The Genomic Instability Group focuses its research on understanding the molecular mechanisms leading to cancer and other age-related diseases, with the ultimate goal of translating this knowledge into novel therapeutic strategies. Our initial investigations centred on Replicative Stress (RS), a type of DNA damage sensed by the ATR kinase, and that is particularly abundant in some cancer cells. Our work in this area led to the discovery of selective ATR inhibitors that were further improved to enable their clinical development as anticancer agents. Next, we became increasingly interested in understanding the mechanisms of drug resistance to specific agents, such as inhibitors of ATR or USP7. More recently, our group has revealed that one of the most frequent mutations in human cancer, inactivation of the tumour suppressor FBXW7, leads to multidrug resistance (MDR). Importantly, we have also discovered strategies to overcome MDR, which is an important area of our current research.

“We have discovered a new mechanism that drives multidrug resistance. In addition, we have shown that the depletion of PD-L1 expressing cells might be a fruitful approach for cancer therapy.”
The Integrated Stress Response as a vulnerability of cancer cells

Last year, we reported that FRK7 mutations lead to multidrug resistance (MDR), limiting the efficacy of most available anticancer agents. Importantly, FRK7 is one of the 10 most frequently mutated genes in cancer due to either inactivating mutations and/or allelic loss. Furthermore, mutations in this gene are among the most significantly associated with poor survival across all human cancers. Interestingly, we discovered that, despite their MDR phenotype, FRK7-deficient cells were preferentially sensitive to therapies targeting mitochondria, such as the antibiotic tigecycline. Surprisingly, these compounds were already known to have hallmarks of ISR activity, was induced by tigecycline and reverted by the ISR inhibitor ISRIB. Moreover, and by searching for additional compounds that could target FRK7-deficient cells, we found another set of seemingly unrelated compounds that did so, all of which activated the ISR (FIGURE 1).

Targeting PD-L1 expressing cells in cancer therapy

The latest advances in immunotherapy for the treatment of cancer have incredibly improved the prognosis of a wide range of malignancies. Not surprisingly, the discovery of the immune checkpoint mediated by PD-1 and CTLA-4 receptors and of how targeting these pathways can be exploited for cancer therapy was awarded the Nobel Prize in Medicine in 2018. Antibodies targeting the PD-1/PD-L1 interaction are among the most widely used immunotherapy strategies, but, despite the indisputable success of these treatments, only 20–40% of the patients respond, and even fewer show durable responses. We hypothesised that the elimination of PD-L1-expressing cells, which may display additional checkpoint mediators on their membranes, could have broader antitumoral effects than targeting only the PD-1/PD-L1 interaction. To address this, we generated mice carrying an inducible suicide reporter allele of PD-L1, which allows the isolation and identification of PD-L1-expressing cells, as well as their selective elimination upon treatment with an otherwise inert compound. Our work with these mice has revealed that the depletion of PD-L1 positive cells potentiates immune responses against different stimuli, such as a septic cytokine storm. In the context of cancer, we found that depletion of PD-L1-expressing cells favoured the clearance of tumour cells in a mouse model of metastatic melanoma and, consequently, prolonged the survival of the animals (FIGURE 2).

This work supports the usefulness of targeting PD-L1+ cells in cancer therapy, and provides the immunotherapy research community with a useful genetic tool for further investigations of the PD-1/PD-L1 checkpoint.