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 2023

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Forschen für das Leben

Research for Life

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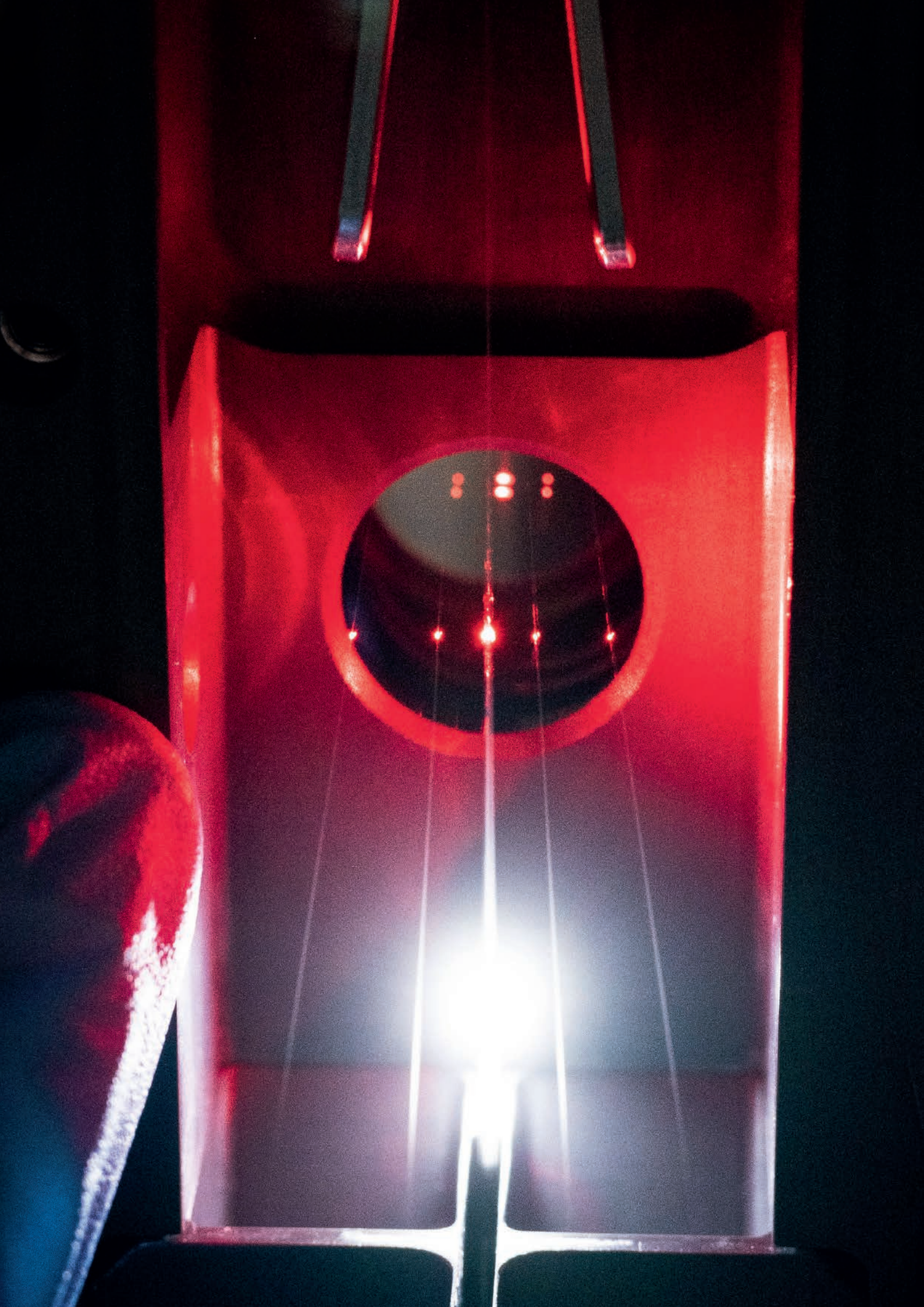

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Liebe Leserinnen und Leser,
liebe Freunde des Georg-Speyer-Hauses,

in diesem Jahr war es uns wieder möglich unseren Regelbetrieb nahezu uneingeschränkt aufzunehmen. Den Beginn des Jahres dominierte sicherlich die Begutachtung durch den Wissenschaftsrat, der nach 12 Jahren erstmalig wieder das Institut zu evaluieren hatte. Nach einer für alle Beteiligten sehr intensiven Vorbereitung konnten wir den Gutachtenden der Arbeitsgruppe des Wissenschaftsrats an zwei Tagen in sehr angenehmer Atmosphäre detailliert die Struktur und Inhalte des Instituts vermitteln und darlegen, wie erfolgreich wir in den letzten Jahren beim Erreichen unserer Ziele waren. Unsere gemeinsam unternommenen Anstrengungen und Erfolge wurden von der Arbeitsgruppe des Wissenschaftsrats erkannt und honoriert und wir freuen uns sehr über das ausgesprochen positive Ergebnis der Evaluation. Wir hoffen nun sehr, dass uns das positive Votum hilft unser übergeordnetes Ziel zu erreichen und das GSH einer dauerhaften institutionellen Förderung als außeruniversitäres Institut durch den Bund und des Landes Hessen zuzuführen. Die die dafür notwendigen formalen Schritte wollen wir im kommenden Jahr initiieren.

Nach 3 Jahren Pause war es uns endlich wieder möglich im Sommer einen wissenschaftlichen Retreat durchzuführen. Organisiert von unseren engagierten jungen Mitarbeiterinnen und Mitarbeitern, die ein spannendes Programm mit hervorragenden Gästen zusammengestellt hatten, kamen bei bestem Wetter Wissenschaft und sportliche Aktivitäten nicht zu kurz. In diesem Sinne sind wir auch froh, dass unsere Seminarreihe wieder Fahrt aufgenommen hat und wir in regulärem Rahmen internationale Sprecherinnen und Sprecher begrüßen konnten.

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

This year, we were able to resume our regular operations with almost no restrictions. The beginning of the year was certainly dominated by the assessment by the German Council of Science and Humanities, which had to evaluate the Institute again for the first time in 12 years. After intensive preparation for all involved, we were able to explain the structure and content of the Institute in detail to the experts from the Science Council's working group in a very pleasant atmosphere and demonstrate how successful we have been in achieving our goals in recent years. Our joint efforts and successes were recognized and rewarded by the Science Council's working group and we are very pleased with the extremely positive result of the evaluation. We now very much hope that the positive vote will help us to achieve our overarching goal of securing permanent institutional funding for the GSH as a non-university institute from the federal government and the state of Hesse. We intend to initiate the necessary formal steps in the coming year.

After a 3-year break, we were finally able to hold a scientific retreat again in the summer. Organized by our dedicated young employees, who had put together an exciting program with outstanding guests; science and sporting activities were not neglected in the best weather. With this in mind, we are also pleased that our seminar series has picked up speed again and that we were able to welcome international speakers on a regular basis.

Besonders zu erwähnen sind einige Veränderungen bei unseren Gruppenleitungen und die damit verbundenen diversen individuellen Erfolge unserer Gruppenleiterinnen. So freuen wir uns für Daniela Krause, die einen Ruf an die Universität Mainz angenommen hat und seit Oktober dieses Jahres dort die Leitung des Instituts für Transfusionsmedizin übernommen hat.

Genauso freuen wir uns für Lisa Sevenich, die einen Ruf an die Universität Tübingen angenommen hat. Lisa Sevenich wird zum Jahreswechsel mit ihrer Arbeitsgruppe umziehen und hat damit sehr erfolgreich einen nahtlosen Übergang ihrer Förderung durch das Max Eder Programm der Deutschen Krebshilfe erreicht. Wir gratulieren beiden und wünschen viel Erfolg bei den neuen Herausforderungen! Überaus erfreulich ist aber auch die Tatsache, dass Canan Arkan im Sommer dieses Jahres den Ruf auf die FCI-finanzierte Professur für Tumormetabolismus angenommen hat. Diese Professur ist am GSH angesiedelt und wird es ihr nun ermöglichen dieses Themengebiet im Kontext des intestinalen Mikrobioms bei uns auszubauen. Weiterhin gelang es uns die dem GSH zugeordnete und durch das DKTK geförderte Nachwuchsgruppe neu zu besetzen und begrüßen Zuzana Tatarova, die im September ihre Arbeit bei uns begonnen hat. Sie wird sich zukünftig mit Fragen der individualisierten Therapie beim Brustkrebs beschäftigen und damit das Themenspektrum unseres Instituts um eine weitere ausgesprochen relevante Erkrankung erweitern.

Wie immer finden Sie einen Überblick über die Fortschritte und Erfolge der individuellen Arbeitsgruppen im Folgenden.

Florian R. Greten, Direktor

Special mention should be made of some changes regarding our group leaders and the various individual successes associated with this. We are delighted for Daniela Krause, for example, who has accepted an appointment at the University of Mainz and has been Head of the Institute of Transfusion Medicine there since October of this year.

We are just as pleased for Lisa Sevenich, who has accepted an appointment at the University of Tübingen. Lisa Sevenich will move with her research group at the turn of the year and has thus very successfully achieved a seamless transition of her funding through the Max Eder Program of German Cancer Aid. We congratulate both of them and wish them every success in their new challenges! We are also very pleased that Canan Arkan accepted the FCI-funded professorship for tumor metabolism this summer. This professorship is based at the GSH and will now enable her to expand this subject area in the context of the intestinal microbiome. Furthermore, we were able to fill the junior research group assigned to the GSH and funded by the DKTK and welcome Zuzana Tatarova, who started her work with us in September. In the future, she will be working on questions of individualized therapy in breast cancer, thus expanding the range of topics at our institute to include another extremely relevant disease.

As always, you will find an overview of the progress and successes of the individual working groups below.


Made in Germany

Forschen für das Leben
Research for Life

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

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

Das Gebäude des Georg-Speyer-Hauses in der Paul-Ehrlich-Straße 42 – 44, 1906 eröffnet, wurde von der Stadt Frankfurt am Main zur Nutzung für Institutszwecke zur Verfügung gestellt. Der gesamte Gebäudekomplex wurde in den Jahren 1995 – 1997 aus Mitteln des Bundesministeriums für Gesundheit und des Hessischen Ministeriums für Wissenschaft und 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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FORSCHUNGSBEREICH 1

Zelluläre Kommunikation
in der Stammzellnische

Prof. Dr. D. Krause
Dr. H. Medyouf

Hygiene-
und Labor-
management

H. Kunkel

ZENTRALE EINRICHTUNGEN

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Präklinische Einheit Mikroskopie
und *invivo* Imaging
Dr. S. Stein
Dr. B. Ritter
Dr. M. Ebert
Dr. T. Alekseeva

Zentrale Einheit Transgenic Core
Genome Regulation
Dr. Ph. Grote

FORSCHUNGSBEREICH 2

Zell-Zell Interaktionen
im Tumorstroma

Prof. Dr. M.C. Arkan
PD Dr. H. Farin
Prof. Dr. F. R. Greten
Dr. L. Sevenich

VERWALTUNG

Personal, Finanzen,
IT, Innendienst, Einkauf,
Arbeitssicherheit

F. Hasslinger-Pajtler

FORSCHUNGSBEREICH 3

Experimentelle Therapie

Dr. Z. Tatarova
Prof. Dr. W. Wels

I

Zelluläre Kommunikation in der Stammzellnische
Cellular Communication in the Stem Cell Niche

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Die Rolle des Knochenmarksmikromilieus bei den Leukämien

The role of the bone marrow microenvironment in leukaemia

leukaemia

bone marrow microenvironment

pharmacological modulation

The bone marrow microenvironment (BMM) is increasingly being considered as a novel target to augment existing therapies for haematological malignancies. This is important, as the overall survival rate for all leukaemias in adults is only 44%, and leukaemic stem cells (LSC) are rarely eradicated. Eradication of cancer stem cells in leukaemia or LSC, however, is thought to be important for cure of a cancer.

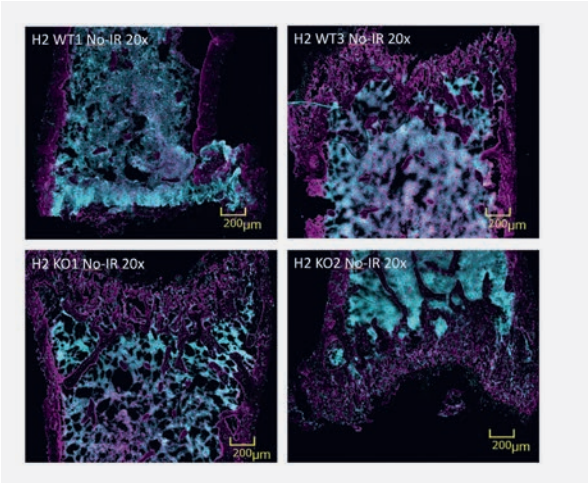


Figure 1. Representative immunofluorescence staining of nuclei (DAPI, blue) and endothelial cells (endomucin, pink) detected in femurs of two WT and two KO mice. Images were taken at 20x magnification.

Trotz verbesserter Therapien, z.B. in Form von Medikamenten aus der Gruppe der personalisierten Medizin, liegt die 5-Jahres-Überlebensrate bei Erwachsenen für alle Leukämien bei nur 40%. Deshalb hat es sich unsere Arbeitsgruppe zur Aufgabe gemacht, neue Therapien, vor allem solche mit neuem Therapieansatz, zu entwickeln.

Eine gezielte Modulation des Knochenmarksmikromilieus (KMM), dem Ort, wo eine Leukämie in der Regel entsteht und voranschreitet, kann eine Verringerung von leukämischen Stammzellen nach sich ziehen. Dies ist notwendig, denn leukämische Stammzellen können zu Therapieresistenz und Krankheitsrückfall führen. Das KMM, welches leukämische Stammzellen vor der Chemotherapie „beschützen" kann, besteht aus verschiedenen Zelltypen wie Osteoblasten, Osteoklasten, mesenchymalen Stammzellen, Endothelzellen, und der extrazellulären Matrix, aber auch azellulären Faktoren wie Zytokine, Ionen oder chemischen Bestandteilen.

Wir haben gezeigt, dass spezifische Interaktionen von Leukämiezellen mit verschiedenen zellulären und azellulären Komponenten des KMMs oder das Alter des KMMs spezifisch den Krankheitsverlauf einer Leukämie beeinflussen können. Ferner sind chemische und metabolische Faktoren im KMM, sowie inflammatorische und qualitätskontrollierende Prozesse in den Nischenzellen des KMMs, aber auch das Gerinnungssystem im KMM der Fokus unserer Arbeitsgruppe.

Auch der Stärkung von normalen hämatopoetischen Stammzellen, den gesunden Gegenstücken der leukämischen Stammzellen, durch eine Modulation des KMMs widmen wir uns.

Figure 2. Representative immunofluorescence staining of nuclei (DAPI, grey)and endothelial cells (endomucin, green) detected in femurs of one WT and two KO mice. In collaboration with Prof. Dr. Bibli, Institute for Vascular Signaling, Frankfurt am Main. Images were taken at 25x magnification.

Based on our previous work our laboratory focuses on various pathways of interaction of leukaemia cells with their surrounding bone marrow microenvironment in an effort to eventually target these interactions and eradicate LSC. The extracellular matrix, the coagulation system, chemical factors, metabolism, inflammation and novel pathways of adhesion to the BMM, studied by various in vitro and in vivo modelling systems, as well as in vivo 2-photon based imaging, hereby, form the basis of our studies.

We studied the role of calcium ions, released during the physiological remodelling of bone, as well as calcium-sensing receptor, a receptor on the surface of leukaemia cells, which senses the calcium concentration in its environment, for the development of leukaemias. This revealed that calcium ions from the bone influence the location of leukaemia cells in the BMM. Secondly, the calcium-sensing receptor has tumour-promoting versus tumour-suppressive roles depending on the type of leukaemia. Lastly, targeting the calcium-sensing receptor in conjunction with chemotherapy can prolong survival in acute myeloid leukaemia. In another project we discovered that leukaemia cells in B-cell acute lymphoblastic leukaemia (B-ALL) condition

hepatocytes to secrete components of the fibrinolytic system. These fibrinolytic agents do not just degrade clots, when they form in the body. They also degrade the extracellular matrix in the BMM which aids the progression of B-ALL. The degradation of the extracellular matrix leads to the release of leukaemia-promoting growth factors stored in the extracellular matrix, as well as easier mechanical spread of the leukaemia. Other projects in the laboratory are involved with quality control pathways in bone marrow niche cells, as well as inflammation and chemical factors influencing leukaemia outcome.

Given the recent pandemic due to SARS-CoV-2, we studied genetic determinants influencing the clinical course of patients infected with SARS-CoV-2. This work was performed in collaboration with the German Red Cross and the Departments of Infectious Diseases, Virology and Bioinformatics

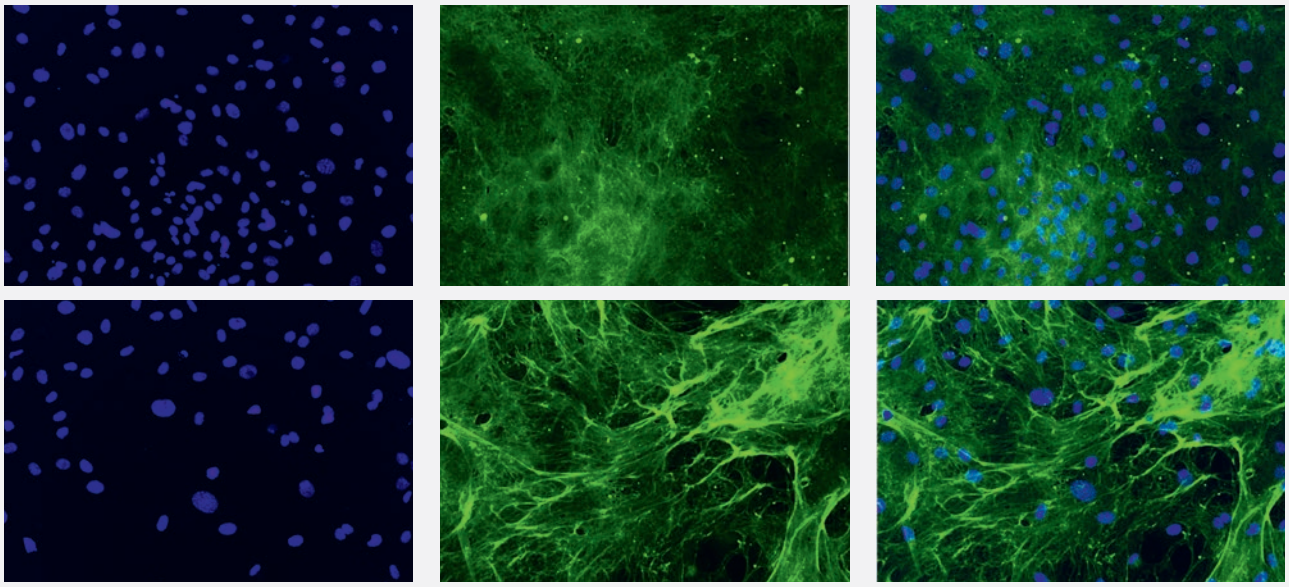
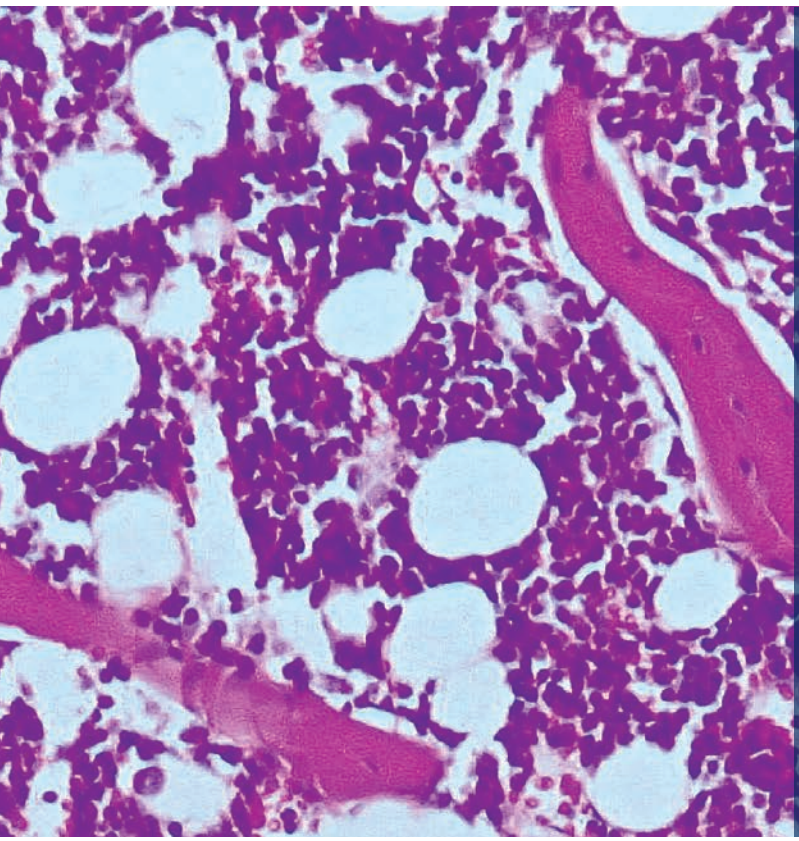


Figure 3. Representative immunofluorescence staining of collagen I (green colour) detected on the secreted extracellular matrix of WT (upper panel) and KO (lower panel) mesenchymal stroma cells from the bone marrow after 14 days of culture. Nuclei were stained with DAPI (blue color). Images were taken at 20x magnification.



