MGTA-456, A First-in-Class Cell Therapy With High Doses of CD34+CD90+ Cells, Enhances Speed and Level of Human Microglia Engraftment in the Brains of NSG Mice

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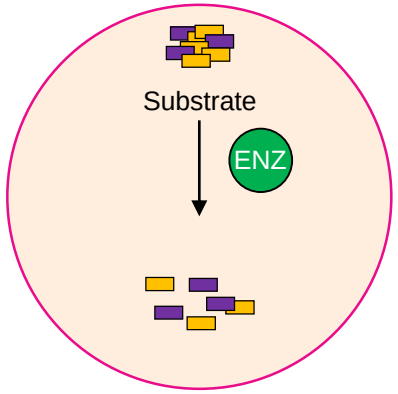
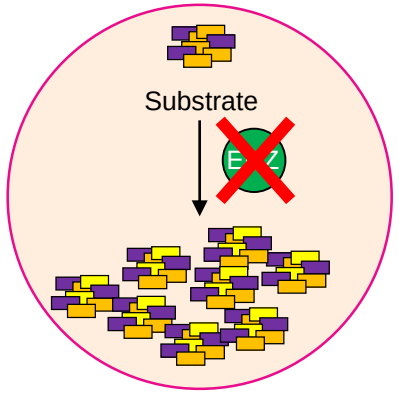
Most Inherited Metabolic Disorders (IMDs) Are Characterized by Defective Enzyme Function In Patients

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

↓

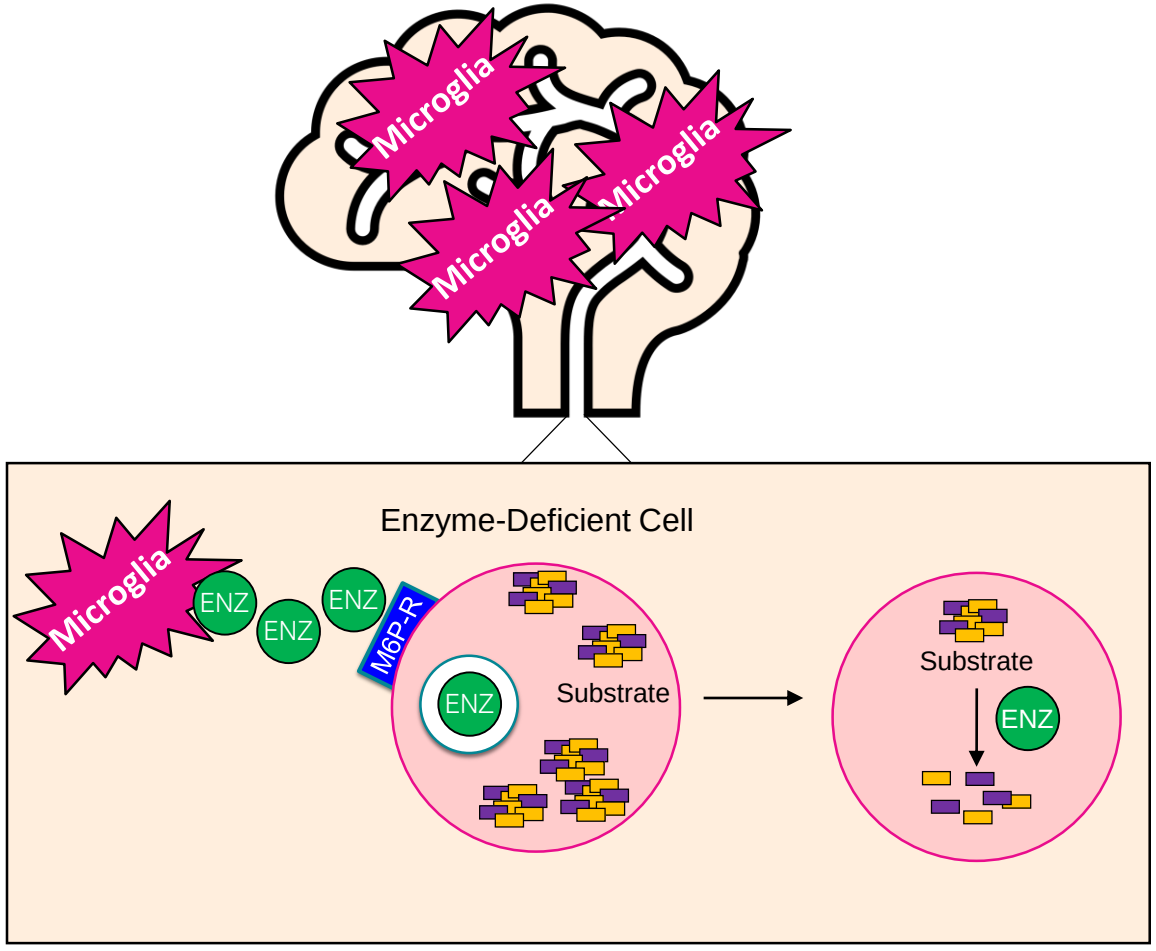
<u>Therapeutic Goal</u>
Restore Functional Enzyme Levels

↓

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

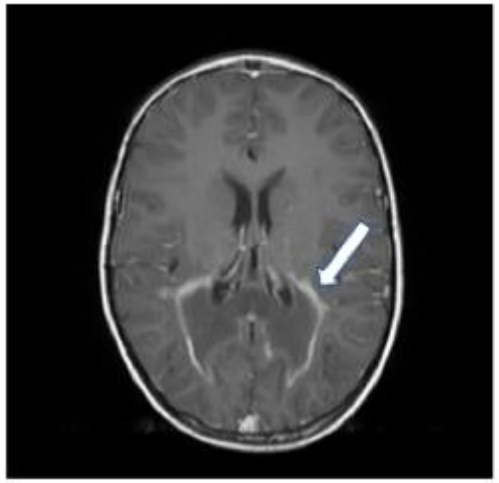
Autologous Gene Therapy

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

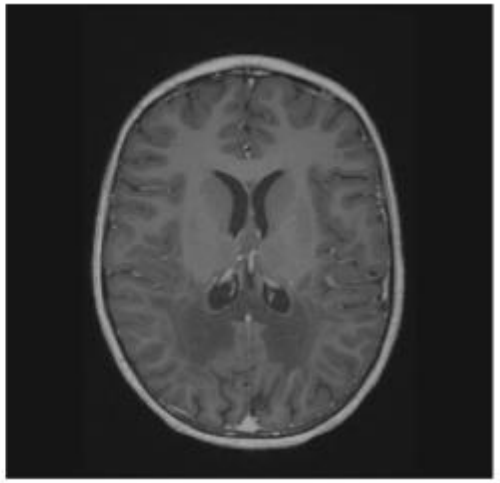
HSC Transplant is Disease-Modifying, but There is Delayed Neutrophil Engraftment and Graft Failure Remains High

REDUCED INFLAMMATION FOLLOWING TRANSPLANT IN CEREBRAL ADRENOLEUKODYSTROPHY

Pre-Transplant



Post-Transplant (Day 28)



