GEORG SPEYER HAUS
INSTITUT FÜR TUMORBIOLOGIE
UND EXPERIMENTELLE THERAPIE

Zelluläre Kommunikation in der Stammzellnische
Zell-Zell Interaktionen im Tumorstroma
Experimentelle Therapie

Annual Report
Georg-Speyer-Haus

2024

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The basic funding of the Georg-Speyer-Haus is provided by the Federal Ministry of Health and the Ministry of Higher Education, Research and the Arts of the State of Hessen.

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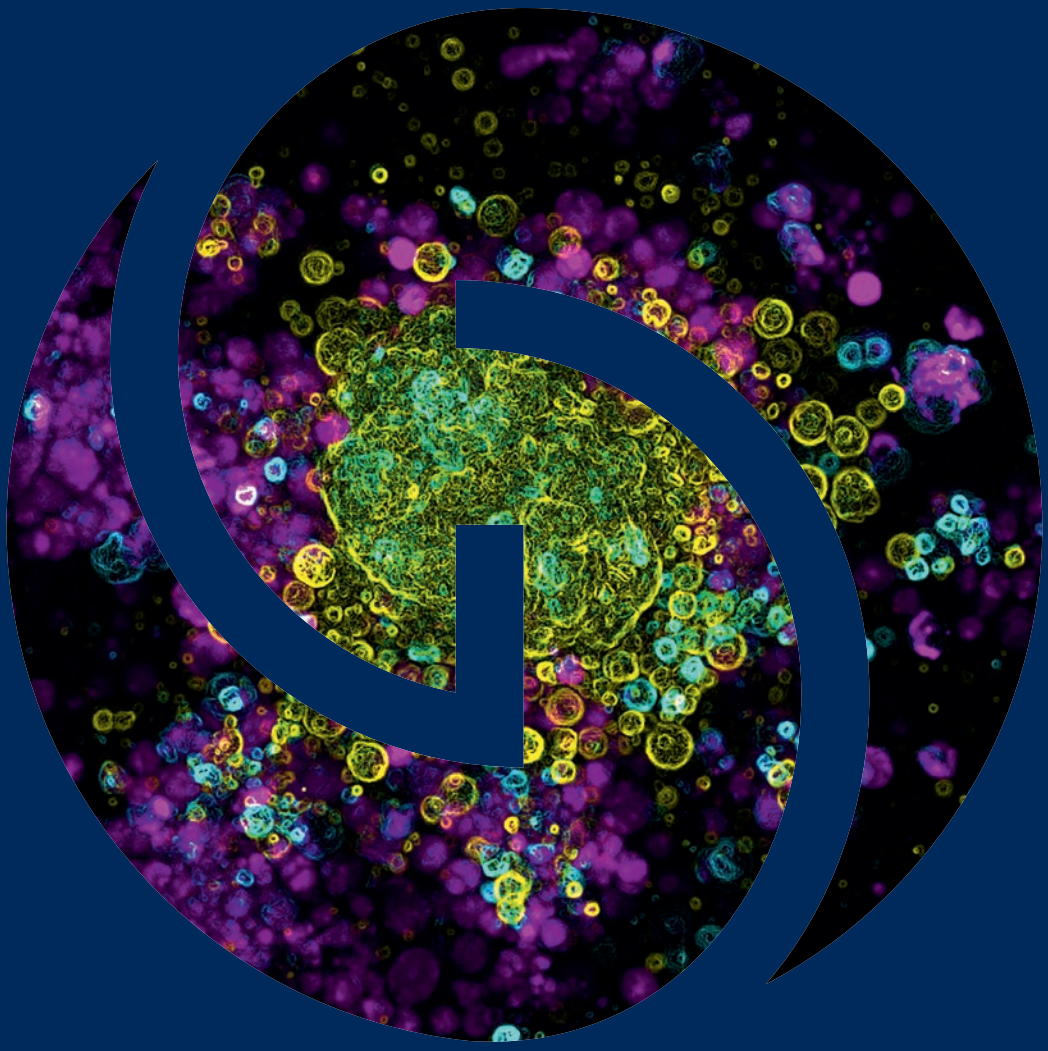

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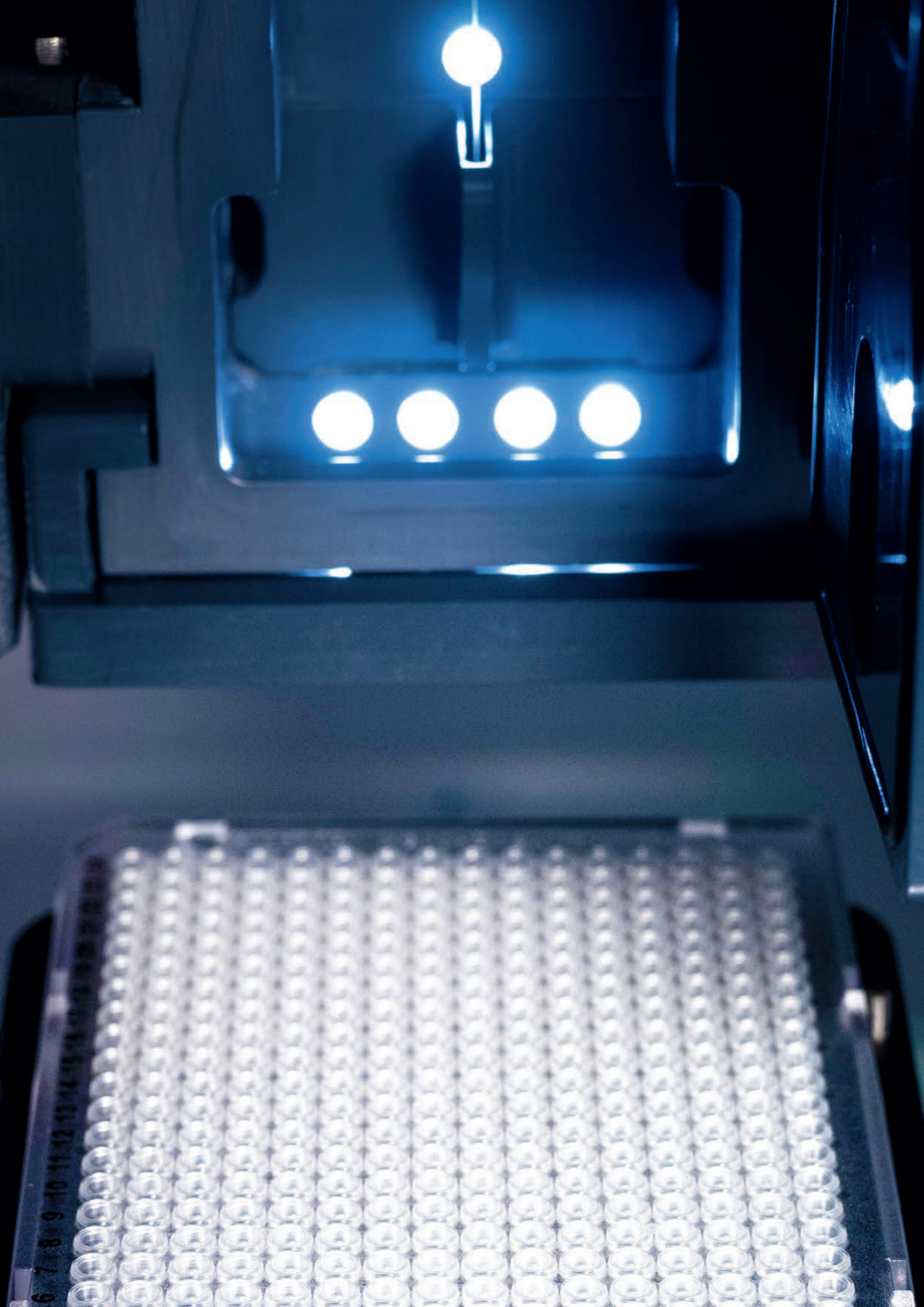

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Liebe Leserinnen und Leser,
liebe Freunde des Georg-Speyer-Hauses,

ein sehr ereignisreiches Jahr liegt hinter uns.

Zutiefst erschüttert waren wir über den Tod von Dr. Rolf-E. Breuer, Ehrenmitglied unserer gemeinnützigen Stiftung im Mai dieses Jahres. Wie viele von Ihnen wissen, prägte Dr. Breuer über vier Jahrzehnte lang das Georg-Speyer-Haus als Vorstands- und späteres Stiftungsratsmitglied, davon viele Jahre als Vorsitzender dieser bedeutenden Gremien. Bis zu seinem Ausscheiden im März 2015 brachte er sich mit unermüdlichem Einsatz und außergewöhnlichem persönlichem Engagement für die Anliegen des Instituts ein. Für diese Verdienste sind wir ihm zu tiefem Dank verpflichtet und werden sein Andenken in Ehren bewahren.

Des Weiteren war das Jahr von verschiedenen personellen Änderungen geprägt. Zu Beginn des Jahres nahm Dr. Melanie Tichet ihre Arbeit als Gruppenleiterin bei uns auf. Finanziert im Rahmen des LOEWE-Zentrums FCI wird sie sich in den kommenden Jahren mit der Rolle und Regulierung suppressiver Zellpopulationen im Tumormikromilieu beschäftigen und sich hier insbesondere auf sogenannte tumorassoziierte Makrophagen fokussieren um die Immunantwort bei soliden Tumoren wie dem Melanom, Pankreaskarzinom und Hirntumoren zu modulieren. Im Sommer stieß Dr. Mike Tyler zu uns, der großzügig unterstützt von der Dr. Rolf M. Schwiete Stiftung, das bei uns am Institut bislang nicht berücksichtigte Feld der *„Computational Biology"* bearbeiten wird und sich mit der Integration verschiedener Datenmodalitäten auf Einzelzellniveau annehmen wird. So wird er entsprechende Datensätze verschiedener Tumorstadien verwenden, um generelle Prinzipien der Tumorentstehung und der Bedeutung des Tumormikromilieus im Zeitverlauf zu identifizieren. Unsere exzellente Kooperation mit der Goethe Universität wurde auch weiter gestärkt. Frau Prof. Sina Oppermann, die im Frühjahr einen Ruf an das Institut für Pharmakologie und klinische Pharmazie des Fachbereich 14 am Campus Riedberg angenommen hatte, bekommt bei uns Laborflächen zur Verfügung gestellt, um sich der funktionellen Profilierung von

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

A very eventful year lies behind us.

We were deeply saddened by the passing of Dr. Rolf-E. Breuer, honorary member of our foundation, in May of this year. As many of you know, Dr. Breuer shaped the Georg Speyer Haus for over four decades as a board member, serving as chairman of this important committee for many years. Until his retirement in March 2015, he contributed tirelessly and with exceptional personal commitment to the institute's mission. For these contributions, we owe him our deepest gratitude and will honor his memory.

This year was also marked by several personnel changes. At the beginning of the year, Dr. Melanie Tichet joined us as a group leader. Funded within the LOEWE Center FCI, she will focus over the coming years on the role and regulation of suppressive cell populations within the tumor microenvironment, with a particular focus on tumor-associated macrophages to modulate the immune response in solid tumors such as melanoma, pancreatic cancer, and brain tumors. In summer, Dr. Mike Tyler joined us, generously supported by the Dr. Rolf M. Schwiete Foundation, to work in the field of "*Computational Biology*," an area not previously covered at our institute. His work will involve the integration of various data modalities at the single-cell level, using datasets from different tumor stages to identify general principles of tumor development and the significance of the tumor microenvironment over time. Our excellent cooperation with Goethe University has been further strengthened. Prof. Sina Oppermann, who accepted a position at the Institute of Pharmacology and Clinical

primären Tumorproben mit Hilfe von Wirkstoffbibliotheken im 2D und 3D Hochdurchsatzverfahren zu widmen. Dies wird die ohnehin schon sehr enge Zusammenarbeit mit den Kollegen am Riedberg im Zuge des FCI weiter intensivieren.

Auch an der Spitze unserer Administration kam es zu einem Wechsel und wir sind ausgesprochen froh, dass es uns gelungen ist mit Herrn Gernot Ruffing einen ungemein erfahrenen Nachfolger für Frau Franziska Hasslinger-Pajtler die sich entschlossen hat eine neue Herausforderung, die näher an ihrem Wohnort liegt zu widmen, gefunden zu haben. Herr Ruffing wird die exzellente Arbeit von Frau Hasslinger-Pajtler nun nahtlos weiterführen und war bereits in der Lage in kurzer Zeit wichtige neue Impulse zu setzen.

Im August hat das Land Hessen einem Antrag zur Aufnahme des GSH in die Leibniz-Gemeinschaft gestellt und wir sind natürlich nach den vielen Jahren der Vorbereitung ausgesprochen gespannt – und vorsichtig optimistisch – auf den Ausgang der nun anstehenden Evaluation.

Sehr stolz sind wir über den Erfolg, dass mit Dr. Henner Farin und Dr. Hind Medyouf gleich zwei unserer Gruppenleitungen erfolgreich im kompetitiven Heisenberg Programm der DFG waren. Dr. Farin hat kürzlich den damit verbundenen Ruf an der Goethe Universität erhalten und wird dem Institut auch in Zukunft mit seiner Arbeitsgruppe erhalten bleiben. Dr. Medyouf hat einen Ruf auf eine W3-Professur der RWTH Aachen angenommen und wird uns in der ersten Hälfte des kommenden Jahres verlassen.

Unser Institut und unsere engagierte Arbeit konnten wir im Juni vielen interessierten Gästen im Rahmen unseres ersten „Open Lab Day“ nahebringen. Bei schönem Wetter gab es eine Reihe von Vorträgen, Führungen durch das Institut sowie angeregte Diskussionen zu unseren Projekten im Garten an den Posterwänden und beim Grillen. Sollten Sie keine Zeit gehabt haben vorbeizuschauen, finden Sie im Folgenden in bewährter Form wieder eine Übersicht über die Fortschritte und Erfolge der individuellen Arbeitsgruppen. Außerdem lade ich Sie herzlich ein unsere überarbeitete Webseite zu besuchen, die wir im Dezember dieses Jahres online nehmen werden.

Florian R. Greten, Direktor

Pharmacy in Faculty 14 on the Riedberg Campus this spring, is being provided with laboratory space at the GSH. She will focus on the functional profiling of primary tumor samples using drug libraries in 2D and 3D high-throughput screening processes. This will further intensify the already close collaboration with colleagues at Riedberg as part of the FCI initiative.

There was also a leadership change in our administration, and we are very pleased to have found an exceptionally experienced successor in Mr. Gernot Ruffing, following the departure of Ms. Franziska Hasslinger-Pajtler, who has chosen to take on a new challenge closer to her home. Mr. Ruffing will seamlessly continue Ms. Hasslinger-Pajtler’s excellent work and has already brought important new ideas to our team in a short time.

In August, the state of Hesse submitted an application for GSH to join the Leibniz Association, and we are, of course, very eager – and cautiously optimistic – about the outcome of the upcoming evaluation after many years of preparation.

We are also very proud of the success of Dr. Henner Farin and Dr. Hind Medyouf, both of whom were successful in the highly competitive Heisenberg Program of the DFG. Dr. Farin has recently received a related appointment at Goethe University and will continue to be part of our institute with his research group. Dr. Medyouf, however, has accepted a W3 professorship at RWTH Aachen and will be leaving us in the first half of the coming year.

In June, we had the opportunity to introduce our institute and our dedicated work to many interested visitors during our first “Open Lab Day.” With beautiful weather, we offered a series of lectures, tours of the institute, and lively discussions about our projects in the garden by the poster boards and during a barbecue. If you were unable to attend, you will find as usual an overview of the progress and achievements of the individual research groups in the following. I would also like to invite you to visit our modernized website, which we will be launching in December of this year.


RUKER

Forschen für das Leben
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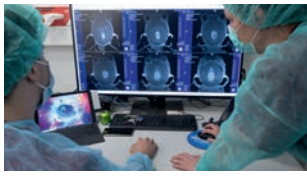
Die Stiftung privaten Rechts „Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus“ wurde 1904 in Frankfurt am Main gegründet, um eine Forschungsstätte für Paul Ehrlich, den ersten Direktor des Hauses, zu schaffen. Die Stiftungsverfassung bestimmt als Zweck der Stiftung die wissenschaftliche Forschung 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 Kunst 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.

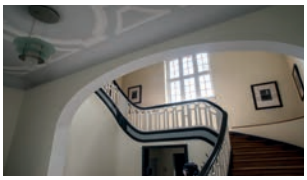
The private foundation “Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus” (Chemotherapeutic Research Institute Georg-Speyer-House) was established in 1904 in order to provide a research institute for Paul Ehrlich, its first director. The constitution of the institute, originating from its foundation, 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 Ministry of Higher Education, Research and the Arts of the State of Hessen. 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.

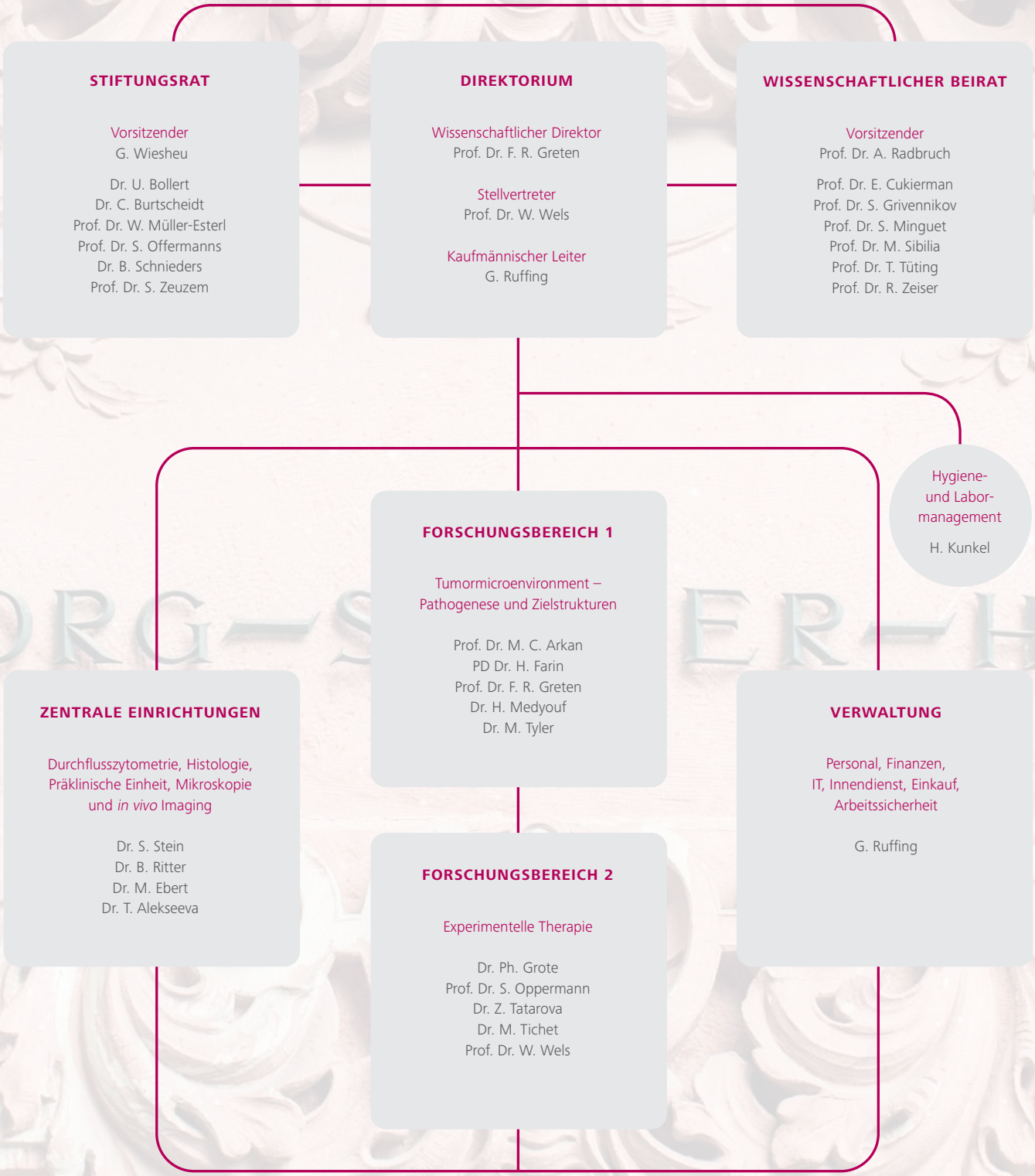
Das Georg-Speyer-Haus wird finanziell vom Bundesministerium für Gesundheit (BMG) sowie vom Hessischen Ministerium für Wissenschaft und Kunst (HMWK) unterstützt. Zusätzlich stehen Mittel aus der Drittmittelförderung öffentlicher und privater Forschungsförderungsorganisationen, aus Kooperationsvereinbarungen 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 Ministry of Higher Education, Research and the Arts of the State of Hessen. 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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I

Tumormicroenvironment – Pathogenese und Zielstrukturen

Tumor Microenvironment – Pathogenesis and Target Structures

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Diät, Energiemetabolismus und Krebs

Dietary and Microbial Modulations in Cancer Therapy

Investigating the Dynamics of Microbial Communities and Their Functions in Cancer Patients 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 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 metabolic processes, dictating how we process nutrients, manage energy, and respond to medications. Disruptions in this internal clock, often caused by irregular sleep patterns, meal timing, or shift work, can lead to metabolic imbalances that may promote cancer development. Emerging evidence suggests that the gut microbiome, a dynamic ecosystem of trillions of microorganisms living in our gut, acts as a critical mediator in this complex relationship. Changes in the composition and function of the microbiome can influence metabolic pathways and interact with the circadian clock, adding another layer of complexity to cancer biology. Our research focuses on the interplay between dietary patterns, metabolism, the circadian clock, and the microbiome, particularly in the context of cancers of the pancreas and intestine.

Ernährung, Stoffwechsel, die zirkadiane Uhr und das Mikrobiom sind eng miteinander verknüpft und spielen jeweils eine wichtige Rolle bei der Entwicklung und dem Progress von Krebs sowie beim Ansprechen auf die Therapie. Die zirkadiane Uhr, die den 24-Stunden-Rhythmus des Körpers regelt, steuert die Stoffwechselprozesse und bestimmt, wie wir Nährstoffe verarbeiten, mit Energie umgehen und auf Medikamente reagieren. Störungen dieser inneren Uhr, die häufig durch unregelmäßige Schlafrhythmen, Mahlzeiten oder Schichtarbeit verursacht werden, können zu einem metabolischen Ungleichgewicht führen, das die Krebsentwicklung fördern kann. Neue Erkenntnisse deuten darauf hin, dass das Darmmikrobiom, ein dynamisches Ökosystem aus Billionen von Mikroorganismen, die in unserem Darm leben, als entscheidender Faktor in dieser komplexen Verbindung spielt. Veränderungen in der Struktur und Funktion des Mikrobioms können Stoffwechselprozesse beeinflussen und mit der zirkadianen Uhr interagieren, was der Krebsbiologie eine weitere komplexe Schicht verleiht. Unsere Forschung zielt auf das Zusammenspiel zwischen Ernährungsgewohnheiten, Stoffwechsel, der zirkadianen Uhr und dem Mikrobiom, insbesondere im Zusammenhang mit Krebserkrankungen der Bauchspeicheldrüse und des Darms.

