High Dose Hematopoietic Stem Cell Transplantation Leads to Rapid Neural and Peripheral Disease Cross-Correction via Robust Hematopoietic and Microglia Recovery

Kevin A. Goncalves, Sharon L. Hyzy, Melissa L. Brooks, Hans J. Hertzler, Anthony E. Boitano, Michael P. Cooke
Magenta Therapeutics, Cambridge, MA

BACKGROUND

- Allogeneic hematopoietic stem cell transplant (HSCT) is a one-time treatment that halts disease progression and prevents or ameliorates neurological damage in selected inherited metabolic disorders (IMDs).
- Donor-derived cells, including microglia in the central nervous system (CNS), limit disease progression post-HSCT via production of normal enzyme in a process called cross-correction.
- A standard cell dose used in HSCT is sub-optimal, resulting in delayed hematopoietic recovery and slower correction of CNS defects (Lund et al BBMT 2019).
- The impact of cell dose on disease outcomes in IMDs like mucopolysaccharidosis I (Hurler syndrome) and mechanism of cross-correction are unknown.
- MGTA-456 is a high cell dose therapy that leads to fast and 100% engraftment in malignant and nonmalignant diseases (Wagner et al., ASH 2017; Orchard et al. AAN 2019).

BRAIN MICROGLIA ENGRAFTMENT IS DOSE-DEPENDENT IN WILD-TYPE C57BL/6 MICE

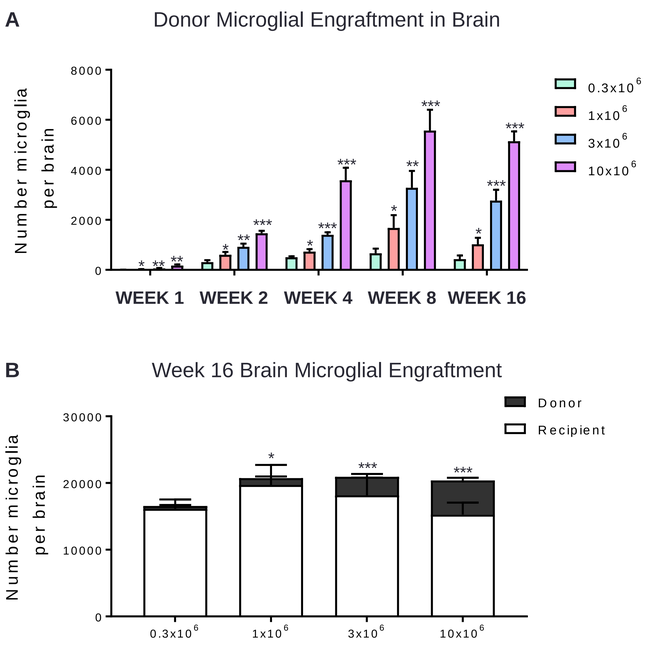

Figure 1. (A) Wild-type C57Bl/6 mice were conditioned with a myeloablative dose of busulfan and transplanted with congenic CD45.1 bone marrow at 0.3-10 x 10^6 cells/mouse. Donor microglia number (CD45.1+CD11b+) was measured by flow cytometry. A dose-dependent increase in microglia was observed as early as 1-week post-HSCT, where 10x10^6 cells led to a 26-fold higher number of donor microglia compared to 0.3x10^6 cells (p<0.01). The proportion of donor microglia number (CD45.1+CD11b+) versus endogenous microglia (CD45.2+CD11b+) was measured at week 16 **(B)**. Bars represent mean ± SEM. Statistics were calculated by one-tailed Student's t-test (*p<0.05, **p<0.01, ***p<0.001, relative to 0.3x10^6 cell dose group).

