Section 2: Executive Summary

Diffuse intrinsic pontine glioma are high grade glial tumours arising in the brainstem with a median survival of 9-12 months, and a distinct biology compared to similar looking tumours arising in the cerebral hemispheres in children and adults. A major challenge to improve outcomes for these tumours is their extensive intratumoral heterogeneity, reflected by differing cellular morphologies and genomic imbalances present within an individual sample. We aim to define the subclonal diversity of DIPG with a view to better understanding the evolutionary dynamics underlying this variation. Firstly, we will use high-depth sequencing to explore the subclonal architecture of a series of DIPG specimens. We will generate direct evidence of subclonal diversity by longitudinal studies of biopsy/autopsy pairs for which multiple topographically distinct samples are available post-mortem. We will further explore the functional consequences of this heterogeneity by studying single cell-derived colonies derived from primary tumour specimens *in vitro*, using advanced high-throughput image analysis linked to targeted resequencing. The long-term goal of such an approach is to provide a framework for preclinical testing of evolutionary biology-driven combinatorial therapies, and to generate data to underpin novel, rationally designed clinical trials in these currently untreatable diseases.