We are investigating how variations in nutrient intake, meal timing, and dietary composition affect not only metabolic processes but also the composition and function of the gut microbiome. In turn, we seek to understand how these factors interact with the circadian rhythm and cancer growth. Disruptions to the microbiome, through diet or medication, can lead to an imbalance known as dysbiosis, which has been linked to both metabolic disorders and cancer progression. By studying these relationships, we aim to uncover how maintaining a stable microbiome and metabolic

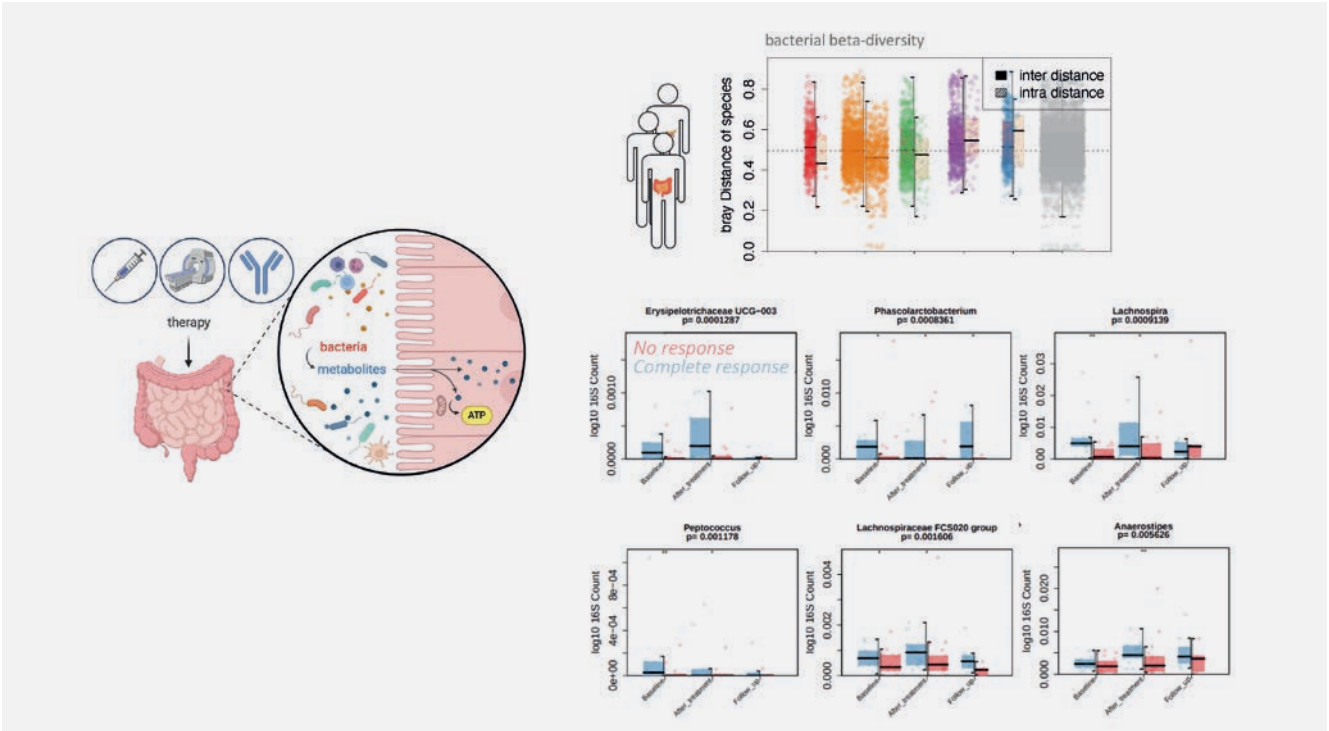
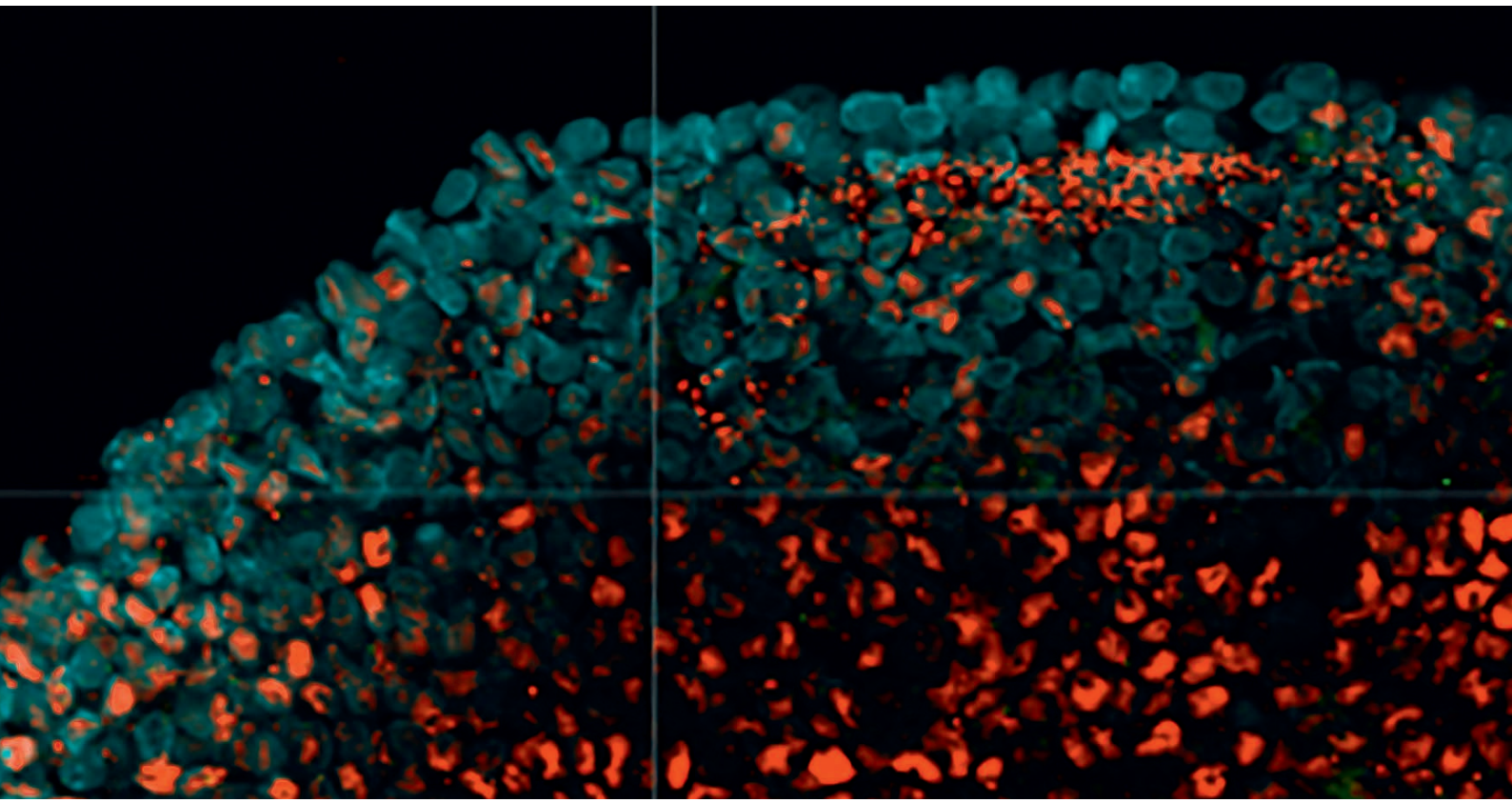


Figure 1. We integrated a correlative multi-omics approach across rectal cancer patient cohorts to leverage microbial community structure and function dynamics during radiochemotherapy not only to predict therapeutic outcomes but also to eventually enhance treatment efficacy.



environment can potentially reduce the risk of cancer or slow its progression.

Incorporating preclinical models and clinical data, we are also exploring how the microbiome influences cancer cell metabolism as well as how treatments further alter bacterial communities. Cancer cells often undergo significant metabolic shifts to support their rapid growth, and these changes are increasingly recognized as potential therapeutic targets. We aim to identify metabolic vulnerabilities in cancer cells by investigating how the microbiome shapes these processes and

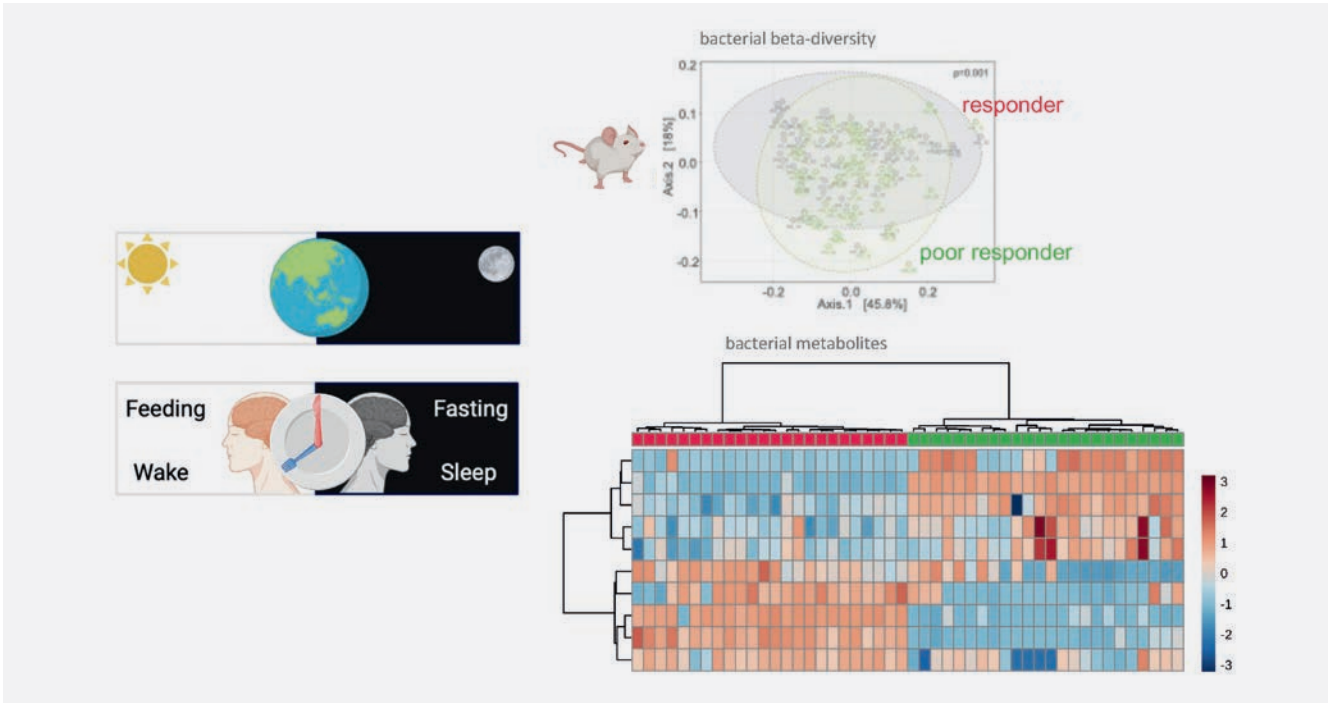
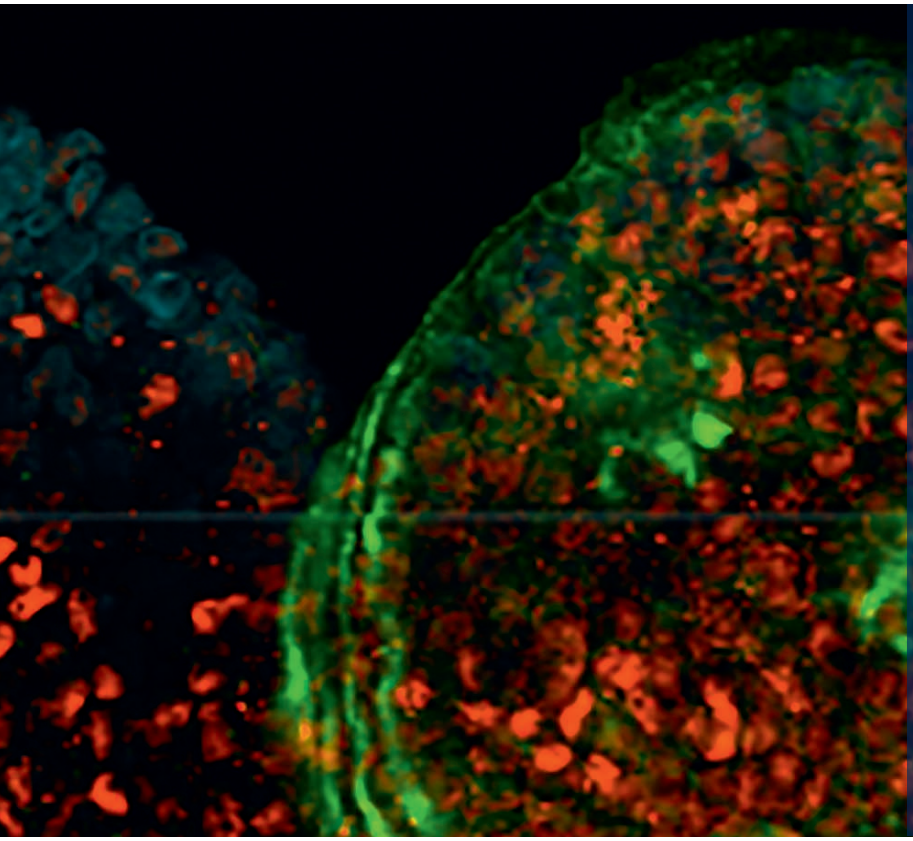


Figure 2. We use preclinical mouse models of colorectal cancer to identify derangements in metabolism during tumor progression and therapy. We then assess the impact of modulating bacterial metabolism on immune cell behavior and tumor response to cytotoxic therapy, employing dietary supplementation or timed eating to target the tumor microenvironment and improve treatment outcomes.



Ausgewählte Publikationen

Khasawneh J, Schulz MD, Walch A, Rozman J, Hrabe de Angelis M, Klingenspor M, Buck A, Schwaiger M, Saur D, Schmid RM, Klöppel G, Sipos B, Greten FR, and **Arkan MC** (2009) *'Inflammation and mitochondrial β-oxidation link obesity to pancreatic cancer'.* ***Proc. Natl. Acad. Sci.*** *USA; 106(9): 3354-9.*

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; accepted.*

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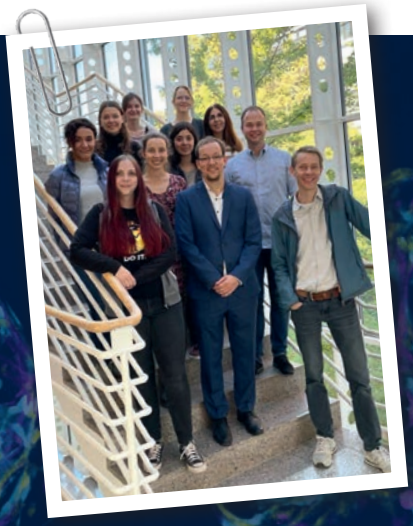
how both diet and circadian rhythms may influence this dynamic. The goal is to uncover microbial metabolic pathways that could be disrupted to weaken cancer cells and enhance the effectiveness of existing therapies (Figure 1).

In addition, we are exploring whether aligning dietary interventions and microbiome with the circadian rhythm could optimize cancer therapies. The timing of treatments, such as chemotherapy or immunotherapy, in relation to the body's natural circadian rhythms, has been shown to influence their effectiveness. By integrating microbiome into this equation, we aim to determine whether certain dietary patterns or defined bacteria, when timed with circadian cycles, can enhance therapeutic responses. This line of research could lead to personalized, time-based dietary strategies that not only improve treatment efficacy but also promote a healthier stable microbiome, ultimately enhancing patient outcomes (Figure 2).

In summary, our research examines the interconnected roles of diet, metabolism, the circadian clock, and the microbiome in cancer development and treatment. By understanding how these factors interact, we aim to uncover new therapeutic approaches that target metabolic weaknesses in cancer cells, while also optimizing the microbiome's role in promoting health. Our studies hold the potential to develop more personalized, circadian-based dietary strategies that improve cancer therapies and enhance patient well-being.



Gewebsinteraktionen und Signalmechanismen im Darmkrebs

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Signaling crosstalk in the colon cancer microenvironment

3D Colon Cancer Models: Using advanced 3D cultures and organoid biobanks from human colorectal cancer

Understanding Cancer Signaling: Study of signaling mechanisms in the cancer microenvironment

Finding New Treatments: Identifying ways to treat colon cancer more effectively

In Germany, colorectal cancer is the third most common type of cancer, with around 59,000 new cases and 24,000 deaths each year. Colon cancers are generally classified into two types: *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 patients with MSI tumors. However, the therapeutic options for patients with MSS tumors are still limited. This is largely due to the high genetic diversity within and between tumors in different patients. 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.

Our research focuses on creating 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

Unsere Arbeitsgruppe untersucht die zellulären und molekularen Mechanismen, die an der Entstehung von Darmkrebs beteiligt sind. Ein besonderer Fokus liegt dabei auf der Kommunikation zwischen verschiedenen Zelltypen innerhalb der direkten Tumorumgebung, dem sogenannten „Tumor-Mikromilieu". Zu diesem Zweck verwenden wir Organoide – ein innovatives, dreidimensionales Gewebekultur-System. Diese Organoide werden unter kontrollierten Kulturbedingungen aus menschlichen Darmstammzellen entwickelt und bilden darmepithel-spezifische Strukturen wie Krypten (Einstülpungen) und Villi (Zotten) nach. Dadurch können wir Stammzellen in einem Gewebe-ähnlichen Zustand expandieren und molekulare Signalwege in einer definierten Mikroumgebung untersuchen. Durch Zugabe von Fibroblasten, Gefäß- oder Immunzellen wird der Gewebekontext nachgebildet.

Im Mittelpunkt unserer Forschung steht die genetische Analyse der Entstehung und des Fortschreitens von Darmkrebs. In Zusammenarbeit mit dem „Frankfurt Cancer Institut" legen wir lebende Biobanken von PatientInnen-abgeleiteten Tumor-Organoiden an. Mithilfe genetischer Methoden wie CRISPR/Cas9 sowie Hochdurchsatzanalysen wie Genom- und RNA-Sequenzierung sowie Proteomanalyse erforschen wir, wie onkogene Mutationen den Tumorphänotyp beeinflussen. Im Rahmen des EU-Projekts „EUbOPEN" nutzen wir Organoid-Modelle zudem für pharmakologische Tests, um neue Ansätze für die zukünftige Behandlung von Darmkrebs zu entwickeln.

3D Matrigel and defined growth factors. Originally developed for the mouse small intestine, the culture conditions have 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 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, our group develops new approaches for genetic modification of 3D organoids.

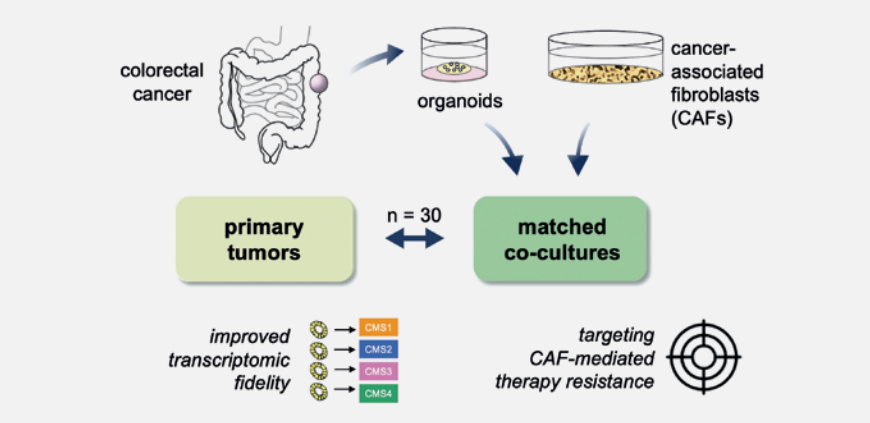
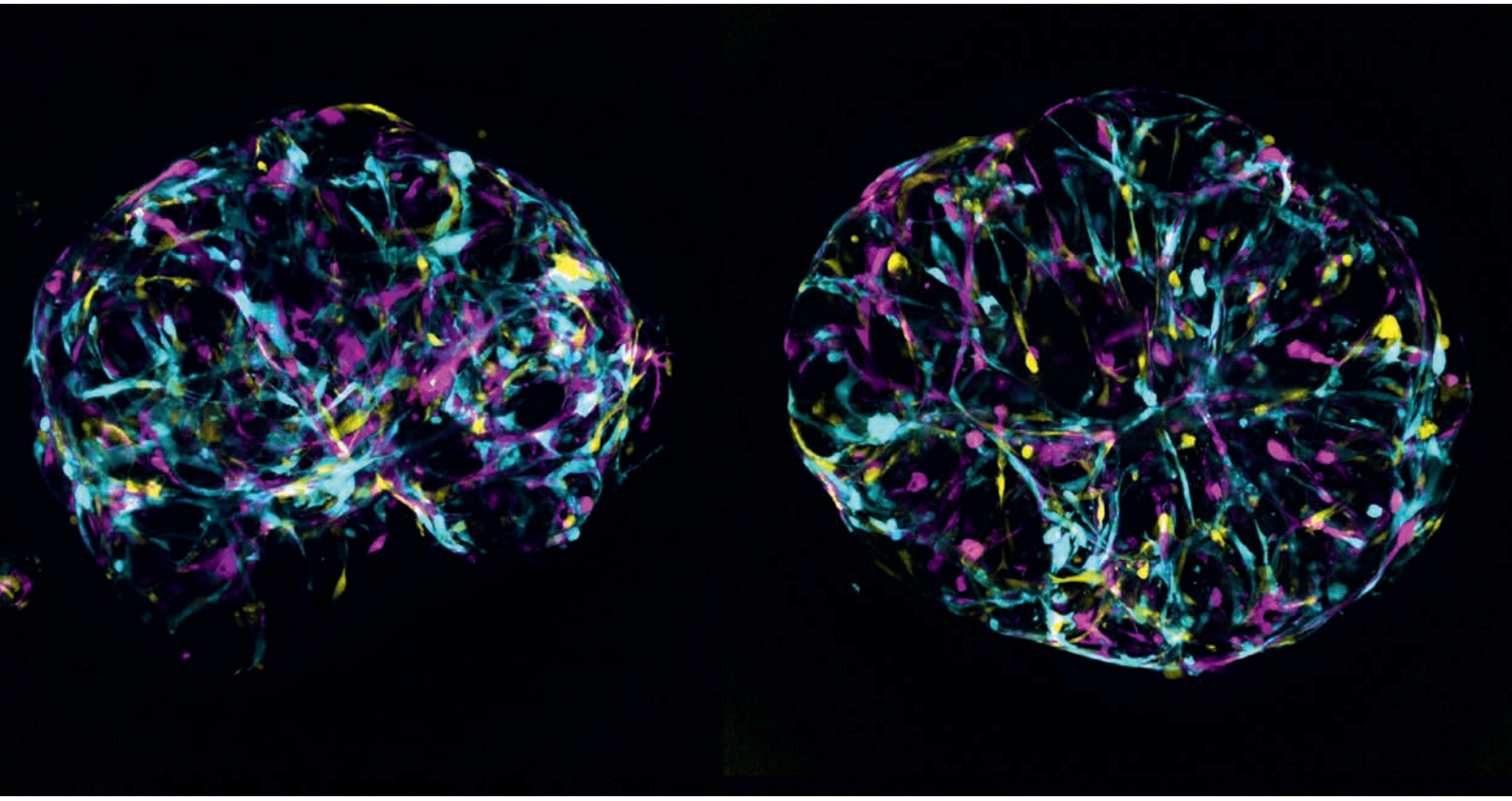


Figure 1.
Colorectal Cancer Organoid-Stroma Biobank. Generation of tumor organoids and cancer-associated fibroblasts (CAFs) from clinical samples. Systematic analysis of co-cultures from 30 patients showed an improved similarity with the corresponding tumor tissues and profound influences of CAFs on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

Main research focus areas are:

I. Study of context-dependency of CRC phenotypes

Although the TME has been recognized as a key determinant for prognosis and therapy response, we currently lack mechanistic insights, how stromal cell interactions control the individual tumor phenotype. To systematically study context-dependency in CRC, we have established the *'CRC organoid-stroma biobank'*. In collaboration with the group of Prof. Florian Greten, an experimental cohort of PDTOs and matched cancer-associated fibroblasts (CAFs) from 30 tumors was generated. All models were subjected to whole exome sequencing to identify tumor mutations. To study CRC subtypes and their regulation, RNA sequencing analysis was performed in original tumors and under diverse experimental settings including xenotransplants and CAF co-culture (Fig. 1; Farin et al., Cancer Discovery 2023). We have identified that PDTOs lose their subtype under standard culture conditions. However, restauration was observed in a stromal context, indicating that the molecular subtype is encrypted in the cancer cell compartment. These co-culture models provide an opportunity to study the underlying cellular mechanisms and



to explore the influence of the tumor microenvironment on therapy responses.

II. Functional genetic screening to identify CRC driver mutations

The impact of CRC mutations strongly depends on the tumor stage, the genetic background, and environmental factors. PDTOs allow to recapitulate this complexity and to study the effect of individual oncogenes and tumor suppressors. By genetic engineering of organoids using the CRISPR/Cas9 technology, we have recently analyzed the transcriptomic and proteomic changes induced by loss of the *APC* gene, which is a main driver of CRC (Michels et al., *J. Exp. Med.* 2019). To facilitate high-throughput testing of many genes in parallel, we have recently developed a protocol for pooled CRISPR/Cas9 library screening in human colon organoids (Fig. 2; Michels et al., *Cell Stem Cell* 2020). This technology permits unbiased detection of hundreds of genes that confer positive or negative growth advantages. We have used custom-generated gRNA libraries to identify tumor suppressors *in vitro* and after organoid xenotransplantation. This powerful platform for phenotypic charac-

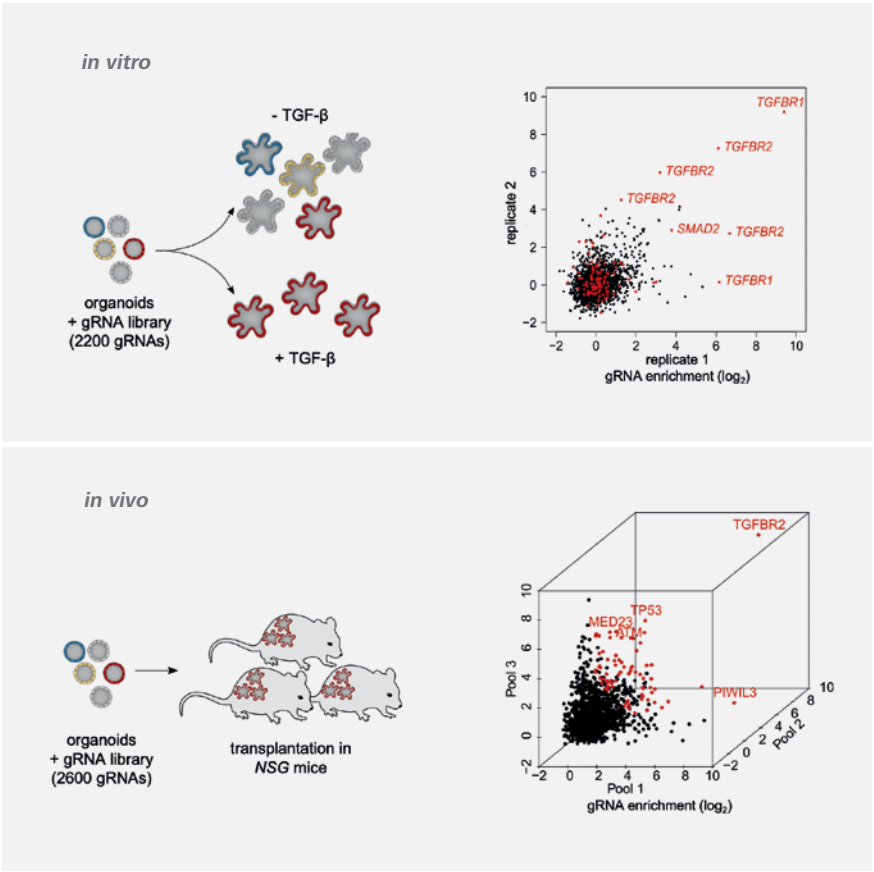
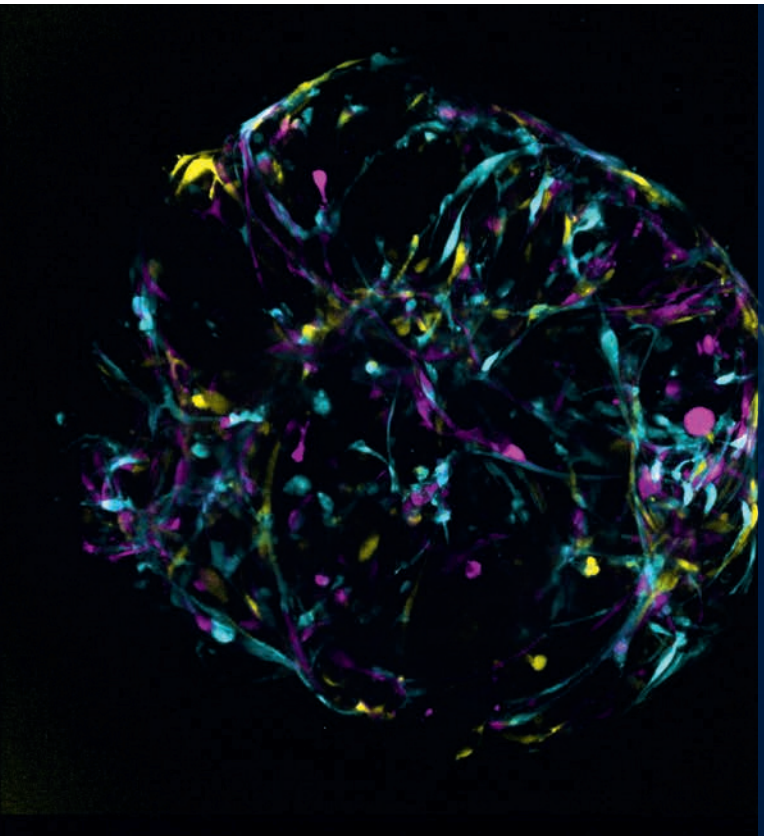


Figure 2. **CRISPR/Cas9 library screening in 3D organoids *in vitro* and *in vivo***
Top: TGF-β resistance screen *in vitro*. Barcode sequencing after phenotypic selection (growth in presence of TGF-β). Bottom: Tumor suppressor screen in human organoids after subcutaneous xenotransplantation. Barcode sequencing in 3 tumor pools. (data from Michels et al., *Cell Stem Cell* 2020).



