MGTA-456, A First-in-Class Cell Therapy, Enhances Speed and Level of Human Microglia Engraftment in the Brains of Transplanted Mice

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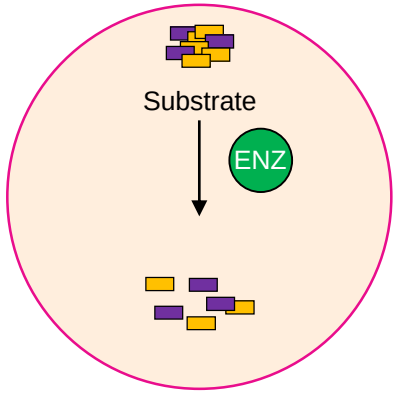
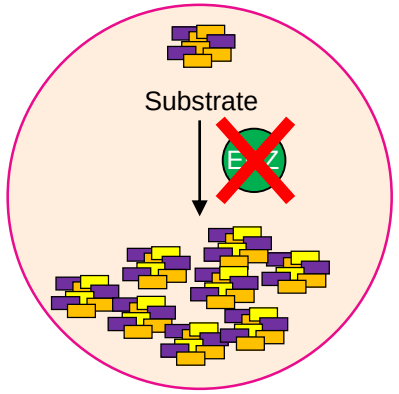
Most Inherited Metabolic Disorders (IMDs) Are Characterized by Defective Enzyme Function In Patients

DEFECTIVE ENZYME FUNCTION IN PATIENTS WITH IMDs

Wild-Type Cell



Enzyme-Deficient Cell



Accumulation of Toxic Substrates

Cell and Tissue Death Leading to Neurological Defects

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

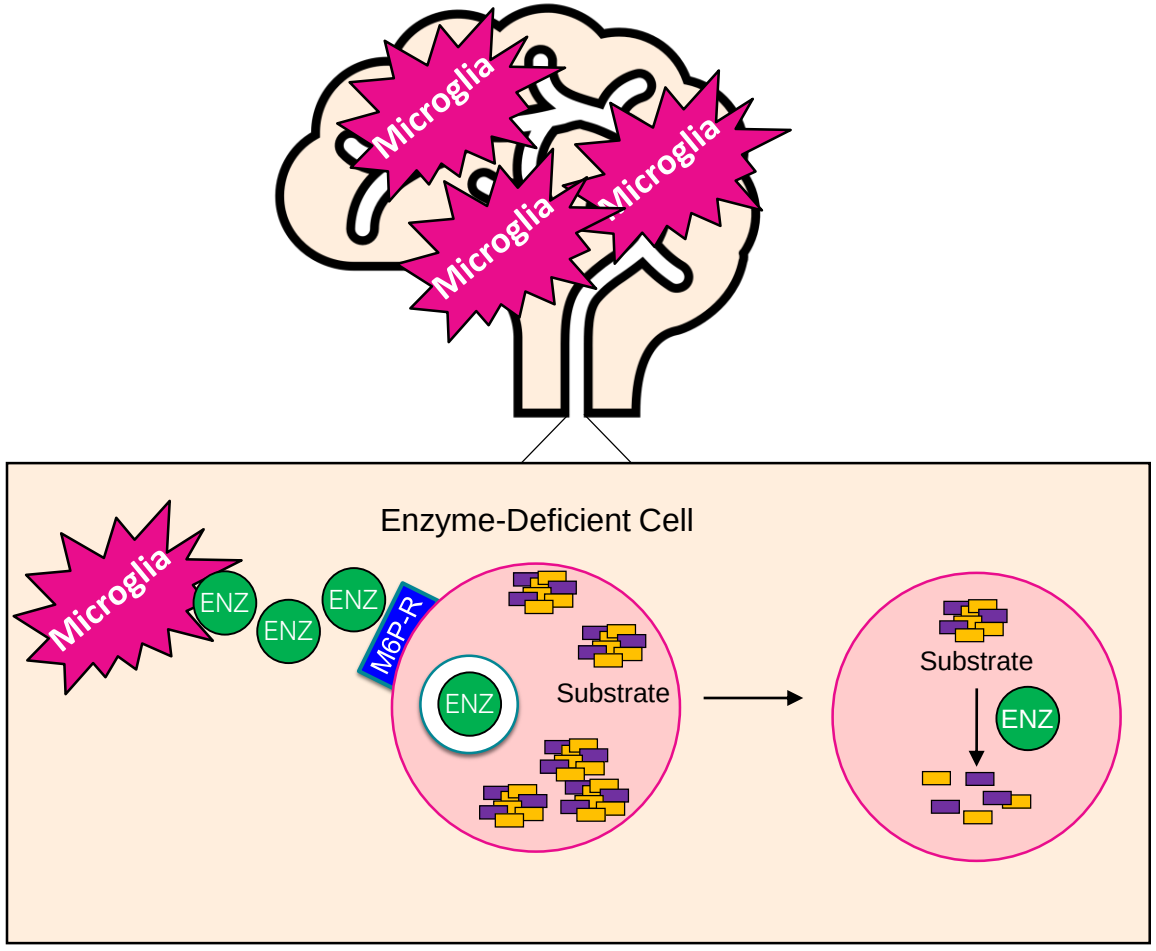
Cerebral Adrenoleukodystrophy

<u>Therapeutic Goal</u>
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

- > 2,000 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

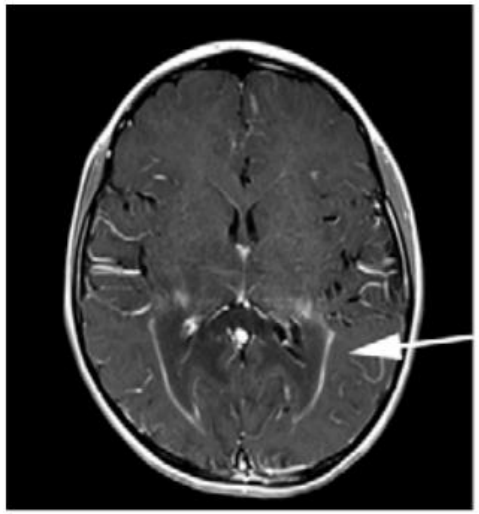
Autologous Gene Therapy

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

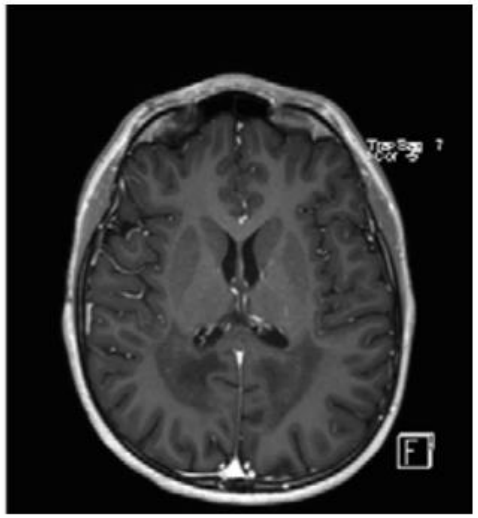
HSC Transplant is Disease-Modifying, but There is Delayed Neutrophil Engraftment and Graft Failure Remains High

