

Doctoral study program: Biomedical Sciences

Form: *doctoral (present)*

Department: Department of Biology

Supervisor: Zdenek Andryšik, Ph.D.

Ph.D. position:

Mechanism of the cell death induced by joint activation of p53 and ISR networks

Annotation:

TP53, which encodes transcription factor p53, is the most frequently mutated tumor suppressor gene in human cancers. Various types of cellular stress induce p53, which then transactivates a broad range of genes involved in numerous anti-cancer programs, including cell cycle arrest, DNA repair, senescence, and apoptosis. However, in most cancer types, targeted induction of p53 by small molecule inhibitors of MDM2 (a key upstream negative regulator) leads to a reversible proliferation block, while the therapeutically desirable elimination of cancer cells by apoptosis remains limited.

Recently, our laboratory identified a novel regulatory mechanism within the p53 network responsible for restraining the apoptotic response upon p53 activation. In this scenario, p53 activity maintains the eukaryotic translation initiation factor eIF2a in a dephosphorylated and fully functional state. Pharmacologically severing this negative feedback loop with eIF2a inhibitors leads to rapid onset of apoptosis in cancer cells *in vitro* and results in stalled tumor growth and improved animal survival *in vivo*. Cell death upon dual activation of the p53 and ISR pathways is accompanied by induction of transcriptional programs governed by p53 and ATF4.

Identifying factors that modulate the apoptotic response can illuminate strategies to further sensitize CRC cells to the p53/ISR-activating treatment. We propose two synergistic approaches to achieve this project's objective: first, to complete genome-wide CRISPR screens in CRC lines; second, to define conserved overlaps of the p53 and ATF4 networks by CUT&RUN. Next, the leading strategies for cancer cells sensitization to the combined activation of p53 and ISR will be tested both *in vitro* and *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.)

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Please quote the Reference Number in your reply.

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>