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Schnalzger TE, de Groot MHP, Zhang C, Mosa MH, Michels BE, Röder J, Darvishi T, Wels WS, **Farin HF**. (2019)
3D model for CAR-mediated cytotoxicity using patient-derived colorectal cancer organoids. ***The EMBO Journal****. 38(12):e100928.*

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Farin HF*, Mosa MH, Ndreshkjana B, Grebbin BM, Ritter B, Menche C, Kennel KB, Ziegler PK, Szabo L, Bollrath J, Rieder D, Michels BE, Kress A, Bozlar M, Darvishi T, Stier S, Kur I-M, Bankov K, Kesselring R, Fichtner-Feigl S, Brune B, Goetze TO, Al-Batran S-E, Brandts CH, Bechstein WO, Wild PJ, Weigert A, Muller S, Knapp S, Trajanoski Z, Greten FR*. (2023)
Colorectal cancer organoid-stroma biobank allows subtype-specific assessment of individualized therapy responses. ***Cancer Discovery****. 13(10):2192–2211.* *corresponding authors

Menche C*, Schuhwerk H*, Armstark I, Gupta P, Fuchs K, van Roey R, Mosa MH, Hartebrodt A, Hajjaj Y, Clavel Ezquerra A, Selvaraju MK, Geppert CI, Bärthel S, Saur D, Greten FR, Brabletz S, Blumenthal DB, Weigert A, Brabletz T**, **Farin HF****, Stemmler MP**. (2024)
ZEB1-mediated fibroblast polarization controls inflammation and sensitivity to immunotherapy in colorectal cancer. ***EMBO reports.*** *25(8):3406–3431.*
*first authors **corresponding authors

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terization may in future allow to identify patient-specific tumor vulnerabilities.

III. Preclinical organoid models for cancer immunotherapy

In CRC, cell-based immunotherapies could help to improve the clinical outcome, because immune checkpoint inhibitors alone are not effective in the majority of MSS patients. Lymphocytes can be engineered to recognize tumor-associated antigens; however, the application of such chimeric antigen receptors (CAR)-modified cells has proven challenging in solid tumors. The immunosuppressive tumor stroma in CRC prevents immune cell recruitment and function and we furthermore lack predictive *in vitro* models. To address these challenges, we have recently developed a CAR-PDTO co-culture system (Fig. 3; Schnalzger et al., *EMBO Journal* 2019). In collaboration with Prof. Winfried Wels (Georg-Speyer-Haus), cytotoxic killing by CAR-modified NK-92 cells was measured in an enzymatic assay and by live imaging, providing a preclinical platform to evaluate efficacy and specificity CAR therapies.

As participant of the EU-consortium 'EUbOPEN' ('Enabling and unlocking biology in the OPEN' 2020-2025), we have developed a PDTO drug screening platform. The EUbOPEN consortium is funded by the Innovative Medicines Initiative (IMI2) and aims to generate an open access chemogenomic library of compounds covering the 'druggable human genome'. Together with our partners from academia and pharmacologic industry, we develop 'Human Tissue Assays' for CRC. We conduct high-throughput pharmacologic screens using our organoid biobank models to identify new therapeutic strategies.

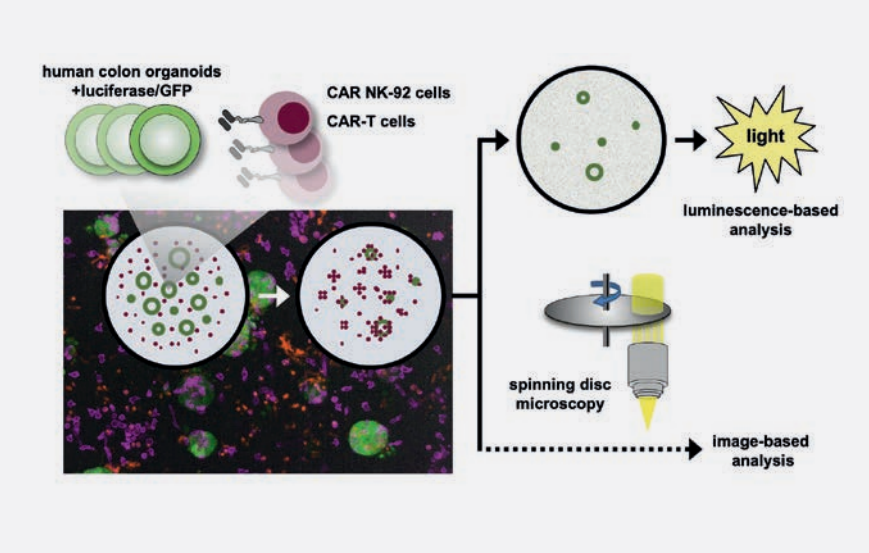

Figure 3. **3D model for CAR-mediated cytotoxicity using patient-derived CRC organoids**
Combination of GFP/luciferase transgenic human colon cancer organoids (green) with CAR-cells (violet). Monitoring of cytotoxic responses by video microscopy and enzymatic read-outs (adapted from Schnalzger et al.,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

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Therapeutische Interventionen in das Tumormikromilieu

Cell Plasticity in the colorectal tumor micro-environment

Tumor microenvironment

Colorectal carcinoma and liver metastasis

IL-17 and IL-17 receptor

Colorectal carcinoma (CRC) is among the three most common cancers in industrialized countries. Despite advancements in preventive colon screenings and treatments, mortality rates remain high, making CRC one of the top three leading causes of cancer-related deaths. The high mortality is primarily due to metastasis, which most commonly affects the draining lymph nodes, liver, and lungs. For many years, surgery or radiation were the primary treatment options, until the development of chemotherapy and, later, immunotherapy expanded the available approaches. This progress was driven by increased research into the tumor microenvironment (TME), revealing that tumors are not merely clusters of mutated cells but complex networks involving cancer cells and surrounding stromal cells such as fibroblasts, immune cells, and endothelial cells that impact all stages of tumor development as well as therapy response (Fig. 1). Focusing on the TME opens up a wider array of therapeutic possibilities. For instance, checkpoint inhibitors like anti-PD-1 can prevent T cell exhaustion and enhance anti-tumor immune responses. These therapies have

Unsere Forschung konzentriert sich auf die Untersuchung des Mikromilieus in gastrointestinalen Tumoren und darauf, die dabei entdeckten Prozesse für therapeutische Ansätze zu nutzen. Hierbei kommen moderne dreidimensionale in vitro Kulturen muriner und humaner intstinaler Epithelzellen, sowie relevante Mausmodelle zum Einsatz, welche die verschiedenen Arten und Stadien der Karzinogenese valide abbilden. Ziel ist die Entwicklung neuer Therapiekonzepte, deren Einsatz wir rasch klinisch überprüfen wollen. Kürzlich konnten wir die gegensätzliche Wirkung des pro-inflammatorischen Zytokins IL-17 in der Progression kolorektaler Tumore in einer Zeit- und Gewebe-abhängigen Weise aufdecken. In frühen Stadien reduziert der Verlust des IL-17-Rezeptors das chemisch-induzierte Tumorwachstum im Mausmodell, während zu einem späten Zeitpunkt eine erhöhte Invasivität und Metastasierung zu beobachten ist. In unserem Modell führt ein Verlust des Rezeptors zu Dysbiose und zur Ausbreitung von Pilzen, was überraschenderweise eine anti-tumorale Wirkung über IL-17RA-Signale in Immunzellen auslöst. IL-17 könnte daher gezielt genutzt werden, um die Metastasierung zu unterdrücken und Immuntherapien zu verbessern.

shown considerable effectiveness in CRC cases characterized by mismatch-repair deficiency or microsatellite instability, conditions associated with a high presence of neoantigens and infiltrating T cells. However, these patients represent only a small fraction of the overall CRC population. This situation underscores the heterogeneity present among patients and tumors, highlighting the necessity for ongoing research and tailored treatment strategies to enhance current therapies.

Unraveling the complex interplay between components of the TME is the main focus of our research group. In addition to the necessary basic research, we are working hard on translational implementation in the clinic. In cooperation with the Department of Radiotherapy at Frankfurt University Hospital, the results of our work (Nicolas et al., 2022) have been implemented in a clinical study that has recently been completed. During neo-adjuvant radiotherapy, patients with CRC received the interleukin 1 (IL-1) receptor antagonist anakinra, which blocks fibroblast-induced resistance mechanisms. Patients tolerated the IL-1 blockade well and we were able to observe very encouraging clinical responses in this first patient cohort. Therefore, we aim now to validate these results in a larger multi-center phase II trial. In another randomized placebo-controlled trial we assessed the effects of the mitophagy inducer urolithin A (UA). UA is a post-biotic metabolite that can be generated by the intestinal microbiome upon pomegranate intake. Recently, we were able to show that UA leads to an expansion of a subset of CD8+ T cells providing them with improved long-term immune functions (Denk et al., 2022). In the clinical trial (MitoImmune) we

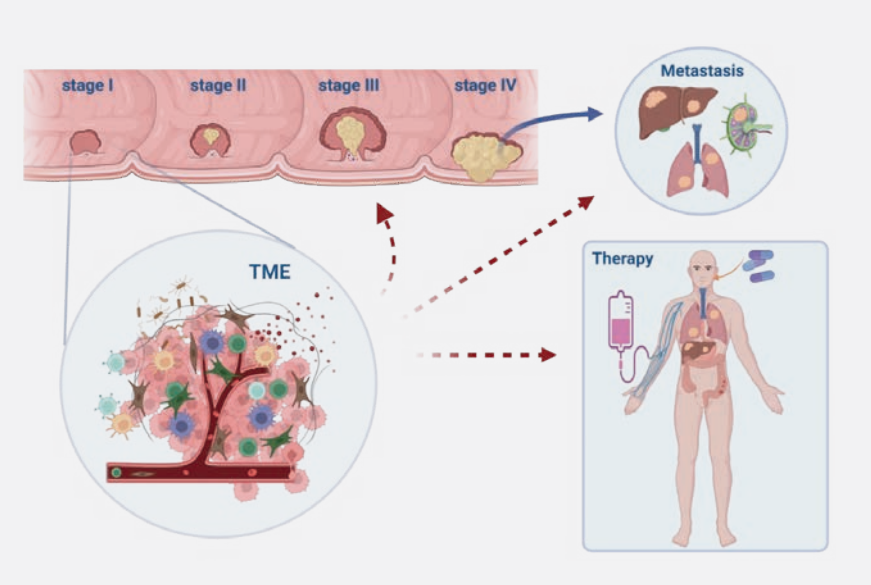
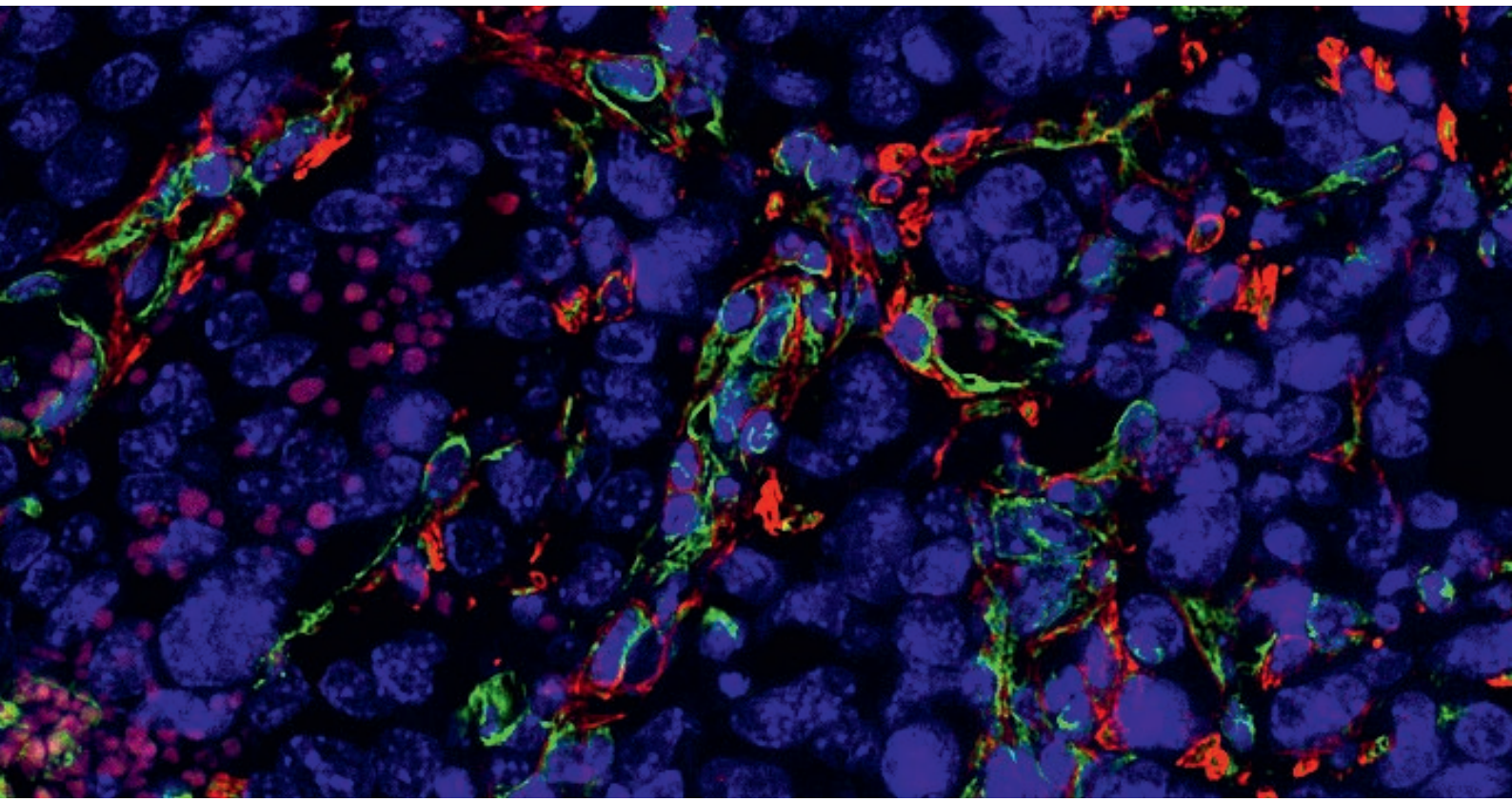


Figure 1: Changes in the composition of the TME start already very early during tumor development and impact the tumor formation throughout its growth. The TMA also has an influence on the development of metastases and plays an important role during therapy response and development of therapy resistance.



assessed now the impact on T cells after one month of oral supplementation in 25 healthy individuals compared to 25 volunteers that were randomly assigned to receive a placebo. As hypothesized, we could confirm a shift in CD8+ T cells and noted further changes in other immune cells as well as in circulating cytokine levels that are generally associated with aging, thus indicating that UA leads to beneficial changes in the immune system already after one month. Next, we plan to assess whether these promising results in cancer patients receiving chemotherapy and/or immune therapy to examine whether UA may lead to an improved immune function and will start the next clinical trial in spring 2025.

In a pre-clinical study we explored the complex role of the cytokine interleukin 17 (IL-17) in colorectal cancer (CRC), showing both its tumor-promoting and very unexpectedly also protective effects, depending on various stages and conditions of the disease. IL-17A and IL-17F, two members of the IL-17 family, bind to the IL-17 receptor A (IL-17RA) on cells. Data from CRC patients revealed that higher IL-17RA levels are linked to improved survival, especially in later stages, suggesting a potential protective role against metastasis – a finding that contrasts with previous studies indicating IL-17's tumor-promoting effect in early-stage CRC. We used a mouse model that mimics human CRC progression, from initial benign polyps to malignant tumors. Using this model, we discovered that IL-17RA deficiency in intestinal epithelial cells (IECs) reduced tumor aggression initially, but by later stages, the lack of IL-17RA led to more

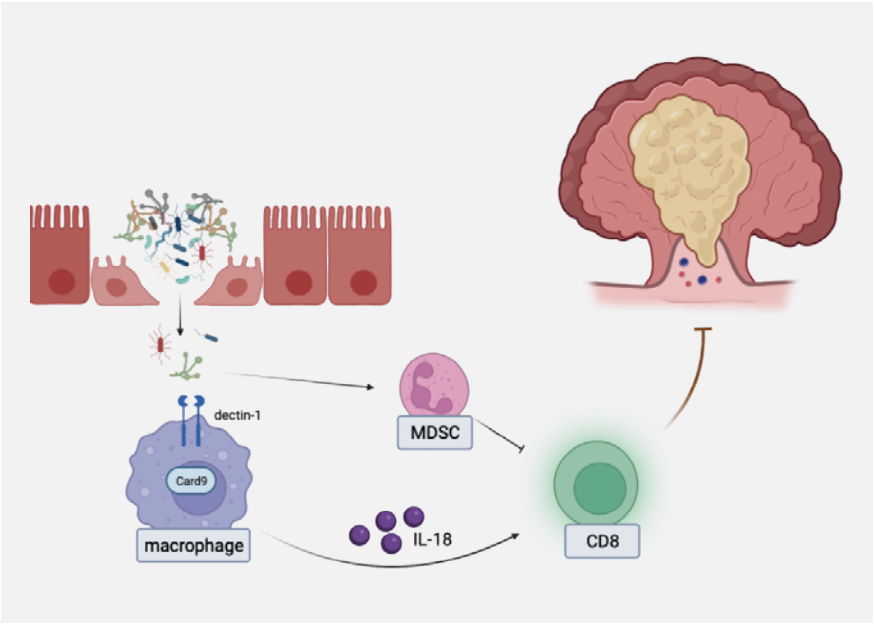
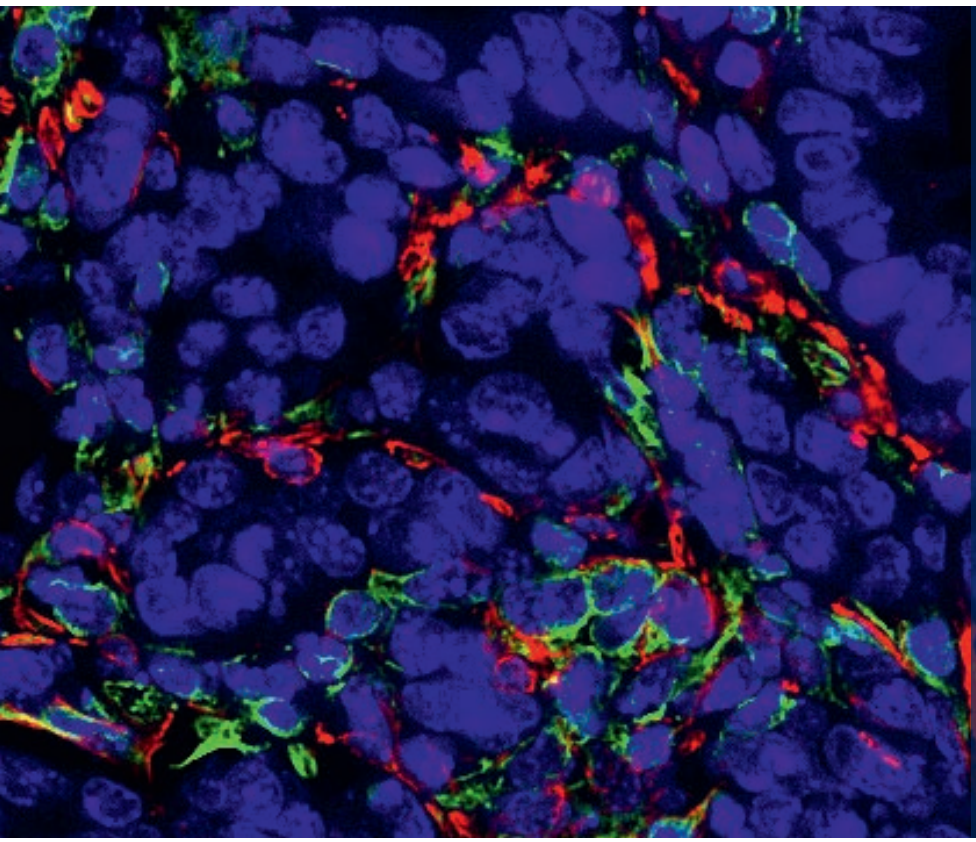


Figure 2: Commensal fungi can activate macrophages during tumor development, which leads to the secretion of IL-18, which in turn enhances CD8 T cell function and suppresses tumor growth. This can be counteracted by activation of myeloid suppressor cells.



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Conche C. & Finkelmeer F.et al.:
Combining ferroptosis induction with MDSC blockade renders primary tumours and metastases in liver sensitive to immune checkpoint blockade. ***GUT*** *2023 Sep;72(9):1774-1782.*

Denk D., et al:
Expansion of T memory stem cells with superior antitumor immunity by Urolithin Ainduced mitophagy, ***Immunity****. 2022 Nov 8;55(11):2059-2073.e8.*

Nicolas A., et al.:
Inflammatory fibroblasts mediate resistance to neoadjuvant therapy in rectal cancer. ***Cell****. 2022 Feb 14;40(2):168-184.e13.*

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invasive carcinomas and higher metastatic burden. This reversal hints that IL-17RA signaling may be protective in more advanced CRC. In a separate experiment with tumor organoids (miniature tumor models), IL-17RA-deficient organoids grew aggressively and spread to the lungs when transplanted into mice, whereas those with intact IL-17RA were less invasive. Interestingly, mice with IEC-specific IL-17RA deletion did not show the same aggressive cancer progression as those with a full-body IL-17RA knockout, implying that IL-17RA in immune cells may play a crucial role in controlling CRC. Without IL-17RA signaling, immune control was compromised, evidenced by fewer immune-suppressive cells but reduced effectiveness of CD8+ T cells, which are essential for anti-tumor activity. In line with this, experiments where IL-17RA-deficient immune cells were reintroduced into mice increased tumor invasiveness, confirming the protective role of IL-17RA in immune cells.

We also examined the impact of the gut microbiome, finding that IL-17RA deficiency led to fungal overgrowth in tumors and could show that fungi may trigger IL-17-related immune responses that help control tumors.

Based on these findings, a therapeutic angle was tested: heat-killed Candida albicans (HKCA) mimicking fungal infection was combined with IL-17 and immune checkpoint inhibitor (ICI) therapy using anti-PD-1. Although CRC is typically resistant to ICIs, the combination of HKCA and IL-17 enabled an effective anti-PD-1 response, significantly reducing tumor growth. This approach highlights a potential novel treatment strategy for CRC by leveraging the immune-stimulating effects of IL-17 in conjunction with ICI therapy.

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Tumornischen Evolution

Tumor niche evolution

Tumor microenvironment

Metastasis/Leukemia

Aging

Overview

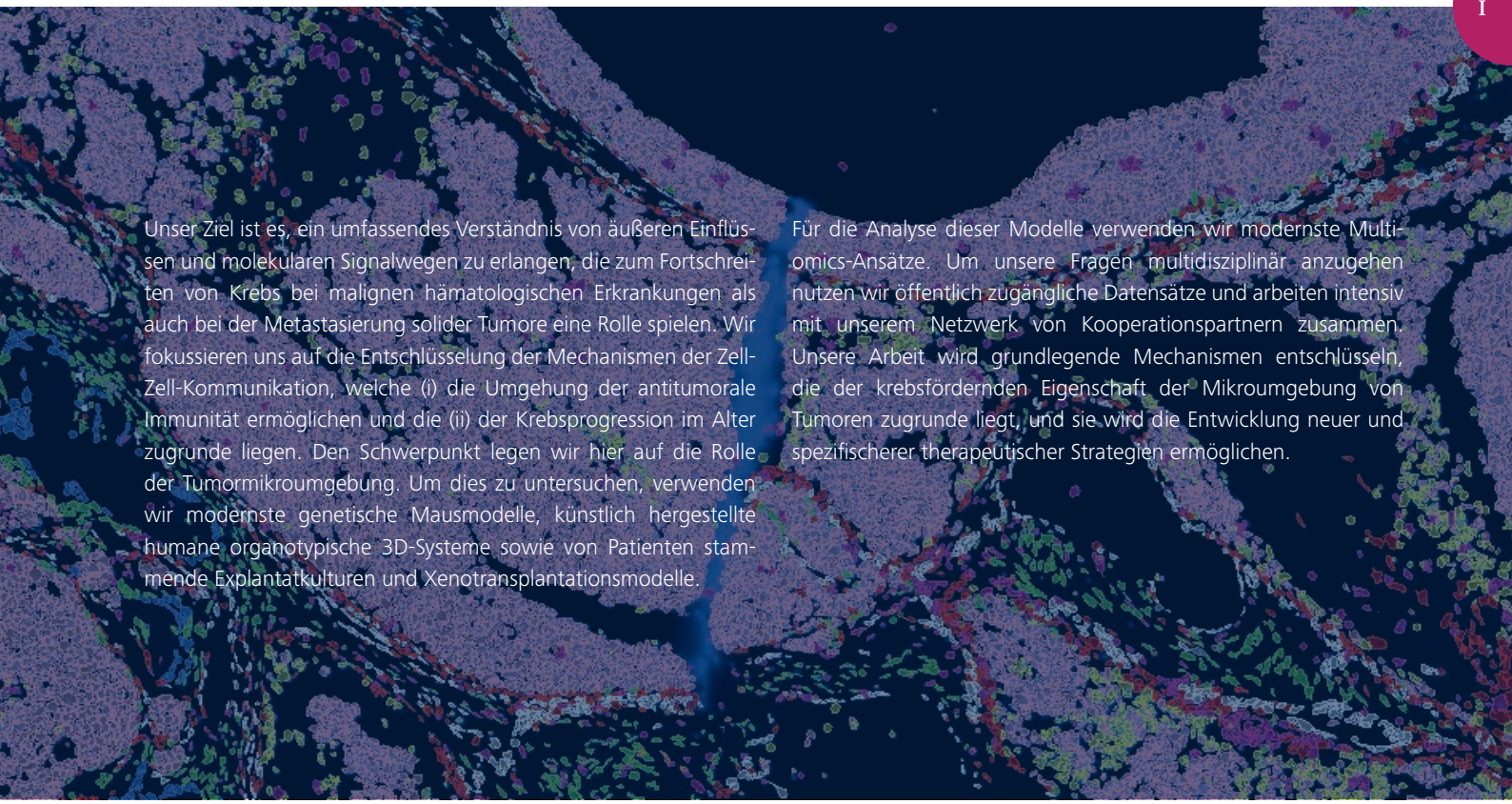
Our understanding of cancer has evolved from a tumor cell centric towards a comprehensive view that incorporates extrinsic inputs from the surrounding tumor microenvironment (TME). The TME is a complex ecosystem in which multi-directional crosstalk between cancer cells and a plethora of surrounding stromal cells shape a local milieu that favors the acquisition of the "hallmarks of cancer", such as the ability to evade immune control or metabolic adaptation that facilitates effective colonization of distant organs[1]. Notably, although they support the acquisition of common cancer traits, TMEs are heterogeneous (e.g. depending on tumor type or organ site) and dynamic (e.g. depending on disease stage or patient age), both in terms of their cellular make up and molecular priming. This implies the need to define niche-dependencies in a time and organ-site resolved manner and adapt niche-directed therapeutic strategies accordingly.

