

TITLE: Immunotherapy for Glioblastoma

**FACULTY MENTOR NAME, EMAIL PHONE NUMBER: Maryam Rahman, MD
mrahman@ufl.edu, 352 273 9000**

FACULTY MENTOR DEPARTMENT: Neurosurgery

RESEARCH PROJECT DESCRIPTION (Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and leads to over 13,000 cancer deaths in the U.S. annually¹. GBM is characterized by treatment resistance, leading to dismal patient outcomes despite aggressive therapeutic measures². Temozolomide (TMZ) is the most effective and commonly used medical therapy for GBM, despite the fact that about half of all GBM patients have TMZ resistance mediated by O(6)-methylguanine-DNA methyltransferase (MGMT), a DNA repair gene³. In addition to this inherent resistance, GBM develops adaptive resistance after exposure to TMZ⁴. Both inherent and acquired resistance make GBM extremely difficult to treat and almost uniformly fatal. Immunotherapy is a promising alternative approach to the treatment of GBM. Immune checkpoint inhibitors are the most recent and exciting addition to the immunotherapy armamentarium. Antibodies against cytotoxic T lymphocyte associated protein 4 (CTLA4) and programmed cell death 1 (PD-1) are immune checkpoint blockers that allow for T cell activation against tumor neoantigens⁵⁻⁷. These drugs have had tremendous success in the treatment of solid tissue tumors^{8,9} and are now being tested for efficacy in GBM. The combination of TMZ with anti-PD-1 therapy for GBM seems logical and compelling. Our ***long-term goal*** is to improve outcomes in GBM patients by implementing ***novel therapeutic strategies to overcome treatment resistance***. The objective of this proposal is to investigate the various dose modified TMZ regimens with immune checkpoint blockade for GBM. We expect the results of this proposal to complement the results from the ongoing clinical trial of anti-PD-1 blockade for GBM. Our ***central hypothesis*** is that *dose-modified TMZ therapy results in changes in host immunity and tumor neoantigen burden that will improve response to anti-PD-1 treatment in TMZ-sensitive and TMZ-resistant GBM.*
Role of Medical Student: Laboratory work that may include cell culture, immunologic assays, PCR, animal work with mice, radiation of tumors, flow cytometry and Western blots.