**Non-technical abstract**

Current treatment of Glioblastoma multiforme (GBM) includes surgical resection followed by concurrent temozolomide (TMZ) and radiotherapy. This therapy results in a modest survival benefit (median 14.6 vs. 12.1 months, two year survival 26.5% vs. 10.4%). TMZ is dose limiting, because it not only kills dividing tumor cells but also normal blood cells, resulting bone marrow toxicity. DNA damage caused by TMZ is repaired by the DNA repair protein AGT. This gene is often expressed at high levels in tumors, making them resistant to tolerated doses of TMZ, and is expressed at low levels in the bone marrow. $O^6$ Benzylguanine (BG) specifically inhibits the activity of AGT, including that in tumors and normal blood cells. Co-administration of BG and TMZ allows the TMZ to more effectively kill the tumors, but also has a detrimental effect on the hematopoietic cells. The key element of this therapeutic proposal is the introduction of a BG-resistant MGMT mutant, the P140K MGMT into hematopoietic stem cells to selectively protect them from the toxicity of BG+TMZ. This mutant gene is resistant to BG. The addition of P140K-MGMT to patients' (CD34+) hematopoietic stem cells by ex vivo transduction will allow these cells to survive the BG/TMZ dosing and to proceed to differentiate and repopulate the blood compartment. The remainder of (non-transduced) blood cells will be deleted by the BG/TMZ treatment, resulting in hematopoesis that is largely or entirely TMZ resistant. This trial will target a subpopulation of GBM patients who benefit less from standard therapy because their tumor expresses high levels of AGT. The goal of this study is to protect bone marrow from the toxic effects of chemotherapy using P140K MGMT to allow TMZ to be administered at much higher levels than currently tolerated, offering real promise to patients with GBM.