Our team devotes substantial effort to *(1) dissect the role of the TME in tumor immune evasion* and *(2) explore the contribution of age-related niche changes to cancer progression and therapy resistance*, across different cancer types. To do so, we develop cutting-edge models and use state-of-the-art technologies, including genetically engineered mouse models, fully human 3D model systems as well as multiplex imaging and single-cell omics approaches.

Project Highlights

Lifting immune suppression to promote cancer control

Cancer is associated with an immune suppressive TME that limits anti-tumor immunity and hampers responsiveness to adaptive immune checkpoint blockade (ICB; anti-PD1/PDL1; anti-CTLA4. etc.). This promotes immune evasion and therapy resistance, respectively. Our goal is to unravel the mechanisms at play to devise new strategies that could lift immune suppression, boost anti-tumor immunity, and elicit susceptibility to ICB thereby enabling lasting therapeutic benefits. We do so in the context of leukemias and brain metastasis, both of which are poorly responsive to systemic immunotherapies using ICB.



Unser Ziel ist es, ein umfassendes Verständnis von äußeren Einflüssen und molekularen Signalwegen zu erlangen, die zum Fortschreiten von Krebs bei malignen hämatologischen Erkrankungen als auch bei der Metastasierung solider Tumore eine Rolle spielen. Wir fokussieren uns auf die Entschlüsselung der Mechanismen der Zell-Zell-Kommunikation, welche (i) die Umgehung der antitumorale Immunität ermöglichen und die (ii) der Krebsprogression im Alter zugrunde liegen. Den Schwerpunkt legen wir hier auf die Rolle der Tumormikroumgebung. Um dies zu untersuchen, verwenden wir modernste genetische Mausmodelle, künstlich hergestellte humane organotypische 3D-Systeme sowie von Patienten stammende Explantatkulturen und Xenotransplantationsmodelle.

Für die Analyse dieser Modelle verwenden wir modernste Multi-omics-Ansätze. Um unsere Fragen multidisziplinär anzugehen nutzen wir öffentlich zugängliche Datensätze und arbeiten intensiv mit unserem Netzwerk von Kooperationspartnern zusammen. Unsere Arbeit wird grundlegende Mechanismen entschlüsseln, die der krebsfördernden Eigenschaft der Mikroumgebung von Tumoren zugrunde liegt, und sie wird die Entwicklung neuer und spezifischerer therapeutischer Strategien ermöglichen.

Acute leukemias are aggressive blood cancers that excel at immune evasion. Due to their low mutational load (i.e. few neo-antigens), leukemias were initially thought to passively escape immune control. Our group recently discovered that leukemia cells actively co-opt macrophages to activate a signaling axis, namely the GAS6/AXL axis, that puts the break on anti-leukemic immunity by hampering the early steps of the "cancer immunity cycle"[2] thus driving the establishment of a suppressive TME. Notably, we demonstrate that targeting AXL, via pharmacological inhibition or genetic ablation in macrophages, not only lifts the barriers towards effective anti-leukemic immunity but also elicits susceptibility to ICB[3]. Ongoing efforts are directed towards clinical translation and assessment of other candidate suppressive mediators in this context.

In the solid cancer arena, we are tackling the challenge posed by brain metastasis (BrM), which represent the most frequent intra-cranial tumor in adults and is associated with a dire outcome. BrM incidence is steadily increasing due to better control of extracranial disease and a higher number of cancer survivors at risk of presenting with BrM. On a cellular level, BrM lesions show a massive recruitment of suppressive myeloid cells which together with other brain resident cells (e.g. glial cells) enforce the establishment of an immune-suppressive TME4 (Fig. 1). Although immune checkpoint blockers (ICB) have been reported to provide clinical benefit in a small fraction of patients, more limited effects are seen in advanced disease[4]. We hypothesize that lifting immune suppression locally in the brain, is a pre-requisite to boost anti-tumor immunity and achieve effective immunotherapies in BrM, a task we currently tackle using a holistic and interdisciplinary approach in the context of two team-science projects, RISEBrain, supported by the European TRANSCAN-3 funding scheme (https://transcan.eu/output-results/funded-projects/risebrain.kl) and the Metastasis working group supported by the LOEWE Centre Frankfurt Cancer Institute. These joint ventures are instrumental to bring together expertise in engineering, imaging, computation, experimental modeling, and clinical care, to uncover and target cellular and molecular drivers of local immune suppression in BrM.

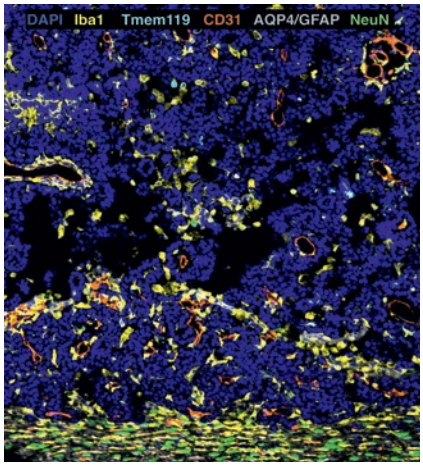
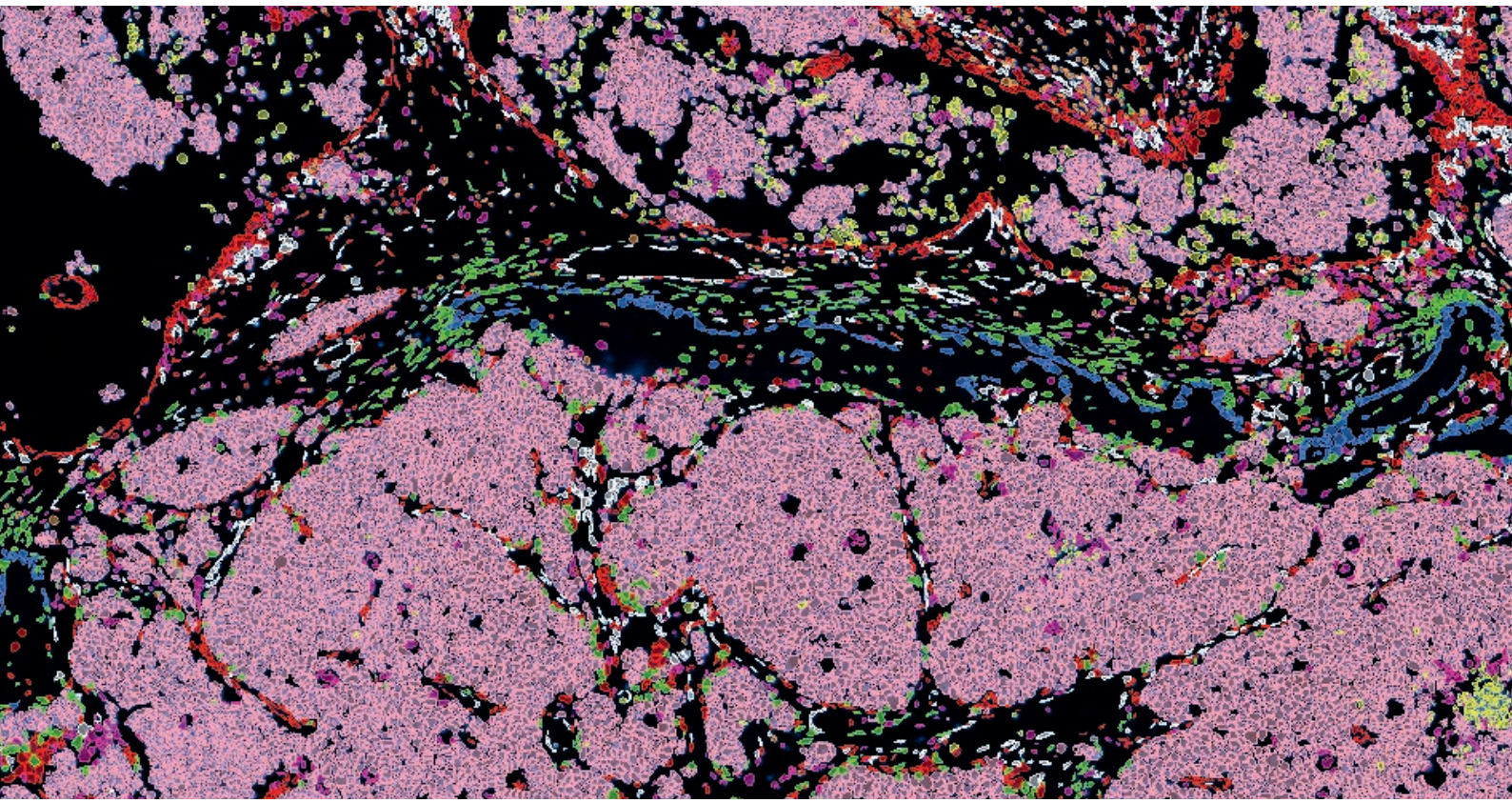


Figure 1. **Cellular architecture inan experimental breast-to-brain metastasis visualized by multispectral imaging.** GFAP and Aquaporine 4=Astrocytes; CD31=Endothelial cells; Iba1= Myeloid cells; Tmem119= Microglia [brain resident macrophages]; NeuN= Neurons; DAPI= Nuclei.

Impact of age-related niche changes on cancer

Physiological aging is accompanied by a progressive decline in health and tissue/organ function as well as a significant



increase in cancer risk. The latter represents a tremendous societal and economic challenge in our aging society. In our lab, we study *how age-related changes in the bone marrow (BM) microenvironment* (cellular architecture, composition, and molecular priming) *impact cancer development/progression in the bone*. We do so in the context of hematological malignancies and solid tumor metastasis to the bone.

In solid cancer, we focus on ER+ breast cancer because it exhibits high tropism to the bone and displays long periods of tumor dormancy, that can last up to decades, before the development of overt metastasis leading to poor quality of life and patient death. Cues leading to the activation of these dormant disseminated tumor cells (DTCs) remain poorly understood, but advanced age is one of the most significant predictors of overt bone metastasis occurrence. As part of the µBone consortium (https://www.microbone.de) we use both syngeneic and patient-derived models, to explore *how age-related alterations in the BM niche drive the awakening of quiescent metastatic cancer cells*. Additional efforts within the Metastasis working group supported by the LOEWE Centre Frankfurt Cancer Institute, aim at leveraging *single-cell and spatial omics approaches to dissect the TME in patient-derived bone metastatic tissue* (Fig. 2). The gained knowledge will be exploited to uncover new means by which we could improve outcome and/or quality of life of patients with bone metastasis.

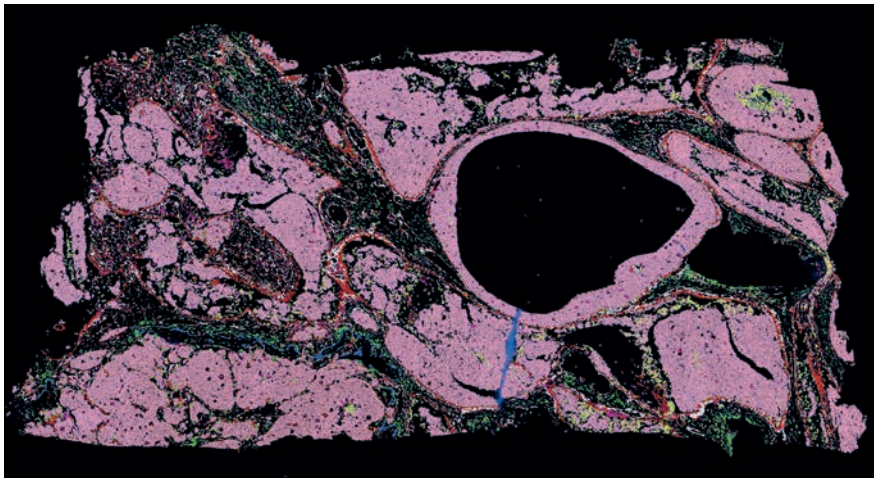
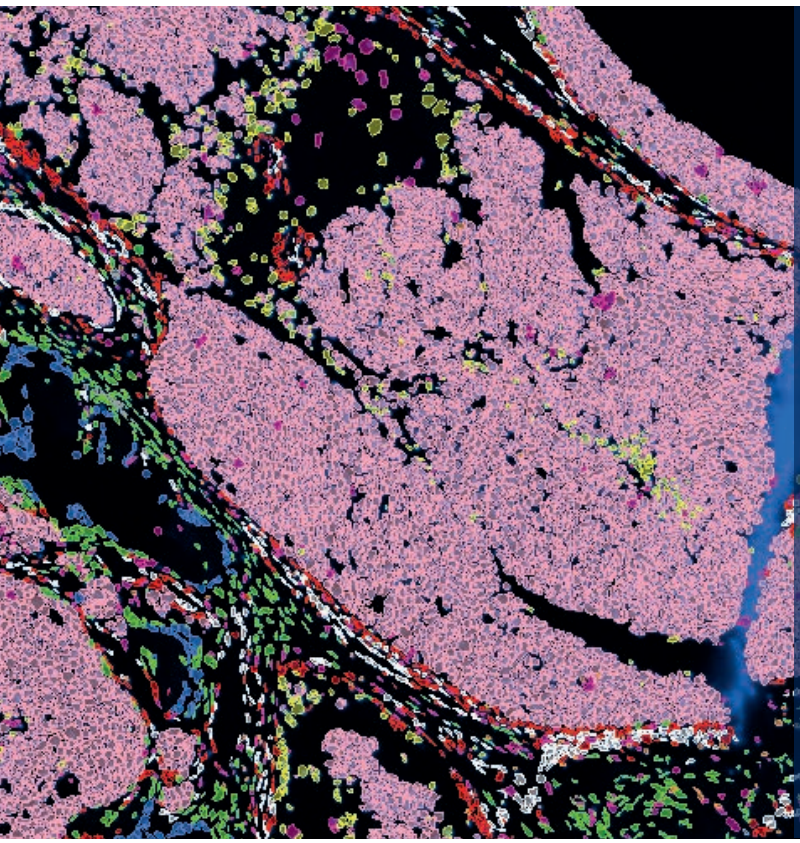


Figure 2. **Single cell spatial transcriptomics of human bone metastasis.** Analysis of TME architecture using FFPE material from a breast-to-bone metastasis sample, using the Xenium platform. Light pink= Tumor cells; Other colors= Cellular constituents of the tumor microenvironment.

In hematological malignancies, we focus on Myelodysplastic Syndromes (MDS)[5,6], a group of syndromes that are characterized by ineffective hematopoiesis with peripheral cytopenia, as well as its precursor state, referred to as clonal hematopoiesis of indeterminate potential (CHIP). We interrogate whether age-related niche changes contribute to the progressive clonal dominance observed in CHIP and MDS as well as the cellular and molecular



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Efficacy and Safety of Bemcentinib in Patients With 1 Advanced Myelodysplastic Neoplasms or Acute Myeloid Leukemia Failing Hypomethylating Agents-The EMSCO Phase II BERGAMO Trial. ***Leukemia. 2023****. In Press*
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Phosphatidylserine Synthase PTDSS1 Shapes the Tumor Lipidome to Maintain Tumor-Promoting Inflammation. ***Cancer Res. 2022*** *Apr 15;82(8):1617-1632.*

Tirado-Gonzalez I*, Descot A*, Soetopo D*, Nevmerzhitskaya A, Schaffer A, Kur IM, Czlonka E, Wachtel C, Tsoukala I, Muller L, Schafer AL, Weitmann M, Dinse P, Alberto E, Buck MC, Landry JJM, Baying B, Slotta-Huspenina J, Roesler J, Harter PN, Kubasch AS, Meinel J, Elwakeel E, Strack E, Tran Quang C, Abdel-Wahab O, Schmitz M, Weigert A, Schmid T, Platzbecker U, Benes V, Ghysdael J, Bonig H, Gotze KS, Rothlin CV, Ghosh S, **Medyouf H**.
AXL inhibition in macrophages stimulates host-versus-leukemia immunity and eradicates naive and treatment resistant leukemia. ***Cancer Discov. 2021****Jun 8:candisc.1378.2020.*
*equal contribution

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mediators underlying this phenotype. This project builds on our previous finding that disease-associated mesenchymal niche cells are essential for MDS maintenance[7] and is part of the MDS-INTERCEPT Innovative Training Network (https://intercept-mds.eu) that brings together 10 European public and private institutions with expertise in leukemia, epigenetics and single-cell approaches to promote early disease interception in the context of clonal myeloid diseases. Experimentally, both research directions are supported by patient-derived xenografts in genetically engineered models with niche alterations that recapitulate those associated with physiological aging[8]. This is complemented by newly developed, highly modular and versatile 3D Human Organotypic Marrow Environments (3D HOMEs), that are easily amenable to experimental manipulation (visualization, CRISPR-editing, drug treatment) and in which malignant cells can be studied in a fully human setting that closely recapitulates the cellular composition and architecture found in the human bone marrow (Fig. 3).

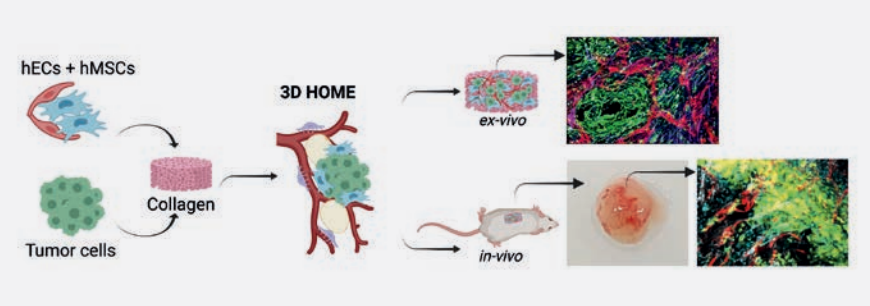

Figure 3. **Schematic view of the 3D HOMEs used to study reciprocal crosstalk between tumor cells and the bone marrow microenvironment.** Representative images show tumor cells in green (GFP+), the vasculature (Red) and stromal cells of mesenchymal origin (Cyan or purple). hEC= human endothelial cells. hMSC= human mesenchymal stromal cells.

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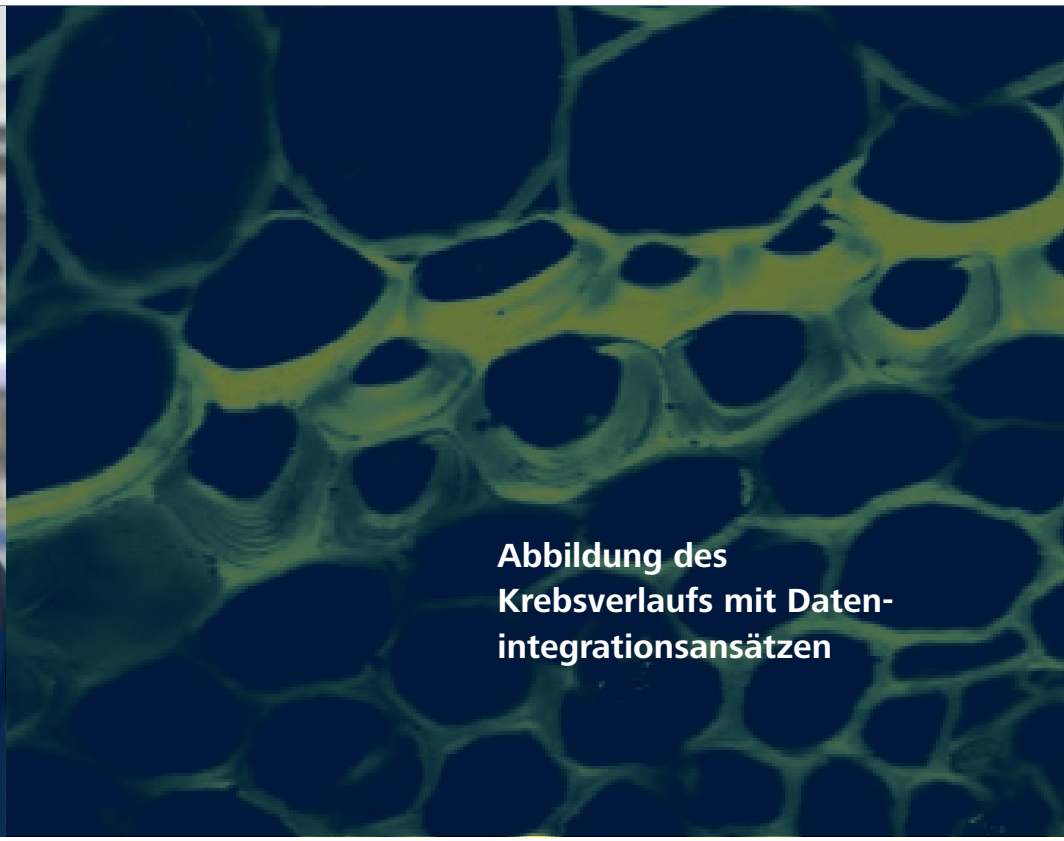


Abbildung des Krebsverlaufs mit Daten-integrationsansätzen

Mapping cancer progression with data integration approaches

mapping cancer progression

data integration approaches

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

Die zelluläre Heterogenität ist eine der größten Hürden bei der Krebsbehandlung. Die Variabilität der Tumorzellstadien und der Zusammensetzung des Mikromilieus zwischen Patienten führt zu unterschiedlichen Behandlungsansprechen, während die Variabilität innerhalb eines einzelnen Tumors auf das Vorhandensein von Zellsubpopulationen hinweisen kann, die in der Lage sind, die Therapie zu überleben und Rezidive und Metastasen zu fördern. Die Rolle dieser verschiedenen Populationen zu entschlüsseln und Möglichkeiten zu identifizieren, sie zum therapeutischen Vorteil zu manipulieren, bleibt eine zentrale Herausforderung in der Krebsforschung. Einzelzell-RNA-seq (scRNA-seq) ist sehr effektiv bei der Entschlüsselung der zellulären Heterogenität, aber einzelne scRNA-seq-Studien erstellen nur wenige Tumorprofile, es fehlen umfassende klinische Annotationen und sie erfassen nur eine Momentaufnahme aus einer langen Zeitspanne der Krebsentwicklung. Diese Herausforderungen behindern die Identifizierung der Zellstadien, die das Fortschreiten der Krankheit am besten vorhersagen. Die Integration vieler Datensätze verschiedener Krankheitsstadien ist ein vielversprechender Weg, um diese Hürde zu überwinden.

Das Ziel unseres Labors ist es, die Veränderungen der Zellstadien und ihre Wechselwirkungen aufzuklären, die das Fortschreiten von Tumoren entlang ihrer gesamten Zeitachse bestimmen, von den frühesten Stadien der malignen Transformation bis hin zu rezidivierenden und metastasierenden Erkrankungen. Wir werden dies erreichen, indem wir Tumorprofile über viele Patienten, Krebsarten und Krankheitsstadien hinweg vergleichen, um Veränderungen zu ermitteln, die (i) bei allen Patienten zuverlässig nachweisbar sind und somit mit hoher Wahrscheinlichkeit die wahre Biologie und nicht technische Effekte widerspiegeln; (ii) über mehrere Krebsarten hinweg konserviert sind, was auf gemeinsame therapeutische Anfälligkeiten hindeutet; und (iii) prädiktiv für das Fortschreiten der Krankheit und Hinweise auf neue Behandlungsmöglichkeiten sind. Wir werden diese Analyse weiter vertiefen, indem wir räumliche Transkriptomik- und Bildgebungsdaten einbeziehen, um die Zusammenhänge zwischen Mikromilieu vollständig zu erfassen. Mit diesen multimodalen Vergleichen werden wir allgemeine Prinzipien der Krebsentstehung aufdecken und neue therapeutische Fenster für eine verbesserte Krebsbehandlung aufzeigen.

