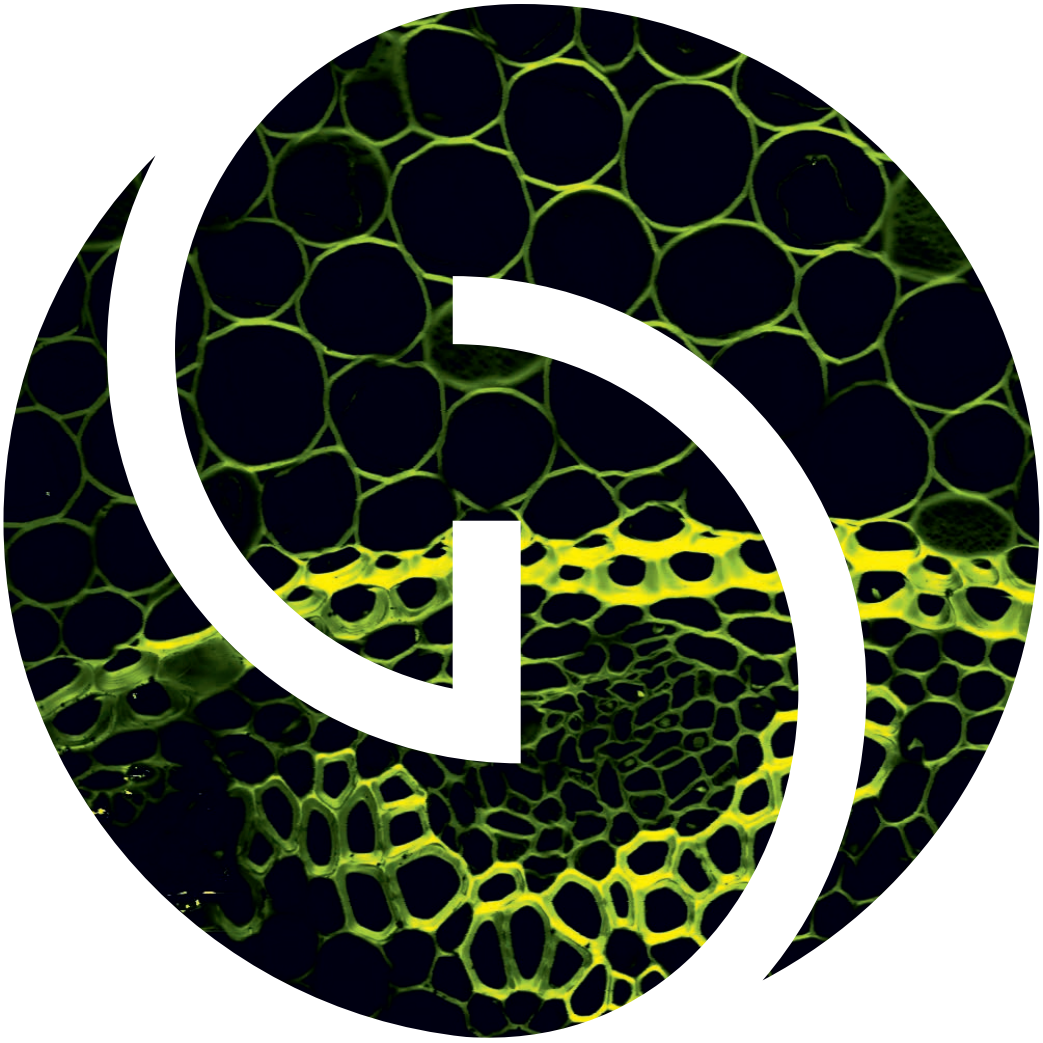
GEORG SPEYER HAUS
INSTITUT FÜR TUMORBIOLOGIE
UND EXPERIMENTELLE THERAPIE



Tumormicroenvironment –
Pathogenese und Zielstrukturen
Experimentelle Therapie

Annual Report
Georg-Speyer-Haus

2025

Gefördert durch:

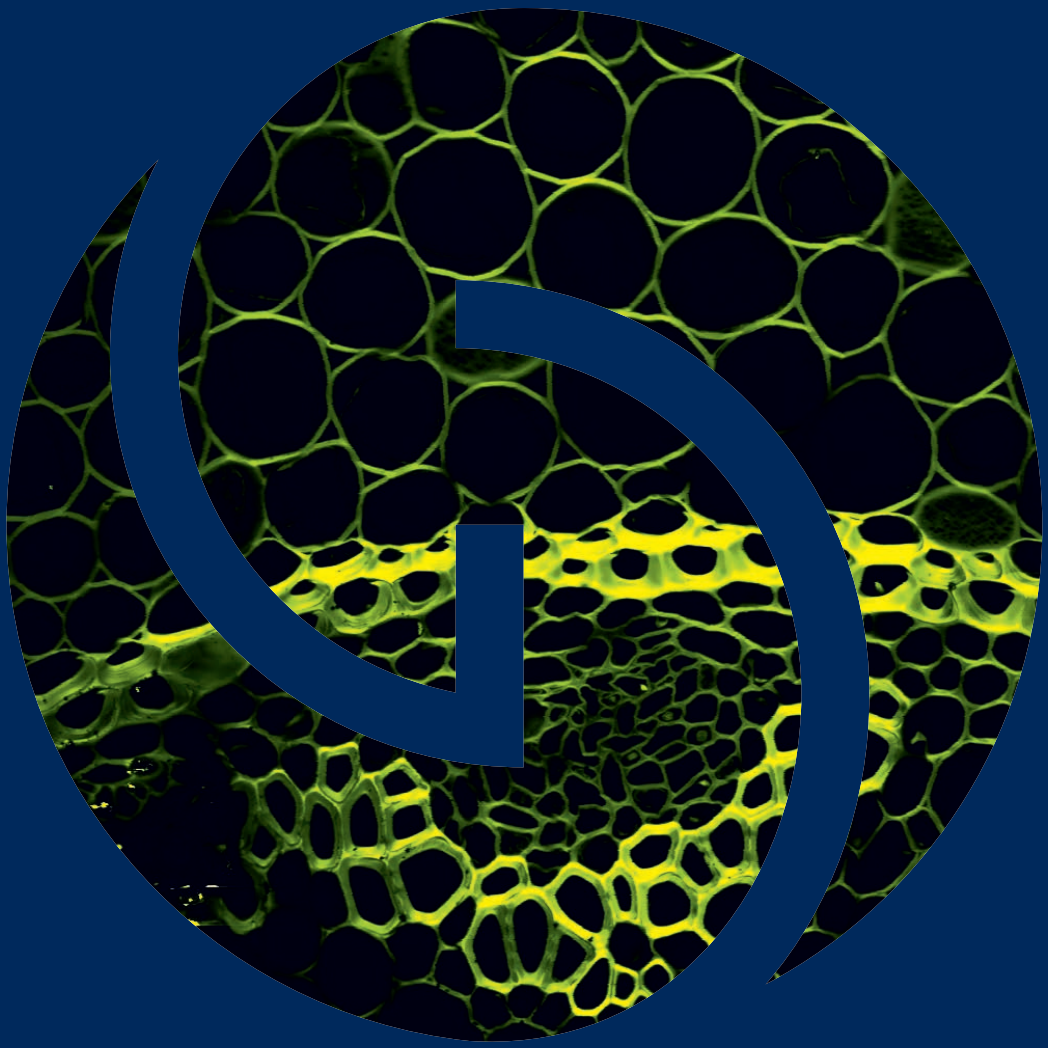
aufgrund eines Beschlusses
des Deutschen Bundestages

Die Grundfinanzierung des Georg-Speyer-Hauses wird vom Bundesministerium für Gesundheit und dem Hessischen Ministerium für Wissenschaft und Forschung, Kunst und Kultur getragen.

The basic funding of the Georg-Speyer-Haus is provided by the Federal Ministry of Health and the Hessian Ministry of Science and Research, Arts and Culture.

Forschen für das Leben

Research for Life



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Liebe Leserinnen und Leser,
liebe Freunde des Georg-Speyer-Hauses,

Der personelle Umbruch in unseren Gruppenleitungen setzte sich auch in diesem Jahr fort. Zu Beginn des Jahres verließ uns Hind Medyouf, um ihre W3-Professur im Rahmen des Heisenberg-Programms an der RWTH Aachen anzutreten. Damit schließt sich ein Kreis: Wir sind sehr stolz darauf, dass alle Gruppenleitungen, die in den vergangenen zehn Jahren ihre Tätigkeit am GSH aufgenommen haben, mittlerweile auf Professuren – entweder an anderen Universitäten oder an der Goethe-Universität – berufen werden konnten.

Nach knapp 28 Jahren am GSH beendete unser stellvertretender Direktor Prof. Winfried Wels Mitte des Jahres seine wissenschaftliche Tätigkeit. Für seine wertvollen Verdienste um das GSH über einen so langen Zeitraum sind wir ihm sehr dankbar. Zugleich bedauern wir, dass seine äußerst erfolgreichen Arbeiten auf dem Gebiet der zellulären Therapie des Glioblastoms bei uns vorerst nicht weitergeführt werden. Mit Spannung verfolgen wir derzeit den Verlauf und die Ergebnisse der klinischen Studie (CAR2BRAIN-Check) zur Kombinationstherapie von NK-92/5.28.z mit dem Anti-PD-1-Antikörper Ezabenlimab, die durch die Pionierarbeit von Prof. Wels ermöglicht wurde. Zukünftig hoffen wir, das Themengebiet der zellulären Therapie durch die Rekrutierung einer neuen Gruppe wieder kompetent besetzen zu können.

Nach einer erfolgreichen Post-Doktorandenzeit in den USA stieß Dr. Marco Seehawer im Sommer zu uns, um seine Arbeit als Gruppenleiter aufzunehmen. Er wird sich zukünftig mit der Bedeutung von Histon-Modifikationen für die Entstehung und Therapie von Mammakarzinomen und Blasenkarzinomen beschäftigen und somit das wichtige Gebiet der Epigenetik am Institut vertreten. Wir freuen uns außerdem, dass wir mit Bianca Kupper die vakante Stelle für unsere Tierhausleitung besetzen konnten. Unterstützt wird sie zunächst durch Dr. Franziska Bayer, die die Tierhaltung des medizinischen Fachbereichs leitet. Für diese anhaltende nachbarschaftliche Hilfe sind wir ausgesprochen dankbar.

Dear Reader,
dear friends of the Georg-Speyer-Haus,

The personnel changes in our group leadership continued this year. At the beginning of the year, Hind Medyouf left us to take up her W3 professorship at RWTH Aachen University as part of the Heisenberg Program. This brings us full circle: we are very proud that all group leaders who joined the GSH in the past ten years have now been appointed to professorships, either at other universities or at Goethe University. In the middle of the year, Prof. Winfried Wels, our deputy director, ended his scientific work at the GSH after almost 28 years. We are very grateful for his valuable service to the GSH over such a long period. We regret that his highly successful work in cellular therapy for glioblastoma will not continue at our institute for the time being. We are currently following the progress of the CAR2BRAIN-Check clinical study into the combination therapy of NK-92/5.28.z and ezabenlimab (an anti-PD-1 antibody), which was made possible by Prof. Wels' pioneering work. In the future, we hope to reoccupy the field of cellular therapy competently by recruiting a new group.

Dr. Marco Seehawer joined us in summer after a successful postdoctoral period in the USA, taking up his position as group leader. He will now focus on the significance of histone modifications in the development and treatment of breast and bladder cancers, representing the important field of epigenetics at the institute. We are also delighted that Bianca Kupper has filled the vacant position of animal facility manager. She will initially be supported by Dr Franziska Bayer, who is responsible for animal husbandry at the Medical Faculty. We are extremely grateful for this ongoing neighbourly assistance.

Eine besonders erfreuliche Nachricht war die Entscheidung des HMWK, unser LOEWE-Zentrum „Frankfurt Cancer Institute“ für zunächst zwei weitere Jahre vollumfänglich zu fördern. Damit können wir unsere vielfältigen, translationalen Forschungsprojekte gemeinsam mit unseren klinischen Partnern am Standort fortsetzen und die dafür essenziellen Unterstützungsstrukturen erfolgreich weiterführen.

Ein weiterer Meilenstein in diesem Jahr war die Bewilligung des Transregios 417 mit dem Titel „Zelluläre Kommunikation im Stroma von kolorektalen Karzinomen- Von der Pathophysiologie bis zur klinischen Translation“. Unter der Sprecherschaft der Goethe-Universität (F. Greten) wird der Verbund gemeinsam mit den Universitäten Freiburg und Erlangen in den kommenden vier Jahren darauf abzielen, das Verständnis der funktionellen Rolle des Tumormikromilieus beim kolorektalen Karzinom zu vertiefen, neue therapeutische Strategien zu entwickeln und diese in klinische Anwendungen zu überführen.

TRR 417
CELLULAR COMMUNICATION IN THE STROMA OF COLORECTAL CANCER

Das von Prof. Arkan organisierte „Microbiome“ Symposium rundete das wissenschaftliche Jahr ab. Ein international hochkarätig besetztes Sprecherfeld referierte über die vielfältigen Facetten des Mikrobioms in der Interaktion mit Tumor und Mensch insbesondere im Kontext von Therapien und setzte einen wissenschaftlichen Höhepunkt zum Jahresende.

Neben all den wissenschaftlichen Leistungen und Erfolgen kamen die persönlichen Interaktionen nicht zu kurz. Ein besonderes Highlight war unser monatlich stattfindender „Happy Midday“, ein gemeinsames Mittagessen für alle Mitarbeitenden, das großzügig durch unseren Förderverein unterstützt wurde. Auch unser Sommerfest und die sportlichen Aktivitäten im Rahmen des Halbmarathons und Marathons – egal, ob in der GSH-Staffel oder als Individualteilnehmer – haben besondere Akzente gesetzt.

Auf den folgenden Seiten finden Sie in bewährter Form eine übersichtliche Zusammenfassung unserer Aktivitäten.

Florian R. Greten, Direktor

Particularly good news was the decision by the HMWK to continue providing full funding for our LOEWE center, the Frankfurt Cancer Institute, for an initial period of two more years. This will enable us to continue our diverse translational research projects together with our clinical partners at the site and to successfully maintain the support structures that are essential for this work.

Another milestone this year was the approval of Transregios 417 entitled “Cellular communication in the stroma of colorectal carcinomas – from pathophysiology to clinical translation.” Under the leadership of Goethe University (F. Greten), the consortium, together with the Universities of Freiburg and Erlangen, will aim over the next four years to deepen our understanding of the functional role of the tumor microenvironment in colorectal carcinoma, develop new therapeutic strategies, and translate these into clinical application.

The “Microbiome” symposium organized by Prof. Arkan rounded off the scientific year. An international panel of internationally renowned speakers gave presentations on the many facets of the microbiome in its interaction with tumors and humans, particularly in the context of therapies, and provided a scientific highlight at the end of the year.

In addition to all the scientific achievements and successes, there was also plenty of opportunity for personal interaction. Our monthly “Happy Midday,” a joint lunch for all employees generously supported by our Society of Friends and Sponsors, is a particular highlight here. Our summer party and sporting activities as part of the half marathon and full marathon – whether in the GSH relay team or as individual participants – also provided special highlights.

On the following pages, you will find a clear summary of our activities in the usual format.


MACHEREY-NAGEL
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Plasmid DNA
Clean-up
RNA
Genomic DNA
Viral RNA and DNA

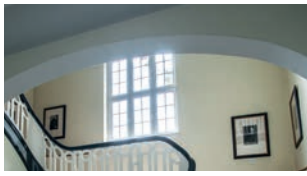
Forschen für das Leben
Research for Life

Die Stiftung privaten Rechts „Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus“ wurde 1904 in Frankfurt am Main gegründet, um eine Forschungsstätte für Paul Ehrlich, den ersten Direktor des Hauses, zu schaffen. Die Stiftungsverfassung bestimmt als Zweck der Stiftung die wissenschaftliche Forschung auf den Gebieten der Chemotherapie und verwandter Wissenschaften, die dem Fortschritt der Biomedizin dienen. Es werden ausschließlich und unmittelbar gemeinnützige Zwecke verfolgt.

Die laufenden Geschäfte des heutigen Instituts für Tumorbiologie und experimentelle Therapie nimmt der Direktor wahr. Er ist in dieser Tätigkeit dem Stiftungsvorstand verantwortlich. Das Georg-Speyer-Haus ist durch einen Kooperationsvertrag mit der Goethe-Universität Frankfurt verbunden.

Das Gebäude des Georg-Speyer-Hauses in der Paul-Ehrlich-Straße 42 – 44, 1906 eröffnet, wurde von der Stadt Frankfurt am Main zur Nutzung für Institutszwecke zur Verfügung gestellt. Der gesamte Gebäudekomplex wurde in den Jahren 1995 – 1997 aus Mitteln des Bundesministeriums für Gesundheit und des Hessischen Ministeriums für Wissenschaft und Forschung, Kunst und Kultur saniert und modernisiert. Er umfasst eine Gesamtfläche von 4710 qm. Die Laboratorien sind für Arbeiten unter verschiedenen biologischen und gentechnischen Sicherheitsstufen 1 und 2 zugelassen.

The private foundation “Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus” (Chemotherapeutic Research Institute Georg-Speyer-House) was established in 1904 in order to provide a research institute for Paul Ehrlich, its first director. The constitution of the institute, originating from its foundation, defines its purpose as an establishment for scientific research in the field of chemotherapy and related sciences. It is an independent institution under public law which is exclusively engaged in non-profit work.



Today’s Institute for Tumor Biology and Experimental Therapy is headed by the Scientific Director who reports to the Board of the Foundation. The Georg-Speyer-Haus has a cooperative agreement with the Goethe University Frankfurt.

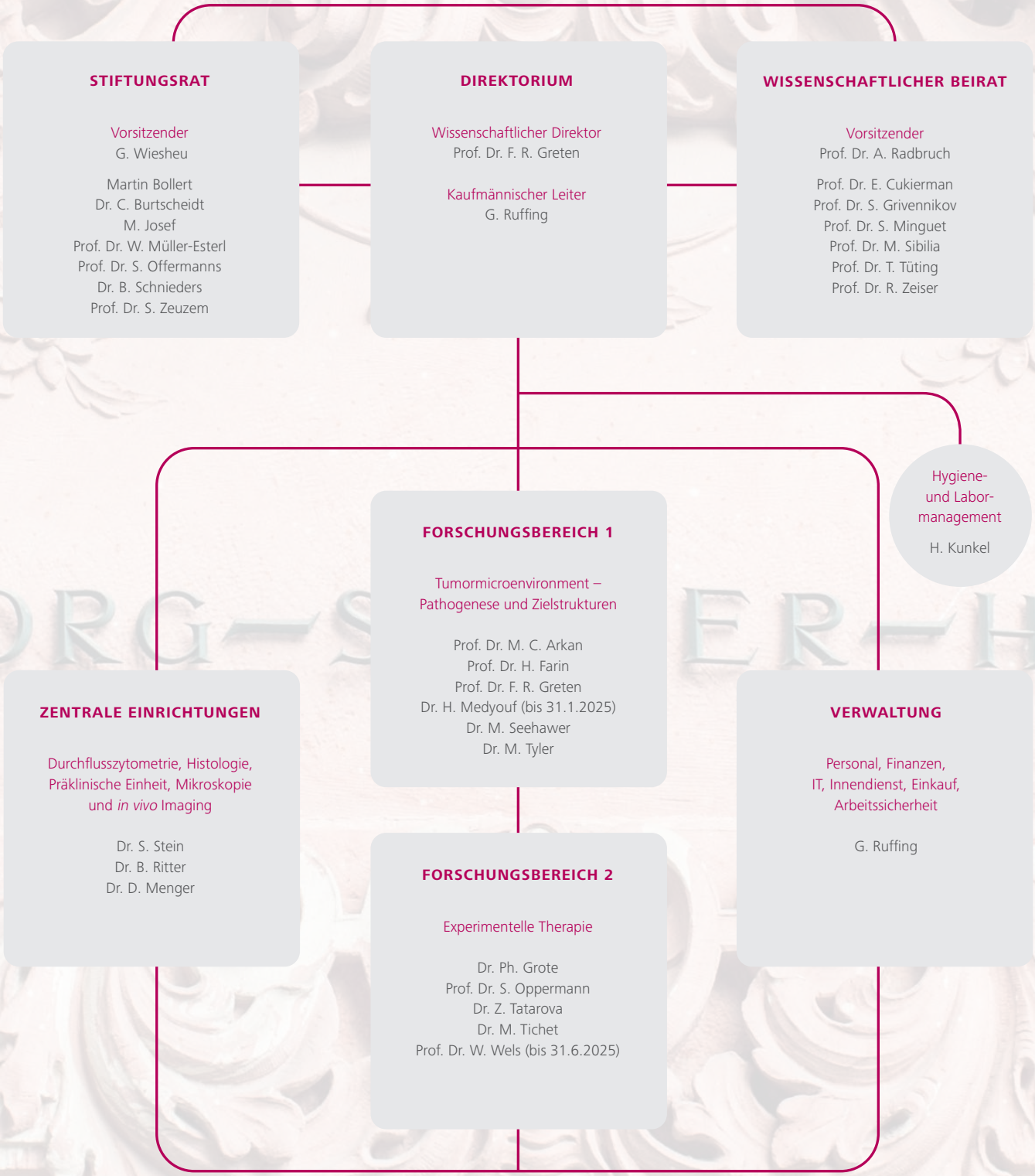
The Georg-Speyer-Haus is located in a building on Paul-Ehrlich-Str. 42- 44, which has been provided by the City of Frankfurt. The building which was opened in 1906 was renovated in the years from 1995 – 1997 with support from the Federal Ministry of Health and the Hessian Ministry of Science and Research, Arts and Culture. It comprises an area of 4710 m^2. The laboratories are certified for work under different biological and gene technology safety regulations 1 and 2.

Das Georg-Speyer-Haus wird finanziell vom Bundesministerium für Gesundheit (BMG) sowie vom Hessischen Ministerium für Wissenschaft und Forschung, Kunst und Kultur (HMWK) unterstützt. Zusätzlich stehen Mittel aus der Drittmittelförderung öffentlicher und privater Forschungsförderungsorganisationen, aus Kooperationsvereinbarungen mit Unternehmen, aus Erträgen des Stiftungskapitals und aus Spenden zur Verfügung.

Als Partner im Universitären Centrum für Tumorerkrankungen (UCT), dem LOEWE Center Frankfurt Cancer Institute (FCI) sowie dem Deutschen Konsortium für translationale Krebsforschung (DKTK) führt das Georg-Speyer-Haus international kompetitive Grundlagenforschung auf dem Gebiet der Tumorbiologie unter besonderer Berücksichtigung des Tumormikromilieus durch. Durch die enge Kollaboration mit den klinischen Partnern der Goethe-Universität im Rahmen der oben genannten Verbünde werden die Ergebnisse aus der Grundlagenforschung in frühe klinische Studien überführt. Darüberhinaus engagiert sich das Georg-Speyer-Haus in der Wissensvermittlung sowie in der Umsetzung neuer Einsichten in therapeutische Applikationen, Dienstleistungen und Produkte und kann so als ein Zentrum der translationalen onkologischen Forschung angesehen werden.

The Georg-Speyer-Haus is supported by the Federal Ministry of Health and the Hessian Ministry of Science and Research, Arts and Culture. Additional funding is provided by competitive grants, by cooperation agreements with companies, by returns from the investment of the foundation and by private donations.

As a strong partner within the University Cancer Center, the LOEWE Center Frankfurt Cancer Institute (FCI) as well as the German Cancer Consortium the Georg-Speyer-Haus is performing internationally competitive basic research in the field of tumor biology with a particular focus on the tumor microenvironment. In close collaboration with clinical partners at the Goethe-University, results are translated into early clinical trials and the Georg-Speyer-Haus can therefore be considered a center of translational oncology.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FORSCHUNGSBEREICH 1
Tumormicroenvironment – Pathogenese und Zielstrukturen
Prof. Dr. M. C. Arkan
Prof. Dr. H. Farin
Prof. Dr. F. R. Greten
Dr. H. Medyouf (bis 31.1.2025)
Dr. M. Seehawer
Dr. M. Tyler
ZENTRALE EINRICHTUNGEN
Durchflusszytometrie, Histologie, Präklinische Einheit, Mikroskopie und *in vivo* Imaging
Dr. S. Stein
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FORSCHUNGSBEREICH 2
Experimentelle Therapie
Dr. Ph. Grote
Prof. Dr. S. Oppermann
Dr. Z. Tatarova
Dr. M. Tichet
Prof. Dr. W. Wels (bis 31.6.2025)
VERWALTUNG
Personal, Finanzen, IT, Innendienst, Einkauf, Arbeitssicherheit
G. Ruffing

Highlights
2025

Marathon
Nach wochenlangem intensiven Training wurde das GSH hervorragend von zwei Teams und zwei exzellenten Einzelläufern vertreten, die alle hervorragende Leistungen und beeindruckende Ergebnisse erzielten.

After weeks of intensive training, GSH was proudly represented by two teams and two brave individual runners, all delivering excellent performances and impressive results.

Midday
Unser monatliches „Happy Midday" bringt das gesamte Team zu einem gemeinsamen Mittagessen mit einer Vielzahl internationaler Gerichte zusammen – oft mit langen Warteschlangen, die sich durch den Flur ziehen.

Our monthly "Happy Midday" brings the entire staff together for a shared lunch featuring a range of international dishes – often resulting in long queues stretching down the hallway.

Sommerfest
Unser traditionelles Sommerfest bot unserem Innendienst erneut die Gelegenheit, seine außergewöhnlichen Koch- und Grillkünste unter Beweis zu stellen. Es war ein Tag voller ausgezeichnetem Essen, entspannter Atmosphäre und viel Spaß für die Mitarbeitenden des GSH sowie deren Familien und Freunde.

Our traditional Sommerfest once again gave our Internal Service Team the chance to showcase their exceptional cooking and barbecue skills. It was a day filled with excellent food, a relaxed atmosphere, and plenty of fun for GSH employees, their families, and friends.

Halbmarathon
Erstes Warm-up für den vollständigen Marathon.

First warm-up for the full marathon.

Besuch von Staatsminister Gremmels
Im November besuchte Staatsminister Gremmels das GSH, um den offiziellen Förderbescheid für die zweijährige Verlängerung unseres LOEWE-FCI zu überreichen. Die Förderung in Höhe von 12 Millionen Euro ermöglicht es uns, unsere starken Kooperationen mit unseren exzellenten Partnern an der Universität, dem Paul-Ehrlich-Institut, dem Max-Planck-Institut für Herz- und Lungenforschung sowie dem DRK-Blutspendedienst – Institut für Transfusionsmedizin und Immunhämatologie fortzuführen und unsere neuen Forschungsergebnisse in Richtung klinischer Prüfung weiterzuentwickeln.

In November, Staatsminister Gremmels visited GSH to present the official funding notice for a two-year extension of our LOEWE-FCI. The €12 million grant will enable us to continue our strong collaborations with our excellent partners at the University, the Paul-Ehrlich Institute, the Max Planck Institute for Heart and Lung Research and the DRK-Blutspendedienst – Institut für Transfusionsmedizin und Immunhämatologie and to advance our novel findings toward clinical evaluation.

