Penn Medicine

CLINICAL BRIEFING™

Department of Neurosurgery • Penn Neurosurgery

Glioblastoma Immunotherapy Research at Penn Medicine

In collaboration with the dedicated Glioblastoma Translational Center of Excellence at the Abramson Cancer Center, investigators with the O'Rourke Laboratory in the Department of Neurosurgery are conducting research in immunotherapy for glioblastoma, including a currently enrolling clinical trial to assess combination CAR EGFRvIII T-cell /pembrolizumab therapy in select newly diagnosed patients.

The highest-grade glial tumor, GBM (grade 4), has an annual incidence of 3.19/100,000 individuals per year (~10,000). Currently, median survival for the disease following standard-of-care surgery, radiotherapy and chemotherapy is 14.6 months; two-year survival remains close to 25%.

The obstacles to GBM therapy are implied in the original descriptive *multiforme*, with its implication of complex, multifaceted disease. In fact, GBM has a prolific capacity to impede standard cancer therapies by manipulating its microenvironment and suppressing the immune system. Neural physiology adds another obstruction to treatment. The blood-brain barrier and meninges are both virtually impermeable to chemotherapy, and the brain structure contributes to the parenchymal spread and infiltration of glial tissue. Genetically, GBM is referred to as a "cold" tumor, with relatively few mutations, unlike a "hot" tumor such as melanoma. Tumor heterogeneity is common, in addition, so the few available mutation targets do not occur uniformly in all patients.

For all of these reasons, the conventional algorithm for GBM (surgery/radiotherapy/chemotherapy) has historically offered at best a temporary hiatus against recurrence and inevitable neurological deterioration. By the same token, the promise of immunotherapy may offer the best hope for the future.

Neuro-Oncology Research at Penn Medicine

One of seven research laboratories devoted to the brain and CNS within Penn Neurosurgery, the O'Rourke Laboratory is devoted to neuro-oncology and has, for several years, been home to a series of vibrant investigations in immunotherapy for GBM. This laboratory is fully integrated into the Center for Cellular Immunotherapies and The Parker Institute for Cancer Immunotherapy in Perelman Building of The Abramson Cancer Center (ACC). The laboratory is led by neurosurgeon Donald M. O'Rourke, MD, who also established and is current Director of the GBM Translational Center of Excellence in the ACC.

Among its current undertakings, the O'Rourke Laboratory is involved in CART-EGFRvIII + Pembrolizumab in GBM (NCT03726515), a clinical trial to assess the safety and tolerability of EGFRvIII T cells in combination with the PD-1 Inhibitor pembrolizumab in a select population of patients with newly diagnosed and confirmed glioblastoma. For further information about this trial, please call **215.662.6264.**

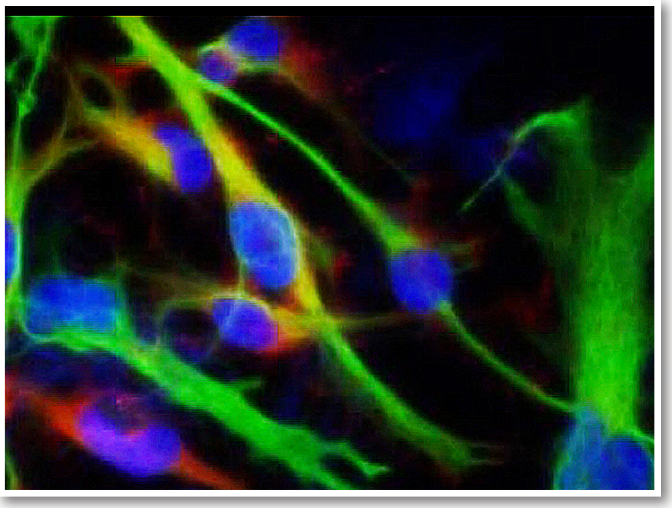

Figure 1: Differentiated gioblastoma cells showing FGAP (green) and Tuj1 (red).

In addition to CAR T therapy, researchers in the O'Rourke Lab are currently focusing upon targeted antibodies and novel proof of concept studies, with the ultimate goal of reversing the immunosuppression native to glioblastoma and stimulating immune activity in the tumor microenvironment. The overarching goal is to create a pipeline of new clinical trials to be used in the care of GBM patients.

Among the recent findings at the O'Rourke Lab:

- GBM organoids can serve as models of tumor heterogeneity to test immunotherapies for glioma;
- CAR T-cells appear to have a synergy with checkpoint blockade in GBM;
- Peripherally infused epidermal growth factor receptor variant III (EGFRvIII)–directed CAR T cells can successfully traffic to regions of active GBM in the brain;
- In tandem with the above study, EGFRvIII–directed CAR T cells mediate antigen loss and induce adaptive resistance in patients with recurrent glioma;
- A highly invasive phenotype associated with the EGFRA289V mutation in glioblastoma may provide a rationale for therapy with newly-designed EGFR-targeted antibodies;
- Functioning SHP2, a cytoplasmic protein tyrosine phosphotase (PTPase) involved in multiple signaling pathways, is required for cell growth and transformation of the glial stem cell compartment in GBM.

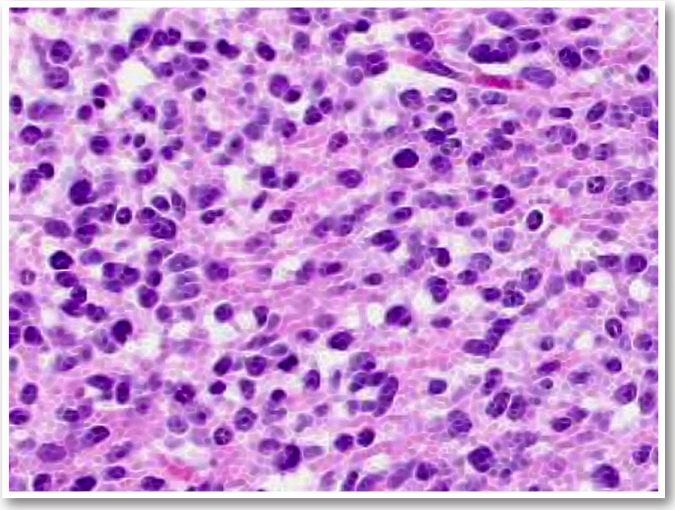

Figure 2: Xenograft H&E demonstrating an invasive high-grade glioma.

Translation to Patient Care

The O'Rourke Laboratory and the Glioblastoma Translational Center of Excellence at Penn Medicine are translating the knowledge gained from clinical trials into effective patient care, narrowing the gap between the clinic and the laboratory, and accelerating the pace of discoveries that will help patients become and remain cancer-free in the future.

Tumor Bank

Dr. O'Rourke serves as the Director of the Human Brain Tumor Tissue Bank, a Penn-Children's Hospital of Pennsylvania joint initiative to preserve tumor tissue and matched blood from Neurosurgery patients for future research. The Human Brain Tumor Tissue Bank has collected blood and tumor samples from over 1,800 patients. These samples are used for research projects both inside and outside of the University of Pennsylvania. The Harvest website is a platform for researchers to access the de-identified inventory of specimens linked to clinical data.

FACULTY TEAM

The Department of Neurosurgery is developing integrated scientific approaches to the treatment of glioblastoma with an interdisciplinary team of experts who lead a large portfolio of targeted cellular immunotherapy clinical trials at Penn Medicine and across other institutions to advance patient care for GBM. The hope is that the many novel treatment approaches and clinical trials will eventually lead to longer life expectancy for patients.

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LOCATION

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