Ausgewählte Publikationen

Kumar R, Pereira RS, Niemann J, Azimpour AI, Zanetti C, Karantanou C, Minka W, Minciacchi VR, Kowarz E, Meister M, Godavarthy PS, Maguer-Satta V, Lefort S, Wiercinska E, Bonig H, Marschalek R, **Krause DS**.
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Distinct and targetable role of calcium sensing receptor in leukaemia. ***Nat Commun.*** *2023 Oct 6;14(1):6242. doi: 10.1038/s41467-023-41770-0.*

... weitere Publikationen
finden Sie auf Seite ▸ 59

at the Goethe University, funded by the Goethe University's Corona-Funds.

In summary, the laboratory focuses on the role of the different constituents of the BMM on the initiation, maintenance and progression of leukaemias in an attempt to develop novel therapies which can augment our existing armamentarium against this intractable disease. Two ongoing projects have led to the discovery of innovative ways of targeting the BMM, which we intend to test in clinical trials in future.

Other activities

We are also coorganizing the 25th international scientific meeting on "Chronic myeloid leukaemia" and the 4th meeting on "The tumour microenvironment in the hametological malignancies" under the umbrella of the European School of Haematology.

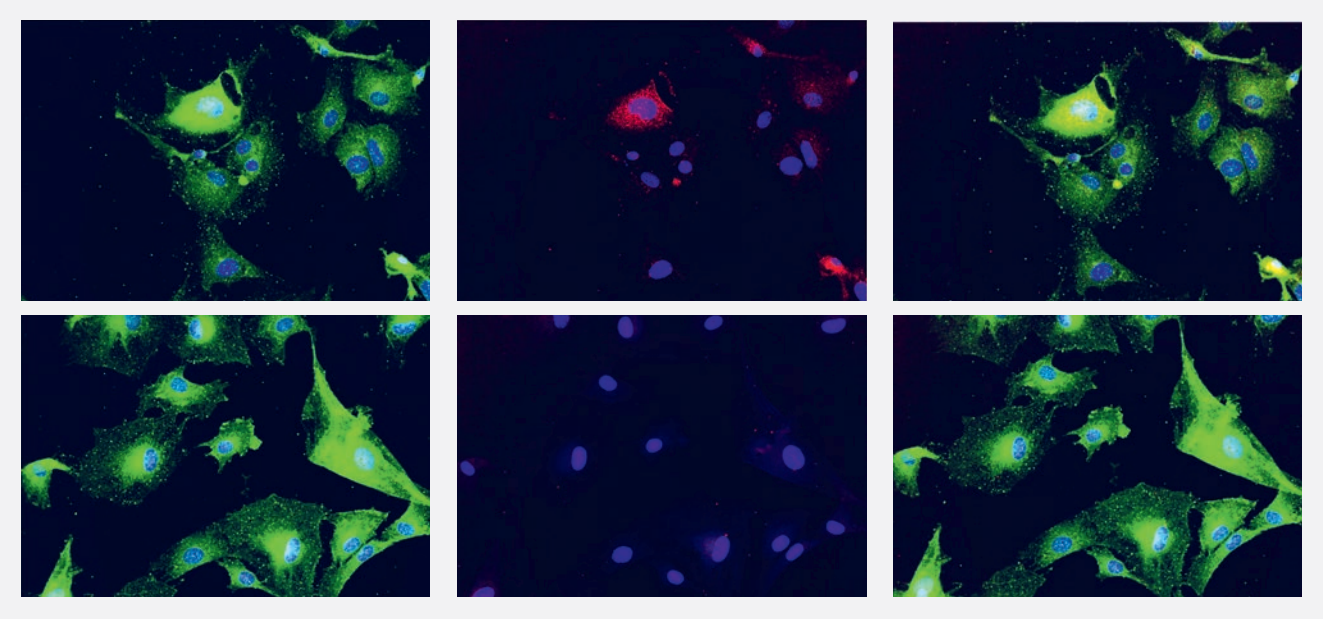

Figure 4. Representative immunofluorescence staining of nuclei (DAPI, blue), LAMP1 (green), LC3 (red) and merged stains of WT (top) and mutant (bottom) mesenchymal stroma cells. Images were taken at 40x magnification.

Tumornischen Evolution

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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.

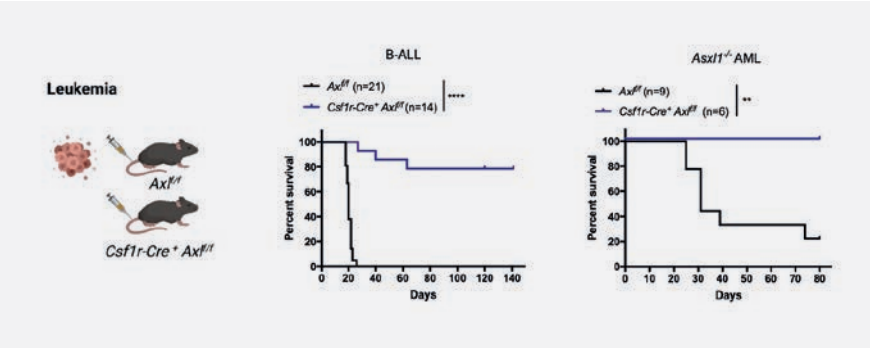


Figure 1. **AXL ablation in macrophages elicits leukemic clearance.** Kaplan-Meier survival of mice with AXL proficient (*Axl*$^{f/f}$) or AXL deficient (*Csf1r-Cre+ Axl*$^{f/f}$) macrophages, challenged with Philadelphia-chromosome positive B-cell acute lymphoblastic leukemia (B-ALL) or acute myeloid leukemia driven by Asxl1 deficiency (*Asxl1*$^{-/-}$ AML).

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. Work from 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 (Fig. 1) 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 TME[4] (Fig. 2).

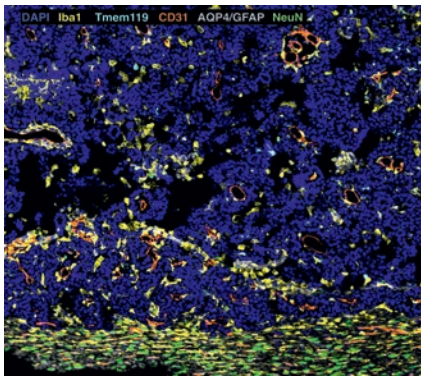
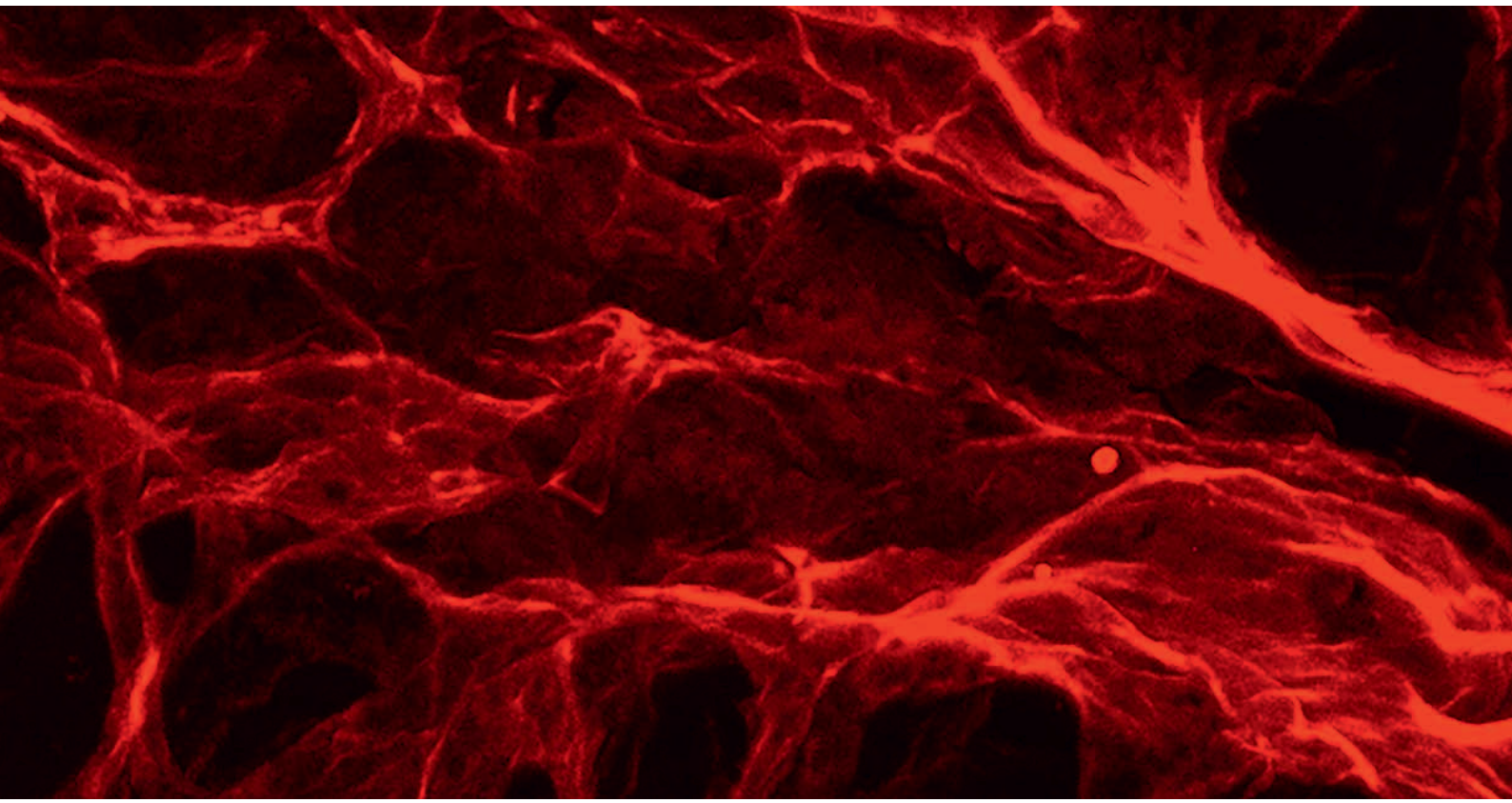


Figure 2. **Cellular architecture of a breast-to-brain metastasis visualized by multispectral imaging.**
Brain metastasis from the 99LN breast cancer line injected into a C57BL/6 syngeneic mouse. Astrocytes are marked by GFAP and Aquaporine 4; Endothelial cells are marked by CD31; Myeloid cells are marked by Iba1; Microglia [the brain resident macrophages] are marked by Tmem119; Neurons are marked by NeuN; Nuclei marked by DAPI.



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 a team-science project, RISEBrain, supported by the European TRANSCAN-3 funding scheme (https://transcan.eu/output-results/funded-projects/risebrain.kl). This joint venture enables us to put together our expertise in engineering, imaging, computation, experimental modeling, and clinical care, to uncover and target cellular and molecular drivers of local immune suppression in BrM.

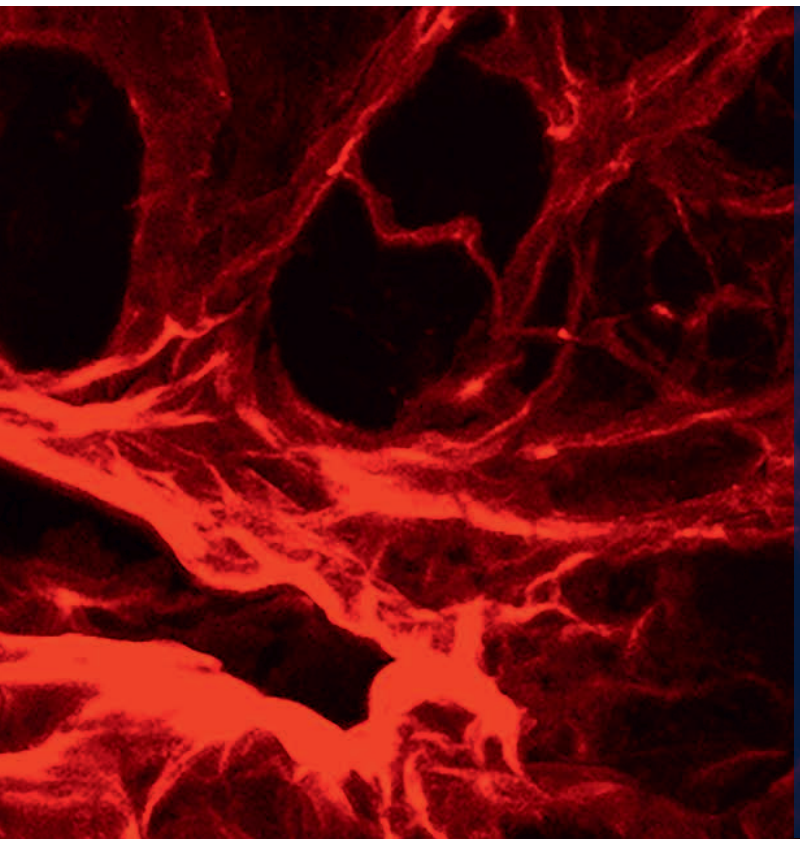
Impact of age-related niche changes on cancer

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 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.micro-bone.de) we explore *how age-related alterations in the BM niche drive the awakening of quiescent metastatic cancer cells* to propose new means by which we could improve outcome and/or quality of life of patients with bone metastasis.

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 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].



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*Co-senior authors

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*equal contribution

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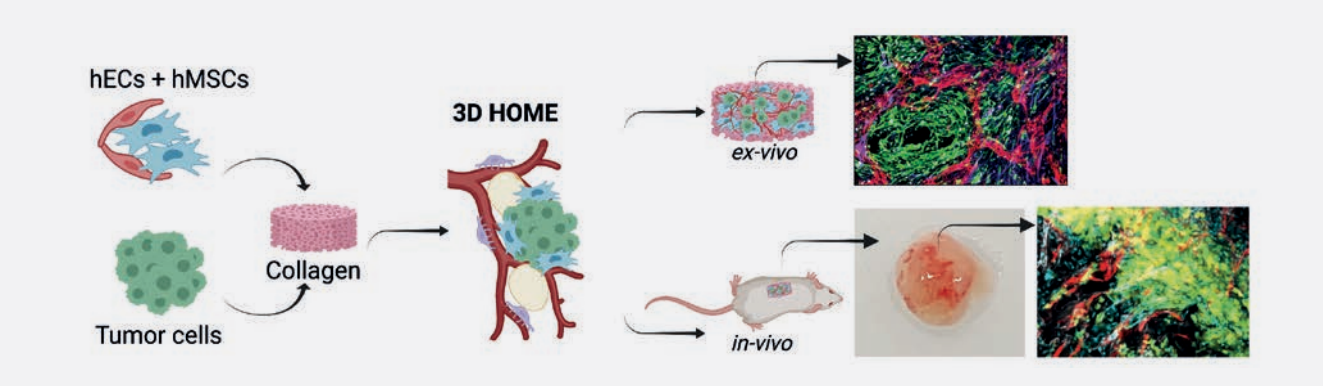

Figure 3. **Schematic view of the 3D HOMEs used to study reciprocal crosstalk between tumor cells and the bone marrow microenvironment.** Representative images show tumor cells in green (GFP+), the vasculature (Red) and stromal cells of mesenchymal origin (Cyan or purple). hEC= human endothelial cells.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

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 are studied in a fully human setting that closely recapitulate the cellular composition and architecture found in the human bone marrow (Fig. 3).

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II

Zell-Zell Interaktionen im Tumorstroma

Cell-Cell Interaction in the Tumor Stroma

Diät, Energiemetabolismus und Krebs

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Diet, Energy Metabolism, and Cancer

Metabolic Derangements during Cancer

Diet, Microbiome, and Cancer

Modeling Host-Microbiome Interactions *in vitro*

Diet is shaped by multiple diverse factors such as culture, nutritional knowledge, price, availability, taste, and convenience. Given the reciprocal interaction between host and environmental factors during carcinogenesis, food consumption is becoming critical. Due to the distinct shifts in agriculture and changes in crops in the last decades, food may have a pivotal role in aggravating disease. Our research aims at delineating how changing diet is associated with cancer initiation and progression at a molecular and cellular level in the pancreas and intestine. Using preclinical models as well as clinical samples, we aim at defining derangements in host, microbial, and tumor energy metabolism in order to define whether there are vulnerabilities that can be targeted during disease or therapy and if customizing diet eventually may pave the way for individual-based interventions.

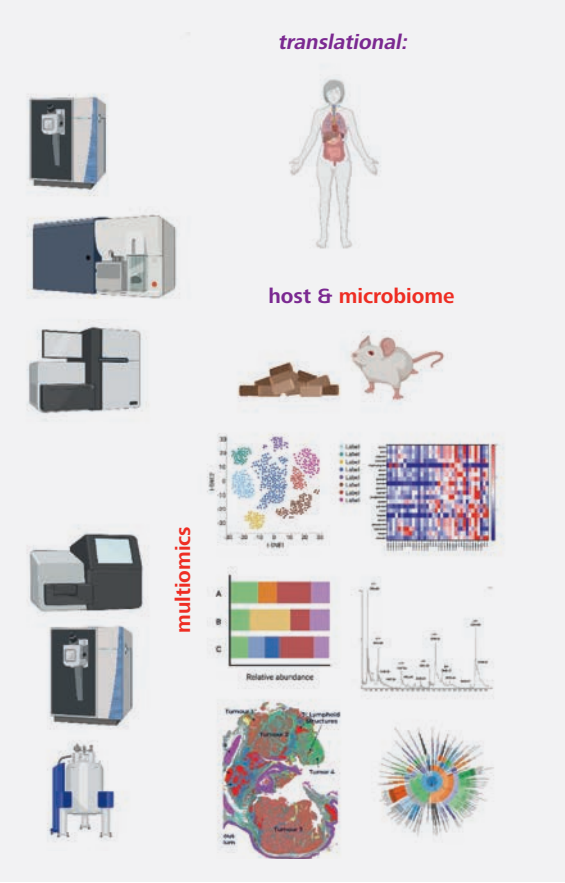


Figure 1.
Through technology platforms established, we investigate alterations in metabolism using clinical samples or preclinical models during disease and therapy.

Die Ernährung wird von vielen verschiedenen Faktoren wie Kultur, Ernährungswissen, Preis, Verfügbarkeit, Geschmack und Bequemlichkeit geprägt. Angesichts der wechselseitigen Wechselwirkung zwischen Wirts- und Umweltfaktoren während der Kanzerogenese, wird der Nahrungsmittelkonsum immer kritischer. Aufgrund der deutlichen Verschiebungen in der Landwirtschaft und der Veränderungen bei den Nutzpflanzen in den letzten Jahrzehnten, können Lebensmittel eine entscheidende Rolle bei der Verschlimmerung von Krankheiten spielen. Unsere Forschung zielt darauf ab, auf molekularer und zellulärer Ebene zu beschreiben, wie eine veränderte Ernährung mit der Krebsentstehung und dem Fortschreiten von Krebs in Bauchspeicheldrüse und Darm verbunden ist. Mit Hilfe präklinischer Modelle und klinischer Proben wollen wir Störungen im Wirts-, Mikroben- und Tumorenergiestoffwechsel definieren, um festzustellen, ob es Schwachstellen gibt, die während der Erkrankung oder Therapie gezielt angegangen werden können, und ob eine angepasste Ernährung schließlich den Weg für individuelle Interventionen ebnen kann.