REDUCED INFLAMMATION FOLLOWING TRANSPLANT IN CEREBRAL ADRENOLEUKODYSTROPHY (cALD)

Pre-Transplant



Post-Transplant (Day 30)



Orchard et al. Blood 2019

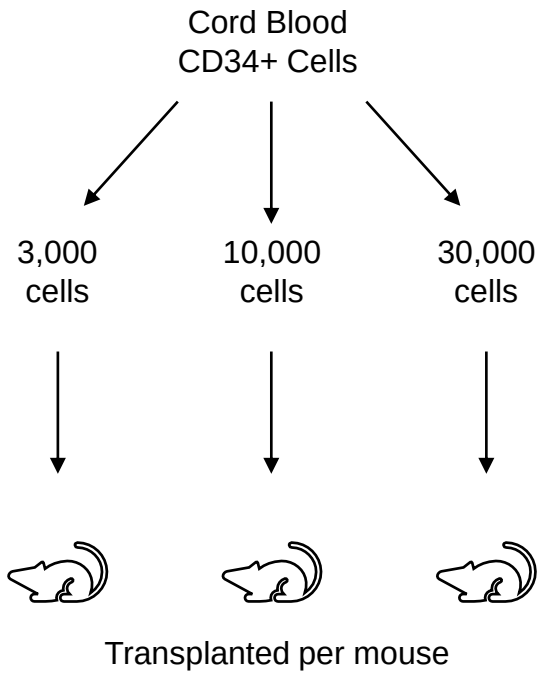
CIBMTR OUTCOMES IN PATIENTS WITH IMDs

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

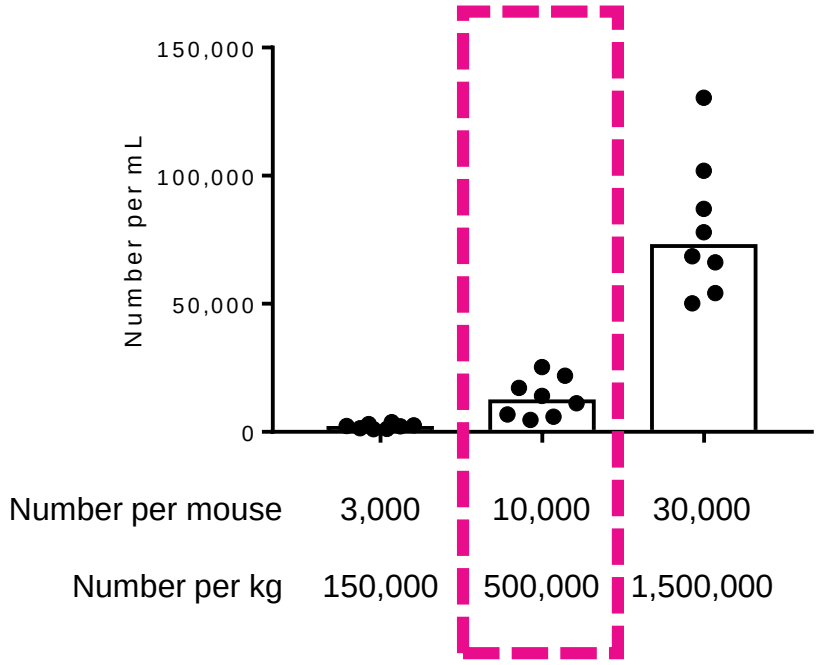
Can Patient Outcomes Be Improved By Increasing Cell Dose?

