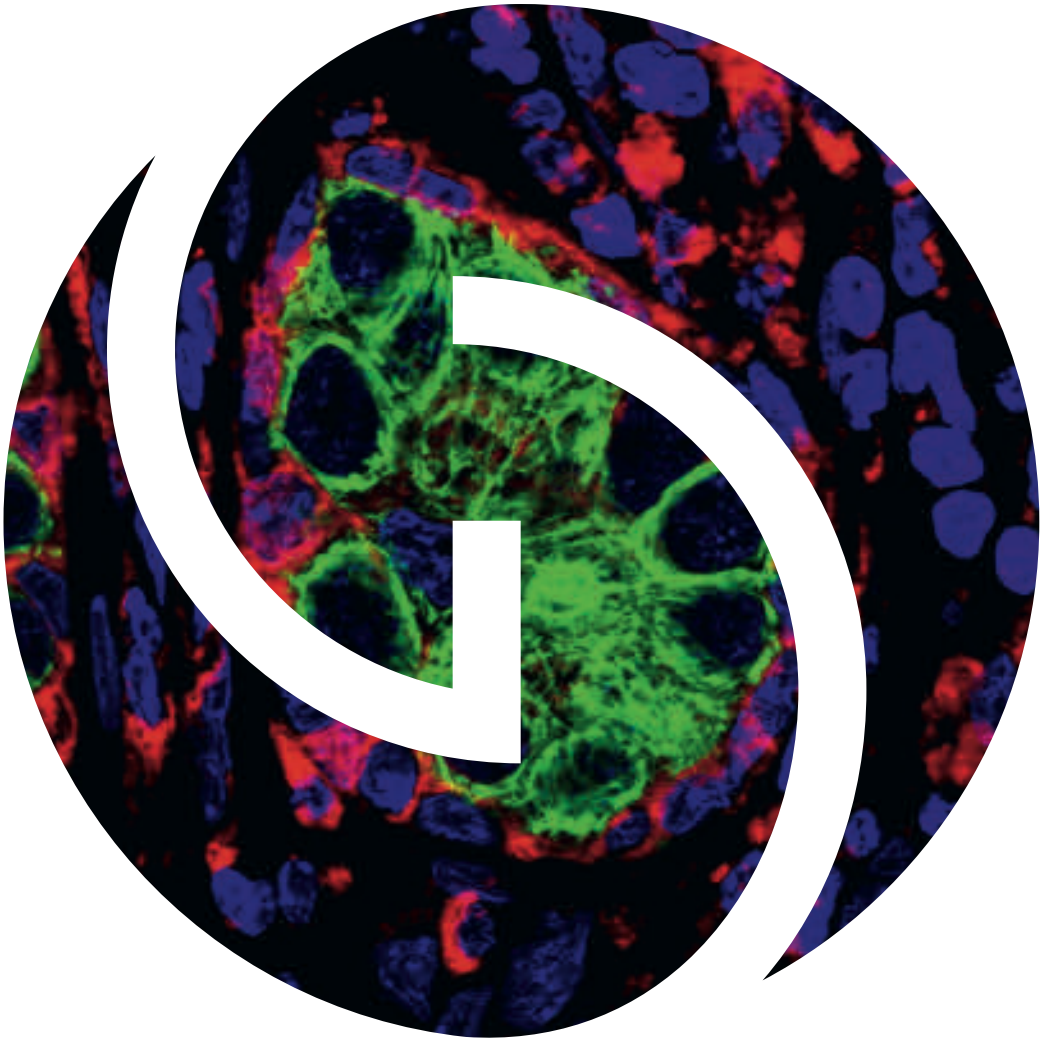
GEORG SPEYER HAUS
INSTITUT FÜR TUMORBIOLOGIE
UND EXPERIMENTELLE THERAPIE



Zellautonome Mechanismen der Karzinogenese
Tumor-Stroma Interaktionen und Tumorimmunologie
Experimentelle Therapie

Annual Report
Georg-Speyer-Haus

2015

Gefördert durch:

aufgrund eines Beschlusses
des Deutschen Bundestages

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

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

Forschen für das Leben
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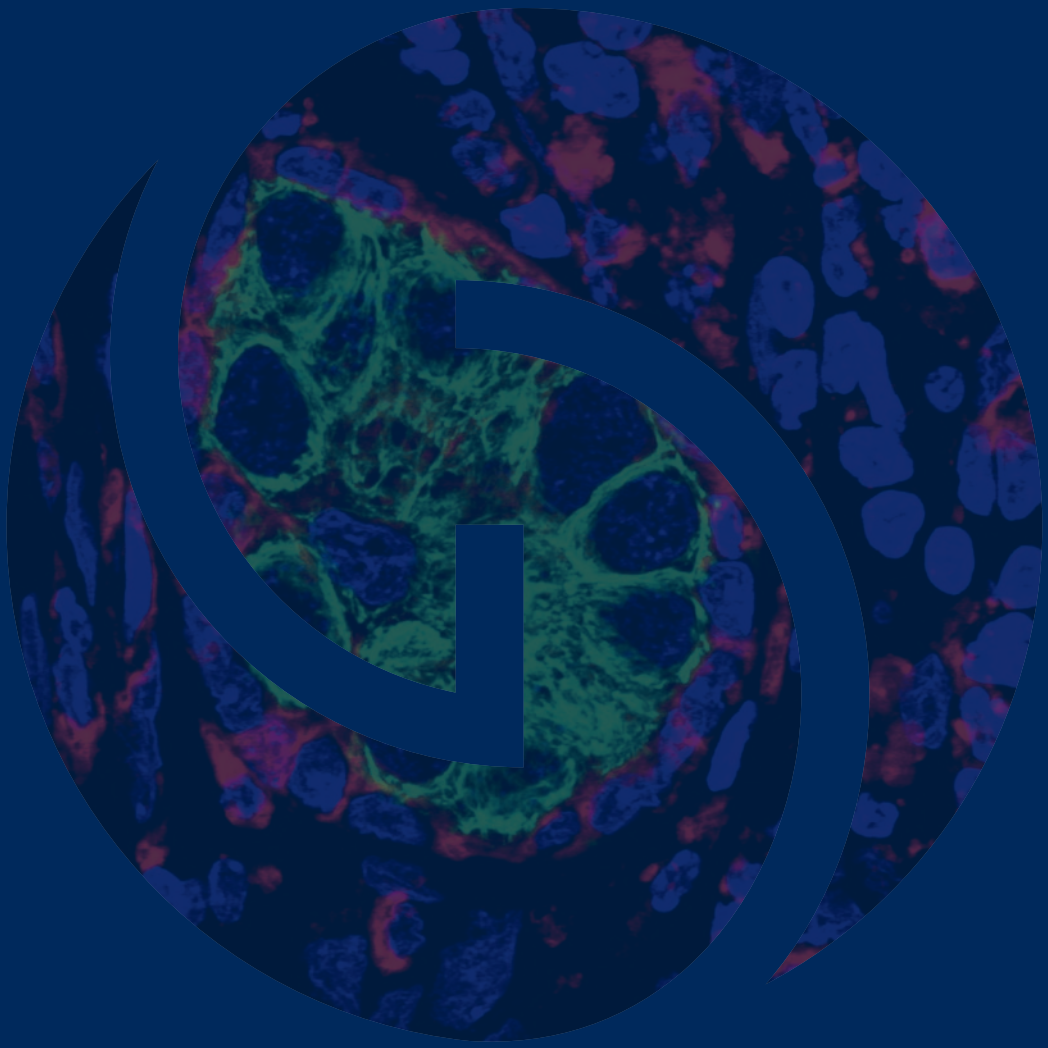

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Liebe Leserinnen und Leser,
liebe Freunde des
Georg-Speyer-Hauses,

Das Jahr 2015 war ein besonderes Jahr für das Georg-Speyer-Haus: vor 100 Jahren, am 20. August 1915, verstarb unser Gründungsdirektor Paul Ehrlich. An seine mannigfachen Entdeckungen und visionären Konzepte in der Mikroskopie und Immunologie sowie die von ihm vorangetriebene Entwicklung der ersten Chemotherapie haben wir daher im November mit einem zweitägigen Symposium erinnert, das unter dem Motto „Paul Ehrlich 2015: From Salvarsan to Personalized Medicine" stand und das wir gemeinsam mit dem Paul-Ehrlich-Institut, der Nationalen Akademie der Wissenschaften Leopoldina und der Goethe-Universität unter der Schirmherrschaft des Bundesministers für Gesundheit, Hermann Gröhe, organisiert haben. Ehemalige Preisträger des Paul Ehrlich- und Ludwig Darmstaedter-Preises und des Paul Ehrlich- und Ludwig Darmstaedter-Nachwuchspreises sowie eine Vielzahl international renommierter Wissenschaftler präsentierten ihre heutige Sicht auf Themen, die Paul Ehrlich bereits vor über 100 Jahren erfolgreich bearbeitete. Einen ganz besonderen Glanzpunkt stellte sicher der Festakt in der Paulskirche am Vorabend des Symposiums dar, der sich insbesondere durch die Festreden des Nobelpreisträgers Stefan Hell und der Urenkelin Paul Ehrlichs Elizabeth Brody auszeichnete.

Ein weiterer wissenschaftlicher Höhepunkt war im Frühjahr der Vortrag von James P. Allison in unserem Hörsaal, der über seine spektakulären Erfolge bei der Entwicklung von Immuntherapien zur Krebsbehandlung berichtete. Für diese Leistungen wurde ihm in diesem Jahr neben dem Paul Ehrlich- und Ludwig Darmstaedter-Preis auch der Lasker – DeBakey Clinical Medical Research Award verliehen.

Auch heute noch verfolgen wir am Georg-Speyer-Haus die bereits von Paul Ehrlich in Grundzügen entwickelte Idee einer zielgerichteten Krebstherapie. So gelang es in den letzten Jahren einem Konsortium von Wissenschaftlern des Georg-Speyer-Hauses, des DRK-Blutspendedienstes und der Goethe-Universität unter der Leitung von Prof. Winfried Wels genetisch modifizierte natürliche Killerzellen (NK-Zellen) zu entwickeln, die einen sogenannten chimären Antigenrezeptor (CAR) exprimieren und damit in der Lage sind, Tumorzellen selektiv abzutöten. Eine Variante dieser CAR NK-Zellen, die spezifisch das Tumorantigen ErbB2/HER2 erkennt, hat die präklinische Entwicklung bereits erfolgreich

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

2015 was a very special year for the Georg-Speyer-Haus: 100 years ago, on August 20, 1915, our founding director Paul Ehrlich passed away. In order to commemorate his manifold discoveries and visionary concepts in microscopy and immunology and his leading role in the development of the first chemotherapy, we have organized together with the Paul Ehrlich Institute, the National Academy of Sciences Leopoldina and the Goethe University under the patronage of the Federal Minister for Health, Hermann Gröhe, a two-day symposium entitled "Paul Ehrlich 2015: From Salvarsan to Personalized Medicine" in November. During this symposium former winners of the Paul Ehrlich and Ludwig Darmstaedter Prize and the Paul Ehrlich and Ludwig Darmstaedter Young Investigator Awards and a number of internationally renowned scientists presented their current views on topics that have already been successfully investigated by Paul Ehrlich over 100 years ago. A highlight of this commemoration constituted certainly the ceremony in the St. Paul's Church on the eve of the symposium, which distinguished itself especially by the speeches of Nobel Prize winner Stefan Hell and the great-granddaughter of Paul Ehrlich Elizabeth Brody.

