Heidelberg Postdoc Symposium / DKTK YAC 2025

Report of Contributions

Contribution ID: **1** Type: **TALK**

Targeted DART-AAVs as in vivo gene delivery platform for the specific transduction of TME cell subsets

In vivo gene delivery has emerged as powerful tool for novel therapeutic concepts. A major challenge is the development of vectors capable of mediating highly selective gene transfer specifically into therapy-relevant cells. For this purpose, we have developed the concept of rational-based receptor-targeting of AAV vectors harnessing designed ankyrin repeat proteins (DARPins) in order to specifically deliver therapeutic genes into particular cell types of the tumor microenvironment (TME) such as CD8+ T cells and tumor cells (DARPin Targeting AAV: DART-AAV).

In our recent work [1], we engineered AAV capsids displaying high-affinity DARPins specific for murine or human CD8 to specifically manipulate CD8+ cytotoxic T cells. The modified vectors exhibit high selectivity for both murine and human CD8+ T lymphocytes. Upon systemic injection, the targeted vectors achieved an impressive in vivo gene transfer rate of up to 80%, which represents a breakthrough in the in vivo modification of T cells with AAV vectors. Most remarkably, near absolute selectivity for CD8+ T cells while detargeted from liver was observed in immunocompetent mouse models.

Building on this platform, we engineered AAV9 for receptor-targeted delivery into tumor cells. Specifically, we developed HER2-AAV9 vectors displaying DARPins against the HER2/neu, resulting in significantly enhanced transduction of HER2+ tumor cells in vitro. These vectors conferred robust checkpoint-inhibitor or IL2 secretion. In mice bearing subcutaneous HER2+ SKOV-3 xenografts, HER2-AAV9 mediated tumor-targeted delivery of a luciferase reporter with minimal hepatic transduction.
Collectively, these receptor-targeted AAV vectors exhibit exceptional efficiency and specificity, opening new avenues for directly modifying therapy-relevant cell populations in vivo. This platform holds promise for basic research and the development of next-generation gene therapy strategies, particularly in the context of tumor-specific immunomodulation.

1- Demircan, Muhammed Burak, et al. “T-cell specific in vivo gene delivery with DART-AAVs targeted to CD8.” Molecular Therapy 32.10 (2024): 3470-3484

Research type

Translational research

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Presenter: DEMIRCAN, Muhammed Burak (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #1

Contribution ID: **2** Type: **TALK**

Pretreatment fatigue in breast cancer patients

Objective:
Cancer-related fatigue is one of the most common burdens of cancer patients. To date, most studies focused on fatigue during or after cancer treatment. However, investigating pretreatment fatigue may identify underlying factors beyond cancer therapy and enable timely fatigue management.
Methods: 232 breast cancer patients and 41 healthy women were recruited via the NCT Heidelberg as part of the CogniFit study. Fatigue (EORTC QLQ-FA12), quality of life related functioning and symptoms (EORTC QLQ-C30), anxiety (STAI), depression (CESD-R), and sleep problems (PSQI) were assessed before start of any therapy. Clinically relevant fatigue was defined based on thresholds of clinical importance (TCI) for C30 fatigue scores. Descriptive and linear regression analyses, as well as logistic regression models adjusted for sociodemographic factors, were performed.
Results: Patients scored significantly higher in physical, emotional and total fatigue. 49% of patients reported clinically relevant fatigue before treatment. Relevant fatigue was associated with being younger, being obese, having low education, or low social support. Higher scores in depression and anxiety, worse sleep quality and health status and poorer functioning were associated with an increased likelihood of scoring above the TCI of fatigue (all p<.001).
Conclusion: Many patients experience clinically relevant fatigue prior to therapy initiation, primarily influenced by psychosocial factors. Early screening and supportive interventions for fatigue seem to be important even before start of cancer treatment.

Research type

Clinical research

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Session Classification: Short talks #3

Contribution ID: **3** Type: **TALK**

Couples who live together longer develop more similar DNA methylation patterns

Pairs of individuals who live together for long periods of time, e.g., spouses, tend to share similar lifestyles, behaviours, and risk events. As environmental exposures can affect the epigenome, it is hypothesised that pairs of long-term cohabiting couples may exhibit greater similarity in their DNA methylation marker patterns.
Using the ESTHER study, a population-representative cohort from Saarland, one hundred and seventy pairs of individuals and their spouses were profiled for genomics, epigenomics, behaviour, and health history cross-sectionally (median age 71.3 years; median cohabitation time 44.7 years). To assess epigenomic similarity, the correlation of functionally normalised DNA methylation values across the entire methylome was calculated per pair.
Linear regression models showed that epigenomic similarity decreased with average age of couples (p=1.48×10⁻⁴), but increased with longer durations of cohabitation (p=1.89×10⁻⁴). Behavioural and health history similarity were also assessed, including smoking, alcohol intake, heart disease, cholesterol, and diabetes, plus the SF-12 Health Survey. Cohabiting couples were found to share smoking and heart disease history at greater than chance, and were correlated in alcohol intake and SF-12 scores. Pairs who shared smoking behaviours were significantly more similar epigenetically (p=0.026), adjusting for age and cohabitation duration. Smoking-related methylation scores suggested a dose-dependent effect of smoke exposure on epigenomic similarity (p=1.96×10⁻³).
Our results support the hypothesis that shared environment can lead to harmonisation of the epigenome through more similar methylation of DNA. Studying cohabiting pairs of individuals could extend research focus beyond genetically-related family members, provide greater control for environmental effects, and increase power for studies of the epigenome, particularly for rare diseases.

Research type

Other

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Presenter: STEVENSON-HOARE, Joshua (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #3

Contribution ID: **4** Type: **POSTER**

The influence of nutrition literacy on diets, nutritional status, and hemoglobin levels of adolescents and youth in sub-Saharan Africa (SSA): Findings from the ARISE-NUTRINT study

Background: Our study explored the pathway from nutrition literacy through diets up to nutritional status and hemoglobin levels of adolescents and youth in SSA.
Methods: The study used data from the ARISE-NUTRINT cohort, which was collected in 2024. A total of 9019 participants aged 10 –24 years were recruited from seven SSA countries. Principal component analysis was used to identify dietary patterns (Dietary Pattern Scores, DPS). These were related to 22 nutrition literacy indicators to obtain a nutrition literacy pattern score (NLPS) through reduced rank regression (RRR).
Results: Underweight, overweight/obese, and anemia were seen in 20.9%, 11.7%, and 14.7%, respectively. Three main dietary patterns, namely western-based, vegan-based, and fish and grains-based diets, were identified. The RRR-derived NLPS explained 6.7% of the total variance in these DPS. The NLPS was characterized by a positive correlation of knowledge of the food pyramid and balanced diet, utilization of the internet for nutrition-related information, engagement in discussions about diet, modification of eating habits based on acquired information, frequent reading of materials on balanced diets, readiness to improve dietary habits, and efforts to influence others to adopt healthy eating practices. A 1-point increase in NLPS was associated with an increase of 0.02 g/dL (95% CI: 0.01, 0.04) in hemoglobin levels. Compared to the lowest score of NLPS (Tertile 1, T1), the highest NLPS (T3) was associated with a 0.13 g/dL increase in hemoglobin. Compared to individuals with normal weight, those with the highest NLPS score (T3) exhibited 1.21 times higher odds (95% CI: 1.00, 1.46) of being overweight/obese. This association was similarly observed with a 1-point increase in NLPS (OR=1.03, 95% CI: 1.00, 1.07).
Conclusion: Nutrition literacy was associated with dietary patterns in this population. Higher nutrition literacy was associated with an increase in hemoglobin levels and overweight/obesity among adolescents and youth in SSA.

Research type

Other

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Session Classification: Poster presentation

Contribution ID: **5** Type: **POSTER**

Immunological impact of PROTAC-mediated HPV16 E6/E7 degradation

High-risk human papillomaviruses (HPVs) are involved in cervical and oropharyngeal cancers, causing over 730 000 new cases and 350 000 deaths worldwide every year. The viral oncoproteins E6 and E7, essential for induction and maintenance of the malignant phenotype, are ideal therapy targets. Proteolysis Targeting Chimeras (PROTACs) are small molecules triggering proteasomal degradation of target proteins, and additionally enhancing MHC-presentation of target protein-derived peptides on the cell surface. The aim of this project is to investigate whether PROTAC-mediated HPV E6/E7 degradation potentiates the efficacy of HPV therapeutic vaccination, by increasing viral antigen presentation on target cells. First, we will characterize HPV16 E6/E7-derived peptides presented on MHC-I after PROTAC-mediated degradation. Therefore, we have developed a highly sensitive mass spectrometry-based immunopeptidomics pipeline to identify HPV-derived peptide candidates, by optimizing the detection of very low abundant and cysteine/methionine-enriched peptides. Because creating PROTACs for new target proteins is challenging, we used the dTAG system consisting of the overexpression of HPV16 E6 and/or E7 fused to the FKBP12F36V tag followed by a treatment with a ligand dTAG. The dTAG molecule binds to the FKBP12F36V tag and recruits an E3 ligase, leading to the degradation of FKBP12F36V -tagged HPV16 E6 and E7. Preliminary data showed that the dTAG system enables the detection of MHC-presentation of the E711-19 peptide, a promising peptide candidate for HPV therapeutic vaccination, demonstrating its suitability for gathering the proof-of-concept of our combined therapeutic approach. Peptides only presented or presented in an increased amount after dTAG-mediated degradation will be considered for immunogenicity assessment. Since not every peptide displayed on a cell surface is immunogenic, tumor immunogenicity will be tested for each identified peptide using a live cell microscopy-based cytotoxicity assay. Altogether, the results will demonstrate whether dTAG-mediated HPV16 E6/E7 degradation increases HPV-related tumor immunogenicity and towards which HPV16 E6/E7 epitopes this happens.

