In our laboratory, we use a combination of genomic analysis, mouse models and primary tumour cell cultures, with the main goal of identifying the molecular mechanisms that could provide the basis for novel therapeutic modalities for GBM patients.

**RESEARCH HIGHLIGHTS**

The molecular basis underlying Glioblastoma (GBM) heterogeneity and plasticity are not fully understood. GBM is a very heterogeneous disease for which multiple transcriptional subtypes have been described. Among these subtypes, the Mesenchymal (MES) GBMs tend to have the worst prognosis. The most frequent genetic alterations — Neurofibromatosis type 1 gene (NF1) copy number loss or mutation — and important regulators of the MES subtype, such as STAT3, CEBPB and TAZ, have been identified. Nevertheless, the mechanisms regulating MES GBMs are still not fully understood. Even though each subtype is associated with specific genetic alterations, there is also considerable plasticity among them. Different subtypes co-exist in the same tumours, and shifts in subtypes can occur over time. This plasticity may be explained by the acquisition of new genetic and epigenetic abnormalities, by stem-like reprogramming or by clonal variation. Using transcriptomic data of patient-derived brain tumour stem cell lines (BTSCs), classified according to GBM-intrinsic signatures, we identified the AP-1 transcription factor FOSL1 as a key regulator of the mesenchymal subtype. We provided a mechanistic basis for the role of NF1, a negative regulator of the RAS/MAPK pathway, in GBM mesenchymal transformation through the modulation of FOSL1 expression. Depletion of FOSL1 in NF1-mutant human BTSCs and Kras-mutant mouse neural stem cells results in loss of the mesenchymal gene signature, reduction in stem cell properties and in vivo tumorigenic potential. Our data demonstrated that FOSL1 controls GBM plasticity and aggressiveness in response to NF1 alterations.