Increased Cell Dose Leads to Increased Hematopoietic and Brain Engraftment

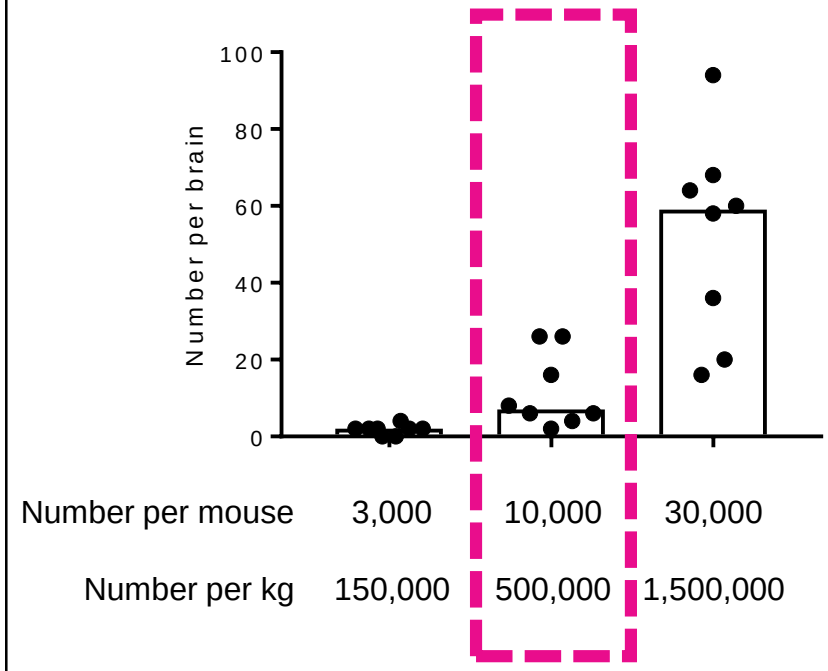
EXPERIMENTAL SCHEMA



PERIPHERAL BLOOD ENGRAFTMENT

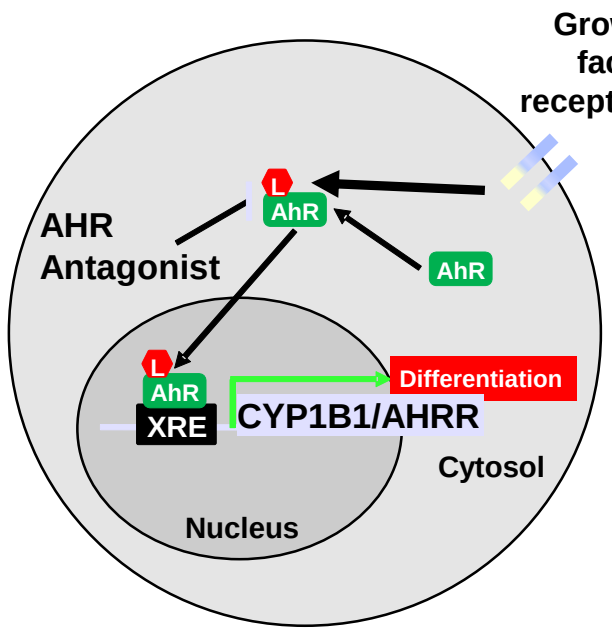


BRAIN ENGRAFTMENT



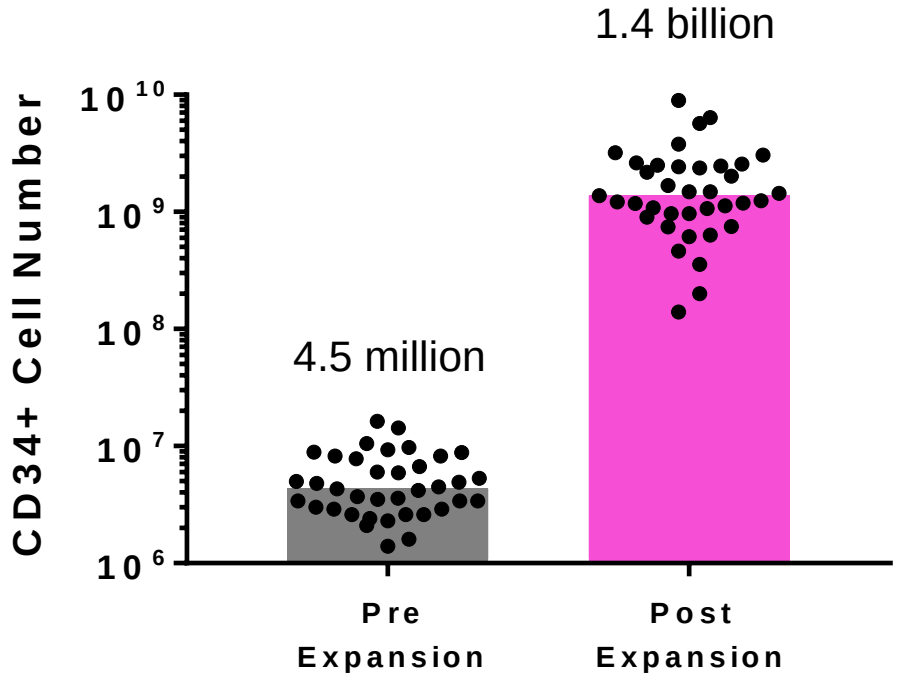
MGTA-456: Aryl Hydrocarbon Receptor (AHR) Antagonism as a Mechanism of HSC Expansion

METHOD TO EXPAND HUMAN HSCs



An AHR antagonist directly binds and inhibits the AHR, blocking induction of CYP1B1 and HSC differentiation

