



Hyundai Hope on Wheels Hyundai Scholar Research

Dr. Tung Thanh Wynn
St. Joseph's Children's Hospital – Tampa, FL

St. Joseph's Children's Hospital's (SJCH) Pediatric Molecular and Cellular Research Laboratory holds the vision for a pediatric cancer-free world and for researching and developing cutting-edge treatment methodologies that are least-painful and most-effective at treating pediatric cancer.

Generous contributions from donors like Hyundai Motor America, partnerships with biotechnology companies, and our own investments have allowed SJCH to create a cutting-edge research program for pediatric cancer treatment. SJCH is proud to be a catalyst for such important work, and takes seriously the understanding that our research provides children with the possibility to live --- cancer-free.

SJCH is very excited about the early study findings of our dedicated team of researchers. In the past five years under the leadership of our Director of Oncology Research Michael Lawman, Ph.D. and his team, SJCH has made tremendous strides in cancer immunotherapy. We respectfully submit Pediatric Oncologist Dr. Tung Wynn as our Hyundai Scholar to facilitate his co-investigation on "Post Transcriptional Silencing of Genes: A Novel Molecular Approach to the Treatment of Pediatric Cancers of the Cerebellum" which may indeed lay the groundwork for the development of a non-invasive and effective therapeutic protocol of medulloblastoma in children – the most common brain cancer.

In recent years, much has been learned about gene regulation of the developing brain. Among the many genes involved, the "hedgehog" family of genes appears to have a pivotal role in the embryonic development in mammals including humans. Likewise, significant data has accumulated regarding the biology and genetics of medulloblastoma. It is evident that certain genes and "signaling" pathways regulate the development of medulloblastoma. Previous data has shown that the dysregulation of sonic hedgehog and *Gli* signaling pathways are a significant contributor to this malignant process.

The inability to down-regulate sonic hedgehog signaling in certain neuron brain cells is the foundation for the development of tumors such as medulloblastoma. Currently, the treatment of medulloblastoma involves surgery, radiation therapy and chemotherapy. While these treatments are successful, they can potentially

cause significant neurological defects and can alter growth and development of young children as well as cause short and long-term psychosocial behavioral problems.

Alternative therapies, based on the molecular biology of the tumor, are needed. The recent discovery of a molecular mechanism termed post-transcriptional gene silencing or RNA interference by which cells are able to shut down the expression of a targeted gene and alter a cellular pathway may offer a means to control such tumors without the side effects associated with conventional treatments. This study proposes to use these RNA interference molecules to “silence” genes within the hedgehog pathway and thereby alter the malignant nature of the cancer cell. This study requires the development of medulloblastoma cell lines, the construction of the RNA interference molecules, the development of methods to target the RNA interference molecules to tumor cells both *in vitro* and to tumors *in vivo* in the both an athymic and transgenic *ptch* mouse model. If successful, this proposed study would open a new avenue in the treatment of tumors in general and medulloblastoma in particular.

However, as we move forward, ***many children are not.*** The truth is that pediatric cancer does exist ***and children are dying today.*** Cancer is the main cause of death in children and adolescents with tumors of the central nervous system account for 22% of all childhood cancers. Medulloblastoma is a malignancy of the cerebellum and the most common brain cancer. Despite significant advances made in the treatment of childhood cancers, brain tumors are still the leading cause of death attributed to childhood cancers. SJCH laboratory has already established in culture two reference medulloblastoma cell lines which is tremendously promising and demands that we continue to move forward to pursue the next step in the research and development of the cancer therapeutic protocol.

Evidence suggests an important role for the Hh signaling pathway in the normal and abnormal development of the brain and in the development of brain tumors such as medulloblastoma. By inhibiting sonic hedgehog expression using RNA interference technology, it should be possible to determine the role of sonic hedgehog, in the development of medulloblastoma. Because the early pre-clinical research outcomes, continuing to advance these efforts is crucial to St. Joseph’s Children’s Hospital and the children and families they will benefit in the future.