THE HARTWELL FOUNDATION

2011 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **G. Praveen Raju, MD, Ph.D.**
Assistant Professor
Department of Pediatrics

Institution: **Cornell University**

Proposal: **Identifying Treatment Resistance Mechanisms for Brain Tumors in Children Using a Novel Approach for Preclinical Drug Testing**

Brain tumors are the leading cause of all cancer-related death in children within the United States. Nearly three thousand children are diagnosed with brain tumors every year in this country with approximately 20% diagnosed with the malignant medulloblastoma. Unfortunately, one-third of all children with medulloblastoma die within five years of diagnosis despite aggressive therapy. Standard of care includes surgery, radiation, and the use of chemotherapy that includes dangerous immunosuppressive drugs. Therapeutic intervention is not effective in one-third of children due to drug resistance and recurrence results in death within five years of diagnosis. The other two-thirds of children are susceptible to devastating side effects such as neurological deficits as well as possible recurrence of the disease. While there is initial response to current therapies for some tumors, many children develop resistance or become refractory to standard treatments. Cancer, in general, is a disease that is believed to originate sporadically from one or a few cells within a tissue as a result of genetic or epigenetic mutations that provide such cells a selective growth advantage over the surrounding normal cells within the tissue. For example, within a tumor microenvironment a few tumor cells may acquire treatment resistance by a range of mechanisms, resulting in recurrence of the tumor. Mouse models of cancer have been generated to study this effect but unfortunately, do not adequately reflect the sporadic nature of tumor formation and tumor recurrence. Raju offers a challenging paradigm shift in cancer therapy: selective targeting of cellular mechanisms responsible for drug resistance. By targeting only the tumor cells that are drug resistant, while sparing normal cells, would increase the effectiveness of chemotherapy and limit side effects. To address this unmet need, he proposes to use a special genetic mouse model of medulloblastoma in combination with a technique that will allow precise control of both spatial and temporal cancer-promoting mutations that provides for the selective identification of recurring tumor cells and their novel gene expression patterns during radiation and drug treatment. His approach will enable more accurate monitoring of the progression of cancer from tumor initiation through later, advanced stages. If successful, Raju will identify therapeutic targets specific to the tumor cell while sparing the normal cell, which will benefit children affected by medulloblastoma by reducing recurrence and decreasing associated morbidity.