Another scientific highlight in spring was the presentation by James P. Allison in our lecture hall, who gave a lecture about his spectacular success in the development of immunotherapies for cancer treatment. For these achievements he has been awarded the Paul Ehrlich and Ludwig Darmstaedter Prize as well as the Lasker – DeBakey Clinical Medical Research Award this year.

durchlaufen. Diese Zellen wurden vor Kurzem an ein US-amerikanisches Biotechnologie-Unternehmen auslizenziert. Dies ermöglicht nun die Untersuchung von Verträglichkeit und möglicher Effektivität der Zellen in einer frühen klinischen Studie bei Glioblastompatienten, die im kommenden Jahr hier am Standort beginnen soll. Die erfolgreiche Entwicklung einer solch komplexen zellulären Therapie bis hin zur klinischen Einsatzreife aus einem akademischen Umfeld heraus stellt sicher eine herausragende Leistung und einen unserer größten Erfolge in diesem Jahr dar.

Das Jahr 2015 war aber auch in anderer Hinsicht ein besonderes Jahr. Dr. Rolf-E. Breuer, der mehr als 40 Jahre lang dem Stiftungsvorstand des Georg-Speyer-Hauses angehörte und über 36 Jahre dessen Vorsitz innehatte, gab dieses Amt im Frühjahr auf. Ein ehrenamtliches Engagement in einer Stiftung über einen solch langen Zeitraum hinweg ohne eine familiäre Bindung ist sicherlich einmalig. Dr. Breuer gebührt der außerordentliche Dank des Georg-Speyer-Hauses für seine unermüdliche und tatkräftige Unterstützung in all diesen Jahren. In Anerkennung seiner Verdienste wurde Dr. Breuer zum Ehrenmitglied des Georg-Speyer-Hauses ernannt und das „Dr. Rolf-E. Breuer-Stipendium" zur Unterstützung ausgezeichneter Nachwuchswissenschaftler ins Leben gerufen. So sehr wir das Ausscheiden von Dr. Breuer aus dem Vorstand bedauern, so dankbar sind wir, dass Herr Gerhard Wiesheu sich nach erfolgter Umstrukturierung der Gremien des Georg-Speyer-Hauses bereit erklärt hat, das Amt des Vorsitzenden des nun anstelle des Vorstands neu konstituierten Stiftungsrats zu übernehmen. Ich freue mich auf eine enge und vertrauensvolle Zusammenarbeit mit Herrn Wiesheu bei der Bewältigung der in den kommenden Jahren vor uns liegenden Aufgaben.

Ziel des Instituts ist eine Fokussierung der onkologischen Forschung auf das Tumor Microenvironment, um neue Therapiekonzepte zu entwickeln, die wir möglichst rasch in klinische Studien überführen können. Diese Konzentration unserer Anstrengungen und die damit verbundene verstärkte Interaktion mit unseren klinischen Partnern an der Goethe-Universität wurde in den letzten Jahren vor allem auch durch die erfolgreiche Rekrutierung von exzellent ausgewiesenen Nachwuchswissenschaftlerinnen und Nachwuchswissenschaftlern vorangebracht. In diesem Jahr ist es gelungen, eine weitere hervorragende Nachwuchswissenschaftlerin zu gewinnen. Dr. Lisa Sevenich kehrte nach einem sehr erfolgreichen

Today we are still working towards the development of a targeted cancer therapy at the Georg-Speyer-Haus, a concept that had already been developed by Paul Ehrlich over 100 years ago. A consortium of researchers from the Georg-Speyer-Haus, the German Red Cross Blood Transfusion Service and the Goethe University, headed by Prof. Winfried Wels, has successfully developed genetically modified natural killer cells (NK cells) over the past years that express a so called chimeric antigen receptor (CAR) and that are thereby able to selectively kill tumor cells. A variant of these CAR NK cells that specifically recognize the tumor antigen ErbB2/HER2, has already successfully completed preclinical development. These cells have been licensed to a US-based biotechnology company recently. This opens up the opportunity to examine the tolerability and potential effectiveness of these cells in an early clinical trial in glioblastoma patients that will be conducted at this site in the coming year. The development of such a complex cellular therapy and its successful implementation into clinical trial from an academic institution constitutes an outstanding achievement and certainly represents one of our biggest successes this year.

The year 2015 was also in other aspects a very special year. Dr. Rolf-E. Breuer, who has been a member of the Foundation Board of the Georg-Speyer-Haus for more than 40 years and has served as chairman of the Board for over 36 years, retired from his post in spring. Voluntary work in a foundation over such a long period of time without any familial ties shows certainly a unique commitment. Dr. Breuer deserves the profound gratitude of the Georg-Speyer-Haus for his tireless and energetic support in all these years. In recognition of his services, Dr. Breuer was appointed honorary member of the Georg-Speyer-Haus and the "Dr. Rolf-E. Breuer Stipendium" has been created to support outstanding young scientists. As much as we regret the resignation of Dr. Breuer from the Board, we are also grateful to Mr Gerhard Wiesheu for agreeing, after the restructuring of the governing bodies of the Georg-Speyer-Haus, to take up the post of Chairman of the newly constituted Board of Trustees. I look forward to a close and trusting collaboration with Mr. Wiesheu in the tasks that lie ahead of us in the forthcoming years.

The aim of the Institute is to put a focus on the tumor microenvironment in oncology research to develop new therapy concepts that we can translate as soon as possible into clinical trials. This focus of our efforts

mehrjährigen Aufenthalt als Post-Doktorandin am Memorial Sloan Kettering Cancer Center in New York nach Deutschland zurück und wird sich in den kommenden Jahren am Georg-Speyer-Haus mit der Rolle von Proteasen bei der Entwicklung von Hirnmetastasen beschäftigen. Besonders bemerkenswert ist in diesem Zusammenhang, dass die Arbeiten von Dr. Sevenich von der Deutschen Krebshilfe im Rahmen des Max-Eder-Programms gefördert werden. Dies ist ein Programm zur Förderung exzellenter Nachwuchswissenschaftler, die sich insbesondere mit kliniknahen Forschungsprojekten beschäftigen. Auch die bereits seit einiger Zeit am Georg-Speyer-Haus tätigen Arbeitsgruppen waren im ausgehenden Jahr wieder ausgesprochen erfolgreich bei der Einwerbung von Forschungsmitteln und der Veröffentlichung wichtiger neuer Forschungsergebnisse. Neben der Beteiligung von Arbeitsgruppen des Instituts an Forschungsverbünden wie dem Deutschen Konsortium für Translationale Krebsforschung (DKTK) als Teil des Standorts Frankfurt/Mainz, der Förderung von Projekten innerhalb des EU-Verbundvorhabens 'NET4CGD' und des BMBF-Spitzenclusters 'Cluster für Individualisierte Immunintervention' (Ci3), des BMBF-Verbundprojekts 'Netzwerk Autoinflammatorische Syndrome bei Kindern und Jugendlichen' (AID-NET), sowie der Beteiligung am DFG-Schwerpunktprogramm 1463 'Epigenetic regulation of normal hematopoiesis and its dysregulation in myeloid neoplasia' ist besonders die Förderung der Arbeiten von Dr. Hind Medyouf mit €1.5 Mio durch den European Research Council (ERC) hervorzuheben.

Fortgeführt wurden in diesem Jahr neben den wie immer gut besuchten von Joachim Koch organisierten Bürgervorlesungen auch die über die Jahre fest etablierte und regelmässig außerordentlich gut besuchte Schülervorlesungsreihe sowie das Schülerpraktikum, organisiert von Dr. Ursula Dietrich, die interessierten Oberstufenschülern die experimentelle Grundlagenforschung nahebringen.

Die erzielten Erfolge bestärken uns in unserer täglichen Arbeit und dem Bestreben, unsere Forschung kontinuierlich weiterzuentwickeln. So wollen wir auch in den kommenden Jahren erfolgreich neue Wege gehen und sind sehr optimistisch, dass dies durch den großen Einsatz und Enthusiasmus aller am Institut Tätigen gelingen wird.

Florian Greten, Direktor

and the associated increased interactions with our clinical partners at the Goethe University have been particularly strengthened in recent years due to the successful recruitment of excellent young scientists. This year we have been able to recruit another excellent young group leader. Dr. Lisa Sevenich returned after a very successful period as a postdoctoral researcher at the Memorial Sloan Kettering Cancer Center in New York to Germany and will investigate the role of proteases in the development of brain metastases at the Georg-Speyer-Haus in the coming years. Particularly noteworthy in this context is that Dr. Sevenich's work will be funded by the Max-Eder-Program of the German Cancer Aid. This is a program for the promotion of excellent young scientists who work particularly on clinically relevant research projects. The already established research groups at the Georg-Speyer-Haus were likewise again very successful in the acquisition of third-party funding and in the publication of important new research results.

In addition to the participation of our research groups in different research networks such as the German Consortium for Translational Cancer Research (DKTK) as part of the Frankfurt/Mainz site, the funding of projects within the EU joint project 'NET4CGD' and the BMBF excellence cluster 'Cluster for individualised immune intervention' (Ci3), the BMBF project 'Network Autoinflammatory Syndroms in Children and Adolescents' (AID-NET), and the participation in the DFG Priority Program 1463 "Epigenetic regulation of normal hematopoiesis and its dysregulation in myeloid neoplasia', I would like to particularly highlight the support of the work of Dr. Hind Medyouf by the European Research Council (ERC) with € 1.5 million.

Our public lecture series organized by Joachim Koch was very well frequented as well as the student lecture series and student internships, organized by Dr. Ursula Dietrich, that allow interested high school students to gain a detailed insight into experimental basic research.

The achieved success encourages us in our daily work and desire to continually develop our research. In the coming years we want to continue to pursue new paths and are very optimistic that we will succeed through the commitment and enthusiasm of all the people at the Institute.

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

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

Das Gebäude des Georg-Speyer-Hauses in der Paul-Ehrlich-Straße 42 – 44, 1906 eröffnet, wurde von der Stadt Frankfurt am Main zur Nutzung für Institutszwecke zur Verfügung gestellt. Der gesamte Gebäudekomplex wurde in den Jahren 1995 – 1997 aus Mitteln des Bundesministeriums für Gesundheit und des Hessischen Ministeriums für Wissenschaft und Kunst saniert und modernisiert. Er umfasst eine Gesamtfläche von 4710 qm. Die Laboratorien sind für Arbeiten unter verschiedenen biologischen und gentechnischen Sicherheitsstufen (L2, L3, S1, S2, S3) 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.