I

Tumormicroenvironment – Pathogenese und Zielstrukturen

Tumor Microenvironment – Pathogenesis and Target Structures

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Ernährungsbasierte mikrobielle Modulationen in der Krebstherapie

Dietary-based Microbial Modulations in Cancer Therapy

Investigating dynamics of microbial communities and their function during therapy

Reconstructing the tumor microenvironment to examine host-microbe interactions *in vitro*

Targeting host-microbiome interactions *in vivo*

Diet, metabolism, the circadian clock, and the gut microbiome are intricately linked, each playing a significant role in cancer development, progression, and treatment response. The circadian clock, which regulates the body's 24-hour biological rhythms, orchestrates a wide range of physiological processes, including nutrient metabolism, energy homeostasis, and drug response. Disruptions in this internal clock, often caused by irregular sleep patterns, shift work or misaligned meal timing can lead to metabolic imbalances. Emerging evidence suggests that the gut microbiome act as a critical mediator within this network. This dynamic ecosystem of trillions of microorganisms living in our gut not only shapes metabolic pathways but also interacts closely with the host rhythms influencing immune responses, drug metabolism, and cancer cell biology. Changes in the composition or function of the microbiome, dysbiosis, have been linked to metabolic disorders and increased cancer risk, emphasizing the importance of maintaining microbial balance. Our research focuses on understanding how dietary patterns regulate this interconnected system.

Ernährung, Stoffwechsel, die innere Uhr und das Darmmikrobiom sind eng miteinander verknüpft und spielen jeweils eine bedeutende Rolle bei der Entstehung, dem Fortschreiten und der Therapie von Krebs. Die zirkadiane Uhr, welche die 24-Stunden-Rhythmen des Körpers steuert, koordiniert eine Vielzahl physiologischer Prozesse, darunter den Nährstoffstoffwechsel, die Energiehomöostase und die Arzneimittelreaktion. Störungen dieser inneren Uhr, häufig verursacht durch unregelmäßige Schlafrhythmen, Schichtarbeit oder nicht mit dem Tag-Nacht-Rhythmus abgestimmte Mahlzeiten, können zu metabolischen Ungleichgewichten führen. Zunehmende wissenschaftliche Erkenntnisse deuten darauf hin, dass das Darmmikrobiom eine zentrale Vermittlerrolle innerhalb dieses Netzwerks einnimmt. Dieses dynamische Ökosystem aus Billionen von Mikroorganismen im Darm beeinflusst nicht nur Stoffwechselwege, sondern interagiert auch eng mit der zirkadianen Steuerung des Wirts und wirkt sich dabei auf Immunreaktionen, Arzneimittelmetabolismus und die Biologie von Tumorzellen aus. Veränderungen in der Zusammensetzung oder Funktion des Mikrobioms, eine sogenannte Dysbiose, wurden mit Stoffwechselerkrankungen und einem erhöhten Krebsrisiko in Verbindung gebracht. Dies unterstreicht die Bedeutung eines stabilen mikrobiellen Gleichgewichts. Daher konzentriert sich unsere Forschung darauf zu verstehen, wie Ernährungsgewohnheiten dieses komplexe Zusammenspiel regulieren. Insbesondere untersuchen wir, wie Variationen in der Nährstoffaufnahme, der Zusammensetzung der Nahrung und dem Zeitpunkt der Mahlzeiten das Mikrobiom, den Stoffwechsel und die zirkadianen Rhythmen im Kontext von Darmkrebs beeinflussen. Durch die Untersuchung dieser Zusammenhänge wollen wir herausfinden, wie die Wiederherstellung oder Aufrechterhaltung eines stabilen Mikrobioms und einer ausgeglichenen Stoffwechselumgebung das Krebsrisiko senken, das Fortschreiten der Erkrankung verlangsamen oder die Wirksamkeit von Therapien verbessern kann.

Especially we check how varitations in nutrient intake, dietary composition, and meal timing influence the microbiome, metabolism, and diurnal rhythms in the context of colorectal cancer. By studying these relationships, we aim to determine how restoring or maintaining a stable microbiome and metabolic environment could reduce cancer risk, slow disease progression, or improve treatment responses.

Inter-individual variability in microbiome composition and function influence patients' response to therapy. Using clinical samples at pre- and post-treatment, we are analyzing the microbiome dynamics in patient cohorts. We are exploring how the microbiome influences metabolism and how therapeutic interventions in turn reshape microbial communities. Cancer cells undergo significant metabolic reprogramming to support their rapid growth, and we are identifying microbial signaling molecules that represent potential therapeutic value. Furthermore, using machine learning classifiers, we are identifying a threshold of specific taxa abundance shifts that can capture the predictive separation between responders and non-responders (Figure 1).

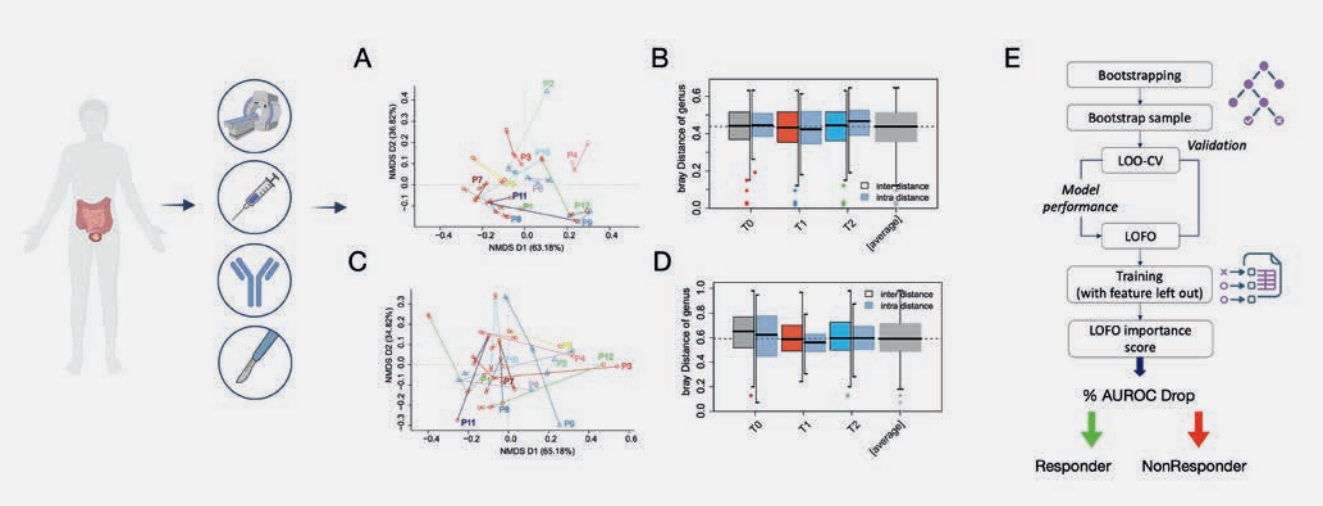
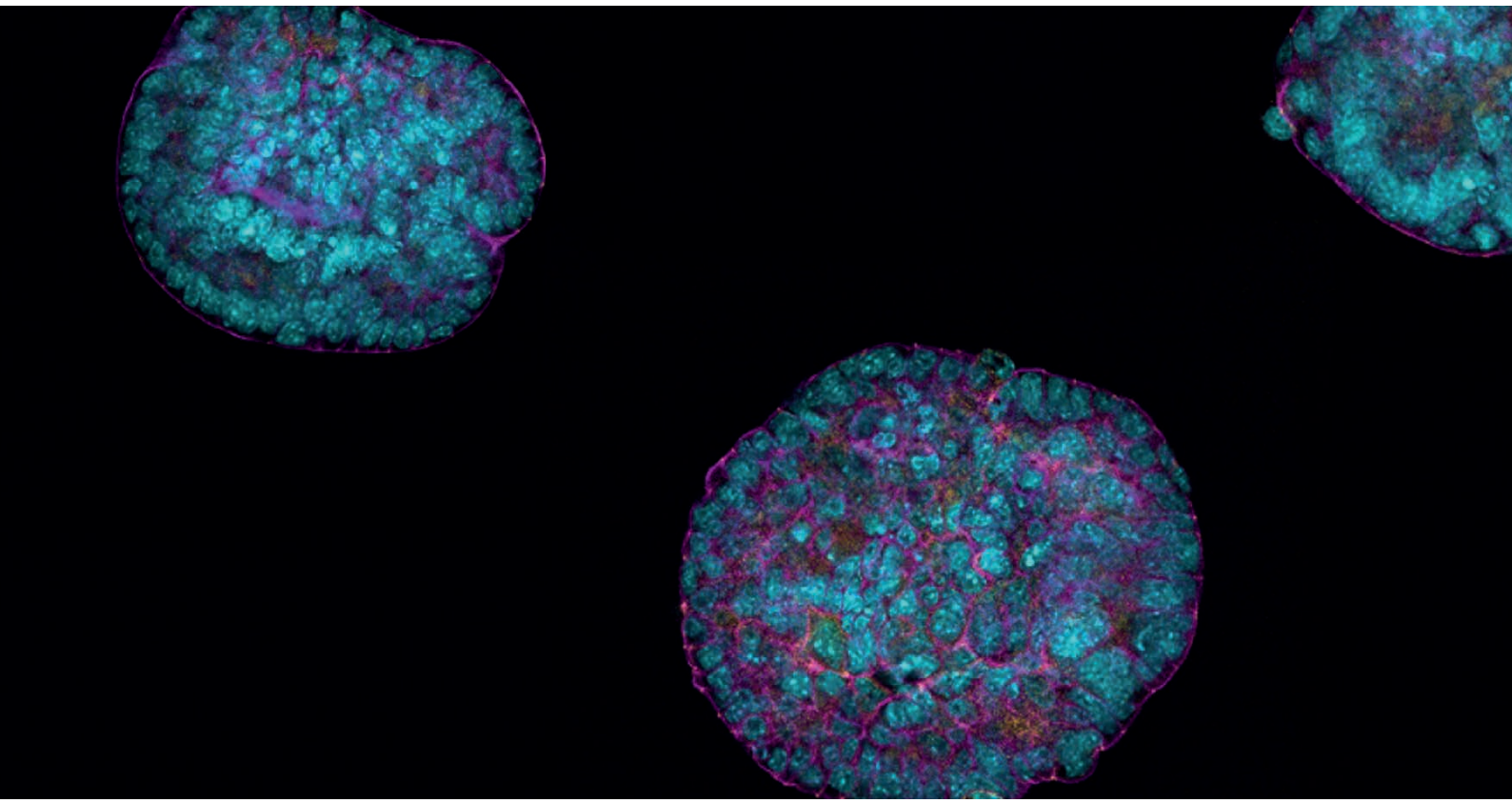


Figure 1. We explore dynamic changes in microbiome during chemoradiotherapy in rectal cancer patients enrolled in a Phase I trial. We integrate a correlative multiomics approach in these patients to understand microbial community structure and function dynamics during therapy whether they can predict therapeutic outcomes. We use machine learning for microbiome modeling and predictive analysis. This presentation was created in BioRender.



An additional focus of our work is aligning dietary interventions and microbiome modulation with host diurnal rhythms to optimize cancer therapies. The timing of treatments such as chemotherapy or immunotherapy relative to the body's biological clock can significantly influence their effectiveness and toxicity. By integrating microbiome dynamics into this cross-

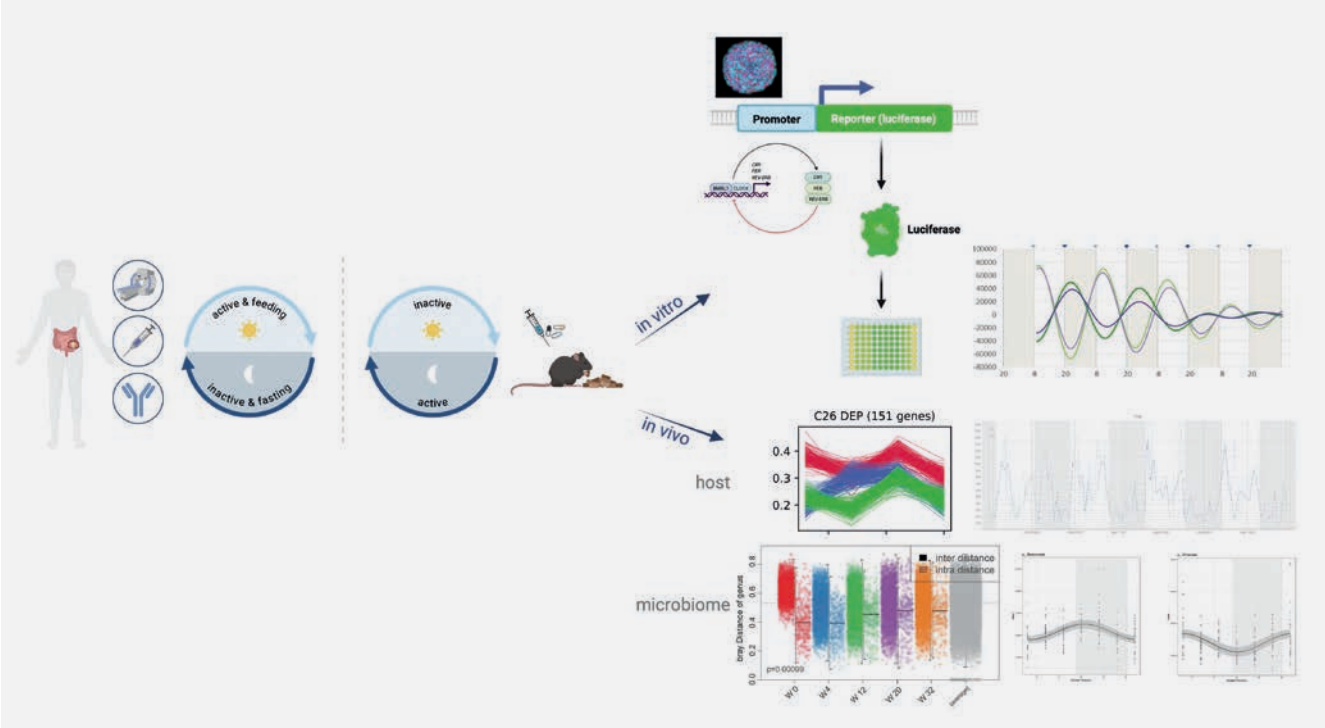
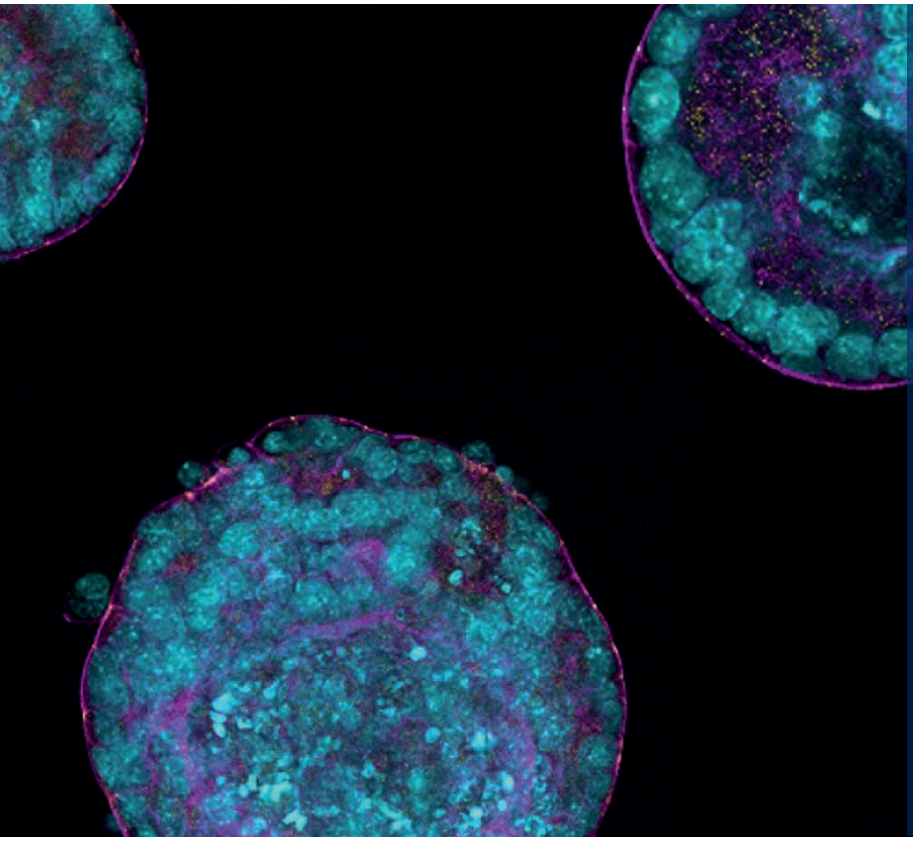


Figure 2. We use preclinical mouse models of colorectal cancer to identify alterations in microbiome structure and function during tumor progression and therapy. Using in vitro and in vivo approaches, we assess host-microbiome interactions by testing the impact of bacterial metabolites on host cell rhythms and responses to cytotoxic therapy. We then employ timed dietary interventions modulating daily rhythms to see whether we can target the tumor microenvironment more efficiently and improve treatment outcomes. This presentation was created in BioRender.



Ausgewählte Publikationen

Schulz MD*, Atay C*, Heringer J*, Romrig FR, Schwitalla S, Aydin B, Ziegler PK, Varga J, Reindl W, Pommerenke C, Salinas-Riester G, Böck A, Alpert C, Blaut M, Polson SC, Brandl L, Kirchner T, Greten FR, Polson SW and **Arkan MC** (2014)
*'High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity'. **Nature**; 514(7523): 508-512.*

Arkan MC (2016)
*'Cancer: Fat and fate of pancreatic tumors'. **Nature**; 536(7615):157-8.*

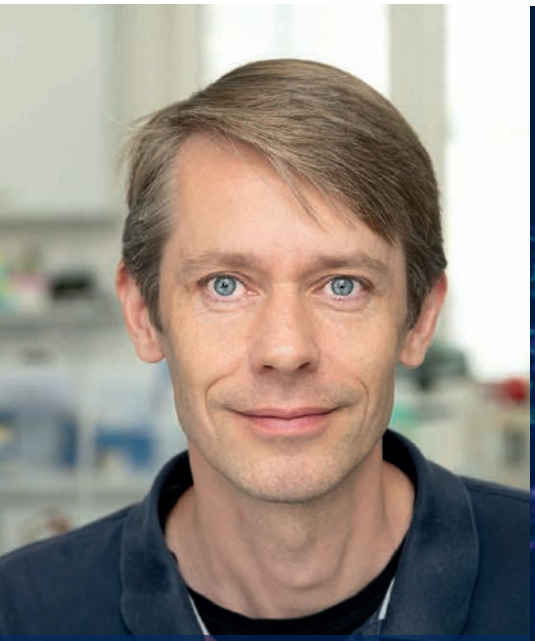
Arkan MC (2017)
*'The intricate connection between diet, microbiota, and cancer: A jigsaw puzzle'. **Semin. Immunol.**; 32: 35-42.*

Greten FR and **Arkan MC** (2024)
Gut microbial carcinogen metabolism–another avenue to cancer. Signal Transduction and Targeted Therapy; 9, 297.

... weitere Publikationen finden Sie auf Seite ▶ 57

talk, we are investigating whether specific dietary regimens when syncronized with diurnal oscillations, can improve therapeutic outcomes. If it did, this research could lead to personalized, timed dietary strategies that not only enhance treatment efficacy but also promote microbial stability and patient well being (Figure 2).

In summary, our research explores the interconnected roles of the microbiome and the potential of dietary interventions aiming to target the microbiome in cancer. By dissecting these complex interactions, we aim to identify therapeutic strategies that use microbiome functionality to influence circadian biology, target weaknesses in cancer cells, and to optimize treatment timing. This approach holds potential to develop personalized, non-invasive interventions that can enhance the effectiveness of cancer therapies and improve patient outcomes.



Gewebsinteraktionen und Signalmechanismen im Darmkrebs

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Signaling crosstalk in the colon cancer microenvironment

3D co-culture models using patient-derived organoids and stromal cells

Genetic and pharmacologic perturbations of the CRC microenvironment

Identifying and testing of new approaches for CRC immunotherapy

In Germany, colorectal cancer (CRC) is the third most common type of cancer, with more than 50,000 new cases and more than 20,000 deaths each year. CRC can be classified into two main subtypes: microsatellite stable (MSS) cancers, which make up about 85% of cases, and microsatellite instable (MSI) cancers, accounting for the remaining 15%. Great advances have been achieved in tumor prevention and immune checkpoint therapy has shown impressive efficacy in MSI patients. However, the therapeutic options for MSS patients are still limited. This is due to the high genetic heterogeneity among patients and within individual tumors. In addition, prognosis and therapy responses are strongly influenced by the tumor microenvironment (TME). To improve our understanding of the link between CRC genotype and phenotype and develop better treatments, new models that can mimic these complexities are needed.

Unsere Arbeitsgruppe untersucht die zellulären und molekularen Mechanismen, die den Verlauf und das Therapieansprechen beim Darmkrebs beeinflussen. Ein besonderer Fokus liegt dabei auf der Kommunikation zwischen verschiedenen Zelltypen innerhalb der direkten Tumorumgebung, dem sogenannten „Tumor-Mikromilieu". Zu diesem Zweck kommen Organoide – ein innovatives, dreidimensionales Gewebekultur-System zum Einsatz. Organoide können unter kontrollierten Kulturbedingungen aus menschlichen Darmstammzellen entwickelt werden und bilden Darmepithel-spezifische Strukturen wie Krypten (Einstülpungen) und Villi (Zotten) nach. Dadurch können wir Stammzellen in einem gewebeähnlichen Zustand expandieren und molekulare Signalwege in einer definierten Mikroumgebung untersuchen. Durch Zugabe von Fibroblasten, Gefäß- oder Immunzellen wird der Gewebskontext nachgebildet.

In Zusammenarbeit mit dem „Frankfurt Cancer Institut" und dem „Universitären Centrum für Tumorerkrankungen" legen wir im Labor lebende Biobanken von Tumor-Organoiden aus klinischen Gewebeproben an. Mithilfe genetischer Methoden wie CRISPR/Cas9 und Genom- und RNA-Sequenzierung erforschen wir, wie onkogene Mutationen den Tumorphänotyp beeinflussen. Im Rahmen des EU-Projekts „EUbOPEN" nutzen wir Organoid-Modelle für pharmakologische Hochdurchsatzanalysen. Dabei kommen zelluläre Assays zum Einsatz, um diverse Therapieformen und Kombinationstherapien zu testen und dadurch neue Ansätze für die zukünftige Behandlung von Darmkrebs zu entwickeln.

Our research is focused on patient-derived tumor organoids (PDTOs) that have emerged as an important preclinical tool. The organoid technology is based on expansion of primary epithelial cells in extracellular matrix and defined growth factors. Originally developed for the mouse small intestine, the method has been adapted to support growth of normal and tumor cells from human colon and other organs. PDTOs can be expanded and cryopreserved to establish 'living biobanks' that represent the tumor heterogeneity among and within patients. In clinical collaboration and supported by Frankfurt Cancer Institute (FCI) and the University Cancer Center Frankfurt (UCT), we are generating a CRC organoid biobank as a research tool to study cancer phenotypes and mechanisms that affect drug sensitivity and therapy resistance. In addition, we study the impact of individual mutations by genetic modification of organoids using the CRISPR/Cas9 technology. To facilitate testing of many mutations in parallel, we have established a protocol for pooled CRISPR/Cas9 library screening in human colon organoids (Michels et al., *Cell Stem Cell* 2020).

Our main research areas are:

I. Study of context-dependency of the CRC phenotype

Although the TME plays a key role for prognosis and therapy efficacy, we currently lack experimental models to study stromal influences in vitro. To systematically investigate TME interactions, we have established the 'CRC organoid-stroma biobank'. In collaboration with

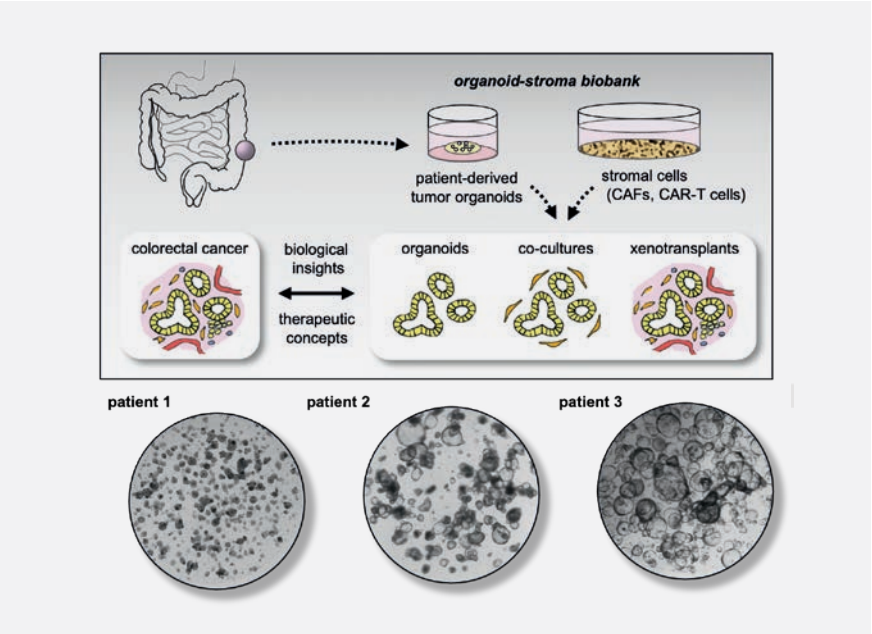
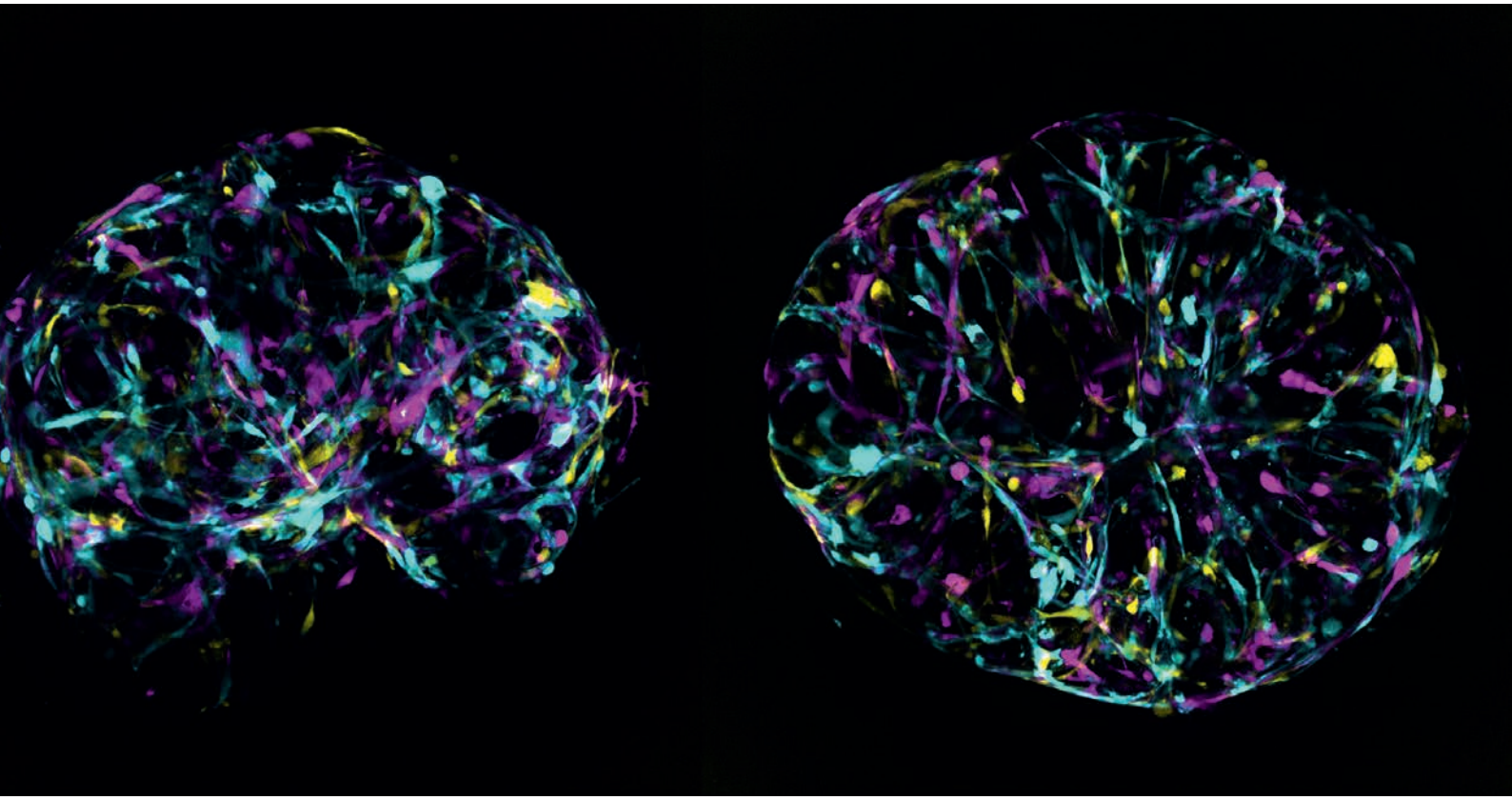


Figure 1.
Colorectal Cancer organoid-stroma biobank. Generation of tumor organoids and cancer-associated fibroblasts (CAFs) from clinical samples. Systematic analysis of co-cultures from 30 patients showed an improved similarity with the corresponding tumor tissues and profound influences of CAFs on the therapy response *in vitro* (adapted from Farin et al., *Cancer Discovery* 2023).



the group of Prof. Greten, a cohort of PDTOs and matched cancer-associated fibroblasts (CAFs) from 30 tumors was generated Farin et al., Cancer Discovery 2023). All models were subjected to whole exome sequencing to identify underlying tumor mutations. To study the impact of the TME, RNA sequencing was performed in tumors and PDTOs under diverse conditions: PDTOs were studied alone, after xenotransplantation and following co-culture with CAFs (Fig. 1). We could show that co-cultures provide an excellent opportunity to recapitulate the stromal crosstalk in CRC tissues. We are currently using single cell RNA sequencing to further describe how stromal cell interactions influence the CRC phenotype.