Research type

Translational research

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Presenter: LEJEUNE, Noémie (Deutsches Krebsforschungszentrum)

Session Classification: Poster presentation

Contribution ID: **7** Type: **POSTER**

Extracorporeal Photopheresis resolves immune checkpoint inhibitor associated colitis through local adiponectin induction

The development of immune-related adverse events (irAEs) in cancer patients receiving immune checkpoint inhibitors (ICIs) cause morbidity, necessitates treatment cessation and limits ICI efficacy. Comparing different first- and second-line irAE treatments, we found that glucocorticosteroids, TNFα blockade, and α4β7-integrin inhibition reduced anti-tumor immunity in mice. We compared these therapies against extracorporeal photopheresis (ECP) and found that ECP has no negative effect on anti-tumor immunity in multiple preclinical tumor models. Based on these findings, we tested ECP in different ICI-colitis models and observed significantly reduced colitis severity after treatment. Mechanistically, we identified that ECP-treated splenocytes accumulate specifically in the inflamed intestinal tract, but not the tumor microenvironment. Apoptotic splenocytes were engulfed by intestinal phagocytes, which rendered these towards an anti-inflammatory phenotype. Immunosuppressive macrophages secreted adiponectin to resolve inflammation in the intestinal tract. Local adiponectin production elicited a tissue-specific effect by reducing pro-inflammatory tissue-resident memory T-cell activation, CD4+IFN-γ+ T-cells and inflammatory myeloid cells, while sparing tumor-specific T-cell development.

Following our preclinical investigations, we tested ECP in a prospective phase-Ib/II trial (EudraCT-No.2021-002073-26) with 30 patients and found low ECP-related toxicity. At week 12 of therapy, the overall response rate (ORR) for all irAEs was 96%; the ORR for colitis was 100%. The colitis-specific complete remission rate was 93%. Glucocorticosteroids could be reduced for all patients after ECP-therapy. The ECP-adiponectin axis reduced intestinal activation in patients with ICI-colitis without evidence of loss of anti-tumor immunity.

In conclusion, we identified ECP-induced adiponectin as an immunomodulatory mechanism to control ICI-induced inflammation without blocking anti-tumor immunity.

Research type

Translational research

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Presenter: BRAUN, Lukas (Deutsches Krebsforschungszentrum)

Session Classification: Poster presentation

Contribution ID: **8** Type: **POSTER**

Regulation of DVL2 Condensates by CK1 and DDX3X in Wnt Signaling

Biomolecular condensates formed via phase separation are emerging as key modulators of signal transduction. In Wnt signaling, Dishevelled proteins (DVL), particularly DVL2, form such condensates ("signalosomes") upon pathway activation, but how these condensates are regulated remains poorly understood. This project investigates the regulatory roles of casein kinase 1 (CK1) and the RNA helicase DDX3X—an oncogene and CK1 activator—in modulating DVL2 condensation and phosphorylation.

We hypothesize that CK1-mediated phosphorylation reduces DVL2 condensation, and that co- condensation of CK1 and DVL2 may inhibit kinase activity due to substrate inhibition, a process that DDX3X can rescue by enhancing CK1 turnover. Using a combination of in vitro reconstitution assays and live-cell imaging of endogenously tagged DVL2, we aim to: (1) determine how phosphorylation influences DVL2 condensation; (2) assess whether CK1-DVL2 condensates lead substrate inhibition on CK1 activity; and (3) test whether DDX3X relieves the substrate inhibition to restore efficient DVL2 phosphorylation; and (4) investigate whether DDX3X-CK1-DVL2 condensates leads to site-specific phosphorylation on DVL2.

By linking kinase kinetics with biomolecular condensation, this project addresses fundamental questions about how phosphorylation is regulated within DVL2 condensate in the Wnt signal pathway. Specifically, it investigates how the physical and biochemical environment of DVL2 condensates influences CK1 kinase activity and how this is modulated by the oncogenic RNA helicase DDX3X. Uncovering these mechanisms will not only shed light on the dynamic regulation of signalosomes in Wnt signaling, but also provide broader insights into how phase-separated condensates fine-tune enzymatic reactions within cells.

Research type

Basic research

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Session Classification: Poster presentation

Contribution ID: **9** Type: **POSTER**

High-resolution imaging of a trypanosome surface coat protein and its interaction with antibodies

The African trypanosome, T. brucei, is a unicellular pathogen responsible for sleeping sickness in humans and nagana in animals. Following transmission by the tsetse fly, the parasite replicates extracellularly in the bloodstream, where it faces constant exposure to the host's immune response. To evade this immune challenge, T. brucei employs an effective strategy of antigenic variation, achieved by switching to a new, antigenically distinct surface coat. This coat is primarily composed of Variant Surface Glycoprotein (VSG), and the trypanosome genome contains a repertoire of over 2,000 VSG genes to facilitate long-term survival.

While significant advancements have been made in elucidating the 3D structures of VSGs, structural information regarding VSG-antibody complexes has remained elusive. We have successfully resolved the cryo-electron microscopy (cryo-EM) structure of a VSG dimer bound to two Fab fragments at an overall resolution of 2.4 Å. This study marks the first detailed examination of a VSG epitope, allowing us to map the amino acids involved in the interaction.

In addition to investigating the interactions of purified VSG-antibody complexes, we aim to utilize cryo-EM tomography to explore antibody interactions on densely packed VSG vesicles and characterize the oligomeric state of VSGs on the trypanosome surface. By elucidating the protein packing, we hope to identify new interaction sites among individual VSG building blocks, which could serve as potential targets for destabilizing the trypanosome coat.

Research type

Basic research

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Session Classification: Poster presentation

Contribution ID: **10** Type: **POSTER**

High-throughput peptide-centric local stability assay extends protein-ligand identification to membrane proteins, tissues, and bacteria

Systematic mapping of protein-ligand interactions is essential for understanding biological processes and drug mechanisms. By using a limited-proteolysis strategy that employs a large amount of trypsin to generate peptides directly from native proteins, we developed the peptide-centric local stability assay, a modification-free approach that achieves unprecedented sensitivity in proteome-wide target identification and binding-region determination. However, its original workflow is limited in throughput, sample compatibility and accessible protein targets. Recently, we introduce a high-throughput adaptation - HT-PELSA - that increases sample processing efficiency 100-fold while maintaining high sensitivity and reproducibility. HT-PELSA substantially extends the capabilities of the original method by enabling sensitive protein-ligand profiling in crude cell, tissue and bacterial lysates, making it possible to identify membrane protein targets in diverse biological systems. We demonstrate that HT-PELSA can precisely and accurately determine binding affinities of small molecule inhibitors, sensitively detect direct and allosteric ATP binding, and reveal off-target interactions of a marketed kinase inhibitor in heart tissue. By enhancing scalability, reducing costs, and enabling system-wide drug screening across a wide range of sample types, HT-PELSA - when combined with next-generation mass spectrometry - offers a powerful platform poised to accelerate both drug discovery and basic biological research.

Research type

Basic research

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Presenter: LI, Kejia

Session Classification: Poster presentation

Contribution ID: **11** Type: **TALK**

3D Imaging and Cellular Barcoding: Novel Spatial Tools for Exploring Cancer Heterogeneity

Breast cancer affects 1 in 7 women, and the risk of death from metastatic (stage 4) disease remains high. In recent years, chemotherapy and mastectomy have improved the overall survival of breast cancer patients and reduced the incidence of breast cancer in at-risk individuals. However, these treatments are non-specific, and do not eliminate the risk of cancer development, patient relapse, or progression to advanced metastatic disease. Understanding the interactions between heterogeneous lesions and the blood vessels that facilitate their spread, will enable better characterisation of these metastasis-initiating cells. New methodologies and technologies are required to facilitate such discoveries and are rapidly developing in the fields of microscopy, spatial omics and cancer. Here, we have developed two novel protocols for the detection of cancer lesions in a murine model of metastatic breast cancer. First, we use light-sheet microscopy and optical barcoding to locate metastases and blood vessels within whole mount organs. Next, we use spatial transcriptomics to detect clones that are labelled with genetic barcodes, in their original spatial context. Here, we reveal the value of spatial information for insight into the behaviour of aggressive breast cancer clones.

