2020 MCC Cancer Center Support Grant (CCSG) Pilot Project Award UCSD-SDSU

RET Inhibition in Neuroblastoma

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Scientific Abstract:

There is a critical need for new treatment options for children with high-risk and relapsed neuroblastoma, and therapies directed against biologically relevant pathways are likely to be more effective with less toxicity. RET expression has been linked to neuroblastoma patient outcomes, but the efficacy of specific RET inhibition has not been established. Getretinib is a novel, specific RET inhibitor that possesses similar potency and improved selectivity to that of other next generation RET inhibitors, but getretinib is half the molecular weight and possesses significantly improved ligand efficiencies towards RET. The efficacy and mechanisms of action of getretinib against neuroblastoma cells and tumors, however, have not been evaluated. We propose that RET inhibition with getretinib will have significant antitumor efficacy against neuroblastoma cells in vitro and xenograft tumors in vivo and that chemical modifications of getretinib to generate RET-specific PROteolysis TArgeting Chimeras (PROTACs) to induce RET degradation within neuroblastoma cells will lead to enhanced potency and efficacy. The potential role of RET in neuroblastoma tumor growth and spread represents an opportunity to identify novel therapies specifically targeting RET, potentially leading to the development of novel RET inhibitors that can be translated into clinical trials in children with neuroblastoma, leading to improved treatment responses and survival rates for children with neuroblastoma.

Lay Abstract:

Children with aggressive neuroblastoma tumors have poor cure rates despite intensive treatment, and new therapies are needed. Treatments that inhibit important proteins and pathways in neuroblastoma tumors are likely to be more effective with fewer side effects. Kinases are proteins that control signals in cancer cells leading to cancer cell growth and spread, and we have determined that drugs that inhibit a specific kinase called RET are effective against neuroblastoma cells in the laboratory. We propose to test a new inhibitor of the RET kinase developed recently at San Diego State University, getretinib, to determine its effectiveness against neuroblastoma cells and tumors, and we will also use strategies and chemical techniques to modify and adjust the structure of getretinib to develop improved drugs that are more effective against neuroblastoma. The results of these studies will determine whether getretinib is effective against neuroblastoma, leading to increased understanding of the role of RET in neuroblastoma tumor growth and spread and to clinical trials using new drugs directed against RET for treatment of children with neuroblastoma.