

High Dose Hematopoietic Stem Cell Therapies, like MGTA-456, Enable Complete Neural, Peripheral, and Skeletal Disease Cross-Correction Through Rapid and Robust Engraftment

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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

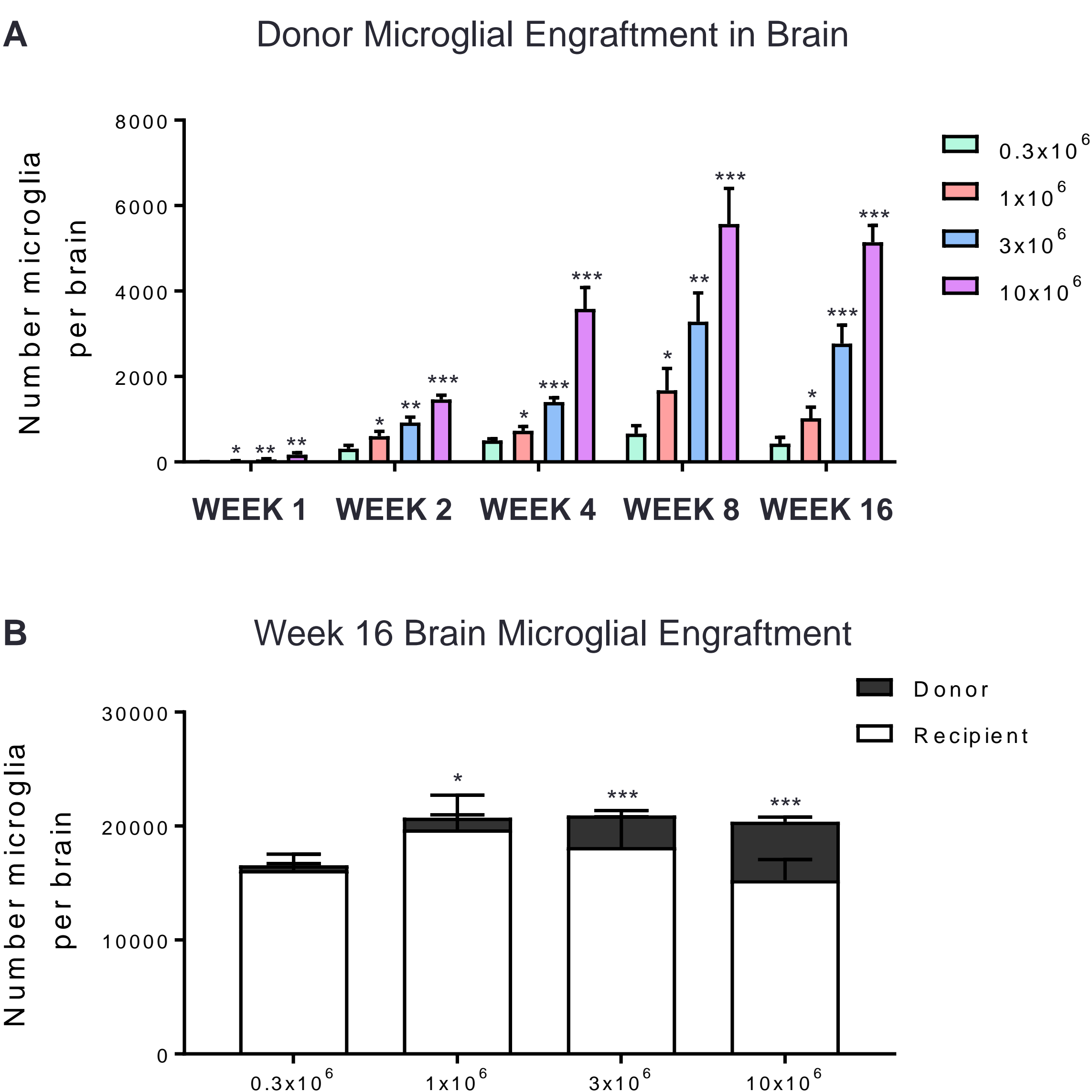


Figure 1. (A) Wild-type C57BL/6 mice were conditioned with a myeloablative dose of busulfan and transplanted with congenic CD45.1 bone marrow at 0.3-10 x 10⁶ cells/mouse. Donor microglia number (CD45.1+CD11b+) was measured by flow cytometry. A dose-dependent increase in microglia was observed as early as 1-week post-HSCT, where 