Research profile for applicants

Name of DKFZ research division/group:	***Molecular Genetics / Cancer Metabolism (B060)***
Contact person:	***Bernhad Radlwimmer; b.radlwimmer@dkfz.de; 06221-42-4580***
Group homepage: *Visit this website for further information on current research and recent publications.*	***https://www.dkfz.de/en/genetics/pages/projects/Tumor-metabolism/Tumor_metabolism.html***
Eligibility:	• ***DKFZ Postdoctoral Fellowships*** • ***Dr. Rurainski Fellowship at DKFZ***

RESEARCH PROFILE AND PROJECT TOPICS

Our group is using -omics approaches to dissect the (epi)genetic basis of glioblastoma phenotypic plasticity. We recently showed that genetically restricting the availability of a co-factor of DNA demethylases, BCAT1, results in a cell-state and phenotypic transition from aggressive to less aggressive tumor phenotypes [Boskovic et al., 2023]. Consistent with this observation, our bioinformatic analysis of patient cohorts shows that DNA methylation is tightly associated with glioblastoma cell states. In addition, we found that the knockdown of a developmental-lineage transcription factor, SOX10, results in a quiescent stem-cell state that can be targeted pharmacologically.

In this project, we will (1) characterize the epigenetic mechanisms of glioblastoma cell state transitions by single-cell sequencing and AI-based computational analysis and (2) test the effects of pharmacologic targeting of epigenetic cell state master regulators.
Toward these aims, we will use CRISPR KO and CRISPR-Csm mediated knockdown approaches to suppress the activity of the BCAT1 and SOX10 and induce the respective cell state transitions in genetically engineered glioblastoma organoid models (collaboration with Haikun Liu, DKFZ) and patient-derived primary cell lines. Samples will be analyzed by single-cell RNA and whole-genome bisulfite sequencing. These data will be integrated with recently published matched scRNA-Seq and scDNA-methylation data [Chaligne et al., 2021]. Cell-state RNA expression signatures and DNA methylation patterns will be linked computationally, and potential epigenetically controlled cell state drivers will be identified. The effects of putative driver genes on cell-state transitions will be tested by in-silico knockout, and master regulators of cell state will be validated experimentally. Finally, we will pharmacologically target selected cell state master regulators to test potential glioblastoma therapy approaches.