



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100762

Project Title:
Enhancing the Anti-Neuroblastoma Activity of Fenretinide by Identifying
and Targeting Sphingolipid Pathways that Confer Resistance

Award Mechanism:
Individual Investigator

Principal Investigator:
Reynolds, Charles

Entity:
Texas Tech University Health Sciences Center

Lay Summary:

High-risk neuroblastoma is a highly lethal childhood malignancy. We showed that intensive chemotherapy and stem cell transplant followed by a vitamin-A-like drug (13-cis-retinoic acid) improved survival for children with neuroblastoma, but many patients still eventually die from disease. Our laboratory studies of fenretinide, another drug derived from vitamin A, have led to clinical trials that have demonstrated complete responses (i.e. patients entering study with tumors had no evidence of tumor after receiving fenretinide) in children with recurrent neuroblastoma. A national Phase III trial of fenretinide in high-risk neuroblastoma is planned in the Children's Oncology Group using our novel fenretinide formulation. Understanding the molecular basis of how cancer cells become resistant to fenretinide will inform future clinical trials. Our preliminary data point toward neuroblastoma cells overproducing sphingosine kinase as a means of resistance to fenretinide, and we have shown a new drug that can inhibit sphingosine kinase (safingol) can overcome fenretinide resistance in cancer cells. This grant will support laboratory studies to understand the molecular basis of resistance to fenretinide, especially resistance caused by sphingosine kinase, and laboratory studies understanding the molecular action of safingol as an anti-neuroblastoma drug. The grant will also support the conduct of phase I clinical trials of fenretinide + safingol (using our novel intravenous formulations for both drugs) initially in adults with cancer and then in children with neuroblastoma. As Phase I clinical trials of our novel intravenous formulation of fenretinide as a single drug in adults have also shown durable complete responses in T-cell lymphomas and activity in adult solid tumors, our proposed fenretinide + safingol laboratory studies and clinical trials will potentially benefit both adult and pediatric patients with a variety of cancers.