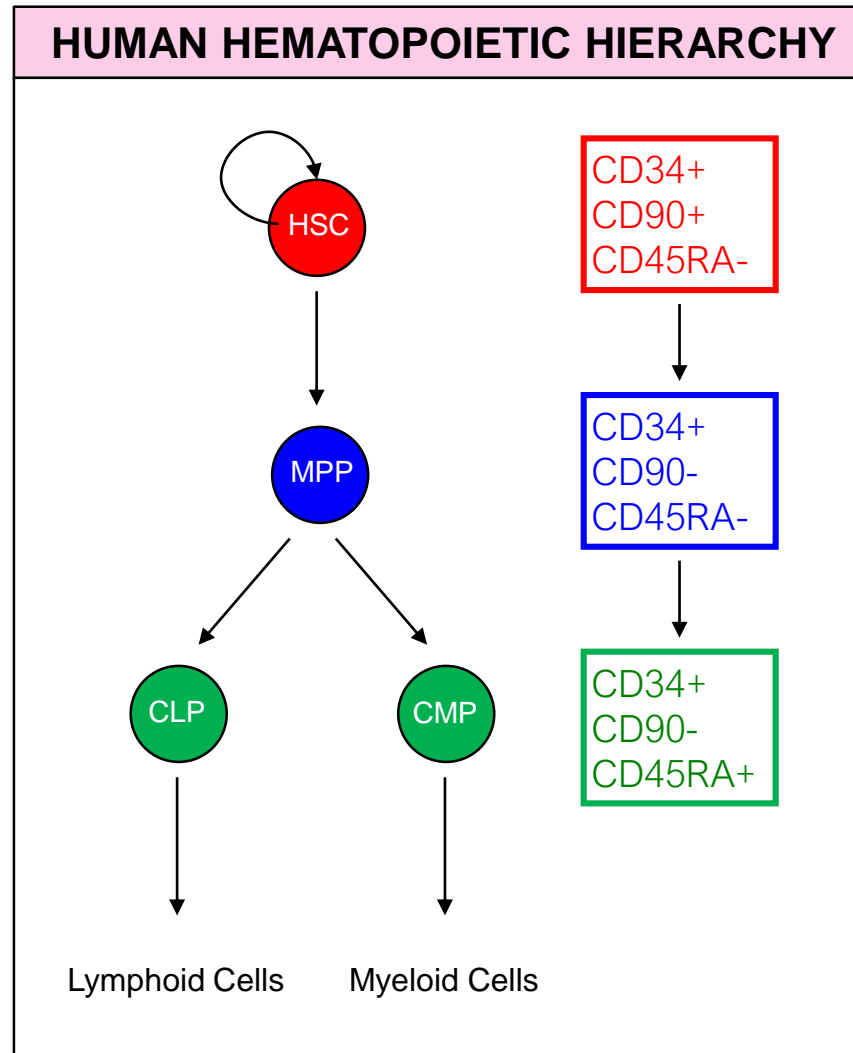


# MGTA-456 Enhances Microglial Engraftment As Early As Two