10x10⁶ cells led to a 26-fold higher number of donor microglia compared to 0.3x10⁶ 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 0.3x10⁶ cell dose group).

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

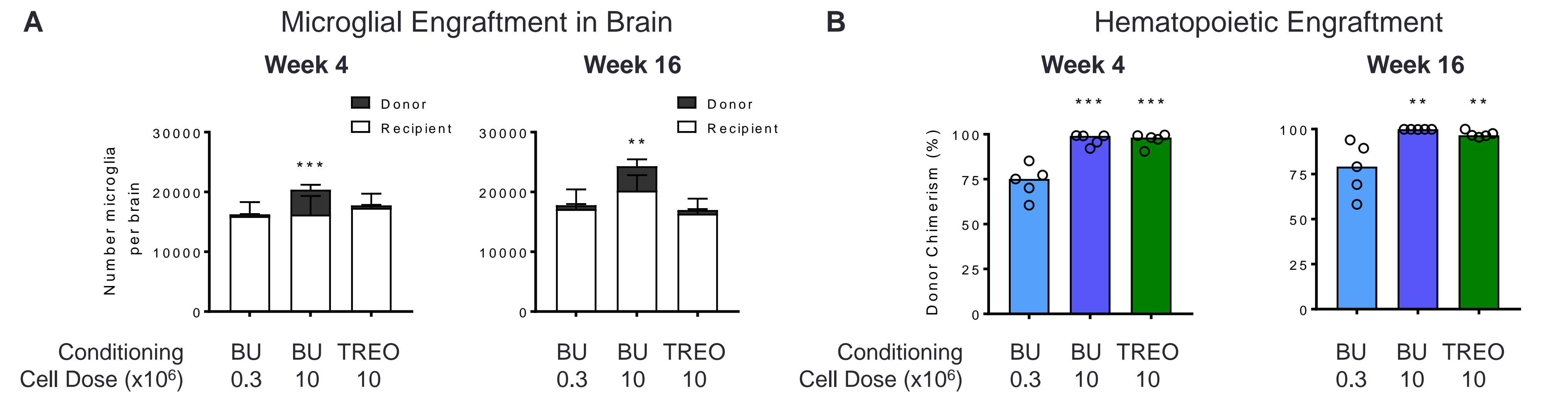


Figure 2. CD45.2 *Idua*^{-/-} mice were conditioned with a myeloablative dose of busulfan (BU) or treosulfan (TREO) and transplanted with 0.3x10⁶ or 10x10⁶ CD45.1 bone marrow cells per mouse (n=5 per group). (A) Microglia number was measured in the brain by flow cytometry. (B) Peripheral blood donor 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 0.3x10⁶ cell dose group.