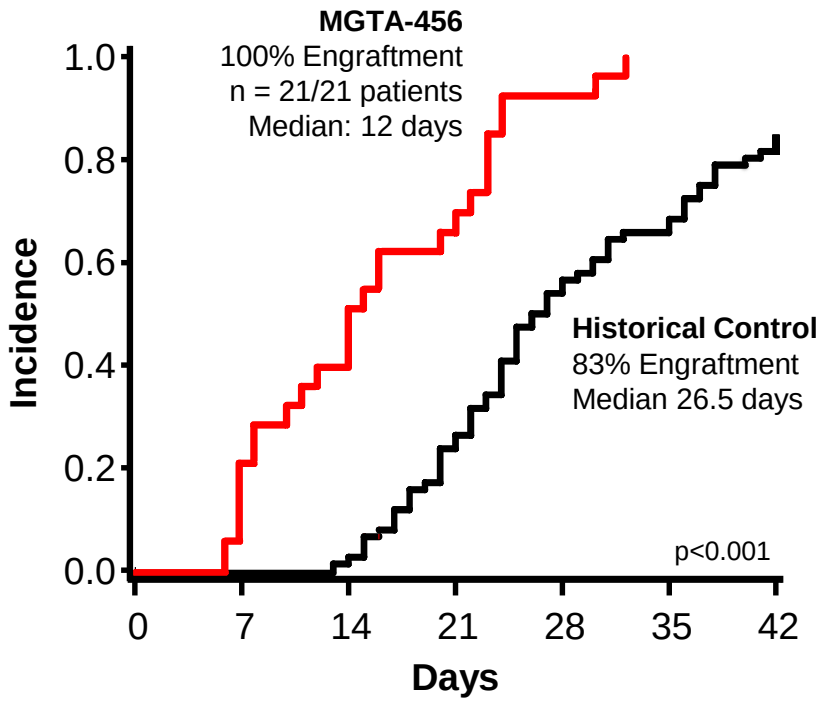
NUMBER OF CD34+ CELLS



Modified from Wagner et al., Cell Stem Cell 2016

MGTA-456 Has Been Clinically-Validated in Multiple Indications

RAPID ENGRAFTMENT WITH MGTA-456 IN HEM/ONC PATIENTS

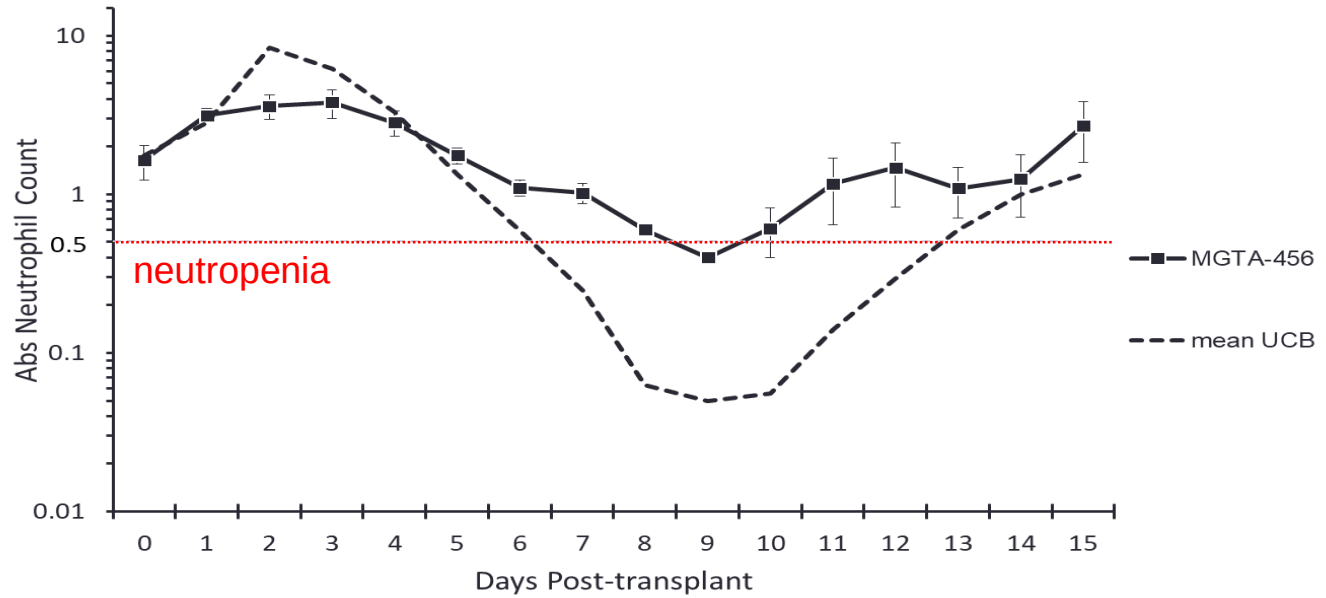


Wagner et al., ASH 2017

RATIONALE FOR Ph2 CLINICAL TRIAL IN IMDs

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

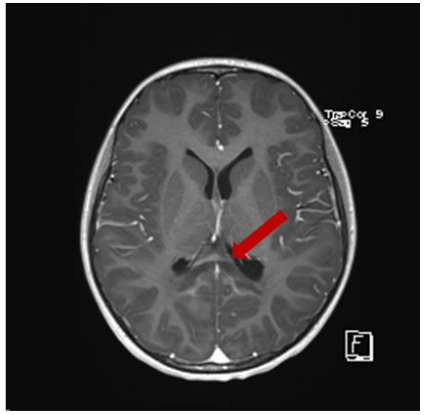
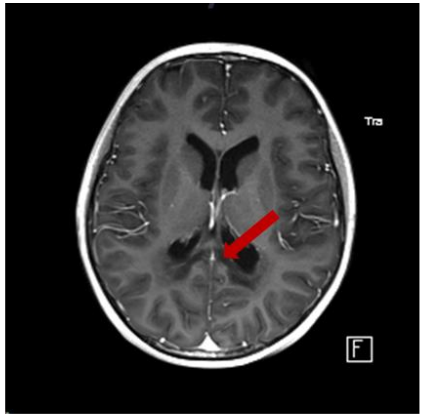
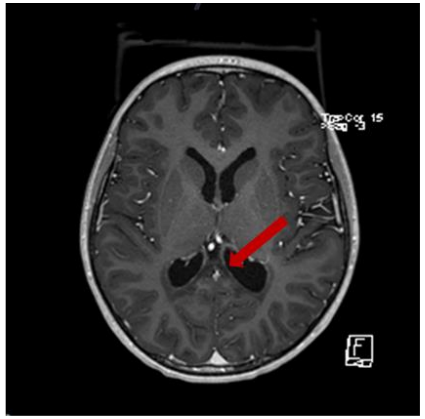
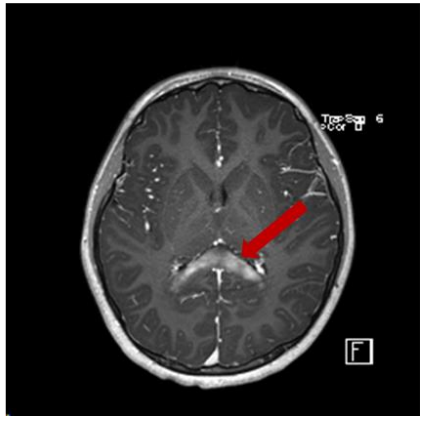
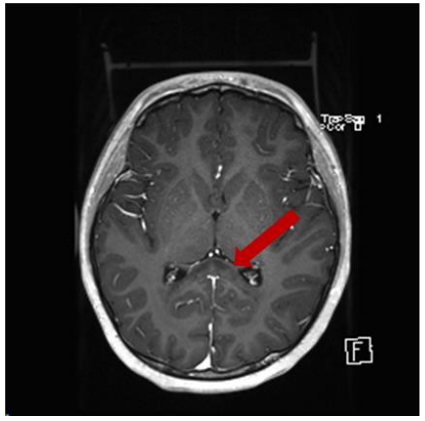
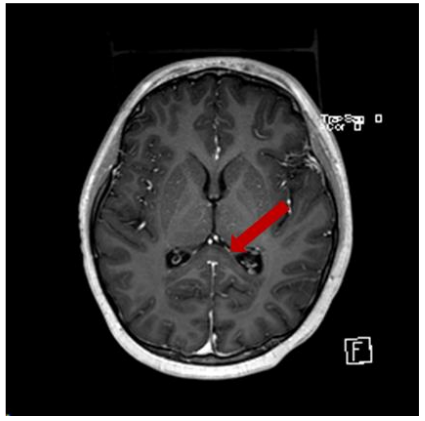
RAPID ENGRAFTMENT WITH MGTA-456 IN IMD PATIENTS



Orchard et al. AAN 2019 P4.6-059

MGTA-456 Shows Durable Improvement in cALD Neuroinflammation

REDUCED INFLAMMATION FOLLOWING TRANSPLANT OF MGTA-456

	Pre-Transplant	Day +28	Day +180
cALD-1			
cALD-2			

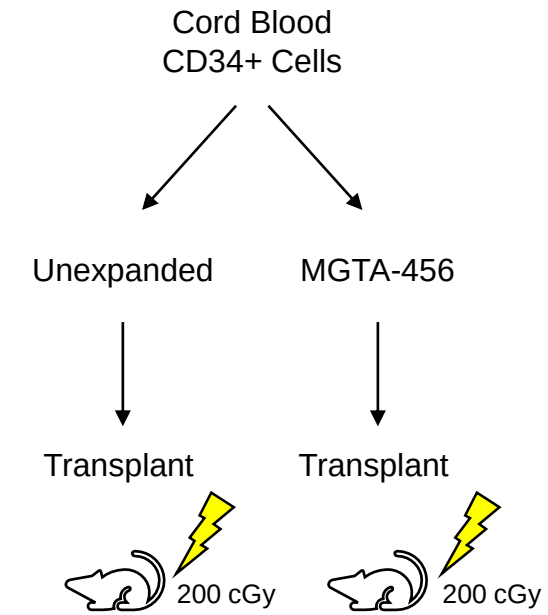
Day post-transplant	Screening	+28	+60	+100	+180
Loes Score	3	3	3	3	3
Gadolinium enhancement	Y	N	N	N	N
Neurologic function score	0	-	-	-	0