Research type

Basic research

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Presenter: Dr LEWIS, Sabrina (Heidelberg University Hospital)

Session Classification: Short talks #2

Contribution ID: **12** Type: **POSTER**

A Patient-Centric Multi-Omics Strategy in Immunotherapy: Uncovering Targets and Markers for Tailored Cancer Treatment

Immunotherapy has revolutionized cancer treatment, yet its efficacy remains limited to a subset of patients due to tumor-intrinsic resistance, variable immune responses, and a suppressive tumor microenvironment (TME). To address this challenge, we are developing a patient-centric reporting system that initially integrates comprehensive genomic and transcriptomic profiling to inform clinical decisionmaking. The report includes classical molecular features (biomarkers) associated with immune activity and treatment response—such as tumor mutational burden (TMB), microsatellite stability status, and the IFN-ɣ signature—as well as tumor antigen burden and tumor neoantigens. By combining these data, we generate a multidimensional view of each patient's TME profile. To streamline interpretation, a large language model (LLM) synthesizes the multi-omic data into concise, clinically actionable summaries to support more informed treatment planning.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **13** Type: **POSTER**

A Comprehensive Targeted Metabolomics Workflow for Efficient Profiling Across Diverse Biological Matrices

Targeted metabolomics workflows are often constrained by limited analyte coverage and high per-sample costs of commercial kit-based assays, leading to incomplete metabolic insights. Here, we present a comprehensive and cost-efficient targeted metabolomics platform that combines broad analyte coverage with high throughput across diverse biological matrices. Utilizing the MetaSci Complete Library - encompassing >1,200 metabolites spanning central carbon, lipid, amino acid, and nucleotide pathways - our method can be tailored from focused analyses of specific compound classes to broad screening of several hundred metabolites per sample. Analytical measurements employ a QTRAP 6500+ mass spectrometer with dual HILIC and reversed-phase chromatography to accommodate polar and nonpolar analytes. We demonstrate the workflow's versatility and robustness through metabolic profiling of mammalian tissues (e.g., mouse liver), plant tissues (e.g., Arabidopsis thaliana leaves), biofluids (e.g., human plasma) and cultured cells (e.g., cancer cell lines). Each matrix yields detection and quantification of hundreds of metabolites within a single analytical experiment. Compared to commercial kit-based assays or untargeted approaches, our platform reduces per-sample costs significantly while maintaining high sensitivity and reproducibility. This user-friendly workflow offers a scalable and modular solution for targeted metabolomics in academic and clinical research settings.

Research type

Other

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Presenters: SAOUD, Mohamad (MCTP); Mr KUPCZYK, Erwin (MCTP)

Session Classification: Poster presentation

Contribution ID: **14** Type: **TALK**

Epigenetic indicators of body mass predict survival outcomes in colorectal cancer patients: patient cohort analysis

Background and Aims: The prognostic value of body mass index (BMI) in colorectal cancer (CRC) remains debated, partly due to disease-related weight loss. DNA methylation (DNAm)-based biomarkers that reflect long-term adiposity may offer more stable prognostic insights. We aimed to evaluate whether blood-based DNAm-BMI scores are associated with mortality in CRC patients and how they compare to self-reported BMI.

Methods: We analyzed data from 2,126 newly diagnosed CRC patients (41.2% women, median age 69) in the population-based DACHS cohort in Germany. Self-reported BMI at diagnosis and up to 14 years earlier, pre-diagnostic weight loss, and five DNAm-BMI scores derived from blood samples were assessed. Outcomes included all-cause, CRC-specific, and non–CRC-specific mortality. Associations were evaluated using Cox proportional hazards models, adjusting for demographic, lifestyle, clinical, and treatment factors.

Results: All DNAm-BMI scores correlated with self-reported BMI (Spearman r = 0.15–0.41, p < .0001). Underweight at diagnosis was linked to higher all-cause mortality (adjusted hazard ratio [aHR] 1.42, 95% CI 1.07–1.88), while obesity was associated with lower risk (aHR 0.83, 0.70–0.99). Weight loss >5 kg before diagnosis was associated with increased CRC-specific mortality (aHR 1.24, 1.04–1.49). Four DNAm-BMI scores showed consistent linear associations with mortality. The 135-CpG score was most predictive (highest vs. lowest quartile for CRC mortality: aHR 1.57, 1.23–1.99).

Conclusions: Blood-based DNAm-BMI scores, reflecting cumulative adiposity exposure, are associated with CRC mortality and may improve risk stratification beyond self-reported BMI.

Research type

Translational research

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Presenter: YUAN, Tanwei (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #3

Contribution ID: **15** Type: **POSTER**

Cerebrospinal Fluid Proteomics Reveals Biomarkers of Response to Anti-Nogo-A Antibody Treatment in Spinal Cord Injury Patients

Spinal cord injury (SCI) is a debilitating neurological condition resulting in partial or complete loss of motor and sensory function. Its complex pathophysiology, involving both immediate mechanical damage and secondary degenerative processes, presents major challenges for treatment. Among neuroregenerative approaches, anti-Nogo-A antibody (NG101) therapy promotes axonal regeneration and has shown promise in enhancing motor outcomes. However, clinical responses remain highly variable, emphasizing the need for biomarkers to predict treatment efficacy and support patient stratification.

To address this, we performed a large-scale, untargeted proteomic analysis of cerebrospinal fluid (CSF) samples from 133 individuals enrolled in a clinical trial: 74 SCI patients treated with NG101, 44 receiving placebo, and 15 healthy controls. CSF was collected pre-treatment and at one and three months post-treatment. Upper Extremity Motor Scores (UEMS) were used to monitor recovery. SCI induced substantial changes in the CSF proteome, involving immune response pathways and processes related to neurogenesis and axonal development. Longitudinal analysis showed largely overlapping protein expression changes in both treated and placebo groups, enriched in cytoskeletal protein binding. Notably, immunoglobulin complex components increased over time, reversing their initial downregulation post-injury.

Despite shared molecular trajectories, proteins associated with motor recovery differed significantly between groups. Using machine learning, we identified a panel of protein biomarkers capable of predicting treatment response and improving current clinical models. This study, the first comprehensive proteomic analysis of both NG101 and placebo-treated patients, provides novel insights into mechanisms of spontaneous versus treatment-mediated recovery and offers a foundation for biomarker-guided therapeutic strategies.

Research type

Clinical research

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Session Classification: Poster presentation

Contribution ID: **16** Type: **POSTER**

Pharmacological inhibition of the Hsf1 pathway as a potential strategy for treating glioblastoma

To overcome stress-induced protein imbalance, cells have evolved a protective mechanism called the heat shock response (HSR). In mammals, this response is primarily regulated by heat shock transcription factor 1 (Hsf1). Under stress conditions, Hsf1 activates genes involved in various cellular processes, including protein folding and degradation, membrane organisation, chromatin regulation, signalling pathways, and apoptosis control, all of which enhance cell survival. Beyond its role in the HSR, Hsf1 is also associated with ageing and various pathophysiological conditions, including cancer, where it is often found overactivated. Importantly, Hsf1 remains minimally active in healthy cells under normal conditions, suggesting that selective Hsf1 inhibitors could potentially target cancer cells while sparing healthy tissues.

Glioblastoma represents an aggressive brain tumour with a particularly poor prognosis. It is responsible for the majority of brain tumour-related deaths among children and adults. Low survival rate classifies glioblastoma as a lethal disease. The current standard treatment, unchanged for nearly 20 years, consists of surgery followed by radiotherapy and temozolomide (TMZ) chemotherapy. First-line therapy only postpones the progression of glioblastoma, with a median progression-free survival of 7 to 10 months. Given these poor outcomes, there is an urgent medical need to develop novel therapeutic approaches for glioblastoma treatment.

In our work, we explore the efficacy of existing Hsf1 pathway inhibitors as both monotherapy and combination therapy (with TMZ and/or radiation) using adult glioblastoma cell culture models. Our findings reveal that Hsf1 inhibition significantly reduces proliferation in adult glioblastoma cell lines, including those resistant to TMZ. Notably, the combination of Hsf1 pathway inhibition and TMZ treatment exhibits an additive effect, potentially enhancing therapeutic impact.

References: Kmiecik SW et al. 2020, 2022; Le Rhun E et al. 2019; Omuro A et al. 2013; Ou A 2020; Dai C et al. 2007; Im CN et al. 2017.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **17** Type: **POSTER**

HAUS architecture as a foundation: Molecular insights into augmin's role in cell division

Accurate organization of microtubules is essential for diverse cellular processes such as intracellular transport and chromosome segregation. Therefore, precise spatial and temporal control of microtubule nucleation is critical, as its dysregulation causes spindle defects and contributes to various diseases, such as cancer. A predominant mechanism for rapid microtubule amplification during spindle assembly is branched microtubule nucleation. Central to this process is the augmin complex—a conserved hetero-octamer composed of HAUS (homologous to augmin subunit) proteins—which functions as a key microtubule branching factor. During mitosis, augmin binds to pre-existing spindle microtubules to recruit the γ-tubulin ring complex (γ-TuRC), the principal microtubule nucleator. This recruitment facilitates the nucleation of new microtubules at defined angles relative to the parental microtubules, ensuring proper spindle architecture. Elucidating the molecular architecture of the augmin complex provides a structural framework for dissecting its functional domains, which underlie its role in microtubule branching. Such insights may offer broader implications for understanding mitotic fidelity and its perturbation in pathological contexts.

