Project Proposal 2022

https://www.unil.ch/crn/en/home/menuinst/research-labs/brain-tumor-biology-and-genetics/monika-hegi.html

TARGETING PATHWAY VULNERABILITIES INDUCED BY EPIGENETIC DISTURBANCE IN GLIOBLASTOMA

The laboratory works at the interphase of basic and clinical research in brain tumors. In the proposed project, we aim at identifying druggable vulnerabilities of cancer relevant pathways revealed upon disturbing the tumor cells by epigenetic drugs, such as Bromodomain inhibitors (BETi). BETi target chromatin readers such as BRD4 that regulate expression of proto-oncogenic genes. We have identified several gene signatures indicative of cancer relevant pathways that are disturbed upon treatment with BETi. Investigating the function of these genes/pathways mechanistically in *in vitro* models and with bio-informatics approaches, 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 for synergistic effects with BET inhibition. Successful combinations will be taken into patient derived orthotopic xenograft models in the mouse. Molecular biomarkers and magnetic resonance imaging/ spectroscopy based response markers will be developed for translation into the clinical setting. [1-4]

References:

1 Gusyatiner, O. & Hegi, M. E. Glioma epigenetics: From subclassification to novel treatment options. *Semin Cancer Biol* **51**, 50-58, doi:10.1016/j.semcancer.2017.11.010 (2018).

2 Gusyatiner, O. *et al.* BET inhibitors repress expression of interferon-stimulated genes and synergize with HDAC inhibitors in glioblastoma. *Neuro Oncol* **23**, 1680-1692, doi:10.1093/neuonc/noab115 (2021).

3 Cudalbu, C. *et al.* Metabolic and transcriptomic profiles of glioblastoma invasion revealed by comparisons between patients and corresponding orthotopic xenografts in mice. *Acta Neuropathol Commun* **9**, 133, doi:10.1186/s40478-021-01232-4 (2021).

4 Morel, D., Jeffery, D., Aspeslagh, S., Almouzni, G. & Postel-Vinay, S. Combining epigenetic drugs with other therapies for solid tumours - past lessons and future promise. *Nat Rev Clin Oncol* **17**, 91-107, doi:10.1038/s41571-019-0267-4 (2020).

Expectations from PhD student:

The project proposed to the student contains a basic question that we would like to address, for which we have outlined the initial experimental / bioinformatics approach.

My goal is to guide and support a graduate student to learn how to address a scientific question, design and implement respective experiments, critically evaluate the results and integrate them into the decisions of the next actions to take. This is a gradual process, and I am always available for advice and critical discussion. The weekly group meetings should foster interaction and synergistic collaborations. I am highly supportive of self-initiative, and welcome input to the project along the interests of the student (where possible), as the ultimate goal is to reach independence, and to acquire the skills to develop, implement, and publish own projects after completion of the thesis.

The lab is situated at the interphase of clinical and basic cancer research. We are associated with neurosurgery of the CHUV and we coordinate the Brain Tumor Bank. This gives us the opportunity to use fresh clinical samples for our research. We have molecular datasets of tumors collected within clinical trials. I encourage the use of these unique resources.

The overreaching goal is to improve outcome of patients, therefore our ambition is to make a difference!

Interested?

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Skills/Qualifications:

We are looking for a highly motivated student with interest in cancer biology and genetics

- Basic molecular biology techniques, (quantitative PCR, Western, etc)
- Cell culture
- Basic skills in bioinformatics (R statistic language)
- Willingness to work with animals

Benefits

- PhD program Immunology and Cancer of the University of Lausanne
- Participation in programs of the Swiss Cancer Center Léman