Weeks



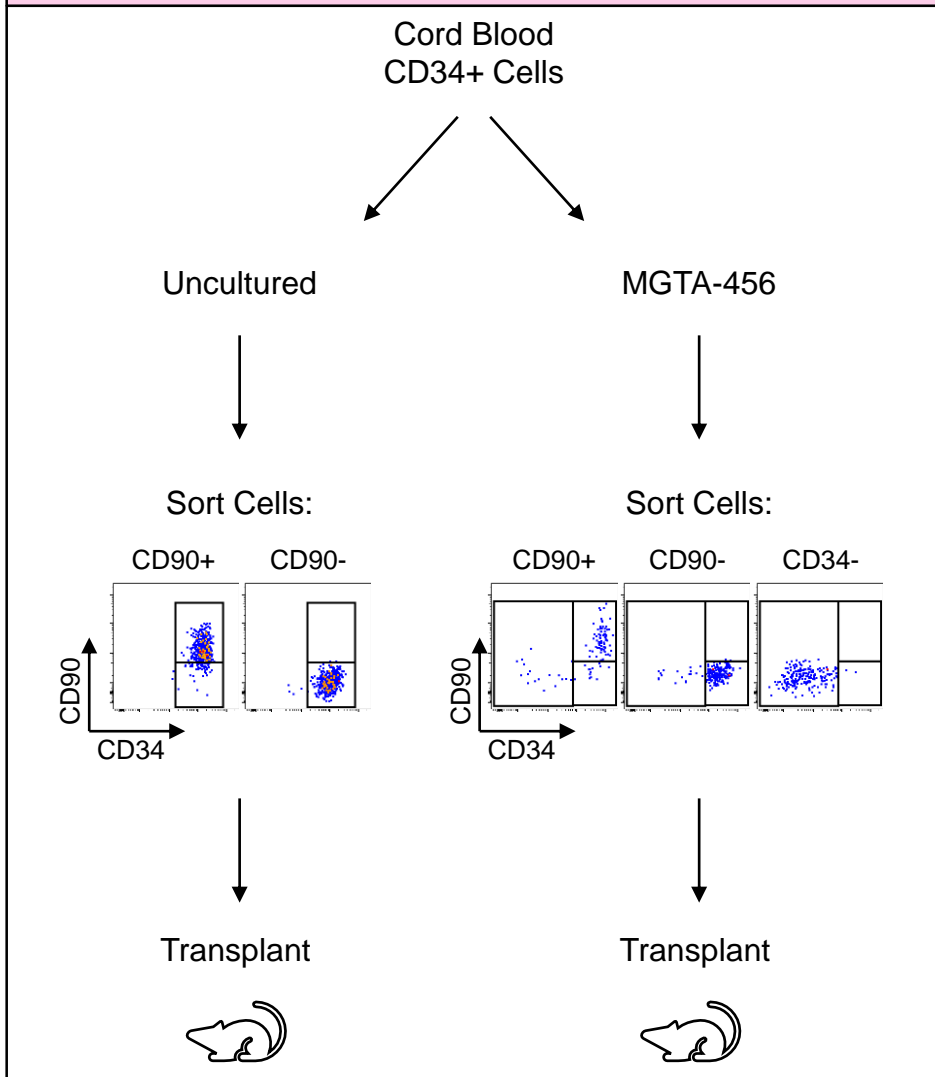
**Which cell type contributes to microglial engraftment?**