Research type

Basic research

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Presenter: WÜRTZ, Martin

Session Classification: Poster presentation

Contribution ID: **18** Type: **TALK**

Investigating TCR T Cell Migration and Cytotoxicity Using 3D Bioprinting

Genetic engineering of T cells to express tumor antigen-specific T cell receptors (TCRs) is a promising approach in cancer immunotherapy. While the cytotoxic potential against cancer of these engineered TCR T cells is critical, their therapeutic efficacy also depends on their ability to migrate, infiltrate, proliferate, and persist within the complex tumor microenvironment (TME). This is particularly challenging in solid tumors, where the TME comprises a heterogeneous mix of stromal cells, immune-suppressive factors, and extracellular matrix components that hinder T cell function. To address these challenges, we evaluate the multifaceted functionality of TCR T cells using 3D bioprinted fully human models. Using a single-chain TCR (scTCR) specific for the HLA-A2.1-restricted p53(264-272) epitope as a model, we encapsulated TCR T cells and p53-high tumor cells in the hydrogel to assess anti-tumor efficacy of the TCR T cells.

This 3D bioprinted tissue allows both end-point histological evaluation and real-time live-cell imaging, providing a versatile platform for studying immune-tumor interactions. Immunohistochemical (IHC) analysis of the formalin-fixed paraffin-embedded (FFPE) tissue revealed that TCR T cells effectively eradicated about 40 % of tumor cells in both the single-cell model and the tumor-spheroid model within two days. Furthermore, analysis of the tumor spheroid model showed that CD8+ T cells constituted the majority of tumor-infiltrating immune cells. Interestingly, multiplex cytokine profiling revealed a robust induction of Th1 cytokines (e.g., IFN-γ, TNF-α) and chemokines (e.g., CXCL9, CXCL10, RANTES).

This 3D bioprinted model represents a significant advancement in preclinical modeling, enabling the evaluation of TCR T cell migration, infiltration, and cytotoxicity within a physiologically relevant TME. By incorporating additional immune components, this model holds promise for optimizing engineered T cell therapies and identifying strategies to overcome TME-mediated suppression, ultimately accelerating the development of effective cellular immunotherapies for solid tumors.

Research type

Translational research

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Presenter: HOLTKOTTE, Xu (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #1

Contribution ID: **19** Type: **TALK**

Disrupting RNA Modification Machinery in Head and Neck Squamous Cell Carcinoma

More than 150 proteins contribute to the formation and regulation of various RNA modifications in humans. These modifications play a crucial role in cell function by influencing RNA splicing, stability, translocation, translation, and ultimately gene expression. To explore the impact of RNA-modifying proteins on cancer cell function, we conducted comprehensive CRISPR-Cas9 dropout screens targeting all known RNA-modifying proteins, both in vitro and in vivo. Our analysis identified a set of RNA-modifying factors essential for the survival of Head and Neck Squamous Cell Carcinoma (HNSCC). Among them, VIRMA, a key subunit of the m6A RNA-modifying enzyme complex, was specifically required for cancer cell survival but not for healthy primary cells. VIRMA depletion significantly reduced HNSCC survival and growth both in vitro and in human tumors xenografted into host mice. Acute depletion of VIRMA using the dTAG system globally inhibited m6A RNA modifications, leading to widespread effects such as reduced proliferation, elevated MHC-I expression, and disrupted DNA damage response. Notably, VIRMA depletion impairs the transcription of bi-directional promoters, which play a crucial role in the DNA damage response. These findings highlight VIRMA as a potential therapeutic target for HNSCC treatment.

Research type

Basic research

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Presenter: Dr XU, Fu (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #2

Contribution ID: **20** Type: **TALK**

Coordinated multicellular programs in the colorectal cancer microenvironment

Tumors are complex ecosystems shaped by both the identity and spatial organization of diverse cell types. Understanding how these factors evolve during cancer progression may help reveal coordinated multicellular behaviors linked to disease outcome. In this study, we profiled 522 colorectal samples using multiplexed ion beam imaging (MIBI-TOF) and a 42-marker panel capturing cell lineage, function, and metabolism. Over 488,000 cells were analyzed to map cellular neighborhoods and metabolic states across disease stages.

We observed metabolic heterogeneity in healthy to malignant samples. Aggressive cancer cells showed malignant adaptation beyond their proliferative state with increased amino acid and oxidative phosphorylation metabolism. Tissue architecture remodeling also tracked with disease progression. Cell composition shifted with increasing tumor stage, including gains in myeloid cells and losses in lymphocytes. Some spatial relationships between cell types were specific of tumors, particularly among macrophages, neutrophils, and fibroblasts. Using machine learning, we identified spatial and molecular features that most strongly predicted tumor stage, such as presence of monocyte clusters.
Finally, a factor analysis framework revealed coordinated shifts in spatial, morphological, and metabolic programs, with distinct cell-type contributions at early versus late stages. These coordinated multicellular programs were strongly associated with clinical variables such as tumor and node invasion stages and microsatellite instability.

Our ongoing work aims to integrate these spatial and metabolic features into predictive models of tumor behavior. Our cross-validation effort suggests spatial lineage and metabolic interactions outperform single-feature predictors. This study supports the view that tumor progression is governed by coordinated multicellular programs, and highlights interpretable features that may inform patient stratification or therapeutic targeting.

Research type

Translational research

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Presenter: VULLIARD, Loan (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #2

Contribution ID: **21** Type: **POSTER**

Optimal enhancement of anti-tumor T-cell immunity through the combined use of selective DGK zeta and DGK alpha inhibitors

Diacylglycerol kinases (DGKs), specifically DGK zeta (DGKζ) and DGK alpha (DGKα), are lipid kinases that regulate T-cell activation by modulating diacylglycerol (DAG) levels at the immunological synapse in a non-redundant fashion. T-cells deficient for DGKζ or DGKα are hyperresponsive and were shown to mediate enhanced immunity against viral infections and tumors. Further experimental evidence suggests that dual DGKα/ζ inhibition may result in maximal T-cell activation. We previously presented the discovery and pharmacology of the DGKζ-selective inhibitor BAY 2965501. In parallel, we developed the DGKα-selective inhibitor BAY2862789, and analyzed its impact on T-cell activation and anti-tumor immunity, both as single agent and in conjunction with DGKζ inhibition, PDL1-blockade and/or depletion of CCR8-positive T-regulatory cells. First-in-human clinical trials with selective DGK inhibitors are currently ongoing.

Both inhibitors enhance in vitro T-cell activation and T-cell mediated tumor cell killing. Pharmacological DGK-inhibition overcomes the suppressive impact of TGFβ and PGE2. T-cell enhancement is more pronounced upon combined DGK inhibition, especially in the context of weaker antigenic TCR-stimulation. Examination of anti-tumor efficacy in different syngeneic mouse models showed that for some tumors maximal effect can already be achieved by DGKζ inhibition alone, whereas for other tumors additional benefit is observed with combined inhibition. Using the available preclinical data, an exposure-response model was developed to predict the T-cell activation for various DGKα/ζ combinations. The predictions are highly correlated to corresponding in vivo efficacy endpoints, which demonstrates the relevance of this in vitro to in vivo extrapolation. The model offers the opportunity to identify optimal combination dosages that pair maximal enhancement of T-cell immunity with minimal probability for on- and off-target adverse events.

The availability of DGKζ and DGKα selective inhibitors allows for hypothesis-driven pharmacology and toxicology studies, and –in combination with the forthcoming single-agent patient exposure data - for a rationally designed dual-agent clinical study.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **22** Type: **POSTER**

Cell organisation and disturbance-mapping using image activated cell-profiling (CODIAC)

Protein localisation and abundance is a key mechanism to regulate cell homeostasis. Furthermore, diseases are frequently associated with aberrant protein localisation. However, high-throughput methods that monitor changes of many proteins at once are missing. Recently, image enabled cell sorting (ICS) has been demonstrated to add spatial and morphological information to classical cell sorting technology. We utilise ICS in combination with improved Cas12a PCR tagging to develop new ways to characterise proteome localisation and expression levels within complex cellular pools. Applying ICS to fluorescently tagged protein libraries and machine learning, we have devised a novel way to assess cell organisation and to map disturbances using image activated cell-profiling (CODIAC). Using image-derived measurements from ICS, we group and isolate cells with fluorescently-tagged proteins of similar visual phenotypes. Sorting cell pools in their native state as well as upon chemical perturbation, we are able to identify changes in protein localisation and abundance in a pooled fashion at a much faster pace than previously established. We hope for this method to have broad applications in the field of high content screening for the identification of novel drug targets and various medical uses.

