UNIVERSITÄTS-
KINDERSPITAL
ZÜRICH | Das Spital der Eleonorenstiftung



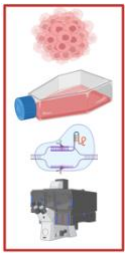
Defining the role of receptor tyrosine kinases in modulating ONC201 response in DMG

We invite students from biology, medicine, bioinformatics, and life sciences to join a 6- to 12-month research project focused on uncovering the receptor tyrosine kinase (RTK) vulnerabilities that shape the response to ONC201 in diffuse midline glioma (DMG), a devastating and currently incurable pediatric brain cancer.



Background: Our research group is dedicated to understanding the biology of pediatric DMG, an aggressive brain tumor with a dismal prognosis of less than one-year post-diagnosis. For children affected by this disease, radiotherapy remains the only standard treatment, offering only temporary symptom relief. ONC201 (dordaviprone), a first-in-class imipridone targeting the mitochondrial protease ClpP, has recently become the first systemic therapy approved for H3 K27M-mutant DMG, yet responses remain partial and the determinants of sensitivity are largely unknown. We therefore performed an arrayed CRISPR-Cas9 screen across the entire family of 58 RTKs and identified IGF1R and INSR as modifiers of ONC201 response, with distinct effects on viability and metabolism. This project will validate these hits genetically and pharmacologically and dissect how RTK signaling and tumor metabolism intersect with the mitochondrial mechanism of ONC201, to design rational combination strategies for children with DMG.

If you are a student:



- with a strong passion for science and discovery
- eager to master cutting-edge techniques to improve treatments for pediatric brain tumors
- curious, driven, and ready to expand your scientific knowledge

<u>This project is especially for you!</u>

General Objectives:

- Validate the CRISPR screen-identified hits (IGF1R, INSR) as modifiers of ONC201 sensitivity in DMG cell models.
- Dissect the signaling and metabolic rewiring behind the response (PI3K/AKT/mTOR axis, glucose handling, mitochondrial function).
- Test rational drug combinations pairing ONC201 with IGF1R/INSR inhibitors and metabolic agents, and assess their potential in vitro.

Opportunities:

- Cell culture and manipulation (lentiviral production, transduction, CRISPR-Cas9 gene editing, generation and characterization of monoclonal knockout lines, drug treatments, etc.)
- Work with bacterial and mammalian systems, performing molecular cloning, plasmid preparation (miniprep, maxiprep), bacterial transformation etc.
- Master a variety of molecular and cellular biology techniques, such as DNA/RNA extraction, Western Blot, Immunofluorescence, automated dose-response and viability/ATP assays, live-cell imaging, CRISPR-based experiments for functional validation etc.

Pre-requisites:

- Basic knowledge in cell/molecular biology and oncology is preferred, but more important is a desire to learn and engage translational research
- Experience with molecular biology techniques (such as cloning, CRISPR, cell manipulation) and familiarity with data analysis (e.g., R, GraphPad Prism) will be an advantage, but not required

Work environment: You will join an international research team embedded within the DMG/DIPG group, in collaboration with the Neuropathology Institute at Universitätsspital Zürich. As part of the team, you will participate in group meetings, one-on-one discussions with the PI, progress reports, and journal clubs, benefiting from a dynamic and research-driven environment**.**

Student will be assisted and guided if/when needed

Project period: Projects can start from January 2027. The starting and ending times of the project can be made flexible for suitable candidates. The duration of the project can be extended for possible publication in high-impact journal.

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