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 recently 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., *bioRxiv*; 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

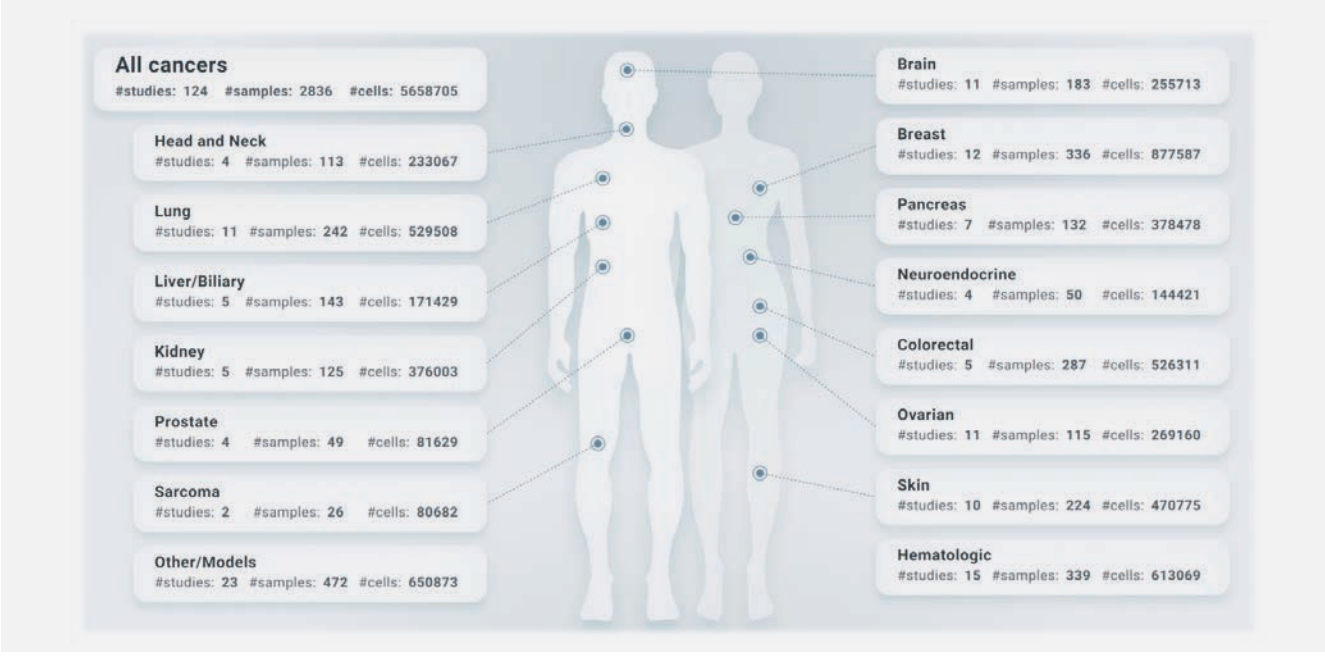
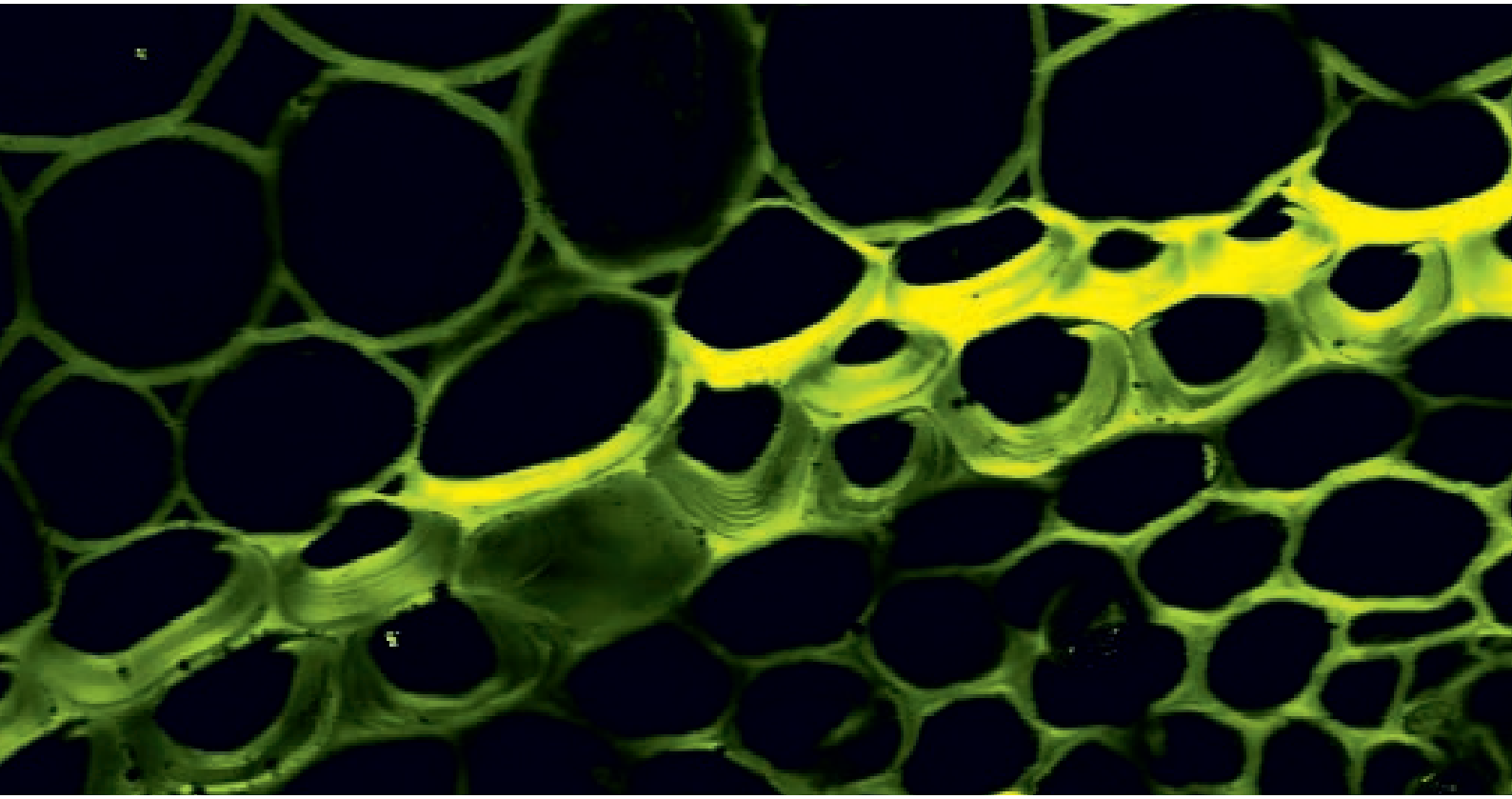


Figure 1. **The Curated Cancer Cell Atlas** (3CA). A repository of published tumour scRNA-seq datasets from 124 studies, curated into a consistent format with verified cell annotations.



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. We are still far from a complete understanding of the tumour timeline, and we are largely unable to predict malignant transformation, treatment response and metastasis. Filling in these knowledge gaps will transform our ability to make precise and effective clinical interventions in cancer.

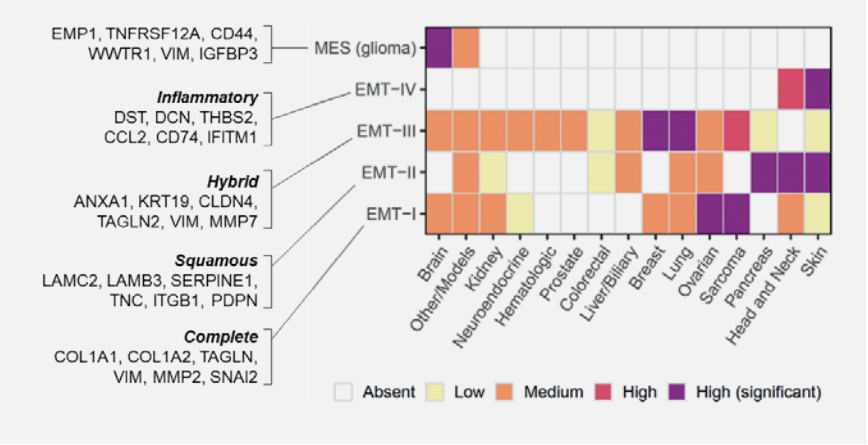
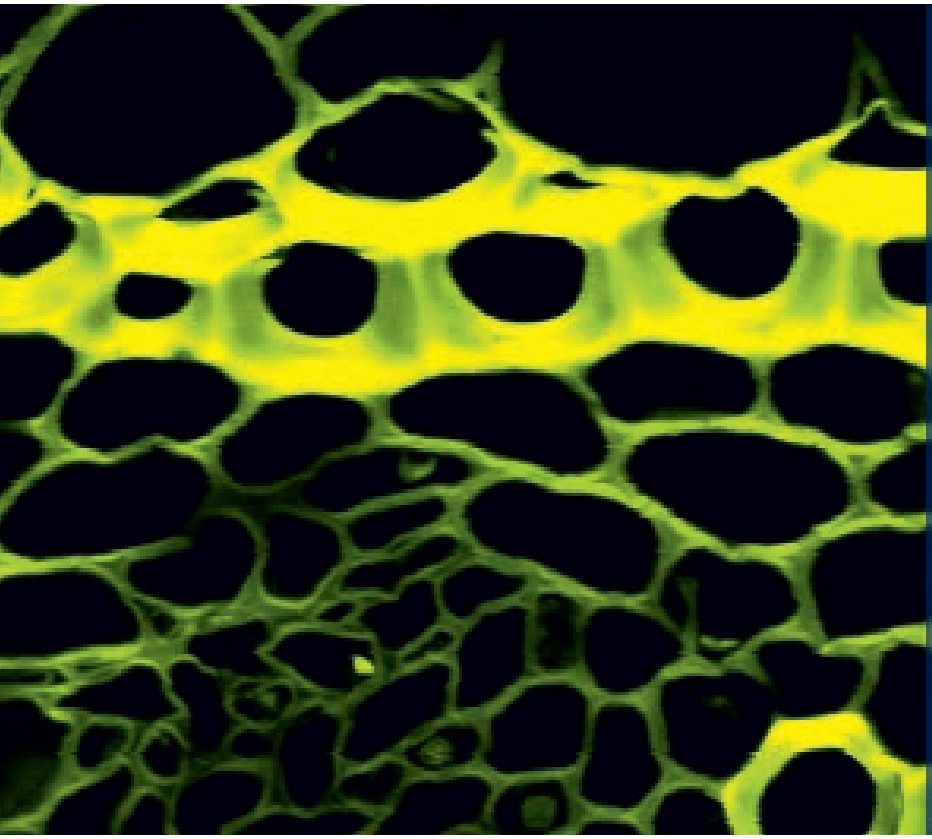


Figure 2. **Extent of EMT-like states in different cancer types.** Pan-cancer expression analysis identified 5 context-specific mesenchymal cell states with different signature genes. This demonstrates that EMT-like states are detectable in every cancer type in some form.



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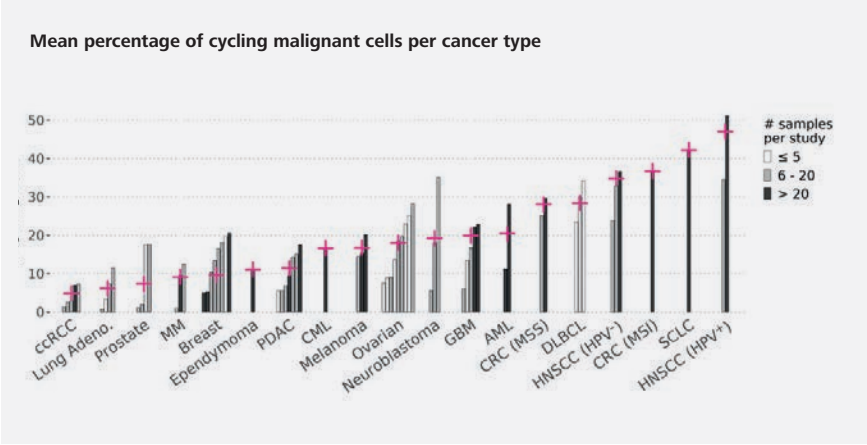

Figure 3. **Pan-cancer quantification of proliferation rates with 3CA.** Bar plot showing the percentage of cycling malignant cells in each study and cancer type. This revealed large variation in proliferation rates between cancer types.

Research objective

My lab will build a pan-cancer, multimodal atlas of tumour progression of an unprecedented scale. We will integrate 3CA with published 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. Our goal is to elucidate the changes in cell states and their 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.

This will be achieved by comparing tumour profiles 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. With these multimodal comparisons, we will uncover general principles of cancer development and reveal new therapeutic windows 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)
Recent advances in genome-editing, particularly the CRISPR/Cas9 technology, have revolutionized the generation of mouse models and Knock-out (KO) mouse models. Combination of CRISPR with homology-directed targeting for insertion of short sequences directly into the genome (Knock-in, KI) opens fresh 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.

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 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.

Die Transgenic Core Facility (TCF) am Georg-Speyer-Haus generiert neue und innovative Mausmodelle für die Krebsforschung durch den Einsatz neuester Technologien der Genommodifikation. Ende 2021 hat Dr. Phillip Grote die Leitung der TCF übernommen. Er bringt seine langjährige Erfahrung in der Entwicklung von transgene Mausmodellen mit und seine Expertise in der Analyse einer neuen Klasse von Genen, den langen, nicht-protein kodierenden RNAs (lncRNAs), die auch in der Krebsforschung ein immer größeres Interesse für möglich Therapieansätze wecken.
Die TCF hat ein starkes Portfolio an etablierten Systemen, um biomedizinisch relevante Mausmodelle zu etablieren. Dazu gehört die Transgen-generierung mithilfe aktueller Versionen der CRISPR/Cas9 Genschere, die es nicht nur erlaubt Bereiche des Genoms einfach zu entfernen, sondern auch kurze Abschnitte gezielt zu integrieren, um krankheitsrelevante Mutation einzubringen, bestimmte Zelltypen zu markieren oder Gene für eine spätere, genetische Inaktivierung in z.B. Tumoren zu markieren. Um einen robusten Ablauf sicherzustellen hat die TCF-Techniken zur Transgen-generierung weiter optimiert und hochwertige Protokolle weiterentwickelt. So kam im Jahr 2024 auch die Möglichkeit dazu, anstatt Gene einfach auszuschalten, stattdessen die Proteine, die von manchen dieser Gene generiert werden, pharmakologisch verschwinden zu lassen, was oft zielgenauer und schneller als klassische Verfahren ist. In Zusammenarbeit mit dem Frankfurt Cancer Institut (FCI) werden auch neue Verfahren für den *in vivo* Einsatz entwickelt.

Der Genklasse der lncRNAs kommt eine immer größere Bedeutung bei der Regulation des Genoms zu. LncRNA Gene sind zelltypspezifischer exprimiert als herkömmliche proteinkodierende Gene und können daher spezifischer manipuliert werden; sie sind daher interessante Zielmoleküle für eine pharmakologische Intervention. Durch gezielte genetische Veränderungen in Mausmodellen konnten wir bisher einige dieser lncRNAs ausschalten und dadurch eine wichtige Rolle bei der Genregulation zeigen (*Handsdown, Sweetheart*). Da die Genklasse der lncRNAs noch relative neu ist wird es in den nächsten Jahren wichtig werden, wie diese in der Zelle genau funktionieren, um neue Ansätze für Therapien auf der Basis der lncRNAs zu entwickeln. Wir haben dahin 135 lncRNAs identifiziert, die in den tumorassozierten MSC Zellen von AML Patienten dereguliert sind. Diese sind derzeit unser zentraler Forschungsschwerpunkt.

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 (+/- 1kb) 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. 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

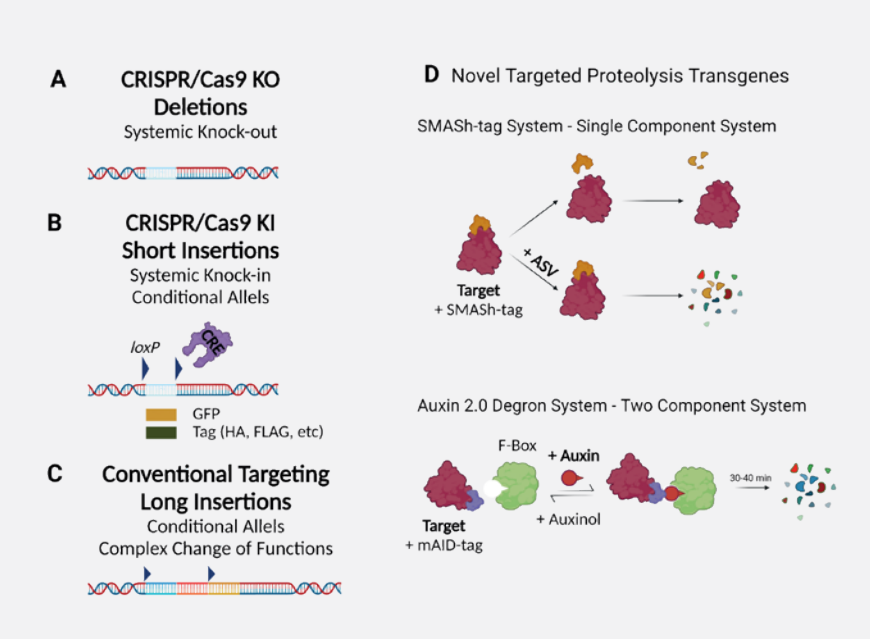

Figure 1.
(A) CAS9 directed gene deletion from several basepairs up to the megabase range that is usable for all techniques shown in Fig 2. (B) CAS9 assisted integration of short genetic elements specific at any site of the genome. This approach is also available for all techniques shown in Fig 2. (C) Complex transgenes require the modification of embryonic stem cells prior to mouse generation (Fig2 top two techniques). (D) The novel transgenic approaches of drug-inducible targeted protein degradation are shown as an example and are currently under development at the TCF. The SMASh-tag either removes itself and gets degraded or, when the drug Asunaprevir (ASV) is present, drags the attached protein along for degradation. 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.
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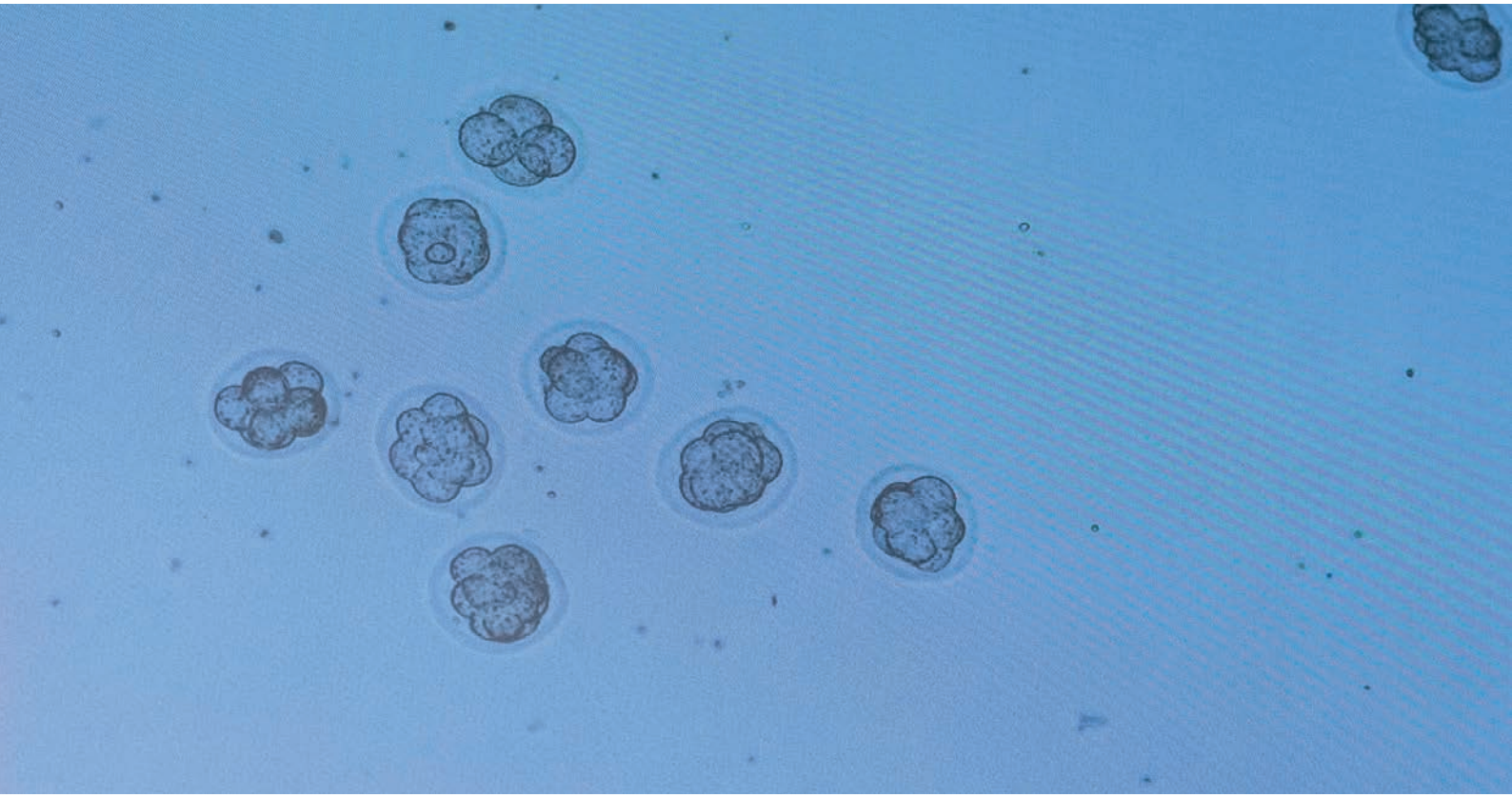


targeted degradation approaches for any protein of interest. In these systems a protein of interest is tagged (see Fig 1B) with short peptide that can bind a small molecule drug. The binding of this drug can induce protein degradation and removal of the drug from the mouse does allow the reappearance 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. Current protocols require the presence of wild type embryos that serve as a host for transgenic embryonic stem cells or to be modified by CRISPR/Cas9 ex vivo (Fig 2). Novel techniques employing CRISPR/Cas9 now allow the direct genetic modification of wild type embryos in the host mother animal, without the need so sacrifice them (i-GONAD) (Fig 2, bottom right). This technique will reduce the number of required animals for generating mouse models drastically and thereby strictly follow the international guidelines for animals experiments to reduce animal numbers when possible. In addition, the process of generating useful mouse lines is faster for simple CRISPR/Cas9 KO or KI (Fig 1A,B) and only takes 2-3 months.

The genome regulation group analyses the *in vivo* function of the gene category of long non-protein coding RNAs (lncRNAs), which are as abundant as 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

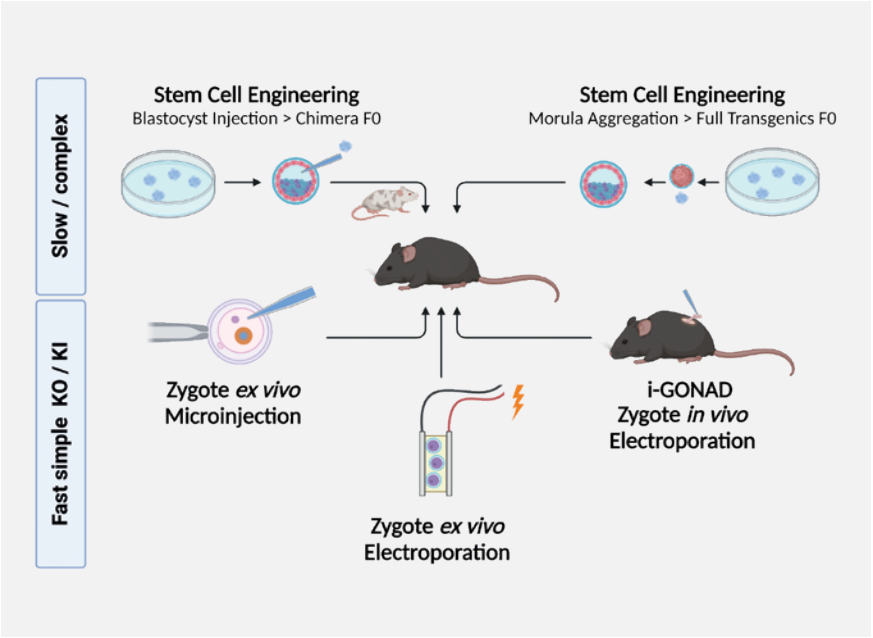
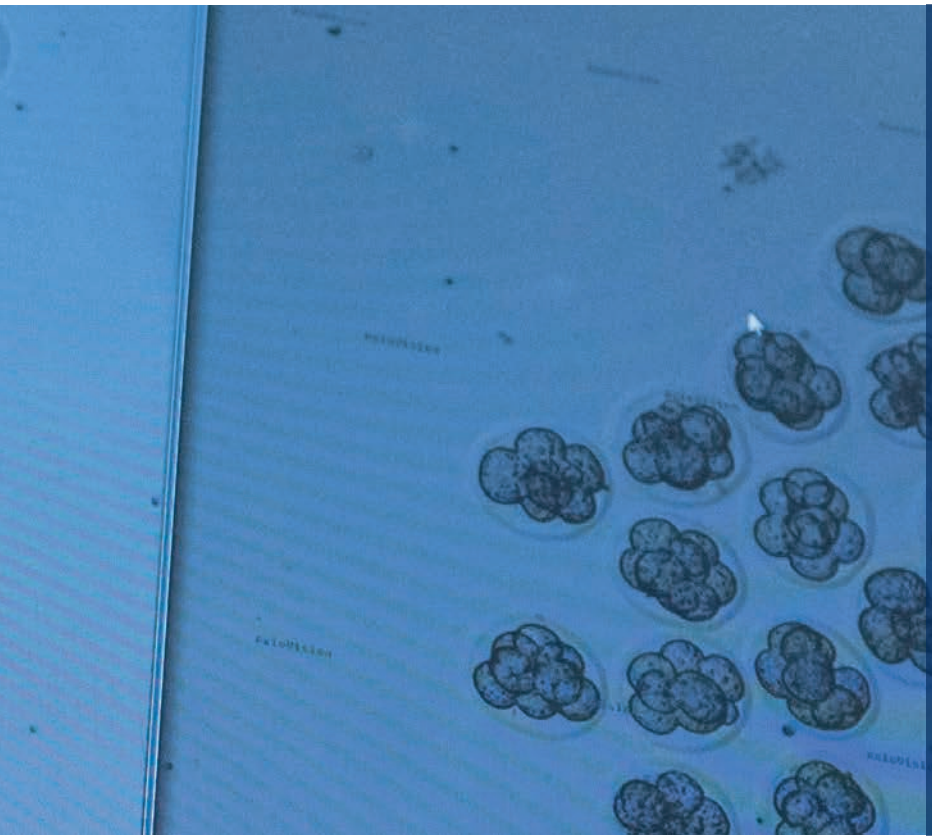


Figure 2.
Techniques for the generation of transgenic mice are available at TCF. The innovative approach i-GONAD is now available as a service from TCF. Created with BioRender.com



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and outcome. We could show that the activity of the lncRNA *Handsdown* is essential for embryo development by adjusting the expression levels of its nearby protein coding gene. 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).

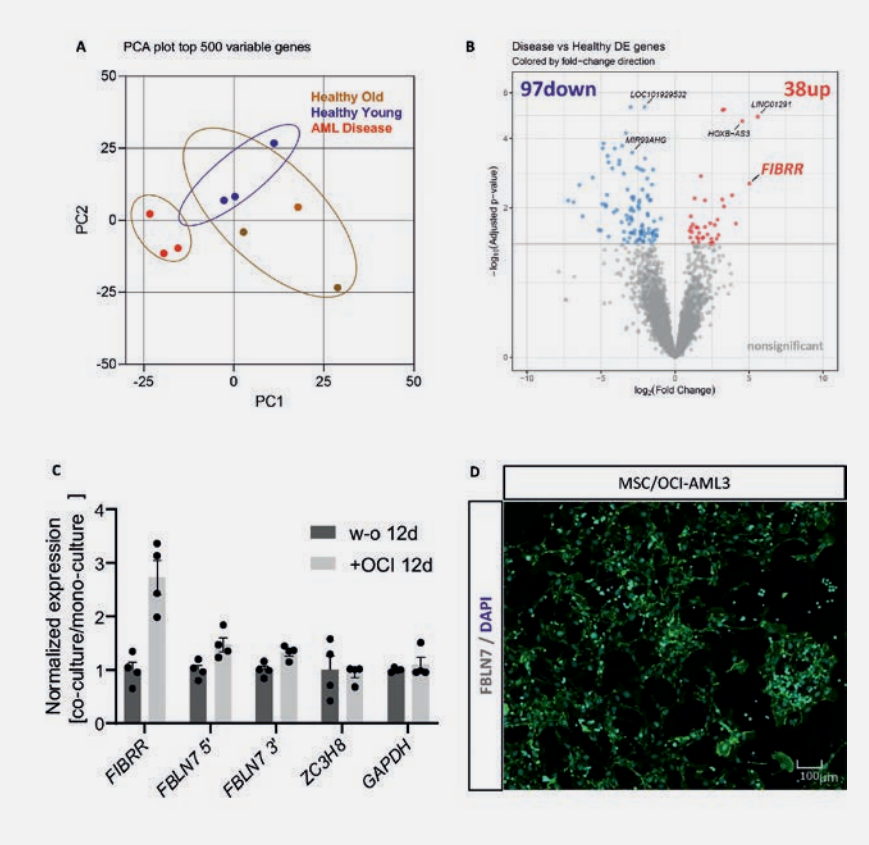

Figure 3.
Dysregulated lncRNAs in MSCs from AML patients (A,B) 135 lncRNAs are dysregulated (C) The lncRNA *FIBRR* is upregulated in MSC upon extended exposure to AML cells. (D) The FBLN7 protein localizes to co-cultured AML cells.

