Project abstract

Name of DKFZ research division/group:	***Applied Functional Genomics (B290)***
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Group homepage: **Please visit our website for further information on our research and recent publications.**	***https://www.dkfz.de/en/applied-functional-genomics***

PROJECT PROPOSAL

Our laboratory works at the interface between basic cancer research and the translation of findings into patient care with the ultimate goal of improving the treatment of cancer patients. We focus on rare cancers, which are associated with poorer patient outcomes compared to common cancers due to limited biological understanding, resulting in a lack of effective therapies. Although the individual subtypes are rare, all rare cancers together account for almost 25% of all malignancies diagnosed each year in Europe, highlighting the immense importance of studying the molecular underpinnings of these diseases.

Strategies we are pursuing to study the biology of rare cancers involve the functional characterization of previously unrecognized recurrent genetic alterations that have been discovered in the prospective precision oncology program DKFZ/NCT/DKTK MASTER (https://www.nct-heidelberg.de/master), which is led by our close and long-standing cooperation partner, Prof. Dr. med. Stefan Fröhling. In addition, we identify rare cancer vulnerabilities using CRISPR/Cas9 small and large-scale screening, followed by the mechanistic in-depth analysis of the discovered gene dependencies.

Frequently used methods in our lab include molecular biology (qPCR, cloning, mutagenesis), cell culture, automated drug testing (IC50 determination), functional cellular readouts (proliferation, migration, invasion, malignant transformation, etc.), flow cytometry, cell sorting, protein biochemistry (Western blotting, immunofluorescence), genetic engineering of cultured cells (CRISPR KO, CRISPRi, lentiviral-mediated gene transfer), next-generation sequencing, automated microscopy, mouse modeling (genetically engineered mice, xenotransplantation), and bioinformatic analyses.

Projects the interested clinician scientist could work on include:

- Mechanistic analysis of a new recurrent genetic alteration we discovered in many sarcoma cases (bioinformatic analysis of the respective next-generation sequencing data is also possible) (similar approach as in *Schöpf et al., 2024*)

- CRISPR screens in *in vitro* germ cell tumor models to identify tumor-specific gene dependencies
- Identify new gene dependencies synergistic with drugs or TBXT inhibition in chordoma using CRISPR screening (*Umbaugh et al., 2025*)

References

Umbaugh CS, Groth M, Erkut C, Lee KS, Marinho J, Linder S, Iser F, Kapp JN, Schröter P, Dolaner S, Kayserili A, Helm D, Schneider M, Hartmann J, Walch P, Barth TFE, Mellert K, Dreier B, Schäfer JV, Plückthun A, Fröhling S*, Scholl C*. Selective targeting of TBXT with DARPins identifies regulatory networks and therapeutic vulnerabilities in chordoma. **Science Advances** 11(36):eadu2796, 2025

Schöpf J, Uhrig S, Heilig CE, Lee KS, Walther T, Carazzato A, Dobberkau AM, Weichenhan D, Plass C, Hartmann M, Diwan GD, Carrero ZI, Ball CR, Hohl T, Kindler T, Rudolph-Hähnel P, Helm D, Schneider M, Nilsson A, Øra I, Imle R, Banito A, Russell RB, Jones BC, Lipka DB, Glimm H, Hübschmann D, Hartmann W, Fröhling S*, Scholl C*. Multi-omic and functional analysis for classification and treatment of sarcomas with FUS-TFCP2 or EWSR1-TFCP2 fusions. **Nature Communication** 15(1):51, 2024