THE HARTWELL FOUNDATION

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Stavroula Sofou, Ph.D.

Associate Professor
Department of Chemical and Biomolecular Engineering

Johns Hopkins University

Curing Glioblastoma by Alpha-Particle Radionuclide Therapy

Glioblastoma is a highly heterogeneous and aggressive brain tumor. It arises from abundant non-neuronal glial cells called astrocytes, which provide structural support and play essential functions in maintenance of the blood brain barrier, neuron survival and synapse formation. The malignancy accounts for 15% of all pediatric brain tumors. Survival can be prolonged with surgery, radiotherapy, and chemotherapy but the location of the tumor is difficult to treat and adverse consequences to peripheral healthy tissue in the developing brain can render treatment prognosis extremely poor in a child. With a 5-year survival of less than 20%, children with glioblastoma have few options. Hence, there is an unmet need for a pediatric therapeutic strategy that will selectively and effectively kill glioblastoma cancer cells, an intervention that will deliver long-lasting remission, improve their quality of life and prolong their survival. Radiation therapy uses high-energy particles or waves (x-rays, gamma rays, electron beams, or protons) delivered either by external beam, a source placed inside the body, or systemically by radiopharmaceuticals. One particularly effective form of internal radiation deploys an element with high atomic number that undergoes relatively rapid spontaneous radioactive decay (radionuclide) by emission of α-particles from its nucleus. A relatively massive amount of energy is deposited by the highly charged α-particles as they traverse tissue and produce complex double strand breaks in DNA that overwhelm cellular repair in diseased tissue at proximity. The α-particles have limited penetration in tissue (short travel distance up to 4 to 5 cell diameters), which is an advantage in limiting peripheral damage but unfortunately, is also related to partial tumor irradiation that is the cause of current glioblastoma treatment failure with alpha-particle therapy. To overcome this limitation, Stavroula proposes a novel strategy for delivery of alpha particles, based on the systemic administration of a short lifetime α-emitter attached to ~4 nM diameter dendrimer-nanoparticles. The nanoparticles are known uniquely to localize in activated brain glial cells (macrophages) at a rate proportional to the extent of existing inflammation and that advantageously, clear quickly from the body and brain when not retained inside the tumor-associated macrophages. She hypothesizes that such dendrimer-nanoparticles loaded with α-emitters will uniformly irradiate the brain tumors at the site of cancer induced inflammation, resulting in maximum killing efficacy of malignant tumor cells and with limited peripheral tissue damage. This strategy, enabled by a nanoparticle platform demonstrated to have an excellent safety profile, represents a new paradigm in radionuclide therapy. If Stavroula is successful, particle-based delivery of alpha-emitters will effectively kill the cancer cells in glioblastoma and related brain tumors, providing a potential cure, if not just extend remission, improve the quality of life, and prolong survival in affected children.