

Bankhead-Coley Cancer Research Program

Hughes, Jeffrey

*Department of Pharmaceutics
University of Florida*

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Project Title: Multifaceted Non-Viral Cancer Gene Therapy

Project Summary: Each year the statistics are published for new cases of brain cancer, and each year the number of cases increases. However, the statistics for the most lethal form of brain cancer, i.e., malignant astrocytoma, remain unchanged ranging from 15,000 to 18,000 new cases per year. Unfortunately, another statistic that does not change is the number of deaths ranging from 12,000 to 14,000 per year. It is the total number of new cases per year rather than the ratio of deaths to new cases that determines whether a pharmaceutical will be developed to specifically treat this lethal disease. Unfortunately, the cost of developing a drug that is solely designed for the treatment of malignant brain cancer can not be justified based on the number of new cases per year. Hence, there is an unmet need in developing a cure. Malignant brain tumors do not metastasize. However, they do migrate away from the primary tumor into the surrounding normal tissue, and it is these migratory cells that give rise to new tumors, ultimately leading to the death of the patient. The migrating cells are highly proliferative creating a high nutrient demand. New blood vessels are found around these lesions in order to supply the needed nutrients. This high demand for nutrients can be taken advantage of in developing a therapy. This grant will take advantage of this property to create a nonviral gene therapy that is safe and effective in treating the malignant tumors. Gene therapy consists of delivering a gene to a cell that instructs the cell to make a protein that will kill the tumor or kill the tumor endothelium or both. This requires that the gene not be delivered to the wrong address. In visualizing the gene therapy approach, the targeting molecule serves as the zip-code. Out of all the addresses in the body, a zip code is put on that gene such that it is only delivered to the blood vessels that feed the tumor. Because the endothelial cells lining the blood vessels in the brain create a highly selective barrier limiting entry of chemicals from the circulation into the brain, the non-tumor endothelial cells are not in a rapid state of cell division because the normal brain tissue is not dividing. However, the endothelial cells in the tumor blood vessels are rapidly dividing to create new blood vessels to keep up with the nutrient demands of the tumor. The gene that is delivered to the tumor cells takes advantage of this difference restricting only those endothelial cells that are dividing to read the gene. For the proposed therapeutic, a circular DNA is packaged to make the tumor endothelial cells think that it is a food particle. A recognition molecule coats the surface of the particle that is recognized only by the tumor endothelium and nowhere else. Once the gene is delivered to the tumor endothelial cells, the tumor endothelial cells begin to make the protein that is encoded by the gene, and they pump the cell-killing protein into the tumor cells that are directly in contact with the blood vessel wall. Hence, the drug is the plasmid DNA. The vehicle used to deliver the gene to the tumor blood vessels is completely biodegradable and non-toxic. Additional safeguards are that only the tumor endothelium can make the cell-killing protein, and it has been engineered to be only secreted from the tumor vasculature into the tumor, thus avoiding potential side effects if the cell-killing protein entered the circulation. If it does enter circulation, it would be in very dilute concentrations so as not to cause any

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problems. Treatment would ensue following surgical resection of the primary tumor or after a combination of surgery plus radiation. A single injection of the targeted gene medicine should pump the cell-killing protein from the tumor vasculature into the tumor for at least 7 days. This would be followed by a second and third injection. This would ultimately be developed as an outpatient setting.