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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Objective:
To optimize bone marrow transplant for treatment of patients with inherited metabolic disorders (IMDs) with neurologic etiology.

Background:
Allogeneic bone marrow transplant (BMT) can prevent or ameliorate neurological symptoms arising from select inherited metabolic disorders (IMDs), including leukodystrophies and Hurler syndrome. Donor-derived microglial cells limit neurological disease progression post-transplant through production of normal enzyme and cross-correction. Cord blood (CB) is the preferred source for IMD patients lacking an HLA-matched related donor, but it is associated with low engraftment and delayed recovery due to few numbers of hematopoietic stem cells (HSCs). MGTA-456, produced by expanding a single CB unit with an aryl hydrocarbon receptor antagonist, contains 100-fold higher numbers of CD34+CD90+ HSCs, the cell type responsible for hematopoietic engraftment (Wagner et al., Cell Stem Cell 2016). As microglia are thought to be derived from HSCs, we hypothesized that the high number of HSCs in MGTA-456 may result in enhanced microglial engraftment.

Design/Methods:
NSG mice were transplanted with CB CD34+ cells or MGTA-456 after 200 cGy irradiation or busulfan (20 or 40 mg/kg). Engraftment was assessed by flow cytometry and immunohistochemistry.

Results:
All animals (n=88) transplanted with MGTA-456 showed robust, long-term immune recovery. MGTA-456 also provided a 60-fold increase in microglial engraftment versus CB CD34+ cells (p<0.001, n=8), with engraftment as early as 2 weeks. MGTA-456 enabled use of low-dose busulfan, showing 21-fold greater microglial engraftment than achieved by standard approaches using high-dose busulfan (p<0.01, n=8). Microglia localized to the non-perivascular region and, mechanistically, neurologic and hematopoietic engraftment was dependent on CD34+CD90+ cells, which are present at high numbers in MGTA-456.

Conclusions:
Transplant of MGTA-456 led to rapid and robust hematopoietic and microglial engraftment due to the high numbers of CD34+CD90+ cells. MGTA-456 was also effective with a reduced-intensity conditioning regimen. These results provide the potential to alter neurologic progression of disease in patients with IMDs.