Oncogenic driver gene activation is one the leading molecular causes of cells' neoplastic, carcinogenic transformation. Among the universal driver oncogenes are mutated *KRAS*, hyperactive *CMYC* and mutated *TP53*, last of which upon acquiring missense mutations switches from a tumor suppressor to a potent driver oncogene. It has been shown by our group and in countless other studies that these and other oncogenic drivers cooperate and complement one another to promote cell transformation and progression of neoplasias. In the same time it is a paradigm that this cooperation and ability of each driver oncogene to be decisive in oncogenesis is different dependent on the molecular background.

During the ongoing project our group has discovered in cancer cell lines that an important dimension of the molecular background is an **"oncogene competition" phenomenon – when one oncogene is taking-over or inhibiting the activity of another oncogene which results in reshaping of molecular programs of both oncogenes.**

This phenomenon has never been described before in cancer research and requires an advanced validation and mechanism study before publishing.

The main project hypothesis is that the competition of the major driver oncogenes is a meaningful process, which may significantly modulate the ability of each oncogene to control the cancer cells' molecular landscape, phenotype, and thus influence cancer diagnosis, prognosis or therapies. In attempt to falsify/validate this hypothesis - we specifically want to study how the trio of common, universal oncogenic drivers – mutant *TP53*, mutant *KRAS* and hyperactive *CMYC* influence one another's molecular programs, what is the mechanism of this interplay and consequences on therapeutic targeting of mutant *TP53* in cancer.

Specific goals of the project are:

1. Determine specific effects of the oncogene competition on cells' transcriptome and phenotype by using untransformed human fibroblasts to sequentially introduce and remove the oncogenic drivers.

2. Validate the effects of the oncogene competition on transcriptome by utilizing a human colon and pancreatic cancer organoid biobank to knock-down endogenous activated oncogenes.

3. Understand mechanistic aspects of the competitive interplay between mutant *TP53* and mutant *KRAS* or hyperactive *CMYC* by using cell lines and organoids.

4. Determine how mutant p53 targeting with preclinical protocols and standard therapies in colon and pancreatic cancer organoids are affected by the oncogene competition.

The ultimate aim of the project is to validate the oncogene competition hypothesis found in cancer cell lines, by using fibroblast and organoid models and *in vivo* organoid-derived xenografts, which allow either more advanced oncogene manipulation or are more closely related to patient tumors, than the cancer cell lines.