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

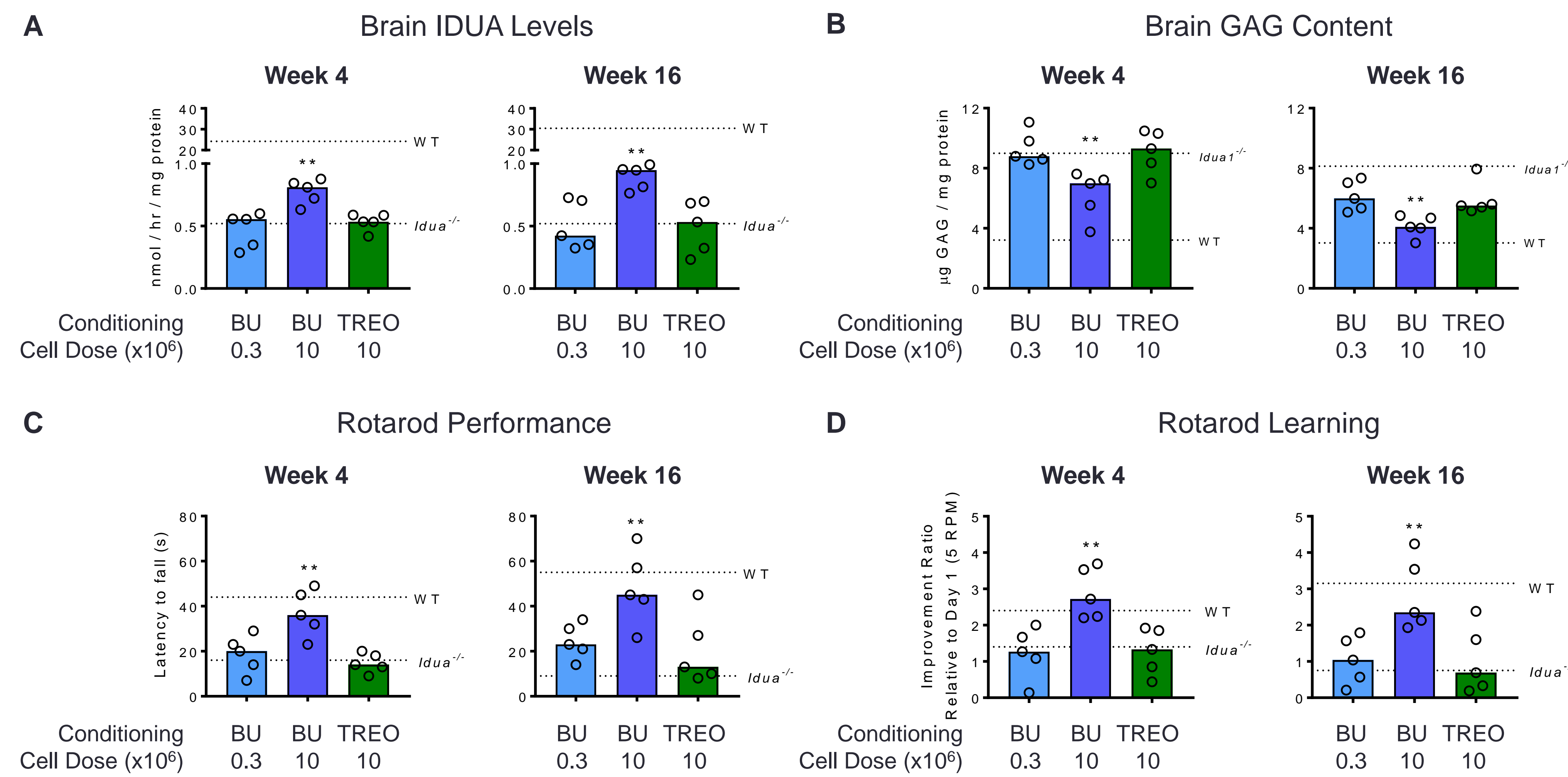


Figure 3. Brain IDUA enzyme levels were increased in high cell dose recipients. Brain IDUA enzyme (A) and GAG levels (B) were measured by colorimetric assays and normalized to protein level. Neurocognition was measured by a rotarod test, as assayed on three consecutive days. Time to fall on day one of 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 0.3x10⁶ cell dose group.