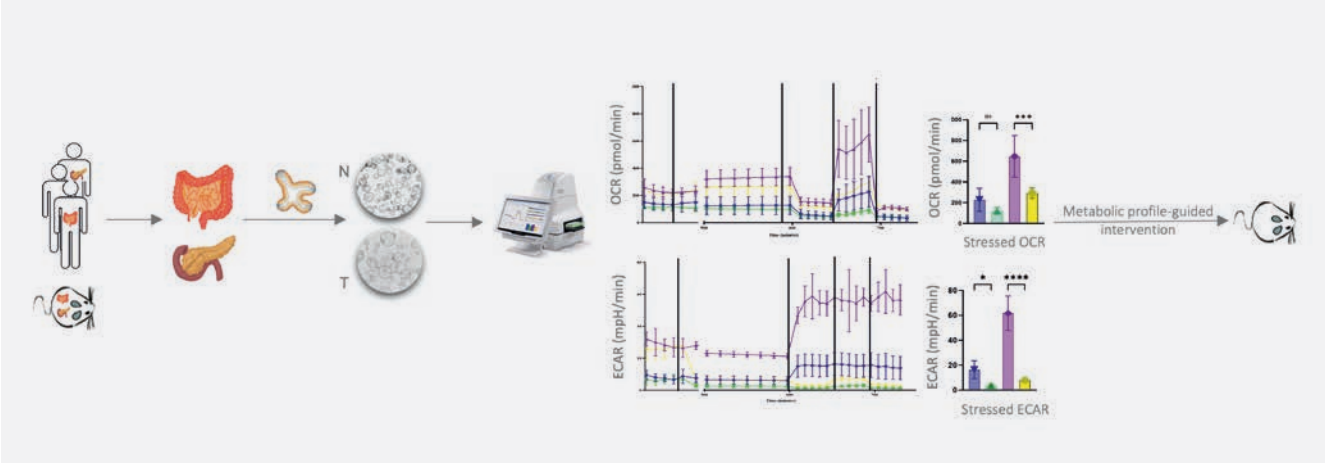
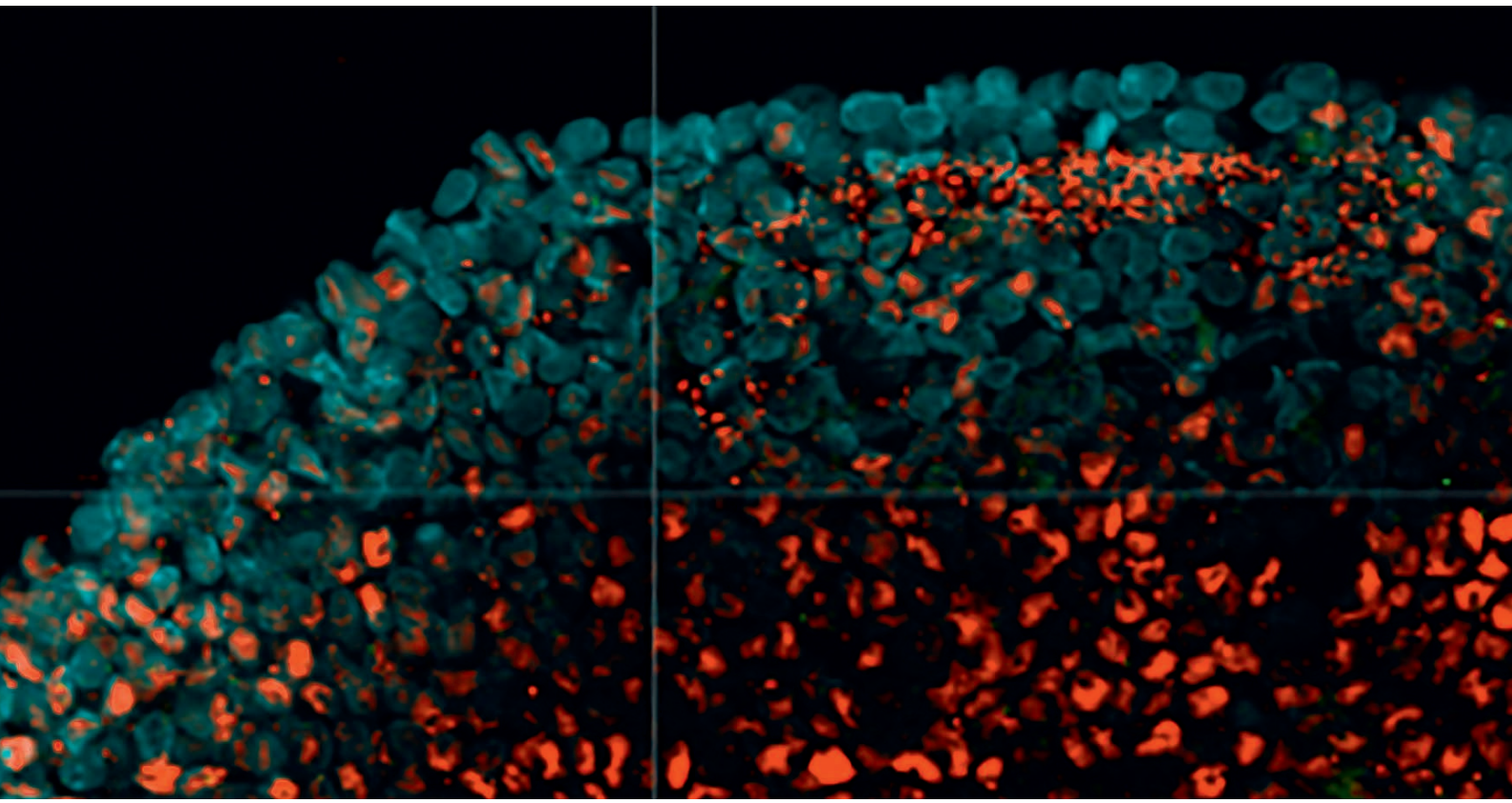


Figure 2.
Derangements in bioenergetic pathways during tumor progression and therapy are investigated using preclinical models to define and target vulnerabilities, which may potentiate therapeutic drug efficacy.

Metabolic Derangements during Cancer

Cancer is marked by dysregulation of the signaling pathways that orchestrate proliferation, cell death, tumor-promoting inflammation, and energy metabolism. Our studies focus on elucidating the host and tumor energy metabolism, delineating the critical alterations that take place during disease initiation and progression, and targeting the metabolic vulnerability of tumor cells genetically or pharmacologically in preclinical mouse models, which may have a diagnostic value in pancreatic and intestinal cancer and can impact therapy response. Using mouse- or human-derived organoids as *in vitro* model system, we characterize the metabolic potentials, and eventually use as a tool to target vulnerabilities in energy metabolism.



Diet, Microbiome, and Cancer

Human gut is inhabited by trillions of bacteria contributing majorly to the regulation of metabolic functions and immune homeostasis. Given microbiota compositional and functional profiles shape susceptibility to cancer under deranged metabolism, dynamics of bacterial community is critical. Nutrition can directly or indirectly modulate microbiome and play a decisive role in disease outcome. Our studies aim at unravelling the impact of varying dietary intake on microbiota structure and function during cancer and therapy. We elucidate whether dietary restrictions can pave the way for individual-based interventions in cancer by regulating microbiome and metabolism.

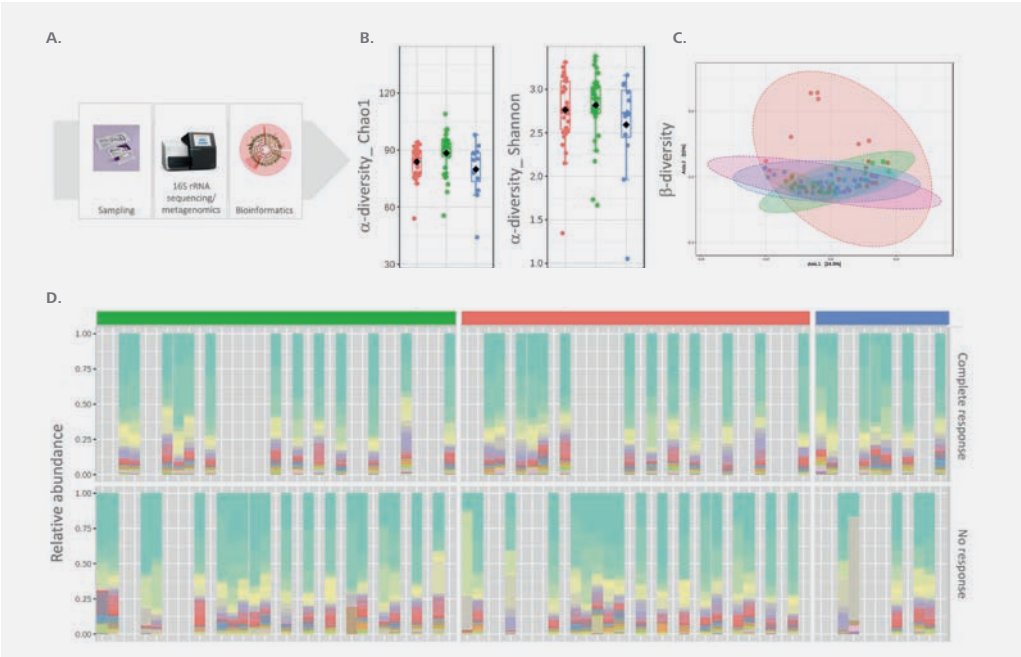
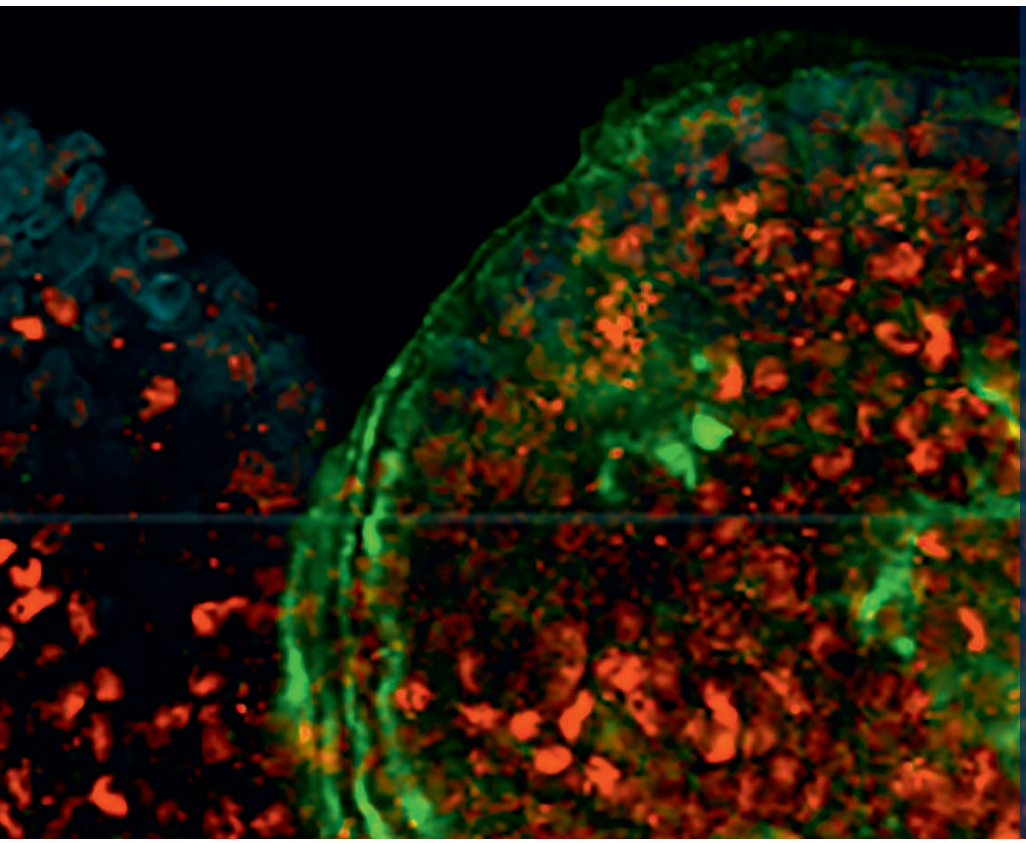


Figure 3.
Our ultimate goal is to define alterations in microbiome and effect of dietary interventions designed to impact microbial community and function during disease and therapy.



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Modeling Host-Microbiome interactions *in vitro*

Many links of microbiota to cancer progression remain only correlative due to lack of modeling host-microbiome connections. This underlies the critical and urgent need for sophisticated *in vitro* model systems to address the issue, which will help not only to gain mechanistic insights into microbial effects on intestinal epithelium but also will lead to development of innovative therapeutic strategies targeting microbial-epithelial interactions. Therefore, our studies include developing innovative tools to fabricate and analyze complex 3D interactions.

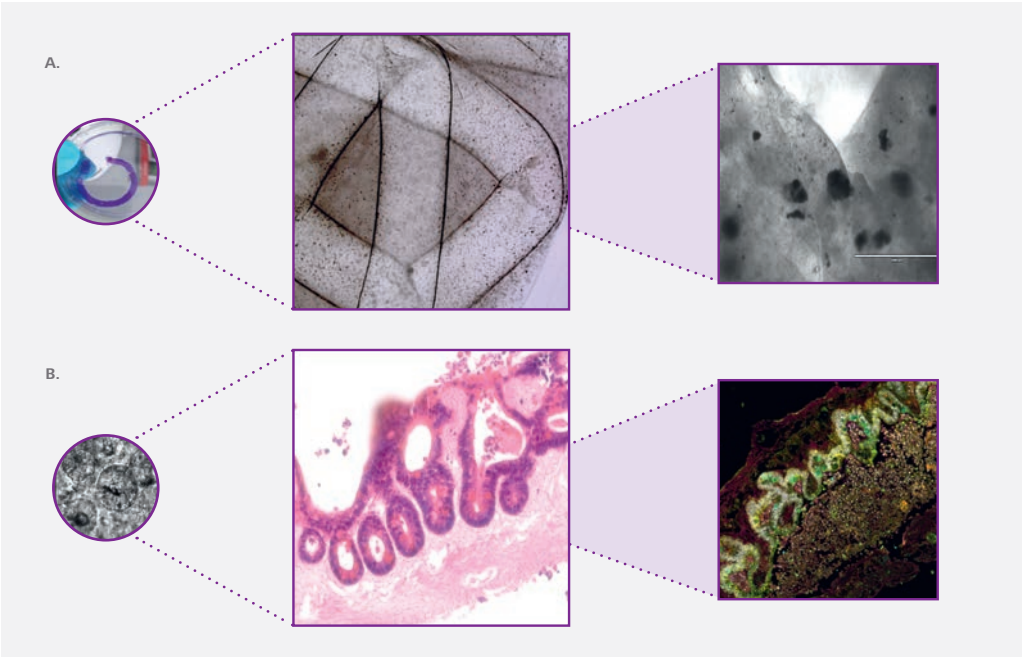

Figure 4.
By reconstructing tissue-specific tumor microenvironment using A) 3D bioprinting and B) scaffold systems, we aim to provide mechanistic insights into host-microbiome interactions *in vitro*.

Gewebsinteraktionen und Signalmechanismen im Darmkrebs

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Signaling crosstalk in the colon cancer microenvironment

3D organoid stroma biobanks from human colorectal cancer

Study of signaling mechanisms in the cancer microenvironment

Identification of therapeutic strategies targeting the colon cancer microenvironment

In Germany, colorectal cancer (CRC) is the third most common cancer type with 59,000 new diagnoses and 24,000 death cases each year. Two major classes can be distinguished: microsatellite stable (MSS, ~85%) and microsatellite instable tumors (MSI; ~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. Main challenges are the high genetic heterogeneity of CRC both at the inter-individual and intratumoral level. In addition, prognosis and therapy responses are strongly influenced by the tumor microenvironment (TME). To better understand the complex link between CRC genotype and phenotype and to develop rational therapies new experimental models are required.

Patient-derived tumor organoids (PDTOs) have emerged as an important preclinical tool. The organoid technology is based on expansion of primary epithelial cells in 3D Matrigel and defined growth factors. Originally developed for the mouse small

Unsere Arbeitsgruppe erforscht die zellulären und molekularen Vorgänge bei der Entstehung von Darmkrebs. Insbesondere interessiert uns die Kommunikation der verschiedenen Zelltypen in der unmittelbaren Umgebung des Tumors, dem so genannten „Tumormicroenvironment". Dabei nutzen wir „Organoide", ein neuartiges dreidimensionales Gewebekultur-System. Organoide können unter definierten Kulturbedingungen aus humanen Darm-Stammzellen etabliert werden und bilden Darmepithel-spezifische Strukturen wie Krypten (Furchen) oder Villi (Zotten) aus. Dadurch können Stammzellen in einem Gewebe-ähnlichen Zustand expandiert werden, was die Untersuchung von molekularen Signalen in einer definierten Mikroumgebung ermöglicht. Durch Zugabe von Fibroblasten, Gefäß- oder Immunzellen, wird der Organkontext nachgebildet. Im Mittelpunkt unserer Forschung steht die genetische Analyse der Entstehung und Progression des Darm-Karzinoms. Im Rahmen einer klinischen Kollaboration am „Frankfurt Cancer Institut" werden dazu „lebende Biobanken" von Patienten-ableiteten Tumor-Organoidlinien angelegt. Mit Hilfe von genetischen Techniken (CRISPR/Cas9) und Hochdurchsatzanalysen wie Genom-/RNA-Sequenzierung und Proteomanalyse versuchen wir zu verstehen, wie onkogene Mutationen den Tumor-Phänotyp beeinflussen. Im Rahmen des EU-Projekts „EUbOPEN" nutzen wir Organoid-Modelle zur pharmakologischen Testung als Ansatzpunkt für zukünftige Therapien beim Darmkrebs.

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.

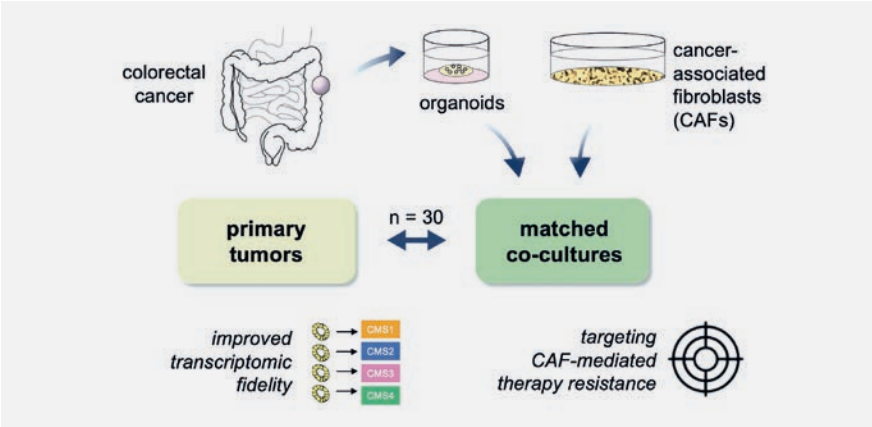
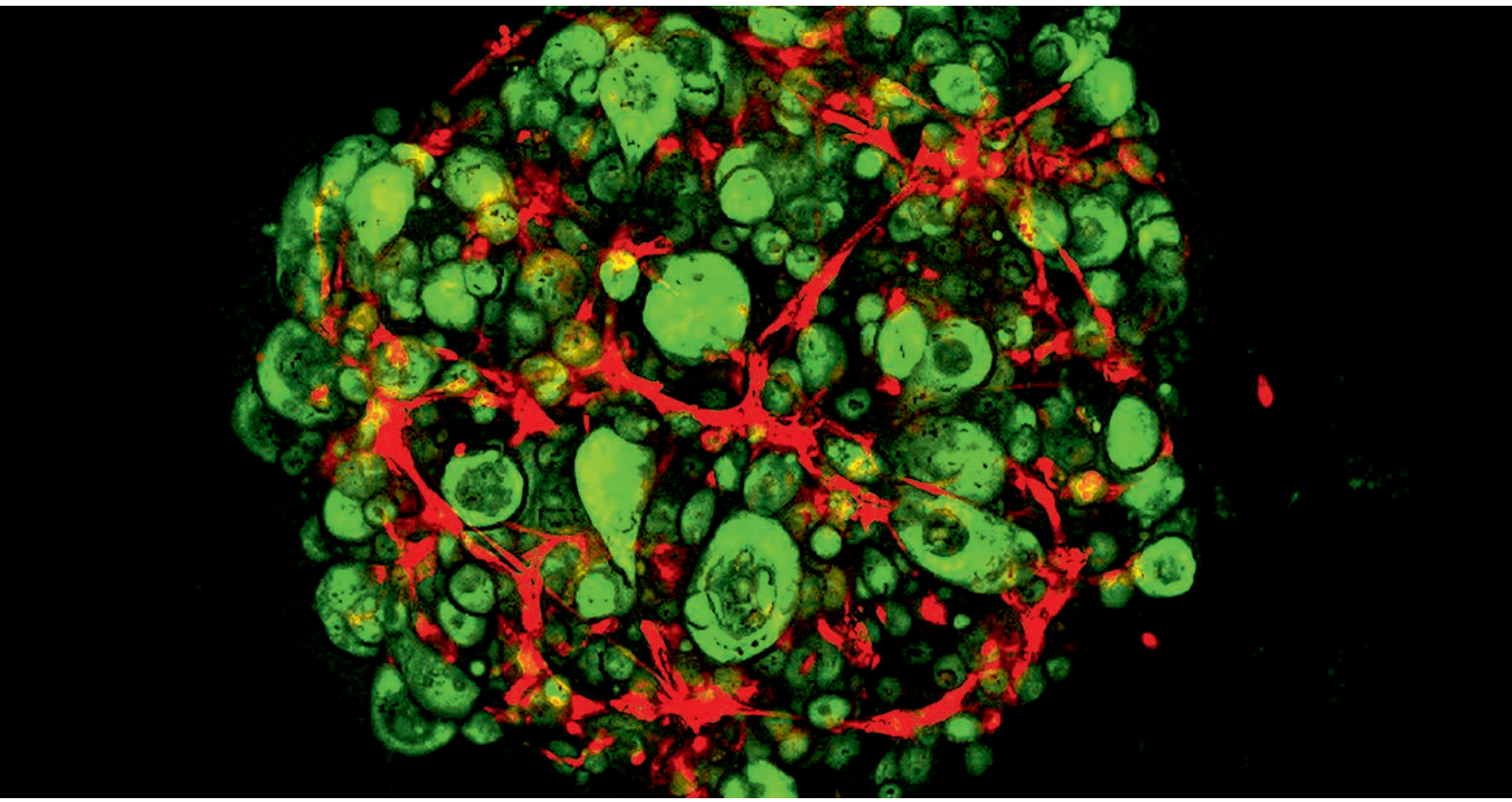


Figure 1.
Colorectal Cancer Organoid-Stroma Biobank. Generation of tumor organoids and cancer-associated fibroblasts (CAFs) from clinical samples. Systematic analysis of co-cultures from 30 patients showed an improved similarity with the corresponding tumor tissues and profound influences of CAFs on 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 tumor microenvironment 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 analyzed. All models were subjected to whole exome and RNA sequencing. To study CRC subtype determination, transcriptomic 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. 3D organoids allow to recapitulate this complexity and to study the effect of individual oncogenes and tumor suppressors. By genetic engineering of patient-derived 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 characterization may in future allow to identify patient-specific tumor vulnerabilities.