II. Preclinical organoid models for cancer immunotherapy

Cell-based immunotherapies hold promise for improving clinical outcomes in CRC, especially for MSS patients who are refractory to immune checkpoint inhibitors. One promising approach is to engineer lymphocytes to recognize tumor-associated antigens through chimeric antigen receptors (CARs). However, the application of CAR-modified cells in solid tumors like CRC faces considerable challenges. Notably, the immunosuppressive TME prevents immune cell recruitment and impairs their function. Moreover existing model systems fail to replicate the complexity of the TME. To address these challenges, we have teamed up with Prof. Winfried Wels (Georg-Speyer-Haus, emeritus) to develop a CAR-PDTO co-culture system.

In this system, the cytotoxic killing of PDTOs by CAR-modified NK-92 cells can be monitored using enzymatic assays and by live imaging (Fig. 2; Schnalzger et al., *EMBO Journal* 2019), providing a preclinical platform to evaluate therapy efficacy.

As participant of the EU-consortium EUbOPEN ('Enabling and unlocking biology in the OPEN' 2020-2025), we have established a PDTO drug screening

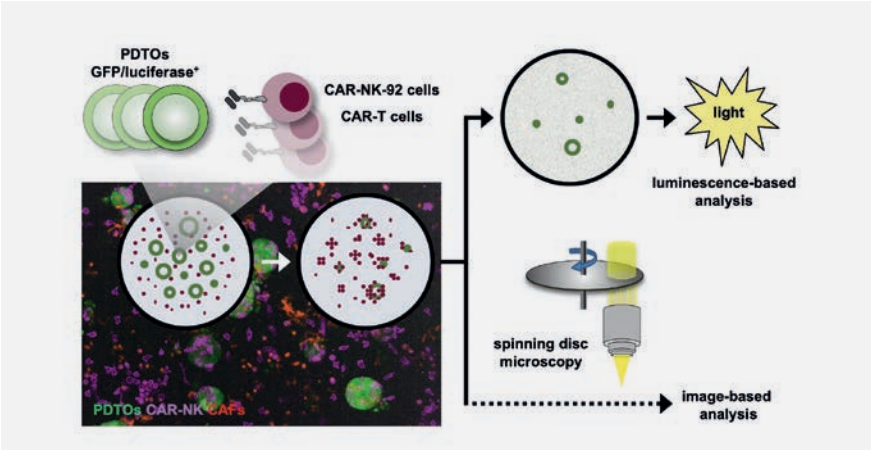
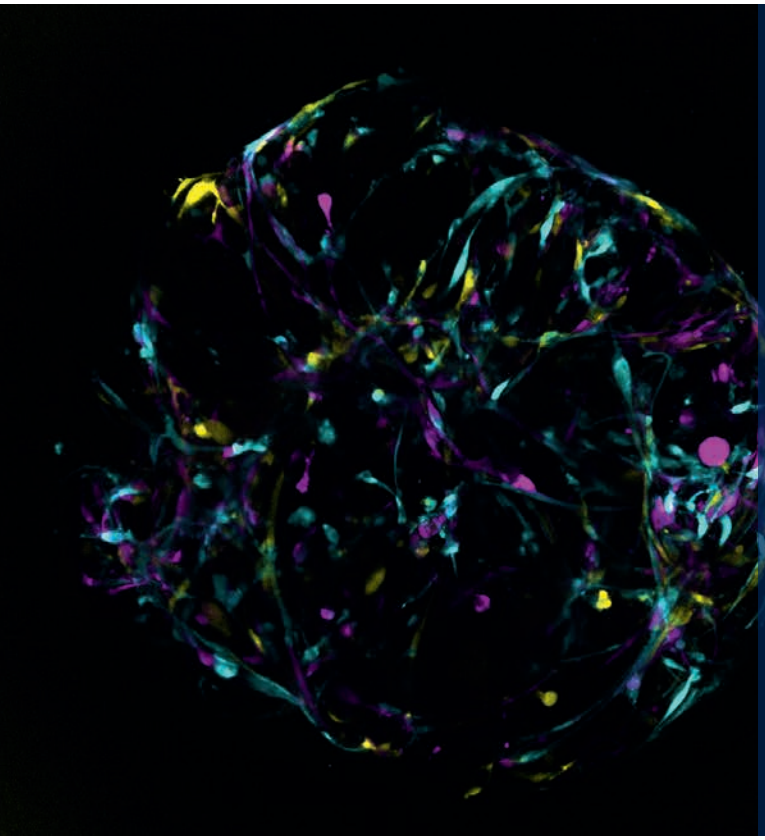


Figure 2. **3D model for CAR-mediated cytotoxicity using patient-derived organoids**
Combination of GFP/luciferase-transgenic CRC organoids (green) with CAFs (red) and CAR-NK cells (violet). Monitoring of cytotoxic responses by video microscopy and enzymatic read-out (adapted from Schnalzger et al., *EMBO Journal* 2019).



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ZEB1-mediated fibroblast polarization controls inflammation and sensitivity to immunotherapy in colorectal cancer. ***EMBO reports.*** *25(8):3406–3431.*
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platform. The EUbOPEN consortium was funded by the Innovative Medicines Initiative (IMI2) to generate an open access chemogenomic library of compounds covering the 'druggable human genome'. Together with our partners from academia and pharmacologic industry, we have developed 'human tissue assays' for CRC. Subsequently, we conducted high-throughput pharmacologic screens using PDTO biobanks to identify new therapeutic targets. As one application, we are currently testing PDTO-based assays for CAR-T cells in collaboration with Prof. Christian Buchholz (Paul Ehrlich Institute).

III. Engineering of heterocellular CRC assembloids

To recapitulate the tissue-complexity in CRC, we have generated a new three dimensional culture method called CRC assembloids. In this system, PDTOs are combined in high density with extracellular matrix, CAFs and other stromal cell types (Fig. 3A). Subsequent culture induces a spontaneous condensation process resulting in self-organization of a tissue-like arrangement. Assembloids can be generated with high reproducibility and display distinct stromal architectures that show resemblance to the histological features of matched tumors (Fig. 3B). Within the newly funded DFG Heisenberg project PHENOMAP (2025-2029), we will use this assembloid platform to study the phenotypic landscape of CRC. Image-based and single cell-resolved analysis of tumor assembloids will allow us to explore the signaling crosstalk in the CRC microenvironment. This could help us to identify new therapeutic concepts and provide a promising alternative to animal experimentation.

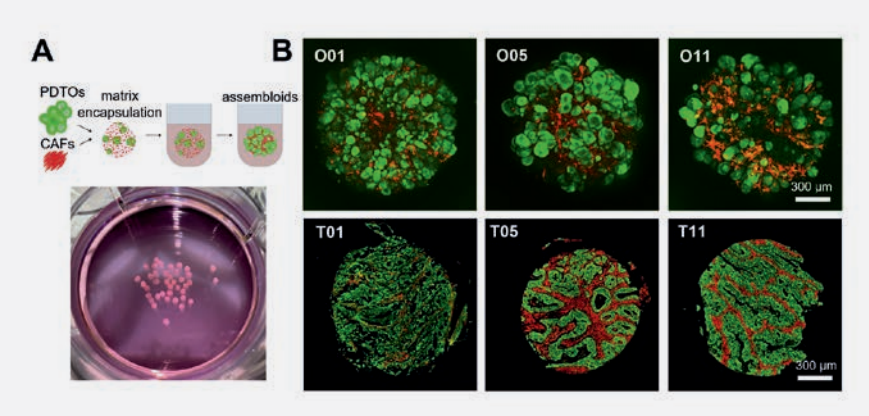
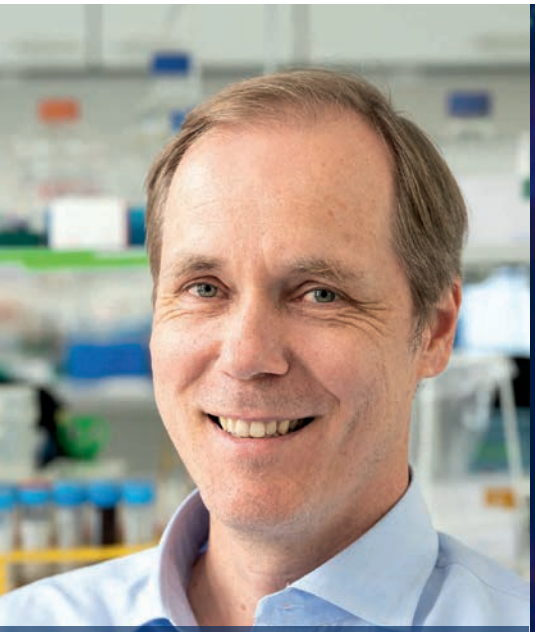


Figure 3. **Self-organization of the TME in human CRC assembloids**
(A) Schematic protocol and morphology. (B) TME architectures in assembloids and matched tumor histology. Assembloids (top) contain GFP+ PDTOs and DsRed+ CAFs. Confocal images (z-projections) after 3 days of culture. Tumor sections (bottom) stained with anti-Cytokeratin (green) and anti-Vimentin (red) antibodies.



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Therapeutische Interventionen in das Tumormikromilieu

Therapeutic interventions in the tumor microenvironment

Effects of Urolithin A on immune cell populations

Immune aging

Clinical translation

Our group focuses on colorectal carcinoma (CRC), its metastasis, and the tumor microenvironment. Although preventive screening and new therapeutic approaches continue to advance, CRC still ranks among the leading malignant diseases in terms of incidence and mortality. Using three-dimensional colorectal organoids derived from mice and humans, along with preclinical mouse models, we investigate the cellular and molecular pathways that drive tumor initiation and metastasis. This helps us better understand the highly complex networks that shape tumor biology. Tumors are composed not only of heterogeneous cancer cells but also of diverse stromal cells. Infiltrating immune cells, for instance, may acquire either an immunosuppressive, tumor-promoting phenotype or an opposing, tumor-fighting role. Additionally, each patient's individual microbiome can profoundly influence both tumor progression and therapeutic responses. Taken together, CRC is shaped by a multitude of factors that contribute to its heterogeneity.

Unsere Forschung konzentriert sich auf die Analyse gastrointestinaler Tumoren und ihres Mikromilieus mit dem Ziel, die dabei gewonnenen Erkenntnisse für neue therapeutische Strategien nutzbar zu machen. Hierfür setzen wir neben modernen dreidimensionalen in-vitro-Kulturen muriner und humaner intestinaler Zellen auch geeignete Mausmodelle ein, die verschiedene Typen und Stadien der Karzinogenese zuverlässig nachbilden.

In unseren präklinischen Studien konnten wir beobachten, dass die durch Urolithin A (UA) induzierte Mitophagie – ein Prozess, bei dem alte oder defekte Mitochondrien abgebaut werden – positive Effekte auf anti-tumorale Immunantworten ausübt. Dieser Effekt war auf zytotoxische CD8-T-Zellen zurückzuführen, die sowohl durch eine verstärkte Aktivierung infolge erhöhter MHC-I-Antigenpräsentation als auch direkt durch UA beeinflusst werden können.

Weitere vielversprechende in-vitro- und in-vivo-Versuche führten uns zur Initiierung einer klinischen Studie, um zunächst den Einfluss von UA auf Immunzellen, insbesondere T-Zellen, in gesunden Probanden zu untersuchen. Dies stellt den ersten Schritt unseres langfristigen Ziels dar, UA in der Krebstherapie einsetzen zu können.

Nach einer einmonatigen täglichen Einnahme von Urolithin A konnten in peripheren Blutzellen der Probandinnen und Probanden verschiedene positive Effekte nachgewiesen werden, die in der Placebogruppe nicht beobachtet wurden. Dazu gehörten ein Anstieg naiver CD8-T-Zellen sowie von NK-Zellen und nicht-klassischen Monozyten. Detaillierte Analysen belegten zudem eine insgesamt verbesserte Funktionsfähigkeit der Immunzellen und eine geringere „Immunalterung". Diese Ergebnisse bilden nun die Grundlage für eine weitere Studie zur Anwendung von UA im Kontext einer Immuntherapie bei Krebspatientinnen und Patienten.

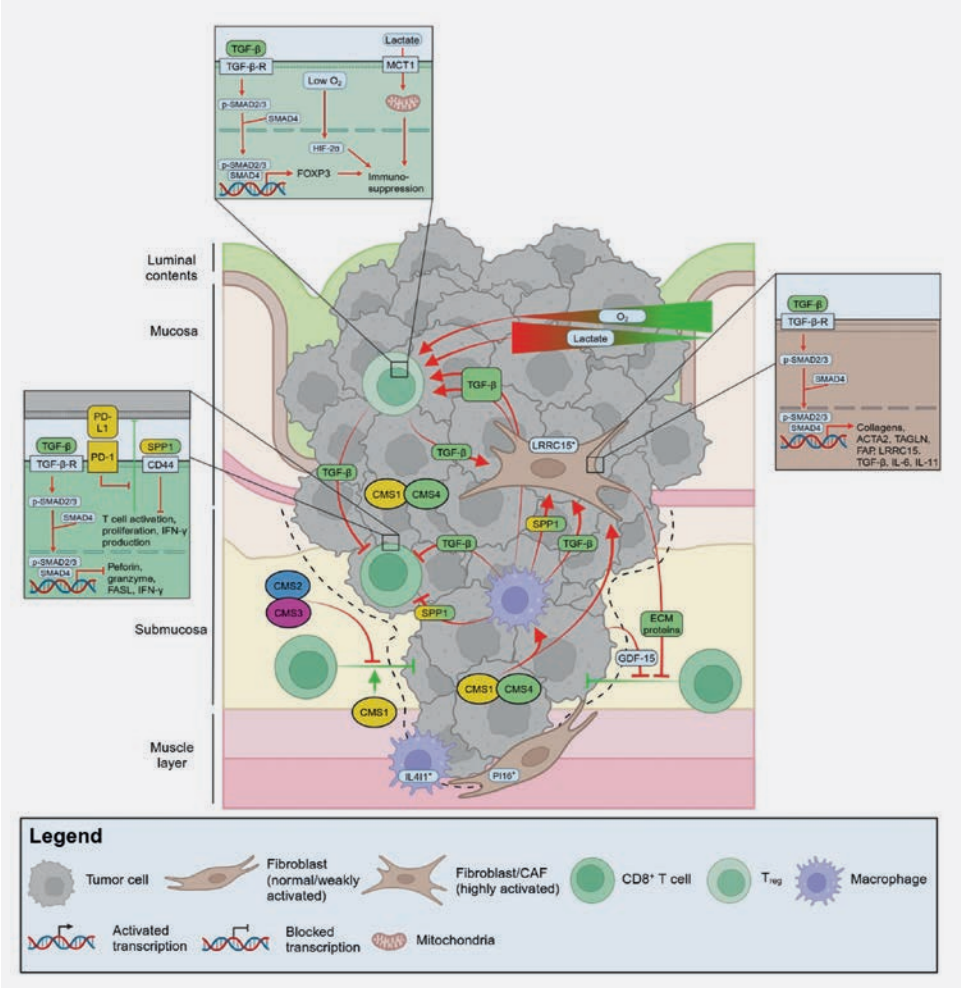
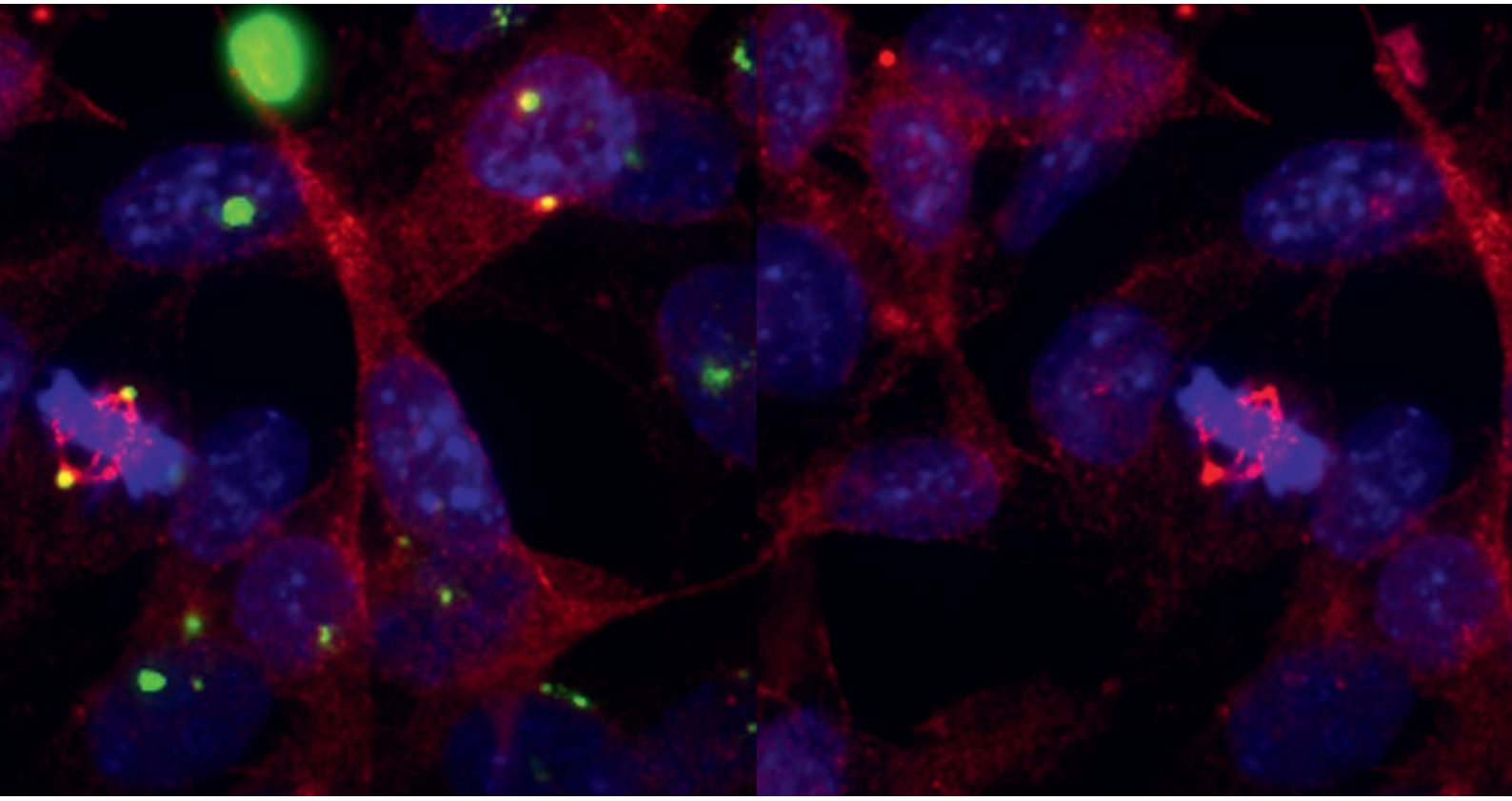


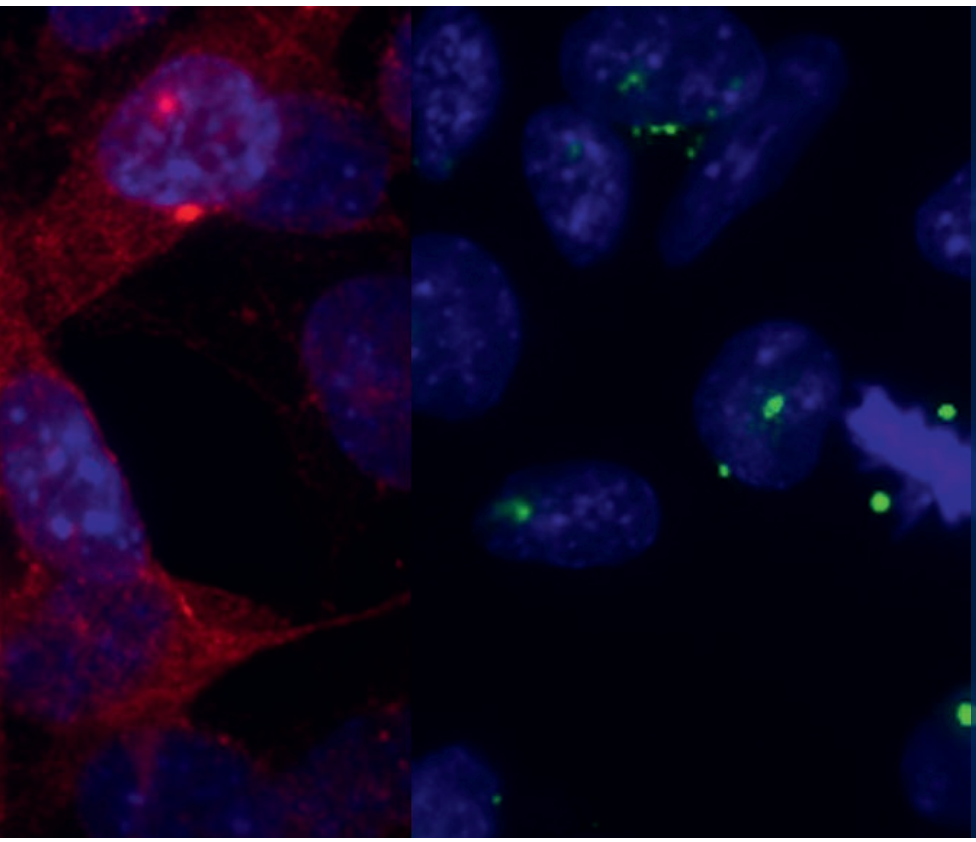
Figure 1:
In invasive CRC, immunosuppression is further intensified, partly due to the accumulation of Tregs and immunosuppressive macrophages that secrete TGF-β and SPP1/osteopontin. TGF-β acts as a central immunosuppressive cytokine by promoting Treg differentiation, inhibiting CD8+ T cell activity, and driving a myofibroblastic CAF phenotype characterized by secretion of ECM proteins, IL-6, and IL-11. Importantly, TGF-β, SPP1, IL-6, and IL-11 are predominantly secreted by TME cells in CRCs of the inflamed MSI-H/CMS1 and mesenchymal MSS/CMS4 subtypes, highlighting their particular relevance in these groups. In contrast, the MSS CMS2 and CMS3 subtypes generally show lower immune infiltration, especially of T cells, suggesting that targeting pro-inflammatory or immunosuppressive pathways may be less effective in these tumors. Additional mediators contribute to immune evasion, including GDF-15, an immunosuppressive cytokine secreted by tumor cells that promotes immune exclusion and resistance to immune checkpoint blockade across multiple cancer types, including CRC. Finally, oxygen and nutrient availability further shape the metabolic state of cancer and TME cells, fostering tumor growth, for instance by enhancing Treg activity. Red connections/fills indicate detrimental interactions/concentrations (Lactate & O_2). Green connections/fills indicate beneficial interactions/concentrations (Lactate & O_2). Arrows indicate stimulatory effects, inhibitors indicate inhibitory effects.
Figure created with BioRender, modified from Kennel, KB & Greten, FR, 2025.



While this complexity is detrimental for patients, it poses both a challenge and an opportunity for clinicians and researchers. Every newly uncovered pathway or resistance mechanism provides a potential lever for developing more effective treatments. This is why our basic research is highly relevant, and we aim to translate our findings into clinical practice whenever possible.

As colorectal tumors progress, they accumulate additional genetic and epigenetic alterations that drive invasiveness and metastasis. Throughout this process, CRCs exploit tumor microenvironment (TME) mechanisms to sustain growth and evade anti-tumor immunity (Figure 1). At the invasive margin, tumor cells directly interact with adjacent normal tissue, eliciting inflammatory responses of variable intensity and quality. The degree of immune cell infiltration – particularly T cells – at this invasion front, is strongly associated with patient survival and may hold therapeutic relevance. Furthermore, the presence of tumor budding at the invasive front, a histological marker of aggressiveness, correlates with reduced immune infiltration and poorer prognosis. This supports the concept that immunosuppression is a defining feature of invasive CRC.

We previously found that the mitophagy inducing agent urolithin A (UA) promotes the expansion of long-lived, naïve-like CD8+ T cells (Denke et al., 2022), which in turn enhances antitumor immunity in colorectal cancer models and synergizes with immune checkpoint blockade. Thus, UA could represent a useful tool to stimulate T cell immunity in cancer therapy. Because our data showed that UA confers functional benefits to human T cells, when treated *ex vivo*, we intended to investigate its impact on immune cells in a clinical trial. We carried out a phase I randomized, placebo-controlled trial in 50 healthy, middle-aged adults (NCT05735886), administering UA or placebo for 4 weeks to assess changes in circulating immunity. The primary endpoints were the proportion of naïve CD8+ T cells among circulating immune cells and alterations in immune cell metabolism indicative of mitochondrial remodeling. Secondary endpoints included functional measures of inflammation and immune response, enabling us to link immune phenotype with functional outcomes. Daily UA supplementation was well tolerated and led to a significant increase in naïve CD8+ T cells compared to both baseline and placebo (Denk et al., 2025). We also observed shifts in circulating monocyte and natural killer cell populations following UA intake. Furthermore, UA enhanced fatty acid oxidation across multiple immune subsets, suggesting mitochondrial remodeling as a potential underlying mechanism. Upon restimulation, immune cells from UA-treated participants exhibited greater bacterial uptake and a stronger proinflammatory response, without exacerbating baseline age-associated inflammation (inflammaging). Transcriptomic profiling of UA-mediated immunity further corroborated these phenotypic and functional findings. Taken together, our results indicate that dietary UA supplementation exerts beneficial effects on human immune aging.



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Based on these encouraging results, we now aim to test whether UA may have a positive impact on patients receiving checkpoint inhibitors. Because colorectal cancer patients do not receive such inhibitors as standard-of-care, we will assess UA in lung cancer and melanoma patients (NCT0716131). Led by a team from the 2nd Department of Medicine this trial exemplifies again the excellent collaboration with our clinical partners that we have established over the recent years within the framework of the LOEWE Center Frankfurt Cancer Institute (FCI).