CIBMTR OUTCOMES IN PATIENTS WITH IMDs

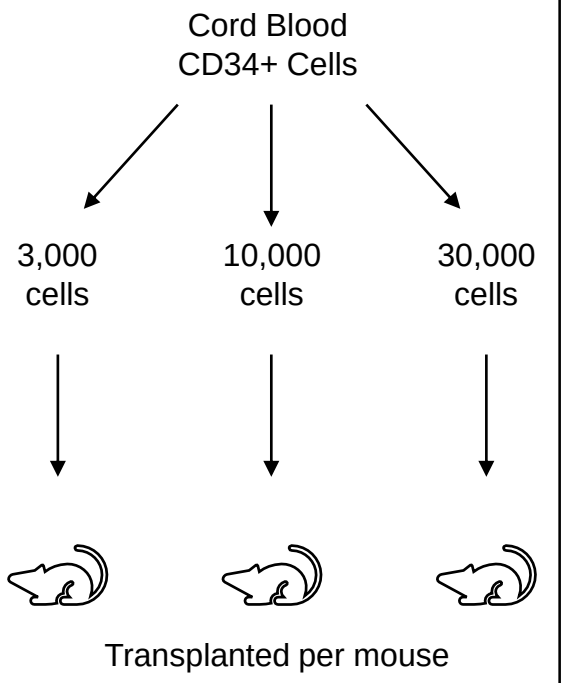
Endpoint	Hurler Syndrome	Adrenoleukodystrophy
Neutrophil Engraftment (Day 28)	84% (95% CI: 79-89%)	80% (95% CI: 73-86%)
Graft Failure (1 year)	21% (95% CI: 15-27)%	24% (95% CI: 17-32%)

Lund et al. ASH 2018 Abstract #4628

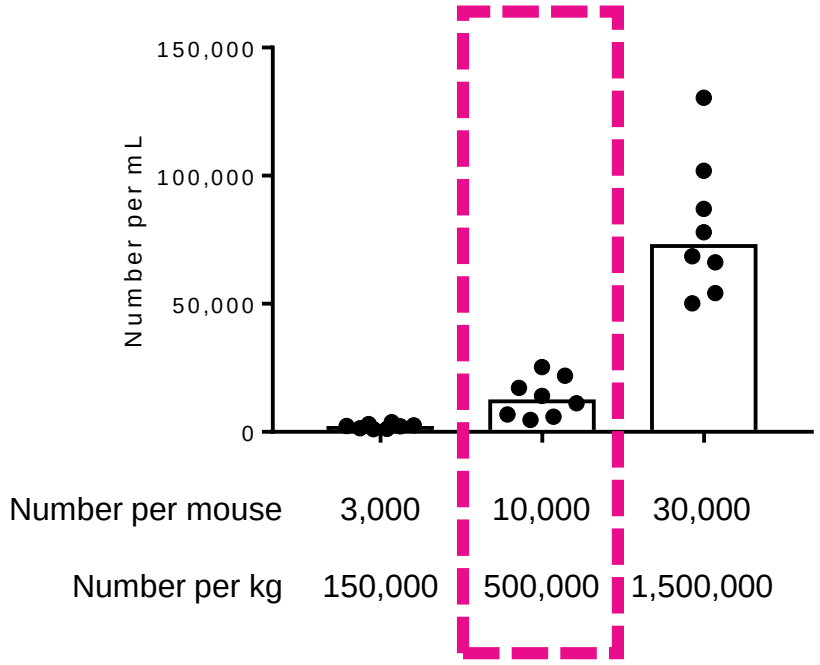
Can Patient Outcomes Be Further Improved By Increasing Cell Dose?