Day post-transplant	Screening	+28	+60	+100	+180
Loes Score	2	2	2	2	pend
Gadolinium enhancement	Y	N	N	N	N
Neurologic function score	0	-	-	-	0

Orchard et al. AAN 2019 P4.6-059

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

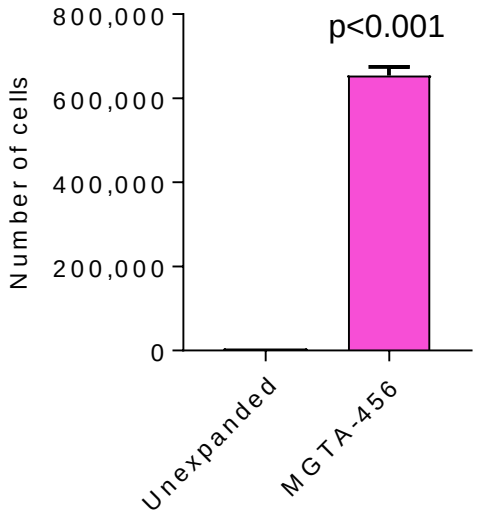
EXPERIMENTAL SCHEMA



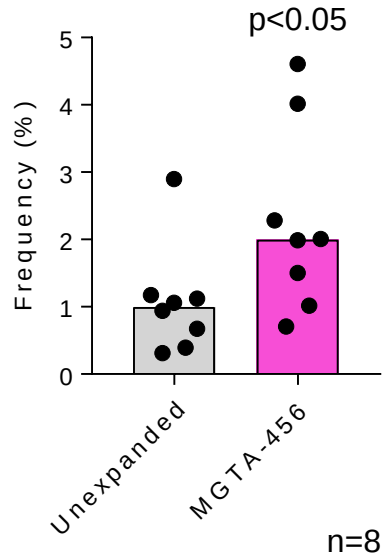
At 3 Months Post-Transplant:

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

CD34+ FOLD EXPANSION OVER 10 DAYS

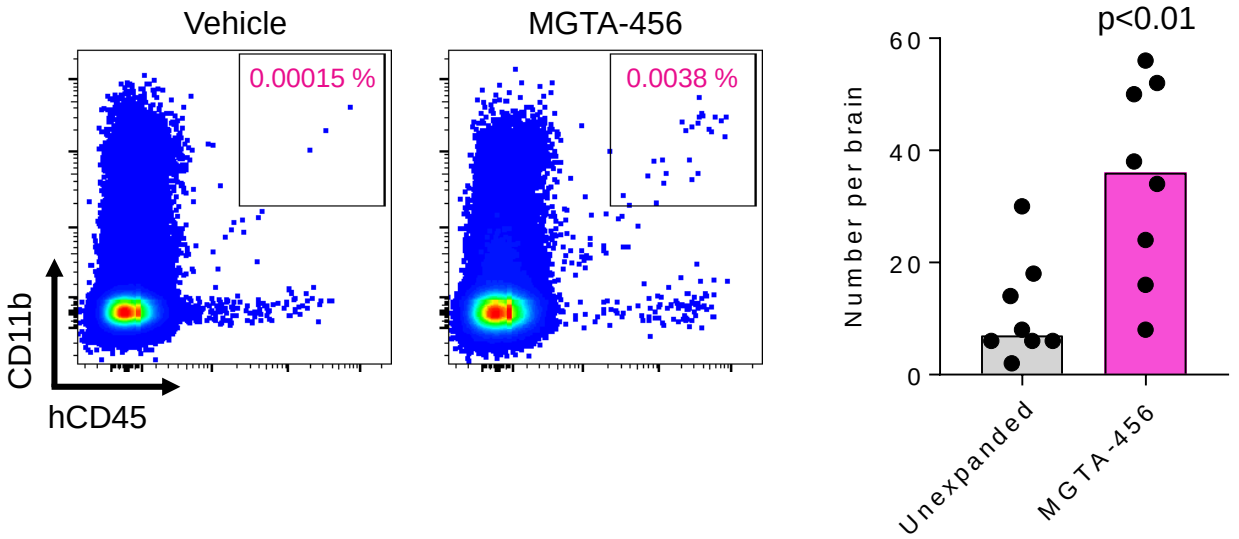


hCD45 FREQUENCY IN PERIPHERAL BLOOD



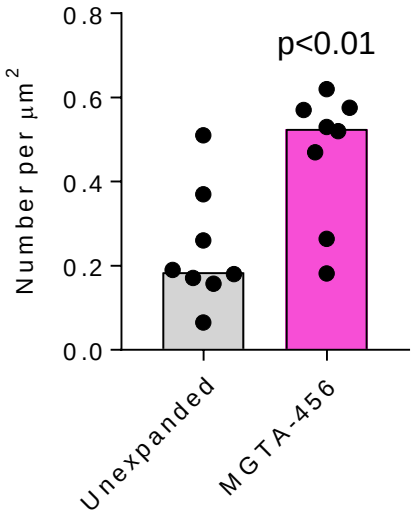
MGTA-456 Leads to Enhanced Brain Engraftment in NSG Mice Relative to Unexpanded Cells, the Standard-of-Care