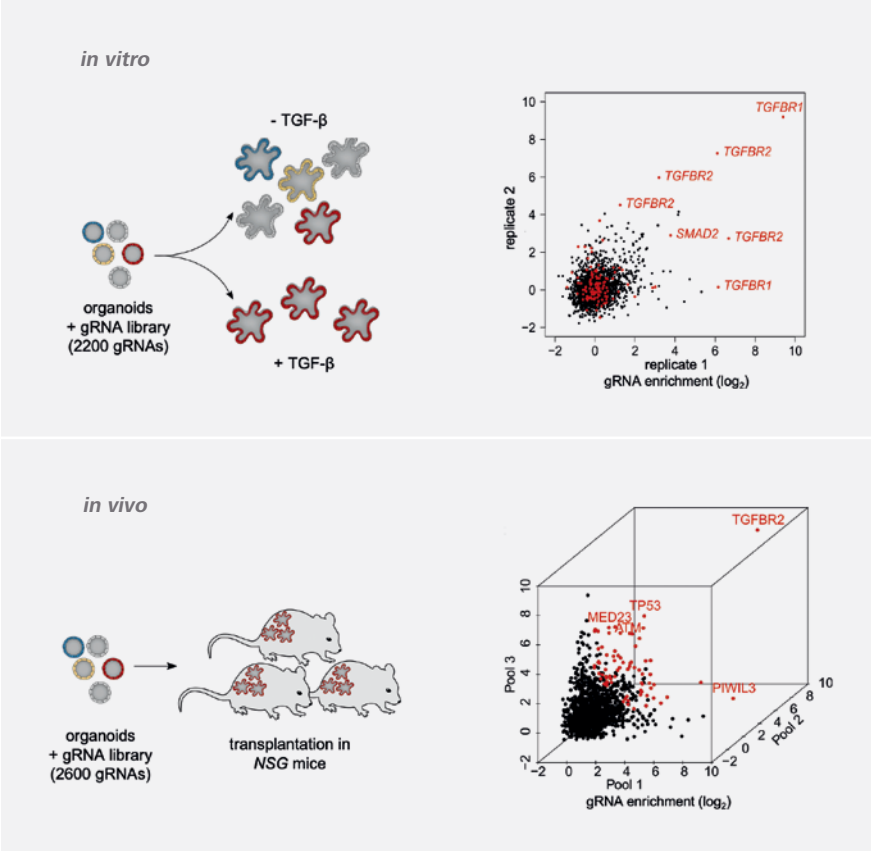
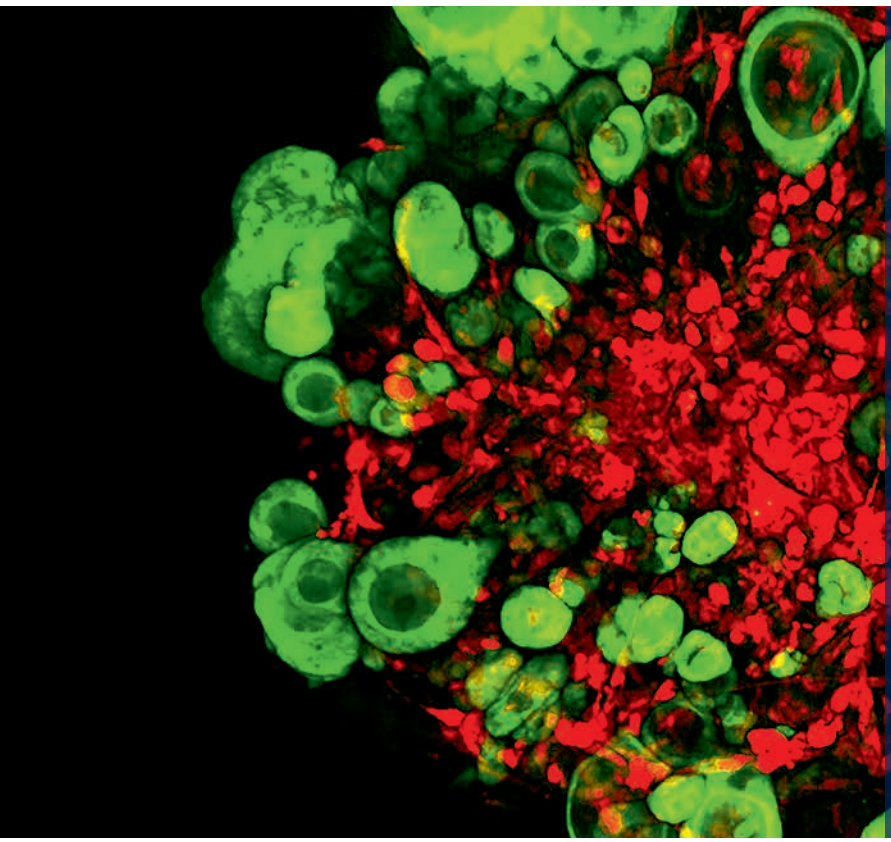


Figure 2.
CRISPR/Cas9 library screening in 3D organoids *in vitro* and *in vivo*
Top: TGF-β resistance screen *in vitro*. Barcode sequencing after phenotypic selection (growth in presence of TGF-β). Bottom: Tumor suppressor screen in human organoids after subcutaneous xenotransplantation. Barcode sequencing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



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Colorectal cancer organoid-stroma biobank allows subtype-specific assessment of individualized therapy responses. ***Cancer Discovery****. CD-23-0050.* *co-corresponding authors

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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.

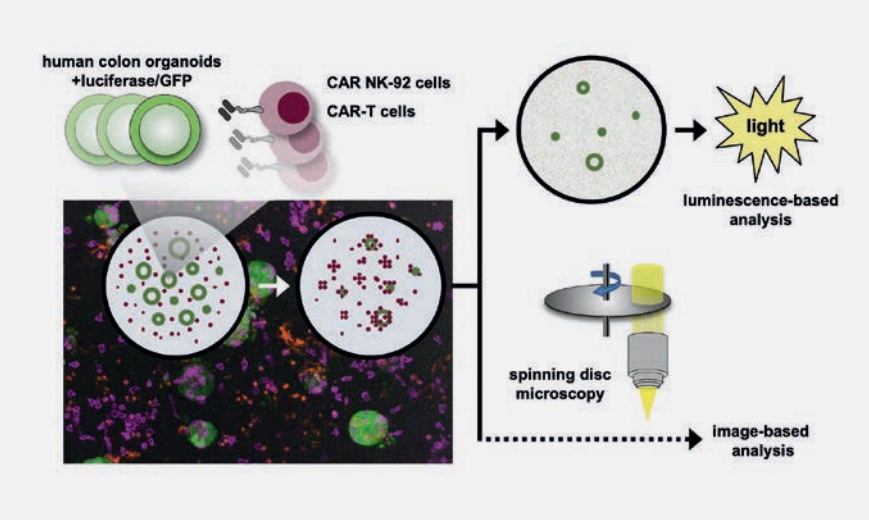

Figure 3.
3D model for CAR-mediated cytotoxicity using patient-derived CRC organoids
Combination of GFP/luciferase transgenic human colon cancer organoids (green) with CAR-cells (violet). Monitoring of cytotoxic responses by video microscopy and enzymatic read-outs (adapted from Schnalzger et al., *EMBO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

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Therapeutische Interventionen in das Tumormikromilieu

Therapeutic interventions in the tumor microenvironment

Tumor microenvironment

Hepatocellular carcinoma

Colorectal carcinoma and liver metastasis

Modulation of immune responses and epigenetic pathways

Human CRC biobank

Colorectal carcinoma (CRC) is one of the three most frequent types of cancer in industrial nations. Despite improvements in preventive colon screenings and therapies, mortality rates remain among the top three cancer-associated causes of death. The mortality is mainly due to metastasis, which occurs predominantly in draining lymph nodes, liver and lungs. Tumors are not just a mass of mutated cancer cells but a complicated network of tumor cells and surrounding stroma cells (e.g. fibroblasts, immune and endothelial cells) that together from the tumor microenvironment. Targeting the tumor microenvironment opens the possibility for a much broader range of therapeutic options. For example, checkpoint inhibitors like anti-PD-1, that prevent T cell exhaustion and increase anti-tumor immune responses. They show great success in mismatch-repair deficient or microsatellite instable CRC, that have a high amount of neoantigens and infiltrating T cells to begin with. Unfortunately, those only comprise a small percentage of CRC. One way to conduct intensive research on individual colorectal tumors is to process patient-derived biopsies into three-dimensional organoids that can be cultured *in vitro*. Together with the group of Henner Farin and support from the University Cancer Center Frankfurt (UCT), the German Cancer Consortium (DKTK) and the Frankfurt Cancer Institute (FCI), we generated a biobank of patient-derived organoids (PDO) from tumor and adjacent normal tissues as well as matched fibroblasts. One shortcoming of PDOs *in vitro* is their lack of stroma, which is known to influence tumor growth and therapy responses. Although they mostly retain the molecular and genetic properties of their parent tumors, the commonly used CRC classification in CMS types (consensus molecular subtype) or the recently further defined IMF classification depend on the presence of stromal cells and therefore cannot be recapitulated exactly. We were able to show, that this could be partly restored by coculturing PDOs with fibroblasts *in vitro* or xeno-transplantation *in vivo* (Farin et al., 2023). Interestingly, the regained CMS signatures were PDO intrinsic and independent of the fibroblast origin. By coculturing PDOs and fibroblasts a platform for drug testing was developed, that showed increased

Der Fokus unserer Forschung liegt auf der funktionellen Analyse des Mikromilieus in gastrointestinalen Tumoren und der Nutzung aufgedeckter Prozesse zur therapeutischen Intervention. 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. Wir verwenden humane Organoide und Fibroblasten, die wir über die letzten Jahre zusammen mit der Arbeitsgruppe von Henner Farin und dem Universitären Centrum für Tumorerkrankungen (UCT) Frankfurt als Biobank aus kolorektalen Karzinomen (CRC), sowie dem zugehörigen Normalgewebe aufgebaut haben. Mit diesen gelang es und zu zeigen, dass die Kokultur mit Fibroblasten die molekularen Subtypen von CRC besser rekapitulieren kann und somit die Vorraussagekraft von Medikamentenscreenings deutlich erhöht. Darüber hinaus verwenden wir aussagekräftige murine präklinische Modelle und konnten so belegen, dass bestimmte Histonmodifikationen insbesondere bei aggressiven rechtsseitigen Tumoren eine wichtige Rolle spielen.

Einen als Ferroptose bezeichneten Prozess des programmierten Zelltodes haben wir in Bezug auf hepatozelluläre Karzinome (HCC) untersucht. Wir konnten zeigen, dass die Induktion von Ferroptose kombiniert mit einer Suppression von myeloiden Zellen Lebertumore und Lebermetastasen für die Behandlung mit Immun-Checkpointblockern empfänglich macht. Dies war jedoch auf ein Wachstum von Tumoren in der Leber beschränkt, primäre kolorektale Tumore reagierten nicht auf die Kombinationsbehandlung. Dies verdeutlicht einmal mehr die Bedeutung des Tumormikromilieus und zeigt eine vielversprechende Therapiestrategie für Tumore und Metastasen der Leber.

predictability then PDO monoculture. CRC is characterized by a high degree of plasticity, as seen by dedifferentiation to stem cell-like states or during epithelial-mesenchymal transition (EMT), an important process for metastasis. The fact that cells convert back and forth between different phenotypes suggests reversible molecular mechanisms responsible for this phenomenon. The transcriptional regulation of gene expression is orchestrated by epigenetic processes like DNA- or histone modifications that either condense or open the DNA for the transcription machinery. Altered trimethylation (me3) of lysine 9 or 27 of histone 3 (H3K9 / H3K27) or lysine 20 of histone 4 (H4K20) has been associated with cancer progression. To investigate if these could be associated with distinct molecular characteristics of colorectal tumors or molecular subtypes Dr. Verawan Boonsanay-Michel evaluated their presence in 30 PDOs from our CRC biobank for her project. Interestingly, there was no distinct pattern in histone 3 trimethylation, while there was a clear separation in high and low H4K20me3 levels. These couldn`t be linked to CMS types or typical oncogenic driver mutations. Instead low levels of H4K20me3 were predominant in organoids from right-sided colon cancer (RCC) [Fig. 1A, B], that generally shows a poorer prognosis and higher recurrence then carcinomas from the left side of the colon (LCC). When transplanted in immunodeficient NSG mice, subcutaneous xenotransplants from RCC-organoids showed a more aggressive growth, that could be treated

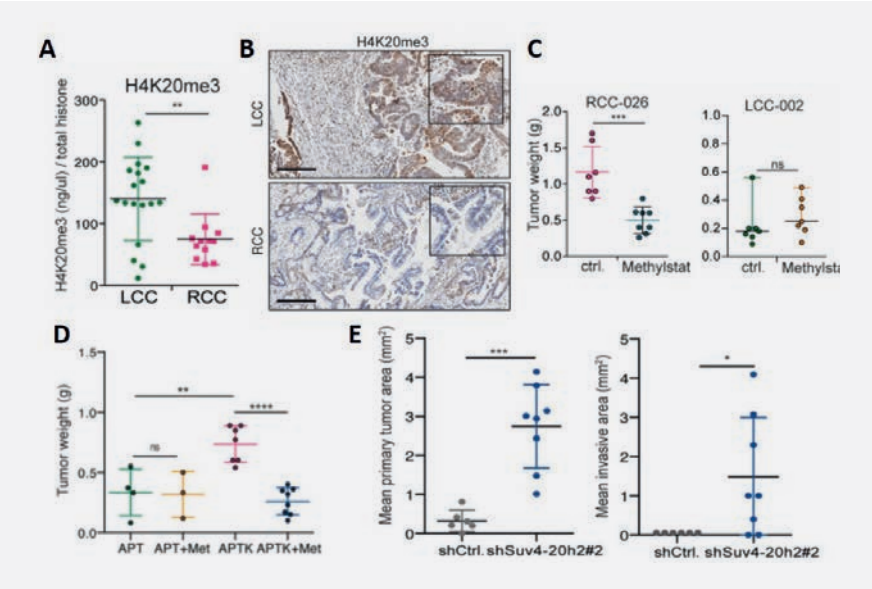
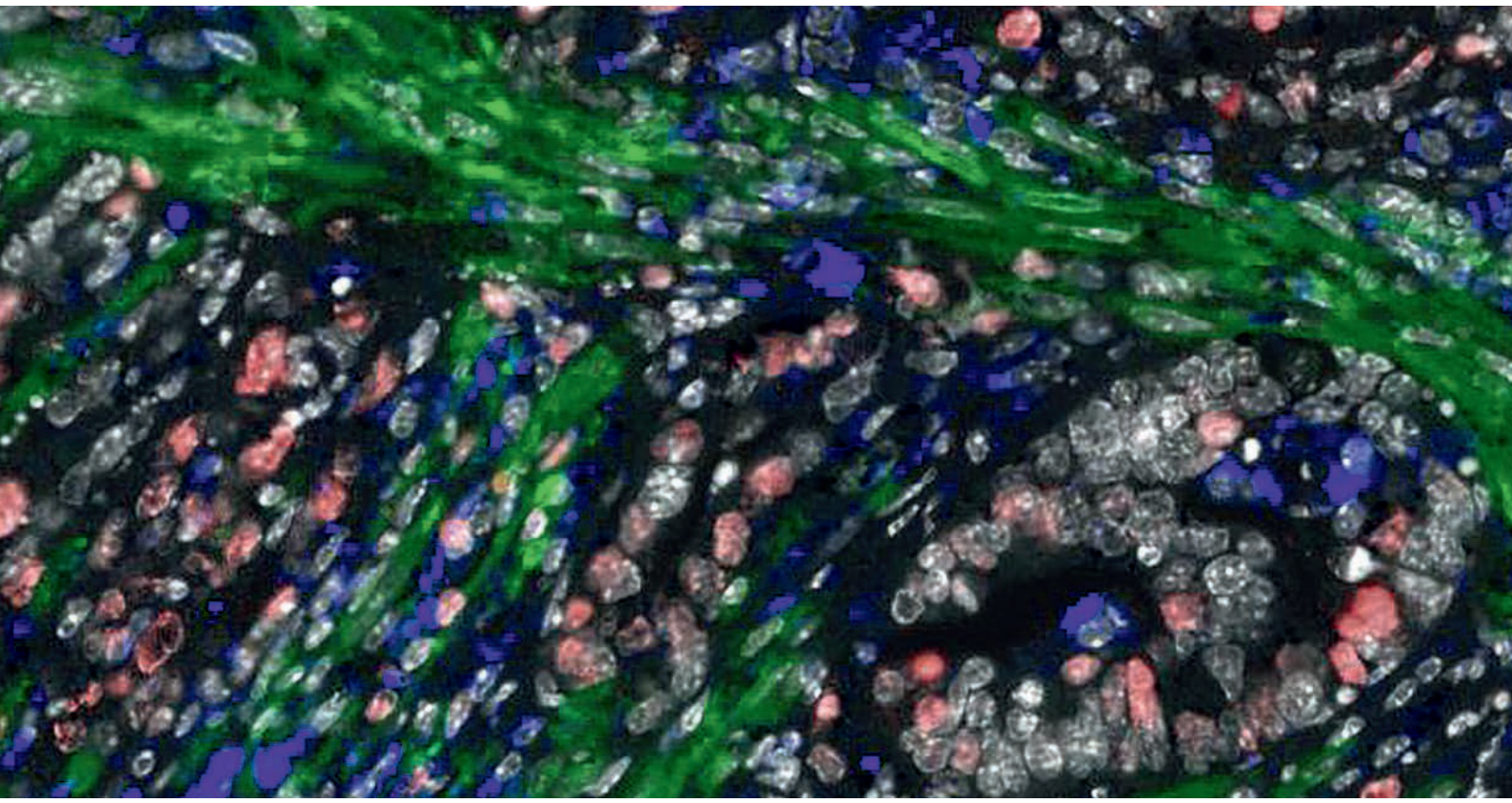
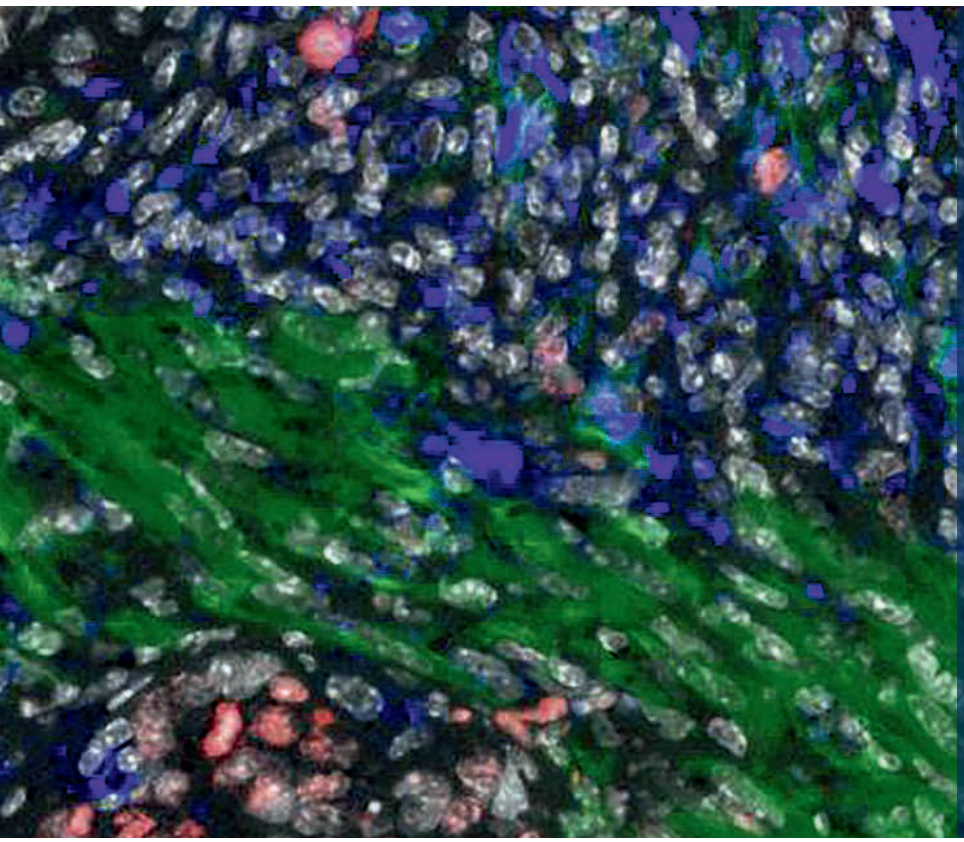


Figure 1: **Effect of H4K20 trimethylation on tumor growth.** (A) Amount of H4K20me3 in human patient-derived organoids from left-sided (LCC) or right-sided colon carcinoma (RCC). (B) Representative staining of H4K20me3 in formalin-fixed paraffin-embedded human tumor tissue. Scale bar = 200µm. (C) Examples of human RCC- and LCC-xenografts, subcutaneously transplanted in NSG mice. Shown are tumor weights after control or methylstat treatment. (D) Tumor weights of s.c. APT or APTK tumors with control or methylstat treatment in C57BL/6 wildtype mice. (E) Tumor size and invasive area of colorectal APT organoids with *Suv4-20h2* or control shRNA. Figure adapted from Boonsanay et al., 2023.



with the small-molecule inhibitor methylstat, which increases H4K20me3 level [Fig. 1C]. We were able to delineate the detailed molecular signaling events responsible for this difference in murine organoid models and could confirm this in human xenografts from RCC-PDOs, that could also be effectively treated with methylstat. Taken together, this study could link an open chromatin structure caused by decreased levels of trimethylated histone 4 K20 to aggressive tumor growth in murine and human tumors.