Increased Cell Dose Leads to Increased Hematopoietic and Brain Engraftment

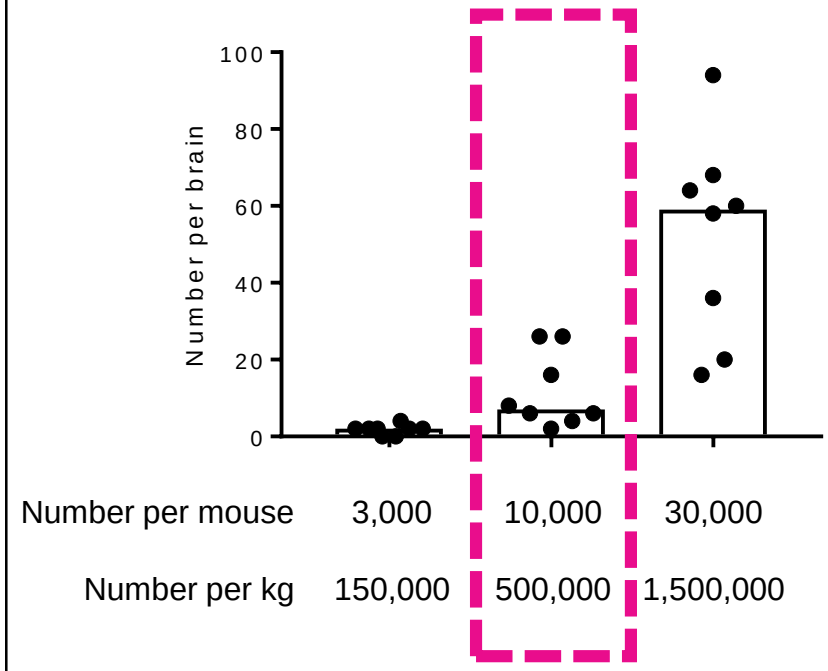
EXPERIMENTAL SCHEMA



PERIPHERAL BLOOD ENGRAFTMENT

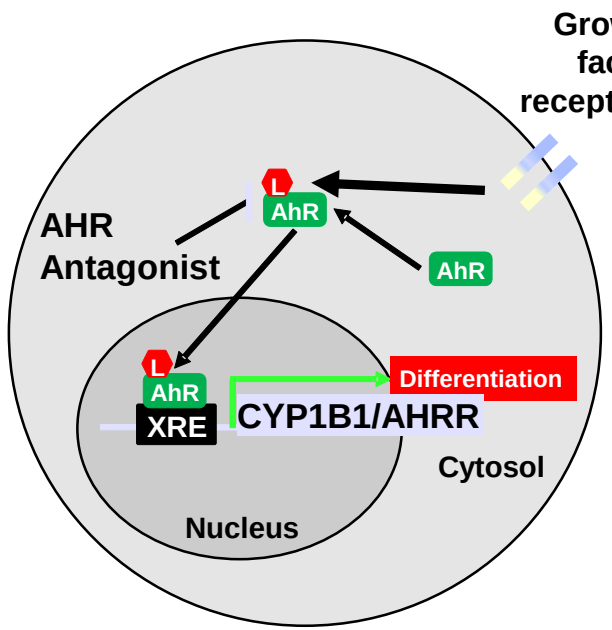


BRAIN ENGRAFTMENT



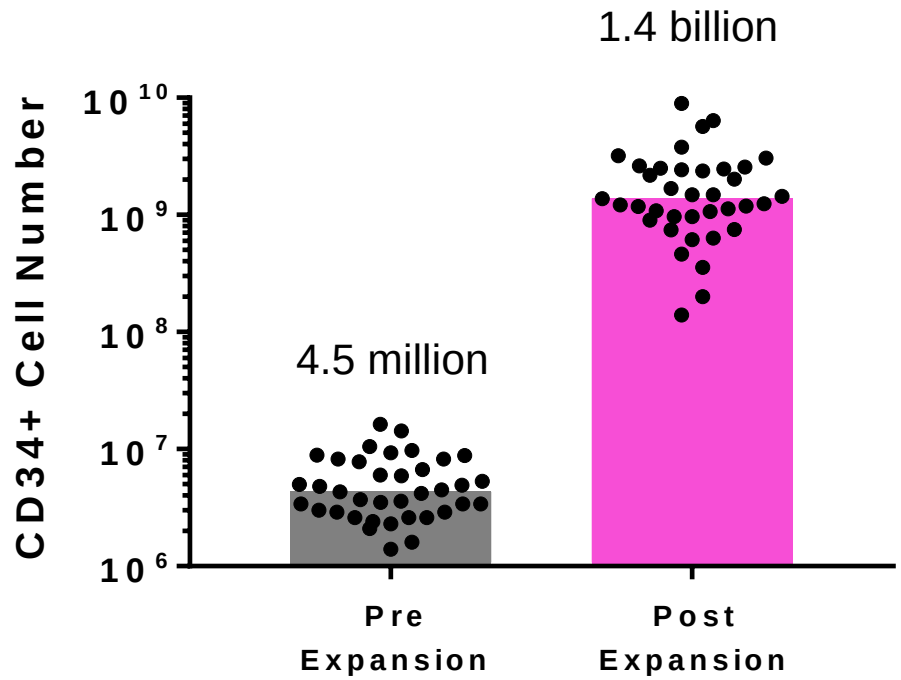
MGTA-456: Aryl Hydrocarbon Receptor (AHR) Antagonism as a Mechanism of HSC Expansion

METHOD TO EXPAND HUMAN HSCs



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

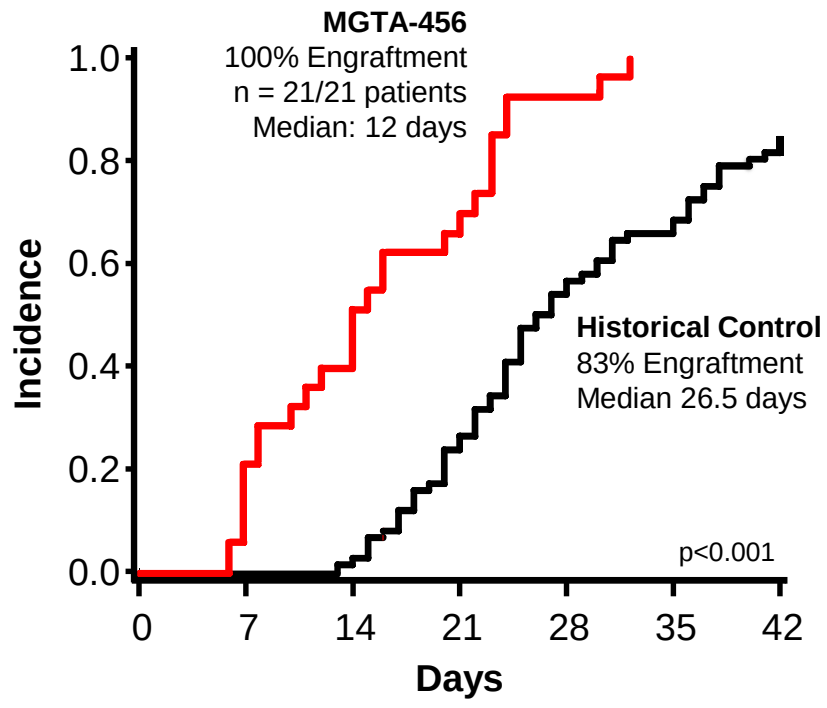
NUMBER OF CD34+ CELLS



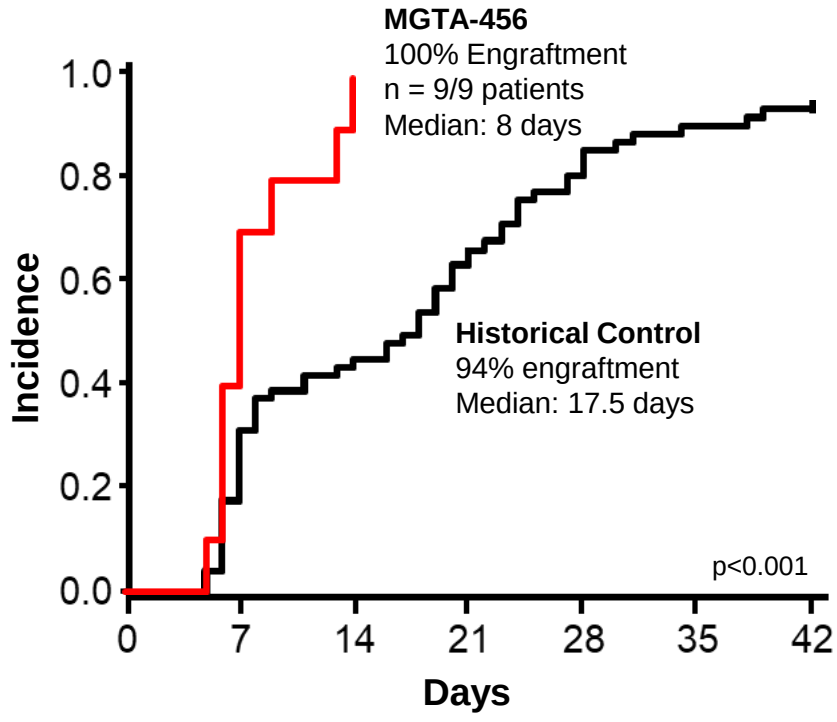
Modified from Wagner et al., Cell Stem Cell 2016

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

WITH MYELOABLATIVE CONDITIONING



WITH NON-MYELOABLATIVE CONDITIONING



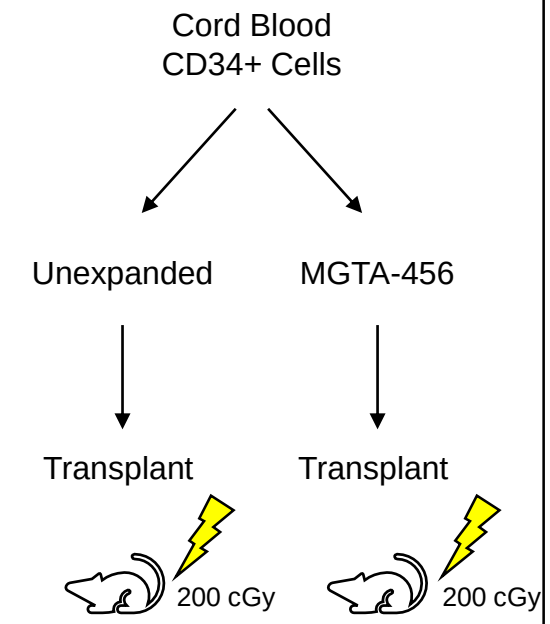
Wagner et al., ASH 2017

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 Relative to Unexpanded Cells, the Standard-of-Care