Research type

Translational research

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Presenter: KRAUSE, Melanie (EMBL Heidelberg)

Session Classification: Poster presentation

Contribution ID: **23** Type: **POSTER**

Identification of TCR-Ligands Using Fractionation and LC-MS Immunopeptidomics

Identifying major histocompatibility complex (MHC)-bound peptides recognized by specific T-cell receptors (TCRs) is key to developing personalized T-cell therapies. We developed an unbiased pipeline combining immunopeptidomics with TCR functional assays in pancreatic ductal adenocarcinoma (PDAC). MHC class I peptides were fractionated by liquid chromatography (LC) and identified via mass spectrometry (MS). Correlating TCR activity with peptide abundance across fractions enabled robust identification of candidate TCR ligands

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **24** Type: **POSTER**

NGS inspired in vitro models of anellovirus infection provide opportunities to study host-pathogen interactions, immunogenicity and their role in carcinogenesis

Anelloviruses are circular ssDNA viruses and endemic in the human population, causing persistent, yet dynamic infections. Due to the lack of *in vitro* models, their interaction with the human host, namely the innate immune system, is largely unknown. However, they must be under constant control through (innate) immune mechanisms, since immunosuppression leads to viral rebound. To date, epidemiologic studies could not conclusively demonstrate a causal connection between anellovirus infection and human pathology. Rather, they are seen as part of the human virome and as such might shape the human immune system.

The high-throughput computational pipelines for virus discovery developed by the Seitz lab, allow the detection and assembly of anellovirus sequences from publicly accessible and protected NGS data sets. Previously, they found that strains of co-occurring anelloviruses (swarms) are closely and specifically associated with certain malignancies. This massive data driven approach does not only provide a rationale to study host-pathogen interaction and innate sensing of anelloviruses, but also a unique opportunity to understand the host cell tropism and genetic background that would allow *in vitro* experiments.

Using modern molecular biology tools, we now want to investigate anellovirus-host interaction in the wet-lab. For this purpose, I will 1) confirm infection events in patient samples on the DNA, RNA and protein level; 2) analyze the immunogenicity of anellovirus infection and anellovirus derived nucleic acids; 3) assess the carcinogenic potential of anellovirus infection; 4) investigate the function of anellovirus ORFs in host-pathogen interaction and immune evasion.

Both the analysis of anellovirus immunogenicity and the study of its carcinogenic potential will benefit tremendously from an *in vitro* infection model, which will be one of the first priorities of our research. We are convinced that this will offer new and fascinating insights into anellovirus host-pathogen interaction.

Research type

Basic research

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Presenter: SCHÜSSLER, Moritz (Deutsches Krebsforschungszentrum)

Session Classification: Poster presentation

Contribution ID: **25** Type: **TALK**

GAG–CCL2 Disruption as a Therapeutic Strategy to Reverse Immune Evasion and Enhance Cancer Immunity

Tumor-associated glycosaminoglycans (GAGs) critically shape the immune landscape by sequestering chemokines such as CCL2, thereby orchestrating the recruitment and polarization of immunosuppressive myeloid cells. However, the therapeutic potential of disrupting GAG-chemokine interactions in solid tumors remains unexplored. Here, we demonstrate that elevated expression of GAG biosynthesis genes and CCL2 in head and neck cancer is linked to poor prognosis, marked immunosuppression, angiogenesis, and epithelial-mesenchymal transition. We evaluated the potential of MMIb, a CCL2 fragment containing a GAG-binding domain, in reprogramming the tumor microenvironment to reverse myeloid-mediated immunosuppression and enhance anti-tumor immunity. *In vitro*, MMIb prevents the immunosuppressive polarization of macrophages in the presence of tumor-derived factors and GAGs. In murine tumor models, MMIb treatment reduces tumor growth, diminishes infiltration by myeloid cells, and attenuates angiogenic and EMT signatures. Proteomic profiling and flow cytometry reveal that MMIb reprograms myeloid cells toward an immunostimulatory phenotype, enhances antigen presentation, and augments interferon signaling, resulting in improved T cell activation and reduced exhaustion. Notably, MMIb is effective both as a preventive and therapeutic intervention in established disease. *Ex vivo*, MMIb limits monocyte migration and suppressive polarization in human tumor explants. These findings establish GAG-CCL2 interactions as a central axis of immune evasion and tumor progression, and identify selective disruption of this pathway as a strategy to reprogram the tumor microenvironment and potentiate anti-tumor immunity. Our work highlights the translational potential of targeting GAG-chemokine interactions for cancer therapy, with broad implications for overcoming immune escape in tumors characterized by high GAG and CCL2 expression.

Research type

Translational research

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Presenter: Dr PYLAEVA, Ekaterina

Session Classification: Short talks #1

Contribution ID: **26** Type: **POSTER**

Associations of sleep characteristics with health-related quality of life in early versus late onset colorectal cancer patients

Introduction
Sleep disturbances and chronotype have been implicated in cancer-related outcomes, yet their impact on health-related quality of life (HRQoL) in colorectal cancer (CRC) patients remains underexplored. This study examines longitudinal associations between sleep characteristics, chronotype, and HRQoL in early onset (EO) (≤50 years) and late onset (LO) (>50 years) CRC patients.

Methods
We included 905 CRC patients from the ColoCare Study in Germany and the USA. Chronotype was assessed using the reduced Morningness–Eveningness Questionnaire, sleep latency and duration by the Pittsburgh Sleep Quality Index. HRQoL scales were measured using the standardized EORTC QLQ-C30 questionnaire. Multivariate linear regression models examined associations between sleep, chronotype, and HRQoL pre-surgery and six months thereafter.

Results
Morning chronotype and favorable sleep characteristics were significantly associated with improved HRQoL among LO-CRC patients at six months. Morning types reported better physical ($\beta = 11.56$, $p = 0.01$), emotional ($\beta = 10.55$, $p = 0.04$), and cognitive functioning ($\beta = 14.41$, $p = 0.002$), along with less fatigue ($\beta = -16.48$, $p = 0.004$), dyspnea ($\beta = -14.39$, $p = 0.02$), and pain ($\beta = -17.64$, $p = 0.003$). Similarly, longer sleep duration (>7 h) was linked to better global health, physical, role, emotional, cognitive, and social functioning (all $p < 0.01$), and fewer symptoms including fatigue, insomnia, nausea, appetite loss, diarrhea, and financial difficulties (all $p < 0.05$). Less symptom burden was also observed in EO-CRC patients with a longer sleep duration (>7 h). Shorter sleep latency (<15 min) was associated with improved global health and psychosocial functioning, and reduced fatigue, insomnia, pain, and constipation. These associations were specific, except for insomnia, to the LO-CRC group and were not observed among EO-CRC patients.

Discussion
These findings suggest that morning chronotype and favorable sleep patterns may play an important role in improving HRQoL among LO-CRC patients.

Research type

Clinical research

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Session Classification: Poster presentation

Contribution ID: **27** Type: **POSTER**

Establishment of ex vivo tumor tissue slice culture from HNSCC xenografts for biomarker discovery

The heterogeneity of locally advanced head and neck squamous cell carcinoma (HNSCC) impacts the response to radio(chemo)therapy, highlighting the need for personalized biomarker-based treatment strategies. Tumor slice culture (TSC) represents an ex vivo model bridging the gap between in vivo and conventional in vitro models, providing an opportunity to reduce animal numbers in experiments while retaining relevance for translational research questions. Here, we establish TSC from four HNSCC cell lines with varying radiosensitivities to implement a robust, reproducible ex vivo assay for biomarker discovery reflecting the heterogeneous response of patients to radiotherapy.

Athymic nude mice were xenotransplanted with five HNSCC tumor models of varying radiosensitivity (SAS –resistant, Cal33, FaDu –intermediate, UT-SCC-14 –sensitive). Tumors were excised and thin vital tissue slices were cut using a Vibratome. Different cutting parameters were tested. The tissue slices were irradiated with 0 –6 Gy X-ray, and immunofluorescence stainings were performed according to standardized protocols. The value of the assay for radiobiological experiments was demonstrated by the analysis of γH2AX foci (https://github.com/jo-mueller/FociCounter), indicative of radiation-induced DNA damage.

Appropriate criteria for tumor induction and harvesting were determined. Cutting parameters considering the model-dependent differences in tumor structure were successfully established. The heterogeneity of the different tumor models should be considered when good-quality slices are to be obtained.The PrestoBlue viability assay showed metabolic activity in the slices over 5-7 days. The preliminary analysis of immunofluorescence images showed a dose-dependent increase of γH2AX foci. Further validation of the assay in the preclinical radiobiology setting and its application for clinical translation will be discussed. The relationship between radiation sensitivity to DNA damage processing and tumor microenvironment heterogeneity will be explored in the future. Furthermore, this assay may be applied to patient samples from resections or biopsies, representing a promising approach to support future personalized radiotherapy concepts.