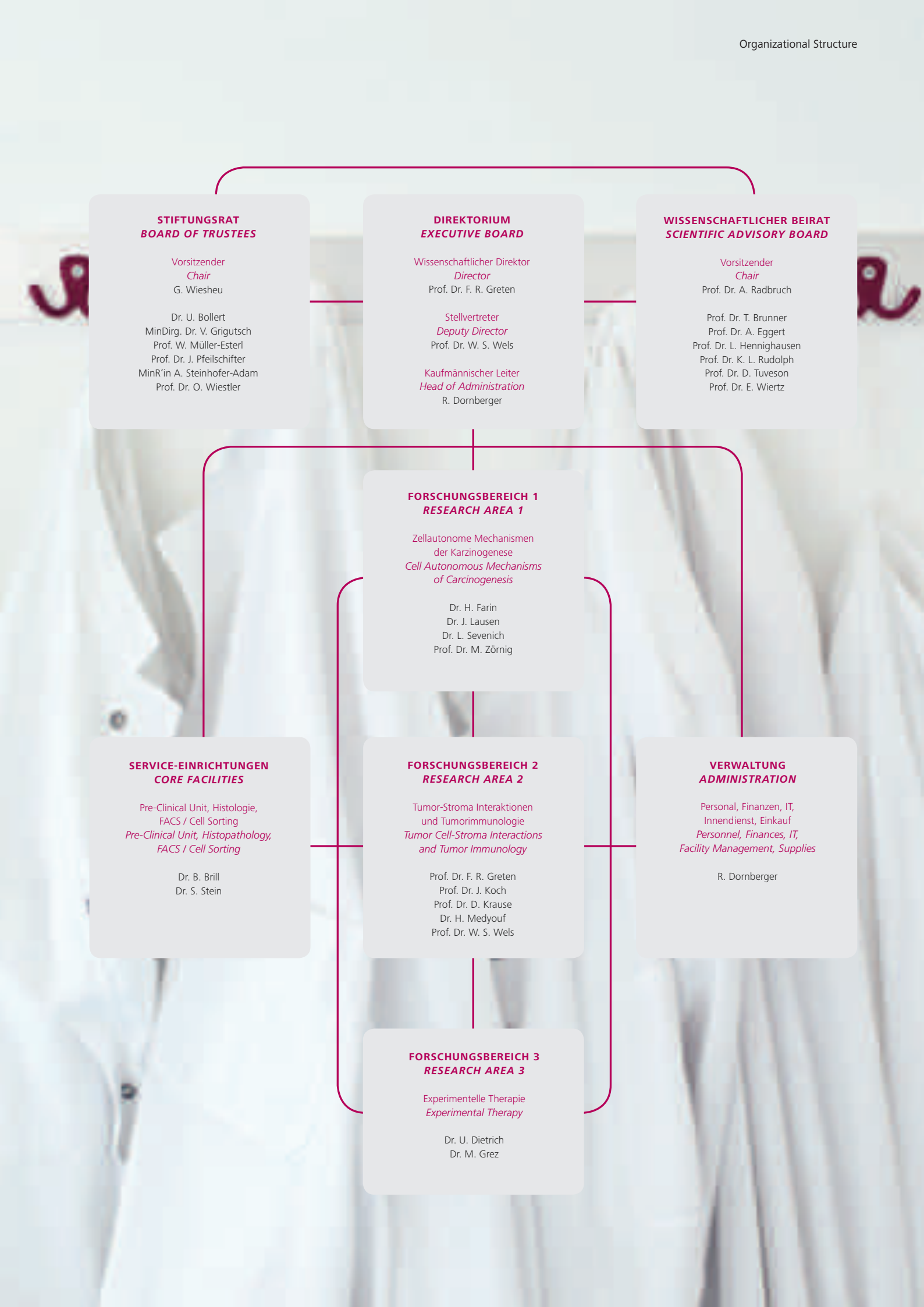
Das Georg-Speyer-Haus wird finanziell vom Bundesministerium für Gesundheit (BMG) sowie vom Hessischen Ministerium für Wissenschaft und Kunst (HMWK) unterstützt. Zusätzlich stehen Mittel aus der Drittmittelförderung öffentlicher und privater Forschungsförderungsorganisationen, aus Kooperationsvereinbarungen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

Als Partner im Universitären Centrum für Tumorerkrankungen (UCT), dem LOEWE Zentrum für Zell-und Gentherapie (LOEWE-CGT) 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.

It comprises an area of 4710 m^2. The laboratories are certified for work under different biological and gene technology safety regulations (L2, L3, S1, S2, S3).

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 für Cell and Gene Therapy 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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der Karzinogenese
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Experimentelle Therapie
Experimental Therapy

Dr. U. Dietrich
Dr. M. Grez

Highlights 2015

Auswahlsymposium zum Paul-Ehrlich- und Ludwig Darmstaedter Nachwuchspreis

Am Montag, 14. September 2015 fand im Hörsaal des Georg-Speyer-Hauses das Auswahlsymposium zum Paul Ehrlich- und Ludwig Darmstaedter-Nachwuchspreis 2016 statt. Wie in den vergangenen Jahren referierten fünf hervorragend ausgewiesene Nachwuchswissenschaftler über eine große Bandbreite aktueller Themen aus der biomedizinischen Forschung. Der mit 60.000 € dotierte Nachwuchspreis wird gemeinsam mit dem „großen" Paul Ehrlich- und Ludwig Darmstaedter-Preis jedes Jahr am 14. März (Geburtstag von Paul Ehrlich) in der Frankfurter Paulskirche verliehen.

Retreat Weilburg 22. – 23. Juli 2015

Der Jahres-Retreat des Georg-Speyer-Hauses fand am 22. – 23. Juli in Weilburg an der Lahn statt. Neben einem wissenschaftlichen Programm mit Beiträgen der 60 Teilnehmer des Instituts waren 7 Gastsprecher eingeladen. Bei sommerlichem Wetter gab es sehr schöne Gelegenheiten die Umgebung zu genießen, z.B. eine Kanutour auf der Lahn.

Verabschiedung Dr. jur. Rolf-E. Breuer aus dem Vorstand des Georg-Speyer-Hauses

Dr. jur. Rolf-E. Breuer wurde am 2. März 2015 nach über 40 Jahren aus dem Stiftungsvorstand des Georg-Speyer-Hauses verabschiedet. In Anerkennung und Würdigung seiner großen Verdienste um das Georg-Speyer-Haus wurde Herr Dr. Breuer zum Ehrenmitglied der Stiftung Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus ernannt.

Der wissenschaftliche Direktor des Georg-Speyer-Hauses, Prof. Dr. Florian Greten überreichte Herrn Dr. Breuer die Urkunde im Rahmen einer feierlichen Verabschiedung im Gästehaus Metzler in Frankfurt-Bonames.

Sommerfest

Kommunikation und Interaktion zwischen allen Gruppen und sämtlichen Mitarbeitern des Instituts machte das GSH-Sommerfest wieder zu einem Highlight. Neben vielen mitgebrachten Köstlichkeiten der Mitarbeiter, wie selbstgezauberten Kuchen und Salaten und einem umfangreichen Grillbuffet, sorgte A. Gresik mit seiner legendären Paella für das leibliche Wohl.

Lauf für mehr Zeit

Am 13. September beteiligte sich das GSH wieder am „Lauf für mehr Zeit" zugunsten der AIDS Hilfe Frankfurt am Main. Das hochmotivierte Läufer-team von links nach rechts, vorne: Divij Verma, Eva Weissenberger, Melanie Meister, Kathrin Koch; Mitte: Canan Arkan, Florian Greten mit Sophie, Lisa Sevenich, Ursula Dietrich, Maren Weisser; hinten: Joachim Schwäble, Oliver Ringel, Jasmin Yillah, Jascha Melomedov (nicht auf dem Bild: Joachim Koch und Sarah Oelsner).

100. Todestag von Paul-Ehrlich – Festakt in der Paulskirche am 22.11.2015

Anlässlich des 100. Todestages des Nobelpreisträgers Paul Ehrlich werden die Leistungen des großen Medizinforschers in drei Veranstaltungen in Frankfurt gewürdigt. Eine seiner großen Forschungsleistungen ist Salvarsan – das erste systematisch entwickelte und spezifisch wirkende Therapeutikum. Damit hat Paul Ehrlich den Grundstein gelegt für eine Pharmakotherapie, bei der gezielt Angriffspunkte für eine Therapie ausgemacht und Wirkstoffe entwickelt werden. 100 Jahre später werden immer häufiger in der Therapie genetische beziehungsweise molekularbiologische Unterschiede zwischen den Patienten genutzt, um die Behandlung zu „personalisieren" und maßgeschneidert die Arzneimittel einzusetzen, die den größten Erfolg versprechen.

I

Zellautonome Mechanismen der Karzinogenese

Cell Autonomous Mechanisms of Carcinogenesis

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Gewebsinteraktionen und Signalmechanismen im Darmkrebs

Mitarbeiter
Mohammed Mosa
Birgitta Michels
Moyo Grebbin
Marnix de Groot
Tahmineh Darvishi

Microenvironmental crosstalk in colon cancer

3-D epithelial cultures from endoscopic biopsies

Identification of paracrine signaling networks

Targeting of the cancer microenvironment

Colorectal cancer (CRC) is the third leading cause of death from cancer among adults in Germany. Cancer genome sequencing programs have identified a heterogeneous spectrum of oncogenic mutations in patients. However we currently cannot predict therapeutic responses based on the genetic composition of a tumor. This is due to the complexity of cell signaling processes that involve an intrinsic crosstalk between all tissue compartments. Our newly established lab explores the 3-D 'organoid' culture system as a solid tumor model. This system allows to expand primary intestinal stem cells under full control of the exogenous 'microenvironment'. Exposure to microenvironmental signals such as inflammatory cytokines, growth factors, microbial and metabolic cues are analyzed to dissect tumor-specific vulnerabilities. Our goal is to understand how tumor cells respond to and influence their microenvironment, to be able to specifically target this cross talk.

The organoid culture system as a human colorectal cancer model. Tumor cells successively acquire mutations that confer unrestricted local

Unsere Arbeitsgruppe erforscht die zellulären und molekularen Vorgänge bei der Entstehung von Darmkrebs. Insbesondere interessiert uns die Kommunikation verschiedener Zelltypen in der unmittelbaren Umgebung des Tumors, dem so genannten "Tumor-microenvironment". 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 (so genannte "Mini-Därme"). Dieses System ermöglicht die Expansion von Stammzellen in einem Gewebe-ähnlichen Zustand, was die Untersuchung von molekularen Signalen in einer definierbaren Mikroumgebung ermöglicht. So kann z.B. durch Zugabe von nicht-epithelialen Zellen wie Fibroblasten, Gefäß- oder Immunzellen der Organ-kontext nachgebildet werden. Im Mittelpunkt unserer Forschung steht die genetische Analyse der Entstehung und Progression des Darm-Karzinoms sowie der Einfluss körpereigener Abwehrmechanismen wie Entzündungsreaktionen. Dazu werden in klinischer Kollaboration Tumorbiopsien expandiert um Patienten-spezifische Signalmechanismen zu identifizieren. Mit Hilfe von genetischen Techniken versuchen wir zu verstehen wie einzelne onkogene Mutationen den zellulären Phänotyp beeinflussen, als Ansatzpunkt für zukünftige Therapien.