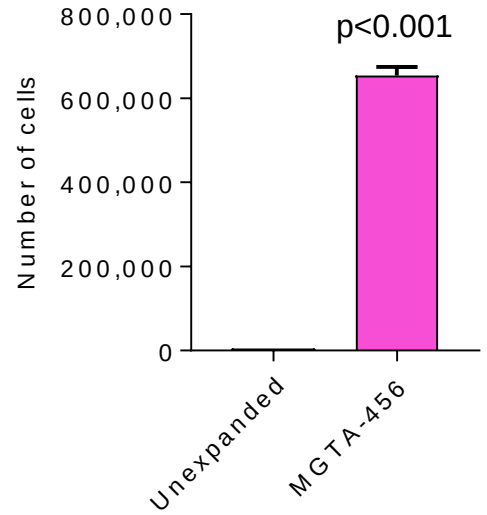
EXPERIMENTAL SCHEMA



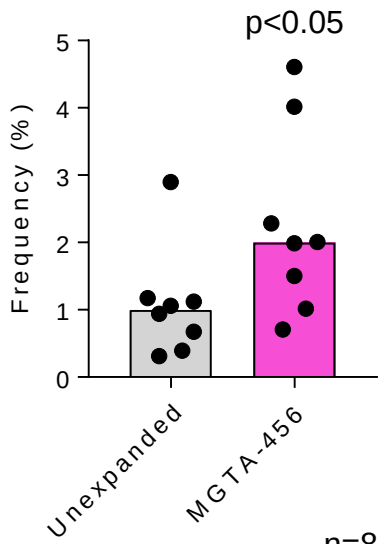
At 3 Months Post-Transplant:

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

CD34+ FOLD EXPANSION OVER 10 DAYS



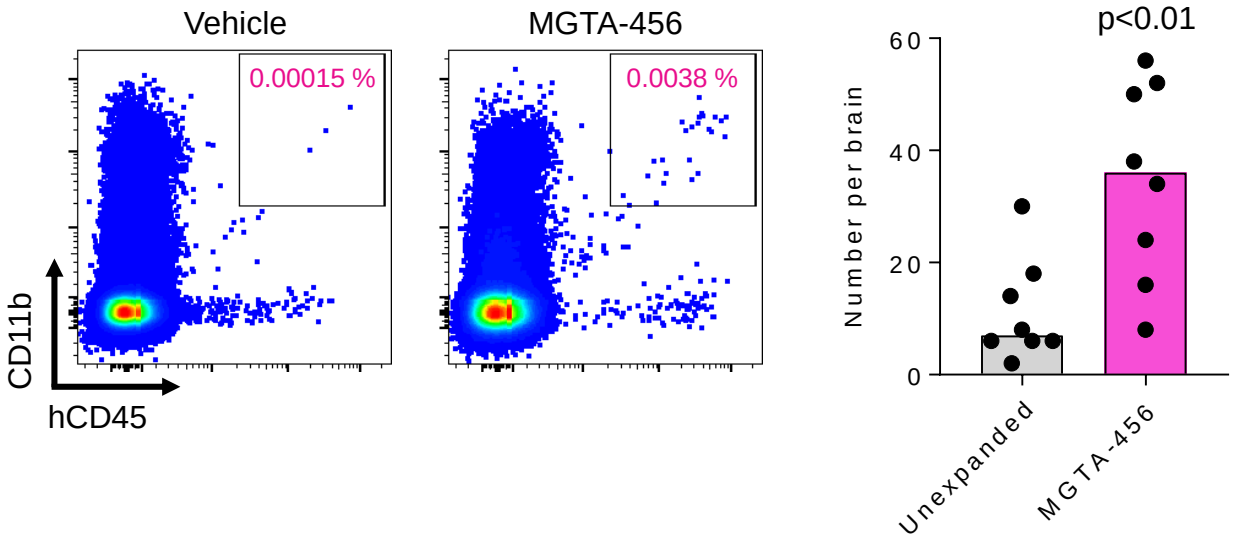
hCD45 FREQUENCY IN PERIPHERAL BLOOD



n=8 mice

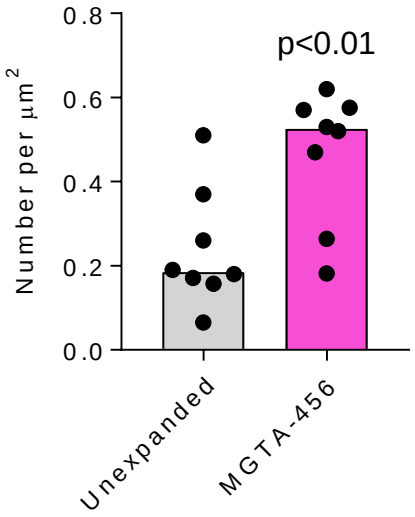
MGTA-456 Leads to Enhanced Brain Engraftment in NSG Mice Relative to Unexpanded Cells, the Standard-of-Care