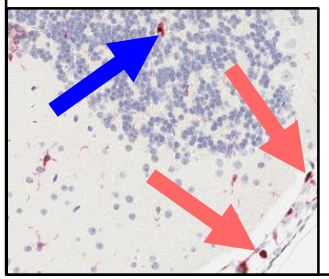
hCD45+CD11b+ NUMBER IN BRAIN



n=8 mice

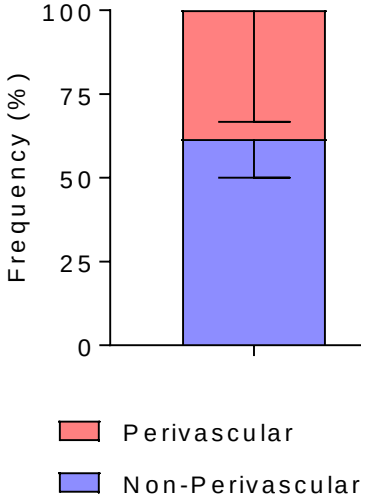
Ku80+Iba-1+ NUMBER BY IHC





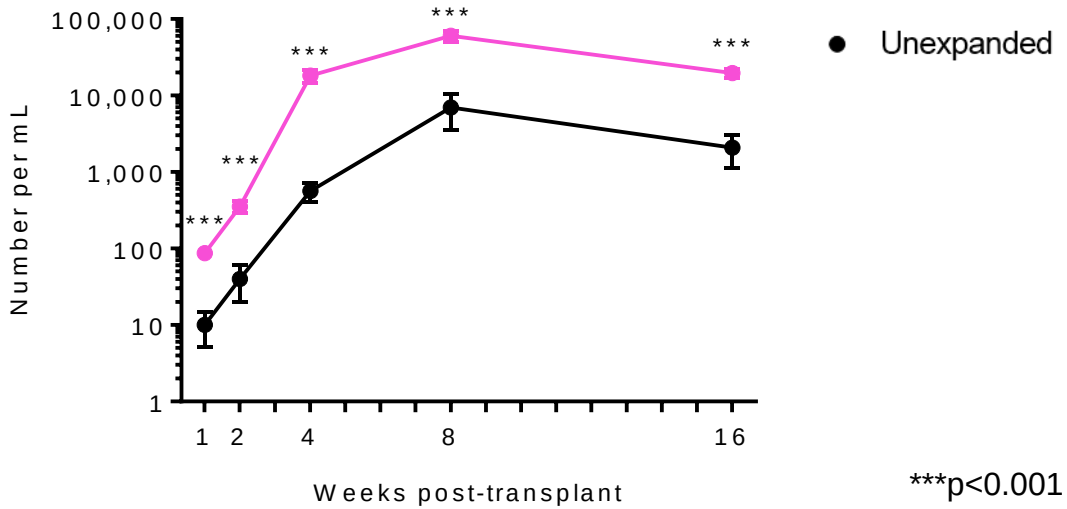
Ku80+Iba1+ microglia indicated by arrows

LOCALIZATION OF Ku80+Iba-1+ MICROGLIA



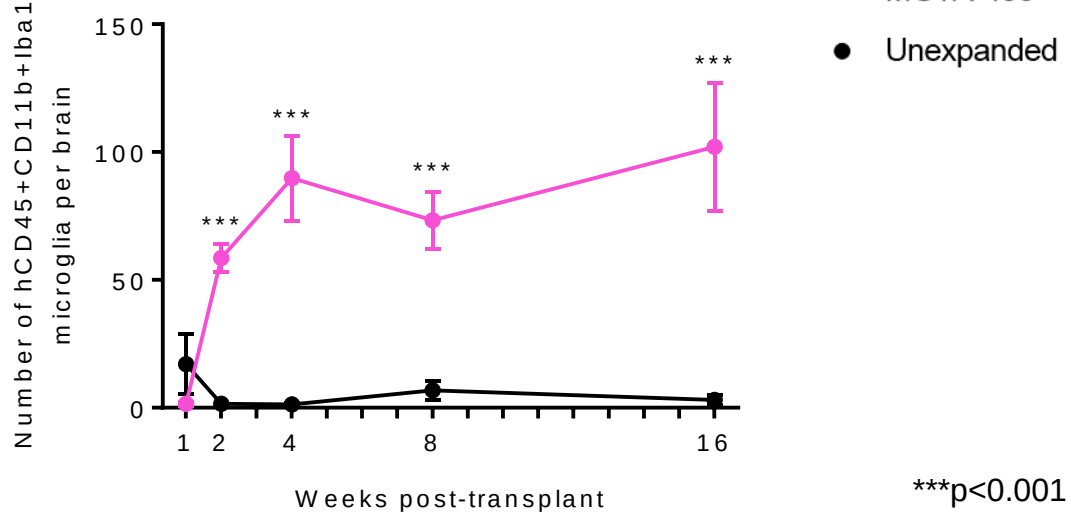
MGTA-456 Enhances Microglial Engraftment As Early As Two Weeks

HEMATOPOIETIC ENGRAFTMENT



***p<0.001
n=8 mice

MICROGLIA ENGRAFTMENT

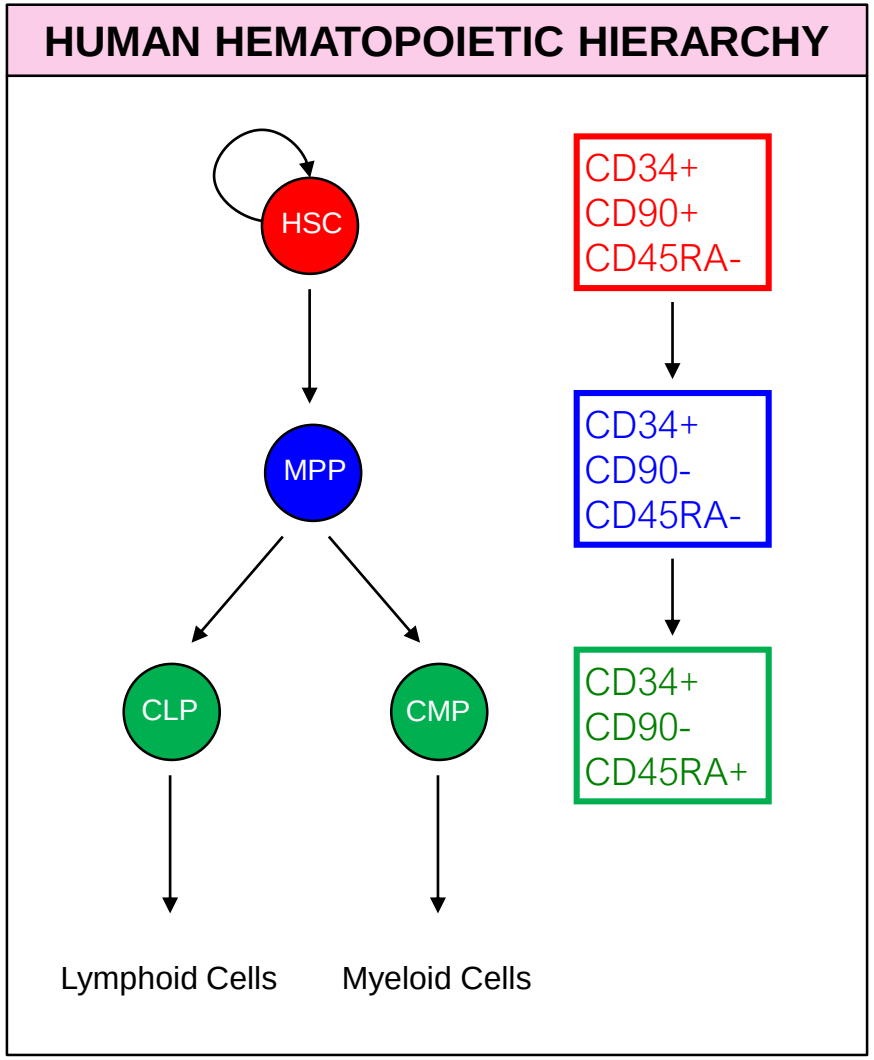


***p<0.001
n=8 mice

Which Cell Type Contributes to Microglial Engraftment?

