TARGETING the CANCER EPIGENOME in GLIOBLASTOMA

Single agent therapies have failed in the treatment of glioblastoma, warranting combination therapies. The challenge is to find a smart combination. The epigenetic landscape is altered in cancer, and may be leveraged for novel treatments. We aim at uncovering cancer relevant pathway vulnerabilities by interfering with the function of epigenetic modifiers (e.g. bromodomain readers, such as BRD4) that have been associated with proto-oncogene activation and drive tumor formation. The perturbation of glioblastoma-derived spheres with an epigenetic drug (BET inhibitor) has uncovered potentially interesting targets that may be actionable with a second drug. The aim of the proposed project is to investigate the drugability of the selected altered pathway by elucidating the underlying mechanism of the interaction and determine the effect on proliferation, cell viability and cell death *in vitro* and *in vivo* models.

APPROACHES

A series of datasets (RNA-seq & ChIP-seq) generated in our lab can be used to explore and discover potential vulnerabilities and resistance mechanisms induced in GBM via BET protein inhibition. Accordingly, relevant pathways can be studied and experimentally tested via multiple *in vitro* approaches. To illustrate, RT-qPCR analysis and Western Blotting are commonly used in our lab to monitor modulation of gene and protein expression, respectively. Moreover, immunofluorescence (IF) imaging, cell viability and proliferation assays using high throughput techniques will be performed. Respective *in vitro* models will be engineered by transducing glioblastoma cell lines with constructs of interest. Promising combinations will be tested in patient derived orthotopic xenograft (PDOX) models in the mouse.

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