As described above, the tumor microenvironment consists of a multitude of cells that communicate via a wide variety of signaling pathways and processes. We investigated a non-apoptotic cell death process called ferroptosis in the context of hepatocellular carcinoma (HCC).
As the name implies, ferroptosis is an iron-dependent mechanism in which lipid peroxidation products accumulate and lead to membrane ruptures. It is normally prevented by glutathione peroxidase 4 (GPX4), which converts lipid peroxides into non-toxic lipid alcohols. To study ferroptosis in HCC, we generated mice with liver-specific deletion of *Gpx4* using the Cre/loxP system (*Alb-cre/Gpx4*$^{F/F}$ or *Gpx4*$^{\Delta/\Delta hep}$). The liver-specific loss of GPX4 is compensated by the amount of antioxidant vitamin E in chow. Deprivation of vitamin E causes ferroptosis in Gpx4-deficient livers and mice succumb to liver failure after the internal reserves are depleted (approximately 3 weeks). Ferroptosis is thought to suppress cancer, however, we could detect an upregulation in several tumor promoting genes in ferroptotic livers, that may counteract tumor suppression by creating a pro-tumorigenic environment. Indeed, in murine HCC model, no difference in tumor load or survival rates could be observed between animals with *Gpx4*-deficient or proficient livers [Fig. 2A]. Further analysis revealed an inflammatory response in tumors of *Gpx4*$^{\Delta/\Delta hep}$ mice with increased numbers of infiltrating CD8^{+} cytotoxic T cells [Fig. 2B], that were attracted by elevated levels of CXCL10 secreted by ferroptotic hepatocytes. Interestingly, although isolated CD8 T cells from these tumors showed increased activity and interferon gamma secretion *in vitro*, they also caused an upregulation of the immunosuppressive programmed death-ligand 1 (PD-L1) in tumor tissue *in vivo* [Fig. 2B]. As a logical consequence, blocking its receptor PD-1 on T cells should overcome the negative effect. Indeed, a single treatment cycle with the checkpoint inhibitor anti-PD-1 (6 times over 16 days) starting at the day of immune cell infiltration, led to significantly prolonged survival in *Gpx4*$^{\Delta/\Delta hep}$ mice. Next to increased numbers of CD8 T cells in ferroptotic liver tumors, also an abundance of tumor-associated macrophages and Gr-1^{+} myeloid cells could be detected [Fig. 2B]. Further analysis confirmed that these were myeloid-derived suppressor cells (MDSCs), with polymorphonuclear MDSC exerting a stronger suppression on T cell proliferation than mononuclear MDSCs *in vitro* [Fig. 2C]. Blocking their chemoattractant HMGB1 prevented MDSC infiltration and increased the survival of *Gpx4*$^{\Delta/\Delta hep}$ mice in the HCC model. When anti-HMBG1 and anti-PD-1 treatment were combined, an even greater advantage could be observed in these mice. In order to verify a clinical application the pharmacological ferroptosis inducer withaferin A (WFA)



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Conche C., Finkelmeier 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.*

Farin H. F., et al.:
Colorectal Cancer Organoid–Stroma Biobank Allows Subtype-Specific Assessment of Individualized Therapy Responses. ***Cancer Discov.*** *2023 Oct 5;13(10):2192-2211.*

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was used, which caused long-lasting T cell infiltration in hepatic tumors of wildtype mice. Experimental animals subjected to triple therapy of WFA, anti-PD-1 and anti-HMGB1 showed greatly prolonged survival rates, with 50 % over 200 days although treatment was only administered over 2 weeks. An even better result was achieved with the MDSC blocking agent SB225002 instead of anti-HMGB1, with 60 % of mice surviving for more than 300 days, at which time they were free of liver tumors [Fig. 2D]. To test whether this promising result could be applied to colorectal cancer, the murine organoids described above (APTK and APTAK with additional AKT mutation) were transplanted subcutaneously in wildtype mice and treated accordingly. However, in contrast to the HCC model, triple therapy could not reduce primary tumor growth [Fig. 2E]. Interestingly, also modified HCC cells didn`t respond to the triple therapy when injected subcutaneously, highlighting the importance of the local tumor microenvironment for efficient therapy response. In contrast, in a CRC liver metastasis the combination of WFA, SB225002 and anti-PD-1 significantly reduced the number of liver metastases [Fig. 2F]. Collectively, these results revealed the niche specific immune responses to ferroptosis, in which two immunosuppressive pathways were triggered, counteracting the induced CD8⁺ T cell activation. Therefore, blocking these suppressive pathways combined with ferroptosis induction may prove to be an effective treatment for liver tumors and metastasis.

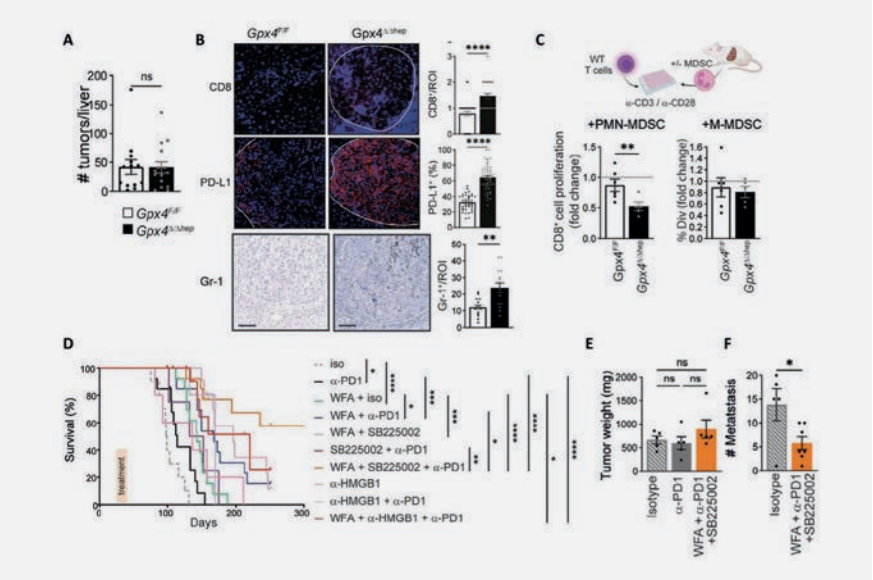

Figure 2: **Ferroptosis-induced immunomodulation.** (A) Number of tumors in *Gpx4*-deficient (*Gpx4*$^{\Delta/\Delta hep}$) and proficient (*Gpx4*$^{F/F}$) livers in a model of hepatocellular carcinoma (HCC). (B) Representative stainings and count of CD8 T cells, PD-L1 and Gr1 cells in liver tumors. (C) Suppressive effect of polymorphonuclear (PMN) and mononuclear myeloid-derived suppressor cells (M-MDSC) from HCC tumors on CD8 T cell proliferation. (D) Survival of wildtype mice after HCC induction. Treatment with isotype (iso), anti-PD-1, withaferin A (WFA), MDSC-blocker anti-HMGB1 or SB225002 or combinations thereof in the indicated time frame. (E) Tumor weight of s.c. transplanted APTK colorectal organoids. (F) Number of liver metastasis of intrasplenically injected APTK colorectal organoids. Figures adapted from Conche and Finkelmeier, et al., 2023.

Die Rolle der Tumormikroumgebung in der Hirnmetastasierung

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Microenvironmental regulation of brain metastasis

CNS immune landscape

Brain metastasis-associated inflammation

Metabolic checkpoints

Resistance mechanism

Brain metastasis remains an unmet clinical need in high demand for novel therapeutic options to overcome tissue-specific limitation of treatment success. Detailed knowledge on cellular and molecular drivers of disease progression and therapy response is required to provide scientific rationale for the development of innovative combination therapies. We therefore seek to gain insight into the complex interplay of cells of the tumor-associated stromal and immune cells and tumor cells at distinct stages of the metastatic cascade.

Adaptive resistance mechanism blunts long-term efficacy of immune-targeted therapies

The development of targeted- or immunotherapies has revolutionized intervention strategies for different primary cancers. However, response rates vary among distinct tumor types and individual patients. Moreover, metastases often show lower response rates compared to primary tumors. The microenvironment represents a critical factor that determines disease progression and the outcome of therapeutic intervention. Given the immune-privileged status of the central

Die Einführung von zielgerichteten- oder Immuntherapien in der Klinik hat große Fortschritte in den Behandlungsmöglichkeiten vieler Krebserkrankungen erzielt. Metastasen stellen jedoch weiterhin die Haupttodesursache bei Tumorpatienten dar, da die verfügbaren Behandlungsmöglichkeiten, insbesondere bei Hirnmetastasen, nur begrenzt wirksam sind. Bei der Entwicklung neuartiger Therapieansätze zur Bekämpfung von Hirnmetastasen ist es daher wichtig, gewebsspezifische Hürden, die zu Therapieresistenzen führen, zu verstehen und diese gezielt zu überwinden.

Das Forschungsziel unserer Nachwuchsgruppe besteht darin, die komplexen Interaktionen zwischen Tumorzellen unterschiedlicher Entitäten (Melanom, Bronchial- oder Mammakarzinom) und hirnresidenten- sowie rekrutierten Zelltypen während der Hirnmetastasierung zu entschlüsseln und Therapieansätze zu entwickeln. Ein besonderer Fokus liegt hierbei auf der Aufklärung von Resistenzmechanismen, die eine dauerhafte anti-tumor Immunantwort verhindern.

nervous system (CNS), brain metastases (BrM) represent a particularly challenging entity for successful immunotherapy. Even though BrM induce the recruitment of myeloid and lymphoid cells into the CNS, the environment poses an immune suppressive pressure to prevent tissue-damaging inflammation. We previously employed different strategies to target either tumor-promoting functions of tumor-associated myeloid cells or reactivate anti-cancer functions of tumor-infiltrating T cells. Our data revealed prominent anti-cancer effects in response to TAM-targeted therapies using the CSF1R inhibitor BLZ945. However, induction of compensatory CSF2-mediated macrophage activation that led to tissue damaging inflammation blunted longer-lasting anti-tumor efficacy. Likewise, we observed anti-tumor efficacy of radio-immunotherapy resulting in enhanced recruitment of T lymphocytes. However, anti-cancer T cell responses were suppressed by monocyte-derived macrophages that show upregulation of immune checkpoint molecules in response to radio-immunotherapy. Hence, immune-modulatory strategies that shift the immune suppressive milieu into an inflamed environment is expected to allow for more efficient and durable anti-cancer T cell responses and synergy with immune checkpoint blockade. We therefore seek to gain detailed insight into the complex interplay between innate and adaptive immunity in BrM to provide scientific rationale for the development of combination therapies that aim to block immune-suppression while promoting effective anti-tumor responses with minimal risk to induce adaptive resistance mechanism (Fig. 1).

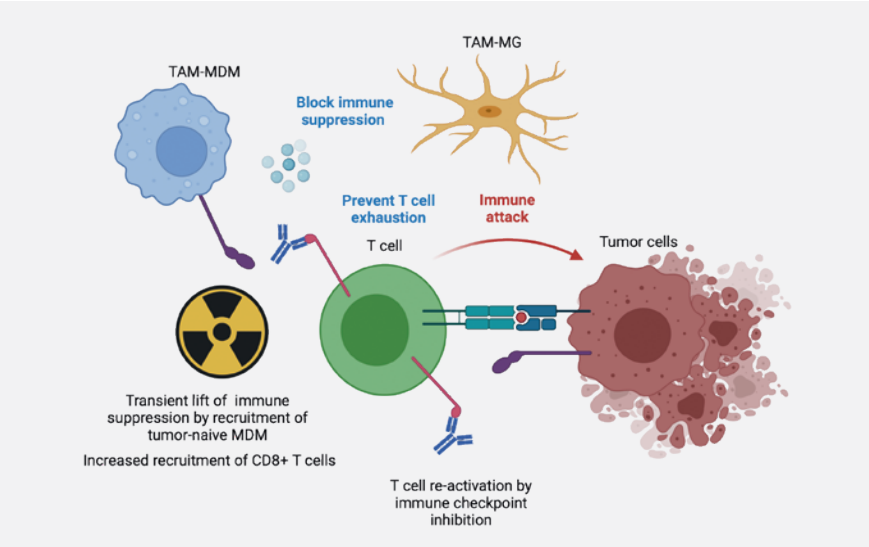
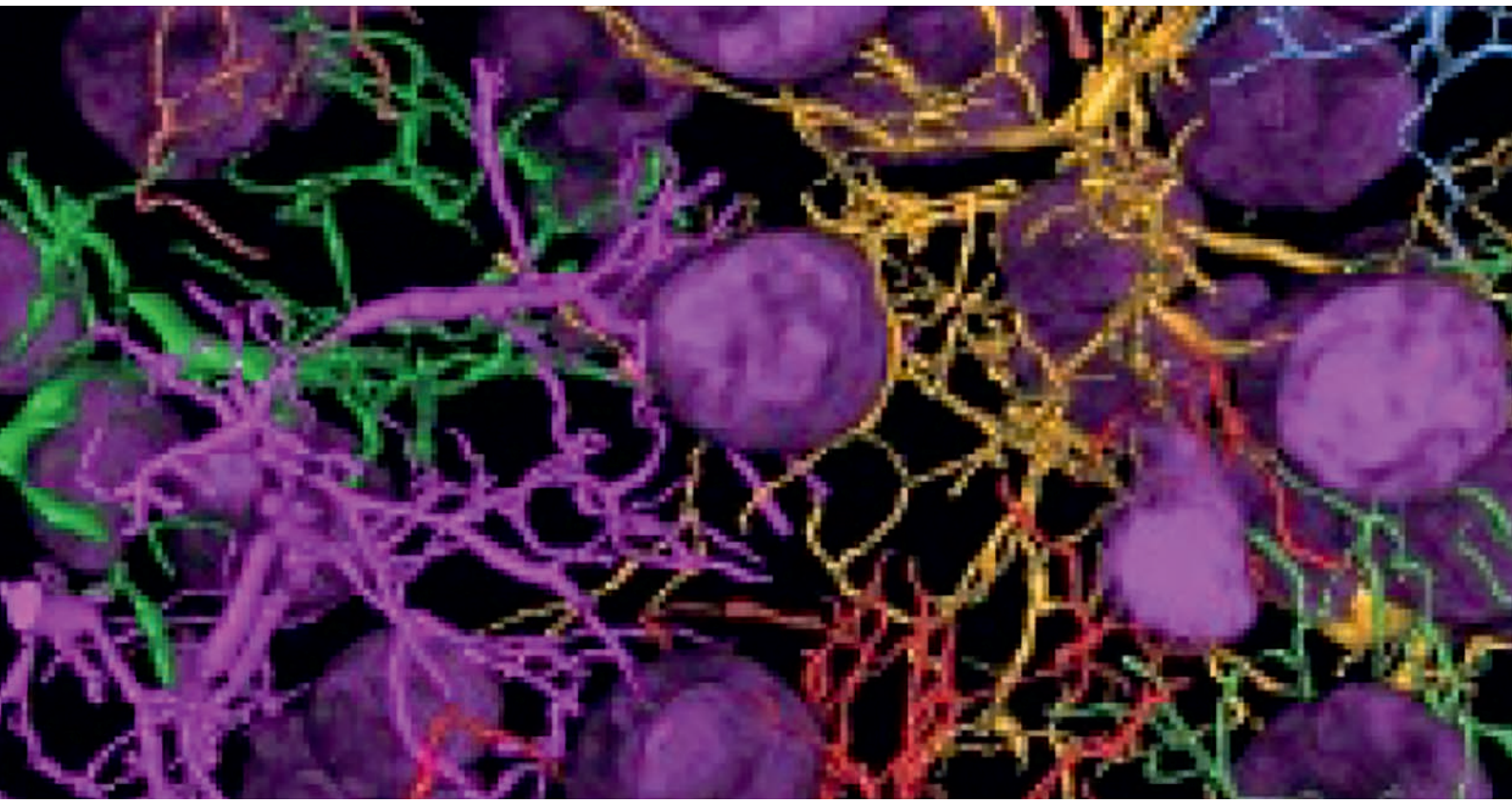


Figure 1.
Model figure summarizing the effects of immune targeted therapy in brain metastases. Lymphoid and myeloid-targeted therapies show limited efficacy in brain metastases due to tissue specific limitations to therapeutic efficacy. Combination therapies have to be developed to target tumor promoting functions of cancer-associated immune cells and to maintain or induce anti-cancer immune responses to achieve sustained tumor control. Fig. was created using BioRender.



Novel concepts for immune-targeted therapies

Major limitations of previously tested strategies stem from the rapid induction of acquired resistance mechanisms. We therefore seek to develop novel therapeutic avenues that allow for specific targeting of disease-associated phenotypes of tumor-infiltrating immune cells concomitant with a local relief of immune suppression for efficient T cell effector functions. Gene expression analysis revealed a critical role of metabolic checkpoints in modulating activation states and effector functions of tumor-associated myeloid and lymphoid cells. In particular the purine-adenosine axis acts as a switch between immune

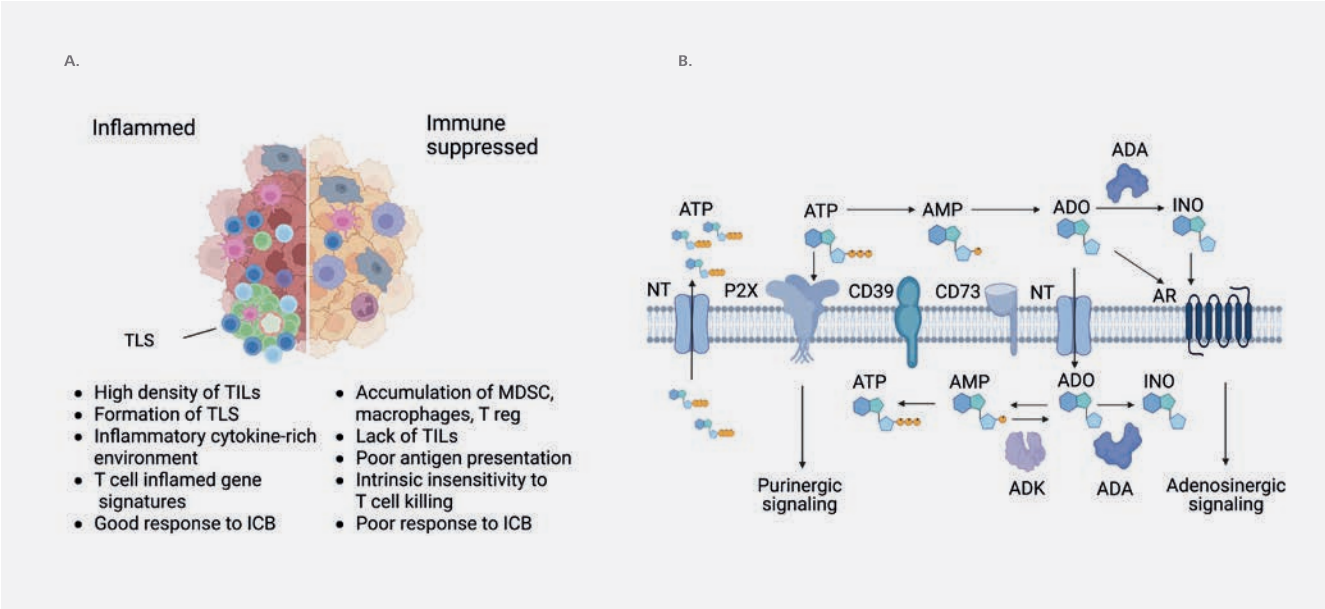
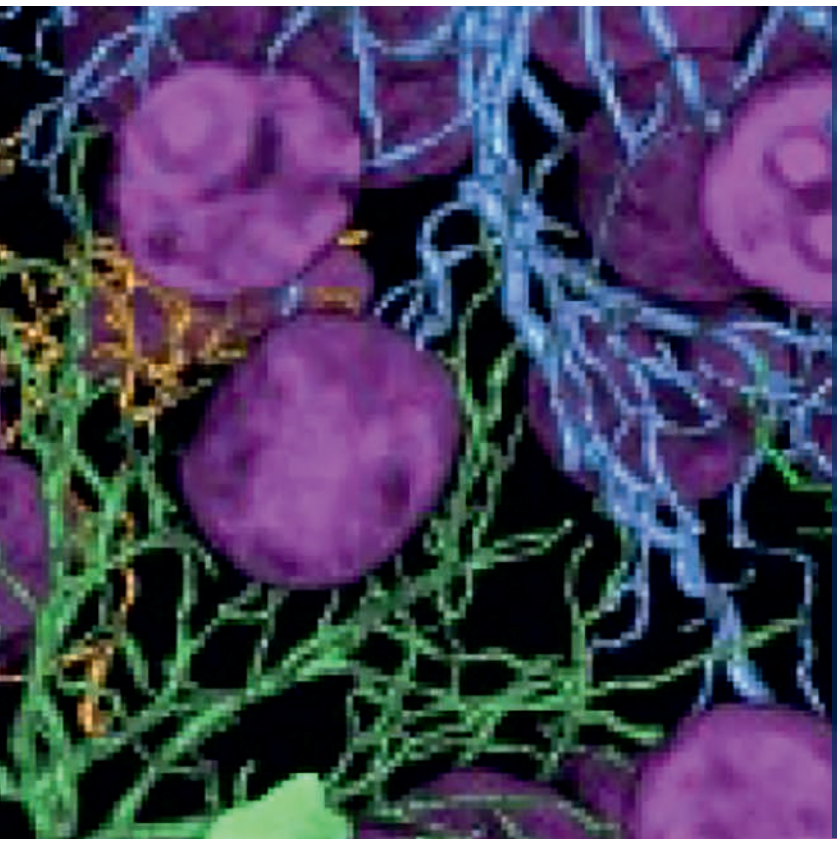


Figure 2.
(a) Tumors can be divided into immunologically hot (=inflamed) and cold (= immune suppressed) environments based different factors such as the ratio of effector cells to suppressive cells and as well as abundance of specific cytokines. (b) The purine-adenosine axis has been identified as an immune modulator in which purinergic signaling drives inflammation, whereas adenosinergic signaling is associated with immune suppression. Figure was created using BioRender.



