Achieving a good efficacy of chemotherapy and an effective activation of the host immune system against the tumor are two major challenges still unresolved in patients with disseminated and metastatic tumors.

The main limitation to the efficacy of chemotherapy is multidrug resistance (MDR), a multiple cross-resistance towards different anticancer drugs. One of the main mechanisms of MDR is the overexpression of integral membrane transporters of the ATP binding cassette (ABC) transporters. All the pharmacological inhibitors of ABC transporters have failed in pre-clinical and clinical stages for their low specificity and high toxicity. However, recent high-throughput screenings of pharmacological libraries progressively identified specific compounds, which were unexpectedly more effective in chemoresistant cells than in chemosensitive ones. The molecular basis of this paradoxical hypersensitivity (“collateral sensitivity”, CS) are far from being understood.

Besides killing MDR cells, the successful tumor eradication depends on the ability of chemotherapy to kill tumor cells in a way detectable by the immune system, i.e. inducing an immunogenic cell death (ICD). Until now, there are no chemo sensitizing compounds with the dual property of inducing selective cytotoxicity (i.e. producing CS) in chemoresistant cells and re-activating the host immune system response (i.e. producing ICD) against MDR tumors.

Our research group works on different chemo-immunosensitive and chemo-immunoresistant tumors (lung and breast cancer, malignant pleural mesothelioma, glioblastoma multiforme). We aim to:

- investigate the molecular and metabolic bases of chemo-immunoresistant phenotype, by exploiting CRISPR KO libraries coupled with multi-OMIC techniques, (including single-cell transcriptomics, untargeted and spatial metabolomics), to identify new therapeutic targets, diagnostic/predictive markers;
- target ER stress proteins and mitochondrial homeostasis as vulnerabilities peculiar of chemo-immuno-resistant tumors that can be exploited to restore sensitivity to chemotherapy and immunotherapy in resistant cells;
- repurpose existing drugs and/or validate new ad hoc synthesized compounds with the dual property of inducing CS and ICD in patient-derived immune-xenografts.