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Histonmodifikatoren bei der Entstehung, Progression und Therapie von Tumoren

Histone modifier in tumor onset, progression, and therapy

histone modifier deregulation as cancer driver

tumorigenesis models

histone modifier-targeting combination therapies

Most cancers arise from normal cells due to specific mutations that activate oncogenes or inactivate tumor suppressor genes, ultimately transforming healthy cells into malignant ones. Beyond genetic alterations, epigenetic dysregulation of gene expression can also drive tumor initiation or enhance the aggressiveness of established cancers. Among the most frequently mutated genes are those encoding histone modifiers, which serve as key regulators of epigenetic mechanisms. Histone modifications can alter chromatin structure or recruitment of further members of the transcriptional machinery. Disruption of the epigenetic landscape can influence cancer cell plasticity, interactions with the tumor microenvironment, and resistance to therapy. Therefore, dissecting these complex networks of epigenetic perturbations is essential not only for understanding the early stages of tumorigenesis but also for guiding the development of targeted combination therapies.

Eine Vielzahl der Tumore entsteht aus normalen Zellen durch Mutationen von Histonmodifikatoren (HM), die epigenetische Mechanismen, z.B. Chromatinstruktur oder Transkriptionsfaktoren regulieren. Eine Störung kann die Plastizität von Krebszellen oder die Therapieresistenz beeinflussen, weshalb wir uns ein besseres Verständnis dieser Deregulationen zum Ziel setzen.

Wir konnten zeigen, dass Deregulationen der HM KMT2C und KMT2D Zellen zum Metastasieren bringen. Insbesondere Gehirnmetastasen waren signifikant erhöht in verschiedenen Zell Modellen (Abb. 1). Es bleibt jedoch unklar, ob der Verlust dieser Proteine ausschließlich für die Metastasierung entscheidend ist oder ob er auch zur Umwandlung normaler Zellen in bösartige Tumore beiträgt.

Wir konnten bereits epigenetische Änderungen infolge deregulierter HM entziffern und das Protein MMP3 identifizieren, das die Metastasierung induziert. Inhibierung eines weiteren HM, KDM6A, konnte MMP3 inhibieren und die Metastasierung verhindern (Abb. 2). Daher kombinieren wir Tumor-Modelle mit genetischen Störungen von HM und modernsten Sequenzierungen, um Tumorplastizität zu charakterisieren.

Die Tumorplastizität ist essenziell für Therapieresistenz, welche oft durch epigenetische Regulation erfolgt. Daher ist die Kombination konventioneller Therapien mit Inhibitoren von HM eine vielversprechende Strategie, um diese zu verhindern und synthetische Letalität aufzudecken. Dafür wollen wir sowohl vorab ausgewählte Wirkstoffkombinationen als auch CRISPR-basierte Screening-Ansätze einsetzen (Abb. 3).

An important regulator of histone modifications is the COMPASS complex, which consists of multiple histone-binding and histone-modifying proteins and is frequently mutated across several cancer types. Our previous work has demonstrated that perturbation of COMPASS members, particularly the histone H3K4 methyltransferases KMT2C and KMT2D, drives non-metastatic breast cancer cells toward aggressive metastatic behavior. Loss of function of these proteins induces widespread alterations in both the histone landscape and transcriptome, specifically upregulating MMP3 which was essential for the initiation of brain metastases (Figure 1). However, it remains unclear whether the loss of these proteins is exclusively critical for metastatic progression or whether it also contributes to the transformation of normal cells into malignant tumors. Moreover, determining whether similar epigenetic and transcriptomic changes occur during tumorigenesis could reveal novel opportunities for targeting early tumor development.

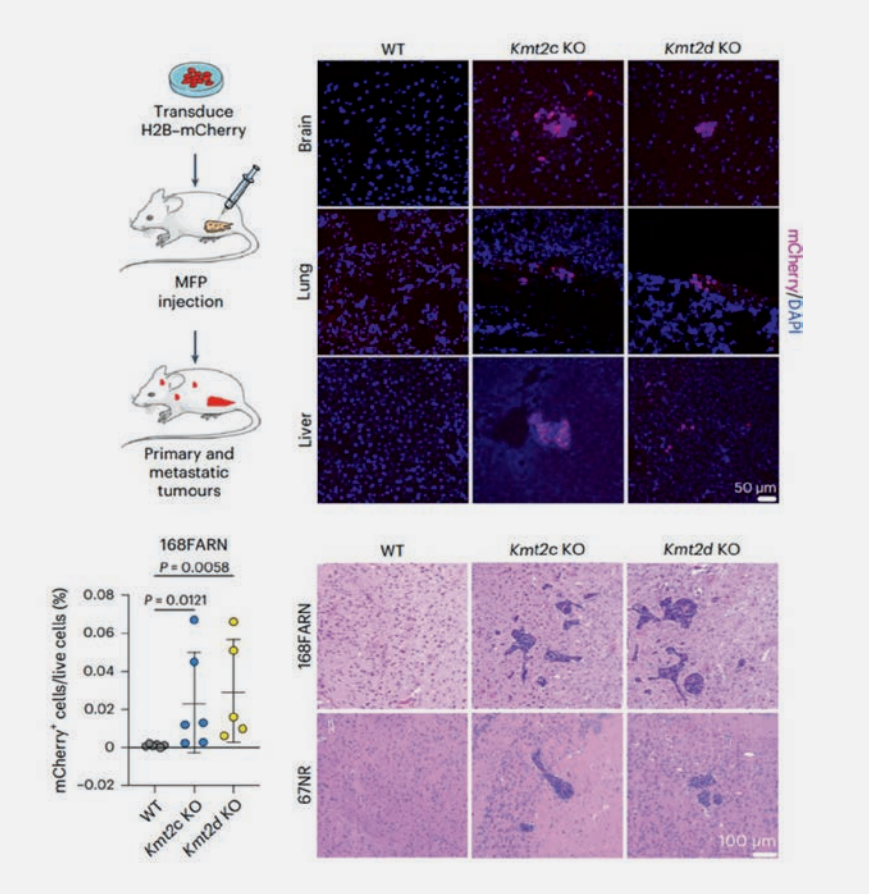
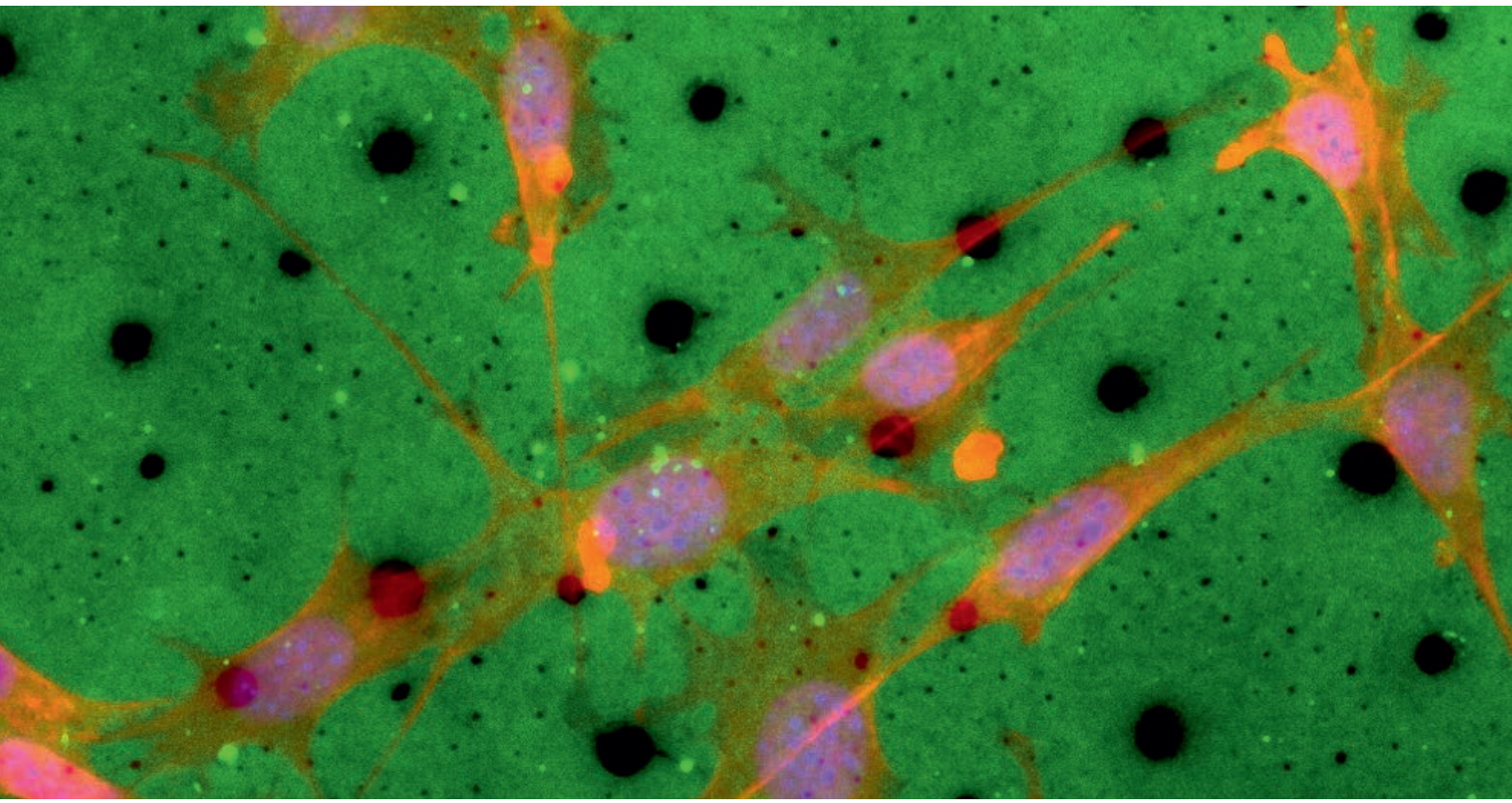


Figure 1. Loss of Kmt2c or Kmt2d induces spontaneous multi-organ metastases from tumors grown in mammary fat pads of mice or after injections of cancer cells into the circulatory system (adapted from Seehawer et al. Nat Cell Biol 2024).



Because the epigenetic network is highly interconnected, the loss of a specific regulator not only affects its direct histone substrate but can also indirectly influence other histone marks or chromatin-modifying complexes. For instance, loss of KMT2C/D not only disrupts H3K4 modifications but also leads to alterations in H3K27 marks. These H3K27 changes are largely dependent on the histone demethylase KDM6A, which presents a potential pharmacological target to counteract metastasis-inducing mechanisms in Kmt2c/d-deficient cells (Figure 2). This illustrates that indirect targeting of histone modifiers may offer promising therapeutic opportunities. To systematically dissect these epigenetic dependencies, our laboratory aims to employ tumorigenesis models that mimic the transformation and progression of normal cells into malignant tumors. By combining functional genetic perturbation of histone modifiers with state-of-the-art sequencing approaches, we will characterize their impact on epigenetic regulation and cellular plasticity.

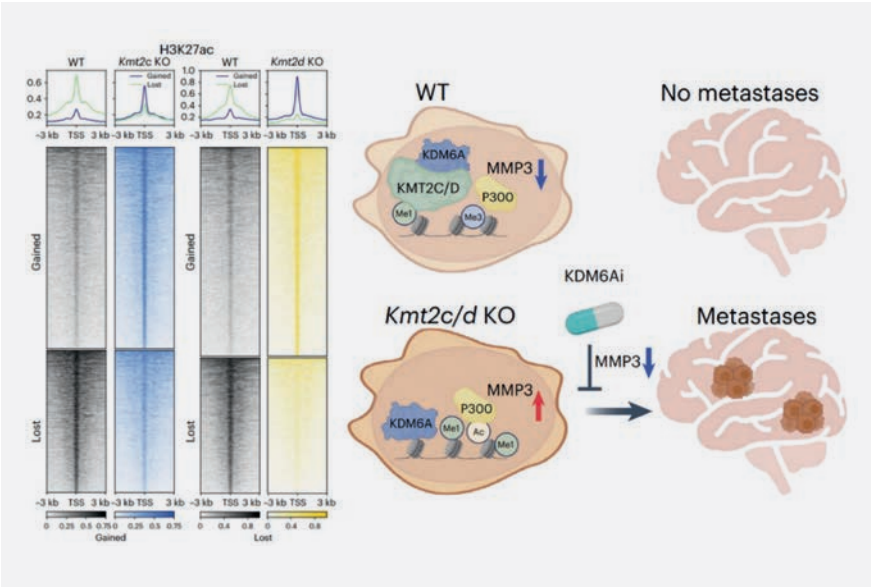
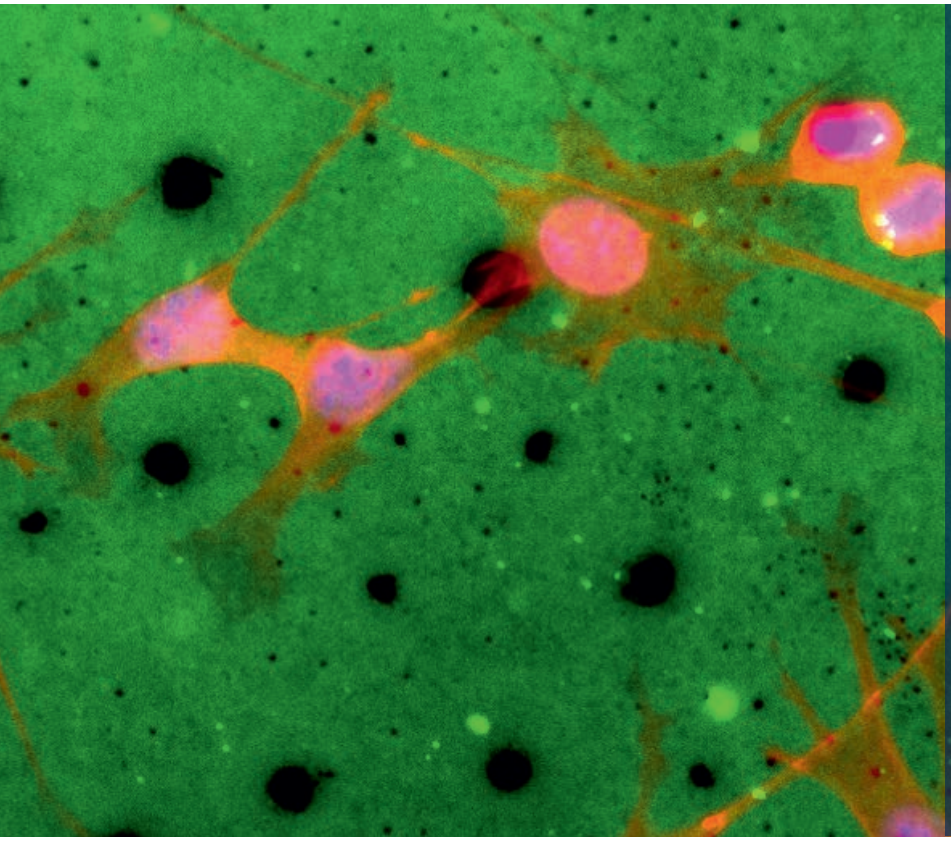


Figure 2. Disruption of Kmt2c/d specifically changes H3K27ac across distinct regions in the genome via altered KDM6A activity resulting in increased MMP3 expression. Pharmacologic inhibition of KDM6A prohibits this mechanism offering potential metastases prevention (adapted from Seehawer et al. Nat Cell Biol 2024).



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Li Z, Peluffo G, Stevens LE, Qiu X, **Seehawer M**, (…), Polyak K.
KDM4C histone demethylase connects redox balance to chromatin remodeling via CTSL-mediated histone H3 tail clipping, ***Nature Genetics*** *(2025)*

Seehawer M and Polyak K
Epigenetic driver of metalloproteinases and metastases, ***Trends in Cell Biology*** *(2025)*

DiCiaccio B, **Seehawer M**, (…) Polyak K.
ZBTB7A is a modulator of KDM5-driven transcriptional networks in basal breast cancer, ***Cell Reports*** *(2024)*

Seehawer M, Li Z, Nishida J, Foidart P, Reiter AH, Rojas-Jimenez E, Goyette M-A, Yan P, Gomez MM, Cejas P, Long HW, Papanastasiou M, Polyak K.
Loss of Kmt2c or Kmt2d drives brain metastasis via KDM6A-dependent upregulation of MMP3. ***Nature Cell Biology*** *(2024)*

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Cellular plasticity is also a major driver of therapy resistance. Under therapeutic pressure, many tumors undergo phenotypic shifts that enable them to evade treatment, ultimately leading to relapse or disease progression. Because epigenetic regulation can occur rapidly, it plays a central role in facilitating such plasticity. Therefore, combining conventional therapies with inhibitors of histone modifiers offers a promising strategy to prevent these adaptive escape mechanisms and thereby suppress therapy resistance. Moreover, perturbation of the epigenetic landscape through inhibition of histone modifiers may also uncover novel opportunities for synthetic lethality. To pursue this, we will employ both pre-selected drug combinations, guided by database analyses, and unbiased CRISPR-based screening approaches to identify effective therapeutic synergies and advance new treatment strategies (Figure 3).

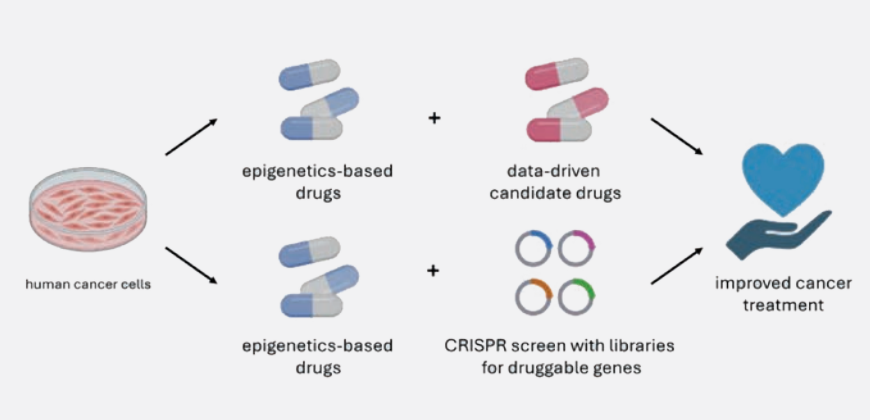

Figure 3. Schematic outline for targeted drug combination or unbiased drug perturbation CRISPR screens to identify epigenetic-based combination therapies (created with BioRender).

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Zelluläre Heterogenität als Schlüssel zur Verbesserung der Krebsbehandlung

Mapping cancer progression with data integration approaches

Cellular heterogeneity in cancer

Tumour initiation and progression

Methods for data integration

Cellular heterogeneity is a major barrier to cancer treatment. Variability in tumour cell states and microenvironmental composition between patients leads to differing treatment responses, while variability within a single tumour may indicate the presence of cell subpopulations able to survive therapy and drive recurrence and metastasis. Deciphering the roles of these different populations, and identifying opportunities to manipulate them for therapeutic advantage, remains a key challenge in cancer research.

Single-cell RNA-seq (scRNA-seq) has proven to be highly effective at illuminating cellular heterogeneity, providing the resolution needed to isolate individual cell types and expression states. However, due to cost and various technical considerations, individual scRNA-seq studies profile relatively few tumours (typically around 5 to 20) and usually lack comprehensive clinical annotations. Moreover, each scRNA-seq profile represents only a snapshot within a long timeline of tumour development. These challenges severely hinder the

Eine der größten Herausforderungen in der modernen Krebsforschung ist die sogenannte zelluläre Heterogenität – also die Vielfalt an Zelltypen und -zuständen innerhalb eines Tumors sowie zwischen verschiedenen Patientinnen und Patienten. Diese Vielfalt beeinflusst direkt den Therapieerfolg: Während manche Zellen auf die Behandlung ansprechen, können andere überleben, sich anpassen und so Rezidive oder Metastasen fördern. Besonders kleine Zellpopulationen mit speziellen Eigenschaften bleiben oft unentdeckt – und genau sie könnten entscheidend für den Krankheitsverlauf sein. Um diese verborgenen Mechanismen sichtbar zu machen, setzen wir auf Einzelzell-RNA-Sequenzierung (scRNA-seq). Damit lassen sich die molekularen Eigenschaften einzelner Tumorzellen hochauflösend untersuchen. Einzelne Studien liefern jedoch meist nur begrenzte Momentaufnahmen ohne umfassende klinische Informationen. Um die Zellzustände zu identifizieren, die das Fortschreiten von Tumorerkrankungen vorhersagen, braucht es deutlich größere, gut annotierte Datensätze über verschiedene Krankheitsstadien hinweg. Diese Herausforderungen erschweren die Bestimmung der Zellstadien, die den Krankheitsverlauf am besten vorhersagen. Die Integration vieler Datensätze verschiedener Stadien ist ein vielversprechender Weg, um diese Hürde zu überwinden. Unser Ziel ist es, die zellulären Veränderungen und Interaktionen entlang der gesamten Krankheitsentwicklung zu erfassen – von den ersten Schritten der Tumorentstehung bis zu fortgeschrittenen, wiederkehrenden oder metastasierenden Stadien. Dafür integrieren wir Einzelzelldaten aus zahlreichen Studien, Patientenkohorten und Krebsarten. So wollen wir Muster erkennen, die (i) bei vielen Patientinnen und Patienten reproduzierbar auftreten, (ii) krebsartenübergreifend konserviert sind und somit auf gemeinsame Schwachstellen hinweisen, (iii) prognostischen Wert besitzen und neue therapeutische Ansatzpunkte aufzeigen.
Zusätzlich erweitern wir unsere Analysen durch räumliche Transkriptomik und Bildgebung, um nicht nur die Zelltypen selbst, sondern auch ihre Lage im Gewebe und ihre Wechselwirkungen im Tumormikromilieu besser zu verstehen.
Mit diesem multimodalen Ansatz wollen wir grundlegende Prinzipien der Krebsbiologie entschlüsseln und gleichzeitig neue therapeutische Fenster identifizieren – mit dem Ziel, personalisierte und wirksamere Behandlungsstrategien für Patientinnen und Patienten zu entwickeln.

power of individual scRNA-seq datasets to identify the cellular states most relevant to cancer progression. Integration of many datasets of different disease stages is a highly promising way to overcome this.

I previously led the development of the Curated Cancer Cell Atlas, a collection of over 120 scRNA-seq datasets comprising over 2800 tumour samples and over 5.6 million cells (Gavish et al., *Nature*, 2023; Tyler et al., *Nature Cancer*, 2025; Fig.1).

With its unrivalled size, this database marked a milestone in computational cancer research, and enabled us to systematically identify robust cell states and commonalities between cancer types. We identified, for example, a

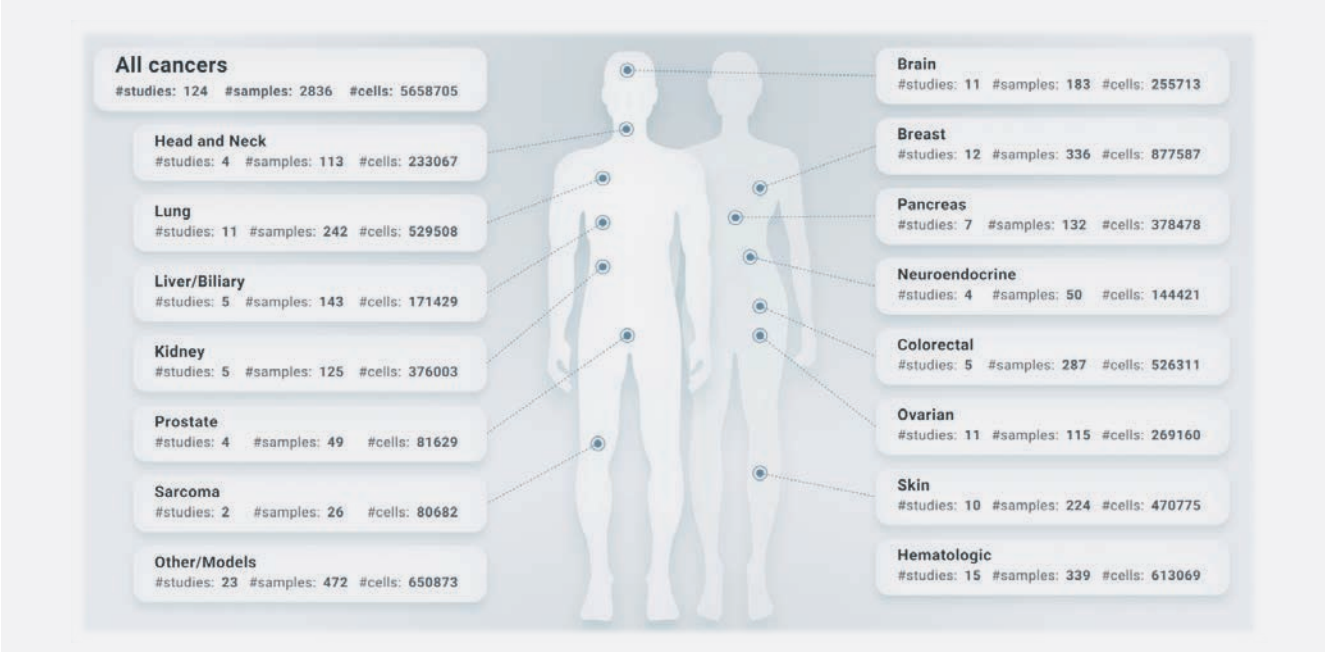
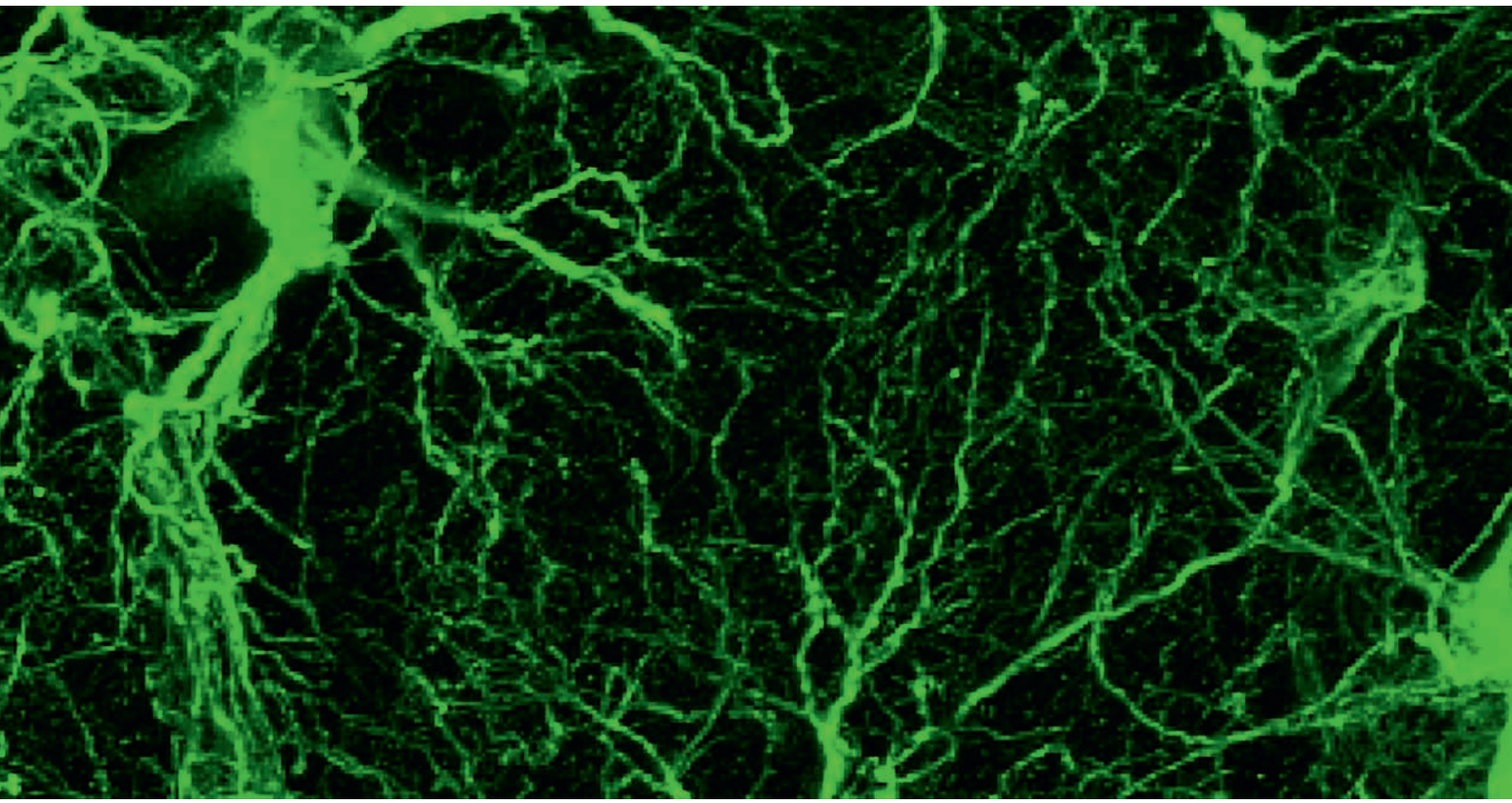


Figure 1. **The Curated Cancer Cell Atlas** (3CA). A repository of published tumour scRNA-seq datasets from 124 studies, curated into a consistent format with verified cell annotations.



mucin-related program that is common to multiple cancer types and correlates with specific mutations in a context-dependent manner. We also identified multiple states resembling epithelial-mesenchymal transition (EMT), confirming EMT as a ubiquitous yet heterogeneous element of cancer (Fig. 2), consistent with our previous work (Tyler and Tirosh, *Nature Communications*, 2021). We also exploited this data resource to fully characterise the variability in cell cycle across cancer types, revealing a large variation in proliferation rates (Fig. 3) and patterns of phase bias linked to mutations in the *TP53* and *RB1* genes.