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

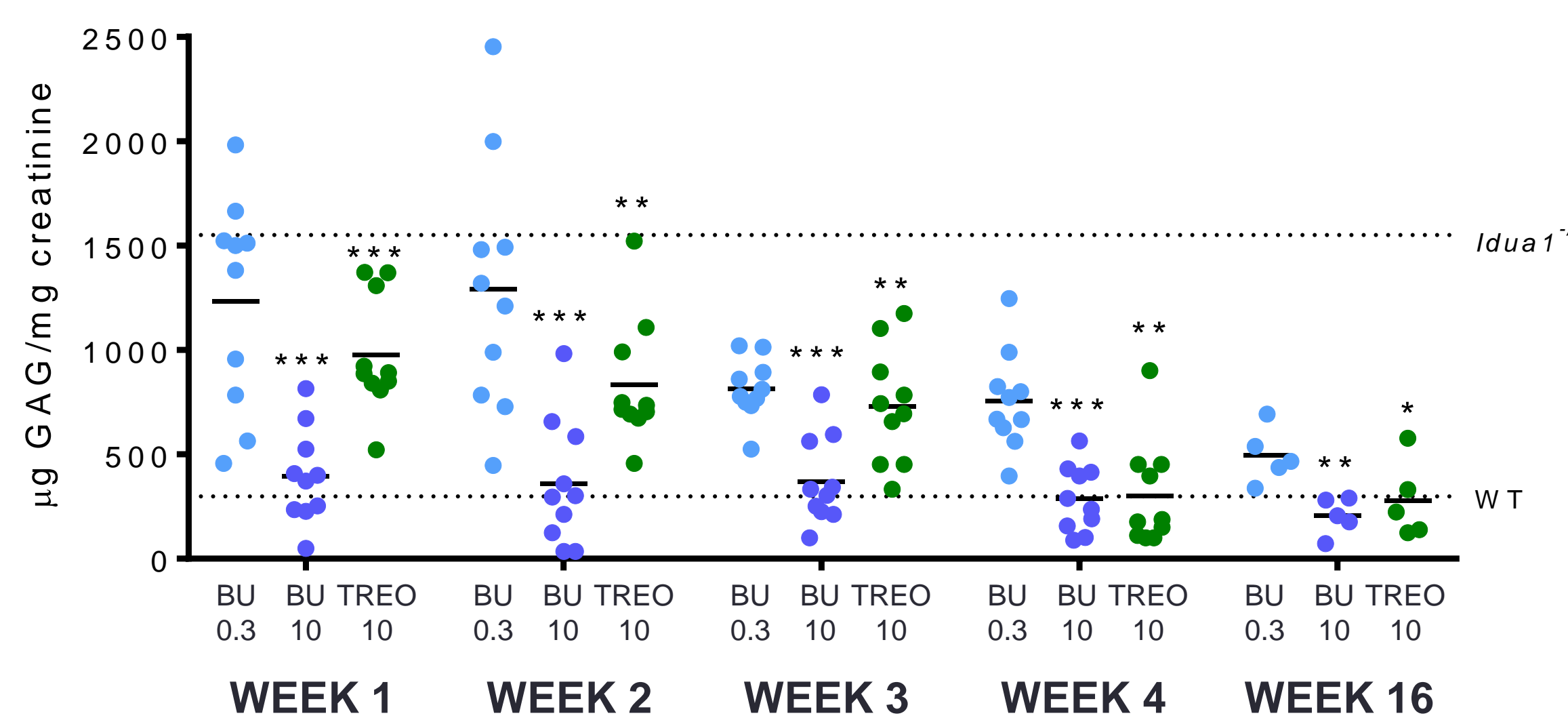


Figure 4. As early as one-week post-HSCT, urinary GAG levels were reduced following high dose HSCT recipients compared to standard cell dose. GAG levels were normalized to creatinine levels. Lines represent median; each symbol represents an individual mouse (n=5-10 per group). Dotted lines represent untransplanted WT or *Idua*^{-/-} controls. *p<0.05, **p<0.01, ***p<0.001 compared to 0.3x10⁶ cell dose group.

