Targeting the Novel Cell Cycle Regulator, Spy1, for Treatment of Medulloblastoma

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Medulloblastoma (MB) is the most common malignant pediatric brain tumour. It occurs in 16-25% of cases, with higher incidence in children between the ages of 1 to 9 years. Current standard of care includes combination radiation, surgery and chemotherapy, this treatment relies on DNA damage to induce death of quickly growing cells. While effective for a small margin of patients the treatment is highly aggressive, is plagued with cytotoxicity and ultimately fails in many patients. One recent approach entering clinical development is the use of synthetic cyclin-dependent kinase inhibitors (CKIs). Finding new drugs and optimizing existing approaches for MB are of high importance.

Our lab studies a cell cycle regulatory protein called Speedy (Spy1), which promotes cell proliferation, even during times of DNA damage produced by chemotherapeutic agents. Spy1 has been implicated in the maintenance and expansion of stem-like populations of tumour initiating cells known to be the most chemo-resistant among solid tumours. It is our hypothesis that Spy1 drives tumour initiating cells in MB and reducing the levels of Spy1 will increase sensitivity of aggressive MB to standard of care and CKI therapy.

To address this hypothesis we have used patient-derived MB cells and have manipulated the levels of Spy1 using a lentiviral system. Using a high throughput platform these cells are injected into zebrafish prior to the establishment of the acquired immune system. We then determine the effect of CKI treatment on these in vivo tumours. To date our results show promise that this approach may sensitize, at least a subset of MB patients, to therapy. Our work may contribute toward optimizing the design of CKIs and the use in combination therapy. This project holds promise for improving survival and quality of life for MB patients.