Despite its utility, 3CA contains mainly primary tumour samples, and as a result, our analyses did not comprehensively capture the full spectrum of cancer stages. Moreover, scRNA-seq is blind to the spatial arrangement of tumours, and elucidating the role of morphology and interactions in the tumour microenvironment requires integration with other data types. Thus, we are still far from a complete understanding of the tumour timeline, and the cellular processes occurring in malignant transformation, treatment response and metastasis remain largely opaque. Filling in these knowledge gaps will transform our ability to make precise and effective clinical interventions in cancer.

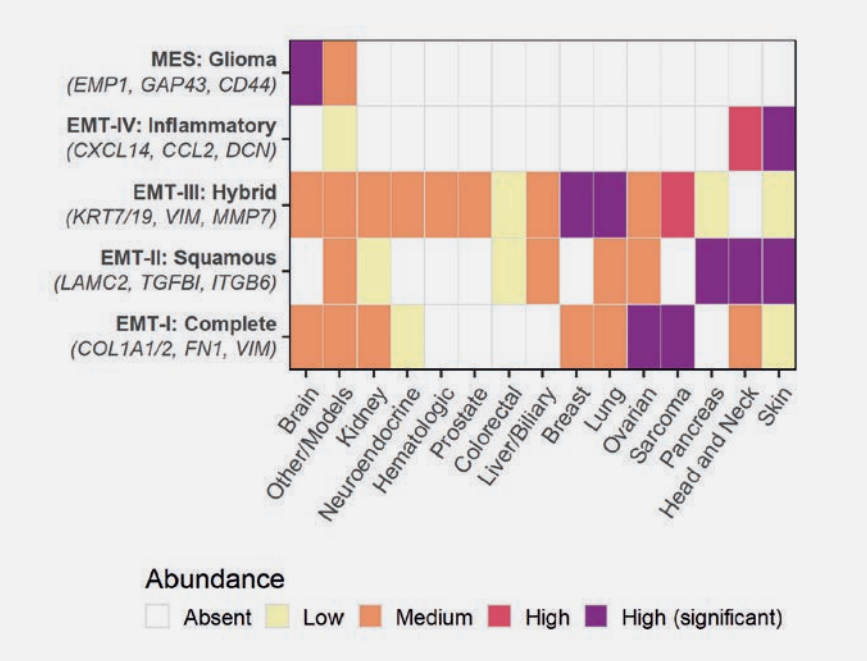
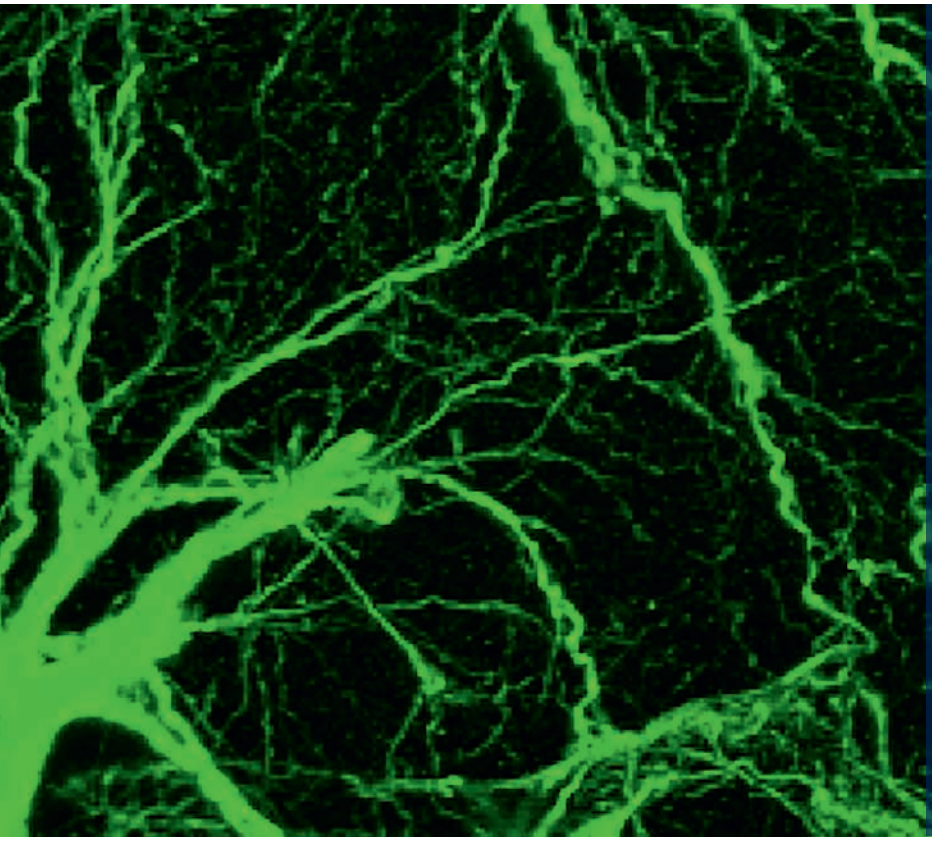


Figure 2. **Extent of EMT-like states in different cancer types.** Pan-cancer expression analysis identified 5 context-specific mesenchymal cell states with different signature genes. This demonstrates that EMT-like states are detectable in every cancer type in some form.



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Tyler M, Gavish A, Barbolin C, Tschernichovsky R, Hoefflin R, Mints M, Puram SV, Tirosh I.
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Hallmarks of transcriptional intratumour heterogeneity across a thousand tumours. ***Nature*** *(2023). doi.org/10.1038/s41586-023-06130-4*

Tyler M and Tirosh I.
Decoupling epithelial-mesenchymal transitions from stromal profiles by integrative expression analysis. ***Nature Communications*** *12, 2592 (2021). doi.org/10.1038/s41467-021-22800-1*

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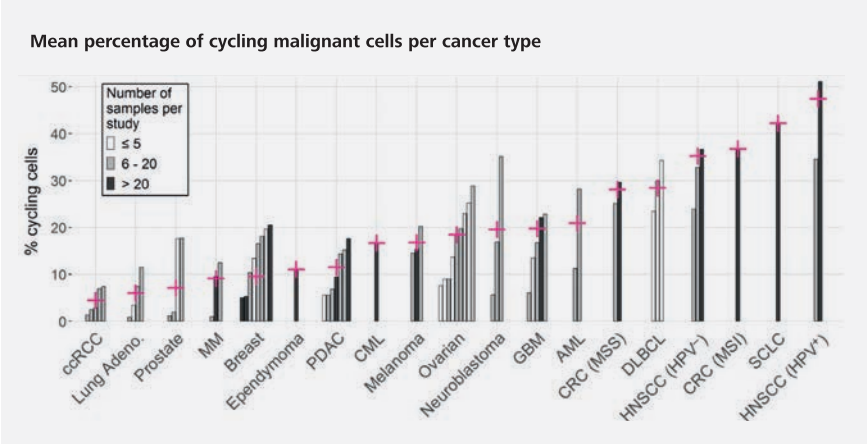

Figure 3. **Pan-cancer quantification of proliferation rates with 3CA.** Bar plot showing the percentage of cycling malignant cells in each study and cancer type. This revealed large variation in proliferation rates between cancer types.

Research objective

The goal of my lab is to elucidate the changes in cell states and interactions that define the progression of cancer along its full timeline, from the earliest stages of malignant transformation all the way to recurrent and metastatic disease. To achieve this, we will first construct a pan-cancer, multi-modal atlas of tumour progression of an unprecedented scale. We will integrate 3CA with published scRNA-seq datasets for normal tissue, premalignant disease and advanced cancer stages, and further deepen this by incorporating spatial transcriptomics and high-resolution imaging data, in order to fully capture microenvironmental relationships. We have already assembled an archive of 290 published datasets, which not only enables our systematic analysis but also highlights research gaps that warrant further profiling efforts, including with premalignant lesions and post-treatment recurrent tumours.

After building this data atlas, we will then develop new methods that compare expression patterns and spatial properties across many patients, cancer types and disease stages, in order to recover changes that are (i) robustly detectable across patients, thus likely to reflect true biology and not technical effects; (ii) conserved across multiple cancer types, suggesting common therapeutic vulnerabilities; and (iii) predictive of disease progression and suggestive of new treatment opportunities. We will further develop a computational framework to map between different data types, including data from scRNA-seq and various spatial transcriptomic and proteomic technologies. With these multimodal comparisons, we will uncover general principles of cancer development and reveal new therapeutic opportunities for improved cancer treatment.

II

Experimentelle Therapie
Experimental Therapy

Zentrale Einheit Transgenic Core und Regulation des Genoms

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Transgenic Core Facility and Genome Regulation

lncRNAs

genome editing

biomedical mouse models

Genetically engineered mouse models (GEMMs)
The CRISPR/Cas9 technology has revolutionized the generation of mouse models and Knock-out (KO) mouse models and is now a central tool for all kinds of genome modifications. The combination of CRISPR with homology-directed targeting for insertion of short sequences directly into the genome (Knock-in, KI) opens additional opportunities in generating biomedical relevant mouse models. In addition, novel approaches for targeted and reversible gene inactivation will further expand the possibilities of generating mouse models for biomedical research. TCF also offers strain conservation and rederivation systems to import new mouse strains from other researchers. In addition, the mouse facility and its database were partially managed by Phillip Grote, until a new head of the animal facility start towards the end of 2025.

The design of the desired genome modification is the fundamental first step in generating any GEMM and a most relevant biomedical mouse model. The desired genetic modification should evoke

Die CRISPR/Cas9-Technologie hat die Erzeugung von Mausmodellen revolutioniert und ist heute das zentrale Werkzeug für Genomveränderungen. In Kombination mit homologiegesteuertem Targeting (Knock-in, KI) ermöglicht sie präzise Insertionen und erweitert die biomedizinische Forschung. Neuartige reversible Geninaktivierungen eröffnen zusätzliche Anwendungen. Die TCF entwickelt, erhält und importiert Mausstämme und integriert kontinuierlich neue Gen-Editing-Techniken.

Mit der TCF-Toolbox lassen sich Knock-outs, Punktmutationen und präzise Deletionen innerhalb von 3–6 Monaten erzeugen. Komplexere Targeting-Strategien für Transgene benötigen bis zu 18 Monate. Neue Systeme erlauben die reversible Kontrolle von Proteinabbau durch kleine Moleküle.

CRISPR/READI und i-GONAD ermöglichen größere oder maternale Genomveränderungen ohne Tierversuche zu erhöhen. Diese Methoden reduzieren Tierzahlen und erfüllen internationale Richtlinien.

Besonderes Augenmerk gilt lncRNAs, die zunehmend als Regulatoren des Genoms erkannt werden. Ihre zelltypspezifische Expression macht sie zu interessanten pharmakologischen Zielmolekülen. Durch gezielte Ausschaltung einzelner lncRNAs (z. B. *Handsdown*, *Sweetheart*) konnten wir ihre Bedeutung für die Genregulation zeigen. Aktuell stehen 135 in AML-assoziierten MSC-Zellen deregulierte lncRNAs im Fokus unserer Forschung.

minimal damage to the normal function of the genome with minimal to none off-target effects. To achieve this a deep knowledge of the genome is required. The complex integration of gene editing techniques is the next important step in the GEMM generation process. The constant development of new applications for the CRISPR system expands the toolbox for gene editing rapidly and any relevant new tool is imported to TCF.

The current toolbox of the TCF allows *ab initio* development of simple gene knockouts by deletion approaches (Fig 1A), point mutations, patient alleles, precise small and large deletions (>10kb), and protein truncations. These approaches usually deliver mouse models within 3-6 months. The next level approach is to employ CRISPR/Cas9 to allow targeted integration of short genetic elements. This can allow the tagging of proteins of interest or marking a gene of interest for subsequent deletion by a CRE recombinase driver line (Fig 1B). Such approaches require prior optimizations and will usually require 4-8 months.

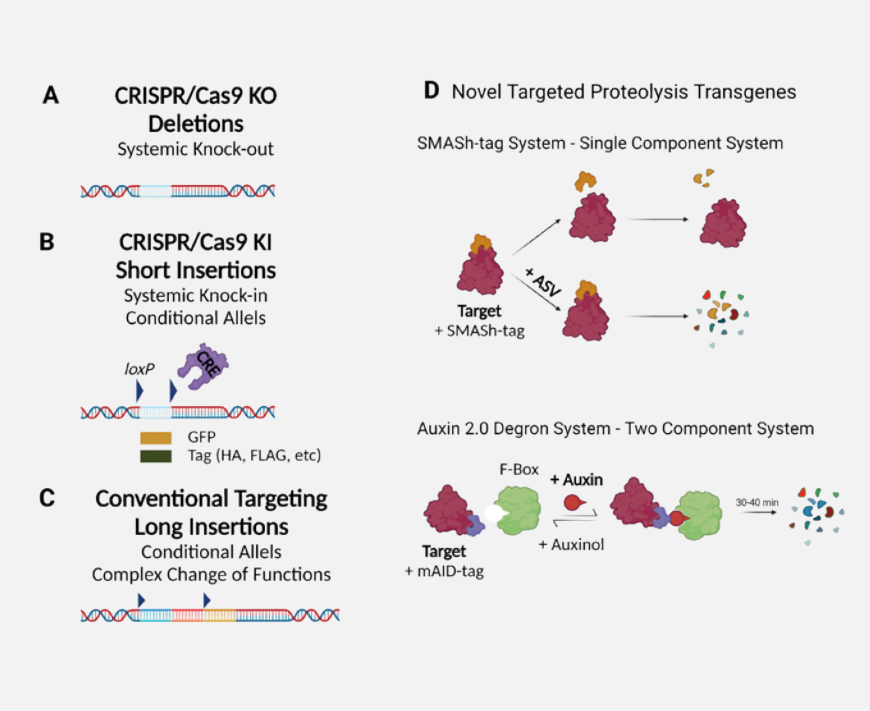
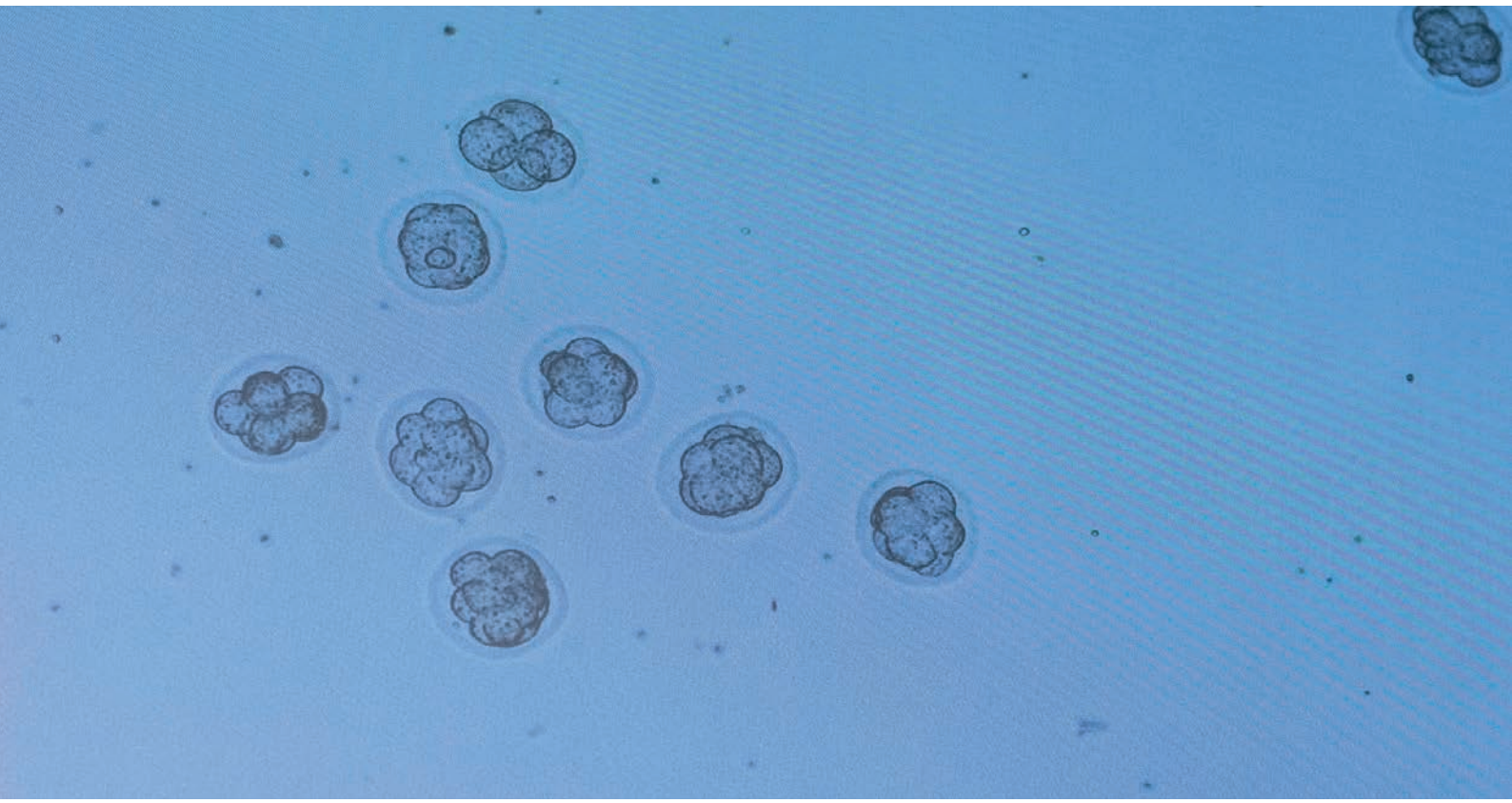


Figure 1.
(**A**) CAS9 directed gene deletion from several basepairs up to the megabase range that is usable for all techniques shown in Fig 2. (**B**) CAS9 assisted integration of short ~80 bp genetic elements specific at most sites of the genome. This approach is also available for all techniques shown in Fig 2. (**C**) Complex transgenes (>4000bp) require the modification of embryonic stem cells prior to mouse generation (Fig2 top two techniques). (**D**) The Auxin system is derived from plants and allows the degradation of the tagged protein of interest when the Auxin drug is present (administered) and the F-box protein (OsTIR1) is available. The second component (OsTIR1) makes this system versatile as this can be directed only to be present in certain cell types of interest. Created with BioRender.com



Standard targeting approaches for complex transgenes can take from 6-18 months (Fig 1C). The expansion of the TCF toolbox with additional mouse strain development will allow us to establish targeted degradation approaches for any protein of interest. In these systems a protein of interest is tagged (see Fig 1B) with short peptide that can bind a small molecule drug. The binding of this drug can induce protein degradation and removal of the drug from the mouse does allow the reappearance of the protein (Fig 1D). These approaches do open new possibilities for biomedical research.

The further development of the CRISPR toolbox also allows us to set up new methods for the generation of transgenic mice. The CRISPR-READI technology builds upon the technology to deliver CAS9 protein for target gene modification via zygote electroporation (Fig 2). Via electroporation one can only deliver short DNA elements for CAS9 assisted insertions at designated target site. CRISPR/READI uses AAV (Adeno-associates virus) particles to allow the delivery of larger DNA constructs (up to 4 kb) and into mouse zygotes for CAS9 assisted genome insertions. The method of i-GONAD allows short alterations of the genome in host mother animal, without the need so sacrifice them (i-GONAD) (Fig 2, bottom right) and is now used routinely at the TCF.

These novel techniques employing CRISPR/Cas9 allow the direct genetic modification of embryos of nearly any genetic background and even with preexisting genetic alterations. This technique will reduce the number of required animals for

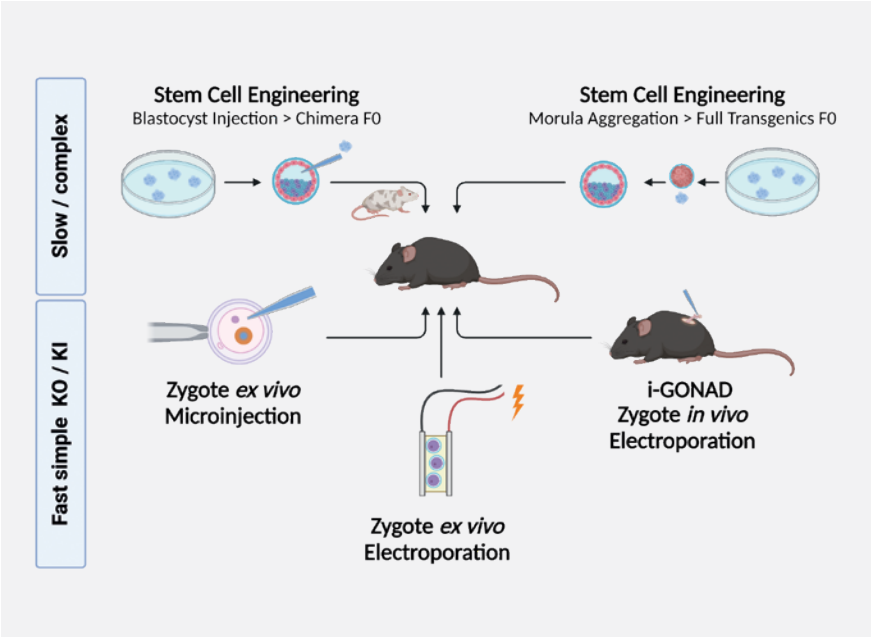
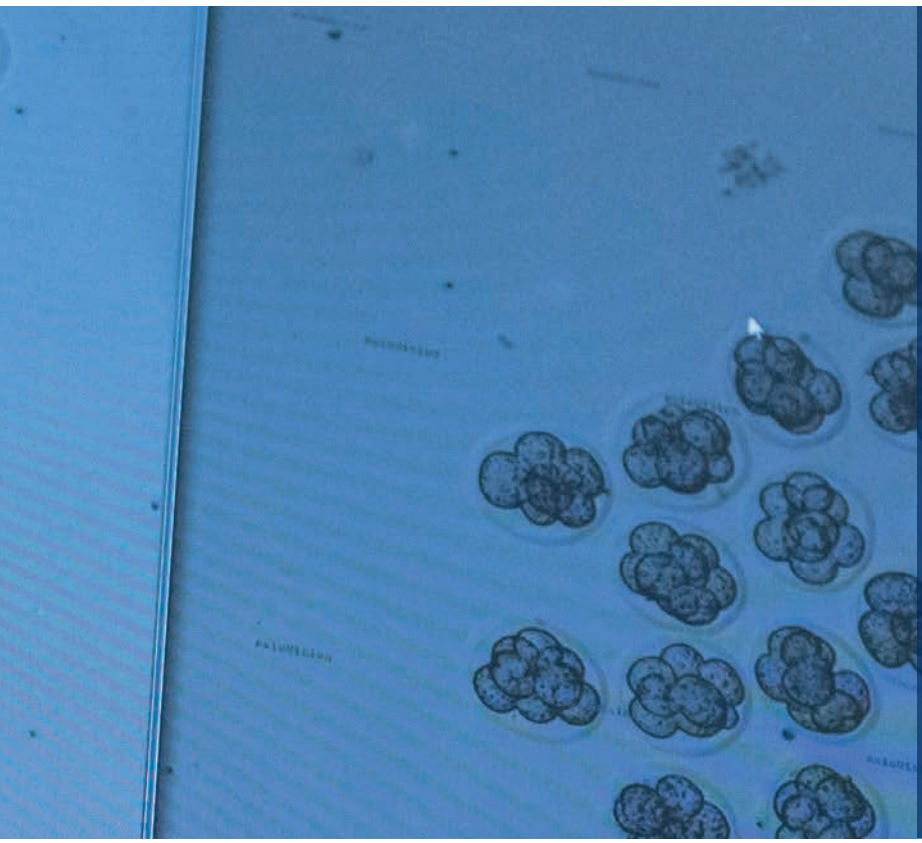


Figure 2.
Techniques for the generation of transgenic mice are available at TCF. The novel techniques of CRISPR-READI and i-GONAD are now established at the TCF. Created with BioRender.com



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Chen, S., Sun, S., Moonen, D., Lee, C., Lee, A.Y., Schaffer, D.V., and He, L. (2019). *CRISPR-READI: Efficient Generation of Knockin Mice by CRISPR RNP Electroporation and AAV Donor Infection.* ***Cell Rep*** *27, 3780-3789 e3784. 10.1016/j.celrep.2019.05.103.*

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generating mouse models drastically and thereby strictly follow the international guidelines for animal experiments to reduce animal numbers when possible.

The genome regulation group analyses the *in vivo* function of the gene category of long non-protein coding RNAs (lncRNAs), which are even more abundant than protein coding RNAs in the genome. These lncRNAs can participate in the fine tuning of gene regulation and thereby are important modifiers of genome activity and outcome. We published the *in vivo* role of the lncRNA *Sweetheart* in the response to acute myocardial infarction. We identified 135 lncRNAs that are dysregulated in mesenchymal stroma cells (MSCs) that are associated with acute myeloid leukemia (AML) cells (Figure 3A,B). We started to investigate them in detail. The lncRNA *FIBRR* seems to respond to extended exposure of MSCs cells to AML cells (Figure 3C) and causing a localization of the protein FBLN7 (Fibulin 7) in MSCs to attached AML cells in our co-culture system (Figure 3D).

