Yanxin Pei - Children's National Hospital, Washington, DC

Inhibiting metastasis and preventing recurrence in MYC-amplified medulloblastoma

Medulloblastoma (MB) is a common form of brain cancer and the leading cause of cancer-related death in children. Among the multiple MB subtypes, the one associated with MYC amplification frequently spread from the primary tumor site in the cerebellum to other parts of the brain and the spinal cord, conferring an extremely poor outcome with an overall survival rate of less than 30%. Although radiotherapy represents an essential component of treatment for patients over 4 years of age, radiation remains ineffective against a substantial fraction of MYC-amplified MB with metastases, ultimately leading to relapse that has proven resistant to available clinical therapies. Moreover, high-dose radiation to the brain and spinal cord often causes serious long-term neurocognitive and other adverse effects. These observations underscore the need to devise new clinically effective therapies for these tumors. Our preliminary data demonstrate that radiotherapy in MYC-amplified MB models eliminates the majority of the tumor cells, but a small number of metastatic tumor cells with strong expression of the transcription factor OLIG2 are resistant to radiation. In the current proposal, we will determine whether these OLIG2-positive metastatic tumor cells contribute to tumor recurrence and whether targeting OLIG2 with a specific inhibitor delivered by nanoparticles can eradicate these cells and prevent tumor recurrence. Successful completion of these studies will support the development of therapies targeting OLIG2 for the treatment of patients with radiotherapy-resistant MYC-amplified MB, with the goal of preventing tumor relapse and metastasis and thereby improving patient survival.

Michael Taylor - The Hospital for Sick Children, Toronto, Canada

Improving therapy by targeting the biological differences between micro- and macro-metastasis in central nervous system tumors

Medulloblastoma (MB) is the most common malignant brain tumor in children. Although termed as one disease, MB can technically be viewed as four different diseases: Wnt MB, Shh MB, Group 3 MB and Group 4 MB. The main tumor mass in the brain is known as the "primary tumor" and it can spread (metastasize) to other surface regions of the brain and spinal cord, forming metastasis. Most children die from medulloblastoma when the tumor spreads, yet the only therapy for metastasis is radiation and that can be very damaging to children. Our overarching research goal is to find new therapies that will effectively target MB metastasis in a manner that will minimize harmfulness to the developing child. In this project, we are studying the progression of metastasis and its various stages. In our MB models and in patients, we have observed small metastases and overt, large metastases which may be the cause of poor clinical outcomes and patient death. Therefore, we hypothesize that there are biological differences between the small and large metastases in MB and that these distinctive characteristics may serve as potential therapeutic targets. Using powerful single-cell sequencing technology to investigate the small and large metastases in our MB models, we have preliminary results that indicate targetable biological

differences between the two states of metastasis. Moving forward, we are designing experiments that explore these potential therapeutic targets with hopes of halting the small metastases in MB from developing into the overt, large metastases.

Alexandra Miller - Memorial Sloan Kettering Cancer Center, NYC, NY
Development of a "Liquid Biopsy" Paradigm for Pediatric Brain Tumor Patient

Pediatric central nervous system (CNS) tumors remain the leading cause of cancer-related death in children and adolescents. Historically, brain tumor diagnosis relied on imaging findings and/or histology. Recently, molecular diagnostic techniques and classification systems have revolutionized our ability to classify and prognosticate CNS tumors, as well as identify patients likely to benefit from molecular targeted therapies ("precision medicine"). We have also learned that as tumors evolve in response to therapy, molecular changes may occur that promote tumor recurrence and/or progression, underscoring the need for longitudinal sampling. This, coupled with the fact that some pediatric brain tumors are surgically inaccessible even at initial diagnosis, illustrates there is an urgent need for a non-invasive tumor sampling for molecular testing.

Recent technological advances have led to the development of a "liquid biopsy," which detects circulating tumor DNA (small fragments of tumor DNA that are shed into the cerebrospinal fluid and bloodstream). After conducting preliminary studies in adult glioma patients, recently published in Nature, we are poised to implement liquid biopsies for pediatric CNS tumor patients at Memorial Sloan Kettering Cancer Center. The proposed "liquid biopsy program" will provide this novel, non-invasive molecular diagnostic test to all pediatric CNS patients at one of the largest Pediatric Neuro-oncology programs in the country and enable us to refine this technology in the context of our precision medicine efforts. Furthermore, we are collaborating with the Pediatric Brain Tumor Consortium (PBTC) to develop applications for this novel diagnostic tool, allowing for patients across the US to benefit.