HIGH DOSE HSCT REVERSES SKELETAL DEFORMITY TO WILD-TYPE LEVELS

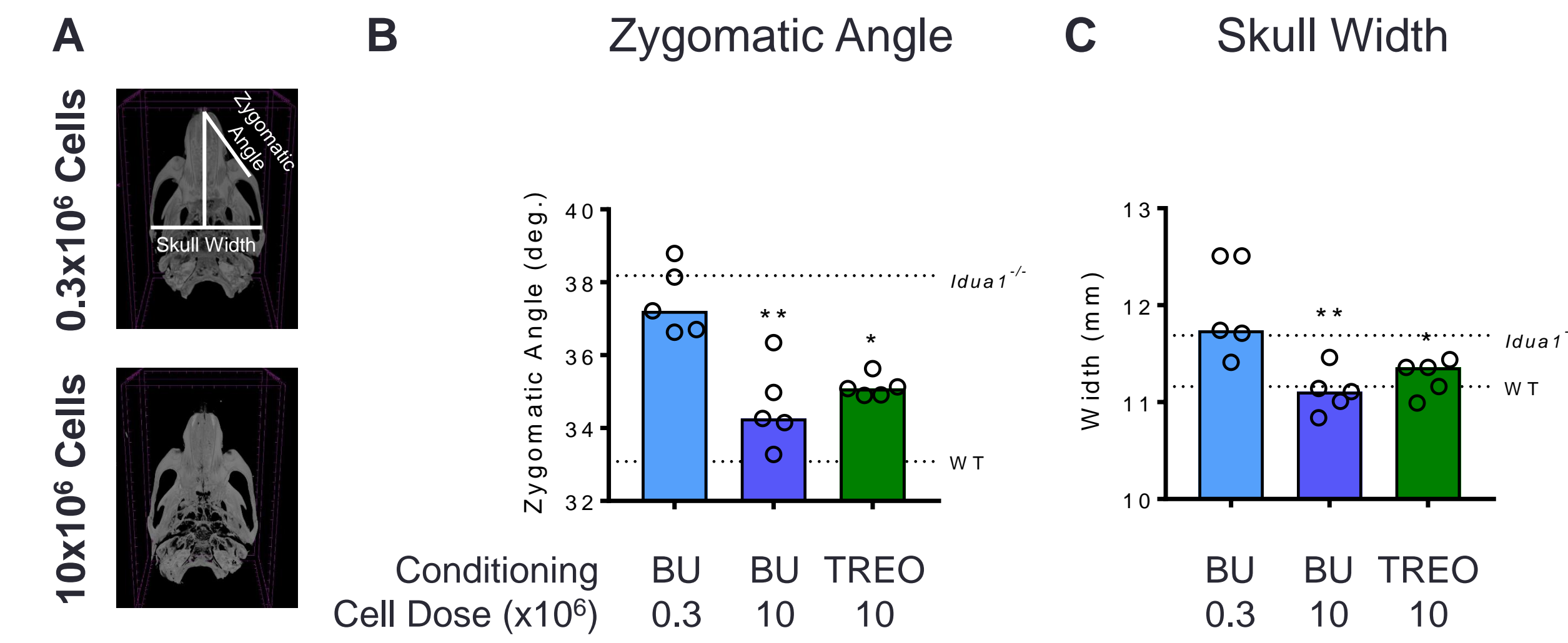


Figure 5. Representative skull images (A), zygomatic angle (B), and skull width (C) at week 16 post-transplant were measured by microcomputed tomography. Bars represent median; each symbol represents an individual mouse (n=5/group). Dotted lines represent untransplanted WT or *Idua*^{-/-} controls. *p<0.05, **p<0.01 compared to 0.3x10⁶ cell dose group.

