Inactivation of the Fanconi anemia (FA) pathway occurs in diverse human tumors including pancreatic cancer and renders those tumors hypersensitive to DNA interstrand-cross-linking agents (ICL). How to treat specificly pancreatic and other cancers harboring FA mutations has recently raised great interest, yet preclinical studies have been hampered by the lack of well-controlled human cancer models.

We endogenously disrupted *FANCC* and *FANCG* in an adenokarcinoma cell line and observed a typical phenotype of FA pathway deficiency (abrogation of FANCD2 monoubiquitination; chromosomal instability, G2M arrest and decreased proliferation upon treatement with ICL, spontaneous chromosomal breakage).

Homozygous deletion was achieved for *FANCC* and *FANCG* but not for *FANCD2* and *BRCA2/FANCD1* in RKO cells, suggesting a detrimental phenotype. It provided direct evidence for the paradoxical assumption that their inactivation could be predominantly selected against in cancer cells.

Using high-throughput screening, we assessed the growth of our isogenic *FANCC* and *FANCG* cells upon treatment with 880 active drugs and 40 000 diverse compounds. The compound having the stronges effect, named 80136342, had a distinct mechanism of action from that of ICL agents. When applied in combination with ICL agents, 80136342 had at least additive toxic effects, excluding interferences on ICL-induced toxicity and facilitating a combinational application.

We then created the first human isogenic cancer cell line model of Brca2 deficiency by deleting a part of exon 11 using homologous recombination. We observed a typical phenotype (loss of Rad51 nuclear foci, increased chromosomal instability, decreased proliferation upon treatment with ICL agents). Two drugs that elicited hypersensitivity may become clinically important (etoposide, NU1025).

Using our *BRCA2* hemizygous (*wt/*Δ*exon*) cells, we generated a novel syngeneic variance library (SyVaL) of exon 27 variants. By applying functional assays to our variants, we were able to evaluate missense mutations of previously unknown significance found in cancer patients as well as to evaluate the importance of various regulatory parts of the gene. SyVaLs thus offer a means to comprehensively annotate gene function, facilitating numerical and unambiguous readouts.

Finally, based on our prior experience with pharmacogenetic studies, we defined the terms pharmacogenetic window and pharmacogenetic synergy.