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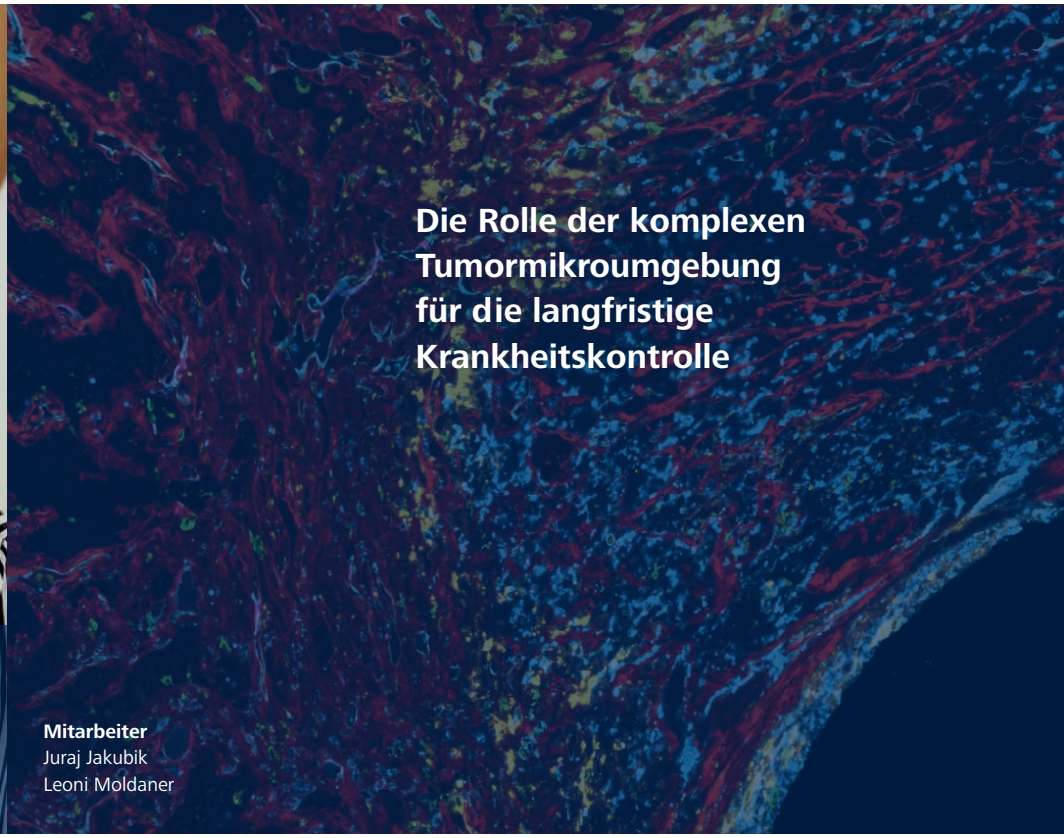
suppression and inflammation and expression of different components of the signaling pathway was found in several tumor-associated immune cell types. Genetic and pharmacological inhibition of adenosinergic signaling in combination with radiotherapy leads to significantly improved survival of brain metastasis bearing mice and results in reactivation of exhausted T cells and induction of anti-cancer immunity. Further immunophenotyping will shed light on immune-modulatory effects in different myeloid and lymphoid subpopulations and functionally link the observed phenotypes with cellular functions. In the future, we seek to expand our studies to additional metabolic checkpoints across different tumor entities that metastasize to the brain as well as other metastatic sites such as liver, bone and lung metastasis.

III

Experimentelle Therapie
Experimental Therapy



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

Cancer complexity impacts neoplastic growth and dissemination but it also impacts responses to therapeutics. Recent integration of tumor devices and high-dimensional computational data from mouse mammary carcinoma studies re-enforced the concept that cancer neighborhood (local tumor microenvironment, TME) can determine the efficacy of anti-cancer therapies. We hypothesize that achieving durable cancer control will require systematic treatment approaches to block resistance mechanisms that result from bidirectional interaction with the TME. Novel strategies will be needed to counter all of these mechanisms via administration (of series) of drug combinations while avoiding systemic toxicities that would reduce quality of life. In the promising era for combination anti-cancer therapeutics, tools to rapidly predict rational immune- and TME-modulating combination treatments on personalized basis are still critically missing.

Recently, we introduced a new analytical tool for this purpose that allows for effective, fast and harmless assessment of TME responses to multiple drugs or drug

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 Therapierfolg 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.

combinations. The system deploys a (i) miniaturized implantable microdevice for localized intratumoral drug delivery and (ii) multiplex immunostaining to measure 30+ proteins in single cells at each drug well. Targeted computational analyses of local drug-induced changes provide information about the composition, functional state and spatial cell organization of the tumor and associated TME rapidly bringing new insights into drug mechanisms of action. This integrative computational/technology tool was termed MIMA for Multiplex Implantable Microdevice Assay (Tatarova et al., *Nature Biotechnology*, 2022; Figure 1). We used MIMA in genetically engineered mouse models of breast cancer to evaluate effects of five FDA-approved targeted anticancer agents (olaparib, palbociclib, venetoclax, panobinostat, lenvatinib) and two chemotherapies (doxorubicin, paclitaxel) and predicted synergistic antitumor effects with anti-PD-1, anti-CD40, anti-CSF1R immunotherapies and vasculature modulating agents.

Among other mechanisms, we found that palbociclib (CDK4/6 inhibitor) induced enrichment of pro-tumorigenic macro-

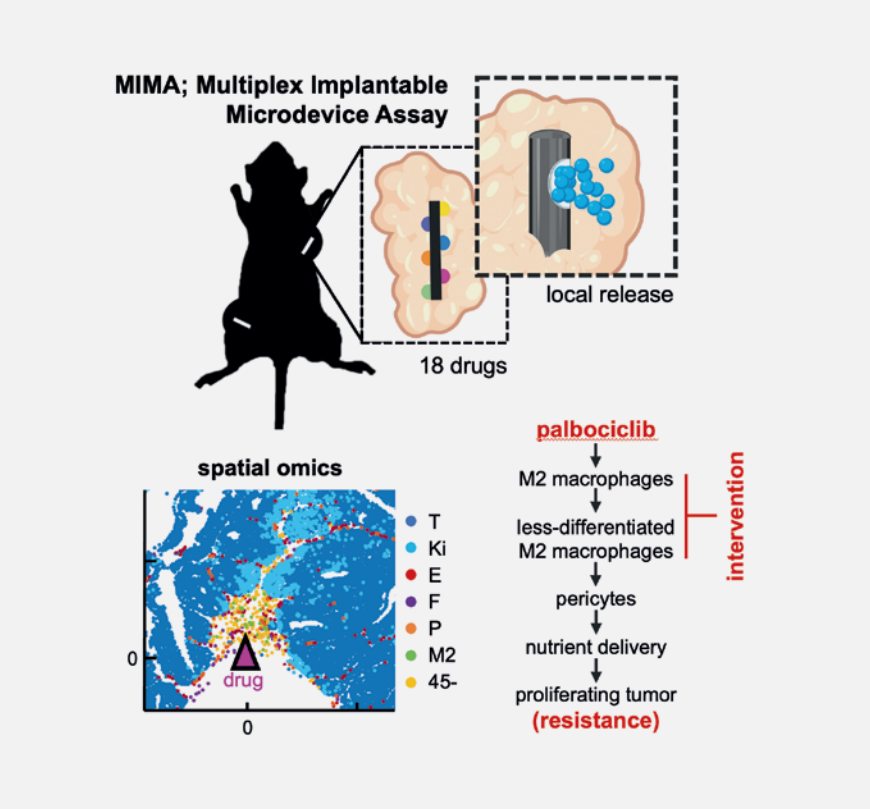
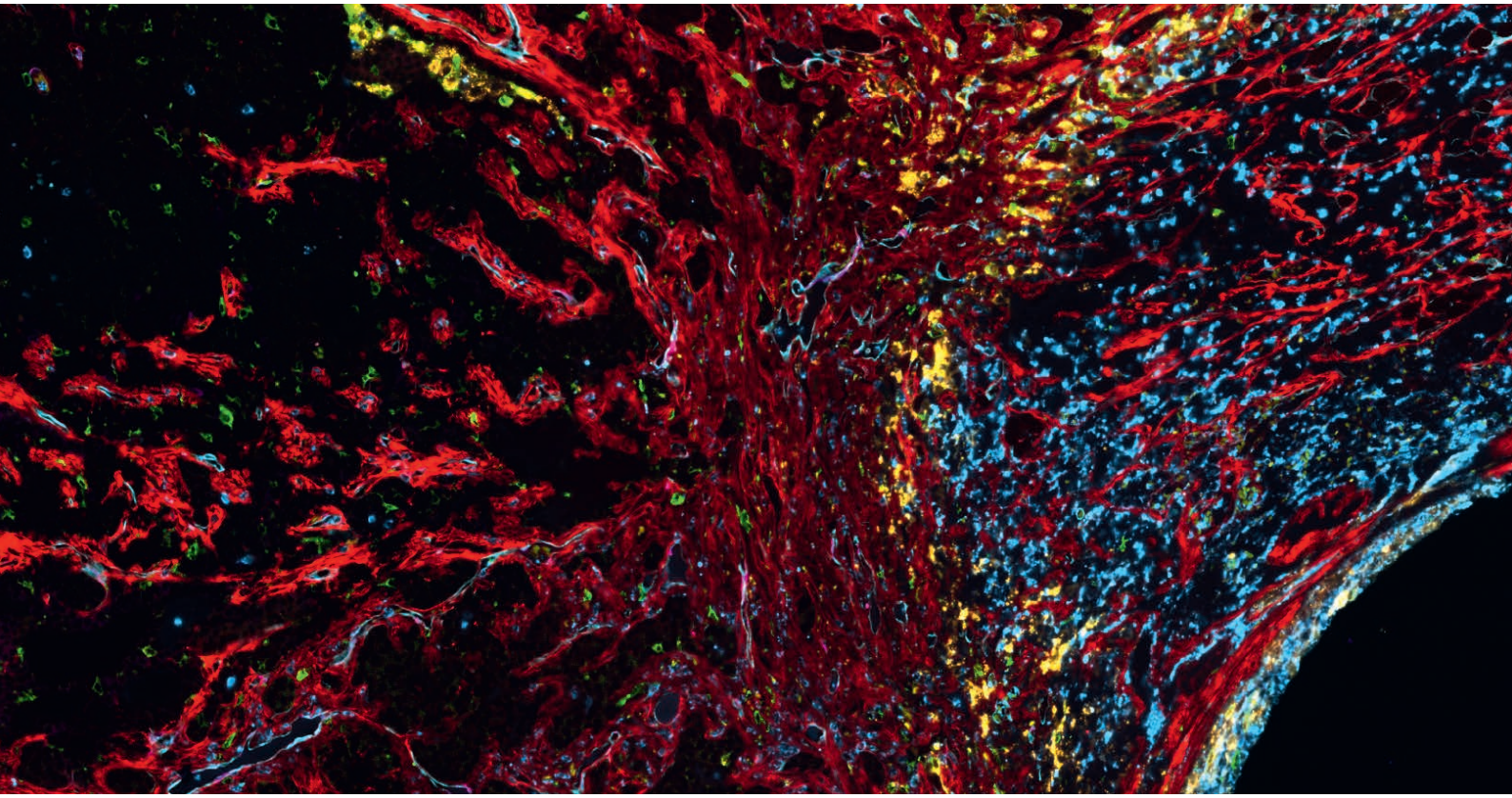


Figure 1.
Integrated Multiplex Implantable Microdevice Assay (MIMA).
An implantable microdevice administers multiple parallel agents into a single living tumor passively at nanodoses; and each condition is being assayed individually using spatial single cell omics to delineate critical cell dependencies translating into models of drug response. Within the models, we look for TME -based therapeutic vulnerability to prevent acquired resistance.



phages associated with endothelial/pericyte branching and increased proliferation of tumor cells in close proximity to the macrophage pericyte network (Figure 1). The results, overall, provided direct evidence how early induced changes in a complex TME can affect course of cellular events to dictate resistance and therapeutic outcome. Predicted triple combination of panobinostat (pan-HDAC inhibitor), venetoclax (BCL-2 inhibitor) and immunotherapy licensing myeloid cells, anti-CD40 agonist (αCD40), resulted in superior therapeutic control with no associated toxicities.
We hypothesize that spatial proximity of dendritic cells in the cancer stem cell (CSC) neighborhood during immunogenic cell death play a role in the long-term breast cancer control (Tatarova et al., *Nature Biotechnology*, 2022, Tatarova et al., *Cells*, 2023). Because our work to date suggests this triple therapy to induce CSC- specific anti-tumor immunity (Figure 2) and because it was effective in three different mouse models of breast cancer, we aim to delineate the efficacy of the compounds alone and in combination to ultimately bring new mechanistic insights which might benefit a large number of breast cancer patients.

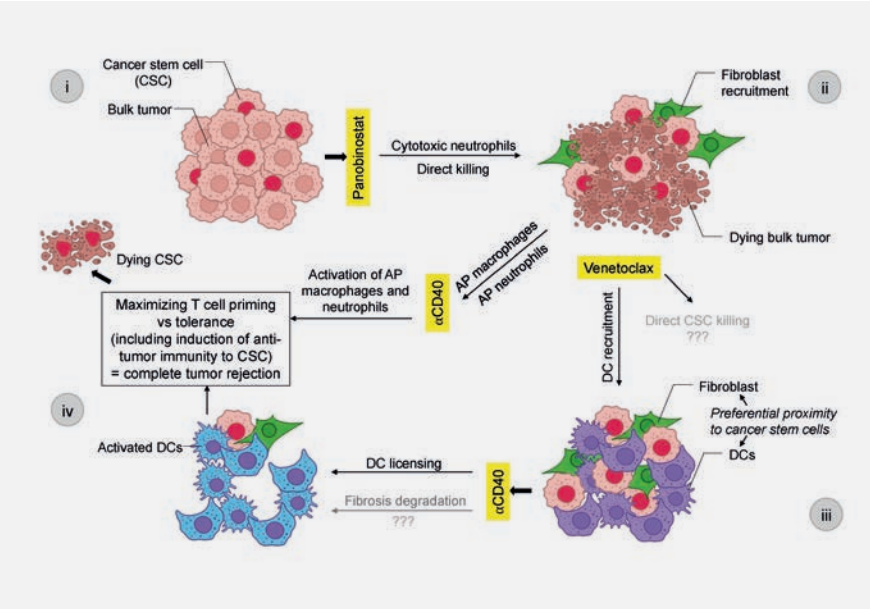
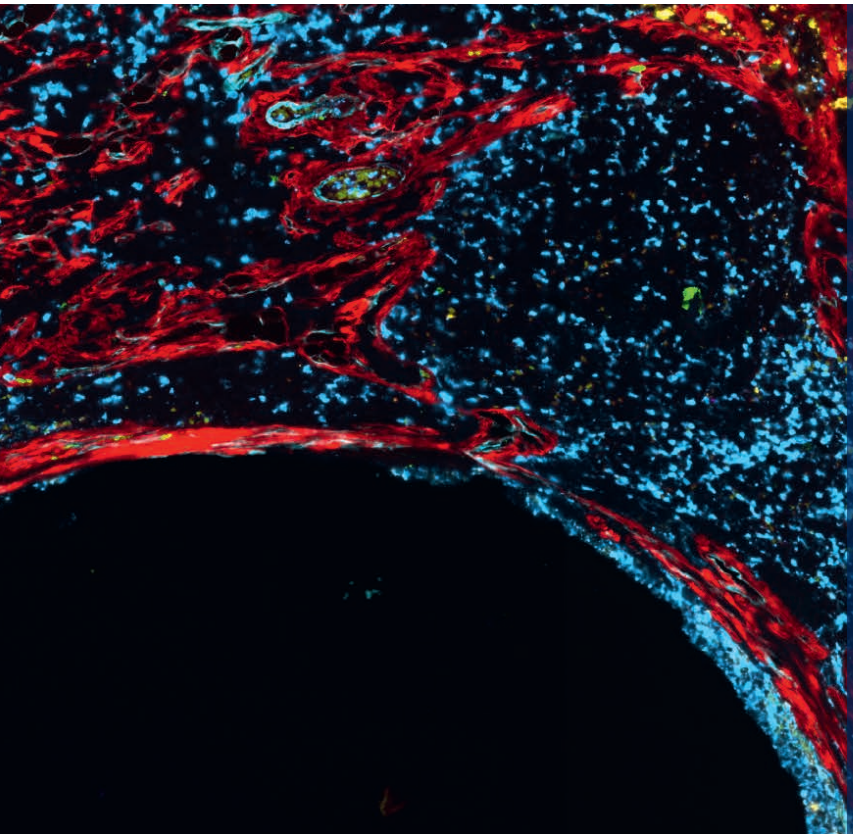


Figure 2.
Hypothetical model maximizing anti-tumor activity in BC through immune modulation.
Tumor is composed of bulk tumor and cancer stem cells (CSCs; i). Panobinostat induces immunogenic cell death of the bulk tumor while CSCs remain resistant (ii). Venetoclax induces recruitment of dendritic cells to tumors which we showed to localize to the CSC niche (iii). We hypothesize that if CD40 ligation induces licensing of DCs which captured and processed antigen from neighboring CSCs, the triple combination potentiates CSC-specific anti-tumor immunity leading to complete tumor rejection (iv). Our research will test this hypothesis.



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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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Research objective: In the first years of operation, our lab will focus on extending the utility of the MIMA system by integrating novel technological and computational strategies to systematically characterize the role of different tumor, immune and stroma cell subsets in panobinostat/venetoclax/αCD40 mechanism of action; with specific focus on luminal breast cancer.

We will perform longitudinal spatial systems analyses to delineate dynamic cell dependencies in immunogenic cell death which will help to understand how the functionally distinct cells developed the acquired state leading to response or resistance. Further, we plan to integrate the implantable microdevice with other single cell technologies including electron microscopy and single cell transcriptomics to link the identified spatial cell states with their molecular and architectural 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.