BRAIN MICROGLIA ENGRAFTMENT IS DOSE-DEPENDENT IN *IDUA*$^{-/-}$ MICE

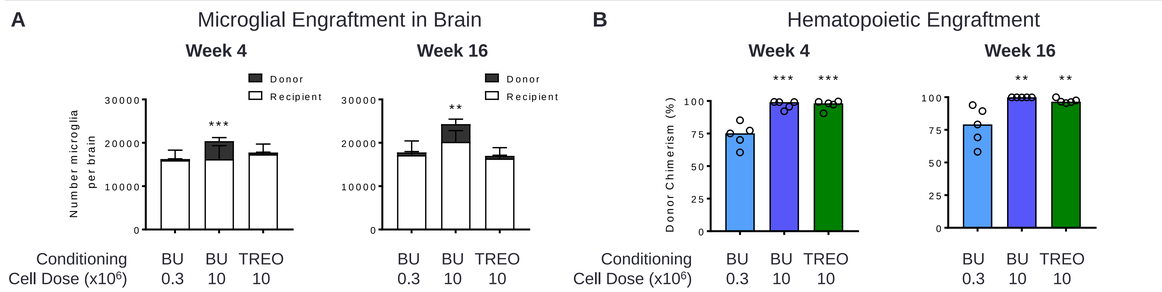

Figure 2. CD45.2 *Idua*$^{-/-}$ mice were conditioned with a myeloablative dose of busulfan (BU) or treosulfan (TREO) and transplanted with 0.3x10^6 or 10x10^6 CD45.1 bone marrow cells per mouse (n=5 per group). **(A)** Microglia number was measured in the brain by flow cytometry. **(B)** Peripheral blood donor chimerism (CD45.1) was measured by flow cytometry. Bar represents median; each symbol represents an individual mouse (n=5 mice per group). Bars represent mean ± SEM (n=5 mice per group). **p<0.01, ***p<0.001 compared to 0.3x10^6 cell dose group.

RAPID AND COMPLETE DISEASE CROSS-CORRECTION IN THE CNS WITH HIGH DOSE HSCT

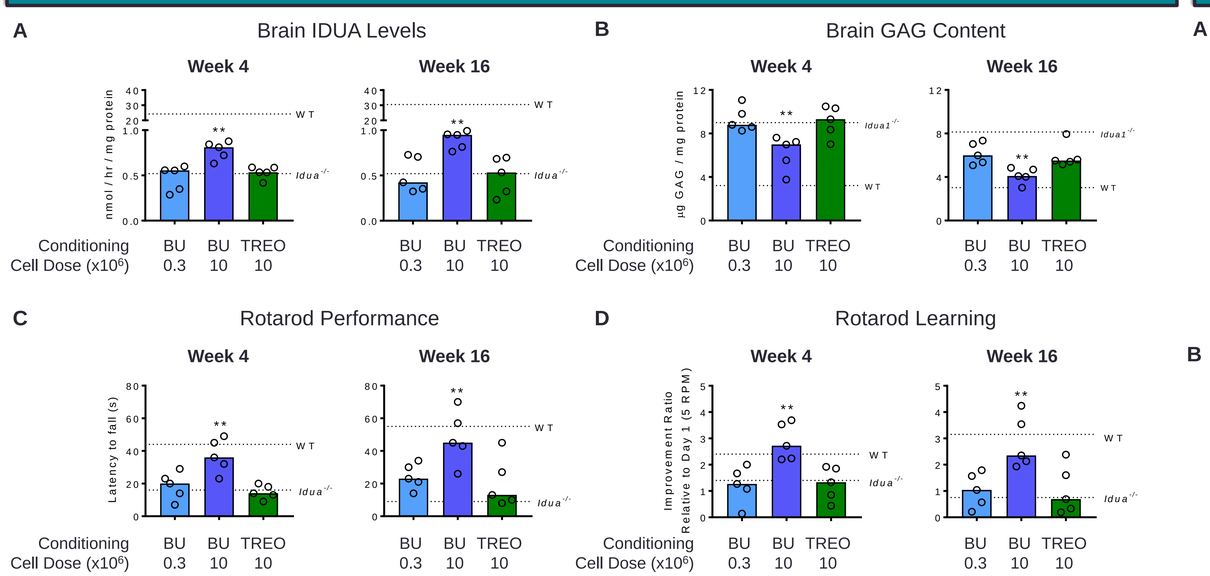

Figure 3. Brain IDUA enzyme levels were increased in high cell dose recipients. Brain IDUA enzyme **(A)** and GAG levels **(B)** were measured by colorimetric assays and normalized to protein level. Neurocognition was measured by a rotarod test, as assayed on three consecutive days. Time to fall on day one of testing **(C)** and ability to learn over three days **(D)** was measured. Bars represent median; each symbol represents an individual mouse (n=5/group). Dotted lines represent untransplanted WT or *Idua*$^{-/-}$ controls. **p<0.01, relative to 0.3x10^6 cell dose group.