Die Stelle wird vom Deutschen Krebsforschungszentrum (DKFZ) im Rahmen des Deutschen Konsortiums für Translationale Krebsforschung (DKTK) am Georg-Speyer-Haus finanziert.

growth before progression to metastatic disease. Although great advances have been achieved in both prophylaxis and therapy of CRC, the clinical options for patients with progressed disease are very limited. Metastatic colonization of distant sites, which is mainly the liver (and also the lungs) often precludes surgical and radiological intervention and the response rates to classical chemotherapy and new targeted therapies are modest with a high degree of relapse. To be able to predict drug efficiency and prevent development of drug resistance, new tumor models are required that closely reflect the signaling processes in CRC. Currently used transformed cell lines have lost important traits of primary tumor cells and cannot reflect the heterogenic nature of the disease. Differences between species restrict the use of animal models to test genetic hypotheses. The recently developed 'Organoid' culture system (Sato et al., Nature 2009) allows expansion of gastrointestinal stem cells over long periods ex vivo. In a 3-D extracellular matrix (ECM) epithelial structures are formed that undergo continuous self-renewal and differentiation, recapitulating

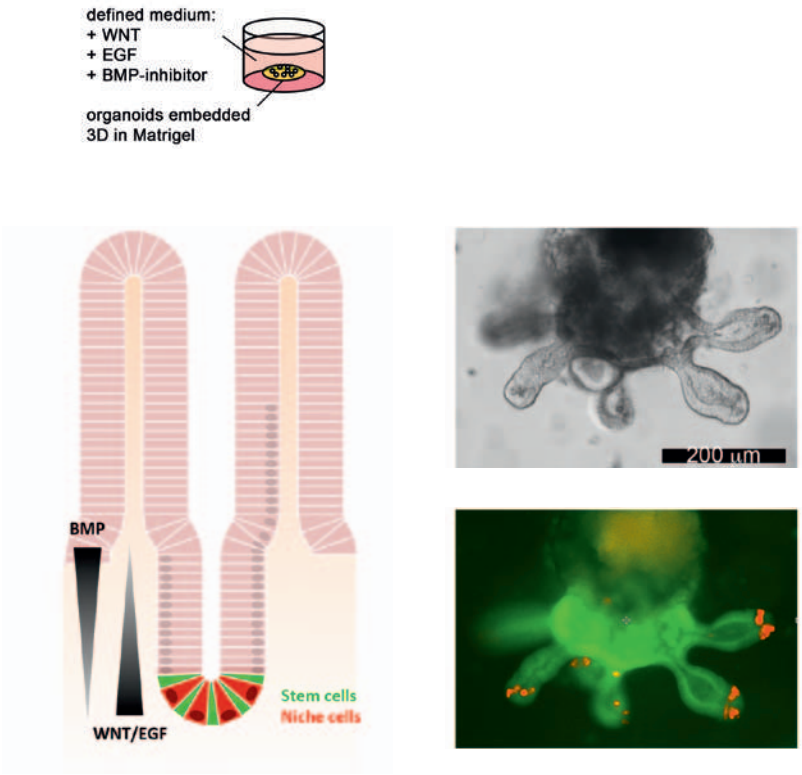
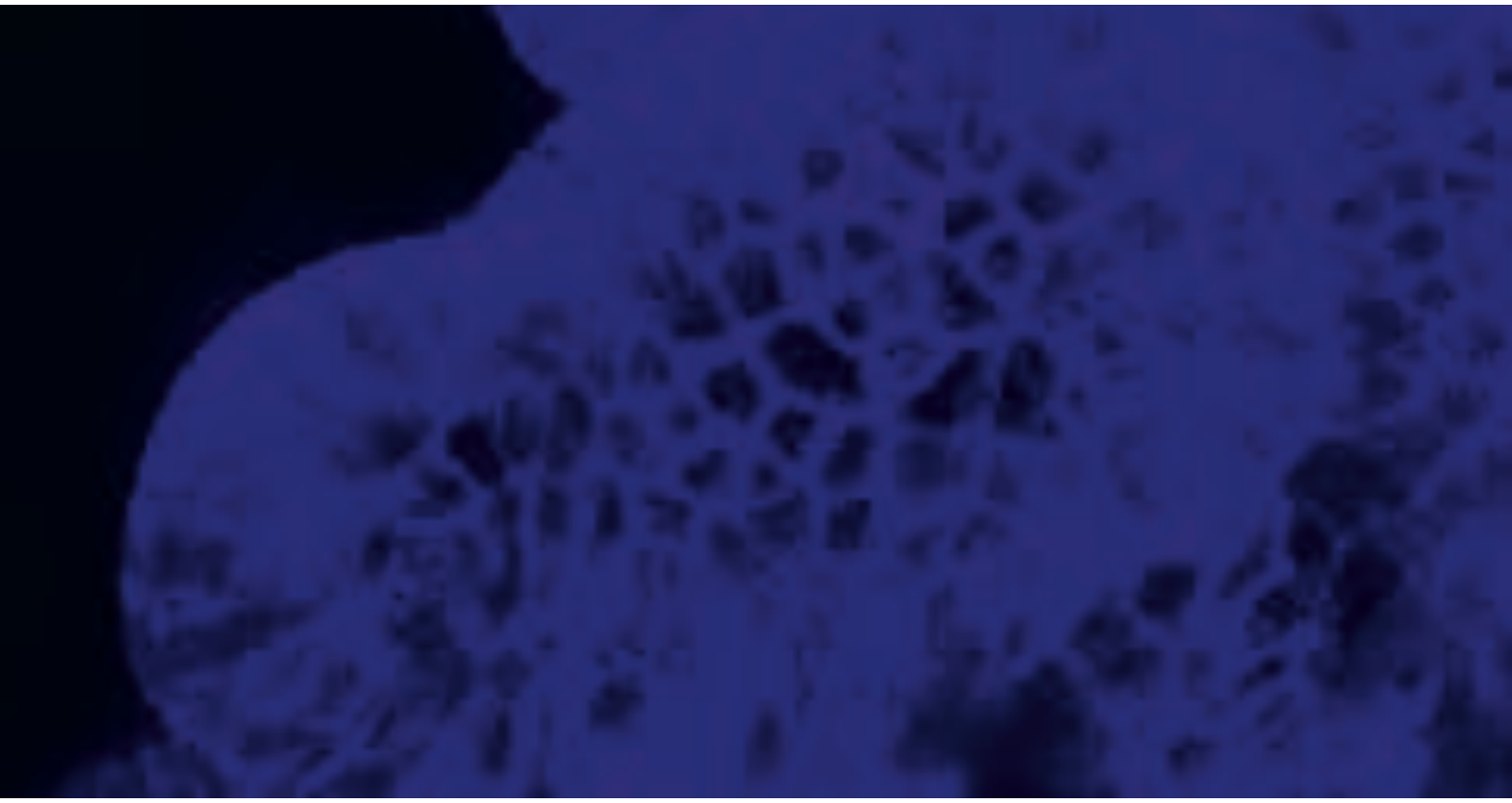


Figure 1.
Organoid cultures recapitulate the intestinal stem cell niche
The intestinal organoid culture system (first described by Sato et al., 2009). The medium composition mimics the stem cell niche environment in the intestine, which is characterized by high WNT/EGF and low BMP signals. In 3-D Matrigel 'mini guts' are formed that contain crypt–like structures, each composed of a stem cell niche compartment (red cells).



a normal crypt-villus architecture (Figure 1). Organoids can be established from endoscopic patient biopsies of normal and tumor tissue (Sato et al., Gastroenterology 2011). Importantly, the culture conditions preserve cells in a native state that depends on niche signals that have to be supplemented with the culture medium. This allows the characterization of individual oncogenic mutations in signaling pathways such as the WNT, EGF or the BMP. We take advantage of our expertize with transgenesis (Koo et al., Nature Protocols 2011), stem cell expansion and differentiation (Yin et al., Nature Protocols 2014) and patient-derived organoids models (Bigorgne, Farin el al., Journal of Clinical Investigation 2013) and have established local clinical collaborations to obtain biopsy material.

The oncogenic microenvironment as a potential therapeutic target.
The gastro-intestinal epithelium is in close

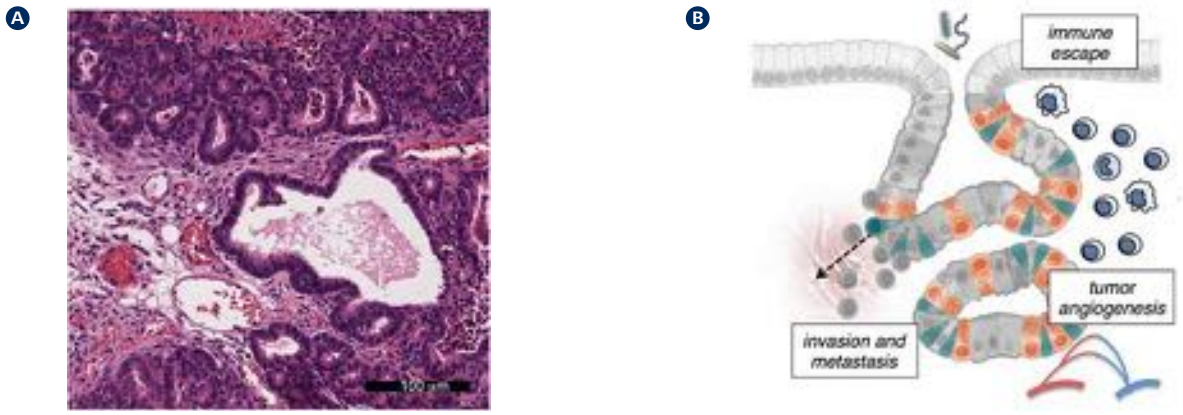


Figure 2.
Paracrine signaling in colon-cancer microenvironment
Tumor progression represents a co-adaptation process: the stroma imposes positive and negative influences on tumor growth and progression.
A Histology (HE staining) of grafted tumor organoids (sub cutaneous). The tumor epithelium shows a glandular architecture. Recruitment of stromal cells is observed (such as blood vessels and fibroblasts).
B Schematic representation of tissue interactions in colon cancer. Boxes highlight cellular processes that offer potential anti-cancer targets.

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contact to surrounding tissues such as mesenchymal, immune and endothelial cells and is furthermore continuously exposed to the gut lumen that contains potentially toxic microbes. In this environment, the stem cell niche secures a normal balance between processes such as proliferation and differentiation. In tumor tissues, however, this homeostasis is disturbed and the transformed epithelium looses its niche-dependence. Oncogenic mutations result in an non-controlled expansion, but also mediate adaptation to a modified microenvironment: Cancer cells need to actively recruit stromal cells such as vasculature and fibroblasts to obtain trophic signals and actively repress immune responses. In order to survive at secondary sites disseminated tumor cells need to re-establish a supportive stroma (Figure 2).

Given the complexity of signaling interactions within the tumor, the study of tumor organoids provides a 'reductionist approach' to dissect and to model epithelial-stromal crosstalk. To this end, we have engineered defined oncogenic mutations in normal human colon organoids using the CRSIPR/Cas9 system (Figure 3). These isogenic lines are characterized in vitro (e.g. by mRNA profiling) and in more complex settings such a co-cultures with stromal cells and Xenotransplantation experiments. Previous research expertize has been gathered in projects addressing mesenchymal-epithelial and immuno-epithelial crosstalk, (Farin et al., Gastroenterology 2012 and Farin et al., Journal of Experimental Medicine 2014). Our goal is to identify new strategies to interfere with stromal crosstalk besides targeting the tumor cells themselves.

The research group is funded by the German Consortium for Translational Cancer Research (DKTK) which is part of the German Cancer Research Centre (DKFZ).

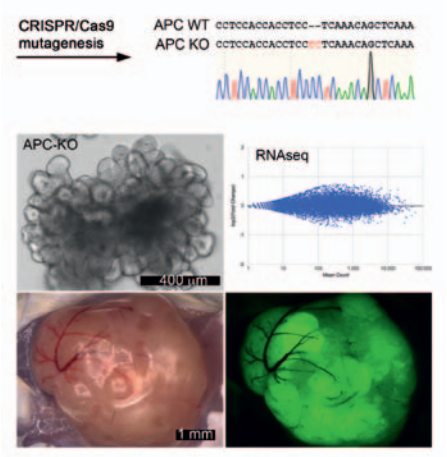

Figure 3.
Colon organoids as a defined cancer model
Human organoids derived from normal biopsies can be engineered using the CRISPR/Cas9 system to generate defined oncogenic mutations. Knock-out (KO) of the human APC tumor suppressor gene is shown. 'Tumor organoid' lines are then characterized by RNA sequencing and xenotransplantation (sub cutaneous graft of GFP expressing organoids is shown).