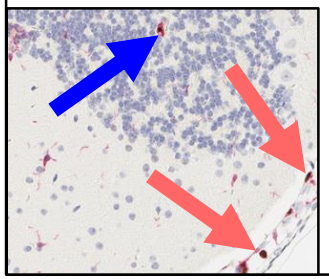
hCD45+CD11b+ NUMBER IN BRAIN



n=8 mice

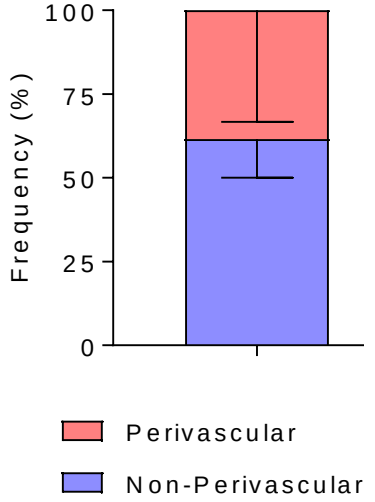
Ku80+Iba-1+ NUMBER BY IHC





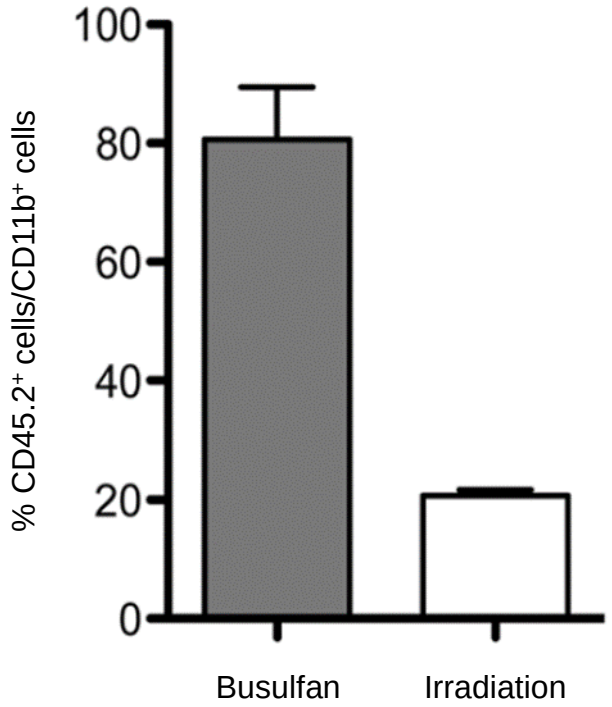
Ku80+Iba1+ microglia indicated by arrows

LOCALIZATION OF Ku80+Iba-1+ MICROGLIA



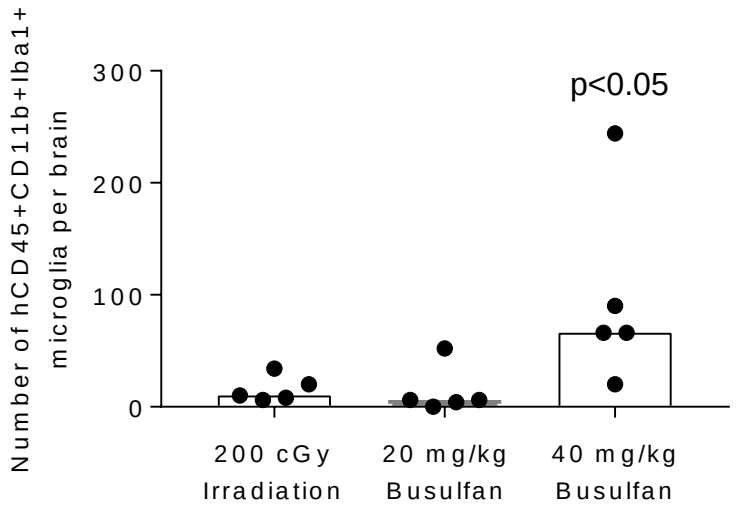
Busulfan Dosing Enables Enhanced Brain Engraftment Compared To Irradiation

MICROGLIA ENGRAFTMENT IN IMMUNOCOMPETENT MICE



Modified from Capotondo et al. Sci Adv 2017

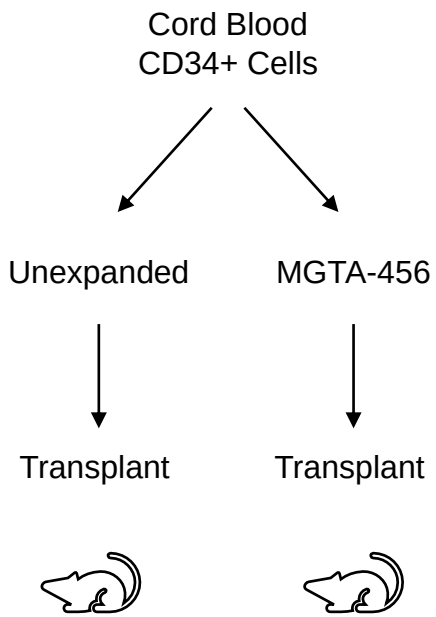
MICROGLIA ENGRAFTMENT IN IMMUNODEFICIENT MICE



n=5 mice

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

EXPERIMENTAL SCHEMA



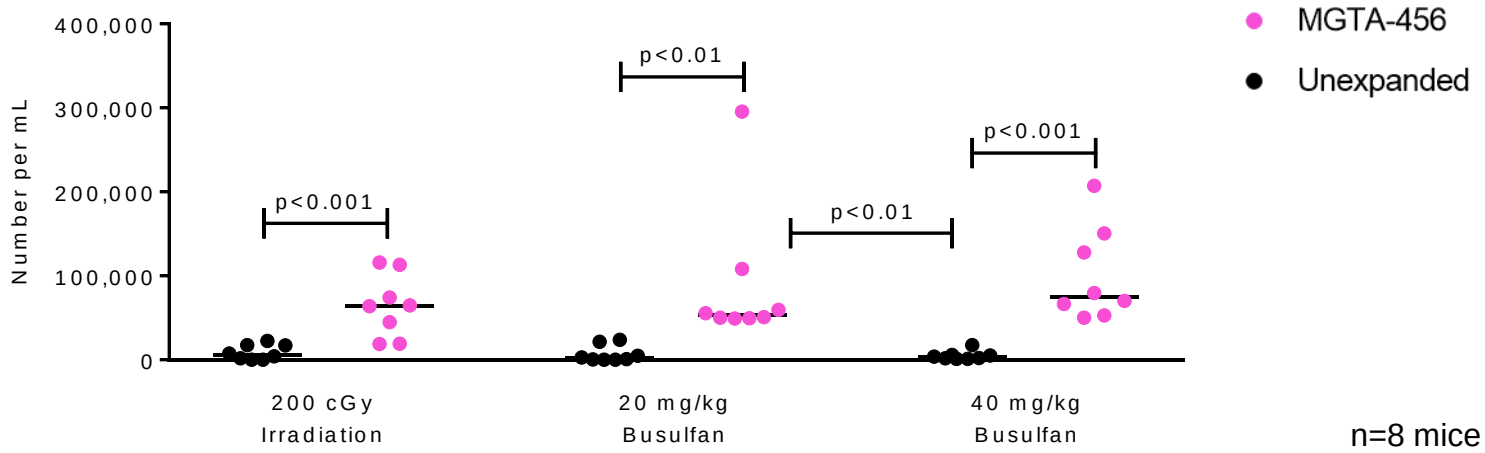
Condition mice with:

Low Dose BU (20 mg/kg)

High Dose BU (40 mg/kg)

