

According to the World Health Organization gastric cancer is the fifth most common global cancer and the fourth most common cause of cancer death (770,000 deaths in 2020). This high mortality highlights the urgent requirement for further investigations and the development of new therapeutic approaches to fight the disease.

Tumor suppressor p53 (encoded by *TP53*) is an important molecule implicated in cancer prevention, however, when mutated, it not only loses its function but may become a driving oncogene at later tumorigenic stages. In gastric cancer, *TP53* is the most frequently mutated gene (approximately 60%), the majority of which are gain-of-function missense mutations. As the role of mutant p53 gain-of-function in tumorigenesis and later cancer progression stages is becoming better elucidated, it is clear how very little we know about mutant p53 and how it functions. It is vital to identify mutant p53 relationships and interactions with other major oncogenes (for example CMYC), and understand both cooperation and competition mechanisms. A better understanding and deeper knowledge of this complex interplay between those molecules could facilitate the design of new, more effective and safer therapeutic approaches for cancer treatment.

To this end, we seek to unravel this complex issue, i.e., is it possible that in parallel to mutant p53 gain-of-function cooperation with CMYC, there exists another level of their interplay: oncogene competition, which is a key process for reshaping molecular programs of co-expressed mutant p53 and hyperactive CMYC? Our comprehensive data sets from next-generation proteomics and RNA sequencing experiments indicated the novel notion of oncogene competition in cancer cells. Such complex datasets have never been gathered before and investigated for mutant p53 gain-of-function, therefore they provide us with an opportunity to study the mechanism of mutant p53 in great detail, like never before. To address this important question we will apply cutting-edge molecular biology techniques (qPCR, CHIP, siRNA silencing, Western blot analysis, microscopy) and advanced cancer models such as 2D cancer cell lines and 3D cancer organoid cultures. Knowledge from this project will directly contribute to deeper understanding of mutant p53 gain-of-function role, function and mechanisms in cancer, and may identify new therapeutic targets for the disease.