Research type

Translational research

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Presenter: MICHLIKOVA, Sona

Session Classification: Poster presentation

Contribution ID: **28** Type: **TALK**

ZBTB7A loss accelerates RUNX1::RUNX1T19a-driven leukemia by enhancing erythroid block and aberrant myeloid progenitor expansion

ZBTB7A is a transcription factor critical for hematopoietic lineage commitment, particularly in promoting erythroid differentiation. In acute myeloid leukemia (AML), ZBTB7A mutations are frequently associated with the t(8;21) translocation, which generates the RUNX1::RUNX1T1 fusion and defines a patient subgroup with relatively favorable outcomes. However, relapse remains a significant clinical challenge, highlighting the need for novel therapeutic strategies. To investigate the cooperative role of ZBTB7A loss in RUNX1::RUNX1T1-driven leukemogenesis, we established a murine model by transplanting sub-lethally irradiated C57BL/6J mice with Cas9-EGFP bone marrow (BM) progenitors transduced with a construct encoding RUNX1::RUNX1T1 (9a variant), tdTomato, and either a Zbtb7a-targeting or non-targeting sgRNA. Strikingly, only mice receiving ZBTB7A knockout cells developed leukemia (latency: 99 days), whereas control mice remained in a preleukemic state for nearly 200 days. Leukemic mice exhibited anemia, elevated leukocyte counts, bone marrow infiltration (>20% blasts), and organomegaly. Immunophenotyping of BM double-positive EGFP and tdTomato leukemic cells revealed a predominant population lacking Sca-1, but positive for c-Kit and CD43, markers consistent with megakaryocyte-erythroid progenitor (MEP)-like leukemia-initiating cells. Besides, approximately 50% of the double-positive cells were also CD71+ and TER119–, indicating a differentiation block at the proerythroblast stage. However, within the Lin–Sca-1–c-Kit+ compartment, a typical MEP population coexisted with an aberrant CD16/32+ CD34–subset, suggesting skewing toward a granulocyte-monocyte progenitor (GMP)-like profile. Ongoing ex vivo colony-forming assays and single-cell RNA sequencing will further elucidate the nature of RUNX1::RUNX1T1 + ZBTB7A-deficient leukemia, with the ultimate goal of identifying novel therapeutic vulnerabilities associated with ZBTB7A loss.

Research type

Basic research

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Session Classification: Short talks #2

Contribution ID: **29** Type: **POSTER**

Towards understanding the molecular mechanisms underlying transient DRE function

Although most cells of an organism carry the same genetic content, they show diverse properties, develop distinct functions and form different tissues. This is enabled by gene regulation, the precise timely and spatially controlled activation and repression of genes. However, how cell-type specific transcriptional induction of genes is initiated, is still not fully understood. One factor presumably impacting transcriptional activation are temporally coordinated gains and losses of contacts between gene promoters and distal regulatory elements (DREs). Our lab has recently identified a type of DREs that transiently interacts with gene promoters during transcriptional activation. While these DREs can affect gene activation, the mechanisms remain unknown, limiting our ability to fully understand distal gene regulation.
To close this gap, I will determine the molecular composition of transiently interacting DREs. Since regulatory elements exert their activity via proteins bound to them, I will first focus on their transcription (co-)factor occupancy. For this, I will combine *in silico* analyses, genomic techniques and temporally-resolved interaction proteomics. Upon determining the TF composition of transient elements, I will assess the effect of the respective factors on gene activation and genome structure using inducible degron technologies. In a final set of experiments, a combination of genetic engineering screens and acute depletion of these TFs will provide insights into their DRE-binding dependence for function.
Preliminary results indicate that transient DREs interacting early during differentiation (2-6 hrs. after induction) display distinct TFBSs compared to their late interacting (24-48 hrs.) counterparts. This project will reveal the proteome of transient DREs at the time point of their promoter interaction and has the potential to identify candidates important for enhancer-driven gene activation. With the understanding of the processes happening at transient DREs we will ultimately be able to understand the dysregulation of these mechanisms in cancer cells.

Research type

Basic research

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Session Classification: Poster presentation

Contribution ID: **30** Type: **TALK**

Sex-Bias Immune Aging and its Interplay with X-Inactivation Escape Genes at Single-Cell Level

The world is aging, and improving the health of the elderly is crucial. Elderly individuals are particularly susceptible to immune system failure, leading to increased vulnerability to infectious diseases. Immune responses exhibit sex-specific patterns due to a combination of hormonal and genetic factors, including the number of X chromosomes and the expression of genes escaping X-inactivation in females. However, which genes escape X-inactivation throughout life and their impact on immune cell functions remain unclear.
Using single-cell multiomics methodologies, we assess whether age-related changes in cellular composition, chromatin accessibility, and transcription are sex-specific in mice. Our findings reveal a similar aging-specific remodeling of the T-cell compartment in both sexes and a pronounced sex influence on the B-cell transcriptome. Moreover, we describe a cell-type-specific landscape of X-inactivation, with escape genes contributing to female-biased expression. Notably, a subset of aged T-cells, which play a key role in aging and cancer progression, demonstrates increased transcriptional activity from the inactive X chromosome, accompanied by heightened chromatin accessibility. Our work sheds new light on the intricate interplay between sex and age, highlighting cell-type-specific escape dynamics in shaping sex-specific immunological trajectories and advantages.

Research type

Basic research

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Presenter: DEL PRETE, Stefania (Deutsches Krebsforschungszentrum)

Session Classification: Short talks #2

Contribution ID: **31** Type: **POSTER**

Towards a better tumour model –bioprinting heterogeneous microtissues of the PDAC

Pancreatic ductal adenocarcinoma (PDAC), responsible for over 90% of pancreatic cancer cases, remains one of the deadliest cancers, with a 5-year survival rate of just ~11%. Its incidence is increasing by 0.5–1% annually due to ageing populations and rising obesity, and it is projected to become the second leading cause of cancer-related deaths.
The Reichert lab at the Technical University of Munich specialises in patient-derived organoid (PDO) models to study PDAC's complex biology and heterogeneity. These models replicate the disease's structure and behaviour in a physiologically relevant environment. The lab is co-spearheading DKTK's strategic initiative "Organoid Biobank"and provides a bulk of this effort's NeoMatch cohort. NeoMatch aims to establish a biobank of longitudinally matched PDOs, before and after neoadjuvant chemotherapy, complemented by sampling cancer-associated fibroblasts (CAFs) and blood samples.
Leveraging this wealth of resources, we focus on creating co-culture systems that simulate the tumour microenvironment (TME), especially interactions with macrophages, T-cells, and CAFs. These components are key to understanding immune modulation and chemotherapy resistance.
To this end, we are using a state-of-the-art bioprinting platform to develop an advanced, high-throughput tumour model for drug screening and immune research. Starting with optimised culture conditions for CAFs and PDO models in the artificial matrix, we will gradually increase complexity. Once established and characterised, the final phase will combine PDOs and cells of the TME in a survival assay using chemotherapeutic drugs and prospectively CAR-T cells to validate the model. This work aims to build a next-generation PDAC model, offering a powerful tool for studying tumour-immune interactions and testing new therapeutic strategies.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **32** Type: **POSTER**

Characterization of Collagen Structure and Tissue Mechanics in Intestinal Biopsies from IBD Patients

Inflammatory Bowel Diseases (IBD), including Crohn's disease and ulcerative colitis, have been estimated to affect between 10 and 40 per 100.000 people in Europe, with an increasing burden over the last few decades [1]. The presence of chronic inflammation associated to these diseases is a known risk factor for the development of colorectal cancer [2]. In this work, we seek to better understand the structural differences between inflamed and healthy pairs of tissues obtained from the same patient. The collagen architecture of the snap-frozen samples was analysed using second harmonic imaging microscopy (SHIM), a non-destructive technique that enables the formation of three-dimensional images of the collagen content encompassing the entire thickness of the sample. Simultaneously, the samples were scanned using a Brillouin microscope to investigate the gradients of stiffness resulting from the fibrotic and healthy regions of the intestine. The use of Brillouin microscopy allows for the contact-free measurements of the mechanical properties of tissue, specifically the longitudinal modulus in the GHz range [3].
The high-resolution scans of the sample pairs could result in improved in-vitro models to be used as a platform for drug development, scaffold design, and 3D cell-culture, among many other tissue engineering applications.

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[3] - Prevedel, R., et al. Brillouin microscopy: an emerging tool for mechanobiology. Nat Methods 2019 16, 969–977.

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Research type

Basic research

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Session Classification: Poster presentation

Contribution ID: **33** Type: **POSTER**

Coordinating the clinical translation of [89Zr]Zr-DFO-trastuzumab: the importance of a multidisciplinary team and key lessons learned

Introduction and aim: The translation of new radiotracers into clinical application use is a complex and often daunting process. The core function of a multidisciplinary team is to bring together professionals with expertise in several areas to expand diagnostic and treatment options for patients. One such tracer, [89Zr]Zr-DFO-trastuzumab, has been successfully implemented in other countries, till now it had not been introduced in Germany. This abstract outlines some considerations of the practicalities of the implementation of [89Zr]Zr-DFO-trastuzumab in Germany.
Methods: Professionals across various disciplines worked together to establish the clinical application of [89Zr]Zr-DFO-trastuzumab, starting from the initial assessment of medical need through to individual manufacturing in accordance with the German Pharmaceuticals Act (§ 13(2b) AMG). Ongoing consultation with local and federal regulatory authorities, along with knowledge exchange through networking with experienced teams routinely producing radiolabelled monoclonal antibodies was undertaken.
Results: The manufacturing of [89Zr]Zr-DFO-trastuzumab was successfully established in compliance with GMP standards, meeting all defined quality specifications. Close communication with regulatory authorities such as the Paul Ehrlich Institute and Federal Institute for Drugs and Medical Devices helped resolve several key questions throughout the process to prepare [89Zr]Zr-DFO-trastuzumab also as an investigational medicinal product (IMP) for prospective clinical trials. It was agreed that no preclinical studies were required due to the extensive supporting literature, and because Herceptin could be replaced with clinically approved biosimilars such as Ontruzant. Regulatory discussions also addressed aspects such as the required time point for sterility testing, and the adjustment of the drug product's shelf life from the initially proposed 72 hours to 24 hours in accordance to the chosen method of dispensing.