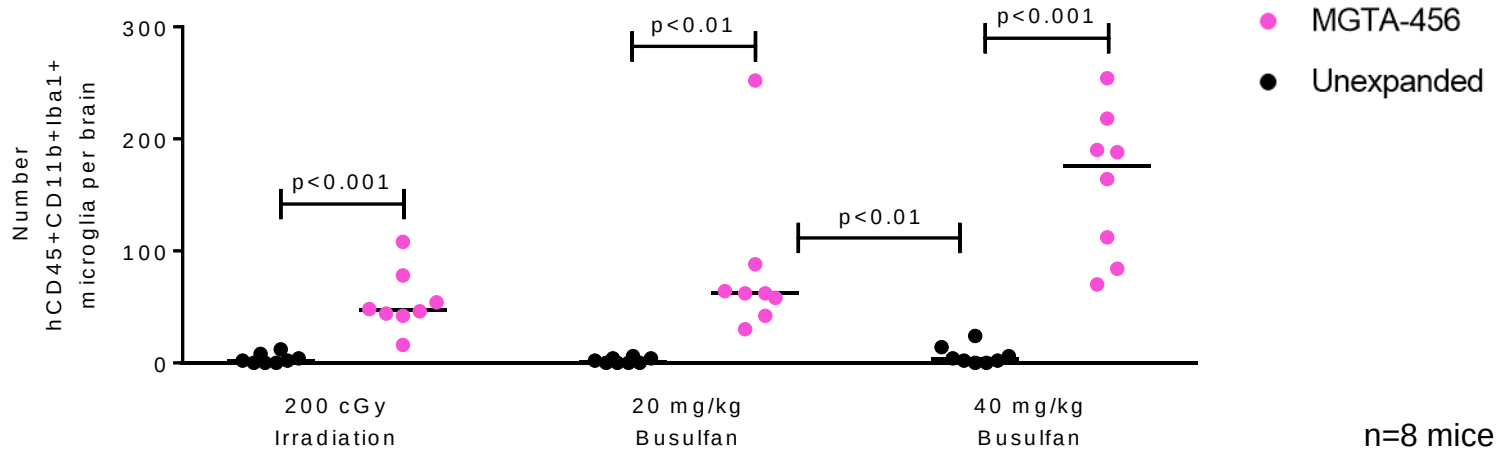
200 cGy Irradiation

HEMATOPOIETIC ENGRAFTMENT



n=8 mice

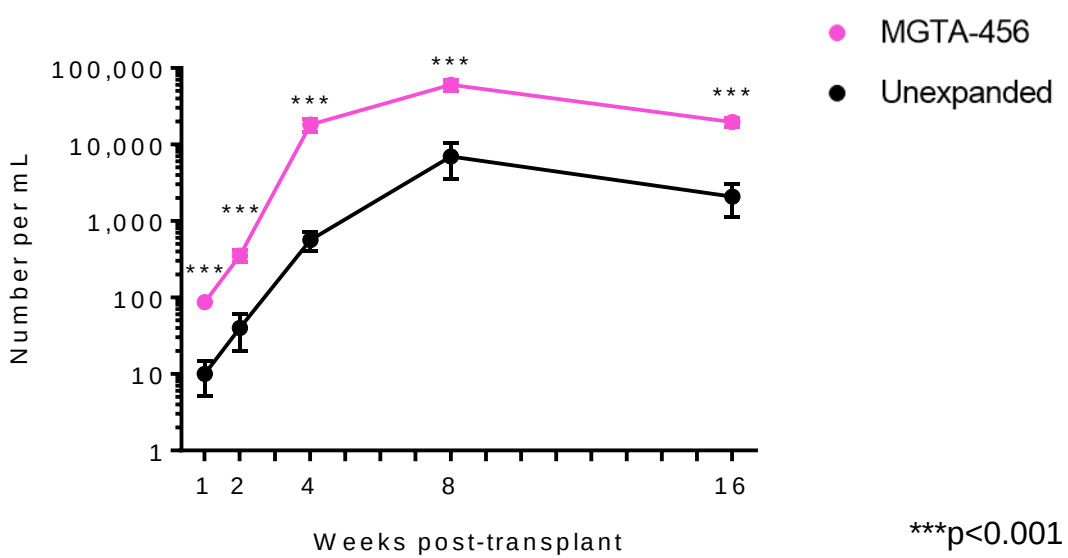
MICROGLIA ENGRAFTMENT



n=8 mice

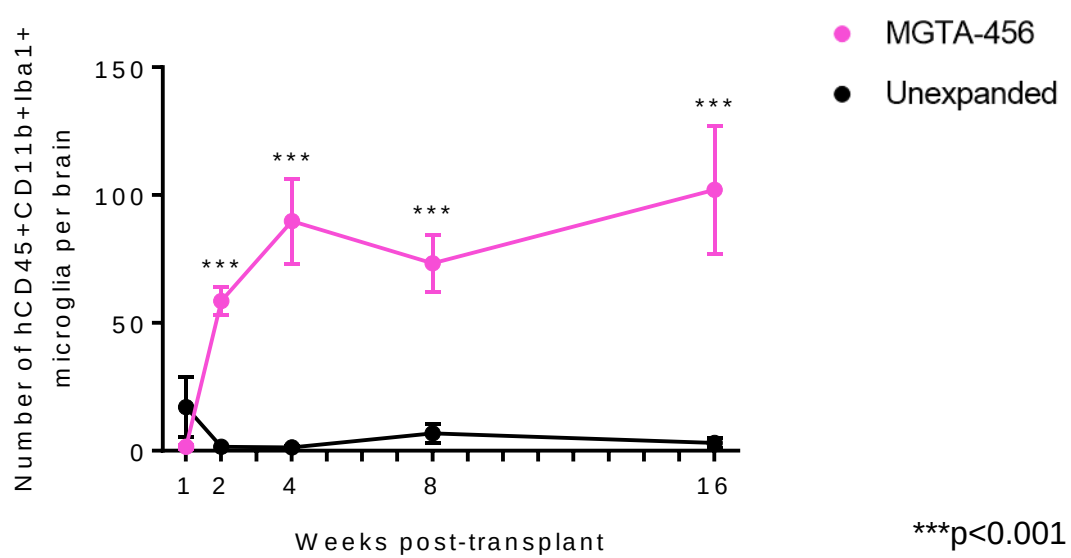
MGTA-456 Enhances Microglial Engraftment As Early As Two Weeks

