Dr. Tannous is focused on developing experimental therapeutics against malignant pediatric and adult brain tumors including diffuse intrinsic pontine gliomas (DIPG) and glioblastomas (GBM). His recent work includes the novel approach of using olfactory cells to carry anticancer therapy to deadly brain tumors. Advanced animal studies have shown the approach is effective in reducing tumor size and prolonging survival.

Gene/Cell therapy has been heralded as a potential revolution in medicine, however, when it comes to cancer in general and brain tumors in particular, this therapeutic strategy has shown limited efficacy due to the restricted delivery to the tumor site. The olfactory ensheathing cell (OEC) is a fully differentiated (not stem cell) glial cell type that closely accompanies the axons as they grow from the olfactory epithelium into the olfactory bulb. OECs naturally migrate from the peripheral nervous system to the central nervous system (CNS). Owing to their strong ability to migrate to the injury site in the brain and their neuroprotective, and immunomodulatory properties, the potential of OECs in neuronal regenerative medicine and spinal cord injury in animal models and the clinic has been widely investigated but were not studied in the context of cancer. Our group was the first to show that OECs can target GBM cells and stem-like cells in the brain of mice upon intranasal injection, the natural route of OECs to CNS, and can efficiently deliver therapeutic transgene to gliomas. We also show that OECs on their own can modulate cancer stemness, proliferation, and activate phagocytosis and anti-tumor immunity in aggressive brain cancer (pediatric and adult) as well as lung cancer models. In addition, we engineered OECs to secrete a single chain antibody against PD-1 and showed that these modified OECs can activate both cancer innate and adaptive immunity leading to efficient immune checkpoint blockade at the tumor site.

OEC offer several advantages over typical stem cell therapy: (1) OECs can be easily obtained from the olfactory epithelium and/or olfactory bulb, a very simple procedure, allowing autologous transplantation; (2) no toxic or tumorigenic potential (since they are fully differentiated cells) with OEC transplantation have been reported to date; (3) OEC natural migration to CNS during olfactory receptor turnover and injury gives them an additional advantage for brain tumor therapy; (4) OECs can also be injected systemically and treat tumors outside the brain, including lung.

**Olfactory Ensheathing Glia: An Unconventional Cell for Cancer Gene/Cell Therapy**

Bakhos Tannous, PhD
Director, Experimental Therapeutics Unit, Director, Viral Vector Core, MGH; Associate Professor of Neurology, HMS
btannous@mgh.harvard.edu

Figure 1. OEC inhibit patient-derived glioma stem cells (GSCs) self-renewal and proliferation.

Figure 2. OECs migrate to GBM through the nasal pathway and induce striking cytotoxic anti-cancer effect and increase survival with 40% of mice survived >150 days and were cancer free.

Figure 3. OEC induces cytotoxic effect in an aggressive lung cancer model.