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"Novel Kinase Inhibitors in Combiation with Retinoic Acid for Neuroblastoma"

Principal Investigators:
Peter Zage, MD, PhD

SCIENTIFIC ABSTRACT
Children with high-risk neuroblastoma have poor survival rates despite intensive treatment, which includes maintenance therapy with the differentiating agent 13-cis-retinoic acid (CRA). Identification of kinases required for neuroblastoma cell survival after CRA treatment will provide new targets for therapeutic development and suggest novel treatment combinations for children with neuroblastoma. Activity of the RAS-MAPK pathway has previously been linked to neuroblastoma differentiation, and we have identified a potential role for the RAS-MAPK pathway in the survival of neuroblastoma tumor cells after CRA treatment. However, the functional roles of RAS-MAPK pathway signaling in the responses of neuroblastoma cells to CRA are unknown. **We hypothesize that RAS- MAPK pathway activity is required for neuroblastoma cell survival after CRA treatment and that increased RAS-MAPK pathway activity results in neuroblastoma cell resistance to CRA**. We propose to determine the efficacy of CRA treatment combined with inhibition of the RAS-MAPK pathway by gene depletion and specific inhibition in neuroblastoma preclinical models, and we will investigate the role of the RAS-MAPK pathway in neuroblastoma tumor cell resistance to CRA treatment. The potential efficacy of treatments combining CRA with RAS-MAPK pathway inhibition represents an opportunity to identify treatment combinations using available, novel kinase inhibitors that can be rapidly incorporated into early phase clinical trials, providing access to novel and potentially effective treatment combinations and potentially leading to improved success of neuroblastoma therapy and improved survival rates for children with neuroblastoma.

LAY ABSTRACT
Children with aggressive neuroblastoma have poor cure rates despite intensive treatment that includes chemotherapy, surgery, radiation therapy, and maintenance therapy with 13-cis-retinoic acid (CRA). Aggressive neuroblastoma tumors frequently relapse after the completion of treatment, likely due to residual tumor cells that are resistant to the effects of CRA. Kinases are proteins that can stimulate tumor cell growth and survival, and a large number of new drugs are available that block or inhibit kinase function, resulting in tumor cell death. Identification of individual kinases needed for neuroblastoma cell survival after CRA treatment will lead to new treatment combinations for children with relapsed neuroblastoma using these new kinase inhibitors combined with CRA. In our initial experiments, we have identified a kinase named "MEK," a member of a key signaling pathway in cancer cells, as a kinase needed for neuroblastoma tumor cell survival after CRA treatment. We propose to evaluate the role of MEK in neuroblastoma tumor cell resistance to CRA and the effectiveness of treatment with CRA combined with new drugs that block MEK activity. The results of these studies will identify treatment combinations using readily available drugs that can be rapidly tested in clinical trials, leading to improved success of neuroblastoma therapy and improved chances of survival for children with neuroblastoma.