HEMATOPOIETIC ENGRAFTMENT



***p<0.001
n=8 mice

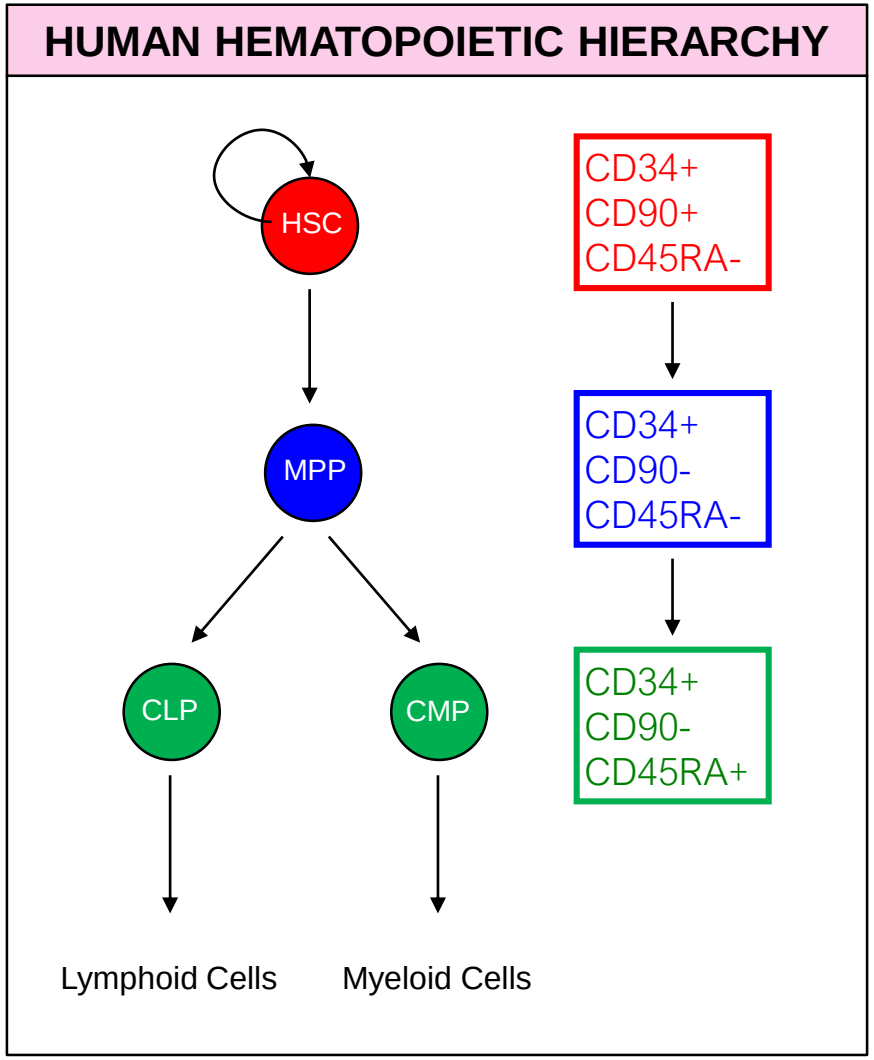
MICROGLIA ENGRAFTMENT



***p<0.001
n=8 mice

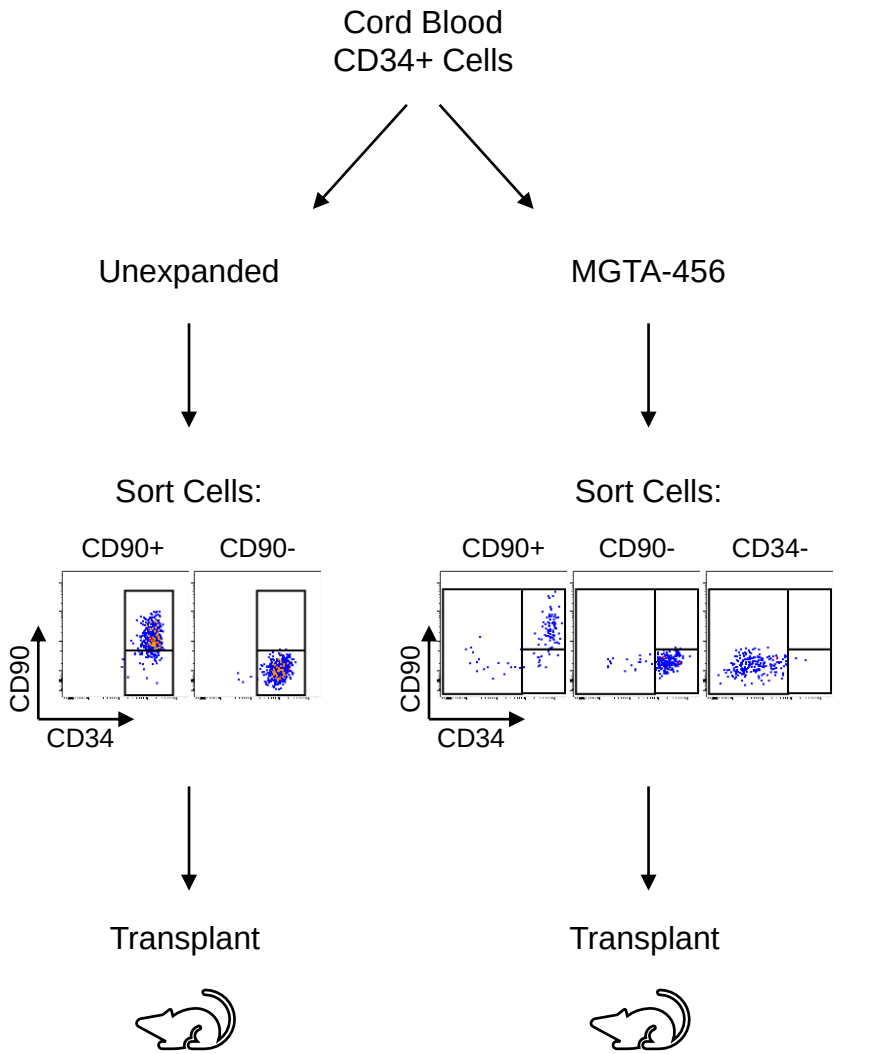
Which Cell Type Contributes to Microglial Engraftment?

Which Cell Type Is Responsible For Engraftment?

