

## Ph.D. projects in progress

1.

**Mentor:** Gyula Timinszky

**Doctoral school:** University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

**Ph.D. student:** Hasan Mamar

**Title of the research topic:** The functional analysis of PARP inhibitor resistance caused by ALC1

**Description of the research topic:** Personalized medicine is one of the most promising strategies in cancer therapy, as it lays the ground to develop new drugs, which specifically attack and eliminate cancer cells with specific genetic alterations, without harming the healthy cells. Among such drugs are the Poly(ADP-ribose) Polymerase Inhibitors (PARPi). PARPi were designed to kill cancer cells with BRCA1 or BRCA2 deficiency. If other gene mutations are identified that are also PARPi sensitive, the therapeutic spectrum of PARP inhibitors could be broadened to the benefit of more patients. With the above premise in mind, we conducted a genome-wide knockout screen to identify novel genes that, when mutated, cause to PARPi sensitivity. The aim of this PhD project is to describe the potential genetic interactions between these mutated candidates and the already known ones, in order to understand the underlying molecular mechanisms. In particular, we focus on ALC1 a PARP-activated chromatin remodeling enzyme and an oncogene. We will study how ALC1 activity leads to PARPi resistance and we will seek to identify ALC1 specific inhibitors, that might be used at the bedside in the future to fight cancer.

2.

**Mentor:** Gyula Timinszky

**Doctoral school:** University of Szeged, Doctoral School of Multidisciplinary Medicine

**Ph.D. student:** Mihály Mérey

**Title of the research topic:** The connection between the EGFR signaling pathway and the mono-ADP-ribosylhydrolases in human osteosarcoma cell lines

**Description of the research topic:** A common feature of cancer cells is uncontrolled growth, frequently due to activating mutations of cell surface receptors, such as the epidermal growth factor receptor (EGFR) that normally responds to growth promoting stimuli. Synthetic lethality was found between EGFR and poly(ADP-ribose) polymerase (PARP) inhibition in human triple negative breast cancer, a particularly aggressive tumor of the breast. However, the underlying molecular mechanisms of the observed synthetic lethality remain unknown. ADP-ribosylation is a post-translational modification regulating an array of cellular processes including DNA repair,

transcription, proliferation and cell death. MacroD2, an enzyme reversing ADP-ribosylation, is frequently amplified or mutated in a number of cancers. When assessing the sensitivity of MacroD2 knockouts to a library of anti-cancer drugs, we find synthetic interactions between MacroD2 knockouts and inhibitors of EGFR signaling. In this PhD project, we investigate the effect of ADP-ribosylation, including MacroD2 and TARG1, on the EGFR signaling pathway in human osteosarcoma (U2OS) cell lines under physiological conditions, as well as upon Epidermal Growth Factor (EGF) hormone stimulation. Receptor internalization and intracellular localization were analyzed under different conditions and in different cell lines using a variety of molecular laboratory techniques. Our goal is to obtain a precise picture how ADP-ribosylation regulates EGFR signaling and identify the underlying molecular mechanisms.

**3.**

**Mentor:** Gyula Timinszky

**Doctoral school:** University of Szeged, Doctoral School of Multidisciplinary Medicine

**Ph.D. student:** Alexandra Mihut

**Title of the research topic:** Functional analysis of MacroD2 in the DNA damage response

**Description of the research topic:** Macrodomains are ancient domains designed to bind or erase different forms of ADP-ribosylation (ADPr), a post-translational modification (PTM) that regulates critical cell processes, including DNA damage repair. MacroD2 is a macrodomain-containing protein with specificity towards mono-ADPr. Up to date research correlates MacroD2 with DNA repair through its ADPr-dependent recruitment at the sites of DNA damage. Cancer studies show that genetic profiles with MACROD2 deletion lead to an aberrant DNA repair response that triggers genomic instability and cancer susceptibility. Furthermore, in response to DNA damage, MacroD2 exports from the nucleus. It remains to be determined what are the biological consequences of this particular behavior with respect to DNA damage. In this PhD project we will identify the targets and regulators of MacroD2 during the DNA damage response using state-of-the-art mass-spectrometric approaches and the identified interactions will be validated in cell biological assays.