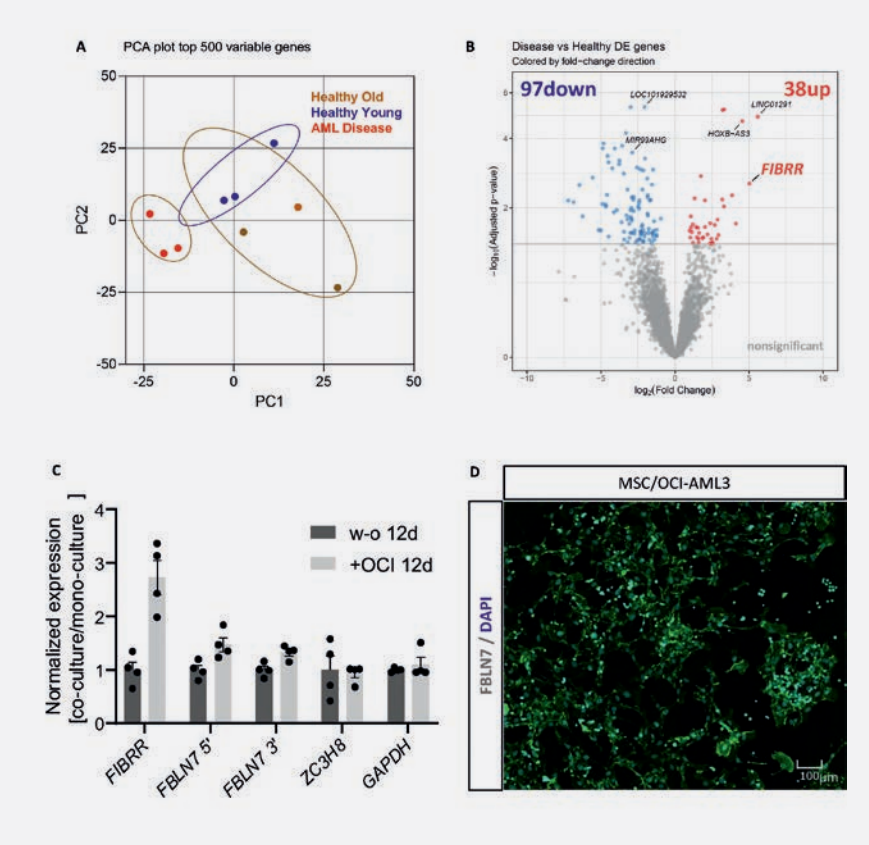

Figure 3.
Dysregulated lncRNAs in MSCs from AML patients (**A**,**B**) 135 lncRNAs are dysregulated (**C**) The lncRNA FIBRR is upregulated in MSC upon extended exposure to AML cells. (**D**) The FBLN7 protein localizes to co-cultured AML cells.

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Funktionelle Präzisionsonkologie

Functional Precision Oncology

To bridge the gap between genomic knowledge and clinical application, comprehensive functional information is needed to identify tumor-specific vulnerabilities. Our group advances **functional precision oncology** by performing ***ex vivo* drug response profiling (DRP)** on **patient-derived tumor cells** to complement genomic data, particularly when genomics fail to guide therapy or tumors are driven by non-genomic factors such as the microenvironment. By providing functional data at single-cell level, we aim to 1) elucidate cancer- and drug-induced phenotypes to discover new efficacies and repositioning opportunities, 2) identify biomarkers and mechanisms underlying drug response and resistance, and 3) directly translate results into clinical application.

In 2024/2025, we achieved significant progress in establishing, standardizing, and validating image-based ex vivo drug response assays and in elucidating mechanisms of therapy resistance in acute myeloid leukemia (AML).

Functional Precision Oncology

Ex vivo Disease Models

High-Content Imaging and AI-Assisted Single-Cell Analysis

Mechanistic Drug Resistance

Rational Combination Strategies

Funktionell-zielgerichtete Präzisionsmedizin bei Krebspatienten – von präklinischen *ex vivo* Studien zur klinischen Anwendung

Unsere Arbeitsgruppe „Functional Precision Oncology" entwickelt experimentelle und bioinformatische Ansätze, um genomische Daten durch funktionelle Analysen zu ergänzen und patientenindividuelle Tumorvulnerabilitäten zu identifizieren. 2025 konnten wir entscheidende Fortschritte bei der Etablierung einer bildbasierten ex vivo Wirkstofftest-Plattform erzielen. Mit Förderung der Rolf M. Schwiete Stiftung wurde ein Hochdurchsatz-Spinning-Disk-Mikroskop (Opera Phenix Plus, Revvity) angeschafft, das nun das Herzstück unserer Forschung bildet. Damit wurden lebendzellbasierte Fluoreszenzassays an AML-Zelllinien etabliert und erste patientenabgeleitete Modelle zur realitätsnahen Abbildung der Tumorheterogenität entwickelt. Hierbei optimieren wir verschiedenste Kulturbedingungen im 2D als auch 3D Format. Parallel entstand eine KI-gestützte Einzelzell-Analyse zur präzisen Quantifizierung zellulärer Wirkstoffantworten.

Ein erster Screen von 135 Substanzen in AML-Zelllinien identifizierte potenzielle Wirkstoff-Repositionierungen und Kombinationsstrategien zur Überwindung von Venetoclax-Resistenzen, insbesondere durch MCL-1-Hochregulation. Aktuelle Arbeiten validieren diese Befunde in primären AML-Kulturen.

Zur Integration der umfangreichen Bild- und Funktionsdaten entwickelt das Team derzeit bioinformatische Analysepipelines und KI-basierte Bildauswertungen, um prädiktive Biomarker und kombinatorische Therapiestrategien zu identifizieren.

Establishment of predictive, image-based *ex vivo* disease models

To functionally characterize tumor-specific vulnerabilities, we are developing advanced *ex vivo* models using patient-derived AML samples from adults and children. Our goal is to generate physiologically relevant short-term cultures that maintain tumor heterogeneity and viability while enabling high-throughput drug testing. To aim this, we optimize 2D and 3D culture protocols mimicking the tumor microenvironment, including cytokine-supported co-cultures, to enhance ex vivo survival and study mechanisms of drug resistance.

With support from the Rolf M. Schwiete Foundation, we installed an automated high-throughput confocal spinning-disk microscopy system (Opera Phenix Plus, Revvity) equipped with an integrated stacker and incubator, forming the core of our imaging platform. This system is used to multiplex live-cell imaging combined with AI-assisted single-cell analysis to assess drug efficacy in AML. Using the MOLM-13 cell line, we developed a robust workflow integrating live-cell dyes (Hoechst, Annexin V, TMRE) with supervised machine learning for automated classification of viable, apoptotic, and dead cells. This scalable, phenotype-resolved 384-well Drug Response Profiling (DRP) workflow is currently being validated in primary AML samples and expanded with immunophenotypic markers to resolve cellular subpopulations and their drug sensitivities.

Functional studies on venetoclax resistance and combinatorial treatment strategies

In parallel, we investigated mechanisms of resistance to the BCL-2 inhibitor

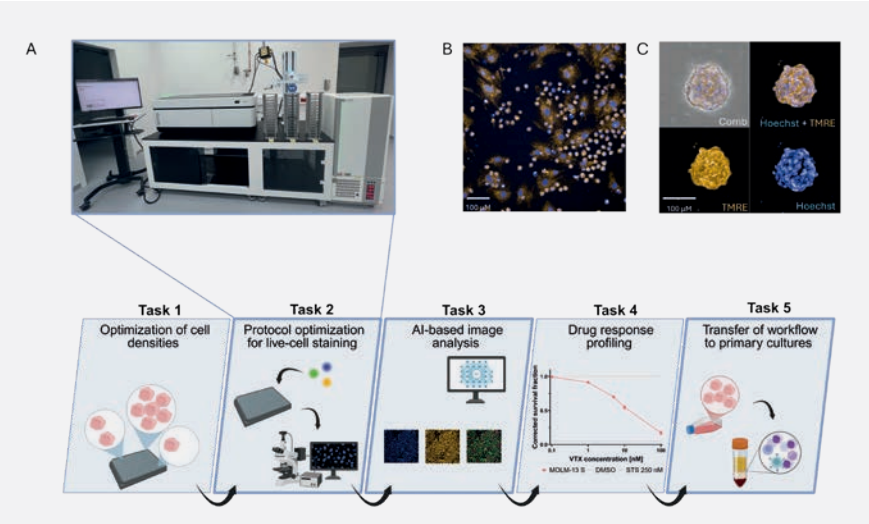
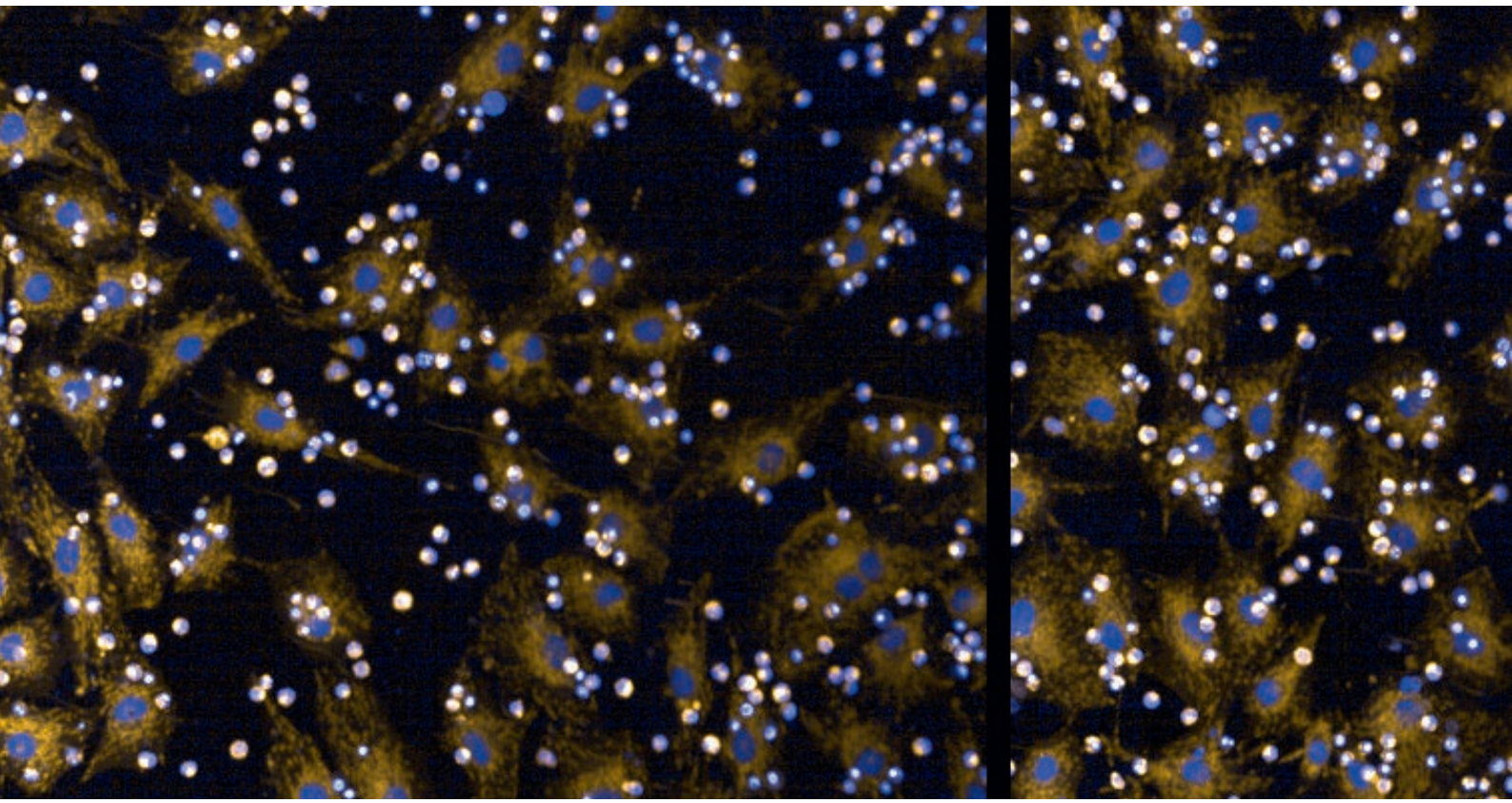


Figure 1. **Optimization and translation of an image-based workflow enabling drug response profiling in AML.** (**A**) Confocal spinning-disc microscopy (Opera Phenix Plus, Revvity). (**B**) Co-culture of MSCs and AML cells imaged by Opera Phenix; nuclei and mitochondrial potential were visualized using Hoechst (blue) and TMRE (orange), respectively. (**C**) Representative MSC spheroids imaged by Opera Phenix, stained with Hoechst (blue) and TMRE (orange).



venetoclax (VTX) in AML and identified rational combinatorial treatment strategies to overcome resistance. Sensitive (MOLM-13 S), BCL-2 G101V mutant (MOLM-13 G), and VTX-resistant (MOLM-13 VR) cells were analyzed using live-cell imaging (Hoechst, Annexin V, TMRE) and CellTiter-Glo assays. Western blotting revealed MCL-1 upregulation in resistant cells, indicating compensatory anti-apoptotic signaling. Dose-response curves showed ~1000-fold reduced sensitivity in resistant lines (IC50 ≈ 5 µM) versus sensitive MOLM-13 cells (IC50 ≈ 5 nM).

To identify potential therapeutic vulnerabilities, we performed a high-throughput screen of 135 compounds as mono- and combination treatments (± VTX at IC_{25}), using a library provided by the Structural Genomics Consortium (SGC). This library includes highly characterized and high-quality chemical probes from industry donations, now screened for repositioning opportunities. The initial screen identified eight compounds reducing cell viability as single agents across all tested AML models and some promising candidates that overcome VTX resistance in BCL-2 G101 V mutant AML cells. Validation studies extend to multiple concentrations, synergy matrices, additional AML lines, and primary blasts. Alongside protein-level resistance analyses, we integrate phenotypic imaging with molecular profiling to study drug-induced cellular and organelle changes. Future DRP experiments on primary AML samples using our oncology-focused drug library aim to advance clinical translation with FDA/EMA-approved drugs, novel targeted agents, and clinical phase II/III candidates.

Current developments and future directions:

We advance automated bioinformatic pipelines to quantitatively evaluate mono- and combination drug responses, integrating functional, molecular, and multi-omics data (ElHarouni et al., *Pharmacol. Res.*, 2022). This framework supports identification of cancer subtype–selective combinations and predictive biomarkers, providing a basis for precision medicine trials, including future basket studies. Concurrently, we enhance high-content

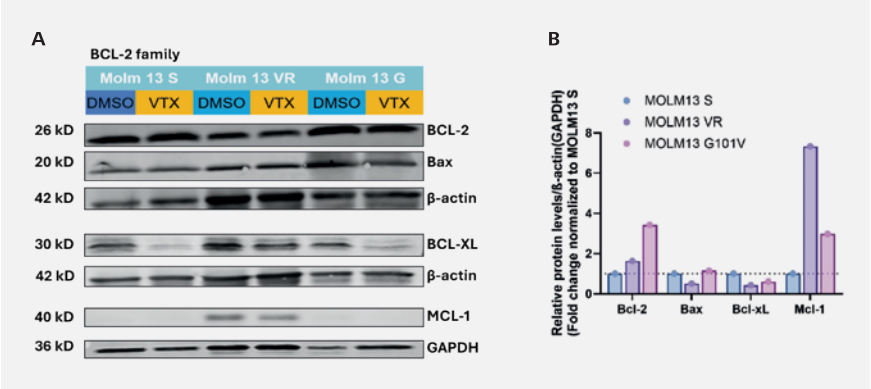
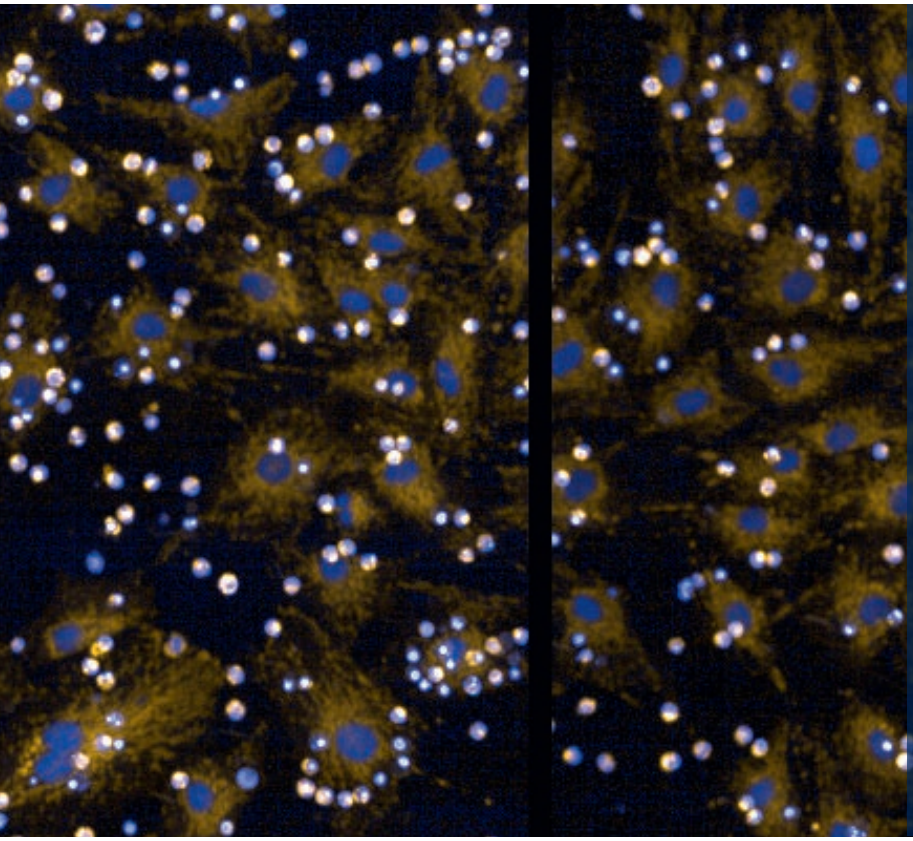


Figure 2. **Protein expression in MOLM13 S, VR, and G101V cells.** (**A**) Western blot of BCL-2 family proteins in MOLM13 S, VR, and G101V cells after DMSO or IC_{50} VTX treatment. The graph shows the fold change in relative protein levels, normalized to β-actin or GAPDH. (**B**) The graph shows the fold change in relative protein levels, normalized to ß-actin and DMSO of MOLM13 S (dotted line).



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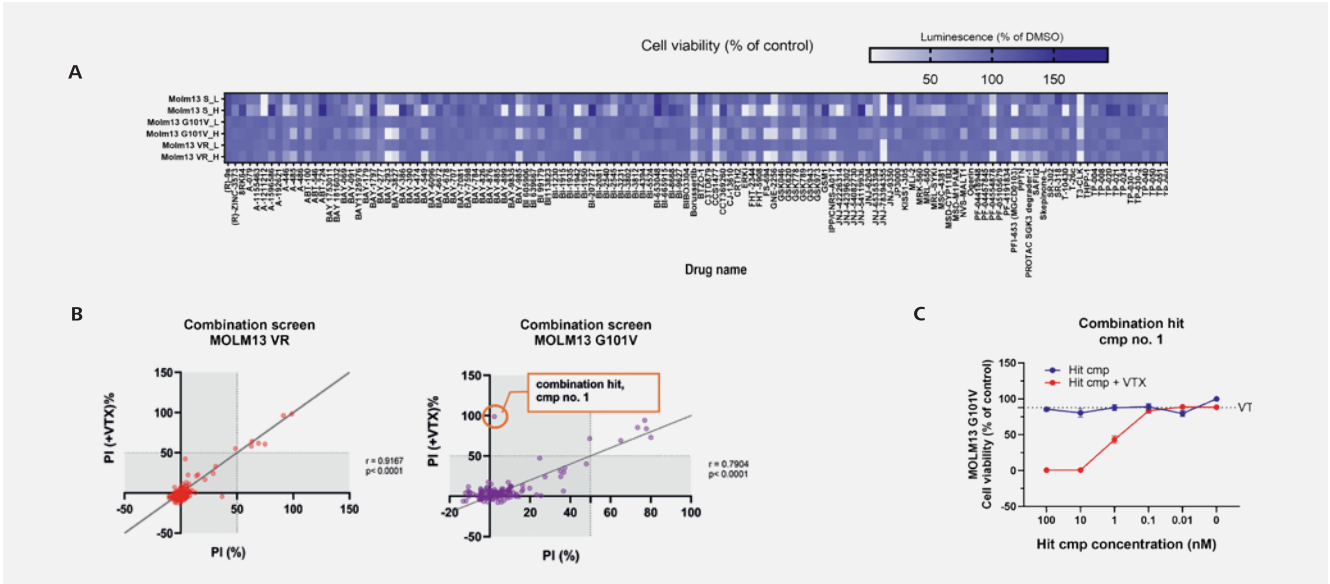

Figure 3: **TACTIC/DCP compounds or combinations screen.** (**A**) High-throughput drug screening heatmap showing cell viability (shown as normalized luminescence signal) of respective MOLM cell lines (S, VR, G) towards 135 compounds in 2 concentrations (L: 0.1 µM and H:10 µM). (**B**) 135 compounds ± VTX (IC25) in MOLM13 VR and G101V cells. (**C**) Cell viability of MOLM13 G101V cells after cmp no 1 as single agent (blue line) and in combination with VTX.

2D and 3D phenotypic image analysis using AI and deep learning. Multi-fluorescent live-cell assays capture single-cell phenotypes, enabling classification of drug responses, subpopulation-specific effects, and cell death mechanisms. Building on our deep transfer learning framework for patient-specific viability prediction prediction (Berker et al., *IEEE Trans. Med. Imaging*, 2022), these pipelines are expanded in collaboration with bioinformatics and AI partners. Together, these approaches create an integrated experimental and computational platform for functional precision oncology, facilitating mechanistic insights, discovery of novel drug combinations, and clinical translation of image- and AI-driven predictive assays. The group is fully affiliated with the Division of Clinical Pharmacy, FB 14, Institute of Pharmacology and Clinical Pharmacy, Goethe University Frankfurt.

Die Bedeutung der Tumormikroumgebung für eine nachhaltige Krebsbekämpfung

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Systems Biology of Breast Cancer in Drug Response

Tumor microenvironment

Integrative model systems

Spatial multi-omics

Therapy Resistance

Breast Cancer

Recent integration of tumor devices and high-dimensional computational data from mouse mammary carcinoma studies re-enforced the concept that cancer neighborhood (local tumor microenvironment; TME) can determine long-term therapy efficacy (Tatarova et al., *Nature Biotechnology*, 2022). We hypothesize that achieving durable control will require systematic treatment approaches that will i) prevent ''rewiring'' that enables therapeutic escape, ii) block resistance mechanisms that result from bidirectional interaction with the TME and iii) reactivate and enhance immune surveillance. Novel strategies will be needed to counter all of these mechanisms via administration (of series) of drug combinations while avoiding systemic toxicities that would reduce quality of life (Tatarova, *Nature Reviews Cancer*, 2024). The latter is particularly important since treatment may extend over months to years. In the promising era for combination anti-cancer therapeutics, tools to rapidly predict rational immune- and TME-modulating combination treatments on personalized basis are still critically missing.

Krebs ist eine vielschichtige Erkrankung, deren Vielfalt die Wirksamkeit therapeutischer Ansätze maßgeblich beeinflusst. Jüngste Mausstudien zum Brustkrebs, die lokal implantierbare Wirkstofffreisetzungssysteme mit computergestützten Auswertungen kombinieren, zeigen: Die unmittelbare Tumorumgebung spielt eine entscheidende Rolle für den Erfolg einer Therapie. Unserer Ansicht nach ist ein tiefgehendes Verständnis sowohl der Krebsbiologie als auch der Tumormikroumgebung notwendig, um i) eine therapeutisch ungünstige Umprogrammierung zu verhindern, ii) Resistenzmechanismen effektiv auszuschalten und iii) das Immunsystem gezielt zu aktivieren und seine Überwachungskapazität zu stärken. Um den komplexen Schutzmechanismen des Tumors entgegenzuwirken, bedarf es innovativer Therapieansätze, insbesondere durch Kombination verschiedener Behandlungsformen. Gleichzeitig müssen unerwünschte systemische Nebenwirkungen und Langzeittoxizitäten vermieden werden, da die Therapiedauer oft mehrere Monate bis Jahre beträgt und die Lebensqualität stark beeinflussen kann. Unser Ziel ist es, durch den Einsatz modernster biotechnologischer und computergestützter Methoden den Einfluss der Tumormikroumgebung bei Brustkrebs und anderen Tumorarten besser zu verstehen, um so neue therapeutische Strategien zu entwickeln. Dies wird die Identifikation standardisierter Biomarker und wirksamer Kombinationsbehandlungen ermöglichen und so zur langfristigen Krankheitskontrolle beitragen.

