

Therapeutic Development Project Highlights

Solving Kids' Cancer (SKC) sponsors a range of scientific projects that include proof of concept, Phase I & Phase II clinical trials, pilot studies, and other directed scientific research designed to improve outcomes for children with the deadliest pediatric cancers. SKC's Therapeutic Development Initiative (TDI) screens clinical research ideas using a novel approach that stresses efficiency, transparency and results through SKC's advisory boards. SKC is an open source organization and encourages its partners to make all results of funded projects publicly available.

Neuroblastoma Drug Discovery Program

In early 2008, SKC partnered with the Hospital for Sick Kids (SickKids) in Toronto to develop the Neuroblastoma Drug Discovery Program. This initiative will act as a centralized platform for screening and evaluating all compounds that SKC researches or funds for the treatment of neuroblastoma. SickKids pioneered the discovery of cancer stem cells and continues to be a leader in using this technology to isolate cutting-edge cancer therapies.

Cancer stem cells are cells within tumors that are thought to cause resistance to chemotherapy and recurrence of neuroblastoma. This new program, built on actual isolated neuroblastoma stem cells, provides a more representative and promising target by which to screen for effective agents, particularly those resistant to standard chemotherapies. To date, in pre-clinical testing, research labs have used cancer cell lines that were developed in the 1970s and have now been modified for many generations. For example, a cancer cell taken from a breast cancer patient in 1973 will have been modified to resemble a neuroblastoma cell. This initiative will provide actual neuroblastoma cells from patients, providing a much clearer picture of how specific cancer cells react to therapeutic agents.

The potential benefits for this therapy are two-fold: the cells themselves have never been specifically targeted with existing and new therapeutic agents preclinically, so this is a completely new approach. More importantly, the collection of tumor initiating cells represents a marked increase in the ability to conduct effective cancer research. This program has already identified anti-cancer properties in drugs used for malaria, bacterial infections, heart conditions and organ rejection. In animal studies, several of these drugs have prevented the growth of neuroblastoma, and one has already been administered to children.

The ultimate goal of this program is to obtain cancer stem cells from every child with neuroblastoma. These cells will be tested for sensitivity to commonly used compounds in order to develop patient-specific therapies against this childhood cancer. Cancer stem cells represent a wholly new target for existing and new agents for cancer therapy.

Nifurtimox Phase I Clinical Trial

Nifurtimox for Refractory or Relapsed Neuroblastoma

This clinical trial is an example of the abundance of basic scientific research that has not been translated into the clinical realm. It was created based on a 2-page abstract detailing a single patient history. Nifurtimox, an antiprotozoal drug, was used to treat an infection called Chagas' disease; the abstract detailed the discovery of an "accidental" therapeutic benefit for neuroblastoma that had been uncovered during the patient's treatment.

In only three months, SKC co-founder John London was able to organize a Phase I Clinical trial using Nifurtimox to treat neuroblastoma. This provides a wholly new therapeutic option for children with this disease.

In keeping with its commitment to prioritize treatment over traditional protocols, the Nifurtimox Phase I trial was designed to be as therapeutically effective as possible. Rather than utilizing Nifurtimox as a single agent, as is typical in a traditional trial for an investigative drug, this study allows for combination therapy, e.g. patients can use chemotherapy agents (cyclophosphamide and topotecan) as well as Nifurtimox to maximize the potential clinical benefit.

This trial was initiated in 2007 by the University of Vermont. Although ongoing, initial results showed a benefit of four to six months in increased survivorship for patients. As a consequence of this trial, a second Phase II trial has been developed to test the drug's efficacy.

Nifurtimox Phase II Clinical Trial

Nifurtimox for Refractory or Relapsed Neuroblastoma or Medulloblastoma

The success of the Nifurtimox Phase I Trial prompted SKC to launch a Phase II Clinical Trial, also in partnership with the University of Vermont, which began in January 2008. This trial has been expanded to include the St. Louis University/Cardinal Glennon Children's Medical Center, M.D. Anderson in Texas, and Children's Hospital in San Diego.

This study has been expanded to include children with medulloblastoma, a cancer with few treatment options. As in the Phase I Trial, this study maintains the combination of agents (cyclophosphamide and topotecan + nifurtimox) as the best design to achieve maximum results against these cancers.

Oncolytic Virus Phase I Clinical Trial

Oncolytic Virus called Vaccinia for neuroblastoma and other pediatric solid tumors

This trial is in partnership with two renowned children's cancer hospitals and Jennerex Biotherapeutics. It is the first clinical trial using an oncolytic virus for children with cancer conducted in the U.S.

The trial will employ a smallpox virus that has shown strong preclinical evidence in treating neuroblastoma and sarcomas. The virus—modified from the strain of vaccinia virus that forms the basis of the standard smallpox vaccine used in hundreds of millions of people around the world—has been engineered to target, attack, and eradicate cancer without harming the surrounding cells.

The virus is activated by genetic pathways that are critical to the vast majority of human cancers, including common solid tumors such as lung, colon, prostate, breast, pancreas and melanoma. A novel primary mechanism of action is used that can deliver therapies including chemotherapy, small molecule tyrosine kinase inhibitors, antibodies, and radiotherapy. Simultaneously, a therapeutic cascade is initiated by viral replication resulting in tumor vasculature shutdown and anti-tumoral immune attack. In addition, the virus is bioengineered with a gene (GM-CSF) to stimulate systemic anti-tumor immune response in the context of DNA replication and death of the infected cancer cells. It is designed to destroy both injected and non-injected metastatic tumors creating a targeted and multi-pronged attack against neuroblastoma and other solid tumors. Although scientists have been manufacturing and genetically manipulating various viruses to attack cancer cells without sickening the individual with the viral disease for several decades, this technique has been introduced into clinical trials for adult cancer patients only in the last five years. The same viruses that cause diseases like influenza and chicken pox could potentially make survivorship possible for some of the deadliest forms of childhood cancer. The phenomenon of individuals' cancers diminishing after they contracted certain viruses has been observed since the late 1800s.

Development Program for Neuroblastoma-specific Oncolytic Virus

Identification of the Optimal Virus Therapeutic for Neuroblastoma

This 'proof of concept' study is in partnership with the Ottawa Health Research Institute. The primary goal of the development project is to identify oncolytic viruses that specifically attack neuroblastoma. The project uses an existing and automated cell-based screening platform to rapidly test panels of viruses. This strategy to identify viruses is employed to find OV's that are effective at infecting and killing pediatric neuroblastoma cells. Next, identified oncolytic viruses are tested *in vivo* on neuroblastoma cell lines, patient samples, and neuroblastoma cancer stem cells to identify lead candidates with optimal safety and efficacy profiles. Identified viruses are then be prioritized for near-term neuroblastoma clinical trials in children.

Natural Killer Cell Transplant Pilot Study

This pilot study is in partnership with the University of Wisconsin. Its goal is to assess the effectiveness of a reduced intensity conditioning regimen plus haploidentical stem cell transplantation (where the parent serves as a stem cell donor) followed by the infusion of donor natural killer (NK) cells in children with acute leukemia and relapsed or refractory solid tumors. Natural Killer (NK) cells are an important component of the immune system, and have been shown to eradicate leukemia cells as well as many different solid tumors (eg, neuroblastoma, Ewing's sarcoma, osteogenic sarcoma).

Eligible patients are treated with chemotherapy and then receive peripheral blood stem cells from the parent-donor. NK cells obtained from the donor are given to the patient to boost immune recovery and facilitate anti-tumor activity. Donor-derived NK cells mediate a potent "graft vs. tumor" effect, without damaging normal tissues.