Drug repurposing to target p53 protein family for improved therapy in the relapsed *TP*53 and *EGFR* mutated lung cancer

Cancer is recognized as one of the leading death threats in humans worldwide. The main challenge in treating cancer patients derives from the high heterogeneity of the disease, low selectivity of the therapies available to date, and the development of the resistant disease. Thus, personalized and affordable treatment is urgently needed to improve the patients' outcomes.

Great potential in treating cancer is in targeted therapeutics, which modulate or inhibit prime cancer cell targets responsible for tumor survival and progression. However, they are at a very early stage of clinical development. My group discovered a new targeted approach for cancer patients using repurposed drugs. Drug repurposing aims to re-use the existing drugs for new indications. My goal is to characterize the biomarkers of resistance/sensitivity to the previously identified drugs in cancer cell lines, animal models, and patient samples for the rapid translation of our findings into clinical practice. For accurate sample analysis, apart from highly sensitive antibodies, we will also apply artificial intelligence.

The overall aim of this project is to identify the factors driving lethal response to repurposed heme analogs to pin down the biomarkers associated with prognosis and treatment resistance. In previous work, with my team, I have identified porphyrins as potent activators of p53 and p73 – key tumor suppressors and important drug targets and, in this work, the mechanism of the anti-tumor action will be elucidated in detail.

In my project, I will evaluate the potential of heme analogs in killing resistant cancer cells. I will use well-characterized cancer cell lines, animal models, and patients' material to build a comprehensive picture of the key factors driving lethal response to repurposed drugs. We will focus on cancers of great unmet need characterized by poor patient outcome. Thus, here we will study the response to repurposed drugs and their combinations of recurrent lung cancer.

Using a high-throughput approach based on CRISPR/Cas9 screen and RNA sequencing, I will describe the networks, which will serve as biomarkers associated with prognosis and treatment resistance for patients treated with heme analogs. I also hope to find new druggable interactions for the design of ready-to-use drug combinations.

My approach, based on drug repurposing, allows for the development of the non-toxic and affordable therapeutic strategy for the tailored treatment of non-small cell lung cancers with *EGFR* and *TP*53 mutations that have developed resistance to frontline Osimertinib.