PROJECT TITLE

Cell-free circulating tumour DNA methylation as a comprehensive biomarker to predict tumour behaviour and response to therapy in central nervous system tumours

PRINCIPAL INVESTIGATOR

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SCIENTIFIC SUMMARY

The current standard of care for brain tumour diagnosis requires tissue biopsy. This has inherent limitations due to the risk of brain surgery and limited sampling timepoints. Therefore, there is a substantial clinical need for non-invasive brain tumour biomarker for diagnosis as well as prediction of tumour behaviour and response to therapy. To this end, our lab has studied the utility of analyzing circulating tumour DNA methylation signatures as a surrogate for direct tumour tissue methylation. The rationale for this approach is that DNA methylation signatures represent a unique fingerprint representative of tissue cell of origin and require significantly less starting DNA material than direct genomic analysis of circulating tumour DNA which can be very low in the context of brain tumours given the blood-brain barrier. We have previously optimized a technique to analyze cell free tumour methylated DNA through immunoprecipitation and sequencing (cfMeDIP-seq) in the context of brain tumours. This technique shows high concordance with the gold-standard whole genome bisulfite sequencing (WGBS) and requires significantly less DNA input. In our previous work we demonstrated cfMeDIP-seq can reliably discriminate between various types of brain tumours. In this proposal, we seek to expand on this foundation by assessing its utility as a biomarker of brain tumour behaviour (recurrence, malignant transformation) and survival outcome when incorporated with other datasets including radiomic, clinical, and histologic/molecular pathology. Additionally, we will investigate the utility of incorporating cfMeDIP-seq in monitoring and predicting response to targeted therapy in Glioma patients. Gliomas represent the most common primary malignant brain tumours, and patients with high-grade gliomas experience rapid disease progression and poor overall survival of 12-18 months despite aggressive standard of care therapy. Molecular studies of gliomas have identified significant intratumoural heterogeneity, thus necessitating for personalized treatment plans. We will assess the ability of cfMeDIP-seq to be used in the context of three phase I/II clinical trials of PARP inhibitors in glioma to determine if a unique signature can be identified from patients who responded to therapy and be used to predict who will benefit from such treatment. If successful, this approach is modular and may act as a valuable addition to clinical trial design of targeted therapies for Glioma and other molecular heterogenous tumours. Overall, in this proposal we aim to develop a novel tool and molecular test for the accurate diagnosis of brain tumour types, as well as the prediction of treatment response, recurrence, and aggressive transformation in gliomas.