Transkriptionsregulation in der Hämatopoese

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Transcriptional regulation during hematopoiesis

transcription

epigenetics

hematopoiesis

leukemia

stem cells

The hematopoietic system is in a constant process of cell proliferation, differentiation and cell death. The progenitor cells produced by hematopoietic stem cells undergo a hierarchical process in which the self-renewal capability is lost and a specific lineage identity is adopted. This differentiation is directed by lineage specific transcription factors, which recruit gene regulatory complexes that contain cofactors with DNA and histone modifying activity to target genes. By these modifications, the chromatin is reorganized locally and genome-wide to initiate and maintain a cell type specific gene expression pattern. Mutations can change the way transcription factors interact with epigenetic cofactors and are therefore the cause of an altered chromatin structure (Figure 1). As a consequence, gene expression can be deregulated in a way that stem cell functions and differentiation processes become imbalanced. This can give rise to a cell population that is able to self-renew and to generate progenitor cells, which exhibit a blockage in terminal differentiation. Because of the role of transcription factors and chromatin

Das Blutsystem befindet sich in einem kontinuierlichen Prozess der Zellbildung, Differenzierung und des Zelltodes. Die Blutzellen werden dabei ständig durch hämatopoetische Stammzellen im Knochenmark nachgebildet. Während der Entwicklung von der Stammzelle zu den verschiedenartigen adulten Zellen wird die zelltypspezifische Genexpression durch linienspezifische Transkriptionsfaktoren epigenetisch festgelegt. Sie bilden dabei genregulative Komplexe mit Chromatin-modifizierenden Kooperationspartnern und bewirken dadurch eine Umorganisation des Chromatins. Mutationen in Transkriptionsfaktoren können die Interaktionsfähigkeit mit diesen Kofaktoren verändern und dadurch eine gestörte epigenetische Wirkung ausüben. Dies kann zu fehlregulierter Genexpression führen und Krebserkrankungen auslösen. Die Identifizierung dieser epigenetischen Kofaktoren ist daher wichtig für das Verständnis der Funktion von Transkriptionsfaktoren in Entwicklung und Krankheit und stellt einen Forschungsschwerpunkt unserer Arbeitsgruppe dar. Außerdem untersuchen wir die Funktion identifizierter epigenetisch wirksamer Kofaktoren während der normalen und gestörten Differenzierung. Die Kombination dieser Forschungsansätze soll das regulative Netzwerk der Expressionskontrolle enthüllen und dadurch potentielle molekulare Ziele für eine therapeutische Manipulation von Transkriptionsfaktoren aufdecken.

modifying enzymes during normal differentiation of cells and in disease, it is important to analyse the normal function of transcription factors and their cofactors. We are investigating transcription factor activity in the hematopoietic system and are analyzing novel transcription factor functions during differentiation. Furthermore, we are identifying cofactors of transcription factors and characterize their epigenetic function in gene regulation. The recent approvals of anticancer therapeutic agents targeting histone deacetylases and DNA methyltransferases highlight the therapeutic potential of drugs, which influence gene expression. Thus, our research aims to unravel molecular targets for manipulation of transcription factor function and we are testing the potential of identified cofactors as targets for a molecular therapy.

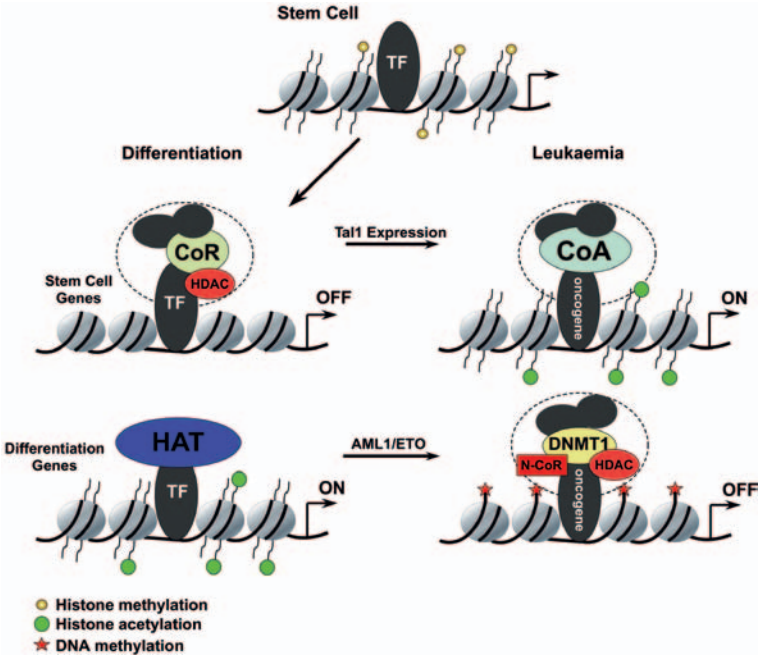
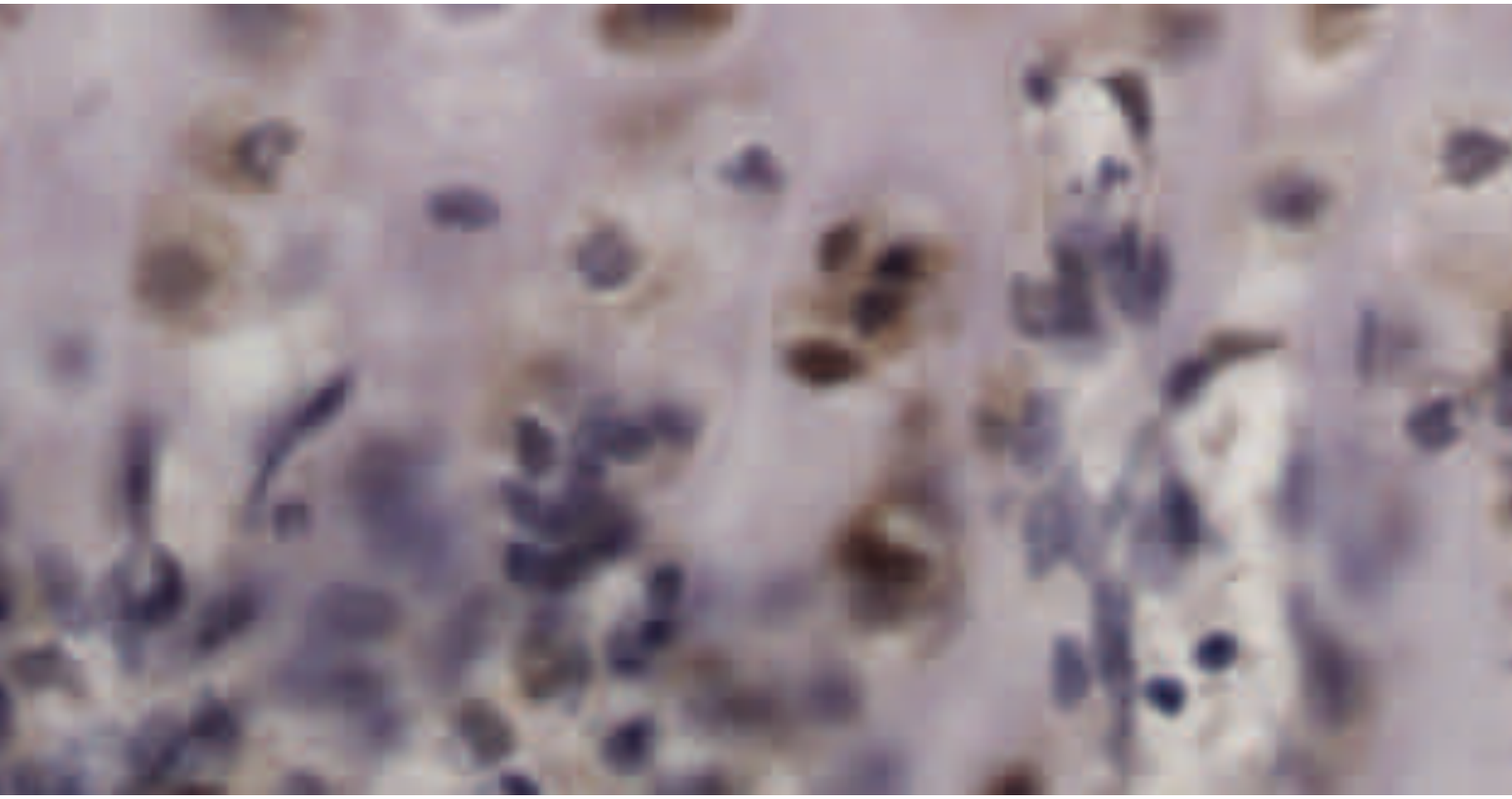


Figure 1.
Deregulated gene expression leads to leukemia.
In stem cells the chromatin is transcriptional competent so that all genetic programs can be activated (upper part). During differentiation, stem cell genes that are responsible for the self-renewing capability are down-regulated by transcription factors that recruit a repressor complex. These complexes contain repressing chromatin modifying enzymes like histone deacetylases (HDACs). At the same time, activating complexes with histone acetylase functions (HAT) turn on differentiation genes. Mutations in transcription factors can interfere with normal differentiation. Here, stem cell genes are expressed because of a mistargeted activating complex caused by Tal1 expression (middle part). On the other hand, mistargeted repressing complexes can silence differentiation genes (lower part). These epigenetic alterations can shift the balance between proliferation and differentiation and ultimately cause cancer. CoR: Corepressor, HDAC: histone deacetylase, HAT: histone acetylase, DNMT1: DNA methyl transferase, N-CoR: Nuclear Corepressor, RUNX1/ETO (or AML1/ETO): Leukemic fusion protein between RUNX1 (acute myeloid leukaemia 1) and ETO (eleven twenty one), Tal1: T cell lymphocytic leukaemia 1.



Tal1 and RUNX1, critical transcription factors in stem cells and in leukaemia

Gene ablation studies in the mouse identified the transcription factors Tal1 (T cell lymphocytic leukemia 1) and RUNX1 (acute myeloid leukemia 1) as critical regulators of hematopoietic stem cell development. Furthermore, both transcription factors play an important role in the development of leukaemia. A deregulated Tal1 expression leads to T cell acute lymphatic leukemia and RUNX1 is mutated in acute myeloid leukemia. The roles of these transcription factors in stem cell and cancer biology implicate that the same functions that contribute to normal stem cell development are deregulated in cancer stem cells. For this reason RUNX1 and Tal1 are being studied in detail to understand the basic mechanisms underlying normal hematopoietic development and leukemia.

