Non-Technical Abstract :

Despite aggressive treatment, Glioblastoma Multiforme (GBM), a malignant primary brain tumor, remains almost universally fatal. Moreover, conventional treatments incapacitate patients as a result of damage to surrounding normal brain and systemic tissues. Use of a vaccine that stimulates the immune system, which is called immunotherapy, offers the prospect of targeting cancer cells more precisely. Dendritic Cells (DCs) are immune cells that interact with T-cells and B-cells in the human body. These cells are endowed with an extraordinary ability to activate specific T-cells called CD4+ and CD8+ T-cells. The DCs have been loaded with antigens, a substance that prompts the generation of antibodies. These antigens, which have been derived from tumor cells, have the potential to induce potent anti-tumor immunity. Unfortunately, genetic instability of tumor cells severely limits the number of immunogenic tumor-specific antigens.

Recently, a subset of tumor cells in GBM, called Brain Tumor Stem Cells (BTSC) have been identified that enjoy a unique capacity to regenerate tumors upon serial transplantation and to resist cell toxicity. These BTSC can be segregated by the neural stem cell surface marker, CD133, and are widely believed to be the cells responsible for tumor development and recurrence. An effective means of specifically targeting these cells then may significantly reduce the need for such intensive conventional therapy and may significantly reduce the risk of tumor recurrence. Therapeutic targets that differentiate these $CD133^+$ cells, however, have not been identified.

Nonetheless, the immune system has the distinct ability to eliminate minimally altered cells with extraordinary specificity. In fact, our multi-institutional Phase II studies in adults with GBM have shown that immunotherapy targeting the tumor-specific EGFR mutation, EGFRvIII, is capable of inducing potent T- and B-cell immunity, producing nearly complete radiographic responses in all patients with residual tumor, universally eliminating tumor cells expressing the targeted antigen, and extending median survival beyond 2½ years without any evidence of toxicity. However, the recurrence of EGFRvIII-negative tumors in a subset of these patients highlights the need for targeting a broader range of tumor antigens expressed in the tumor cells that contribute to disease recurrence. Immune responses directed against unique antigens expressed in BTSC then could serve as a way of specifically eliminating these crucial BTSC without the untoward side effects of conventional therapy.

We and others have successfully employed the use of DCs loaded with total tumor RNA as an innovative strategy to induce cellular immune responses against the repertoire of, as yet, largely uncharacterized antigens present in malignant brain tumors. $CD133^+$ BTSC are often present as a minority subpopulation of GBM cells that cannot be reliably isolated or multiplied in sufficient quantity to serve directly as a source of antigen for use in human vaccination protocols. We have, however, been able to reproducibly amplify the RNA content from as few as 500 sorted $CD133^+$ tumor cells using an amplification technique called RT-PCR to generate RNA libraries in sufficient quality and quantity for clinical scale DC-based vaccination. We have also used a technique that compares the expression of RNA from normal brain and $CD133^-$ tumor cells to enrich for antigens expressed exclusively within $CD133^+$ BTSC.

In this protocol, we will determine if vaccination with BTSC mRNA-loaded DCs or TTRNA DCs in patients with first recurrent GBM is safe and leads to enhanced immune responses directed against BTSC antigens.