2021 ACG-IRG Pilot Grant

A Targeted Protein Degradation Approach for Discovery of Improved Therapies in Pediatric Oncology

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Abstract:

Brain and central nervous system tumors are the second most commonly occurring pediatric tumor with over 4,000 children diagnosed each year, and are the number one cause of death from pediatric cancer (CBTRUS Statistical Report[1], NCI[2]). The standard treatment for pediatric brain tumors (PBTs) is surgical resection followed by radiation therapy and cytotoxic chemotherapy. This aggressive regime achieves remission in a subset of patients, but results in profound delayed toxicity and poor quality of life in long-term survivors. High dose radiation is severely toxic to the rapidly developing central nervous system and results in devastating side effects for the child. The survivors of PBT frequently experience significant neurocognitive impairment, with only one third able to maintain employment and a normal lifestyle in adulthood.[3] Targeted therapies, which turn off the functions of oncogenes, such as kinases, have revolutionized treatment of cancer over the past 20 years, and are the cornerstone of modern precision medicine. However, few targeted therapies have been approved for PBTs, due to the challenge of developing molecules with adequate brain exposure at well-tolerated doses (FDA). *A key challenge in neuro-oncology is to identify effective PBT treatments with reduced toxicity, which can replace or reduce the use of high-dose chemotherapy and craniospinal radiation.* In this proposal, we will develop a targeted protein degradation approach to achieving tissue specific drug activation, with the goal of widening the therapeutic index of experimental targeted therapies for PBT. Our hypothesis is that E3-ligases expressed only in CNS tissues can be hijacked for tissue-specific targeted protein degradation of PBT-relevant oncogenes. Our specific aims are to (1) identify ligands for these ligases, (2) use these ligands to survey tractable target space, and (3) develop targeted protein degraders of PBT-relevant oncogenes.

This project aims to develop targeted therapies for pediatric brain tumors with reduced toxicity relative to current standard-of-care.