Funktionell-zielgerichtete Präzisionsmedizin bei Krebspatienten

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Functional Precision Oncology

To bridge the gap between the genomic knowledge of individual cancers and what can be directly applied in the clinic, comprehensive functional information is needed to identify the vulnerability of the respective tumor. Our group functional precision oncology is addressing this need by performing functional *ex vivo* drug efficacy testing on patient-derived tumor cells to complement genomic approaches, particularly for cases in which genomics fail to guide treatments or in which the tumor is driven by non-genomic factors, such as the tumor microenvironment. By providing functional information at the individual tumor cell level, we aim to 1) better understand cancer- and drug-induced phenotypes to discover new drug efficacies and drug repositioning opportunities; 2) to investigate possible biomarkers and underlying mechanisms for the drug effects seen as well as for the resistances that emerge, and 3) to ultimately translate the results directly into the clinic.

CNS immune landscape

Brain metastasis-associated inflammation

Metabolic checkpoints

Resistance mechanism

Von präklinischen *ex vivo* Studien zur klinischen Anwendung

Unsere Arbeitsgruppe „Funktionelle Präzisionsonkologie" hat das Ziel, die derzeitigen molekularen und immuntherapeutischen Präzisionsmedizin-Programme durch funktionelle Informationen über das Ansprechen individueller Tumorzellen auf eine Vielzahl von Wirkstoffen zu ergänzen.

Ausgehend von frischem Tumormaterial individueller Patienten entwickeln wir neue prädiktive 3D-Tumorzell-Modelle, welche über eine standardisierte *ex vivo* Drug Testing Plattform auf Sensitivität und Resistenz gegenüber großer Medikamentenbibliotheken getestet werden.

Wir verfolgen dabei drei Ziele: 1) die Untersuchung von krebs- und wirkstoffinduzierten Phänotypen, um neue Therapien und Neupositionierungen von bereits zugelassenen Medikamenten zu identifizieren; 2) die Identifizierung möglicher Biomarker für individuelle Sensitivitäten und Resistenzen sowie 3) die direkte Translation der Ergebnisse in die Klinik. Methodisch setzen wir hierzu die Hochdurchsatz-Mikroskopie (HCM, Bioimaging) ein, die eine schnelle Testung großer Wirkstoffbibliotheken an limitiertem Tumormaterial sowie eine Analyse auf Einzelzellebene ermöglicht. Mittels multiparametrischer KI unterstützter Analysen, Integration von funktionellen, sowie genomischen und proteomischen Daten der jeweiligen Tumorproben sollen letztlich personalisierte Therapien für individuelle Krebspatienten mit bislang unheilbaren Erkrankungen zu entwickelt und klinische Studien unterstützt werden.

We are carrying out the following projects:

1. Predictive *ex vivo* cancer models
2. Functional drug response testing
3. High-content phenotypical image analysis using artificial intelligence

As the ultimate goal is to implement the functional precision medicine approach into a widespread clinical use, we aim for a high standardization of our functional assays to ensure reproducibility and reliability or our protocols and results as well as quick turnaround time of results within a maximum of a couple of weeks allowing direct clinical translation.

Establishment of predictive and advanced *ex vivo* disease models:
We receive fresh and fresh-frozen patient-derived tumor material, which is used to establish predictive disease models. Current main cancer entities cover adult and pediatric leukemia (CLL, AML) as well as selected solid tumor entities. Here, we focus on establishing *ex vivo* tumor models that closely reflect the situation in the human body *and* at the same time are suitable for high-content drug testing in multi-well formats. We are investigating different culture protocols that mimic the tumor microenvironment and the influence of cellular matrices, including 2D (co-)cultures as well as 3D spheroid cultures with emphasize on short-term models that allow a relevant clinical turn-around time of our drug testing results. In reverse translation studies, co-culture systems including stromal cells, immune cells and/or cytokine signaling are established (Oppermann et al., Blood, 2016) to particularly investigate possible factors leading to *in vivo* drug resistance.

Functional drug response profiling:
Key methodology of our functional *ex vivo* drug sensitivity and resistance profiling ('drug response profiling', DRP) platform is the use of high-content fluorescent spinning-disc confocal microscopy (HCM, bioimaging) allowing to test large drug libraries for their effect on human-derived cancer cells in a medium- to high-throughput format and to distinguish between different cell types within one well. We test different compound libraries, including donated chemical probe library obtained through the Structural Genomics Consortium (SGC) as well as customized drug libraries

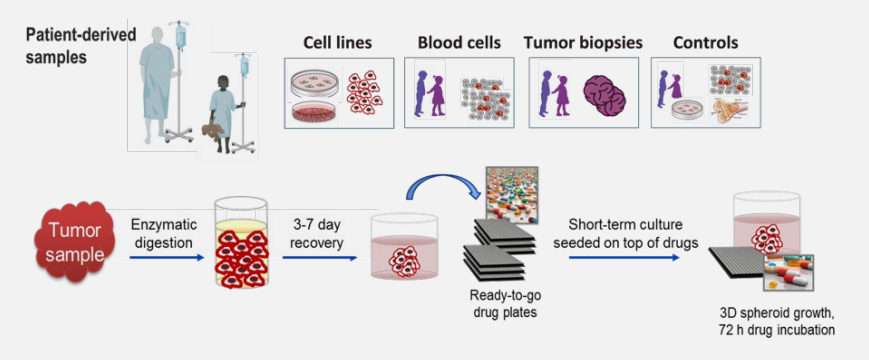
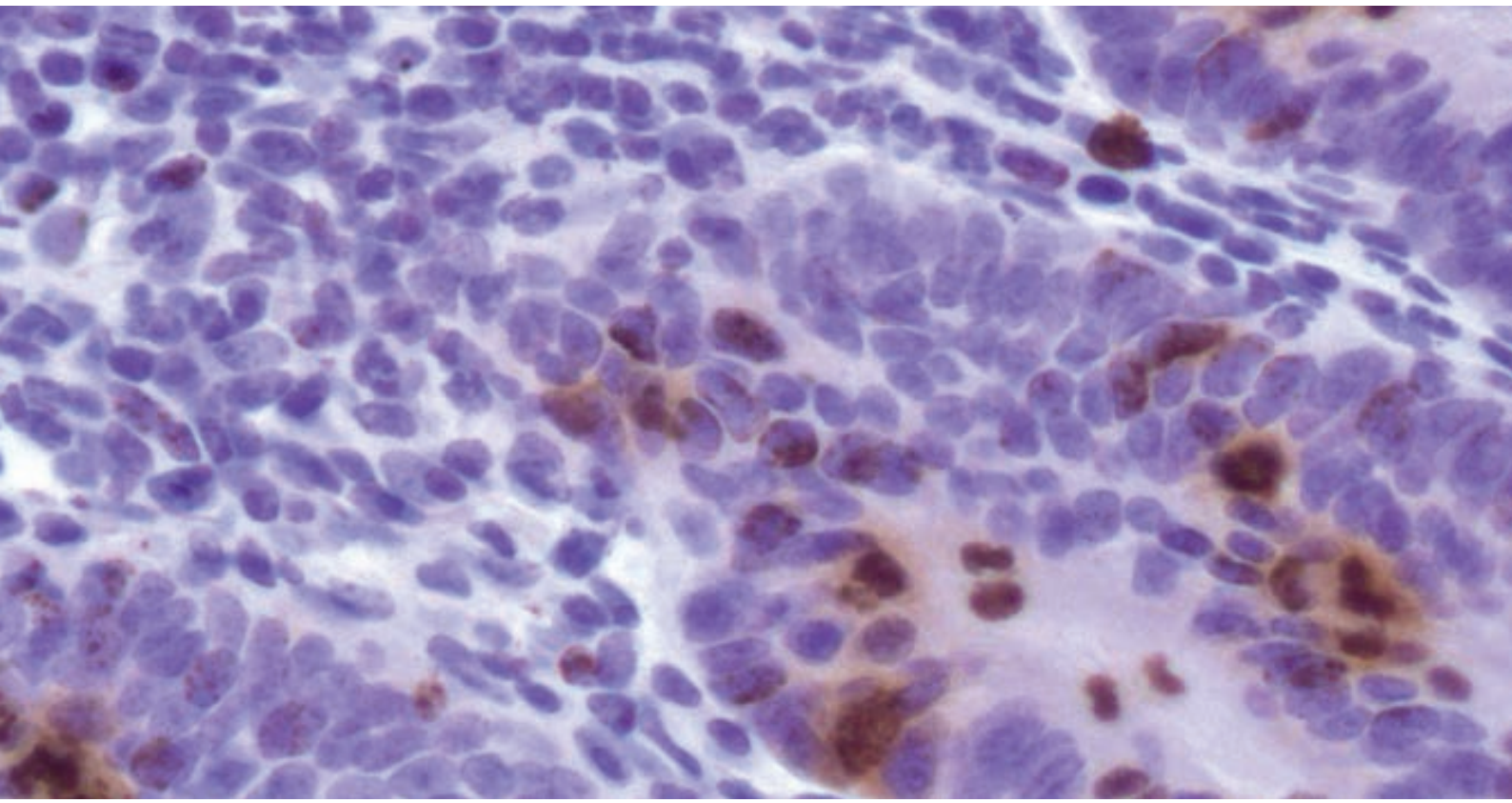


Figure 1. generated with biorender.com and further modified.



consisting mainly oncology drugs, that are FDA/EMA approved, a variety of targeted new drugs (e.g., (multi) kinase inhibitors) and compounds currently tested in clinical late phase (Phase II/III) for the respective diagnoses. Drugs are tested in a minimum of 5 concentrations covering the clinical achievable plasma and steady state concentration and replicates, mainly in a 384 multi-well format.

As automated analysis tools are crucial for handling and management of big data and timely feedback to the clinic, we develop bioinformatical drug analysis pipelines allowing the quantification of mono- and combination therapy responses for individual patients and cohorts and mapping of drug hits with drug target genes and multi-omics data (ElHarouni et al., Pharmacol Res., 2022). Together with the molecular profiling of the respective tumor samples, the functional information is used for the establishment of hypotheses on cancer subtype-selective drug combinations and their predictive biomarkers and further supports the optimal design of new clinical trials (e.g., new basket trials).

High-content phenotypical image analysis using artificial intelligence: We apply high-content 2D and 3D image analysis to phenotypical drug response profiling of the patient-derived tumor cell cultures. Here we use the multiplex/cell painting approach, combining different fluorescent dyes to extract phenotypical information of single cells and applied drugs. Using this approach, we investigate how the different drugs affect different subpopulations of tumor and non-tumor cells and further classify induced cell death mechanisms as well as entity- and patient-specific phenotypes and drug response. We employ both classical image analysis approaches (MIP (2D), volumetric 3D analysis, 3D and 2D nuclei and single cell

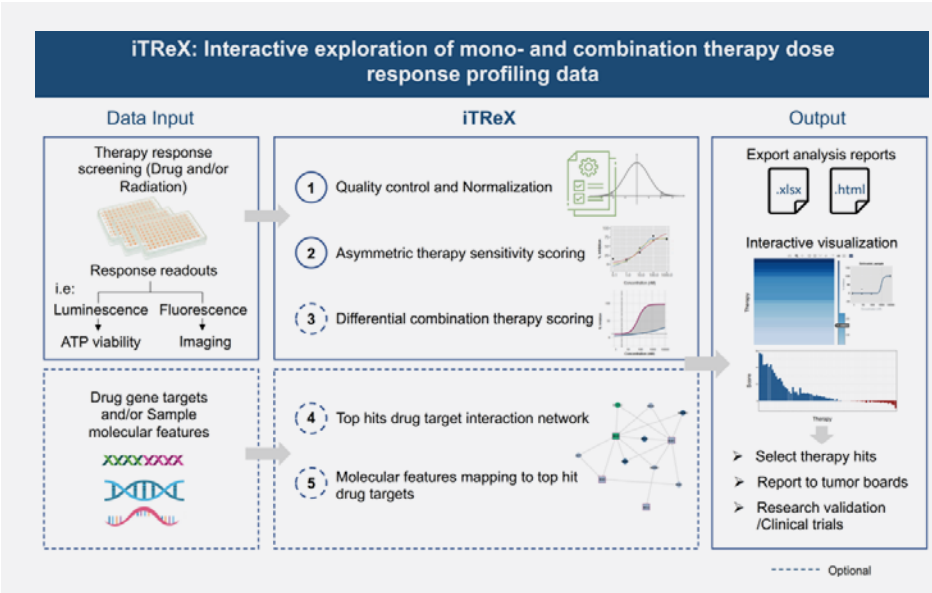
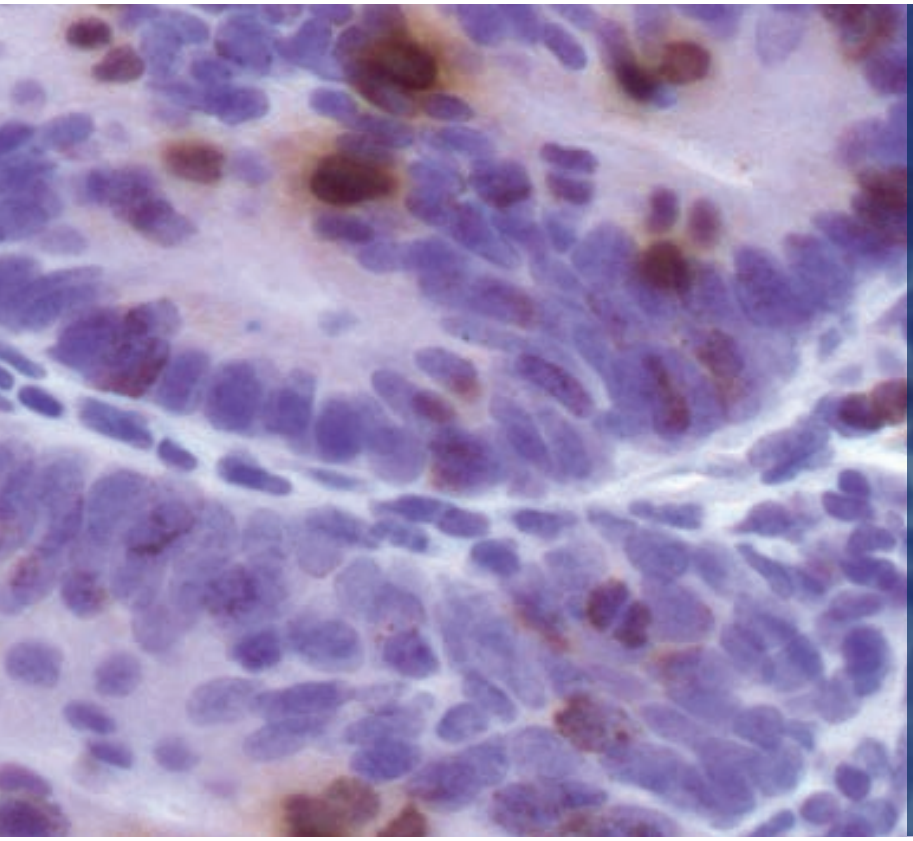


Figure 2. iTReX: ElHarouni et al., Pharmacological Research, 2022; https://itrex.kitz-heidelberg.de/



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ElHarouni D, Berker Y, Peterziel H, Gopisetty A, Turunen L, Kreth S, Stainczyk SA, Oehme I, Pietiäinen V, Jäger N, Witt O, Schlesner M, **Oppermann S.**
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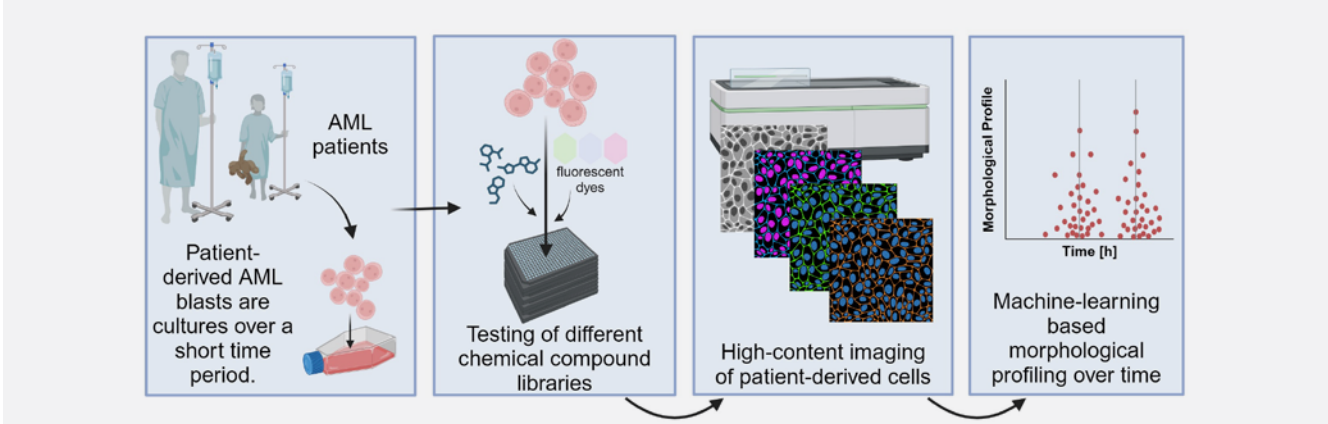
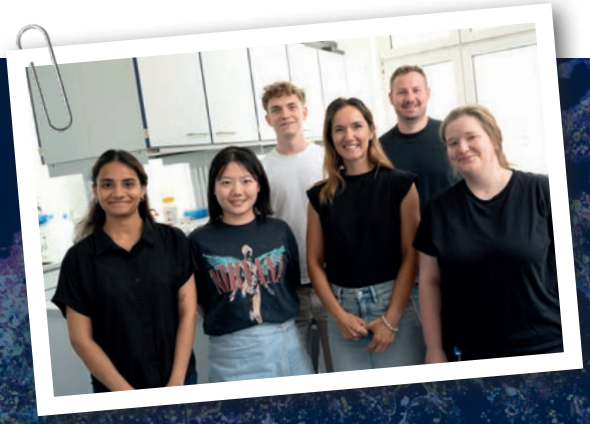


Figure 3: Example workflow for functional drug response testing on patient-derived AML blasts.

segmentation, advanced feature extraction (i.e morphology, shape, intensity, texture), supervised and unsupervised phenotype clustering) as well as end-to-end deep learning with the aim to gain more complex and detailed information of drug response and cellular behavior. We have previously developed a patient-by-patient deep transfer learning method using a convolutional neural network which transfers image information into image-based cell viabilities (Berker Y. et al., IEEE-Trans Med Imaging (TMI), 2022). Our group is now building up on the established pipelines and is developing new and advanced AI-based image analysis models in close collaborate with the local and international bioinformatics, AI and image-analysis groups.

The group is co-affiliated with the group of Clinical Pharmacy, FB 14 at the Institute of Pharmacology and Clinical Pharmacy, Goethe-University, Frankfurt am Main.



Die Rolle der komplexen Tumormikroumgebung für die langfristige Krankheitskontrolle

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Systems Biology of Breast Cancer in Drug Response

Tumor microenvironment

Integrative model systems

Spatial multi-omics

Therapy Resistance

Breast Cancer

Conventional anti-cancer agents have been primarily designed to target tumor intrinsic vulnerabilities. Recent studies including ours support the concept that cells surrounding the cancer cells (i.e. the local tumor microenvironment; TME) can determine efficacy of anti-cancer therapies. Systems understanding of the complex interactions between drugs, neoplastic cells and cells of TME can serve to predict effective treatment combinations with direct inhibitory effects on cancer cells and indirect anticancer effects on TME. Tools to effectively predict such combinations are still critically missing. We have developed an integrated analytical platform called the Multiplex Implantable Microdevice Assay (MIMA, Figure 1) to rapidly find TME drug responses and biomarkers with predictive value for combination therapy efficacy. The system deploys a (i) miniaturized implantable microdevice for localized intratumoral drug delivery, (ii) high-dimensional multiplex immunostaining and (iii) integrated computational analyses providing single cell information about the functional state and spatial cell organization bringing new insights into treatment mechanism

Krebs ist eine komplexe Erkrankung, deren Heterogenität den Therapieerfolg verschiedener Behandlungsarten stark beeinflusst. Neuste Brustkrebsstudien an Mäusen, welche intratumoral implantierbare Systeme für die gezielte Wirkstofffreisetzung im Tumor und computergestützte Analysen kombinieren, konnten zeigen, dass die lokale Tumormikroumgebung die Wirksamkeit von Krebstherapien entscheidend mitbestimmt. Wir denken, dass für eine dauerhafte Krebskontrolle ein tiefgreifendes Verständnis der Komplexität des Krebses und der Tumormikroumgebung erforderlich ist, um i) eine „Umprogrammierung", die den Therapieerfolg schwächt, zu verhindern, ii) Resistenzmechanismen zu blockieren und iii) die Überwachung durch das Immunsystem zu reaktivieren und zu verbessern. Daher werden neuartige Therapiemodelle, wie die Kombination mehrerer Behandlungsstrategien benötigt, um den vom Tumor ausgehenden Mechanismen entgegenzuwirken. Gleichzeitig müssen aber systemische Nebeneffekte und Toxizitäten vermieden werden, welche die Lebensqualität beeinträchtigen können, da Krebsbehandlungen über Monate bis Jahre dauern können. Unser Ziel ist es, den Einfluss der Tumormikroumgebung bei Brustkrebs und anderen Krebsarten mit Hilfe von hochentwickelten computergestützten und biotechnologischen Methoden zu verstehen und dadurch Therapiemöglichkeiten verbessern zu können. Dies wird letztendlich zur Entdeckung von neuen standardisierten Biomarkern und neuen therapeutischen Kombinationsmöglichkeiten führen und somit für wirksamere Behandlungen und eine langfristige Krankheitskontrolle sorgen.

of action. The prototyped studies suggest wide use of the MIMA system to develop systems control strategies providing long-term cancer control by creating strong anti-tumor microenvironments (Tatarova, *Nature Reviews Cancer,* 2024).

The breast cancer tumor microenvironment is critical determinant of drug responses. In situ cellular interactions that govern favorable responses to the targeted drug panobinostat have been deciphered recently, and provided a synergistic therapy prognosis for combining panobinostat with immune checkpoint blockade therapy (Tatarova et al., *Nature Biotechnology*, 2022). We have extended those early spatial studies to identify mechanisms of resistance that likely restricted a durable systemic antitumor response. We found an acquired resistance to panobinostat in our mouse model of breast cancer to be multifaceted and describe molecular diversity of cancer stem cell niche establishment, spatial deposition of cellular mesenchymal stroma and high-density collagenous

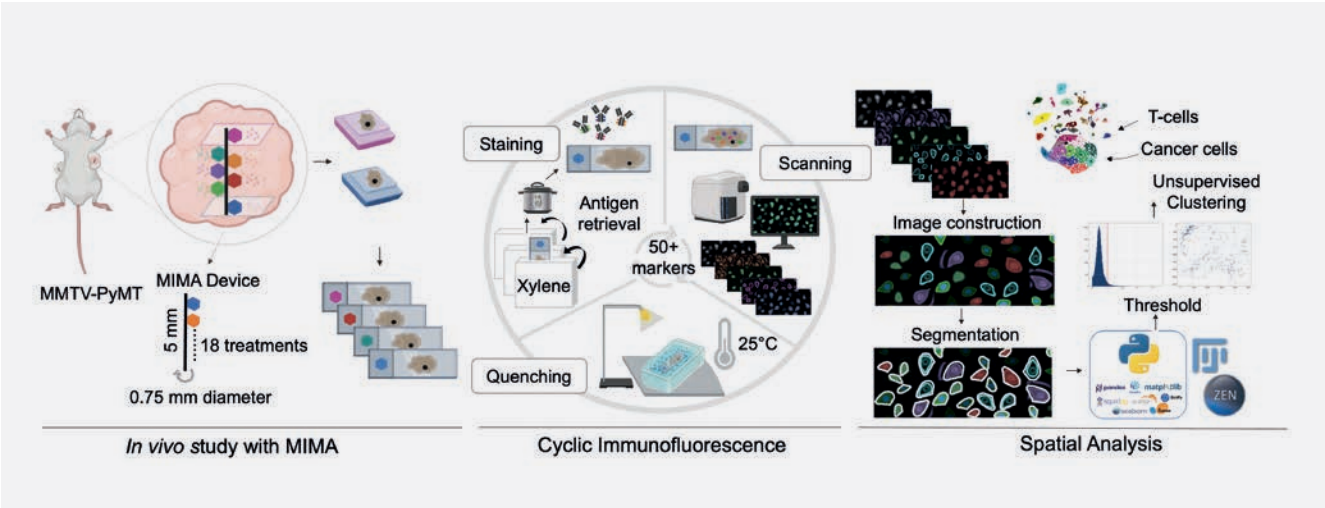
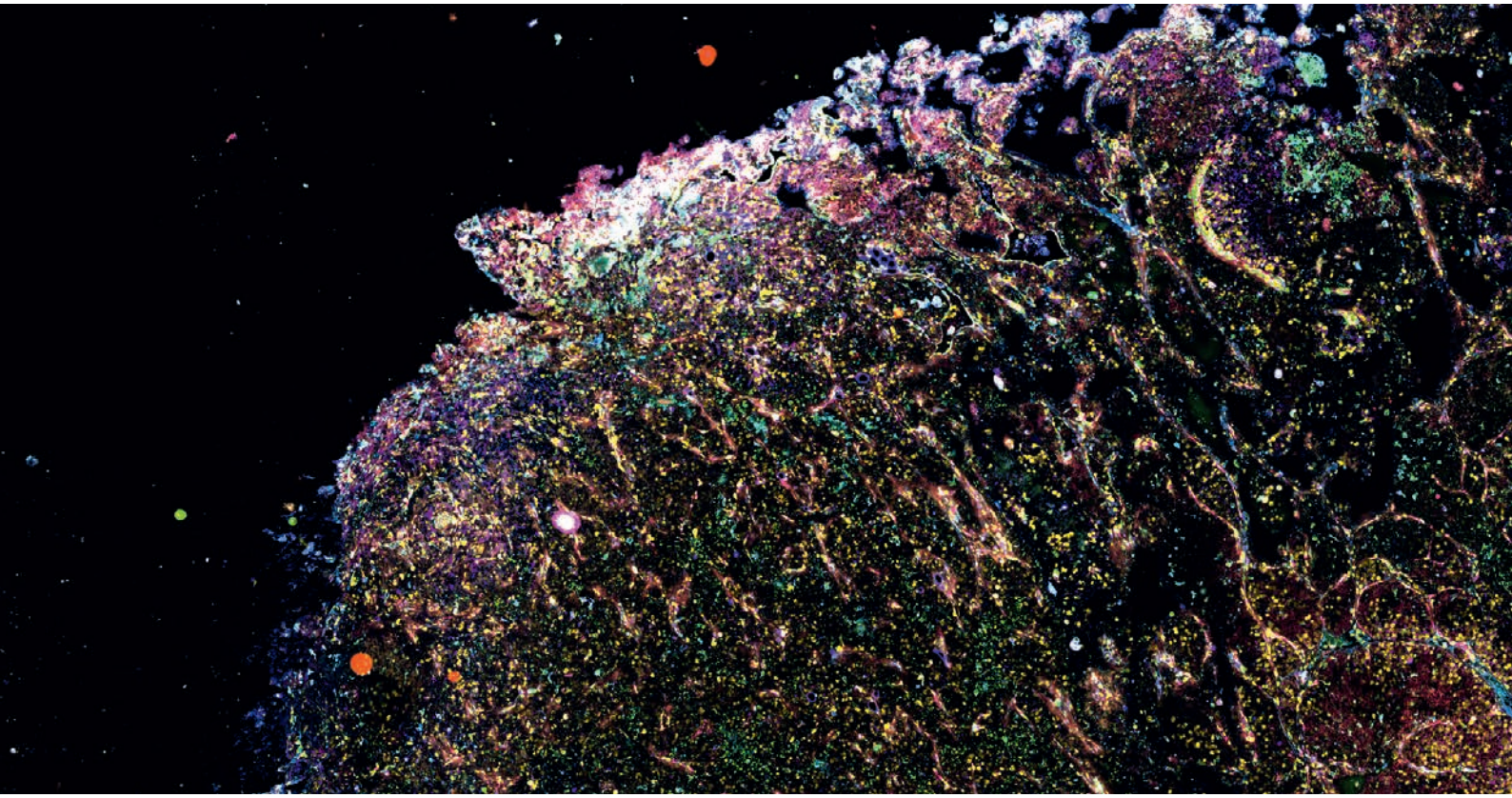


Figure 1.
Integrated Multiplex Implantable Microdevice Assay (MIMA). An implantable microdevice administers multiple parallel agents into a single living tumor passively at nanodoses; and each condition is being assayed individually using spatial single cell omics to delineate critical cell dependencies translating into (i) predictive biomarkers, (ii) mechanisms of actions and (iii) effective combination treatment strategies.



matrix content, alongside extracellular matrix breakdown and cancer cell invasiveness. The identified spatial patterns developing in response to local drug stimuluses could be systemically translated and serve as predictive biomarker for beneficial treatment combinations.