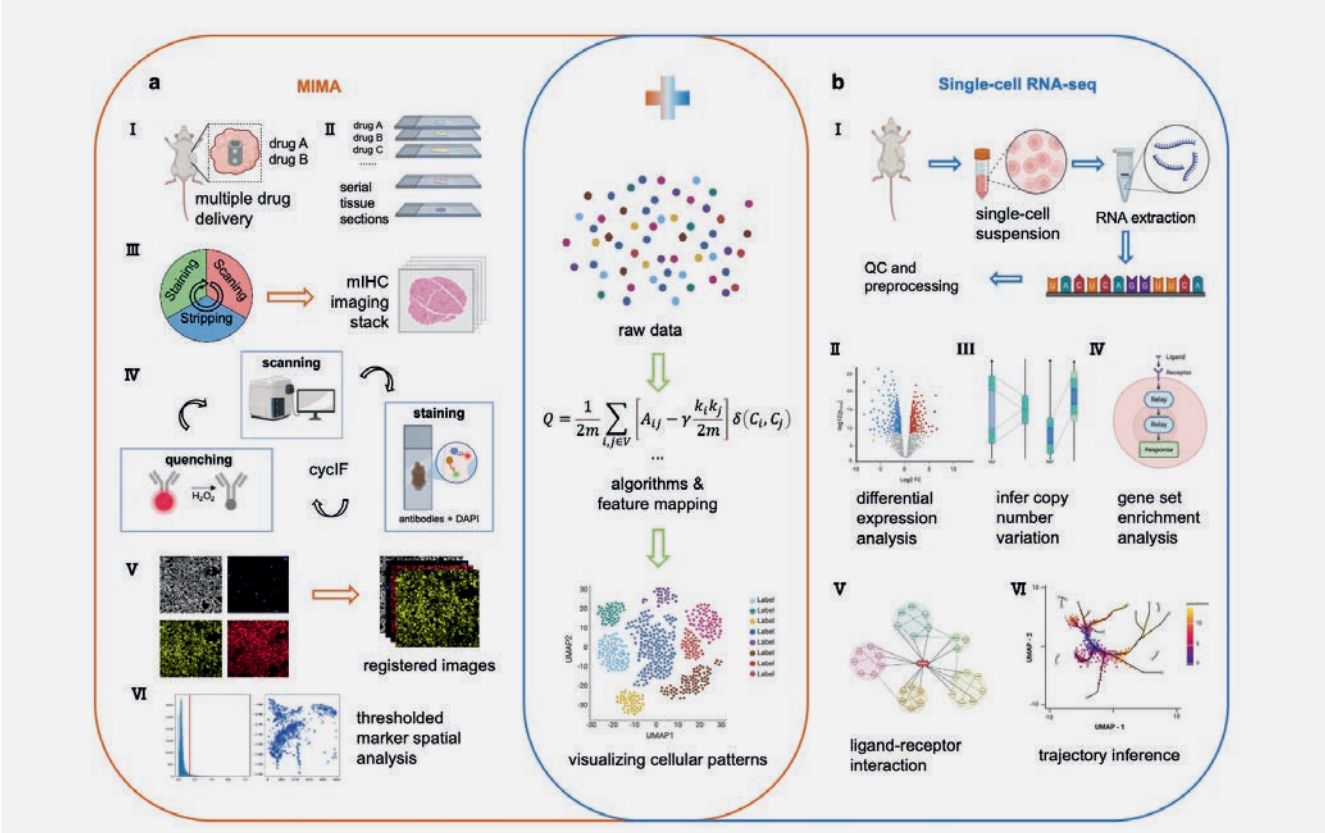
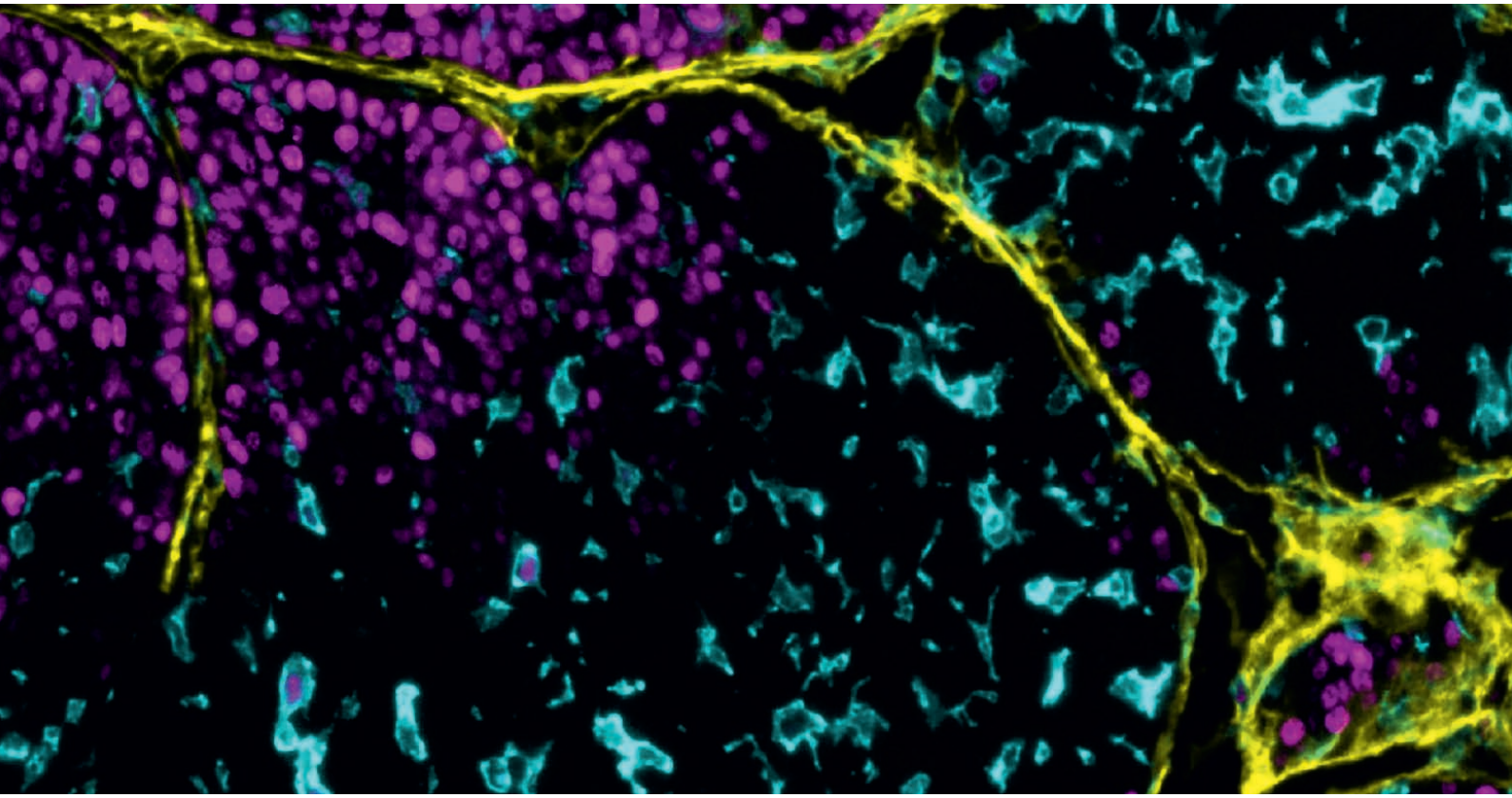


Figure 1. **Workflow integrating multiplex imaging and single-cell RNA sequencing. a,** MIMA: An implantable microdevice (I) releases localized nanodoses into tumors. After sectioning (II), tissues undergo cyclic staining, image registration and spatial marker analysis (III–VI), enabling spatial marker analysis with supervised and unsupervised methods (center). **b**, scRNA-seq: Tumors are dissociated and sequenced (I), followed by clustering, differential expression, copy number, cell–cell interaction, enrichment, and trajectory analyses (II–VI). Schematics partly created with BioRender.com.

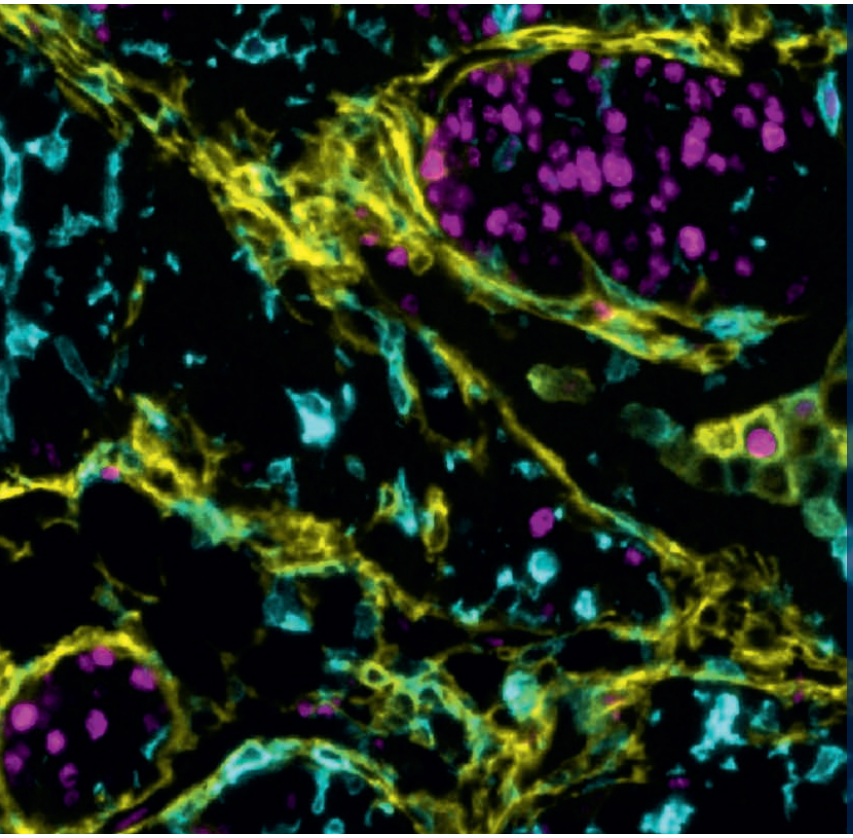


Using systems biology approaches, our laboratory develops and identifies the most promising integrative computational and bioengineering tools to decompose tumor microenvironment complexity in luminal breast cancer ultimately leading to discovery of new (i) standardized biomarkers with predictive value and (ii) effective combinations of immune- and conventional therapies.

The cellular composition of and the interactions in the TME influences all stages of cancer progression, including mediation of therapy resistance. Recent studies implementing MIMA revealed molecular and architectural signatures that predicted combining targeted anti-cancer agent panobinostat with anti-PD1 checkpoint blockade to be effective in breast cancer, though emerging resistance limited the long-term efficacy. We expanded on these early spatial observations and found that cancer stem cells, and CD8 T cells embedded in high-density collagen, along with cells of invasive front, contributed to evasion of drug treatment over time. Multiple cell types were implicated in tissue desmoplasia and matrix breakdown, including drug-enriched activated cancer-associated fibroblasts. We hypothesized that combination with non-immune stroma normalizing drug could improve the immunotherapy outcomes, and this triple therapy delayed disease progression in a mouse model of breast cancer. Our findings highlight the molecular and spatial cellular diversity driving resistance in mammary carcinoma while proposing novel biomarkers that might achieve improved specificity in clinical setting.

Further, we combined the multiplex implantable microdevice assay with single-cell RNA sequencing (Figure 1) to dissect the molecular mechanisms underlying treatment resistance and immune modulation in breast cancer. Our findings demonstrate that combining panobinostat (a pan-HDAC inhibitor) and venetoclax (a BCL-2 inhibitor) enhances intratumoral immune infiltration, particularly of neutrophils, macrophages, and dendritic cells. Further, the addition of anti-CD40 myeloid-compartment immunotherapy amplifies tumor cell killing, reprograms the immune cells to promote anti-tumor immunity. Notably, this triple therapy effectively reduces cancer stem cells, with the remaining population expressing class I MHC, highlighting potential vulnerabilities for immune targeting. By integrating advanced analytical approaches, our work provides a promising framework for overcoming treatment resistance in breast cancer and underscores the potential of the triple-drug regimen in targeting cancer stem cells by reshaping the tumor microenvironment.

Therapeutic resistance hinders the efficacy of single-agent cancer treatments, often mediated by the TME. Significant endothelial cell enrichment following local doxorubicin treatment has been proposed as a resistance mechanism in breast cancer (Tatarova et al., *Nature Biotechnology*, 2022). We applied the tumor vasculature normalization principle using an anti-angiogenic drug combination delivered locally using the high-throughput MIMA in mouse models of breast cancer. Spatial single-cell proteomic profiling paired with unsupervised learning methods confirmed doxorubicin-mediated pro-angiogenic changes, including pericyte detachment and sprouting angiogenesis. A combina-



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Köse H, Schneeweis C, Putze P, Contreras CT, Ferreiro L, Witte L, Deidda I, Herzberg F, Ebert S, Jakubik J, Moldaner L, Todorovic J, Träger I, Zang C, Demel UM, Hessmann E, Kirchner M, Rhein S, Hoffmann J, **Tatarova Z**, Ghadimi M, Saur D, Kappert K, Mertins P, Schneider G, Keller U, Wirth M.
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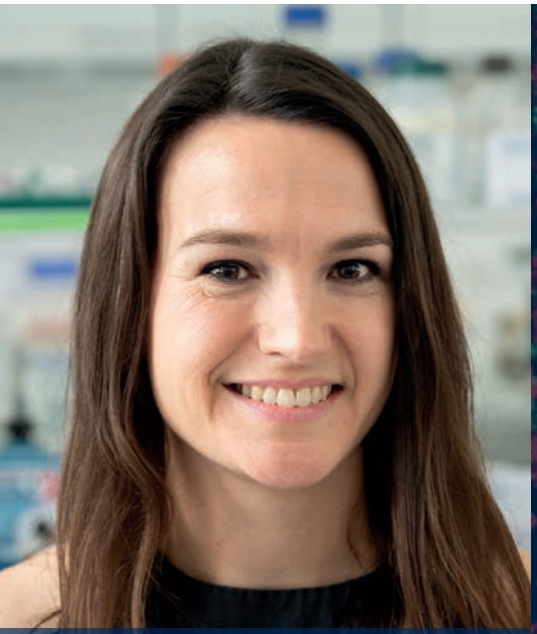
tion with cabozantinib depleted endothelial cells and increased tumor antigenicity by inducing immunogenic cell death with recruitment of leukocytes including neutrophils, and T cells. Leveraging this immune modulatory activity, we tested a systemic triple combination with anti-PD1 immunotherapy, which led to a significant and complete tumor regression. Our study demonstrates a rational drug combination that improves doxorubicin efficacy to overcome microenvironment-driven resistance for long-term breast cancer control.

After successful establishment of the Cyclic immunofluorescence (cycIF) method in the laboratory we continue performing the highly multiplexed protein staining and analysis, enabling simultaneous detection of numerous markers on a single histological tissue sample. The method involves iterative rounds of staining, imaging, and target inactivation, allowing for a comprehensive analysis of cellular phenotypes and tissue architecture. We apply cycIF to mouse and human tissues using approximately 65 distinct antibodies that are tested for specificity, sensitivity, target localization, and biological function maintaining the accuracy and reliability of the ongoing longitudinal studies. The successful translation of this technique to human samples promises to expand its utility, providing a powerful tool for detailed cellular and molecular investigations as has been shown by fruitful collaborations.

In summary, we prototyped the use of MIMA by testing FDA approved drugs (targeted anti-cancer agents and chemotherapies) in mouse models of breast cancer and discovered spatial association predictive of immune and non-immune stroma targeting therapy efficacy. Some of the most effective combinations have not been previously reported. Integrations of the implantable device with other modalities such as transcriptomics, metabolomics and electron microscopy map cellular, architectural and molecular features. Development of these integrative systems can serve as a template when translating the tool to clinical practice in breast, and possibly other cancer types. Use of the novel single cell spatial omic techniques will identify actionable cellular axes which will open novel opportunities in in silico modeling and might ultimately help to identify effective treatment strategies in individual cancer patients.

Events: In April 2025, the Tatarova Laboratory of Therapy Resistance warmly welcomed colleagues and visitors during the **"Explained by GSH Colleagues"** tour. This event provided an insightful look into the cutting-edge research of the lab focused on tumor devices unraveling the complex tumor organization and boosting immunotherapy effectives. The core themes of the research were translated into five languages, helping to engage the international audience of the GSH. Additionally, **Boys' Day at the GSH: One day in a biology lab** was organized by Leoni Moldaner. Students of the Martin-Niemöller-Schule in Riedstadt had the opportunity to dive into cancer biology research working in a lab environment ultimately fostering a balanced representation in the field.



Immunregulatorische Mechanismen in der Tumormikroumgebung und Therapieresistenz

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Immunoregulatory mechanisms in the tumor microenvironment and resistance to therapy

Tumor microenvironment

Cancer immunotherapy

Resistance mechanism

Metastases

Immunosuppression

Advances in cancer treatment have stemmed from understanding oncogenic signaling, the tumor ecosystem, and cancer immunobiology. Targeted therapies lead to, in some tumor types, remarkably high clinical responses, but are often followed by relapse. Conversely, immunotherapies, particularly checkpoint inhibitors, have revolutionized cancer treatment by producing long-lasting responses through the activation of anti-tumor immunity, albeit only in a subset of patients. The complex and dynamic interactions within the tumor microenvironment (TME) between cancer cells and their surrounding ecosystem drive tumor progression, enabling tumors to evade immune detection and develop innate or acquired resistance mechanisms to therapies. Understanding this intricate cellular communication and the barriers within the TME is essential for designing effective combinatorial anti-cancer. Non-responsiveness to immunotherapies often stems from the presence of various immunosuppressive mechanisms that cancer cells employ to evade detection and destruction by the immune system. These barriers include immunoinhibitory

Unsere Forschung untersucht, wie Krebs- und Stromazellen innerhalb der Tumormikroumgebung (TME) interagieren, um Barrieren zu errichten, die eine Umgehung des Immunsystems und Therapieresistenz ermöglichen. Wir konzentrieren uns darauf, Schwachstellen in suppressiven Immunzellen, insbesondere tumorassoziierten Makrophagen (TAMs), zu identifizieren und zu verstehen, wie deren Regulation Resistenz und Tumorrezidive fördert. Unser Ziel ist es, Mechanismen zu identifizieren, die die Tumorimmunität schwächen und diese Erkenntnisse in therapeutische Strategien umzusetzen.

Um die durch die Mikroumgebung vermittelten Mechanismen der Therapieresistenz und des Wiederauftretens von bösartigen Tumoren besser zu verstehen, untersuchen wir erworbene und angeborene Resistenzen, die mit Veränderungen in der Aktivierung von Makrophagen und ihren Effektoren verbunden sind, welche die T-Zell-gesteuerte Tumorimmunität als Reaktion auf Therapien und im Zusammenhang mit dem Metastasierungsprozess unterdrücken. Methodisch verwenden wir immunkompetente, gentechnisch veränderte Mausmodelle (GEMMs), die die Tumorentstehung, das Fortschreiten und die Therapieresistenz genau nachahmen, sowie ergänzende Ex-vivo-Systeme. Dazu gehören Co-Kulturen von murinen und humanen Immunzellen mit Tumorzellen oder deren Sekretomen/extrazellulären Vesikeln sowie organotypische Kulturen. Zusammen bieten diese Ansätze einen robusten Rahmen für die Identifizierung von Zielmediatoren und Signalwegen, stromalen Schwachstellen und die Entwicklung von Reprogrammierungsstrategien zur Induktion immunstimulierender Signale innerhalb der TME. Neben diesen funktionellen Ansätzen führen wir umfassende „Omics"-Profilierungen durch, um Mediatoren der Immunsuppression und Therapieresistenz zu identifizieren.

Schließlich analysieren wir in Zusammenarbeit mit Klinikern Patientenproben und bestehende Datenbanken. Durch die gegenseitige Filterung von Erkenntnissen aus Maus- und menschlichen Tumoren wollen wir umsetzbare Ziele aufdecken, die experimentell validiert und möglicherweise in neue Therapien umgesetzt werden können.

signals, corrupting resident and recruited immunosuppressive cell populations, such as macrophages, myeloid cells, and regulatory T cells, as well as T cell exhaustion and dysfunctional angiogenic vasculature.

Research Program

Our research focuses on unraveling the complexity of the interaction between cancer and stromal cells in the tumor microenvironment (TME), as tumors build multiple barriers to evade immune destruction, leading to non-responsiveness to treatments. Indeed, cancer cells can corrupt the resident and recruited stromal cells, thereby supporting their tumor progression, metas-

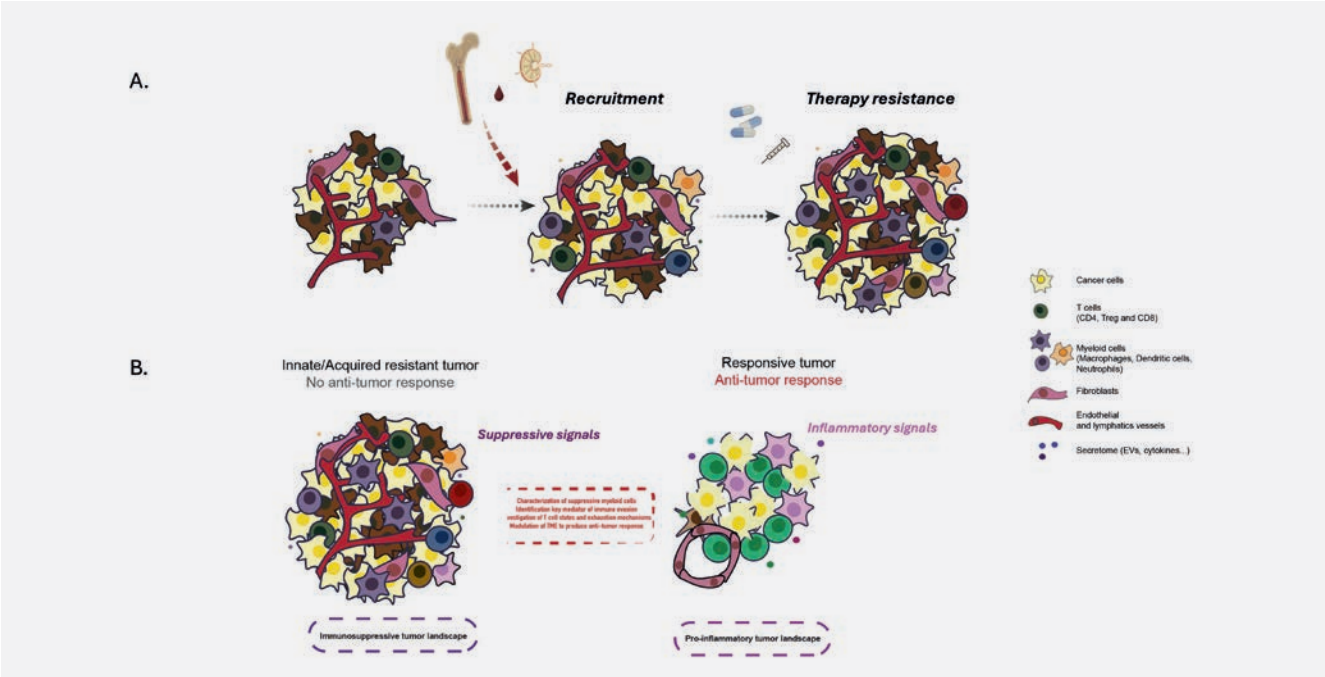
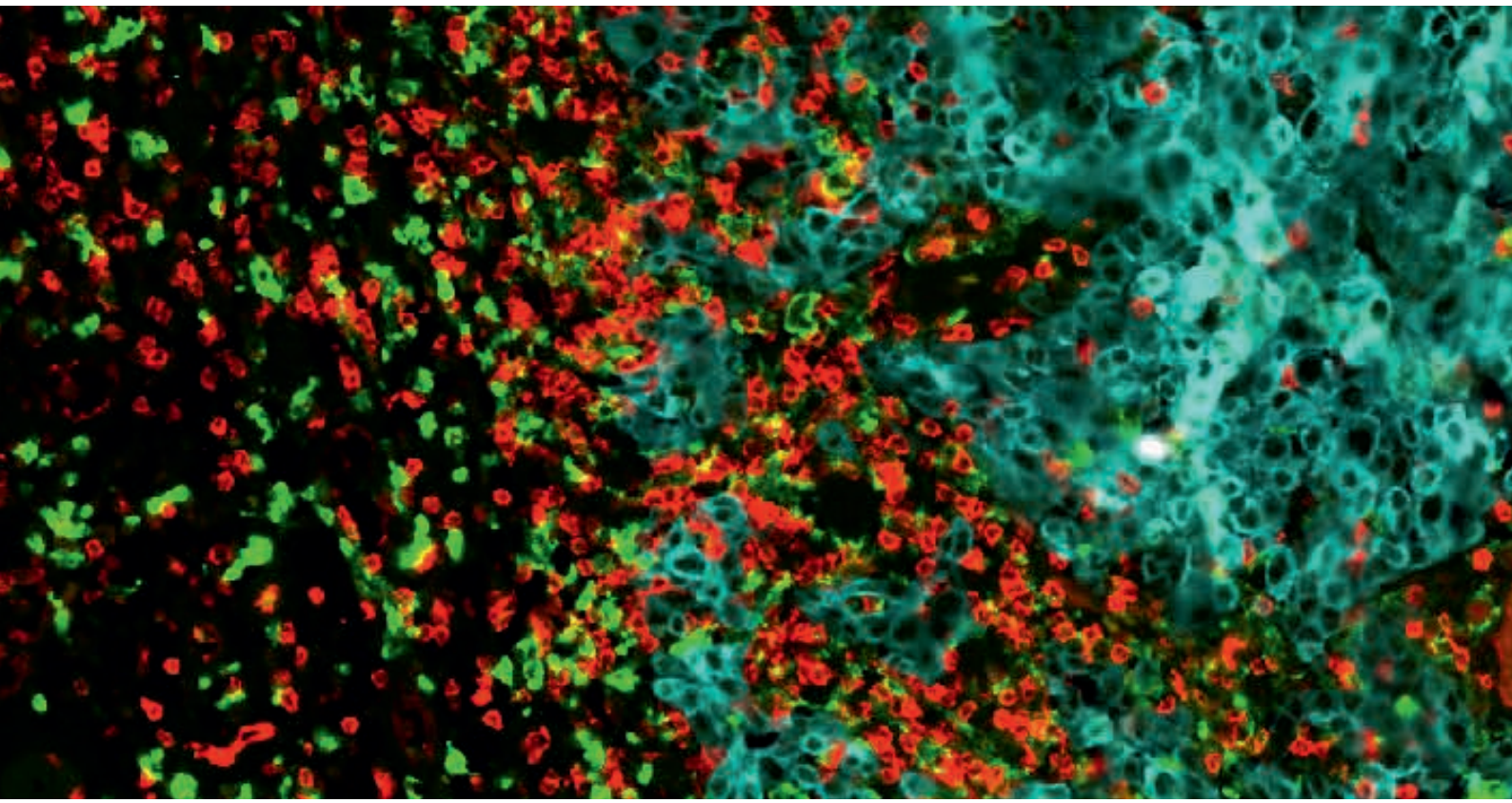


Figure 1. **Model summarizing the immunosuppressive vs the pro-inflammatory tumor microenvironment. A.** Tumors are complex ecosystems: Resident/recruited immune and stromal cells are silenced and/or corrupted to support cancer progression and therapy resistance. **B**. Suppressive TME, notably myeloid cells, limits T cell infiltration/activation, leading to non-responsiveness to immunotherapies. In the middle red box are all the axes to better understand suppressive TME and unleash anti-tumor responses.



tasis, and resistance to therapies (Figure 1). Therefore, we are exploring the roles and regulation of suppressive cell populations to identify vulnerabilities in cancer and stromal cell crosstalk that can be targeted therapeutically. To better understand the microenvironment-mediated mechanisms of therapeutic resistance and recurrence in malignancies, we are investigating acquired and innate resistances related to alterations in the activation of suppressive populations (e.g., tumor-associated macrophages) and their effectors in suppressing tumor immunity in response to therapies (Figure 2).

Mouse cancer models demonstrate the potential to both reveal functional and molecular mechanisms of resistance and serve as testing platforms for new therapeutic drugs and combinatorial strategies. Our laboratory's research program focuses on mouse models, in which oncogenes and tumor suppressor mutations predispose mice to develop organ-specific cancers. Importantly, tumorigenesis and the histological progression of tumors phenocopies the biology of human tumors. We are studying genetically engineered mouse models that develop cancers in several locations (the pancreas, the skin, and the brain). Our investigations have revealed that myeloid cells, especially tumor-associated macrophages (TAMs), are predominantly polarized toward a pro-tumoral "M2-like" phenotype producing inhibitory factors and exhibiting immunosuppressive capabilities, underlying their role in suppressing anti-tumor immunity (Figure 2). We assessed reprogramming agents that effectively convert immunosuppressive TAMs into pro-inflammatory, tumor-antagonizing macrophages upon combination with standard-of-care therapies, leading to T cell infiltration and mediating anti-tumor immunity and tumor destruction.

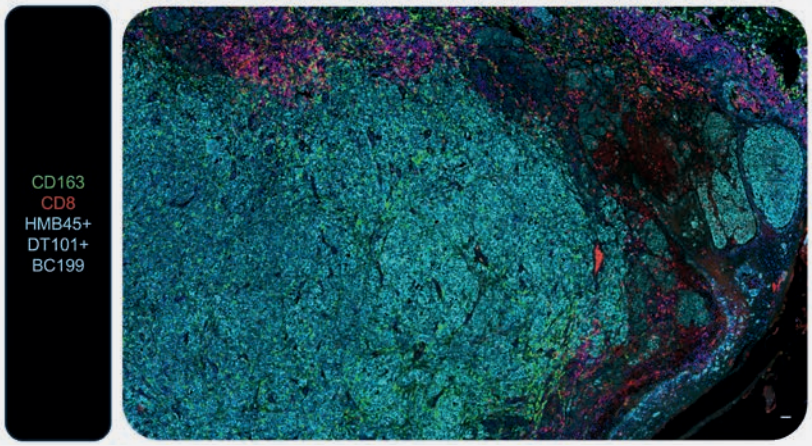
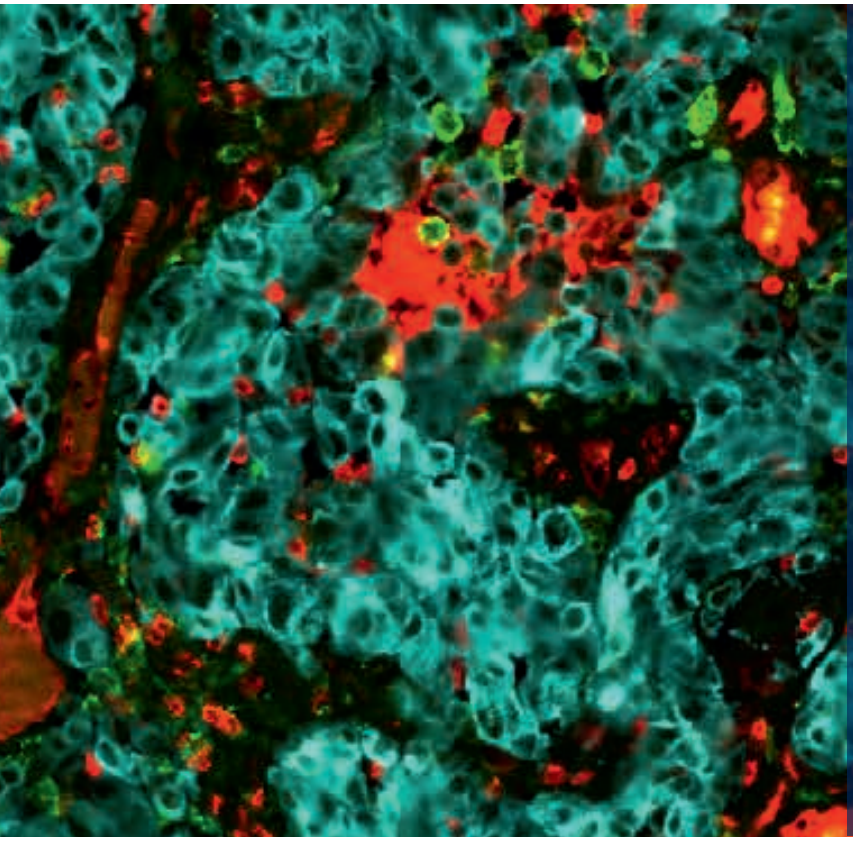


Figure 2. **Immunofluorescent image of a melanoma tumor from a patient resistant to immunotherapy.** IF staining for CD163 (TAMs - green), CD8 (CD8 T cells - red), and HMB45+DT101+BC199 (melanoma cells- cyan). Tumor is infiltrated with suppressive TAMs while CD8 T cells are excluded. Scale bar 50 µm.