CAR-exprimierende Lymphozyten für die adoptive Krebs-Immuntherapie

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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 chain or 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 maintaining 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-

Ziel unserer Arbeiten ist die Erforschung und Entwicklung effektiver Immuntherapien zur Behandlung von Krebserkrankungen. Einen Schwerpunkt bilden dabei natürliche Killerzellen (NK-Zellen), die Teil des angeborenen Immunsystems sind und eine wichtige Rolle bei der Abwehr maligner Zellen spielen. 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 gerichtete zytotoxische Aktivität der Effektorzellen aus. Daneben modulieren CAR-NK-Zellen über die Ausschüttung von Zytokinen indirekt auch die endogene adaptive Anti-Tumor-Immunantwort. 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).

derived allogeneic NK cells are preferred 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 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

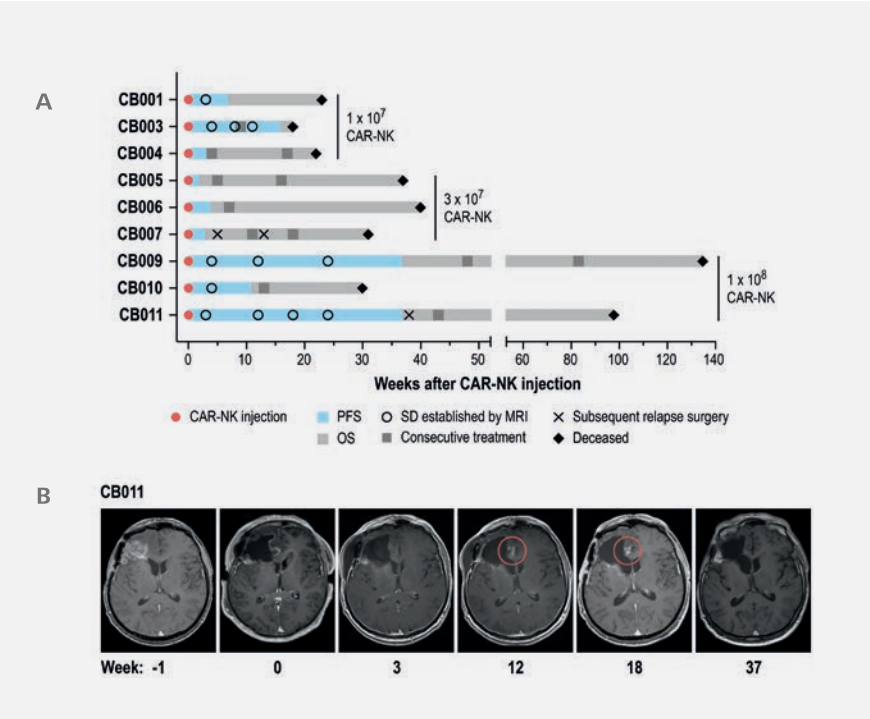
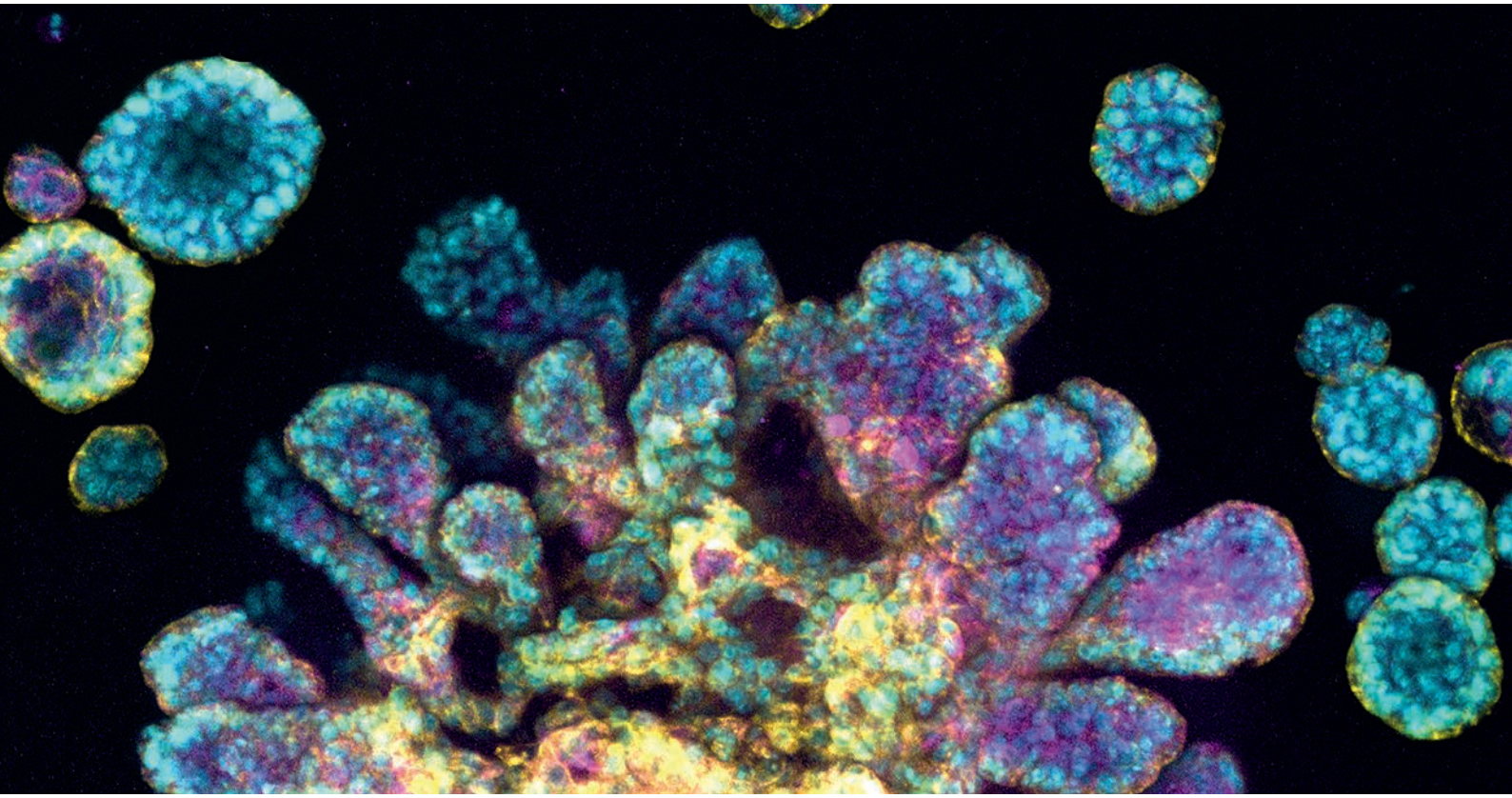


Figure 1.
Progression-free (PFS) and overall survival (OS) of glioblastoma patients of the dose-escalation cohort of the CAR2BRAIN phase I clinical trial. (A) Patients were treated with a single dose of NK-92/5.28.z cells injected into the resection margin during relapse surgery. Dose levels, time points of initiation of consecutive treatments, and subsequent additional relapse surgeries are indicated. Best response was stable disease (SD) for patients CB001, CB003, CB009, CB010, CB011, and progressive disease (PD) for patients CB004, CB005, CB006, CB007. (B) Magnetic resonance imaging (MRI) showing spot-like contrast enhancements in the resection margin in patient CB011 detected 12 and 18 weeks after local NK-92/5.28.z injection as a possible correlate of a treatment-induced immune activation.



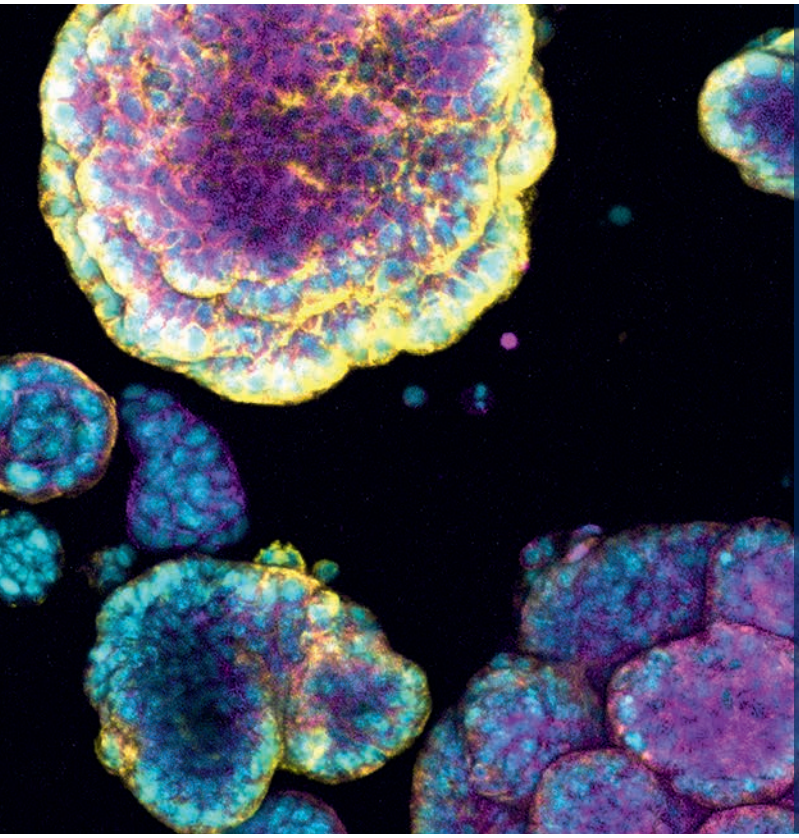
NKG2D-dependent immune surveillance. To enable tumor-specific targeting of NKG2D-expressing effector cells independent of membrane-anchored NKG2D ligands, we generated bispecific antibodies which can simultaneously bind to NKG2D and a tumor-associated surface antigen like ErbB2 (HER2), epidermal growth factor receptor (EGFR) or PD-L1. On their own, such NKAB molecules 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 enhance 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 (Fig. 1). Also, treatment and follow-up of patients of the expansion cohort has recently been concluded. These patients 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 endogenous antitumor immunity, an additional cohort of patients is currently treated with repeated local injections of NK-92/5.28.z cells in combination with a systemically applied immune checkpoint inhibitor. 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.

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,



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suggesting this strategy as a promising approach for further development of functionally enhanced cellular therapeutics.

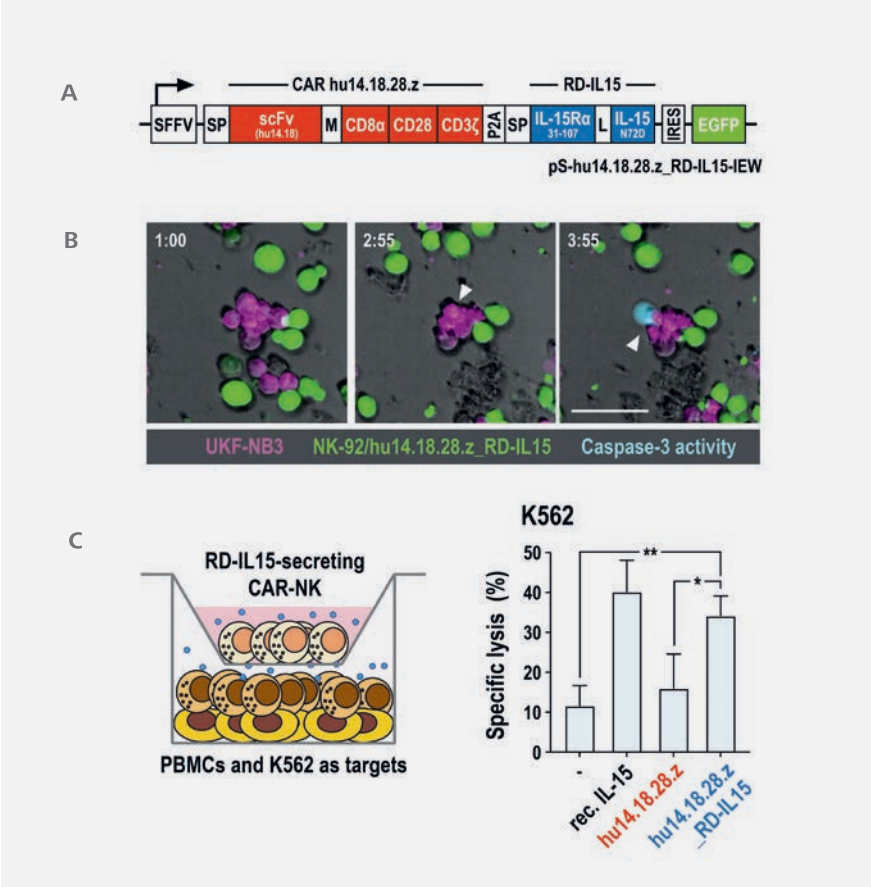
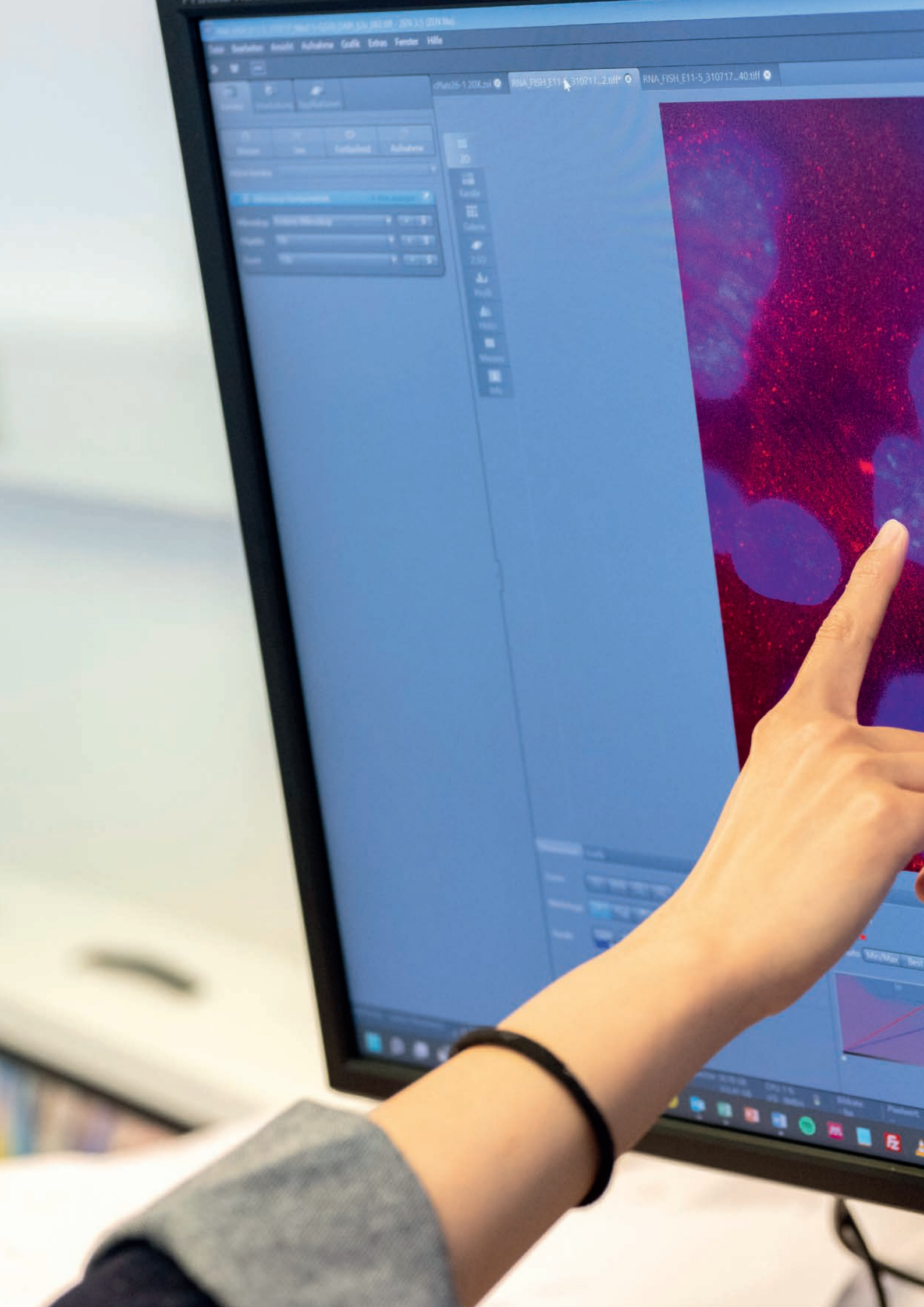


Figure 2.
Functional enhancement of CAR-NK cells by co-expression of an IL-15 superagonist. (A) Lentiviral vector encoding chimeric antigen receptor hu14.18.28.z under control of the Spleen Focus Forming Virus promoter (SFFV). The CAR includes a signal peptide (SP), a single chain fragment variable (scFv) antibody domain specific for the disialoganglioside GD_2, a Myc-tag (M), a CD8α hinge region (CD8α), transmembrane and intracellular domains of CD28, and the intracellular domain of CD3ζ. For co-expression of the IL-15 superagonist RD-IL15, a sequence encompassing a second SP, the IL-15Rα sushi domain (IL-15Rα$_{31-107}$), a peptide linker (L), and mutated IL-15 (IL-15$_{N72D}$) was fused to the CAR via a self-cleaving peptide (P2A). The transgenes are followed by an internal ribosome entry site (IRES) and enhanced green fluorescent protein (EGFP) cDNA. (B) Interaction of NK-92/hu14.18.28.z_RD-IL15 cells (green) expressing the GD_2-CAR and RD-IL15 with GD_2-positive UKF-NB3 neuroblastoma cells (magenta) was analyzed by time-lapse microscopy. Shown are images of a representative field taken at the indicated time points (hours:minutes). Membrane blebbing (white arrowheads) and caspase-3 activation (cyan) indicate target cell lysis. E/T ratio: 5:1; scale bar: 50 µm. (C) Peripheral blood mononuclear cells (PBMCs) from healthy donors were co-cultured in IL-2-free growth medium with NK-92/hu14.18.28.z_RD-IL15 cells placed in transwell inserts. Then, K562 cells were added to the pre-stimulated PBMCs at an E/T ratio of 20:1, and target cell killing was determined after 2 hours of co-incubation. For comparison, samples co-cultured with NK-92/hu14.18.28.z cells that lack RD-IL15 expression were included. Primary lymphocytes cultured without CAR-NK cells or stimulated with recombinant IL-15 served as controls. Mean values ± SD are shown; n=3 different donors.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Zentrale Einheit Transgenic Core / Genome Regulation

Transgenic Core Facility / Genome Regulation

Zentrale Einheit Transgenic Core und Genome Regulation

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Genetically engineered mouse models (GEMMs)

lncRNAs

genome editing

biomedical mouse models

Recent advances in genome-editing, in particular the CRISPR/Cas9 technology, have revolutionized the generation of mouse models and Knock-out (KO) mouse models in particular. Combination of CRISPR with homology-directed targeting for insertion of short sequences directly into the genome (Knock-in, KI) opens novel 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. The 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. A complex integration of gene editing techniques is the important next step

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 aktuellster 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 2023 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. Da die Genklasse der lncRNAs noch relativ 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.

in the GEMM generation process. The constant development of novel applications for the CRISPR system expands the toolbox for gene editing rapidly and any relevant new tool is imported to the 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 are usually quite fast to 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 to establish targeted degradation approaches for any protein of interest. In these systems

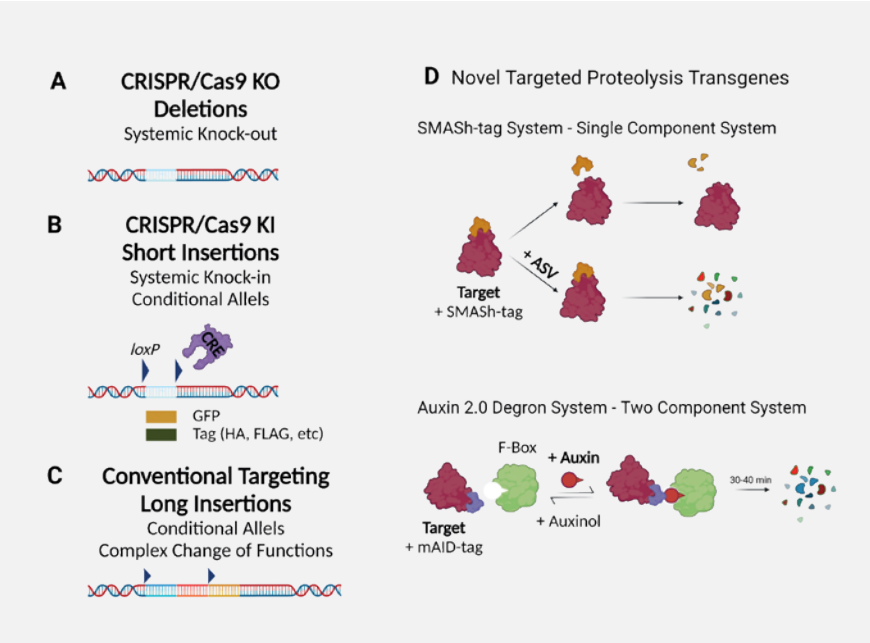

Figure 1.
(A) CAS9 directed gene deletion from several basepairs up to the megabase range that is usable for all techniques shown in Fig. 2. (B) CAS9 assisted integration of short genetic elements specific at any site of the genome. This approach is also available for all techniques shown in Fig. 2. (C) Complex transgenes require the modification of embryonic stem cells prior to mouse generation (Fig. 2 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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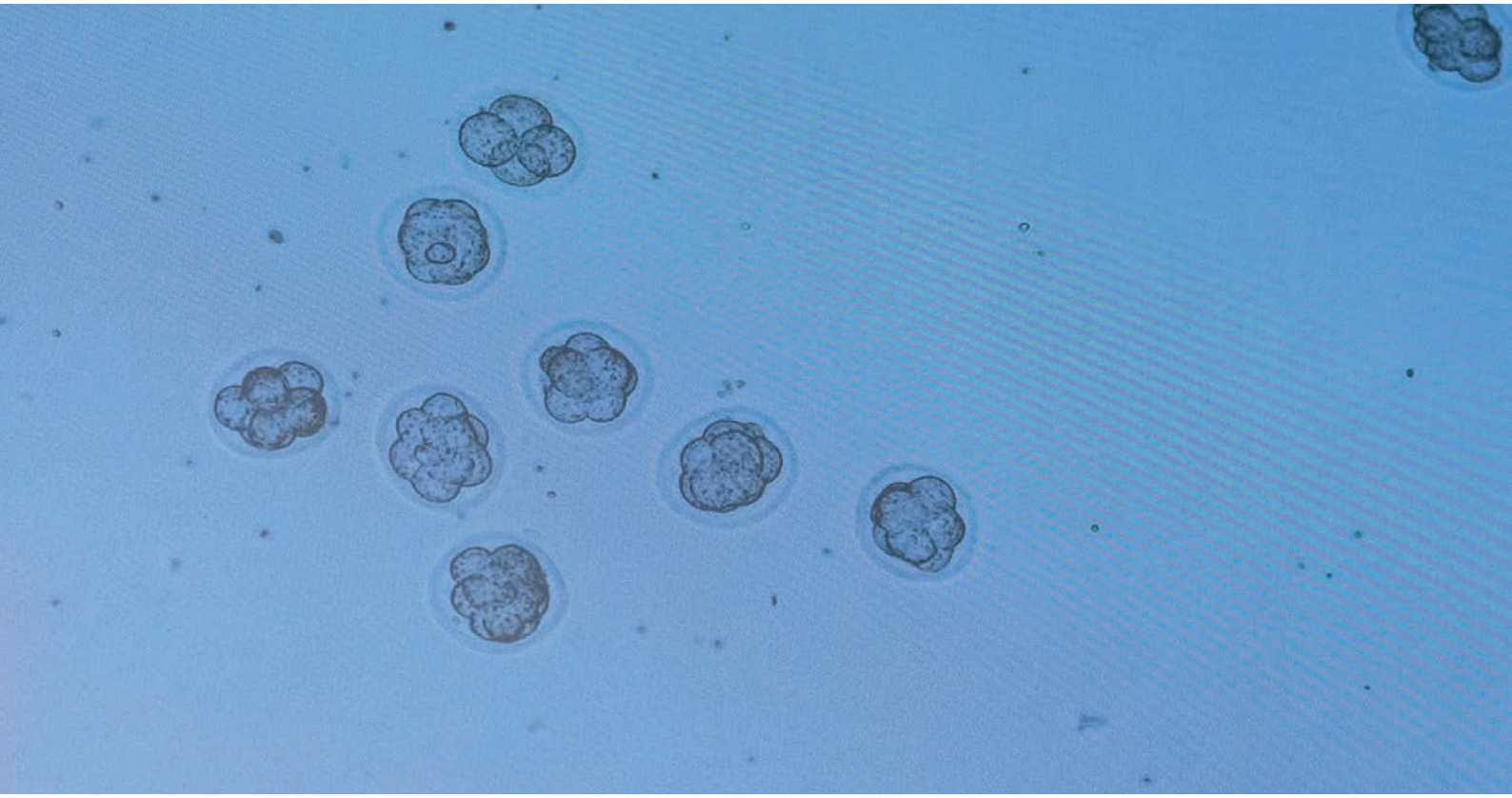


a protein of interest is tagged (Fig. 1B) with short peptide that can bind a small molecule drug. The binding of this drug can induce protein degradation and removal of the drug from the mouse does allow the reappearance of the protein (Fig. 1D). These novel approaches do open up new possibilities for biomedical research.

