Customizing treatment in cancer patients & uncovering cancer vulnerabilities

Project

Prof. Dr. med. Chantal Pauli

RAS proteins are among the most important members of the MAPK pathway, a signaling cascade relevant for cell growth and survival. Altered RAS genes (*HRAS*, *KRAS* and *NRAS*) represent the most frequently mutated gene family in human cancers, with *KRAS* being accountable for the development of roughly 35% of lung adenocarcinomas, up to 50% of colorectal cancers and even up to 95% of pancreatic cancers. Despite intensive research efforts, effective inhibition of mutated *KRAS* remains a major obstacle in the battle against cancer. The recent development of $KRAS^{G12C}$ mutation-specific drugs has shed some light on this specific variant, but clinical success of these compounds is very limited, and first resistance mutations have already been reported. As these efforts in inhibiting *KRAS* have not been successful, the research focus has shifted towards the inhibition of MEK1/2, a regulator found downstream of the MAPK pathway. However, as resistance mechanisms are rapidly emerging, the notion that *KRAS*-mutated tumors remain unassailable persists. It is therefore of great importance to develop other strategies in the identification of cancer vulnerabilities.

In the era of precision medicine, strategies to confirm therapeutic efficacy and the identification of additional treatment options have become essential to both clinicians and patients. The functional tumor pathology group, led by Prof. Dr. med. Chantal Pauli and located in the Department of Pathology and Molecular Pathology at the University Hospital Zurich, has developed a platform incorporating the genetic features of individual patient tumors and the functional testing of patient-derived tumor organoids (PDTO). The overall goal is to identify effective therapeutic strategies for individual patients by performing a screen of cancer-relevant drugs. This approach has resulted in the identification of a novel synergistic drug combination involving a MEK inhibitor and a purine analogue. Interestingly, this synergy was not found in all tumor organoids, but was restricted to those with a mutation in the MAPK pathway.

This project will further examine the therapeutic potential of the identified drug combination in a larger cohort of PDTOs, and help to understand the genetic features responsible for this vulnerability seen in certain tumors. As resistance mechanisms against $KRAS^{G12C}$ are arising, we plan to test if our combination is able to bypass the resistance mechanisms and affect the tumor's viability. Ultimately, we seek to identify patients likely to benefit from this synergistic drug combination and elucidate mechanisms of patient-related drug sensitivities or resistances.