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Bakiri L, **Tichet M**, Marques C, …, Hanahan, D, and Wagner EF (2025).
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Additionally, by utilizing integrative omics analyses, we have developed a gene signature for "suppressive TAM associated with therapy resistance" that was found to be significantly associated with non-response to ICB in melanoma patients and poor survival, supporting the concept of cross-resistance mechanisms. Spatial imaging further revealed the infiltration of these TAMs in resistant patient tumors.

Our projects, therefore, focus on the roles and regulation of suppressive cell populations to identify vulnerabilities in cancer and stromal cell crosstalk that can be targeted therapeutically. To better understand the microenvironment-mediated mechanisms of therapeutic resistance and recurrence in malignancies, we are investigating acquired and innate resistances associated with alterations in the activation of macrophages and their effectors to suppress T cell-driven-tumor immunity in response to therapies and in the context of the metastatic process. We also aim to understand the T cell biology and mechanisms of exhaustion and dysfunction induced by the suppressive TME to improve and sustain the anti-tumor response.

We are working with preclinical in vivo models, human and mouse ex vivo and in vitro cellular models, and “omic” analyses (Figure 3). We are investigating different mediators; once we identify the key ones involved in tumor evasion within the TME, we will develop refined GEMM models with cell-specific Cre-inducible systems and CRISPR editing to examine cell-dependent immunostimulatory mechanisms. Furthermore, we are studying cognate human tumors using available databases and patient samples enabled by clinical collaborations (omics analyses, multispectral imaging, and immunochemistry). By cross-filtering mouse and human tumors, we aim to identify actionable targets that are functionally validated preclinically, operative, and potentially translatable to the clinic.

Publikationen

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Deniz Sagir,
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Kathrin Diestel (Forschungspraktikum im Masterstudiengang „Molekulare Medizin" der Goethe Universität Frankfurt): *„Optimierung von CasRX/Cas13d zur Genmodulation in Darmkrebs Organoiden"* am 25.08.2025 - 02.10.2025

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Akademische Ausbildung
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Engineering adeno-associated virus (AAV) vectors for in vivo delivery of interleukin-18 (IL-18)
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AG Seehawer

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Reviews and Book Chapters

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Akademische Ausbildung

Idan Ben-Horin: *„Targeting non-small cell lung cancer with chimeric antigen receptor-engineered natural killer cells“*, Doktorarbeit im Fachbereich Biologie der Technischen Universität Darmstadt, 2025.

Jordi Pfeifer Serrahima: *„Development of NKG2D-specific killer cell engagers for cancer immunotherapy“*, Doktorarbeit im Fachbereich Chemie der Technischen Universität Darmstadt, 2025.

Maren Prüfer: *„Arming NK cells against leukemia and lymphoma with CARs and bispecific killer cell engagers“*, Doktorarbeit im Fachbereich Biologie der Technischen Universität Darmstadt, 2025.

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Die Abteilung Finanzen und Administration verantwortet jährlich ein Finanzvolumen von etwa 12 Millionen Euro und betreut dabei rund 100 Mitarbeitende. Sie wird seit Juli 2024 von Herrn Gernot Ruffing geleitet, der dabei von Herrn Robert Dornberger unterstützt wird. Besonderer Fokus der Administration liegt wie bei jeder Verwaltung auf den Themen Finanz- und Rechnungswesen, Controlling, Informationstechnologie, Digitalisierung & Forschungsdatenmanagement, Datenschutz, Gebäudemanagement, Einkaufsmanagement, Arbeitssicherheit, Nachhaltigkeit, Compliance, Diversity, Personalmanagement, Personalbindung und -entwicklung sowie der Vereinbarkeit von Beruf und Familie.

Frau Giuseppina Virgillito im Personalbüro bearbeitet alle Themen der Personalsachbearbeitung. Frau Belinda Gehrmann verantwortet das Personalmanagement und unterstützt den kaufmännischen Leiter bei allen administrativen Themen. Frau Ilka Grau bearbeitet in der Finanzbuchhaltung und Drittmittelverwaltung die Projektfördermittel des Bundes, der DFG, des Landes Hessen und allen weiteren Geldgebern. Herr Luca Fabisch ist verantwortlich für die Kreditorenbuchhaltung und Herr Lars Fischer unterstützt bei sämtlichen Aufgaben in der Finanzbuchhaltung. Frau Brigitte Huth ist für die Abrechnung der Reiskosten der Mitarbeitenden zuständig. Frau Dr. Alina Jurcoane ist die Ansprechpartnerin für alle Belange, welche die Drittmittel der Europäischen Union betreffen sowie die Graduiertenschule PEGS.
Für das Museum im Georg-Speyer-Haus und für die historischen Fragestellungen fungiert Herr Dr. Klaus Cußler als Ansprechpartner; er bietet regelmäßig Museumsführungen für Interessierte an.

Herr Adrian Gresik ist verantwortlich für die vielfältigen Aufgaben des Innendienstes und koordiniert gemeinsam mit Frau Hana Kunkel die anspruchsvollen Umbau- und Sanierungsvorhaben des Instituts. Das Team des Innendienstes mit Herrn Krzysztof Data und Herrn Heinrich Krompiec kümmert sich primär um die Gebäudetechnik und unterstützt zudem bei der Organisation von wissenschaftlichen Tagungen und Veranstaltungen. Ansprechpartner in der Telefonzentrale und am Empfang ist Herr Bernd Würdemann.

Frau Yasemin Piskin, Frau Lacramioara Pulpan und Frau Neriman Sarac sind u.a. für die Laborreinigung, die ordnungsgemäße Abfallentsorgung, Hygiene und Recycling im gesamten Haus sowie für die Laborbedarfsversorgung verantwortlich.

The Finance and Administration Department manages an annual financial volume of approximately 12 million euros and oversees around 100 employees. Since July 2024, it has been led by Mr. Gernot Ruffing, who is supported by Mr. Robert Dornberger. A key focus of the administration, as in any management structure, is on areas such as financial and accounting matters, controlling, information technology, digitization and research data management, data protection, building management, procurement management, occupational safety, sustainability, compliance, diversity, personnel management, employee retention and development, as well as work-life balance.

Ms. Giuseppina Virgillito in the personnel office handles all personnel-related matters. Ms. Belinda Gehrmann is responsible for personnel management and assists the commercial director in all administrative issues. Ms. Ilka Grau, working in financial accounting and third-party funds management, oversees project funding from the federal government, the DFG, the state of Hesse, and other funding bodies. Mr. Luca Fabisch is in charge of accounts payable, and Mr. Lars Fischer provides support with all tasks related to financial accounting. Ms. Brigitte Huth is responsible for the reimbursement of employee travel expenses. Dr. Alina Jurcoane serves as the contact person for all matters related to European Union third-party funds as well as the PEGS graduate school. Dr. Klaus Cußler is the contact person for the museum at the Georg-Speyer-Haus and for historical inquiries; he regularly offers museum tours for those interested.

Mr. Adrian Gresik is responsible for the diverse tasks of internal services and, together with Ms. Hana Kunkel, coordinates the institute's complex renovation and refurbishment projects. The internal services team, consisting of Mr. Krzysztof Data and Mr. Heinrich Krompiec primarily handles building technology and also assists with organizing scientific conferences and events. The contact person at the telephone switchboard and reception is Mr. Bernd Würdemann.

Ms. Yasemin Piskin, Ms. Lacramioara Pulpan and Ms. Neriman Sarac are responsible for cleaning the laboratories, ensuring proper waste disposal, hygiene, and recycling throughout the building, as well as supplying laboratory materials.

Wissenschaftlicher Service

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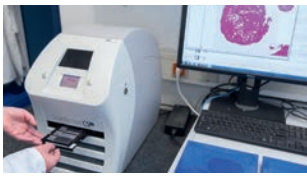
Zentrale Einheit Histologie
Zur Anfertigung von histologischen Präparaten betreibt das Georg-Speyer-Haus eine Histologie-Serviceeinheit unter der Leitung von Dr. Birgit Ritter. Hier werden von Frau Petra Dinse meist automatisiert die Gewebeaufarbeitung sowie immunohistochemische Färbungen und Standardfärbungen durchgeführt. Weiterhin verfügt das Labor über ein automatisiertes Präparate-Scanner- und Bildanalysesystem, Aperio ScanScope CS2, einen Färbeautomat Leica Autostainer XL, einen Leica BOND max sowie ein Lunaphore COMET zur Anfertigung von automatisierten Immunfärbungen.

Core Facility Histology
The Georg-Speyer-Haus operates a histology core facility. It is supervised by Dr. Birgit Ritter. Petra Dinse is responsible for the mostly automated procedures of tissue processing and immunohistochemistry as well as hematoxylin / eosin staining. The laboratory is equipped with a slide scanner and image analysis system, Aperio ScanScope CS2, a Leica AutostainerXL, a Leica BOND max and a Lunaphore COMET for automated immunostaining.



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Zentrale Einheit Durchfluss-zytometrie (FCU)
Die zentrale Durchflusszytometrie-Einrichtung (FCU) betreut drei Zellanalyse-Geräte (BD LSRFortessa, BD FACSCantoII, Cytek Aurora) und zwei Zellsorter (BD FACSAriaI, BD FACSAria Fusion). Zusätzlich werden in der Einrichtung ein Bioplex200 zur Multiplex-Analyse, ein ABC Blood Counter zur Blutzellanalyse und ein Chromium X zur Einzelzellanalyse betrieben.

Geleitet wird die Serviceeinheit von Dr. Stefan Stein, der auch Ansprechpartner für allgemeine Fragen zur Durchflusszytometrie und bei der Entwicklung und Anpassung neuer Mess- und Sortieransätze ist. Unterstützt wird er bei den anfallenden Hochgeschwindigkeits-Zellsortierungen durch Frau Annette Klemke (zurzeit vertreten durch Herrn Felix Kienzle). In einigen Fällen fungiert Herr Thorsten Geyer als zusätzlicher Operator am Fusion-Zellsorter.

Flow Core Unit (FCU)
The Flow Core Unit (FCU) of the Georg-Speyer-Haus operates three flow cytometer instruments (BD LSRFortessa, FACSCantoII, Cytek Aurora) and two cell sorters (BD FACSAriaI and BD FACSAria Fusion). In addition, the facility runs a Bioplex200 for multiplex analysis, an ABC Blood Counter for blood cell analysis, and a Chromium X for single cell analysis.

Dr. Stefan Stein manages the performance of the core facility and is available for scientific questions regarding flow cytometry in general and the establishment of new flow-based assays. He is supported by Annette Klemke (currently substituted by Felix Kienzle) for the high-speed cell sorting tasks. In some cases, Thorsten Geyer acts as an additional operator on the Fusion cell sorter.

Nachhaltigkeit
Zuständiger Ansprechpartner für alle Fragen rund um das Thema Nachhaltigkeit im Georg-Speyer-Haus ist Dr. Dominic Menger. Mit Hilfe der bestehenden „GSH Nachhaltigkeitsrichtlinien" wird jedem Mitarbeitenden ein Dokument zur Verfügung gestellt, welches ein nachhaltigeres Handeln der Belegschaft begünstigen soll. Darüber hinaus unterweist Dr. Dominic Menger alle Mitarbeitenden und berät sie bei Nachhaltigkeitsfragen, sowohl innerhalb des Labors als auch bei der täglichen Arbeit.

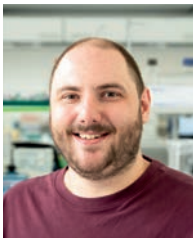
Zentrale Einheit für Bildgebung
Die Zentrale Einheit für Bildgebung (ICF) bietet sowohl Mitarbeitenden des Georg-Speyer-Hauses als auch externen Nutzer*innen Zugang zu modernsten Bildgebungsgeräten. Die ICF am Georg-Speyer-Haus ist ausgestattet mit einem 7T-MRT-Gerät für Kleintiere (BioSpec 70/16, Bruker), einem In-vivo-Bildgeber mit Computertomographie (IVIS Spectrum CT, Revvity), einem Lichtblattmikroskop (Ultramicroscope Blaze, Miltenyi), einem Spinning-Disc-Konfokalmikroskop (CQ1, Yokogawa), einem Laser-Scanning-Konfokalmikroskop (SP5, Leica) und einer Vielzahl von Fluoreszenz-/Lichtmikroskopen (z. B. AxioImager, Zeiss). Weitere Arbeitsstationen mit Softwaretools stehen zur Verfügung, darunter Imaris (Oxford Instruments), CellPathFinder (Yokogawa) und Living Image (Revvity).

Dr. Dominic Menger ist für die Schulung, Koordination und Wartung verantwortlich. Er ist der Ansprechpartner für alle Anfragen im Zusammenhang mit den Bildgebungsgeräten sowie für Beratung zu Versuchsaufbauten, der Entwicklung neuer Analysepipelines und allgemeinen Fragen zur Bildgebung. Am MRT wird Dr. Dominic Menger in Teilzeit von Marco Lolies unterstützt, der für die routinemäßigen Messungen für interne und externe Nutzer zuständig ist.

Sustainability
Dr. Dominic Menger is the contact person responsible for all questions relating to sustainability at Georg-Speyer-Haus. With the help of the existing "Green GSH Guidelines", every employee is provided with a document that is intended to promote more sustainable action by the workforce. In addition, Dr. Dominic Menger instructs all employees and advises them on sustainability issues, both within the laboratory and in their day-to-day work.

Imaging Core Facility
The Imaging Core Facility (ICF) is offering access to state-of-the-art imaging equipment for both Georg-Speyer-Haus staff and external users. The ICF at Georg-Speyer-Haus is equipped with a small animal 7T MRI (BioSpec 70/16, Bruker), an in vivo imager with computed tomography (IVIS spectrum CT, Revvity), a light-sheet microscope (Ultramicroscope Blaze, Miltenyi), a spinning disc confocal microscope (CQ1, Yokogawa), a laser scanning confocal microscope (SP5, Leica) and a variety of fluorescent/light microscopes (e.g. AxioImager, Zeiss). Further image processing stations with software tools are available, including Imaris (Oxford Instruments), CellPathFinder (Yokogawa) and Living Image (Revvity).

Dr. Dominic Menger is responsible for the training, coordination and maintenance. He is the designated point of contact for all enquiries related to the imaging equipment, as well as for advice on experimental set-up, the development of new analytical pipelines and general imaging-related queries. At the MRI, Dr. Dominic Menger is supported part-time by Marco Lolies, who is responsible for taking care of routine measurements for internal and external users.



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IT
Dirk Haas leitet die IT. Er nimmt die zentralen Tätigkeiten der Unterstützung der Mitarbeitenden des Hauses in allen Fragen der IT, der Serverbetreuung, des IT-Projekt Managements, der Netzwerkadministration und des Einkaufs war.

IT
Dirk Haas heads IT. His main tasks are the maintenance of the servers, IT project management, administration of the networks, and the support of the colleagues in the institute.

Dr. Stefan Stein
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Geräte und Biologische Sicherheit
Dr. Stefan Stein berät bei der Beschaffung der nötigen wissenschaftlichen Arbeitsgeräte. Außerdem kümmert er sich als Beauftragter für biologische Sicherheit (BBS) um die Arbeitssicherheit und ist zuständig für die Kommunikation mit den entsprechenden Aufsichtsbehörden.

Devices and Biological Safety
Dr. Stefan Stein attends for lab equipment and devices. As biosafety officer (BBS), he is responsible for biological safety at the institute and for communication with respective authorities.

Dipl. Biol. Thorsten Geyer
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Arbeitssicherheit und Strahlenschutz
Thorsten Geyer ist am Institut die Fachkraft für Arbeitssicherheit und berät die Mitarbeitenden und verantwortlichen Gruppenleitungen in allen Belangen des betrieblichen Arbeitsschutzes. Als Strahlenschutzbeauftragter ist er für die Organisation der entsprechenden Einrichtungen und die Kommunikation mit den Aufsichtsbehörden zuständig.

Occupational safety and radiation protection
Thorsten Geyer is the specialist for occupational safety at the institute and advises the employees and responsible group leaders in all matters relating to occupational health and safety. As radiation protection officer, he is responsible for organizing the relevant facilities and communicating with the supervisory authorities.

Hana Kunkel
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Hygiene- und Labormanagement
Hana Kunkel ist verantwortlich für das institutsweite Labor- und Hygienemanagement inklusive Laborausstattung. Weiterhin koordiniert sie im Team mit Adrian Gresik die gesamten Renovierungs- und Umbaumaßnahmen des Georg-Speyer-Hauses, um modernste Forschung im denkmalgeschützten Institut zu ermöglichen.

Facility- / Lab Management
Hana Kunkel is responsible for institute-wide laboratory and hygiene management, including laboratory equipment. Together with Adrian Gresik she coordinates all renovation and remodeling work at the Georg-Speyer-Haus, enabling state-of-the-art research to be conducted at the institute, which is a listed building.

Wissenschaftsmanagement
Dr. Sandra Schmitz ist für den Bereich Wissenschaftsmanagement verantwortlich. Zu ihren Aufgaben gehören insbesondere die Koordination wissenschaftlicher Verbundprojekte unter der Federführung von Prof. Dr. Greten von der Antragstellung über die Durchführung bis zum Abschluss. Derzeit betrifft dies das LOEWE-Zentrum (seit 2019 einschließlich der Vertretung des GSH im FCI-Forschungsbauprojekt), den SFB/Transregio 417 „Cellular Communication in the Stroma of Colorectal Cancer" sowie weitere Kooperationsprojekte. Ab November übernimmt Dr. Ann-Kathrin Mehnert den SFB/Transregio 417.
Dies geschieht durch eine zielgerichtete, koordinierte Durchführung, Budgetverwaltung und Berichterstattung der Projekte. Darüber hinaus ist Dr. Schmitz für die Kommunikation und Öffentlichkeitsarbeit des Instituts zuständig. Dazu zählt unter anderem die Betreuung der Website und des LinkedIn-Auftritts, um die Forschung des Instituts sichtbar zu machen.

Science management
Dr. Sandra Schmitz is responsible for science management. Her tasks include, in particular, coordinating research associations under the leadership of Prof. Dr. Greten, from the application stage through implementation to completion. Currently, this concerns the LOEWE Center (since 2019, including representation of the GSH in the FCI research building project), the SFB/Transregio 417 "Cellular Communication in the Stroma of Colorectal Cancer," and other collaborative projects. Dr. Ann-Kathrin Mehnert will take over SFB/Transregio 417 as of November.
This is achieved through targeted, coordinated implementation, budget administration, and reporting of the projects. In addition, Dr. Schmitz is responsible for the institute's communication and public relations. This includes maintaining the website and LinkedIn presence to raise awareness of the institute's research.

TRR 417
CELLULAR COMMUNICATION IN THE STROMA OF COLORECTAL CANCER

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Die Zentrale Tierhaltung am Georg-Speyer-Haus

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Tierhaus im Umbruch – und wo soll die Reise hin?
Mit dem Weggang der vormaligen Tierhausleitung waren personelle, rechtliche und organisatorische Hürden zu nehmen. Wir sind unseren Kolleginnen und Kollegen der Goethe Universität dankbar, dass mit Frau Dr. Schubert und Frau Dr. Bayer eine Interimslösung für die Leitung und tierärztliche Betreuung des Tierhauses gefunden werden konnte. Aufgaben, die nicht unbedingt seitens der beiden übernommen werden mussten, wurden hausintern aufgeteilt. Herr Dr. Grote unterstützt das Tierhaus als Ansprechpartner vor Ort in technischen und organisatorischen Belangen. Dies ermöglichte einen reibungslosen Betrieb und eine Fokussierung auf die tierärztliche Betreuung.

Wir freuen uns, dass ab Oktober durch den Beginn von Frau Kupper die tierärztliche Versorgung wieder in Vollzeit sichergestellt ist und Frau Dr. Bayer nach wie vor für die Leitung zur Verfügung steht.

In Zukunft möchten wir gemeinsam mit der Tierpflege und den Wissenschaftlerinnen und Wissenschaftlern in der Tierhaltung das Thema Culture of Care und Stressreduktion stärker in den Fokus nehmen. So werden wir gemeinsam ein Tiertraining erarbeiten, um die Tiere besser auf das Geschehen im Versuch vorzubereiten. Hierdurch soll Stress bei Tier und Forschenden reduziert und die Tierpflege besser in die Versuche eingebunden werden.

Wer ist die „Zentrale Tierhaltung“?
An erster Stelle stehen die Tierpflegenden, die tagtäglich mit viel Hingabe und Motivation für das Wohl der Tiere sorgen. Neben den Aufgaben der Tierversorgung helfen unsere Mitarbeitenden auch bei der Durchführung von Versuchen, z.B. bei Blutentnahmen durch die aktive Mitarbeit in der Transgenic Core Facility und bei eigenständiger Zuchtführung von Linien. Gemeinsam mit der Tierhausleitung erfolgt die Ausbildung zweier Tierpflegerinnen, Fachrichtung Forschung und Klinik.

Eine weitere zentrale Rolle übernimmt das Personal der Spülküche. Verschmutztes Material muss gereinigt, wieder befüllt und anschließend autoklaviert werden. Nur so kann der hohe Hygienestandard im Tierhaus sichergestellt werden.

Die tierärztliche Versorgung und rechtliche Verantwortung für die Tierhaltung wird von der Tierhausleitung getragen. Wir sind Ansprechpartner in allen Belangen rundum Tierhaltung, Tierwohl und gelebten Tierschutz.

Frau Dr. Wagenblast ist unsere Tierschutzbeauftragte. Sie berät die Kolleginnen und Kollegen in Forschungs- sowie die Tierhausleitung in Tierschutzfragen. Außerdem wird Frau Dr. Wagenblast die fachliche Weiterbildung von Frau Kupper begleiten.

Animal facility in transition – where is the journey headed?
With the departure of the former animal facility management, personnel, legal, and organizational hurdles had to be overcome. We are grateful to our colleagues at Goethe University for finding an interim solution for the management and veterinary care of the animal facility in the form of Dr. Schubert and Dr. Bayer. Tasks that did not necessarily have to be taken on by the two of them were divided up internally. Dr. Grote supports the animal facility as a local contact person for technical and organizational matters. This enabled smooth operation and a focus on veterinary care.
We are pleased that, with Bianca Kupper starting in October, full-time veterinary care will once again be ensured and that Dr. Bayer will continue to be available for management duties.

In the future, we would like to work with the animal care staff and scientists in animal husbandry to focus more strongly on the topics of culture of care and stress reduction. Together, we will develop an animal training program to better prepare the animals for the experiments. This should reduce stress for both the animals and the researchers and better integrate animal care into experiments.

Who is the "Central Animal Facility"?
First and foremost are the animal caretakers, who work with great dedication and motivation every day to ensure the well-being of the animals.

In addition to their animal care duties, our employees also assist in conducting experiments, e.g., blood sampling, through active participation in the Transgenic Core Facility and independent breeding management of lines. Together with the animal facility management, two animal caretakers are being trained in research and clinical care.

The staff in the scullery also play a central role. Dirty equipment must be cleaned, refilled, and then autoclaved. This is the only way to ensure the high standard of hygiene in the animal facility.

Veterinary care and legal responsibility for animal husbandry are the responsibility of the animal facility management (photo: Franziska, Bianca). We are the point of contact for all matters relating to animal husbandry, animal welfare, and animal protection in practice.

Dr. Wagenblast is our animal welfare officer. She advises colleagues in research as well as our animal facility management on animal welfare issues. In addition, Dr. Wagenblast will accompany Ms. Kupper's professional training.

Der Verein „Freunde und Förderer des Georg-Speyer-Hauses“

The Association “Friends and Sponsors of the Georg-Speyer-Haus”

Innovative Forschung und wissenschaftlicher Fortschritt in unserer Gesellschaft sind nur möglich durch das Engagement der Wissenschaftler/innen und die aktive Unterstützung von Forschungsförderern aus Öffentlichkeit, Wissenschaft und Wirtschaft. Diesem Engagement hat sich der Verein „Freunde und Förderer des Georg-Speyer-Hauses“ verpflichtet: Sein Ziel ist es, über die Grundfinanzierung durch Bund und Länder hinaus für weitere erforderliche Mittel zu sorgen und so das hohe Niveau der Grundlagenforschung zu sichern.

Mitglied im Verein kann werden, wer den wissenschaftlichen Fortschritt im Bereich der Krebsforschung und der experimentellen Therapie zum Wohle der Allgemeinheit fördern möchte und Interesse hat am Forschungsprozess und am Diskurs über Ergebnisse und deren Nutzen für die Allgemeinheit.

Neben der einfachen Mitgliedschaft (Freund/innen) und der Forschermitgliedschaft (Wissenschaftler/innen, Student/innen) besteht die Möglichkeit der fördernden Mitgliedschaft für Einzelpersonen oder Firmen. Förderer können im Jahrbuch und auf der Spendentafel aufgeführt werden.

Da der Verein eine gemeinnützige Einrichtung ist, sind Mitgliedsbeiträge und Spenden im Rahmen der zulässigen Höchstbeträge von der Steuer absetzbar.

Innovative research and scientific advances are only possible through generous financial support from public and private sponsors. The association „Friends and Sponsors of the Georg-Speyer-Haus“ has committed itself to this task. The major goal of the association is to raise the necessary funds to supplement the basic financing provided by the federal and state governments. This should ensure a continuing high quality of basic research.

Everybody who would like to support research in the fields of cancer and experimental therapy is welcome to join the association. Private persons can become supporting members („friend“) or research members (scientists and students). Moreover, private individuals and companies may obtain corporate membership. Sponsors will be listed in both the annual report and the table of benefactors in the Institute.

Since the association is a non-profit organisation, all membership fees and donations are tax deductable.

Jährliche Mitgliedsbeiträge
Annual membership fees

Forschermitglied
Scientist
100,– €

Studenten
Students
12,– €

Freund
Friend
150,– €

Förderer
Sponsor
1000,– €

Firmenmitgliedschaft
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5000,– €

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„Wer nicht neugierig ist,
erfährt nichts.“

Johann Wolfgang von Goethe