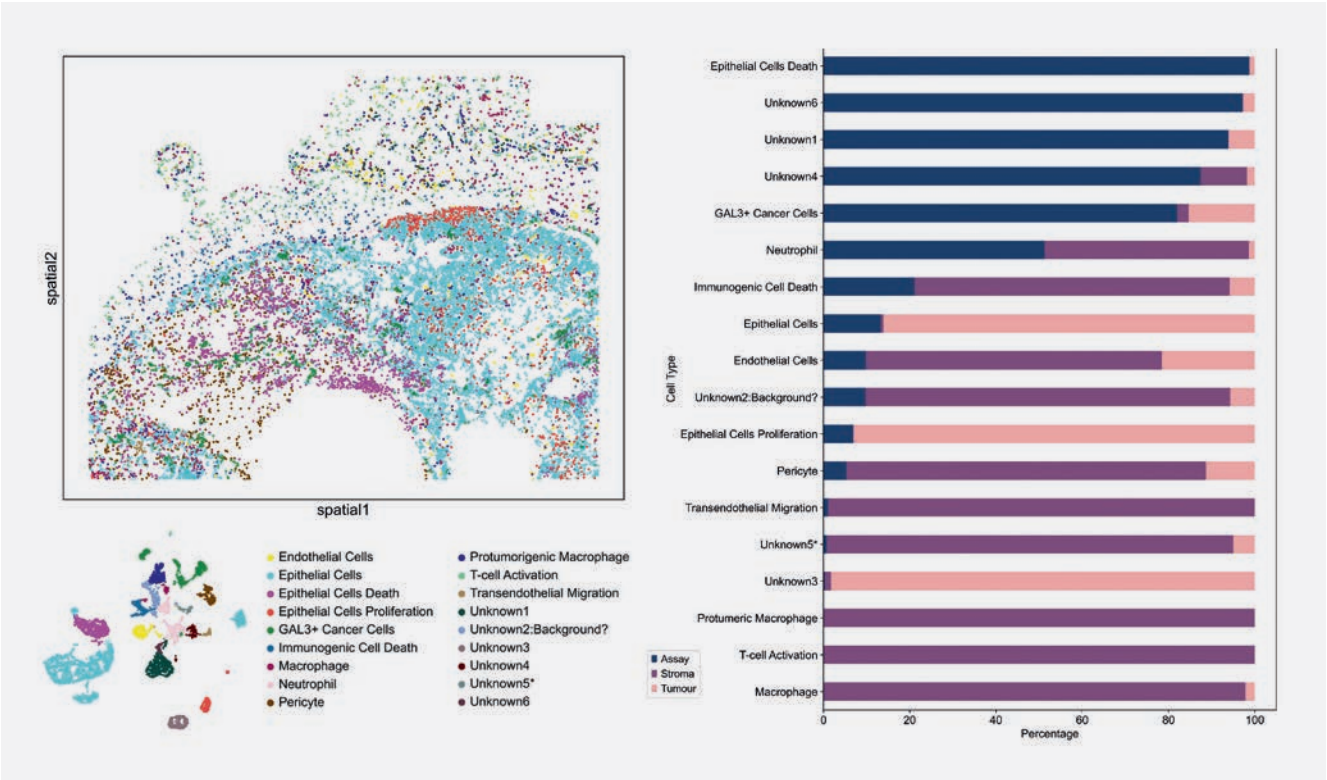


Figure 2. **Cellular phenotypes discovered at the doxorubicin/cabozantinib combination treatment site by MIMA.**

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Tatarova Z, Blumberg DC, Bensen A, Mills GB, Jonas O.
Panobinostat Induced Spatial In Situ Biomarkers Predictive of Anti-PD-1 Efficacy in Mouse Mammary Carcinoma. ***Cells.*** *2023 Jan 13;12(2):308. doi: 10.3390/cells12020308. PMID: 36672243; PMCID: PMC9856407.*

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MYC Deregulation and PTEN Loss Model Tumor and Stromal Heterogeneity of Aggressive Triple-Negative Breast Cancer. ***Nat Commun.*** *2023 Sep 13;14(1):5665. doi: 10.1038/s41467-023-40841-6. PMID: 37704631; PMCID: PMC10499828.*

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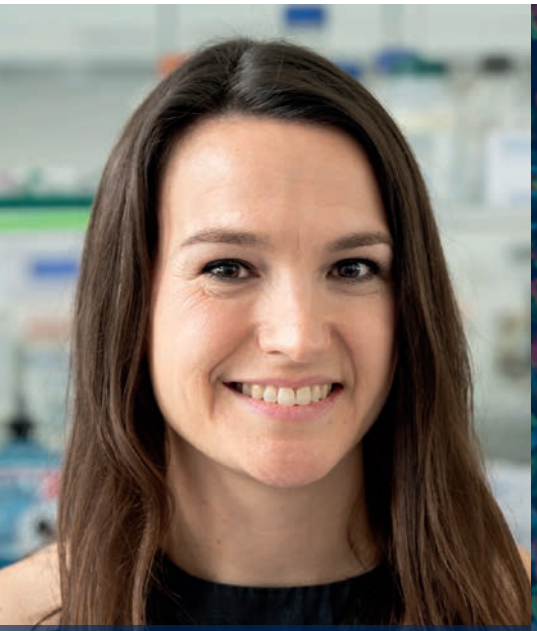
An increasing amount of evidence suggested that cancer stem cells exist within tumors, contributing to therapy resistance. Initial single-cell RNA sequencing analysis involving preprocessing, unsupervised clustering and ligand-receptor analysis suggested increased interaction frequency between CSCs, dendritic cells and macrophages to be important for a superior therapeutic control. By linking ligand to the target genes, we found APOE-TREM2 interaction to stand out as one of the most significant, suggesting a potentially crucial communication pathway between macrophages and dendritic cells (DCs) through cell death phagocytosis. The most significant ligand-receptor pairs between DC and CSCs were MIF-CD74 and APP-CD74, both of which are related to immune regulation in tumors. A differential gene expression analysis showed a higher metabolic efficiency to be needed for therapeutic control as shown by high expression of certain mitochondrial genes. CSCs notably expressed H2-D1, while both CSCs and DCs highly expressed H2-K1, suggesting potential MHC class I protein binding activity and peptide antigen binding activity. Given previous spatial DC/CSC co-localization observations (Tatarova et al., *Nature Biotechnology*, 2022), proficient antigen presentation might play critical role in eliminating CSCs.

Therapeutic resistance is also a major challenge to the efficacy of single-agent chemotherapies such as doxorubicin resistance due to a significant enrichment of endothelial cells (Tatarova et al., Nature Biotechnology, 2022). We normalized doxorubicin-treated vasculature using anti-angiogenic drug combination. We investigated drug effects on the TME with the multiplex implantable microdevice assay on murine breast cancer model and multiplexed imaging. An unsupervised Leiden clustering strategy confirmed doxorubicin-mediated endothelial cell enrichment and the first combination with cabozantinib showed endothelial cell population reduction. The latter revealed an immunogenic cell death phenotype with the recruitment of active immune cells. This immune modulatory activity was used to test doxorubicin, cabozantinib, and anti-PD1 immunotherapy triple combination, which showed significant tumor remission. The study confirmed a rational drug combination that improves doxorubicin chemotherapy efficacy for long-term breast cancer control.

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. Our aim is to develop and identify the most promising integrative computational and bioengineering systems to decompose tumor microenvironment complexity in cancer ultimately leading to discovery of new (i) standardized biomarkers with predictive value and (ii) effective combinations of immune- and conventional therapies.



Immunregulatorische Mechanismen in der Tumormikroumgebung und Therapieresistenz

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Immunoregulatory mechanisms in the tumor microenvironment and resistance to therapy

Immunotherapies

Cancer immunotherapy

Resistance mechanism

Immunosuppression

Tumor-associated-macrophages

T cells

Pancreatic neuroendocrine tumor

Melanoma

Glioma

Breakthroughs in cancer treatment have come from understanding oncogenic signaling, the tumor ecosystem, and cancer immunobiology. Targeted therapies provide – in some tumor types – remarkably high clinical responses followed, unfortunately, by relapse. In contrast, immunotherapies, especially checkpoint inhibitors, have revolutionized cancer treatment and induce long-lasting responses by activating anti-tumor immunity, albeit only in a subset of patients. The complex and dynamic crosstalk within the tumor microenvironment (TME) interactions between cancer cells and their surrounding environment drive tumor progression and help tumors evade immune detection and develop innate or acquired resistance mechanisms to therapies. Understanding this intricate cellular communication and the barriers erected in the TME is crucial for designing effective combinatorial anti-cancer.

One explanation for non-responsiveness to immune therapies is the presence of multiple immune suppressive mechanisms erected by cancer cells to avoid detection and destruction by the immune system. These barriers include immuno-inhibitory

Unsere Forschung untersucht die komplexen Wechselwirkungen zwischen Krebs- und Stromazellen innerhalb der Tumormikroumgebung (TME), in der Tumore Barrieren aufbauen, um der Zerstörung durch das Immunsystem zu entgehen und gegenüber Therapien resistent zu werden. Wir konzentrieren uns darauf, therapeutische Schwachstellen zu identifizieren, indem wir unterdrückende Immunzellpopulationen und deren Regulation untersuchen. Unser Ziel ist es, besser zu verstehen, wie diese Zellen zur Therapieresistenz und zum Wiederauftreten von Tumoren beitragen, insbesondere durch ihren Einfluss auf die Tumorimmunität.

Mithilfe von genetisch veränderten Mausmodellen, die die menschliche Krebsbiologie genau nachbilden, untersuchen wir Resistenzmechanismen und testen neue therapeutische Strategien. Unsere Arbeit hat die Rolle von tumorassoziierten Makrophagen (TAMs) hervorgehoben, die überwiegend einen pro-tumorales, immunsuppressives Phänotyp annehmen. Durch die Reprogrammierung dieser TAMs in proinflammatorische, tumorantagonisierende Zellen, insbesondere in Kombination mit Standardtherapien, wollen wir die T-Zell-vermittelte Tumorzerstörung verstärken.

Unsere Forschung integriert präklinische in vivo Modelle sowie ex vivo und in vitro zelluläre Systeme sowohl vom Menschen als auch von der Maus. Wir nutzen zudem umfassende „Omics"-Ansätze, um wichtige Mediatoren der Tumorausweichung in der TME zu identifizieren. Sobald diese identifiziert sind, verwenden wir fortschrittliche genetische Werkzeuge, wie Cre-induzierbare Systeme und CRISPR-Editing, um zellspezifische Immunmechanismen zu untersuchen. Darüber hinaus untersuchen wir verwandte menschliche Tumore mit Hilfe verfügbarer Datenbanken und Patientenproben, die durch klinische Kooperationen ermöglicht werden. Durch Querfilterung von Maus- und Humantumoren wollen wir Angriffspunkte identifizieren, die präklinisch funktionell validiert, operativ und potenziell in die Klinik übertragbar sind.

signals, reprogramming and recruitment of immunosuppressive cell populations, such as macrophages, myeloid cells and regulatory T cells, exhaustion of T lymphocytes, and a dysfunctional angiogenic vasculature.

Research Program

Our research focuses on unraveling the complexity of the interplay between cancer and stromal cells in the tumor microenvironment (TME), as tumors erect multiple barriers to evade immune destruction, resulting in non-responsiveness to treatments. Therefore, we are delving into 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 suppressive populations (i.e., tumor-associated macrophages…) and their effectors to suppress tumor immunity in response to therapies (Figure 1).

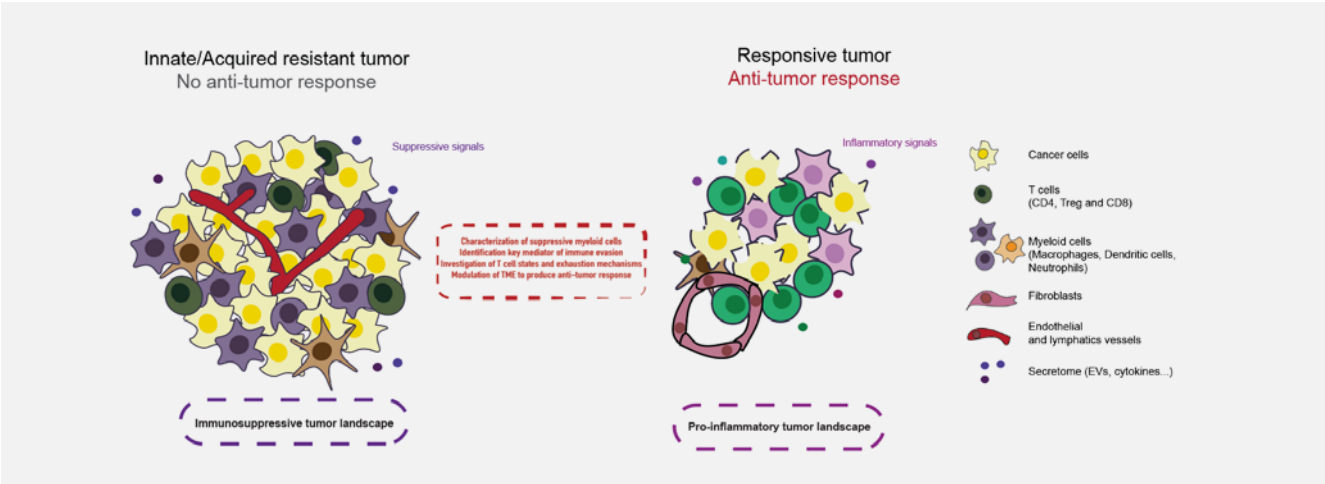
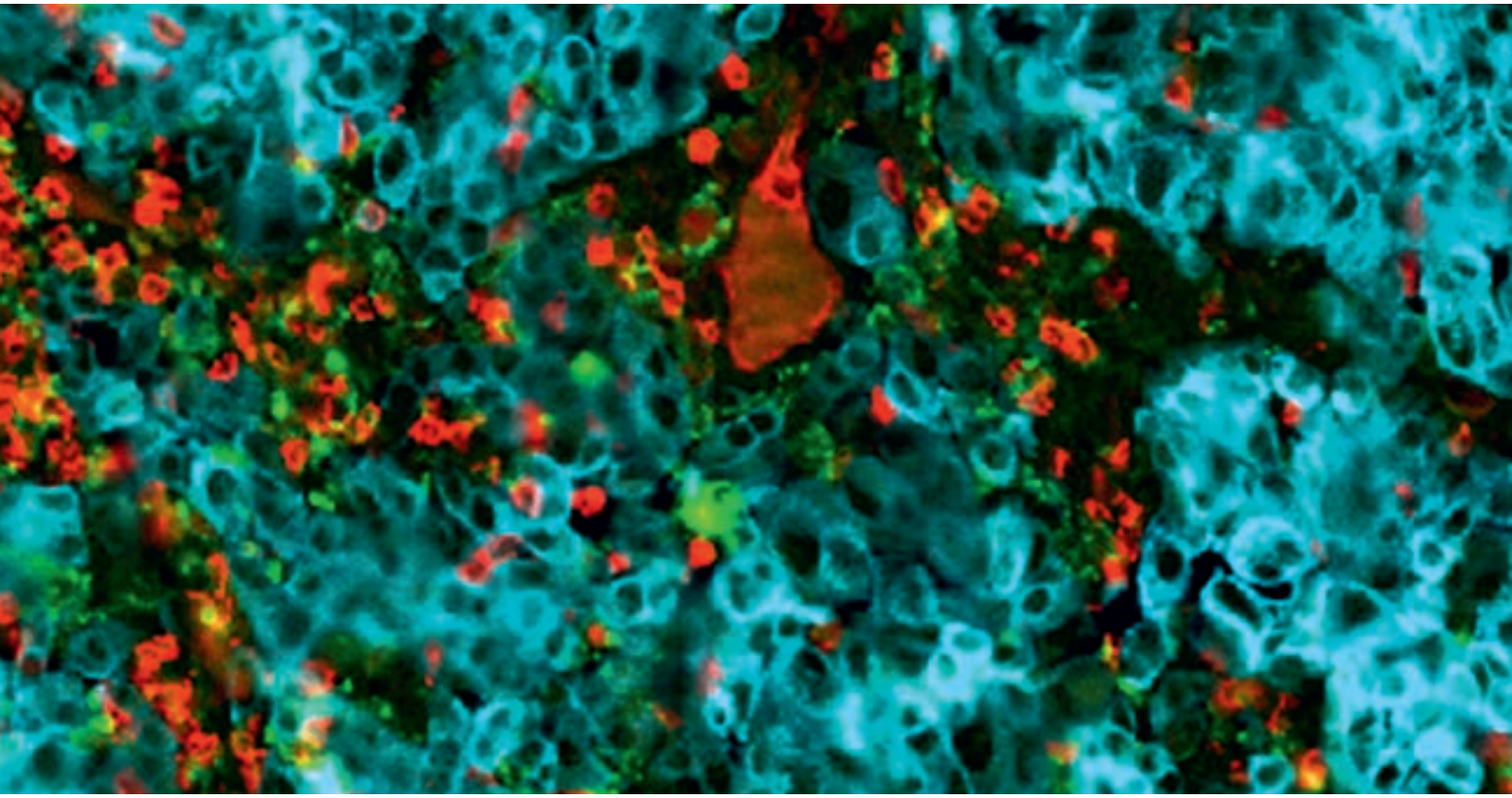


Figure 1. **Model summarizing the immunosuppressive vs the pro-inflammatory tumor microenvironment.** Suppressive TME (myeloid cells notably) limit the T cell infiltration/activation leading to non-responsiveness to immunotherapies. In the middle red box are all the axes to better understand suppressive TME and unleash anti-tumor responses.



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 is focused on mouse models, wherein 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 effectively converting immunosuppressive TAMs into pro-inflammatory, tumor-antagonizing macrophages upon combination with standard-of-care therapies leading to T cell infiltration mediating anti-tumor immunity and tumor destruction.

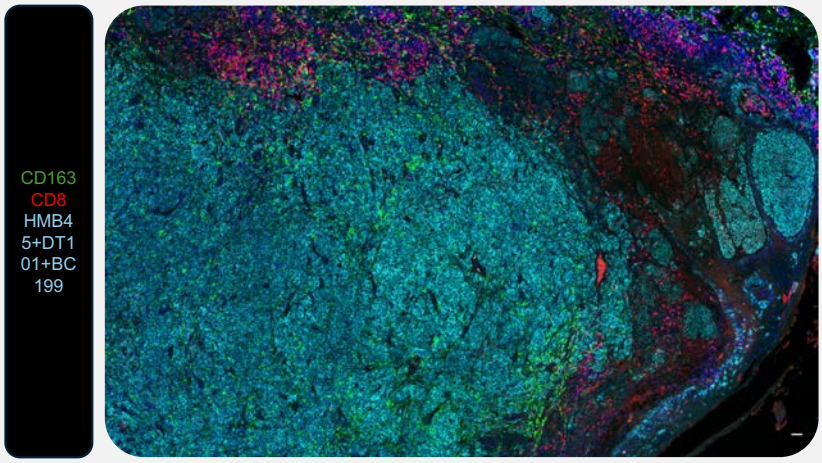
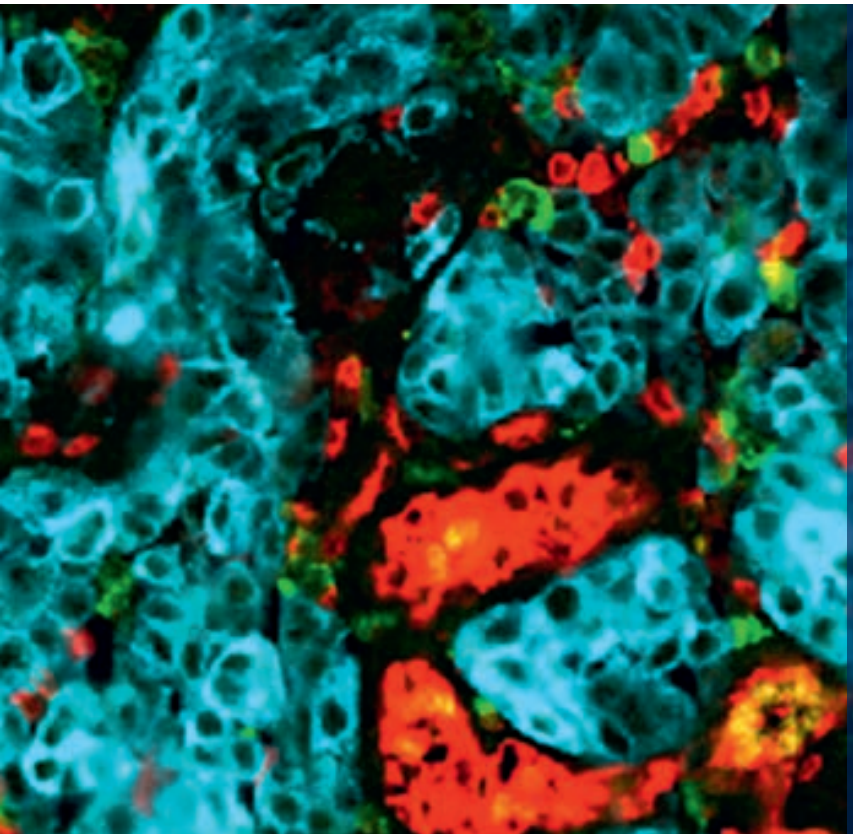


Figure 2. **Immunofluorescent image of a melanoma tumor from a patient resistant to immunotherapy.** IF staining for CD163 (TAMs - green), CD8 (CD8 T cells - red), and HMB45+DT101+BC199 (melanoma cells- cyan). Tumor is infiltrated with suppressive TAMs while CD8 T cells are excluded. Scale bar 50 um.

Our projects are focusing 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 will investigate 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. We also aim to understand the T cell biology and mechanisms of exhaustion and dysfunc-



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tion induced by the suppressive TME but also the T cell-intrinsic mechanisms (such as chronic TCR signaling) 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). Once we have pinpointed critical mediators of tumor evasion in the TME, we will create refined GEMM models with cell-specific Cre inducible systems and CRISPR-editing to study cell-dependent immunostimulatory mechanisms. Furthermore, we are investigating 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 intend to identify actionable targets functionally validated pre-clinically, operative, and potentially translatable to the clinic.

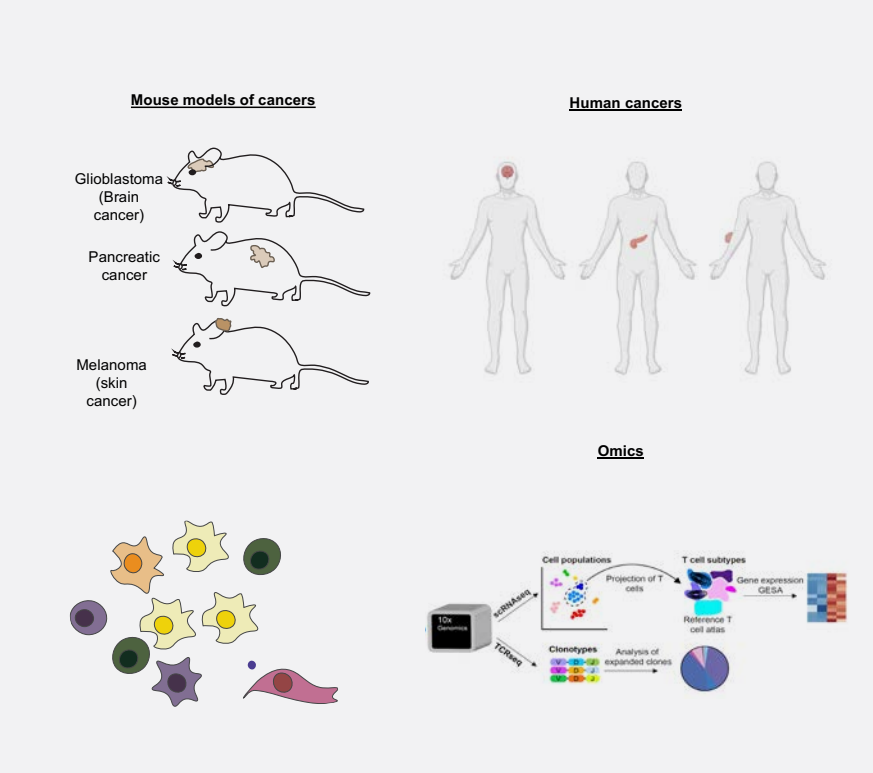

Figure 3. **Scientific approaches and models.** *Mouse models of cancers* (melanoma, pancreatic cancer and glioma) - recapitulate human cancer development and resistance to treatment; used for pre-clinical therapeutic trials combining standard-of-care therapies and TAMs reprogramming to unleash anti-tumor immunity and induce therapeutical benefits; *Human cancers* - tumor characterization; *Cell-based assays* - Cells (cancer, immune, vessels…) are isolated from human and murine tumors and collected for experiments and analyses. *Omics analyses* (scRNAseq, secretomics…) - comprehensive approaches for the analysis of complete genetic and molecular profiles of human and mouse cancer cross-comparison.

