DNA Methylation signatures associated with Neurofibromatosis type 1

Context: The neurofibromatoses (NF) consist of three genetically distinct disorders (NF1, NF2 and schwannomatosis), characterized by the growth of peripheral nerve sheath tumors (Bakker et al 2017; Kresak and Walsh 2016; Philpott et al. 2017). NF1, the most common of these disorders, affects 1/3000 individuals and can occur spontaneously or be inherited within families due to mutations in the NF1 gene. A significant challenge in the context of treating this disorder is that although major advances have been made in understanding the molecular biology of NF1 over the last 20 years, few approved therapies have been identified and developed to specifically treat the characteristic tumours that occur. A recent position paper (Bakker et al. 2017) written by scientists affiliated with the Children's Tumour Foundation (CTF; previously the National NF Foundation in the US) highlights the unmet needs in the NF1 patient and research community. These include the needs for biomarker discovery and development that would be critical to better understand the disorder's course and the treatment's timing. As well, innovative target-based drug discovery is key to identify innovative NF specific drug candidates.

Our expertise here: Scientists and Clinician Scientists within the CHRI's Genetics and Development Division focus on unravelling the mysteries of childhood genetic disorders and to use that information to provide better quality of life through prevention, early diagnosis and treatments. Of note is our current initiative on "epigenetics", a branch of biomedical science aimed at identifying and understanding the factors that influence how the activity of genes is controlled. One of our CHRI Scientists (Dr. D. Rodenhiser) is an epigenetics researcher who has had a past research background studying the neurofibromatosis gene (Haines et al 2004; Zou et al 2001). Other research undertaken here at the

CHRI and our associated London Health Sciences Centre focuses on developing new epigenomic technologies that will improve diagnostic aspects of a variety of genetic and epigenetic disorders (Schenkel et al. 2017; Aref-Eshghi et al. 2017).

Our proposed research: Epigenetics research has advanced significantly over the past few years with the advent of new technologies that can scan and map epigenetic changes across the entire genomes of patient and tumour DNA. This has lead to the development of new cancer therapies to target the epigenetic patterns found in a variety of cancers. At the CHRI we have the expertise in mapping distinct methylation signatures across the genes in human tissues (Aref-Eshghi et al. 2017). These 'DNA methylation' signatures allow us to show which genes may be wrongly turned on (or off) in patient samples including tumours, and thus contribute to disease. **In our proposed study**, we will undertake a novel pilot project to identify such DNA methylation signatures in tumours from NF1 patients (accessed from tissue and tumour biobanks and databases). We will be specifically asking whether NF1 tumours have individual or shared patterns of DNA methylation and whether these signatures can identify specific targets for therapies already available in treating cancer. As well our innovative research could identify novel targets or pathways that are specific to the causation and progression of NF1 tumours and symptoms, with the goal of advancing biomarker discovery and developing new NF1-specific therapies.

References: **Bakker et al. (2017)** Prog Neurobiol. 152:149-165. **Philpott et al. (2017)** Hum Genomics. 11(1):13. **Kresak and Walsh (2016)** J Ped Genet. 5(2):98-104. **Zou et al. (2004)** Oncogene. 23(2):330-9. **Haines et al. (2001)** Dev Biol. 240(2):585-98. **Schenkel et al. (2017)** J Pediatr Genet. (1):30-41. **Aref-Eshghi et al. (2017)** Epigenetics Epub ahead of print.