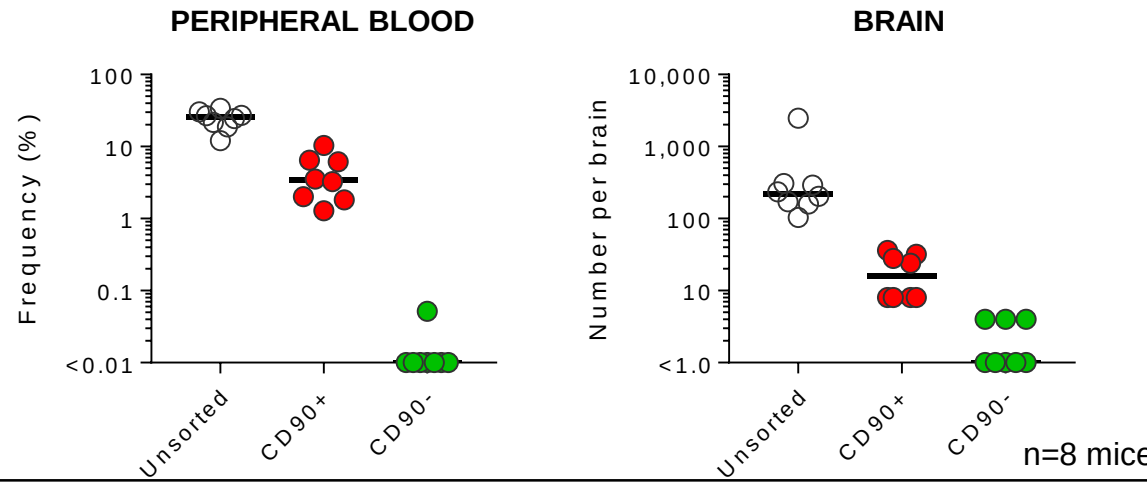


Only CD90+ Cells Contribute to Microglial Engraftment

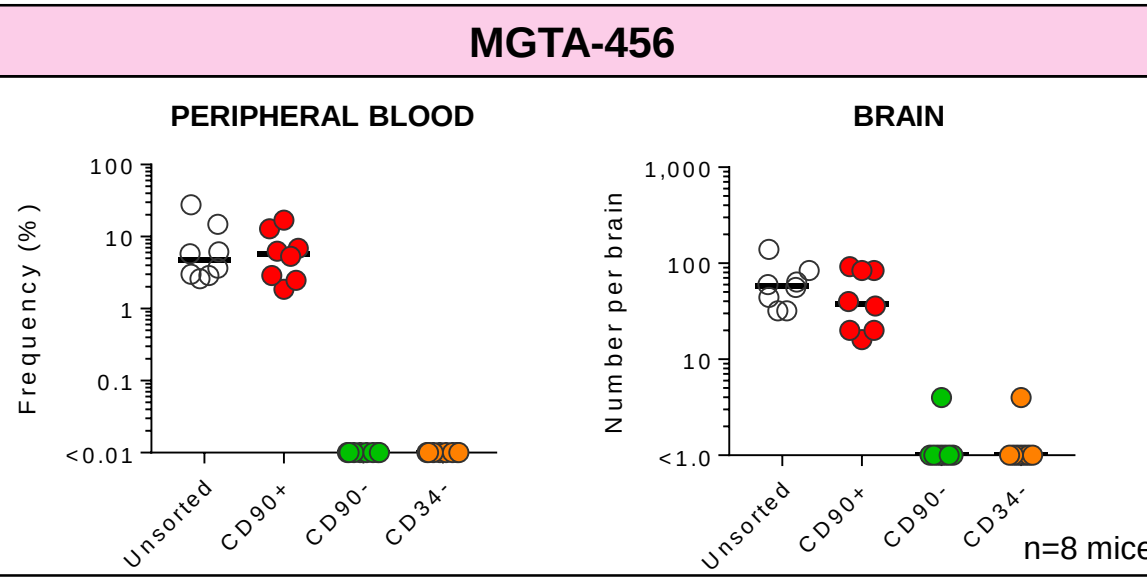
EXPERIMENTAL SCHEMA



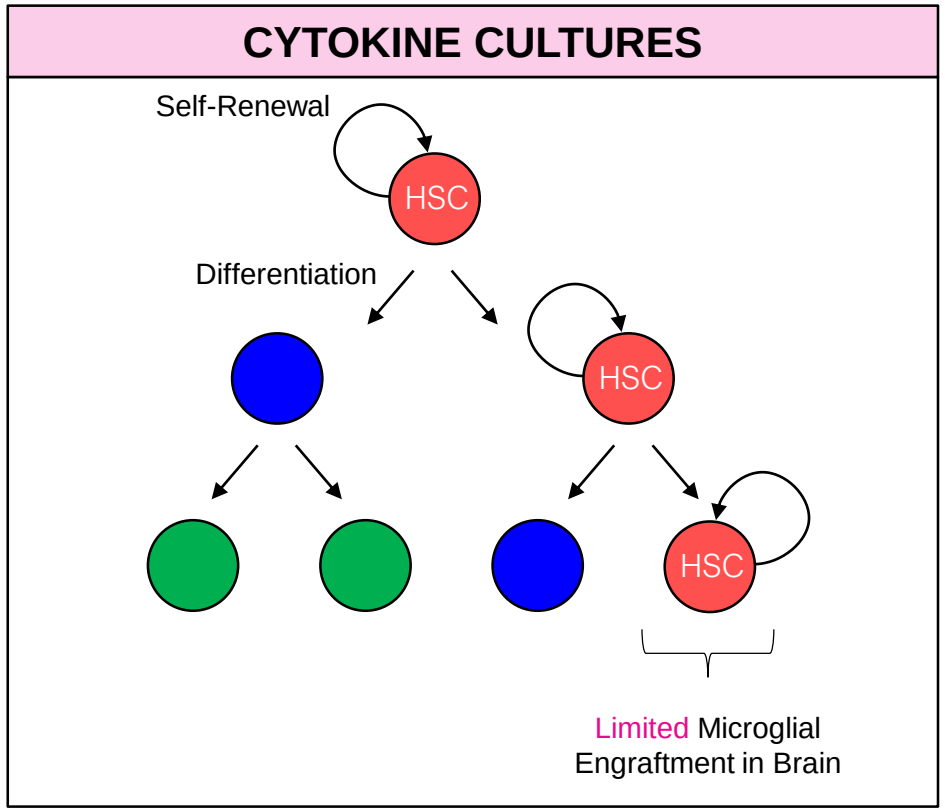
UNCULTURED

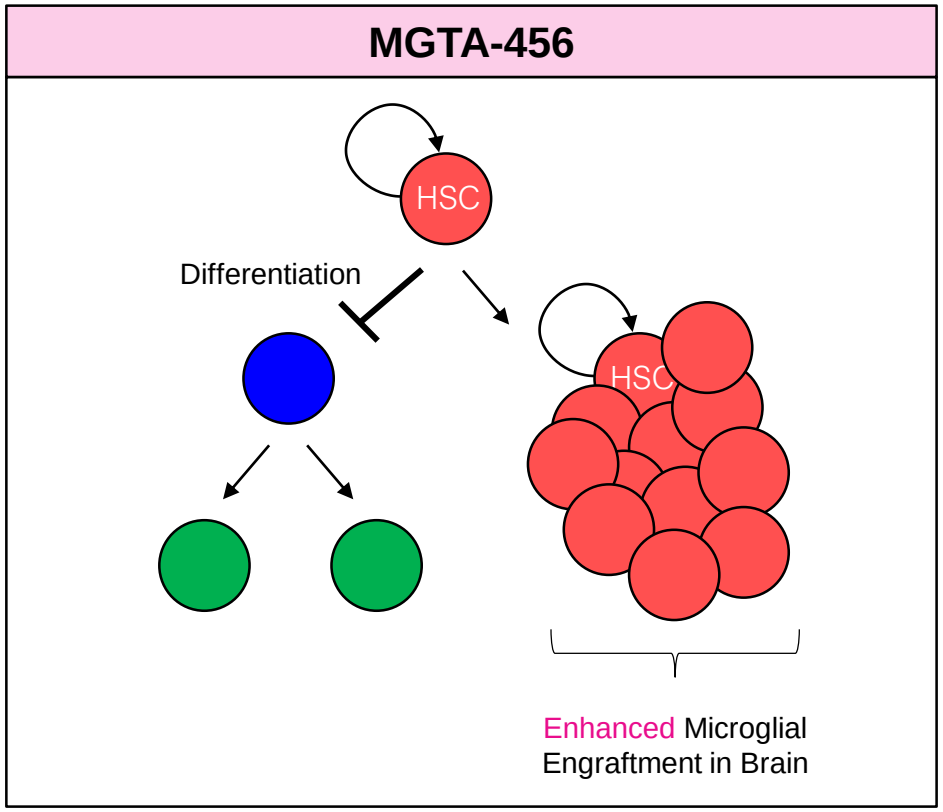


MGTA-456



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)

Acknowledgments

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