I. Epigenetic mechanisms in hematopoiesis

During hematopoietic differentiation, the progenitor cells produced by stem cells undergo a hierarchical progression, in which the self-renewal capability is lost and a specific lineage identity is adopted. Throughout this process gene expression needs to be tightly controlled to allow for cell-type and cell-stage specific gene expression. This is achieved by key transcription factors, which recruit epigenetic

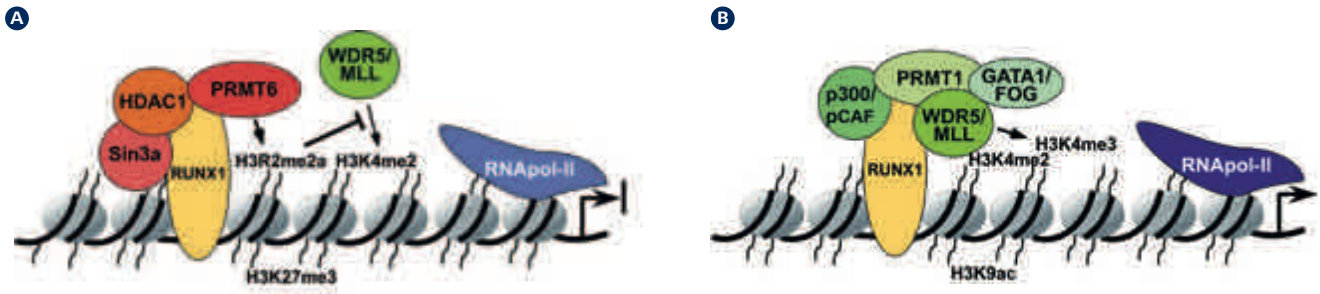
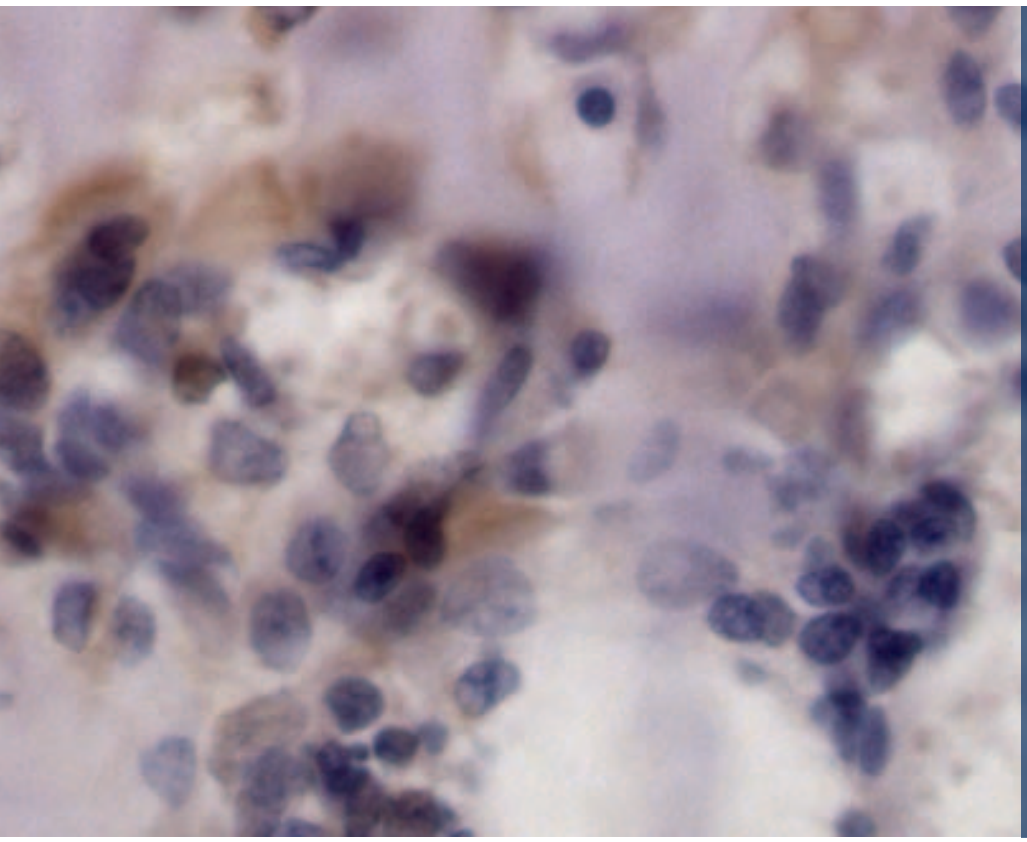


Figure 2.
Model of PRMT6 activity with RUNX1.

A RUNX1 recruits a corepressor complex with PRMT6, Sin3a and HDAC1 in progenitor cells, which supports a repressive chromatin environment with H3R2me2 and H3K27me3. The promoter is in an intermediate state, H3K4me2 is present at the promoter, but H3K4me3 is inhibited due to a block of WDR5 recruitment.

B The corepressor complex is exchanged with a coactivator complex upon differentiation, containing p300, PRMT1, WDR5 and GATA1/FOG1. Loss of PRMT6 leads to diminished H3R2me2 and an enhanced recruitment of WDR5. As a consequence, the activating histone modifications H3K4me3 and H3K9ac are established and RNA polymerase drives transcription.



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cofactors to target genes. These cofactors can change the chromatin environment by posttranslational modifications of the histone tails in a way that transcription is activated or repressed. It is very critical during hematopoietic differentiation that differentiation specific genes are repressed in progenitors, but are maintained in a state that allows for later activation. This epigenetic state is characterized by the concomitant presence of activating and repressive histone marks and is termed as a poised or intermediate state. The mechanism how transcription factors contribute to the establishing and maintenance of the intermediary state of genes is largely unknown. We have discovered that the central hematopoietic transcription factor RUNX1 interacts with the protein arginine methyltransferase 6 (PRMT6). We found that RUNX1 recruits PRMT6 to megakaryocytic target genes in CD34+ hematopoietic progenitor cells. Here, PRMT6 contributes to the maintenance of an intermediate chromatin state at target loci by triggering a specific histone mark, which blocks transcriptional activation. During differentiation, an activating complex replaces this repressive RUNX1/PRMT6 complex, which augments gene expression (Figure 2). These results shed light on gene expression control in hematopoietic stem cells and progenitor cells by hematopoietic transcription factors. The discovery of an epigenetic activity of PRMT6 in conjunction with RUNX1 may open a road to therapeutically manipulate epigenetic states during normal hematopoietic stem cell differentiation and in RUNX1 dependent leukaemia. It has been recognized that epigenetic mechanisms play a central role in gene regulation and in human disease. Furthermore, the recent approvals of anticancer therapeutic agents targeting histone deacetylases and DNA methyltransferases highlight the therapeutic potential of drugs, which influence gene expression. Whereas DNA binding transcription factors mostly lack enzymatic activity on their own, they recruit histone and DNA modifying cofactors to target genes. These histone-modifying proteins have enzymatic pockets, which can be targeted by small molecule drugs. Therefore we are testing the potential of identified cofactors of the oncogenes Tal1 and RUNX1 as targets for a molecular therapy.

II. Identification and characterisation of coregulators of transcription factors

The transcription factor Tal1 is a critical regulator of gene expression in hematopoiesis and angiogenesis. We have identified peptidyl arginine deiminase 4 (PADI4) as a cofactor of Tal1 by affinity purification of Tal1 interaction partners and SILAC based mass spectrometry. We show that PADI4 differentially inhibits epigenetic histone arginine methylation marks at the Tal1 target gene IL6ST (gp130). IL6ST is a key molecule for cytokine signalling. At the IL6ST promoter, PADI4 counteracts the repressive H3R2me2a mark triggered by PRMT6 and augments IL6ST expression. A small molecule inhibitor of PADI4 influences this epigenetic function of PADI4. Our results demonstrate for the first time that PADI4 can act as an epigenetic coactivator through influencing H3R2me2a. Furthermore, we found that PADI4 influences myeloid differentiation in a colony forming assay using human CD34+ progenitor cells. The function of PADI4 as a cofactor of Tal1 opens the possibility to pharmacologically influence the oncoprotein Tal1 in leukemia.

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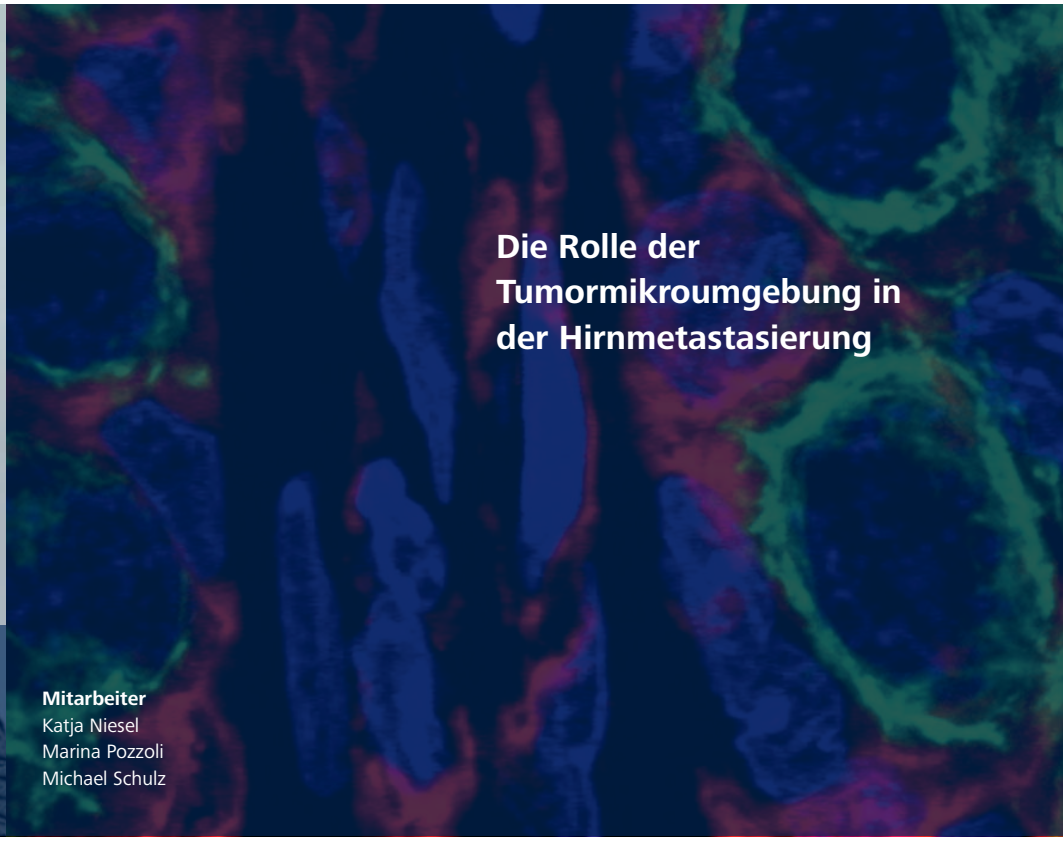


Die Rolle der Tumormikroumgebung in der Hirnmetastasierung

Mitarbeiter
Katja Niesel
Marina Pozzoli
Michael Schulz

Microenvironmental regulation of brain metastasis

Cancer-associated inflammation in brain metastases

Therapy-induced inflammatory respsonse

Tumor microenvironment targeted therapy

Metastasis represents a major clinical issue with limited effective therapies for patients with brain metastases in particular. The median survival following diagnosis of brain metastases is only a few months with a 1-year survival rate of approximately 10%. These dismal statistics emphasize the urgent need for detailed mechanistic insight and development of novel therapies to combat this lethal disease. One such paradigm is the recognition that reciprocal interactions between tumor cells and non-cancerous stromal cells in the tumor microenvironment critically contribute to disease progression at the primary site and regulate site-specific metastasis. The brain represents a unique tissue environment in which the blood-brain barrier (BBB) limits the entry of inflammatory cells from the periphery. Immune functions are therefore performed by, microglia, the brain-resident macrophages that derive from the yolk sac and populate the brain parenchyma before the development of the BBB. Brain metastases and CNS inflammation disrupt the integrity of the BBB thus allowing infiltration of inflammatory cells from the periphery. Brain metastatic progression

Viele Krebserkrankungen können dank intensiver Forschung und den daraus resultierenden Therapiefortschritten erfolgreich behandelt werden. Metastasen stellen jedoch weiterhin die Haupttodesursache bei Tumorpatienten dar, da die verfügbaren Behandlungsmöglichkeiten, insbesondere bei Hirnmetastasen, nur begrenzt wirksam sind. Die Entwicklung neuartiger Therapieansätze zur Bekämpfung von Hirnmetastasen ist daher von großer Bedeutung. Neuere Studien verdeutlichen den Einfluss der Gewebsumgebung auf die Tumorprogression und die organspezifische Metastasierung. Die Mikroumgebung von Hirnmetastasen weist aufgrund des Vorhandenseins hirn-spezifischer Zelltypen, wie z.B. Mikroglia oder Astrozyten, im Vergleich zu anderen Organen einige Besonderheiten auf. Der Einfluss dieser hirn-residenten Zelltypen sowie weiterer Entzündungszellen, die in Hirnmetastasen einwandern, ist derzeit weitgehend unbekannt. Das Forschungsziel unserer Nachwuchsgruppe besteht darin, die komplexen Interaktionen zwischen Tumorzellen unterschiedlicher Entitäten (Melanom, Bronchial- oder Mammakarzinom) und hirnresidenten- sowie rekrutierten Entzündungszellen während der Hirnmetastasierung zu entschlüsseln. Ein besonderer Fokus liegt hierbei auf der funktionellen Analyse der Mechanismen, durch die Krebszellen tumor-fördernde Entzündungsreaktionen im Gehirn hervorrufen sowie der Fragestellung wie Strahlen- bzw. Chemotherapie diese Vorgänge auf zellulärer und molekularer Ebene beeinflusst.

is accompanied with accumulation of brain resident cells as well as recruitment of inflammatory cells from the periphery in particular monocytes/macrophages and granulocytes (Figure 1). There is accumulating evidence that oncogene-driven signals activate tumor-promoting inflammatory pathways and block host defense mechanisms to escape immune surveillance and to foster tumor growth.