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CAR-exprimierende Lymphozyten für die adoptive Krebs-Immuntherapie

CAR-engineered lymphocytes for adoptive cancer immunotherapy

natural killer cells

chimeric antigen receptors

bispecific antibodies

Expression of chimeric antigen receptors (CARs) in cytotoxic lymphocytes constitutes a promising strategy for adoptive cancer immunotherapy with effector cells of defined specificity. CARs consist of a tumor-specific single-chain antibody fragment (scFv) connected via a flexible spacer and a transmembrane domain to intracellular signaling domains such as CD3ζ combined with one or more costimulatory protein domains. CAR-engineered T cells have demonstrated remarkable clinical efficacy in patients with malignancies of B-cell origin. Natural killer (NK) cells represent another valuable effector cell population for adoptive cancer immunotherapy, with CAR-NK cells gaining increasing interest. NK cells are part of the innate immune system and play an important role in cancer immune surveillance. NK cells can also modulate T-cell mediated antitumor immune responses by shaping the quality of dendritic cells and enhancing the presentation of tumor antigens. Nevertheless, in cancer patients NK cells are often functionally compromised due to the immunosuppressive activity of the tumor. Hence, for adoptive cancer immunotherapy donor-derived allogeneic NK cells are preferred

Ziel unserer Arbeiten ist die Erforschung und Entwicklung effektiver Immuntherapien zur Behandlung von Krebserkrankungen. Einen Schwerpunkt bilden dabei natürliche Killerzellen (NK-Zellen). Diese sind Teil des angeborenen Immunsystems und spielen eine wichtige Rolle bei der Abwehr maligner Zellen. Durch Expression sogenannter chimärer Antigenrezeptoren (CARs) generieren wir genmodifizierte NK-Zellen, die Tumorzellen selektiv abtöten. CARs tragen ein extrazelluläres Antikörperfragment mit Tumorzellspezifität, das über eine flexible Verbindungsregion und eine Transmembrandomäne mit intrazellulären Signaldomänen verbunden ist. Damit lösen die Rezeptoren nach Zielzellerkennung eine gerichtete zytotoxische Aktivität der Effektorzellen aus. In ähnlicher Weise setzen wir bispezifische Antikörper für die Aktivierung von zytotoxischen Lymphozyten gegen Tumorzellen ein. Als Zielantigene nutzen wir tumorassoziierte Oberflächenantigene wie das zelluläre Proto-Onkogen ErbB2 (HER2), den epidermalen Wachstumsfaktor-Rezeptor EGFR, Liganden des Rezeptors NKG2D und Differenzierungsantigene wie CD19 und CD20. Eine in enger Kooperation mit akademischen Partnern am Standort Frankfurt generierte ErbB2-spezifische Variante der klinisch nutzbaren humanen NK-Zelllinie NK-92 wird gegenwärtig in einer Phase-I-Studie bei Patienten mit rezidiviertem, ErbB2-positivem Glioblastom eingesetzt (CAR2BRAIN; NCT03383978, clinicaltrials.gov).

since they do not recognize tumor cells as 'self', thereby bypassing inhibitory signals.

Tumor-specific natural killer cells

Similar to donor-derived primary NK cells, the continuously expanding human NK cell line NK-92 has been safely applied in clinical trials as an allogeneic cell therapeutic, with durable responses observed in some of the cancer patients treated. In previous work we demonstrated that this therapeutic utility of NK-92 cells can be further enhanced by expression of CARs which specifically recognize tumor-associated surface antigens expressed by hematologic malignancies or solid tumors. Together with colleagues at the Frankfurt University Hospital we also extended this strategy to primary NK cells and cytokine induced killer cells. In a current approach, we harnessed the broad tumor specificity of the activating receptor Natural Killer Group 2D (NKG2D) in a CAR design. NKG2D has multiple membrane-anchored ligands, which are widely expressed in almost all cancer types. However, shedding or downregulation of such ligands can prevent NKG2D activation, resulting in escape of cancer cells from NKG2D-dependent immune surveillance. To enable tumor-specific targeting of NKG2D-expressing effector cells independent of membrane-anchored NKG2D ligands, we generated bispecific antibodies which can simultaneously bind to NKG2D and a tumor-associated surface antigen like ErbB2 (HER2) or epidermal growth factor receptor (EGFR). Together with colleagues at the Technical University Darmstadt, we derived a panel of novel NKG2D-binding antibody domains for the generation of such

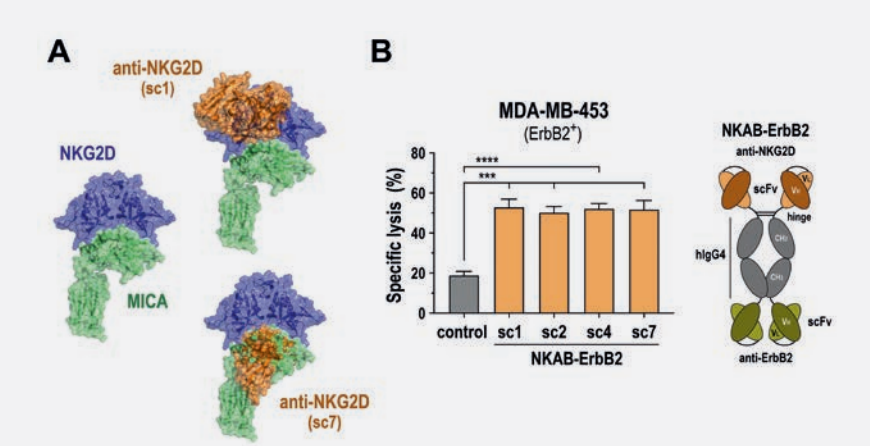
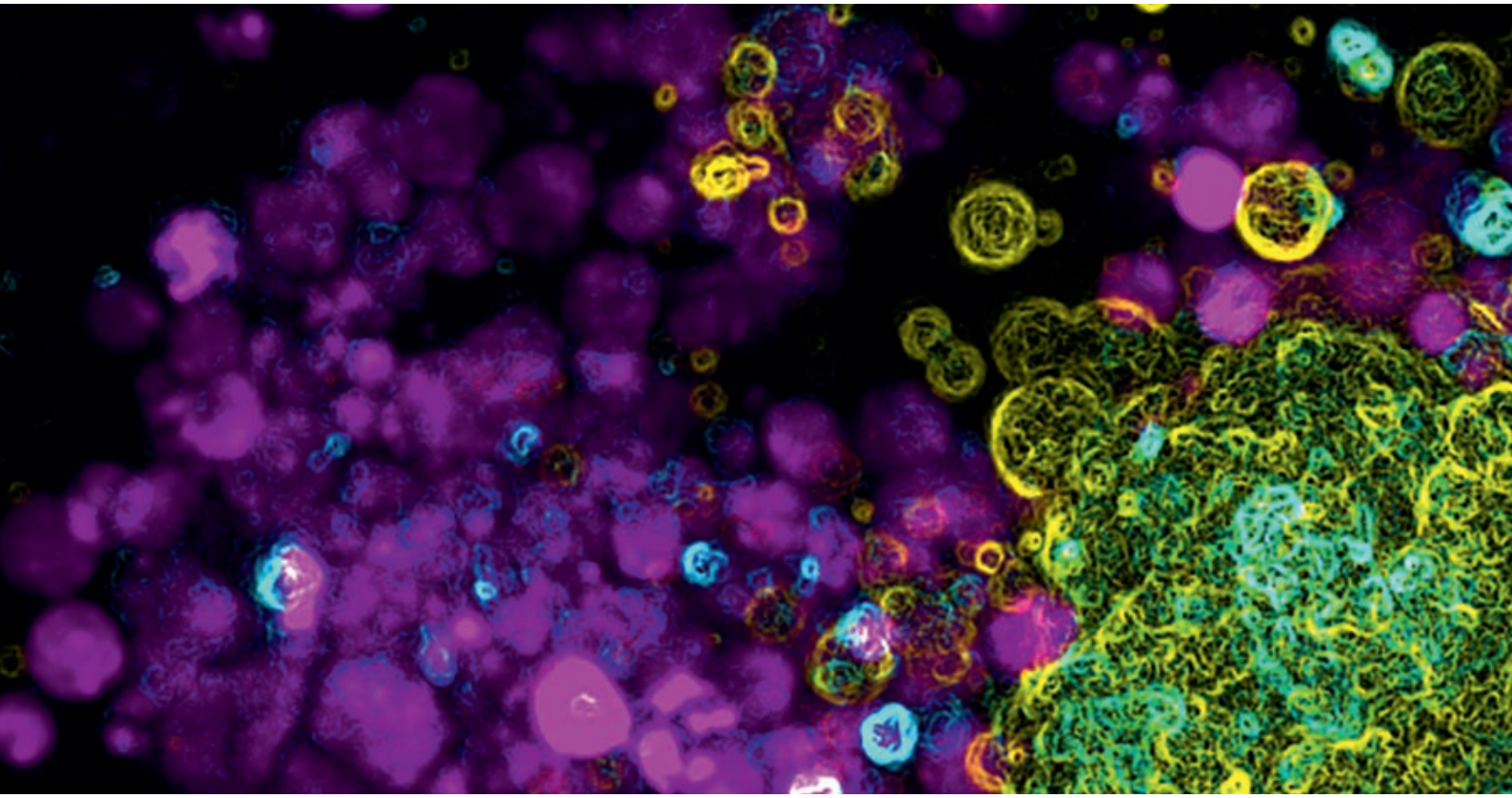


Figure 1. **Redirection of NKG2D-CAR engineered NK cells by bispecific NKAB antibodies.** (A) Structure of the extracellular domain of activating receptor NKG2D (blue) in complex with the natural NKG2D ligand MICA (green) based on published crystal structure data (left). The interaction of NKG2D-binding antibody fragments sc1 and sc7 (orange) with NKG2D was modeled and superimposed into the NKG2D-MICA complex (right), indicating in agreement with experimental data competition of MICA binding by sc7 but not sc1. (B) Cytotoxic activity of NKG2D-CAR engineered NK-92 cells (NKAR-NK-92) against ErbB2-positive MDA-MB-453 breast carcinoma cells in the presence of 0.64 nM of bispecific NKAB-ErbB2 molecules based on NKG2D-binding antibody fragments sc1, sc2, sc4 or sc7 was determined after 3 hours of co-incubation at an effector to target cell ratio of 5:1. An ErbB2-specific antibody fusion protein unable to interact with human NKG2D was included as control. A schematic representation of an NKAB-ErbB2 protein is shown on the right.



bispecific NKAB molecules (Figure 1). On their own, the resulting bispecific antibodies can mediate lysis of antigen-positive cancer cells by NK and T cells that naturally express NKG2D. Furthermore, when applied together with NK cells transduced with an NKG2D-CAR vector, targeted cell killing and antitumor activity are greatly enhanced. Hence, this combination strategy represents a powerful approach to simultaneously amplify tumor-antigen-specific as well as NKG2D-CAR and natural NKG2D-mediated cytotoxicity, which may be particularly useful to target tumors with heterogeneous target antigen expression.

CAR-NK cells for clinical applications

To assess safety and antitumor activity of CAR-NK cells in a clinical setting, together with colleagues from the Institute for Neurooncology, the Department of Neurosurgery and the German Red Cross Blood Donation Service in Frankfurt we are conducting a phase I clinical trial of intracranial injection of the clonal ErbB2-specific CAR NK-92 cell line NK-92/5.28.z in patients with recurrent ErbB2-positive glioblastoma (CAR2BRAIN; NCT03383978, clinicaltrials.gov). No dose-limiting toxicities were encountered in the completed dose escalation part with single-dose injection into the wall of the resection cavity during relapse surgery, demonstrating safety and feasibility of our approach. Subsequently, patients of an expansion cohort received additional weekly injections of NK-92/5.28.z cells through an implanted catheter and reservoir. To further enhance the desired stimulatory effect of the CAR-NK cells on

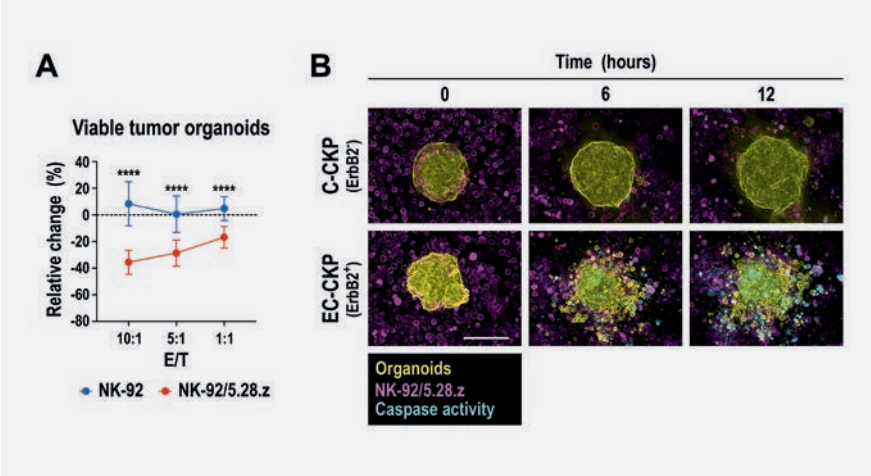
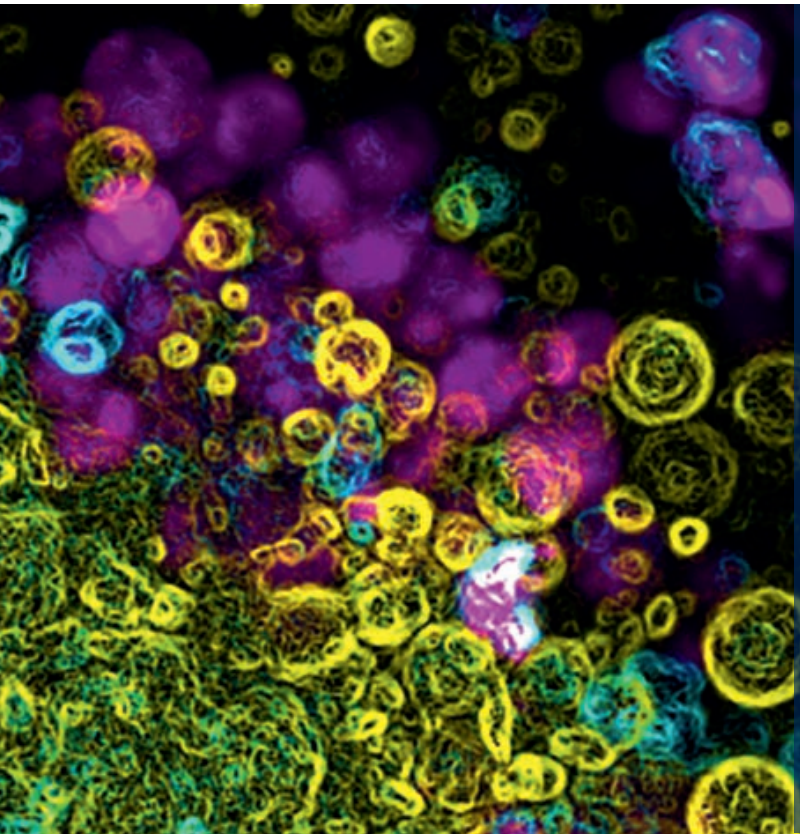


Figure 2. **Selective cytotoxicity of CAR-NK cells against breast cancer organoids.** As a model system, malignant transformation of murine mammary epithelial cells was induced by Cre-mediated deletion of p53 and expression of activated KrasG12V (C-CKP cells), and the resulting cells were further modified to express the tumor-associated antigen ErbB2 (HER2) (EC-CKP cells). C-CKP and EC-CKP cells were grown as organoids, mimicking the three-dimensional structure of a tumor. (A) Organoids of ErbB2-positive EC-CKP breast cancer cells carrying a luciferase reporter gene were co-cultured with ErbB2-specific NK-92/5.28.z or parental NK-92 cells at the indicated effector to target cell (E/T) ratios for 4 hours. Then the relative change in bioluminescence as a measure of viable tumor cells was determined in luciferase assays. (B) For microscopic analysis of target cell killing, ErbB2-negative C-CKP and ErbB2-positive EC-CKP organoids (yellow) were co-cultured with NK-92/5.28.z cells (magenta) for 12 hours. Shown are processed maximum intensity projections of images taken at the indicated time points. Induction of target cell apoptosis was visualized with a fluorescent caspase-3/7 substrate (cyan). Scale bar: 100 µm.



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endogenous antitumor immunity, repeated local injections of NK-92/5.28.z cells were combined with a systemically applied immune checkpoint inhibitor, with patients of this CAR2BRAIN-Check treatment cohort still in follow-up. To extend this approach to other ErbB2-expressing cancers such as breast carcinoma and non-small cell lung carcinoma, we are currently testing the activity of NK-92/5.28.z cells in respective preclinical models (Figure 2).

Functional enhancement of CAR-engineered NK cells

In addition to direct killing of tumor cells, CAR-NK cells can contribute to tumor control by recruitment of and crosstalk with other immune cells through cytokines and chemokines secreted after effector cell activation. In immunocompetent glioblastoma mouse models, treatment of syngeneic murine tumors expressing human ErbB2 with ErbB2-specific NK-92/5.28.z cells induced endogenous humoral and cellular antitumor immune responses resulting in tumor rejection and long-term protection of the animals against tumor rechallenge. In ongoing work, we investigate means to further enhance this immunostimulatory effect of CAR-NK cells through modulation of their cytokine profile. One such approach is based on co-expression of a CAR together with an IL-15 superagonist (RD-IL15). Production of this molecule by CAR-NK cells resulted in self-enrichment and targeted cell killing in the absence of exogenous IL-2 (Fig. 2). Furthermore, co-culture with RD-IL15-secreting CAR-NK cells markedly enhanced proliferation and cytotoxicity of bystander immune cells in a paracrine manner, suggesting this strategy as a promising approach for further development of functionally enhanced cellular therapeutics.

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Promotion im Fachbereich 16 Medizinische Fakultät, Goethe Universität Frankfurt

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Akademische Ausbildung
Visiting PhD students
04/2024-06/2024 Eve Dias
(ITN Network secondment)
06/2024-09/2024 Maria Magallon Mosella
(EHA scientific exchange fellowship)
05/2024-11/2024 Alessia Andrea Ricci
(EU-TRANSCAN Network student)
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Djenna Dalencourt: Internship
15.06.2024 – 15.09.2024

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Akademische Ausbildung

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Finanzen und Wissenschaftlicher Service

Financial Affairs and Scientific Services

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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 neben den klassischen Aufgaben einer Verwaltung Finanz- und Rechnungswesen, Controlling, Einkaufsmanagement Arbeitssicherheit, und Personalmanagement, auf den Themen, Informationstechnologie, Digitalisierung & Forschungsdatenmanagement, Datenschutz, Gebäudemanagement, Nachhaltigkeit, Compliance, Diversity, 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.

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, Herrn Heinrich Krompiec und Herrn Michael Paul 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 Ayfer Aktas 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.

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, Mr. Heinrich Krompiec, and Mr. Michael Paul, 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. Ayfer Aktas 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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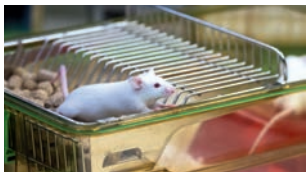
Tierhaltung am Georg-Speyer-Haus

Am Georg-Speyer-Haus wird eine Vielzahl unterschiedlicher Mausmodelle gezüchtet und in genehmigten Experimenten eingesetzt. Die Tierhaltung erfüllt hierbei alle aktuellen gesetzlichen Anforderungen und steht im Einklang mit der europäischen Verordnung 2010/63/EU sowie den deutschen Gesetzen zum Schutz der für wissenschaftliche Zwecke verwendeten Tiere. Die Tierpflege und alle wissenschaftlichen Arbeiten orientieren sich grundsätzlich am ethischen „3R" Prinzip des Verringerns, Verbesserns und Vermeidens von Tierversuchen. Alle Mitarbeiter sind erfahren im Umgang mit Mäusen und konsequent dem Tierwohl verpflichtet. Fortlaufend geschultes und sachkundiges Tierhaltungspersonal ermöglicht eine gute und umfassende Pflege der Tiere sowie wissenschaftliche Assistenz bei der Durchführung der Versuche.

In der GSH Tierhaltung können unterschiedliche Bildgebungsverfahren eingesetzt werden. Beispielsweise verfügt das Institut über einen 7 Tesla Hochleistungstomographen (PharmaScan 7T, Bruker Biospin) für anatomische, funktionelle und metabolische Untersuchungen sowie ein modernes in-vivo Bildgebungsverfahren (IVIS Lumina II, PerkinElmer) für Biolumineszenz- und Fluoreszenzanalysen in kleinen Nagetieren. Das SARRP System (Small Animal Radiation Research Platform, Xstrahl Medical) bietet Möglichkeiten der therapeutischen Strahlentherapie bei Mäusen. Weitere Geräte erlauben eine Ganzkörperbestrahlung kleiner Nagetiere (BioBeam, Gamma Medical) und die Generierung sogenannter „humanisierter" Mausmodelle. Mit Hilfe einer endoskopischen Apparatur (Coloview, Karl Storz) können Darmspiegelungen bei der Maus durchgeführt werden beziehungsweise konfokale endomikroskopische Untersuchungen der Darmschleimhaut (Cellvizio, Mauna Kea Technologies) erfolgen.

Animal Husbandry at the Georg-Speyer-Haus

Our Animal Facility is designed and run in line with the recent legislation and meets all requirements of the directive 2010/63/EU on animal welfare and the German law on the protection of animals used for scientific purposes and consistently adheres to the ethical „3R" principle of reduction, refinement and replacement. All scientists are experienced in laboratory animal care and advised on animal welfare and legal requirements. Ongoing training of qualified staff responsible for animal housing enables a comprehensive service that includes both experienced care and scientific assistance.



The experimental area of the GSH animal facility is equipped with an ultra-high field magnetic resonance imaging system (PharmaScan 7T, Bruker Biospin) for anatomical, functional and metabolic imaging and an in vivo imaging system (IVIS Lumina II, PerkinElmer) for quantitative fluorescent and bioluminescent imaging of small rodents. The small animal radiation research platform (SARRP, Xstrahl Medical) provides opportunities for therapeutic treatment that bridge basic research and clinical translation. Other experimental procedures enables whole-body irradiation (BioBeam, Gamma Medical) and creation of variable humanized mouse models. Further scientific research tools are an endoscopic system (Coloview, Karl Storz) for colonoscopic examination and a probe-based in vivo confocal laser endomicroscopy platform (Cellvizio, Mauna Kea Technologies).

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 sowie einen Leica BOND max 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 and a Leica BOND max for automated immunostaining.

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Zentrale Einheit Durchflusszytometrie (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 Herrn Thorsten Geyer. In einigen Fällen fungiert Herr Felix Kienzle 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 Thorsten Geyer for the high-speed cell sorting for all research groups. Occasionally, Felix Kienzle serves as an additional sorting operator at the Fusion sorter.

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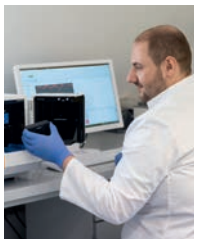

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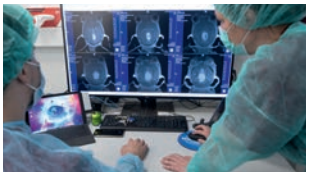
Zentrale Einheit Mikroskopie und *in vivo* Imaging

Die Imaging Core Facility bietet Zugang zu den hochentwickelten Bildgebungsinstrumenten im GSH, zu denen derzeit ein 7T-Kleintier-MRT (Bruker), ein konfokales Spinning-Disc Mikroskop (CQ1, Yokogawa), ein konfokales Mikroskop (SP5, Leica), Fluoreszenz-/ Lichtmikroskope (AxioImager, Zeiss) sowie Bildverarbeitungsstationen (CQ1- Bildanalyse und CellPathFinder) gehören. In diesem Jahr wird die ICF-Flotte durch Light-sheet Ultramicroscope Blaze und IVIS Spectrum CT ergänzt.

Verantwortlich für die Schulung, Koordination und Wartung ist Dominic Menger. Er dient als zentrale Anlaufstelle für alle Fragen im Zusammenhang mit den Bildgebungsgeräten sowie für die Beratung zum Versuchsaufbau, zur Entwicklung neuer Analyseansätze und zu allgemeinen Fragen im Zusammenhang mit der Bildgebung. Am MRT wird Dominic Menger in Teilzeit von Marco Lolies unterstützt, der sich um Routinemessungen für interne und externe Nutzer kümmert.

Imaging Core Facility

The Imaging Core Facility provides access and training to the sophisticated imaging instruments in the GSH, currently including a small animal 7T MRI (Bruker), spinning disc confocal microscope (CQ1, Yokogawa), confocal microscope (SP5, Leica), fluorescent/light microscopes (AxioImager, Zeiss) as well as image processing stations (CQ1 image analysis and CellPathFinder). This year, ICF fleet will be complimented by Light-sheet Ultramicroscope Blaze and IVIS Spectrum CT.



Responsible for the training, coordination and maintenance is Dominic Menger. He serves as single point of contact for all questions related to the imaging equipment as well as advice on the experimental set up, development of new analytical pipelines and general enquiries related to imaging.

At the MRI, Dominic Menger is supported part time by Mr Marco Lolies who is taking care of routine measurements for internal and external users.
All services are available to both staff at GSH and external users.

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 Netzwerk-administration und des Einkaufs wahr.

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.

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

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

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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 radia-tion protection officer, he is responsible for organizing the relevant facilities and communicating with the supervisory authorities.

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Hygiene- und Labormanagement
Hana Kunkel achtet auf die Einhaltung der geltenden Laborstandards und Ar¬beits¬sicherheitsbedingungen. Sie verantwortet den Spülküchenbereich und koordiniert die Reinigungsdienstleistungen. Darüber hinaus ist Sie Ansprechpartnerin der Gruppenleitungen für die Laborplanung und Laborausstattung.

Facility- / Lab Management
Hana Kunkel ensures compliance with the applicable laboratory standards and work safety regulations. She is responsible for the scullery area and coordinates all cleaning services. In addition, she is the contact person for all group leaders concerning laboratory planning and laboratory equipment.

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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.

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FREUNDE UND FÖRDERER DES
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Die Grundfinanzierung des Georg-Speyer-Hauses wird vom Bundesministerium für Gesundheit und dem Hessischen Ministerium für Wissenschaft und Kunst getragen.

Funding of the Georg-Speyer-Haus

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Paul Ehrlich