

## Non-Technical Abstract

Myelosuppression remains a major dose limiting toxicity of many chemotherapeutic agents. In an effort to combat this, a number of gene therapy approaches have been initiated to overexpress drug resistance genes in hematopoietic progenitors [HPs] with the intent of reducing chemotherapy induced myelosuppression. In the proposed clinical trial, bone marrow progenitor cells will be transduced with a retroviral vector, MFG-mutant-MGMT-G156A ( $\Delta$ MGMT). This will transfer the drug resistance gene [MGMT] for the chemotherapeutic agent, BCNU, a potent nitrosourea currently used in cancer treatment, into human CD34 hematopoietic progenitor cells. The mutant MGMT protein contains a single amino acid change which renders it resistant to a potent inhibitor of the protein, O6-benzylguanine [BG]. BG has been shown to markedly sensitize drug-resistant tumors to BCNU. The combination of BG and BCNU is currently in phase 2 clinical trials in patients with cancer, but in phase 1 trials has been found to cause bone marrow suppression which may limit its therapeutic efficacy. In mice transplanted with  $\Delta$ MGMT transduced cells, a significant survival advantage over control animals was observed when the mice were given repetitive doses of BG & BCNU. These mice also showed enrichment of the transduced progenitors *in vivo*. The protective effect observed was much better than when mice were infused with marrow cells transduced with the normal, wild type MGMT gene and treated with BCNU alone. On this basis, we propose that retroviral expression of  $\Delta$ MGMT in human hematopoietic progenitors will reduce myelosuppression after therapy with BG & BCNU. As a consequence, therapy with BG & BCNU can be optimized by sensitizing the tumor with BG and making hematopoietic cells resistant to BG with  $\Delta$ MGMT. This strategy represents a uniquely different approach to drug resistance gene therapy.

We plan to conduct a clinical study consisting of 12 evaluable subjects to determine the feasibility and biologic relevance of this approach with the following objectives:

- 1 To evaluate the feasibility of expressing the  $\Delta$ MGMT gene in hematopoietic progenitors taken from advanced solid tumor patients using a safety modified retroviral vector MFG.
- 2 To determine the toxicity associated with reinfusion of *ex vivo* transduced hematopoietic cells into patients with advanced cancer.
- 3 To find  $\Delta$ MGMT transduced and BG & BCNU resistant hematopoietic cells in patients infused with  $\Delta$ MGMT transduced cells.
- 4 To enrich for the transduced hematopoietic progenitors in patients by repeated treatment of patients with BG & BCNU.
- 5 To evaluate the toxicity of repeated BG & BCNU treatments in patients who received  $\Delta$ MGMT transduced cells.