MUNI
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Doctoral study program: Biomedical Sciences
Form: *doctoral (present)*
Department: Department of Biology
Supervisor: Zdenek Andrysik, Ph.D.

Ph.D. position:
Overcoming resistance in tumor subpopulations treated with MDM2 and ISR inhibitors

Annotation:

TP53 is recognized as the most frequently mutated tumor suppressor gene in human cancers. The p53 protein functions as a transcription factor that controls several cellular programs constraining cancer progression, including cell cycle arrest, senescence, and apoptosis. However, in most cancer cell types, targeted activation of p53 by small molecule inhibitors of its endogenous repressor MDM2 is insufficient for triggering apoptosis. Therefore, investigating the mechanisms controlling cell fate choice upon p53 activation could illuminate strategies to overcome this critical shortcoming of p53-based cancer *monotherapies*.

Within this context, we recently discovered a negative feedback mechanism whereby p53 activation inhibits the Integrated Stress Response (ISR) and restrains the apoptotic branch of the p53 network. These findings allowed us to design an innovative combinatorial treatment strategy and demonstrate that targeted pharmacological induction of the ISR enhances activity of the p53 network, leads to rapid apoptosis in cancer lines resistant to MDM2 inhibitors, and results in tumor growth arrest *in vivo*. The overall goal of this project is to improve tumor response to the combined induction of p53 and ISR through two complementary approaches focused on potentiating the apoptotic response in resistant tumor subpopulations.

First, we will develop a reporter system for monitoring and optimizing p53/ISR pharmacological induction *in vivo*. Efficiencies of both p53- and ISR-activating drugs in vivo differ greatly, and efficacy information for CRC treatments is limited. We hypothesize that bioavailability of MDM2 and eIF2a inhibitors and their respective CRC-specific efficiencies are variable. Therefore, we propose to examine p53/ISR activities in orthotopic CRC xenograft tumors following oral administration of 3-4 leading compounds from each group using a fluorescence reporter system, as activities of both pathways can be monitored easily at the transcription level. Specifically, we will generate a reporter system for both monitoring tumor growth and activation of p53 and ATF4. We will test the system *in vitro*, implant reporter-expressing organoids in mouse cecum, and identify the most efficacious MDM2/eIF2a inhibitors for in vivo CRC tumor treatment.

Second, we will test strategies for overcoming treatment resistance in tumor subpopulations. Our preliminary data revealed variable p53/ISR induction throughout the tumor. We hypothesize that treatment-resistant subpopulations of tumor cells can be targeted pharmacologically to elicit strong p53/ISR activation triggering apoptosis. Therefore, we will use spatial transcriptomics data from CRC tumors to rank subpopulations based on p53/ISR activity. Next, we will identify druggable targets in cells with low p53/ISR scores and validate top sensitizing strategies *in vivo*.

Funding of the research:
State external sources of PhD position funding

Information on funding PGS positions:
The program requires that all PhD students have some means of financial support of min. 25 000 CZK per month. This is often a combination of various sources (grants, scholarship etc.)

Requirements for the student according to the Doctoral Board:
The student's minimum publication activity within the course of study is one first-author publication with an IF value above the median in the field or 2 first-author publications in journals with an IF value in the 3rd quartile in the field (Q3). A condition for successful completion of the studies is also a foreign internship of at least 1 month, which is an inseparable part of the studies. As part of their studies, students will also participate in the teaching.

Information about supervisor:
https://biology.med.muni.cz/en/research/zdenek-andrysik/about