The further development of the CRISPR toolbox also allows to setup novel 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 novel technique will reduce the number of required animals for generating mouse models drastically and thereby strictly follows the international guidelines for animals experiments to reduce animal numbers when possible. In addition, the process of generating novel mouse lines is faster for simple CRISPR/Cas9 KO or KI (Fig. 1A, B) and only takes 2-3 month.

The genome regulation group analyses the *in vivo* function of the novel gen 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 and outcome. We could show previously that the activity of the lncRNA

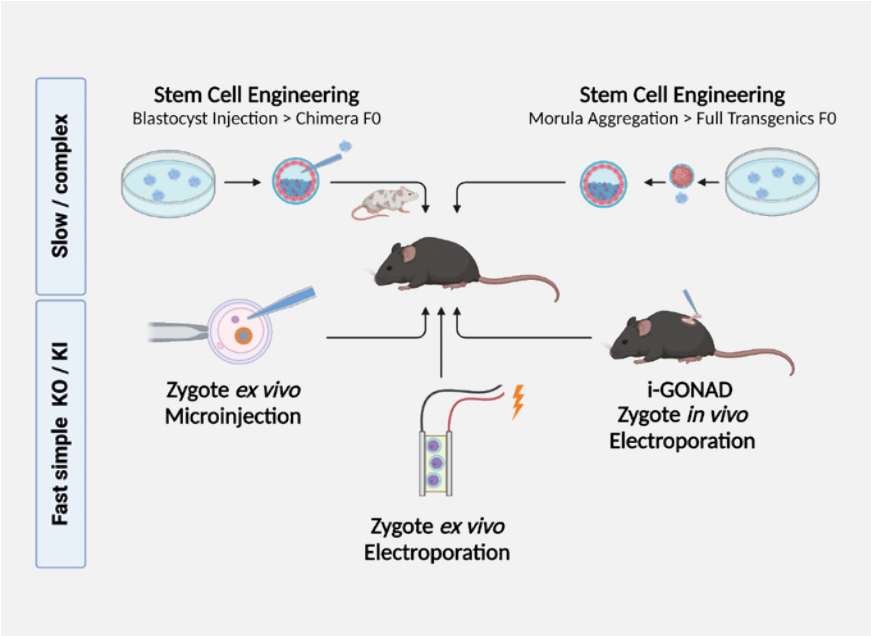
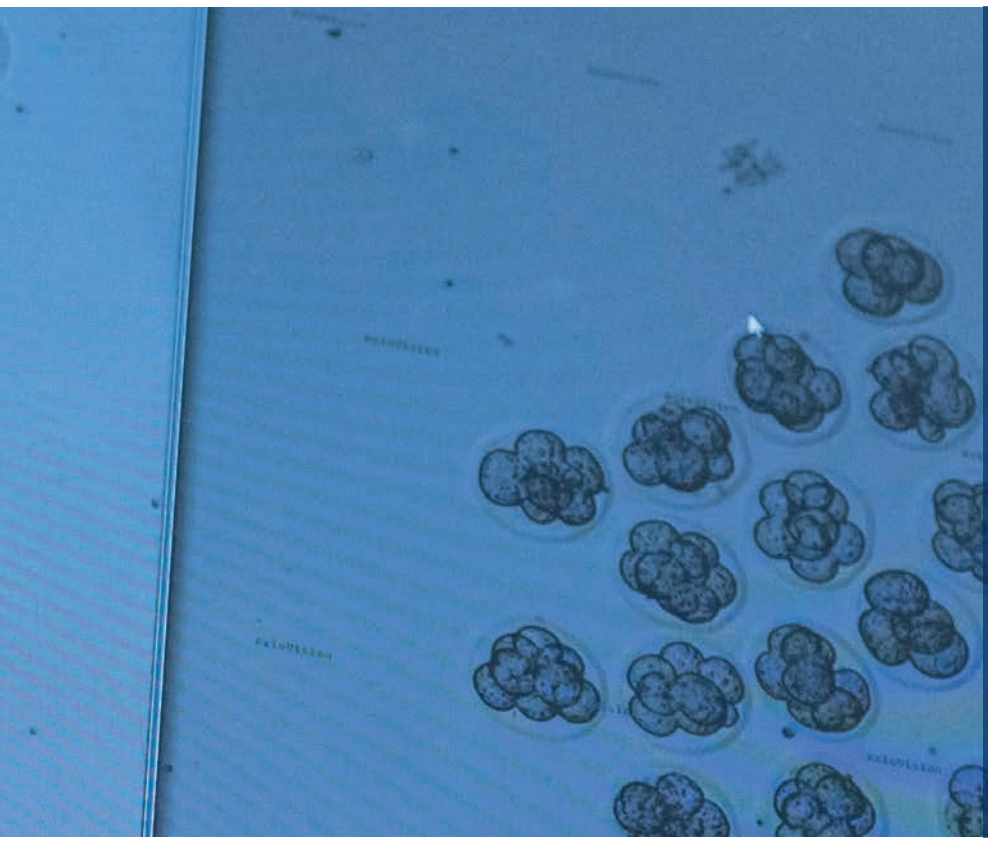


Figure 2.
Techniques for the generation of transgenic mice available at the TCF. The novel approach i-GONAD is now available as a service from the TCF. Created with BioRender.com



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Handsdown is essential for embryo development by adjusting the expression levels of its nearby protein coding gene. Recently, we got a manuscript accepted that describes the role of the lncRNA *Sweetheart* in the response to acute myocardial infarction. Another lncRNA that is currently under investigation is the lncRNA *cPlatr26*, which we can show that it regulates the alternative splicing of its neighboring protein coding gene *Itga6* (Fig. 3), which is not only important in heart development but also an important marker for tumor metastasis.

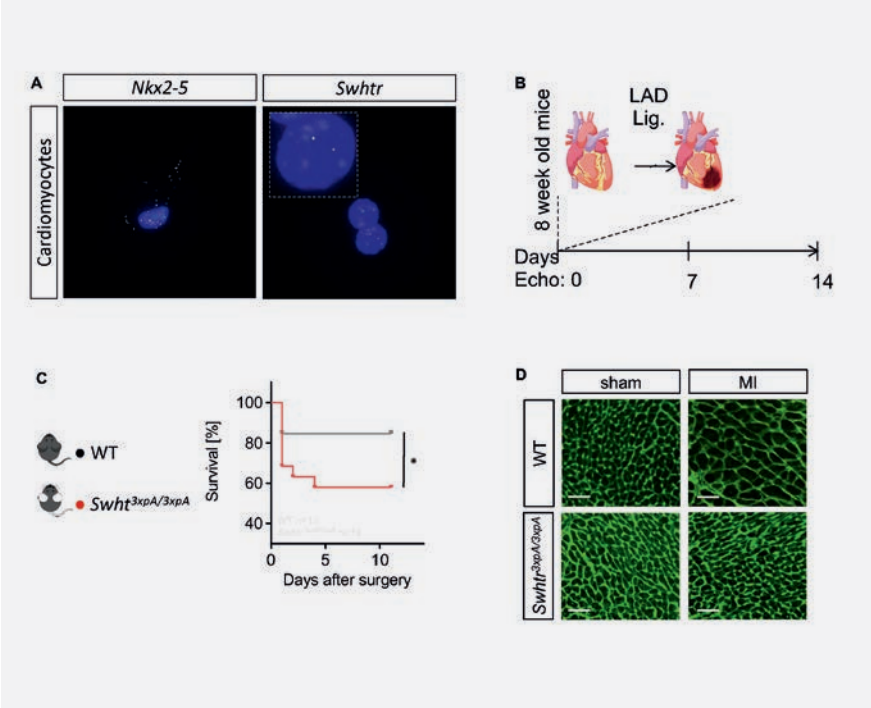

Figure 3.
The lncRNA *Sweetheart* is required for survival and hypertrophy of mice and cardiac tissue after myocardial injury. (A) The *Sweetheart* RNA localizes in the nucleus of cardiomyocytes. (B) Mouse model for severe heart attack (C) Reduced survival of *Sweetheart* mutant adult mice after heart infarct (D) Lack of hypertrophy in *Sweetheart* mutant cardiac tissue after myocardial infarction.

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Akademische Ausbildung
Bachelor- und Masterarbeiten
2023-2023 Helene Markmann
2023-2023 Laura Deuster
2022-2023 Theresa Krack
2022-2022 Lara Paulini
2021-2022 Wahyu Minka
2021-2021 Celina Reiter
2020-2021 Bianca Gregorz
2020-2021 Alessia Cais

Doktorarbeiten
2022 Costanza Zanetti
2022 Raquel S. Pereira
2021 Christina Karantanou

AG Medyouf

Kubasch AS, Peterlin P, Cluzeau T, Götze KS, Sockel K, Teipel R, Jentzsch M, Attalah H, Sebert M, Chermat F, Gloaguen S, Puttrich, M, Cross M, Schneider M, Kayser S, Schipp D, Giagounidis A, Tirado-Gonzalez I, Descot A, Van de Loosdrecht A, Weigert A, Metzeler K, Fenaux P, **Medyouf H***, Platzbecker U*, Ades L*.
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*Co-senior authors

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*equal contribution

Akademische Ausbildung
Doktorarbeiten
Ewelina Czlonka (Ph.D.)
07/2021
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Masterarbeiten
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Internship
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AG Arkan

Schmitt M, Ceteci F, Gupta J, Pesic M, Böttger TW, Nicolas AM, Kennel KB, Engel E, Schewe M, Callak Kirisözü A, Petrocelli V, Dabiri Y, Varga J, Ramakrishnan M, Karimova M, Ablasser A, Sato T, **Arkan MC**, de Sauvage FJ, Greten FR.
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Akademische Ausbildung
Nergiz Karagöz
Summer Internship
1.7. – 1.9.2023

Deniz Sagir
M.Sc. Thesis Study
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AG Farin

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*.
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Chantal Harth:
„Patient derived colorectal cancer organoids for personalized T cell therapies" Masterarbeit im Studiengang "Molecular Medicine" Goethe University Frankfurt am Main.

Mara Romero Richter:
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Constantin Menche:
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Kennel KB, **Greten FR**
Immune cell – produced ROS and their impact on tumor growth and metastasis. ***Redox Biol,*** *2021 Feb 5;101891.*

Akademische Ausbildung
Sophie Heinzen / MD:
„Evaluating Immune Checkpoint Inhibition in Colorectal Cancer"
Promotion im Fachbereich 16 Medizinische Fakultät, Goethe Universität Frankfurt

AG Sevenich

Möckl A and **Sevenich L**
Take my breath away – TAMing anti-cancer immunity in hypoxic niches (2023) ***Immunity*** *Aug8; 56(8): 1704-1706 doi 10.1016/j.immuni.2023.07.010*

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Bemmerlein L, Deniz IA, Karbanova J, Berg-Jacobi A, Drukewitz S, Link T, Goebel A, **Sevenich L**, Taubenberger A, Wimberger P, Corbeil D and Kulmann JD
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Akademische Ausbildung
Vanessa Arnold:
„Closing the gap: establishment of brain metastasis assembloids to mimic the establishment of brain metastases in vitro" Masterarbeit im Studiengang Molekulare Medizin, Goethe Universität Frankfurt

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AG Wels

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Akademische Ausbildung
Malena Bodden: *„GD2-spezifische CAR-NK-Zellen für die adoptive Krebsimmuntherapie"*, Doktorarbeit im Fachbereich Biologie der Technischen Universität Darmstadt, 2023.

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Finanzen und Wissenschaftlicher Service

Financial Affairs and Scientific Services

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Die Abteilung Finanzen/Administration setzt jährlich ein Finanzvolumen von etwa 12 Millionen Euro um und betreut dabei rund 100 Mitarbeitende. Sie wird seit September 2019 von Franziska Hasslinger-Pajtler geleitet, die dabei von Robert Dornberger unterstützt wird. Besonderer Fokus der Administration liegt neben den klassischen Kernaufgaben einer jeden Verwaltung aktuell auf den Themen Compliance, Datenschutz, Digitalisierung & Forschungsdatenmanagement, Diversity, Nachhaltigkeit, Personalbindung und -entwicklung sowie der Vereinbarkeit von Beruf und Familie.
Giuseppina Virgillito im Personalbüro bearbeitet alle Themen der Personalsachbearbeitung. Ilka Graus Fokus in der Finanzbuchhaltung/Drittmittelverwaltung liegt auf der Betreuung der Projektfördermittel des Bundes, der DFG und des Landes Hessen. Luca Fabisch ist verantwortlich für die Kreditoren und Lars Fischer unterstützt beide bei sämtlichen Aufgaben in der Finanzbuchhaltung. Brigitte Huth bearbeitet die Reisekostenabrechnungen des Hauses. Sabine Finger erstellt die Bilanz. Frau Dr. Alina Jurcoane ist die Ansprechpartnerin für alle Belange, welche die Drittmittel der Europäischen Union betreffen. Belinda Gehrmann arbeitet im Team rund um die Kaufmännische Leitung und unterstützt außerdem das Personalbüro. Für das Museum im Georg-Speyer-Haus und historische Fragestellung fungiert Dr. Klaus Cußler als Ansprechpartner.
Adrian Gresik ist verantwortlich für die vielfältigen Aufgaben des Innendienstes und koordiniert gemeinsam mit Hana Kunkel die anspruchsvollen Umbau- und Sanierungsvorhaben des Instituts. Das Team des Innendienstes mit Krzysztof Data, Heinrich Krompiec und 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 Bernd Würdemann.
Yasemin Piskin, Lacramioara Pulpan, Merve Cetin und Neriman Sarac sind für die Laborreinigung, die ordnungsgemäße Abfallentsorgung und Recycling sowie die Laborbedarfsversorgung verantwortlich.

The Finance/Administration department with its yearly budget of approximately 12 million Euros manages around 100 staff members. Since September 2019 it has been headed by Franziska Hasslinger-Pajtler, who is supported by Robert Dornberger. In addition to the classic core tasks of any administration, the Administration Department is currently focusing in particular on the topics of compliance, data protection, digitization & research data management, diversity, sustainability, staff retention & development and work-life balance. Giuseppina Virgillito in the HR office handles all HR-related issues. Ilka Grau's focus in financial accounting is on the management of project funding from the federal government, the DFG and the state of Hesse. Luca Fabisch is in charge of accounts payable and Lars Fischer supports both with various tasks in financial accounting. Brigitte Huth processes the travel expense reports of the house. Sabine Finger prepares the balance sheet. Dr. Alina Jurcoane is the contact person for all matters concerning third-party funds from the European Union. Belinda Gehrmann assists in the team around the commercial management and also supports the personnel office. Dr. Klaus Cußler is the contact person for the museum in the Georg-Speyer-Haus and historical issues. Adrian Gresik is responsible for the diverse tasks of the Building Services department and coordinates the demanding reconstruction and renovation projects in cooperation with Hana Kunkel. The Building Services department team with Krzysztof Data, Heinrich Krompiec and Michael Paul primarily takes care of the building services, various constructions and installations, and also supports the organization of scientific conferences and events. The contact person in the switchboard and at the reception is Bernd Würdemann. Yasemin Piskin, Pulpan Lacramioara, Merve Cetin and Neriman Sarac are responsible for laboratory cleaning, proper waste disposal and recycling, and laboratory supplies.

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).

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Zentrale Einheit Histologie

Zur Anfertigung von histologischen Präparaten betreibt das Georg-Speyer-Haus eine Histologie-Serviceeinheit unter der Leitung von Dr. Birgit Ritter. Hier werden von Frau Petra Dinse, meist automatisiert, die Gewebeaufarbeitung sowie immunohistochemische Färbungen und Standardfärbungen durchgeführt. Weiterhin verfügt das Labor über ein automatisiertes Präparate-Scanner- und Bildanalysesystem, Aperio ScanScope CS2, einen Färbeautomat Leica Autostainer XL 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 Geräte zur Zellanalyse (BD LSRFortessa, BD FACSCantoII, Cytek Aurora) und zwei Zellsorter (BD FACSAriaI, BD FACSAria Fusion). Zusätzlich werden in der Einrichtung ein Bioplex200 zur Multiplex-Analyse und ein ABC Blood Counter zur Blutzellanalyse 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 hierbei durch Frau Annette Trzmiel, die die anfallenden Hochgeschwindigkeits-Zellsortierungen durchführt und für den einwandfreien Zustand aller Durchflusszytometrie-Geräte am Institut verantwortlich ist. In einigen Fällen fungiert Herr Thorsten Geyer als zusätzlicher Operator an den Zellsortern.

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 and an ABC Blood Counter for blood cell analysis. Dr. Stefan Stein oversees the performance of the core facility and is available for scientific questions regarding flow cytometry in general and the establishment of new flow based assays. He is supported by Annette Trzmiel who is responsible for high-speed cell sorting as operator for all research groups. Annette also takes care of the maintenance and functionality of the flow cytometers in the institute. Occasionally, Thorsten Geyer serves as an additional sorting operator.

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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 Dr. Tijna Alekseeva. Sie 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 Dr. Alekseeva 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 Dr. Tijna Alekseeva. She 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, Dr. Alekseeva 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.

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IT
Steffen Luft leitet als Chief Information Officer (CIO) die IT. Er nimmt die zentralen Tätigkeiten der Unterstützung der Mitarbeitenden des Hauses in allen Fragen der IT, der Serverbetreuung, des IT-Projekt Managements, der Netzwerkadministration und des Einkaufs wahr.

IT
Steffen Luft is Chief Information Officer (CIO) of the Institute. 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 Beschaffung 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 equipment and devices. As biosafety officer, he is responsible for biological safety at the institute and for communication with respective authorities.

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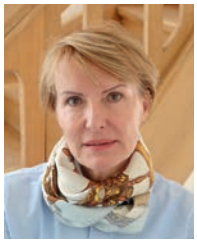
Arbeitssicherheit und Strahlenschutz
Thorsten Geyer ist am Institut die Fachkraft für Arbeitssicherheit und berät die Mitarbeitenden und verantwortlichen Gruppenleitungen in allen Belangen des betrieblichen Arbeitsschutzes. Als Strahlenschutzbeauftragter ist er für die Organisation der entsprechenden 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 radiation 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.

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.

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Jährliche Mitgliedsbeiträge
Annual membership fees

Forschermitglied
Scientist
100,– €

Studenten
Students
12,– €

Freund
Friend
150,– €

Förderer
Sponsor
1000,– €

Firmenmitgliedschaft
Company membership
5000,– €

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GEORG SPEYER HAUSES E.V.

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„Man muss ihn lieben wie ein Kind, er ist am Forschen interessiert wie ein Kind an seinem Spielzeug.“

Robert Koch über Paul Ehrlich