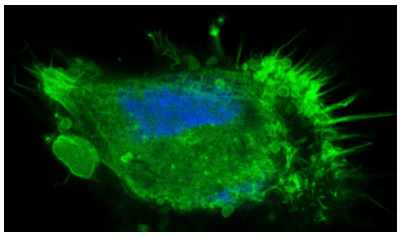
University of Zurich[UZH] | UNIVERSITY CHILDREN'S HOSPITAL ZURICH — Children's Research Center CRC | PEDIATRIC MOLECULAR NEURO-ONCOLOGY RESEARCH

MASTER'S THESIS PROJECT:

Impact of therapeutic targeting of FGFR signaling on subcellular Ca^{2+} balance in medulloblastoma



Description of research: Medulloblastoma (MB) is the most common malignant brain tumor in children. Aggressive growth and metastatic spread of MB together with lack of targeted therapy options represent a major therapeutical challenge. Deregulation of cell signaling in tumor cells contributes to tumor growth and tissue invasion. Ca^{2+} ions act as secondary messengers of multiple signaling pathways, and Ca^{2+} transients inside tumor cells control cellular functions relevant for tumor growth and tissue invasion. Intracellular Ca^{2+} transients in MB tumor cells are induced for example by growth factor signaling, direct-cell-cell communication or pharmacological modulation of Ca^{2+} channels. A better understanding of subcellular Ca^{2+} transients in MB tumor cells, and their control by growth factor signaling or alteration under treatment will provide mechanistic insights in the impact of therapeutic targeting on tumor cell signaling.

Project: FGFR siganling, which promotes MB tumor growth and invasiveness, is associated with an altered Ca^{2+} signature. The experimental small molecule ligand of FRS2 (F2i)[1], the receptor proximal adaptor protein of FGFR, represses downstream signaling and restricts tumor cell invasion. The analysis of putative off-targets of F2i hints towards altered mitochondrial Ca^{2+} functions. Based on the on- and off-target effects of F2i, we hypothesize that tight control of localized Ca^{2+} transients in MB tumor cells is essential for maintaining oncogenic functions. The visualization and quantification of subcellular Ca^{2+} transients in tumor cells would thus provide essential insights in oncogenic signaling and the efficacy of anti-tumor treatments.

Objective:
To characterize normal and drug disturbed subcellular Ca^{2+} transients as a real-time molecular read-out for oncogenic signaling and drug response.

The aims of the Master's thesis project are:

1. To establish quantitative analysis of mitochondrial and plasma membrane-proximal Ca^{2+} transients in MB tumor cells
2. To assess physiological and drug-altered Ca^{2+} transients
3. To determine the impact of genetic interference with suspected regulators of Ca^{2+} transient function

What you will learn:

- Cell biological and biochemical approaches to study cell signaling and Ca2+ transients in cells
- Cloning, lentivirus handling and cell line generation
- Confocal and quantitative imaging, live cell imaging using fluorescent sensors

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Requirements: Genuine interest in the cell biology of cancer and cancer cell signaling. Motivation to work in a wet-lab environment and to explore fundamental biological questions, curiosity. Some experience in wet lab work/and or imaging/computing is an asset.

Starting date: Start after August 2023, upon agreement

1. Santhana Kumar K, Kopp LL, Brunner C, Schuster M, et al. Discovery of a small molecule ligand of FRS2 that inhibits invasion and tumor growth. *Cell Oncol*. Published online 2022:331-356.