SWIFT PERIPHERAL CROSS-CORRECTION WITH HIGH CELL DOSE HSCT IN *IDUA*$^{-/-}$ MICE

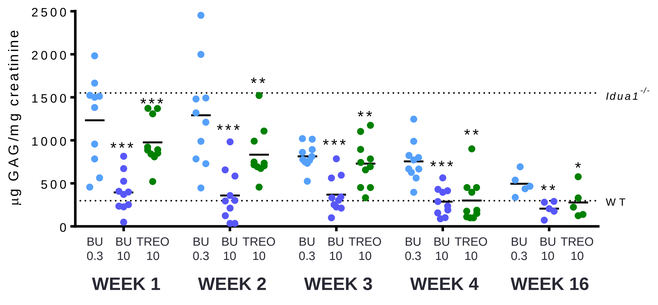

Figure 4. As early as one-week post-HSCT, urinary GAG levels were reduced following high dose HSCT recipients compared to standard cell dose. GAG levels were normalized to creatinine levels. Lines represent median; each symbol represents an individual mouse (n=5-10 per group). Dotted lines represent untransplanted WT or *Idua*$^{-/-}$ controls. *p<0.05, **p<0.01, ***p<0.001 compared to 0.3x10^6 cell dose group.

HIGH DOSE HSCT REVERSES SKELETAL DEFORMITY TO WILD-TYPE LEVELS

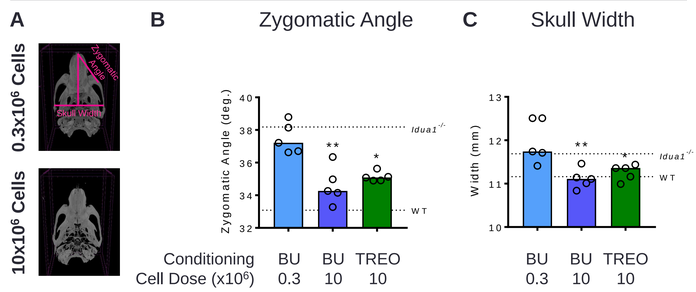

Figure 5. Representative skull images **(A)**, zygomatic angle **(B)**, and skull width **(C)** at week 16 post-transplant were measured by microcomputed tomography. Bars represent median; each symbol represents an individual mouse (n=5/group). Dotted lines represent untransplanted WT or *Idua*$^{-/-}$ controls. *p<0.05, **p<0.01 compared to 0.3x10^6 cell dose group.

MGTA-456: A HIGH DOSE CELL THERAPY THAT LEADS TO RAPID AND ROBUST ENGRAFTMENT

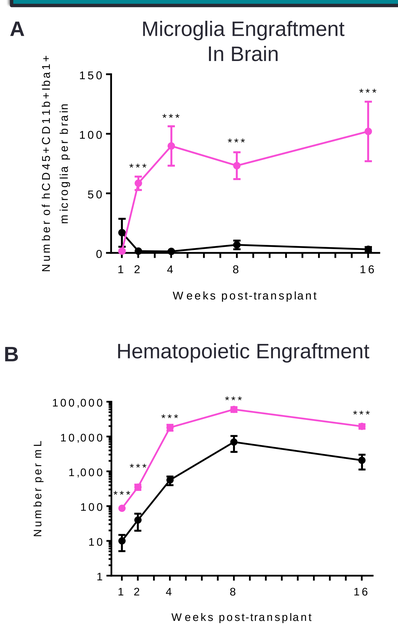

Figure 6. hCD45+CD11b+Iba1+ microglia brain engraftment **(A)** and hCD45+ peripheral blood engraftment **(B)** after transplant with 4,000 unexpanded cord blood CD34+ cells (standard of care) or MGTA-456 (n=8 mice per group). Lines represent mean ± SEM. Statistics were calculated by one-tailed Student's t-tests, ***p<0.001.

CONCLUSIONS

- High dose HSCT leads to rapid and durable resolution of CNS, peripheral, and skeletal abnormalities associated with IMDs.
- Improved disease cross-correction is achieved via robust donor hematopoietic engraftment.
- Strategies to increase cell dose, such as MGTA-456, may accelerate halting of disease in patients with IMDs.
- Similar approaches could be used to improve microglial function in other neurodegenerative diseases where defective microglia have been implicated.
- Magenta-sponsored Phase 2 trial for MGTA-456 in patients with IMDs (NCT03406962) is currently enrolling patients.

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