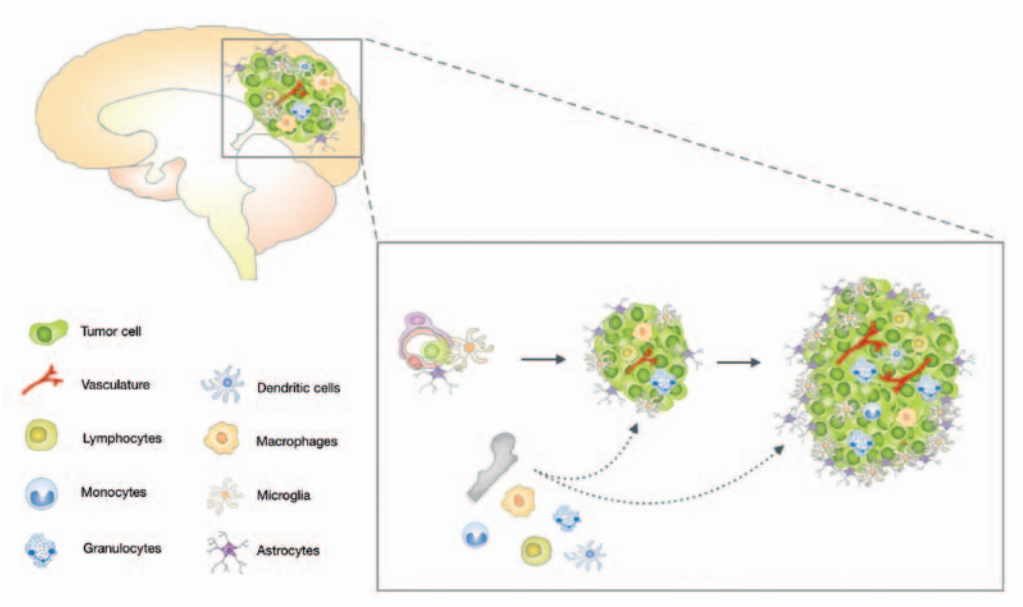
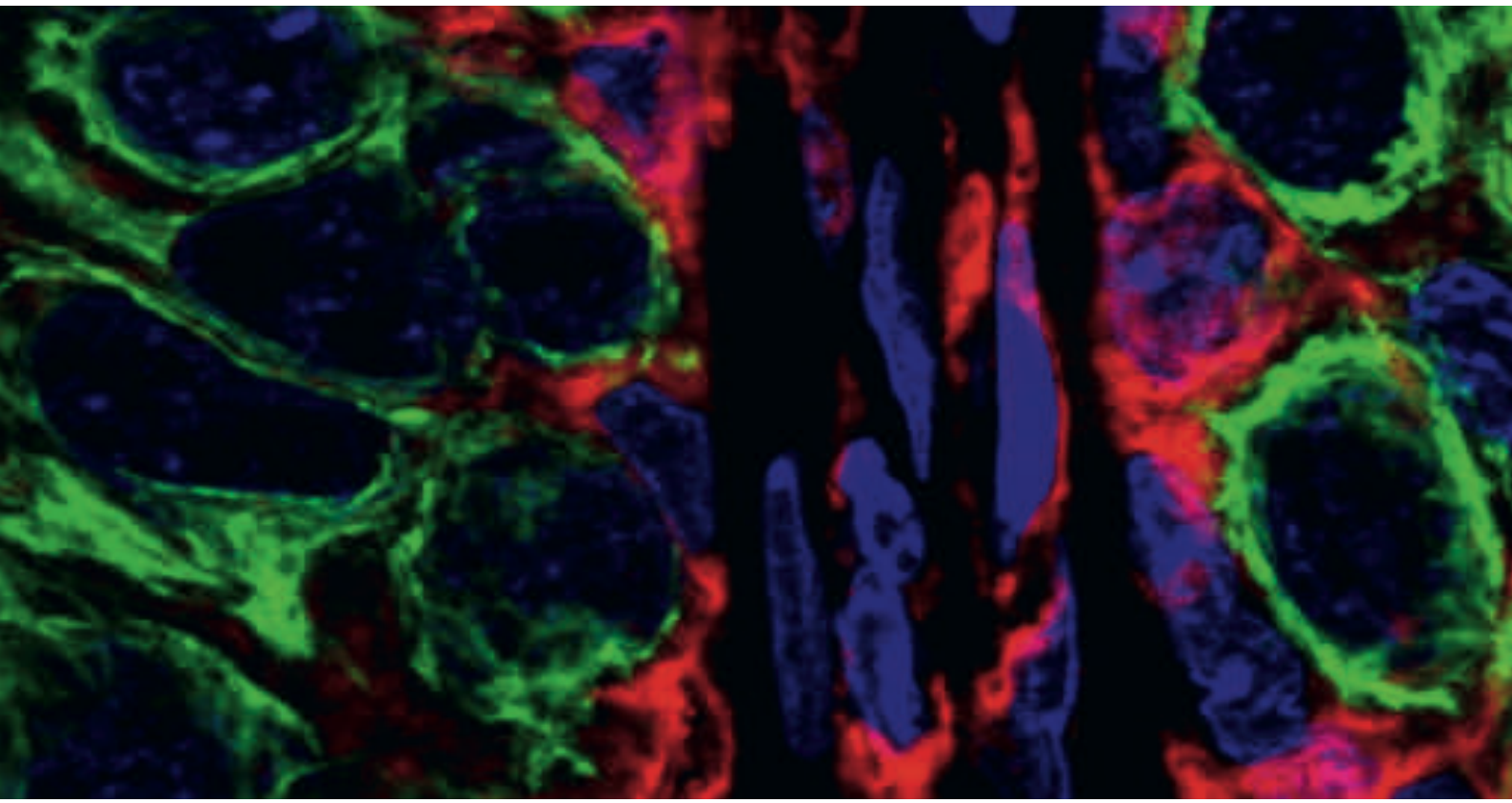


Figure 1.
The brain metastases microenvironment. Brain metastasis is accompanied with a gradual increase stromal cell recruitment. Tumor cells get in close contact with brain resident cell-types such as astrocytes and microglia already during extravasation. Inflammatory cells from the periphery are recruited to the brain after the integrity of the blood-brain barrier is impaired. Brain-resident and recruited stromal cell types form the complex tumor microenvironment that regulates different steps within the metastatic cascade.



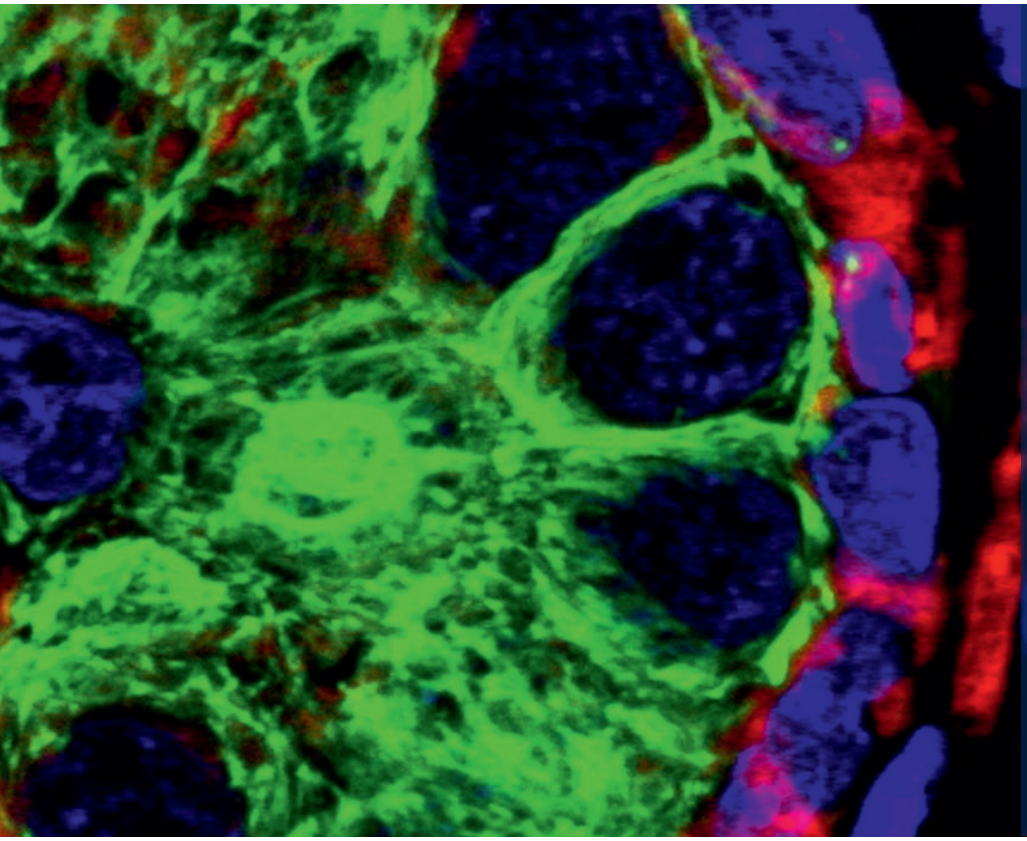
Tumor – stroma interactions as potential therapeutic targets

Given the important role of the tumor microenvironment (TMEM) in primary tumor growth and metastasis, TMEM-targeting strategies are emerging to interfere with paracrine loops between tumor cells and stromal cells. The research goal of our recently established junior group is to dissect complex tumor – stroma interactions in brain metastasis. We are particularly interested in the functional analysis of the mechanism by which tumor cells from different entities such as melanoma, breast- or lung cancer induce tumor-promoting inflammatory pathways in brain-resident or recruited immune cells to support metastatic seeding and outgrowth. We seek to develop strategies that interfere with the tumor – stroma crosstalk with the goal to maintain or induce anti-tumor effector functions in brain metastases-associated immune cells (Figure 2).

Effects of standard of care therapy on the brain metastases microenvironment

The majority of patients with brain metastases receive radio- or chemotherapy as standard of care. The therapeutic use of local ionizing radiation (IR) or cytostatic drugs has been largely guided by the dogma that terminally differentiated cells, including macrophages/ microglia and astrocytes are inherently radio- or chemoresistant because of their post-mitotic state. However, it has recently been demonstrated that IR and chemotherapy affect bystander cells leading to changes in their gene expression and effector functions with profound effects on disease progression or therapeutic response. Combination of standard of care and immune modulatory drugs has shown improved therapeutic efficacy in several primary tumor types. To date, very little is known how IR or chemotherapy affect the tumor microenvironment in brain metastases on the cellular or molecular level. We will therefore specifically investigate the effects of IR or chemotherapy on brain metastases-associated inflammation. Our goal is to identify critical regulators of therapy-induced inflammatory responses and to test the efficacy of immune modulatory drugs in combination with standard of care (Figure 2).