# Which Cell Type Is Responsible For Engraftment?

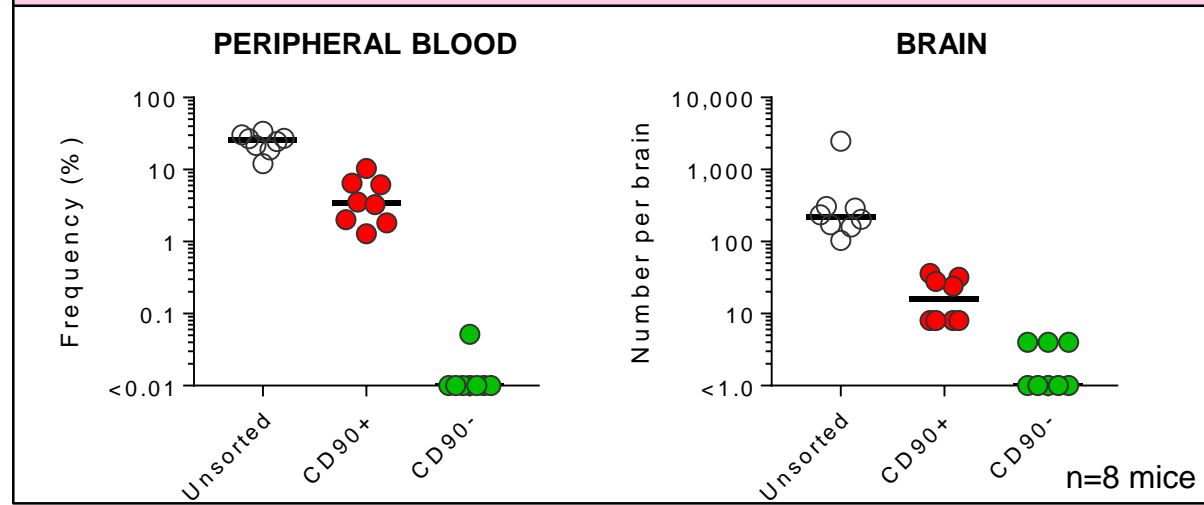


# Only CD90+ Cells Contribute to Microglial Engraftment

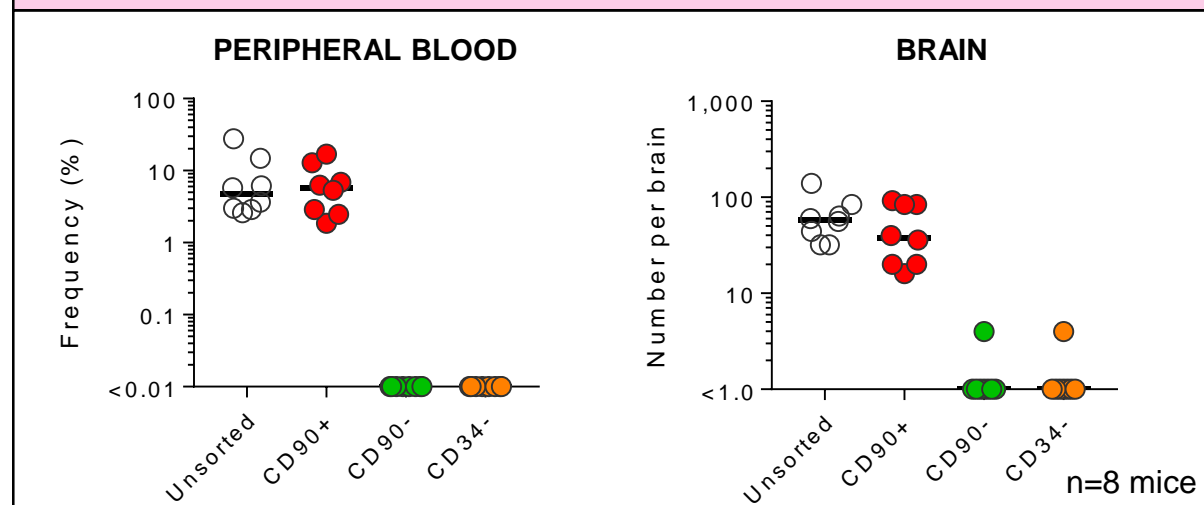
## EXPERIMENTAL SCHEMA



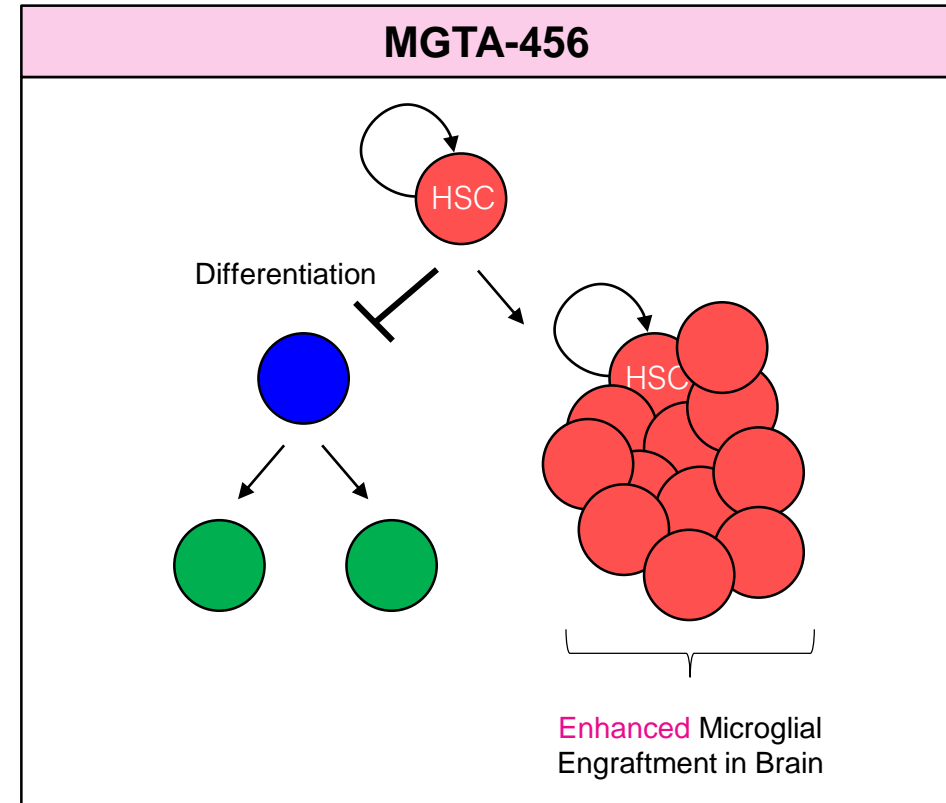
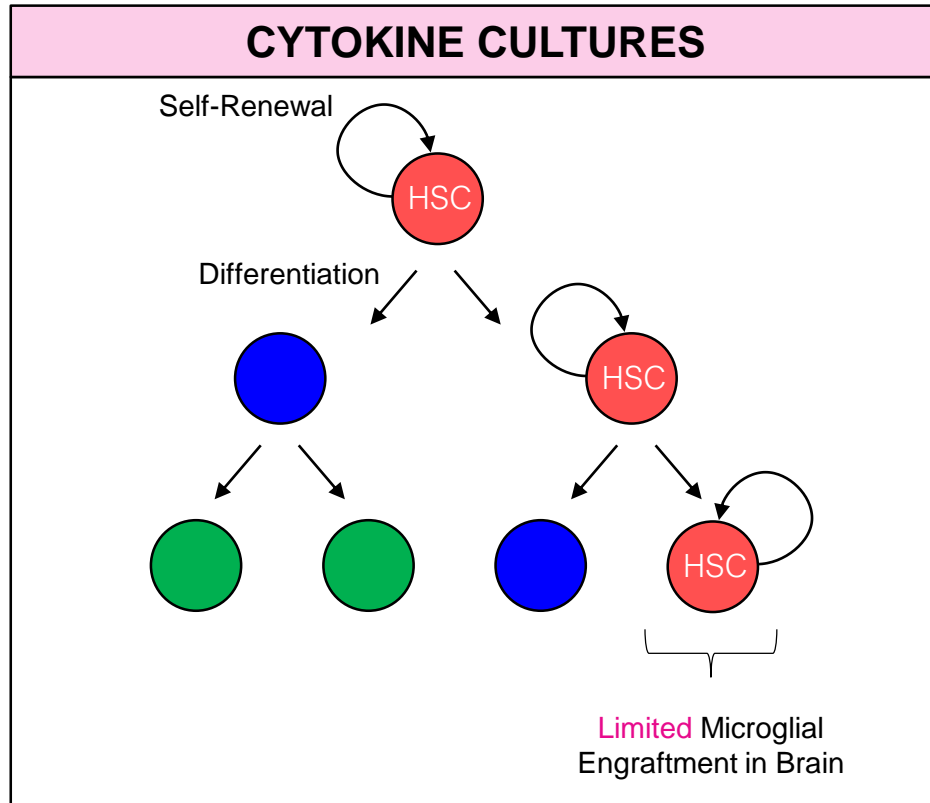
## UNCULTURED



## MGTA-456



# MGTA-456 Results in Faster and Greater Hematopoietic and Brain Engraftment



- *Ex vivo* expanded human cord blood CD34+ cells, MGTA-456, significantly improves hematopoietic engraftment and number of human microglia in the brains of NSG mice
- CD90+ cells are the only cells to contribute to microglia engraftment under these treatment conditions
- Magenta-sponsored trial for MGTA-456 in patients with IMDs

# MGTA-456 in Pediatric Patients with IMDs

## **ABSTRACT #3467**

Preliminary Phase 2 Results Demonstrate Engraftment with Minimal Neutropenia with MGTA-456, a CD34+ Expanded Cord Blood Product in Patients Transplanted for Inherited Metabolic Disorders

John Wagner, M.D.

Sunday, December 2, 2018 6:00 – 8:00 PM



# Acknowledgments



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