The Translational Sarcoma Research Group (Group Leader: Sebastian Bauer, MD)

https://tumorforschung.uk-essen.de/index.php?id=3222
www.sarcoma.eu
www.sarkomtour.de
www.husarc.org

Research interests:

- Oncogenic signaling pathways in soft-tissue sarcomas
- Mechanisms of resistance to targeted treatments
- Small molecular kinase inhibitors
- Development of novel soft-tissue sarcoma models (cell lines and PDX models)
- Development and validation of preclinical diagnostic techniques/methods for GIST and other soft-tissue sarcomas

About us:

The Translational Sarcoma Research Group is embedded into the dynamic research environment of the West German Cancer Center (inside the WTZ Research Building)and integral part of the Sarcoma Center (www.sarcoma.eu), one of the largest clinical sarcoma programs in Europe. A large clinical trial program including a broad spectrum of early clinical trials, including first-in-human trials, has in recent years allowed us to study novel treatments in sarcomas and look into mechanisms of resistance in parallel to ongoing clinical trials. The center's outstanding surgical program provides the sarcoma research group with clinical samples that provide a unique opportunity for both model development and to study sarcoma biology.
We are one of the most active research groups for Gastrointestinal Stromal Tumors (GIST), a paradigmatic disease with strong oncogenic addiction to receptor tyrosine kinases KIT or PDGFRA. We constantly study mechanisms of resistance to inhibitors of KIT and other kinases relevant in GIST and try to recapitulate these mechanisms in disease-specific models using CRISPR/Cas9 and other gene-editing technologies. We believe that strong models are a pre-requisite for successful translation of preclinical research. To this end, a long-standing research collaboration with the drug-development group "chemical biology" at the TU Dortmund (Prof. D. Rauh) has been established to discover and develop novel compounds in genetically well-defined cancer models.
Our lab is primarily working with genomically distinct cell lines (many isogenic models available) but for many years we also sustain a continuous PDX-program for both drug validation studies and in-vivo transplant models in several sarcoma subtypes. Our lab has a track-record in cancer kinase-signaling and associated methods (immunoblots, flow cytometry, apoptosis-assays) and we routinely perform CRISPR/Cas9 techniques, ORF expression, or lentiviral knockdowns to validate variants of unknown significance. As part of the DKTK Master initiative (led by NCT Heidelberg/Prof. Fröhling) we are leading some subprojects to discover therapeutic vulnerabilities in difficult-to-treat sarcomas such as clear cell sarcomas. Together with Johannes Köster, computer scientist with a focus on algorithm engineering and data analysis in bioinformatics at the Institute of Human Genetics, Essen, we have set up a bioinformatic workstation that allows analyses of exome/genome and transcriptome datasets in our lab using state of the art workflows (https://snakemake.github.io/). We are further interested in exploring the opportunities and limits of circulating tumor DNA using both next generation sequencing and ultra-sensitive techniques such as digitial PCR.

Background and project description:

Sarcomas are a heterogeneous group of mesenchymal cancers with more than 150 genomically distinct subtypes. While the majority of sarcomas have complex karyotypes with few recurrent genomic alterations, approximately one third of sarcomas show recurrent translocations. With introduction of RNA-sequencing into routine pathological work-up of sarcomas, more and more novel translocations are found. However, little is known on their impact on prognosis or if these alterations can be exploited therapeutically.

The need for subtype-specific, genomically well-defined models is high – as of to date, only a fraction of subtypes is represented in preclinical models. Our recently started HUSARC (www.husarc.org) sarcoma model initiative aims to greatly expand these models and their availability.
Other sarcomas, such as GIST, have recurrent activating mutations of oncogenes that are successfully targeted with kinase inhibitors. The current challenge is to better understand, treat and prevent the increasing complexity of resistance in GIST patients. NGS panel sequencing of both tumor and plasma have revealed a multitude of alterations apart from KIT and PDGFRA mutations. Particularly plasma sequencing may reveal the genomic heterogeneity of resistance, when highly sensitive methods are used.
We have shown that recapitulating those alterations in a GIST-specific context may allow us to validate the impact on resistance and test novel drug approaches.

The overarching aim of this project is to further expand our model pipeline (in vitro and in vivo) both by characterizing and validating novel translocation-positive cell lines that have emerged from primary cultures as well as validating variants of unknown significance in well-established cell line models. We would like to further develop and expand our plasma sequencing capabilities by setting up a hybrid-capture based NGS pipeline in collaboration with the Institute of Pathology. We expect these studies to consolidate and expand our innovation pipeline that is fed by the constant observation of novel variants in our clinical practice. This work will be a starting point for drug discovery projects, functional studies of novel fusions and validation of novel mechanisms of resistance or oncogenic progression. Candidates will receive comprehensive mentoring and collaborative support.

Methods:

Cell culture with established cell lines as well as primary culture, single cell isolation
In vivo model validation and drug treatments
Variant validation using CRISPR/Cas9 gene editing as well as site-directed mutagenesis
Plasma-sequencing (panel NGS, digital PCR)
Establishment of Hybrid Capture-Based Next Generation Sequencing
Bioinformatic analyses and interpretation
Cytotoxicity and apoptosis assays
Flow Cytometry
qRT-PCR
Western Blot