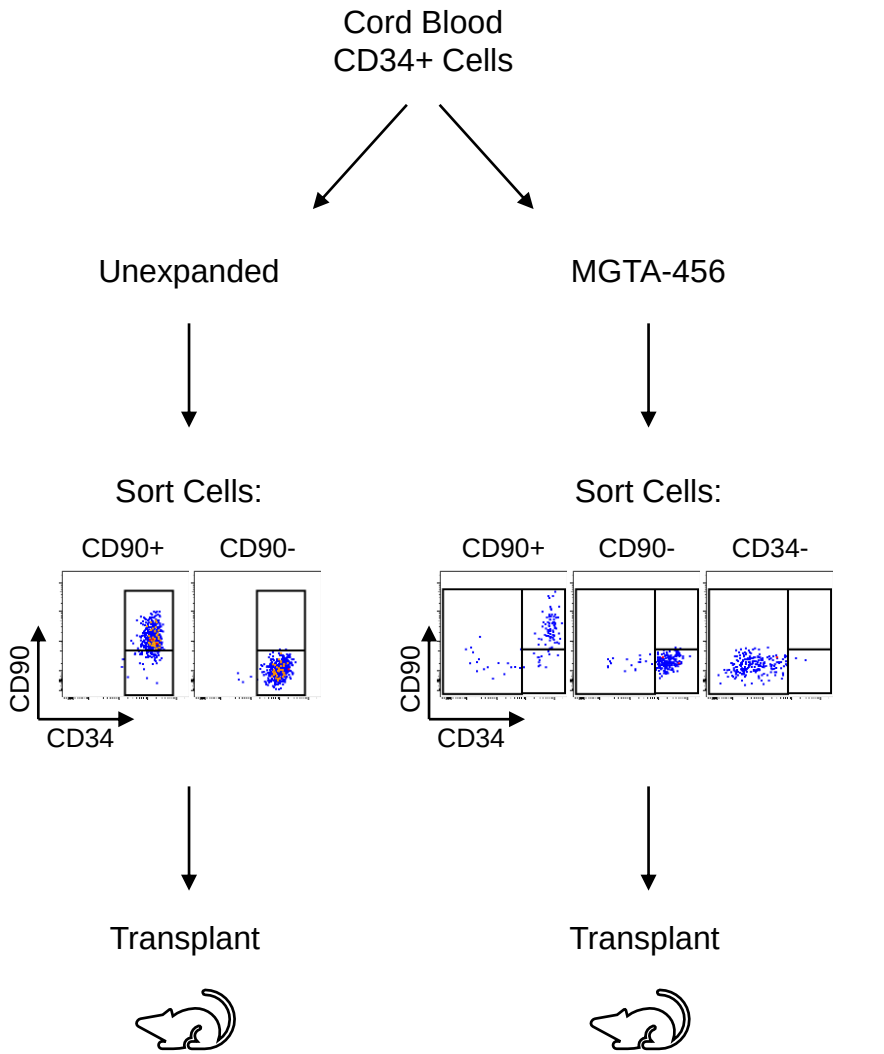
Mice were conditioned with 40 mg/kg Busulfan

Which Cell Type Is Responsible For Engraftment?