Conclusion: Early engagement with regulatory authorities and experts in the field proved crucial in positively shaping the manufacturing process of [89Zr]Zr-DFO-trastuzumab, ensuring the reliable production of a safe drug product and administration to patients.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **34** Type: **POSTER**

Building of a cryo-super-resolution microscope for cryo-correlative light and electron microscopy (cryo-CLEM)

Cryo electron microscopy (cryo EM) has been at the center of many new advances and discoveries in biology. The ability to freeze biological samples in vitreous non-crystalline ice, allows us to study biological matter in its native unperturbed environment with molecular resolution. It avoids using chemicals to fix the samples which has been shown to perturb the native environment. This has allowed us to understand the structure-function relationships in the sub-cellular context and also to study interactions between sub-cellular structures and proteins which provided deep insights into the mechanisms governing different processes of life. In-spite of the progress made so far, cryo EM is limited in its ability to provide specificity of the sub-cellular structures and to identify rare-events. One approach to overcome these limitations is to combine it with light microscopy and perform correlative light and electron microscopy (CLEM). So far, there have been rapid developments for cryo-CLEM. However, when correlating light and electron microscopy images, one needs to mind the resolution gap imposed by the wave nature of light or the diffraction limit. One way to overcome the resolution gap is to develop techniques for cryo superresolution microscopy (cryo SRM) and correlate it to cryo EM. For localization-based cryo SRM techniques, there are two possible approaches based on the design of the cryostat used for cooling the vitrified samples. These are open and vacuum based cryostat designs, each with its own advantages and drawbacks. In this poster, I will present a theoretical comparison between the two types of designs and discuss the planning and progress in building a vacuum-cryostat based cryo single molecule localization microscope (cryo-SMLM) to study vitrified biological samples.

Research type

Basic research

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Session Classification: Poster presentation

Contribution ID: **36** Type: **TALK**

Synergistic Efficacy from Menin and PRMT5 Co-Inhibition against NPM1 Mutated and KMT2A-Rearranged Leukemia

Menin inhibitors represent a novel class of targeted therapies for acute myeloid leukemia (AML), particularly in patients with *KMT2A* rearrangements (*KMT2A*-r) and *NPM1* mutations (*NPM1*mut). These inhibitors disrupt the Menin-KMT2A complex, silencing leukemogenic gene expression, promoting differentiation, and leading to disease eradication. However, the precise mechanisms by which the Menin-KMT2A complex regulates leukemic gene expression remain incompletely understood. We hypothesized that the Menin-KMT2A complex may recruit additional protein partners to the complex that might contribute to leukemogenesis and could represent druggable targets. Using a high-resolution CRISPR/Cas9 domain scan of *KMT2A* and *MEN1*, we identified PRMT5, a putative binding site in Menin, as a strong dependency in NPM1mut AML cells. The arginine methyltransferase PRMT5 has been reported to interact with Menin, is implicated in the pathogenesis of myeloid neoplasms, and represents a promising target. CRISPR/Cas9-mediated PRMT5 knockout was lethal to *NPM1*mut AML cells and PRMT5 inhibition suppressed viability of various AML cells. We demonstrated that PRMT5 inhibition synergizes with Menin inhibition to reduce cell viability in *KMT2A*-r and *NPM1*mut AML cell lines and patient-derived *NPM1*mut AML cells. This combination induced differentiation, triggered apoptosis *in vitro* and reduced leukemia burden, and prolonged survival significantly in an *NPM1*mut AML xenograft model. RNAseq analysis revealed that Menin and PRMT5 co-inhibition suppresses Menin-KMT2A target genes and reported PRMT5 targets, including those regulated by the E2F and ATF4 transcription factors. Integration of these transcriptional data with CUT&RUN and ChIPseq analyses revealed chromatin co-occupancy of Menin and PRMT5 on a subset of the Menin-KMT2A targets loci as well as at the loci of E2F/ATF4-regulated genes. These results are consistent with a suppression of complementary pathways as a potential mechanism of drug synergy. Our findings provide a strong rationale for combining Menin and PRMT5 inhibitors in *NPM1*mut or *KMT2A*-r AML, a drug regimen already available for clinical testing.

Research type

Translational research

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Session Classification: Short talks #1

Contribution ID: **37** Type: **POSTER**

mRNA-Based Strategies for Targeted Tumor Microenvironment Modulation to Enhance Antitumor Immunity

The tumor microenvironment (TME) is a complex and dynamic ecosystem composed of cancer cells, stromal cells, immune cells, various signaling molecules, and extracellular matrix components. Dynamic processes within the solid TME drive response or resistance to treatment, highlighting the importance of developing tools capable of precisely targeting these intricate mechanisms. Beyond vaccination, mRNA technology provides a versatile tool for fine-tuning specific targets within the TME, enabling modulation of complex processes such as immune cell migration, activation, and engagement. In this study, we used *in vitro* transcription to synthesize reporter protein and cytokine mRNAs, which were then encapsulated in various lipid nanoparticle (LNP) formulations to evaluate and optimize their efficiency in delivering mRNA to target cells. The mRNA-LNPs efficiently transfected human PBMCs and multiple cell lines *in vitro*, and outperformed commercial Lipofectamine. Interleukin 12 single-chain (IL-12sc) mRNA-LNPs induced robust production of bioactive IL-12p70, as demonstrated by the activation of PBMC-derived human T cells. Subsequently, we applied IL-12sc-LNPs *ex vivo* to primary colorectal cancer and liver metastasis specimens. Expression of IL-12sc in these tissues was associated with elevated levels of CD3+ cells and inflammatory cytokines. Thus, LNP-encapsulated mRNA holds strong potential as a tool for immune modulation within the TME and may offer a promising avenue for innovative cancer therapies.

Research type

Translational research

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Presenter: WISSFELD, Jannis (Deutsches Krebsforschungszentrum)

Session Classification: Poster presentation

Contribution ID: **38** Type: **POSTER**

Design and synthesis of steroid-based agents targeting estrogen and progesterone receptors for breast cancer radiotheranostics

Due to the high variation in surface receptor expression, breast cancer (BCa) is a highly heterogeneous disease presenting significant challenges for early detection and treatment. Four molecular subtypes have been identified including estrogen receptor (ER)- and progesterone receptor (PR)-positive BCa. ER and PR are overexpressed in ≈ 80% of all BCa which promotes cell proliferation. The expression of PR in target tissues is highly dependent on the presence of ER conducting in less than 1% of ER-negative/PR-positive BCa. Estradiol, an estrogen steroid and the major female sex hormone, possesses a high affinity for ER. Katzenellenbogen and coworkers have developed the clinically approved radiotracer 16α-[18F]fluoro-17β-estradiol ([18F]FES) for BCa diagnostic by positron emission tomography (PET). However, due to its high lipophilicity, [18F]FES is rapidly metabolised in the liver resulting in a high hepatic uptake and background signal preventing its use in targeted radionuclide therapy (TRT). This group has proposed derivates of estradiol and progesterone radiolabelled with fluorine-18, technetium-99m and rhenium-188 for theranostics but their high lipophilicity has prevented further studies. This project aims to develop steroid-based ligands suitable for radiotheranostics applications in ER/PR-expressing BCa. For this purpose, versatile DOTA chelator was selected for complexation of various diagnostic and therapeutic radionuclides. DOTA-lysine-estradiol has been synthesised on solid phase with a yield of 15% and purity of >95%. Coupling of estradiol was achieved by Copper(I)-catalysed Azide-Alkyne Cycloaddition (CuAAC) between ethynylestradiol and lysine-resin. DOTA was then coupled using classic amidation method. The synthesis of other DOTA-estradiol and DOTA-progesterone derivatives are currently ongoing. These derivatives will be radiolabelled using [177Lu]LuCl3 (~5 MBq, 0.4 M NaOAc pH 5, 95℃, 30 min). Internalisation assays of 177Lu-conjugates will be performed on ER/PR-positive and -negative cell lines with the aim to validate radioligands targeting ER and PR to improve the early detection and stratification of BCa patients followed by TRT.