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

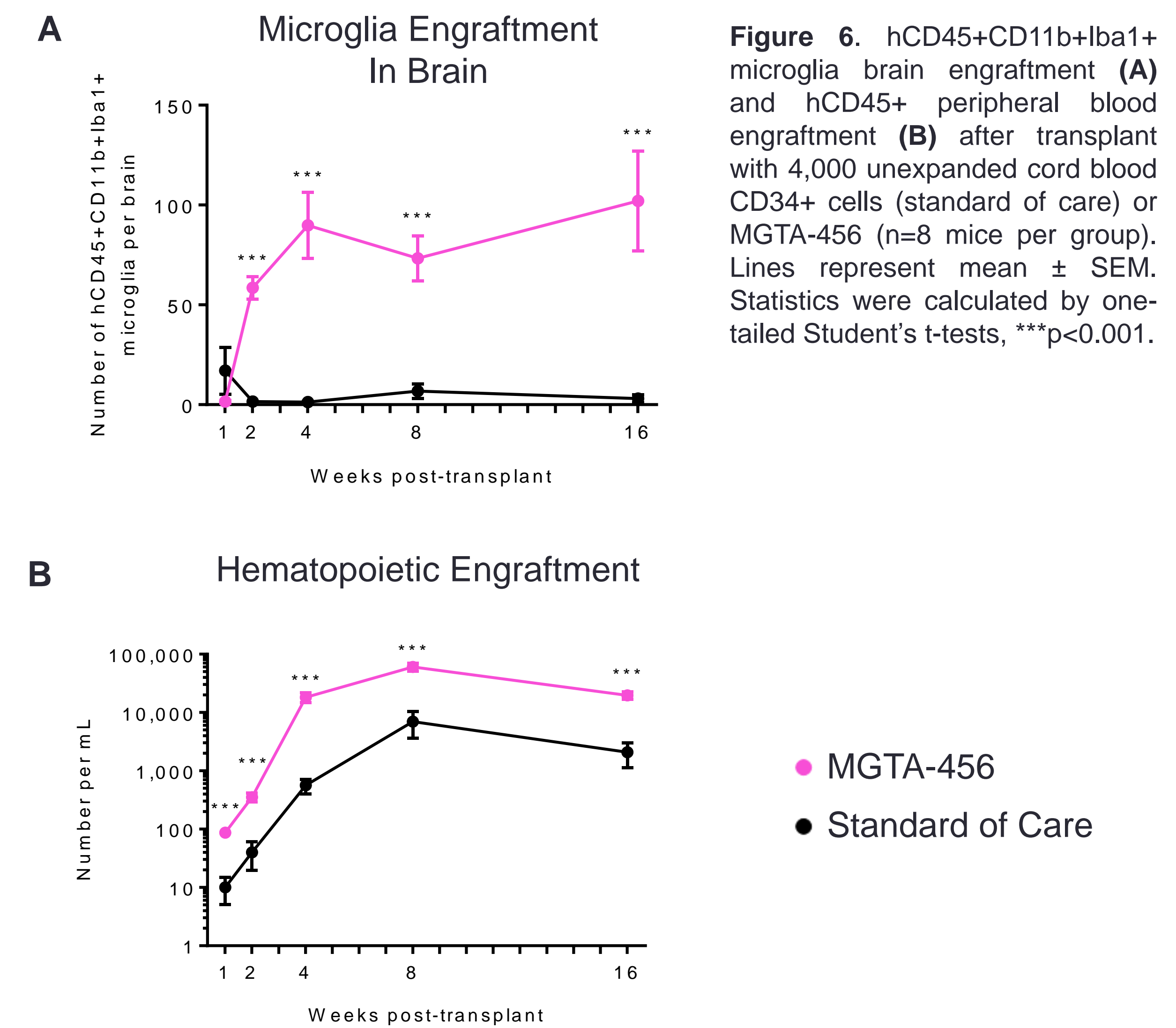


Figure 6. hCD45+CD11b+Iba1+ microglia brain engraftment (A) and hCD45+ peripheral blood engraftment (B) after transplant with 4,000 unexpanded cord blood CD34+ cells (standard of care) or MGTA-456 (n=8 mice per group). Lines represent mean ± SEM. Statistics were calculated by one-tailed Student's t-tests,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