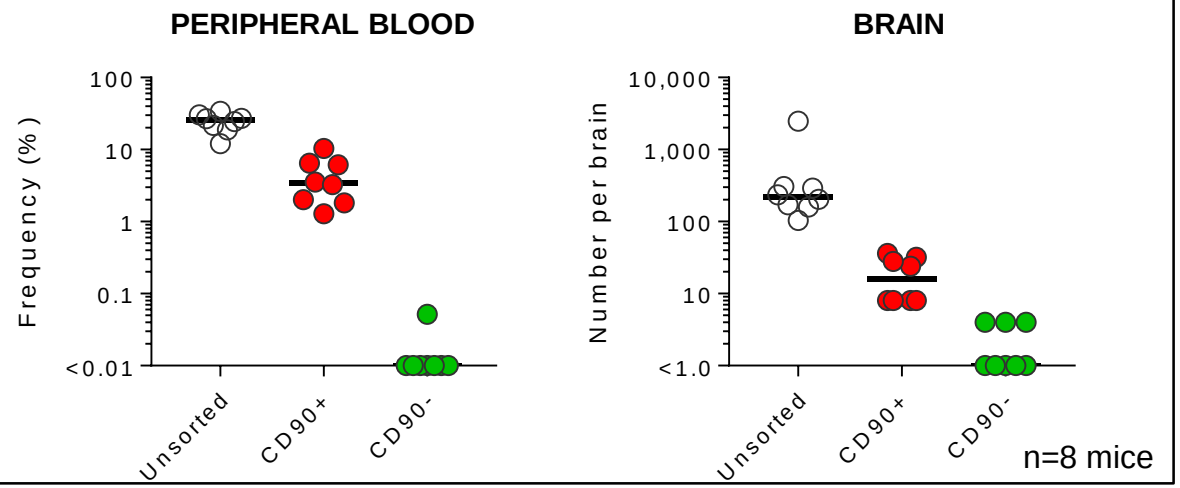


Only CD90+ Cells Contribute to Microglial Engraftment

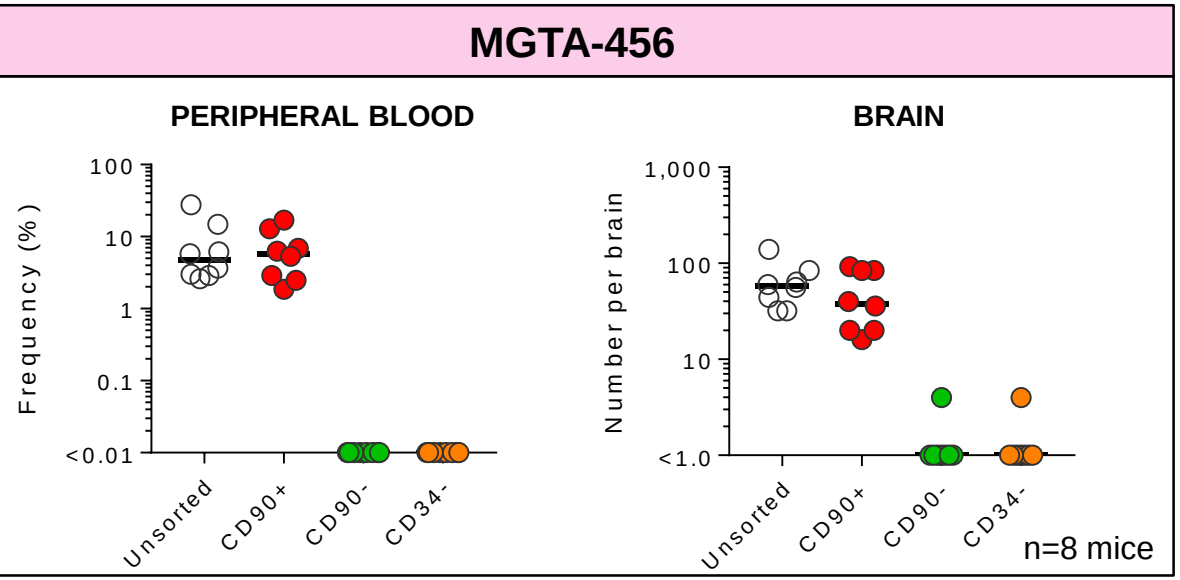
EXPERIMENTAL SCHEMA



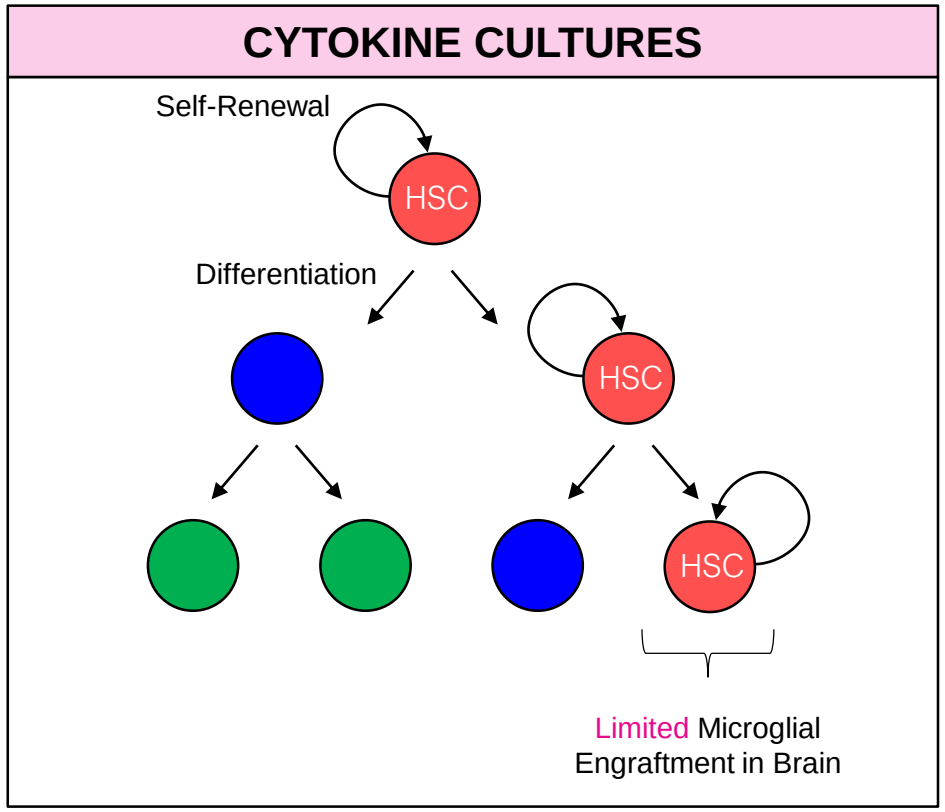
UNCULTURED

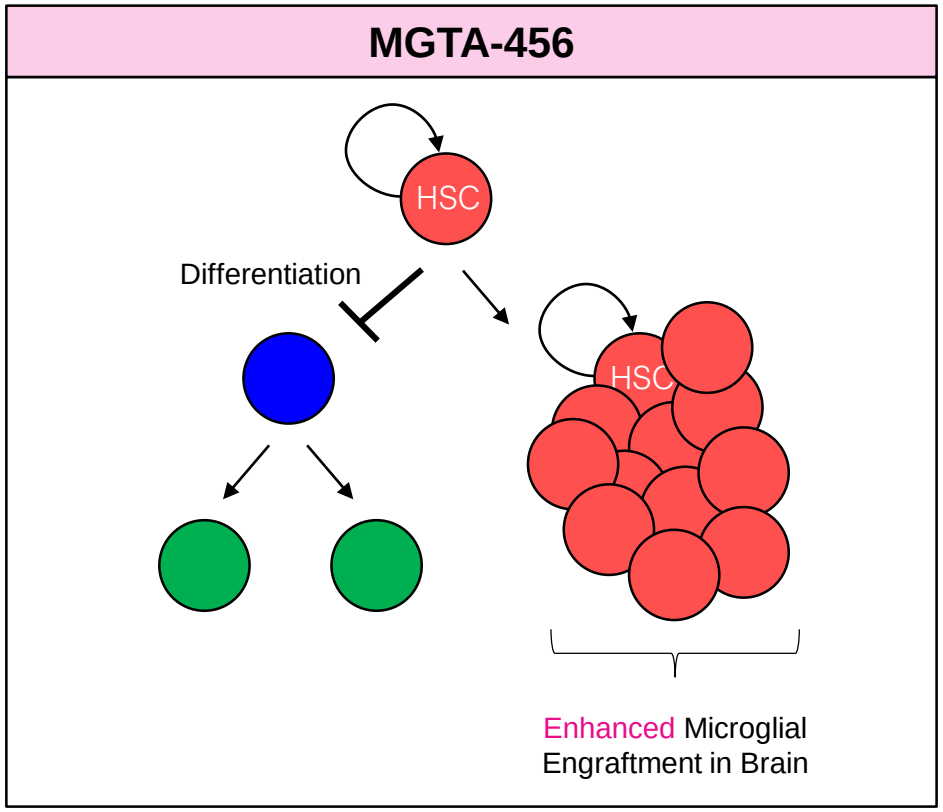


MGTA-456



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





- *Ex vivo* expanded human CD34+ cells derived from cord blood, 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 (NCT03406962) shows an early disease benefit (AAN 2019 P4.6-059: Orchard et al)

Acknowledgments

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