Research type

Basic research

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Presenter: WAGNER, Laurène (Deutsches Krebsforschungszentrum)

Session Classification: Poster presentation

Contribution ID: **39** Type: **POSTER**

Evaluation of EpCAM Peptide Binding and Internalization for Breast Cancer Radiotheranostic Applications

Breast cancer is a heterogeneous disease and remains one of the most prevalent cancers among women worldwide, highlighting the urgent need for more effective diagnostic and therapeutic approaches. Epithelial Cell Adhesion Molecule (EpCAM) is a transmembrane glycoprotein involved in cell adhesion, proliferation and differentiation and is overexpressed in several types of cancer including breast, gastric, prostate, ovarian and colorectal. EpCAM expression demonstrates a context-dependent impact on cancer prognosis, correlating with tumor progression, metastasis and poor prognosis in breast and ovarian cancers, but with favorable outcomes in colorectal and gastric cancers. Due to its position on the cell surface, EpCAM presents a promising target for molecular imaging and targeted radionuclide therapies. We successfully synthesized two peptides EpCAM-1 (SNFYMPL) and EpCAM-2 (EHLHCLGSLCWP) via automated solid-phase peptide synthesis at high chemical purity and conjugated with DOTA chelator and Alexa Fluor-488. The aim of this study is to evaluate the specific binding and internalization of the peptides [177Lu]Lu-EpCAM-1 and [177Lu]Lu-EpCAM-2 in breast cancer cell lines using internalization assays and flow cytometry with EpCAM-1 Alexa-Fluor-488 and EpCAM-2 Alexa-Fluor-488 conjugates. For internalization assays, these peptides will be radiolabeled with [177Lu]LuCl3 (~5 MBq) in 0.4 M NaOAc (pH 5), at 95℃, for 30 min. Cells will be seeded in 24-well plates 24 h before the experiment. The cells will be incubated with 20 and 100nM [177Lu]Lu-EpCAM-1 or [177Lu]Lu-EpCAM-2 in 150 µL Opti-MEM for 1 h at 37℃. For flow cytometry studies, cells will be incubated with different concentrations of EpCAM-1 Alexa-Fluor-488 and EpCAM-2 Alexa-Fluor-488 conjugates for 60 min at 4 and 37℃. These results will allow us to determine the potential of EpCAM for prospective radiotheranostic applications in breast cancer.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **40** Type: **POSTER**

Analysis of KiSS-1R Receptor Dynamics Through Kisspeptin-Derived Ligands for Breast Cancer Radiotheranostics

Currently, theranostic options for triple-negative breast cancer (TNBC) are critically lacking. As a promising strategy, the KiSS-1 receptor (KiSS-1R) has been reported for potential molecular imaging and targeted radionuclide therapy. The interaction of kisspeptins (KPs) and their receptor (KiSS-1R) is vital for the reproductive axis and has been reported to exhibit tumor-suppressing properties. Controversially, metastasis-promoting characteristics have been observed in various cancer types, e.g. TNBC. This led to the synthesis of radiolabeled metal-chelator conjugates of endogenous KP-10 (Gallium-68, Lutetium-177) and KP-54 (Gallium-68) for potential radiotheranostic application. However, these compounds suffer critically from proteolytic degradation and low tumor uptake, while the role of KiSS-1R in cancer biology remains unclear and must be investigated further.

For this purpose, DOTA- and Alexa-Fluor-488 (AF-488)-conjugated KPs were synthesized in high purities (>99%) and of (sub-)nanomolar affinities towards KiSS-1R, verified *via* functional Ca^{2+} release assays. Target expression analysis was conducted using commercial antibodies and synthesized ligands in native human and transfected cell lines expressing KiSS-1R. Conventional analysis methods failed due to rapid receptor internalization, but live cell imaging microscopy using AF-488 labeled KPs successfully visualized KiSS-1R on CHO-KiSS-1R cells.

Additionally, rapid internalization dynamics were verified through internalization assays using promising DOTA-KPs radiolabeled with Lu-177, obtained in high radiolabeling efficiency (>95%) and good radiolytic stability. Despite variable total uptake and internalization rates among different KPs, [^{177}Lu]Lu-KiSS-34-DOTA showed highest internalization of >40% of total uptake. Positron emission tomography (PET) studies with Ga-68 labeled DOTA-KPs in healthy BALB/c mice revealed [^{68}Ga]Ga-KiSS-34-DOTA as favorable due to improved solubility and *in vivo* stability compared to endogenous ligands, KP-10 and KP-54.

In summary, DOTA- and AF-488-conjugated KPs demonstrate functionality for receptor validation and interaction studies, suggesting potential in theranostic applications against TNBC. Further evaluation of KiSS-1R biology in native cancer cell lines remains essential before further translational approaches.

Research type

Translational research

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Session Classification: Poster presentation

Contribution ID: **41** Type: **POSTER**

Getting to Grippe With Influenza: An Investigation of Why the Disease Is Called That

We investigated two competing terms for influenza in English, Spanish, German, French, and Italian: “influenza” and “grippe” to determine what may have driven the choice in disease name under these competing options. Of the two, “grippe” is more commonly used in Indo-European languages. Using minimum edit distance (Levenshtein distance) we determined the available space in each language for an incoming disease name from a justification of if one term is too similar to words already in use, the other may be preferred. This explains partially why influenza is called what it is in the European languages considered.

Research type

Basic research

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Session Classification: Poster presentation

Contribution ID: **42** Type: **POSTER**

The Role of RNF145 in Renal Epithelial Cell Metabolism: Lipid and Oxygen Sensing Mechanisms

In diabetic patients, factors such as dyslipidemia and hypoxia drive kidney damage. Our previous research using induced renal epithelial cells (iRECs) and a pharmacological mouse model of diabetes combined with a high-fat diet demonstrated that palmitic acid (PA), a saturated fatty acid induces ER stress and lipotoxicity in proximal tubular cells in vitro and in vivo, whereas monounsaturated oleic acid (OA) does not. Moreover, in a transcriptomic approach to assess genes differentially regulated by lipid saturation we uncovered the ring-finger protein 145 (RNF145), an E3-ubiquitin ligase that targets adiponectin receptor 2 (ADIPOR2) a protein with antidiabetic effects.

Our major aim is to uncover the role of RNF145 in PA-mediated toxicity and in hypoxia adaptation as well as to identify the metabolic cues regulating RNF145 and ADIPOR2 levels. To this end Rnf145, knockout (KO) iRECs were analyzed for cell viability, protein, and mRNA expression and bioenergetic profiling under both lipotoxic and hypoxic conditions.

Depletion of Rnf145 partially protected iRECs against PA-mediated lipotoxicity by upregulating ADIPOR2, reducing ER stress and cell death. Furthermore, both chemical and physiological hypoxia downregulates RNF145 levels, leading to the stabilization of ADIPOR2. In parallel, RNF145 deficiency enhanced cell survival in hypoxia. Potentially due to the normoxic upregulation of genes typically induced by hypoxia. In addition, RNF145 KO cells showed higher basal mitochondrial respiration and reduced glycolysis.

Collectively, our findings suggest that RNF145 serves as a key regulator of lipid homeostasis and oxygen sensing shaping the metabolic profile of renal epithelial cells, highlighting its potential as a Reno-protective target in both lipid-mediated toxicity and the adaptation to hypoxia.

Research type

Basic research

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Welcome

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High-resolution mass spectrometry for quantitative analysis of drugs, biologicals and biomarkers in clinical and preclinical research

The quantification of therapeutics and associated biomarkers is crucial for understanding drug efficacy and patient response in personalized medicine, and in clinical studies. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) offers unique advantages for high resolution quantitative analysis of small-molecules, peptides and even proteins that are used as therapeutics (including monoclonal antibodies, bispecific antibodies and antibody-drug conjugates). Mass spectrometry offers quantitative analyses with higher specificity and sensitivity compared to traditional immunoassays.

We have developed and validated a broad spectrum of LC-MS/MS methods for quantitative analyses of drugs and metabolites as well as biomarkers, with high standards needed for pharmacokinetic (PK) and pharmacodynamic (PD) studies. We also offer therapeutic drug monitoring for patients in vitro diagnostic quality. We enable analyses in various matrices such as in plasma, urine, tissue, cultured cells, organoids, and dried blood spots (DBS). Our workflow incorporates advanced sample preparation techniques and targeted proteomics approaches, ensuring full compliance with key validation parameters such as accuracy, precision, selectivity, linearity, recovery, matrix effect, carry-over, and stability.

In various clinical and in vitro research projects, we have successfully analyzed a wide range of antineoplastic small molecule drugs, including tyrosine kinase inhibitors (TKIs), phosphodiesterase inhibitors, ion channel inhibitors, immunomodulators, neuropsychiatric agents, and MDM2 inhibitors. We have successfully expanded our methods for analysis of peptides and proteins for quantification of biotherapeutics such as monoclonal antibodies and antibody-drug conjugates.

Our current focus extends to the simultaneous quantification of biotherapeutics while monitoring relevant biomarkers, providing comprehensive molecular-level insights into individual bioavailability and treatment response. This integrated approach enables the study of efficacy and safety of biological therapeutics, as well as the identification of novel protein biomarkers associated with treatment response and disease progression. Our LC-MS/MS platform represents a powerful tool for advancing biotherapeutic development and personalized medicine, supporting preclinical and clinical drug development.

Research type

Clinical research

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