

Project Proposal Hegi Lab 2019/20

TARGETING PATHWAY VULNERABILITIES INDUCED BY EPIGENETIC DISTURBANCE IN GLIOBLASTOMA

Glioblastoma is the most malignant brain tumor in adults, and one of the most difficult tumors to treat. It is notorious for its resistance to treatment, with a median outcome of less than two years despite recent insights in the evolution of the disease gained from multi-dimensional OMICs. An important contribution comes from cancer associated epigenetic alterations that reprogram the cells in a tumor type specific manner and comprise epigenetic silencing of key genes mediated by DNA methylation, and remodeling of the chromatin landscape.

The failures of single agent treatments tested in clinical trials over the last 10 years have dramatically shown that combination therapies are necessary for improving outcome of patients affected with glioblastoma. However, the rational choice for successful combination therapy is a big challenge.

In this project we aim at identifying druggable vulnerabilities of cancer relevant pathways revealed upon disturbing the tumor cells by Bromodomain inhibitors (BETi). BET inhibitors are a new class of drugs that act on Bromodomain and extra-terminal (BET) family proteins that are chromatin readers, such as BRD4. BRD4 is an important regulator of gene enhancers and super enhancers regulating cancer relevant genes. We have identified several gene signatures indicative of cancer relevant pathways that were disturbed upon treatment with BETi. Investigating the function of these genes/pathways mechanistically will inform on their suitability to serve as targets for treatment, and the biological function will guide the choice for the second drug to use. Hits will be tested *in vitro* for synergistic effects with BET inhibition. Successful combinations will be taken into *in vivo* models. The treatment in mouse orthotopic xenograft models will be followed by magnetic resonance imaging (MRI) and spectroscopy (MRS) that may provide early response markers that can be used to translate into the clinical setting.

Taken together, this innovative study may not only uncover **potentially druggable pathways/targets**, but may in addition provide **non-invasive tools** for ***in vivo* monitoring of treatment response** that eventually can be **translated into the human setting**.

(Gusyatiner and Hegi, 2018; Gusyatiner et al., 2018)

References:

Gusyatiner, O., and Hegi, M.E. (2018). Glioma epigenetics: From subclassification to novel treatment options. *Semin Cancer Biol* 51, 50-58.

Gusyatiner, O., Pham, M.D.T., Lei, Y., Park, J.H., Bady, P., Delorenzi, M., and Hegi, M. (2018). BET inhibitors synergize with HDAC inhibitors and downregulate expression of interferon response genes in glioblastoma. In 109th Annual Meeting of the American Association for Cancer Research, Abstr #2923, AACR, ed. (Chicago, Illinois: AACR).