To address these objectives, we will employ a comprehensive set of strategies including syngeneic and xenograft mouse models of brain metastasis, organotypic- and in vitro co-culture systems, gene expression profiling, pre-clinical trials, and analysis of patient samples. Our long-term goal is to translate these findings into clinical applications for the development of targeted- or immune therapies that block tumor – stroma interactions or modulate cancer-associated inflammation in brain metastasis to provide better treatment options for brain metastases patients.



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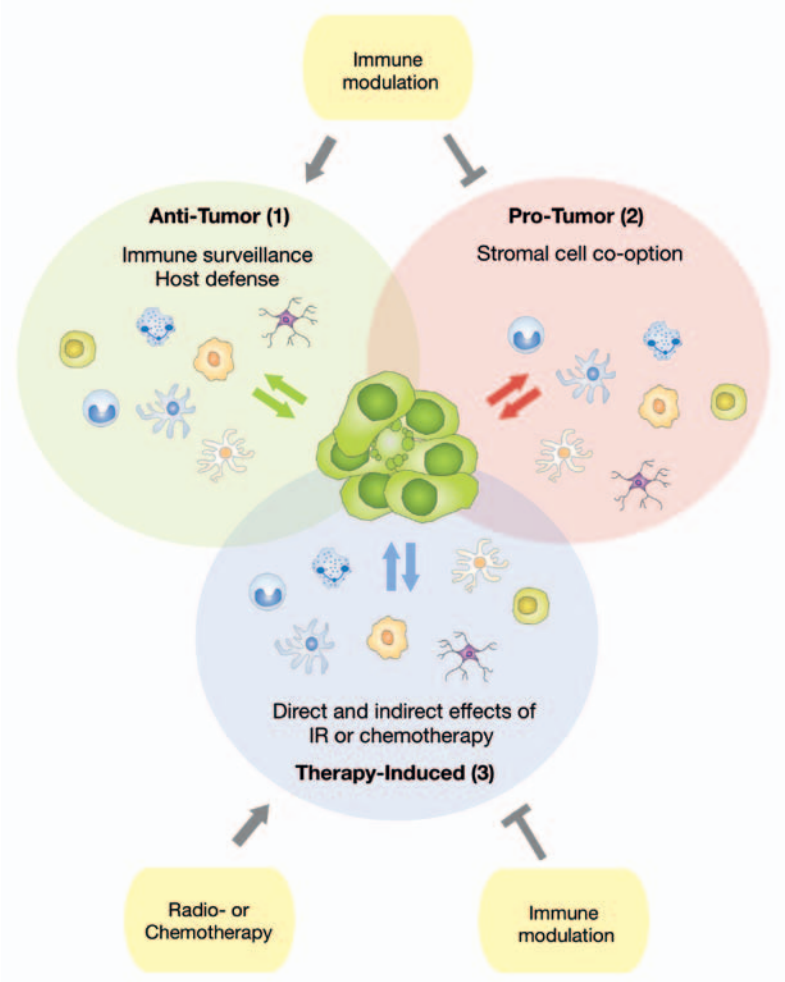

Figure 2.
Cancer-associated inflammation in brain metastases. Reciprocal interactions between cancer cells and inflammatory or other stromal cells determine the polarization of the cancer-associated immune response. Pro-inflammatory cytokines are often associated with anti-tumor responses in which the immune system limits tumor growth and spread through host defense mechanisms (1). However, many tumor types secrete factors that induce tumor-promoting responses (stromal cell co-option) (2). Ionizing radiation and chemotherapeutics have been shown to affect effector functions of stromal cells, which often leads to induction of tumor-promoting inflammation (3). Tumor microenvironment-targeted therapies that modulate cancer-associated inflammation are thus emerging as promising mono- or adjuvant therapies to inhibit tumor-promoting inflammation and to maintain or induce anti-tumor responses.

Regulationsmechanismen des programmierten Zelltodes (Apoptose)

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Regulation and deregulation of apoptosis

Regulation of the mitochondrial apoptosis pathway

Targeting of anti-apoptotic oncoproteins

Transcriptional control of hematopoietic and tumor stem cell self-renewal by FUBP1

Alteration of the control mechanisms of cell death contributes to the pathogenesis of many human diseases, including cancer and neurodegenerative diseases. Our group is interested in identifying novel anti-apoptotic oncoproteins that are responsible for tumor initiation, progression and/or therapy resistance in particular cancer entities. We are analyzing the precise molecular mechanisms how these proteins inhibit cell death and support tumor growth, and we are validating their potential as targets for future molecular therapies. At the same time, we are investigating their physiological role in vivo to predict potential side effects of molecular targeting strategies.

Identification of novel mammalian proteins that regulate apoptosome activity

Several apoptotic stimuli, including cancer treatment regimens of radiation and chemotherapy, ultimately result in the activation of the mitochondrial apoptosis pathway. Inhibition of apoptotic cell death "downstream" of Cytochrome c release would appear advantageous for tumor development, as malignant cells success-

Unsere Arbeitsgruppe beschäftigt sich mit der Identifizierung und Analyse neuer anti-apoptotischer Onkogene, die für die Tumorentstehung sowie für Therapieresistenzen verantwortlich sind. In der Vergangenheit konnten wir in einem selbst entwickelten „Hefe-Survival-Screen" mehrere interessante anti-apoptotische Kandidatengene identifizieren, die in bestimmten Tumorentitäten überexprimiert werden. Wir untersuchen diese Moleküle in Zellkulturexperimenten und in geeigneten Mausmodellen in vivo daraufhin, welche Rolle sie während der Tumorentstehung und -progression spielen, und ob sie sich als Zielstrukturen für zukünftige molekulare Krebstherapien eignen. Parallel sind wir auch daran interessiert herauszufinden, welche Funktion diese Gene im gesunden Organismus ausüben. Letzteres erlaubt auch die Abschätzung möglicher Nebenwirkungen bei molekularen Therapien, in deren Verlauf die tumorrelevante Funktion solcher Gene gestört werden soll. Für ein „Targeting" geeigneter Kandidatengene bzw. der entsprechenden Onkoproteine versuchen wir, kleine inhibitorische Moleküle und shRNA-basierte Strategien für therapeutische Zwecke zu entwickeln, um eine Resistenzentwicklung der Tumorzellen zu umgehen und diese für weitere Behandlungen zu sensitisieren.

fully evade cell death during tumorigenesis. Therefore, it is important to identify and characterize novel anti-apoptotic proteins that inhibit Caspase-9 activation within the apoptosome complex. We used a functional yeast survival screen to isolate human genes that inhibit cell death at the level of the apoptosome, and we isolated promising candidates as potential targets for cancer therapy: FUBP1 binds to single-stranded DNA and activates transcription of the c-myc proto-oncogene, represses the cell cycle inhibitor gene p21, and regulates additional target genes. We isolated FUBP1 from a breast carcinoma-derived cDNA library and studied its involvement in tumorigenesis. FUBP1 is overexpressed in more than 80% of hepatocellular carcinomas (HCCs) and supports HCC tumor growth by inhibiting pro-proliferative and anti-apoptotic genes. We are currently developing small molecule inhibitors of FUBP1 for HCC therapy, and we are testing these inhibitors in several different systems, including liver organoid cultures (Fig. 1). In parallel studies, we are analyzing the physiological function of FUBP1 in suitable mouse models. Our studies unravelled a crucial role of FUBP1 for the maintenance

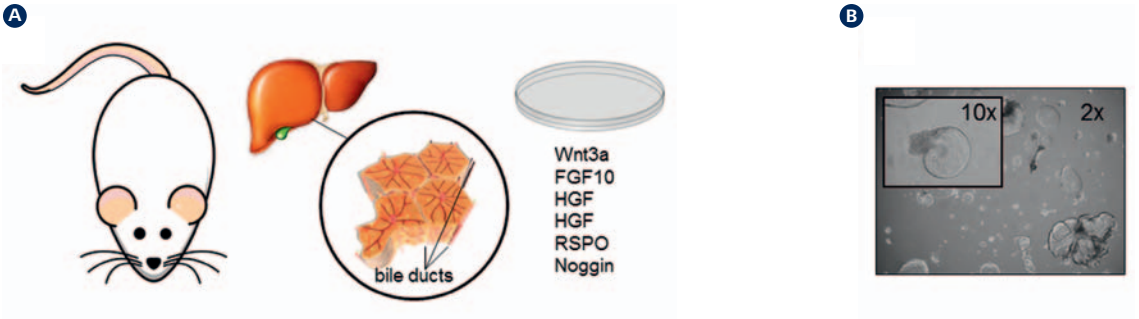

Figure 1.
Establishment of liver organoids to test the therapeutic potential of novel FUBP1 inhibitors.
A To generate liver organoids, bile ducts were isolated by digestion of a mouse liver, embedded in matrigel and cultured in medium containing special growth factors.
B Picture of liver organoids at day 7 (following passage 1).

and self-renewal of both, adult and fetal, hematopoietic stem cells (HSCs) by regulating relevant target genes.

The anti-apoptotic protein AVEN was also isolated in one of our yeast survival screenings, and it interacts with various regulators of apoptosis, such as the apoptosome adaptor protein APAF-1. Our studies revealed that AVEN requires proteolytic processing by the lysosomal protease cathepsin D to unleash its full anti-apoptotic potential, thereby implying that AVEN may be involved in the lysosomal apoptotic pathway. Published data indicate a strong association between poor prognosis in acute childhood lymphoblastic leukemia and AVEN expression, suggesting that AVEN has oncogenic activity. We established a transgenic mouse line with T cell-specific overexpression of the full-length AVEN protein, which accelerates leukemogenesis in heterozygous p53+/- knockout mice. Moreover, the downregulation of AVEN in T-ALL cell lines reduces tumor growth in xenograft experiments. Both findings demonstrate the significant oncogenic potential of AVEN.

AVEN has also been implicated in both DNA repair and the activation of ataxia telangiectasia mutated (ATM) protein kinase, a major regulator of the cell cycle and the DNA damage response. We developed and analyzed a constitutive Aven-/- knockout mouse model, and the results suggest that AVEN plays a vital role in embryonic development. Lack of AVEN expression leads to accumulation of DNA damage and growth arrest, thereby resulting in embryonic lethality at approximately day E9.5. To further study the physiological role of AVEN in adult mouse organs and tissues, and to investigate its oncogenic function in leukemia and breast carcinoma, we established conditional Aven-/- knockout mice. The heterozygous Aven+/- animals allow to monitor endogenous Aven promoter activity by lacZ staining (Fig. 2).

The detailed analyses of FUBP1 and AVEN activity will help to further clarify the mechanism by which apoptosome assembly and Caspase-9 activation are regulated in response to mitochondrial Cytochrome c release. Based on this knowledge, we aim to develop inhibitors for therapeutic intervention targeting the anti-apoptotic activity of these molecules.

Recently, long non-coding RNAs have been shown to promote both tumor suppression and oncogenesis in a variety of tumor entities. MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is a long non-coding RNA of 8 kb that has been reported to be overexpressed in various human solid carcinomas. MALAT1 has been linked to gene regulation, and it seems to play an important role in metastasis. We isolated several MALAT1 cDNA clones from melanoma- and leukemia-derived tumor libraries in our functional yeast survival screen. Cell culture experiments confirmed increased apoptosis rates in the absence of MALAT1 expression. We established a conditonal Malat1 knockout mouse model that is currently being used to study the physiological function of Malat1 and its influence on tumor development, progression, and metastasis. Interestingly, homozygous Malat1-/- knockout mice are born and appear normal, suggesting that Malat1 is not required for normal murine development.

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[1] these authors contributed equally to the work

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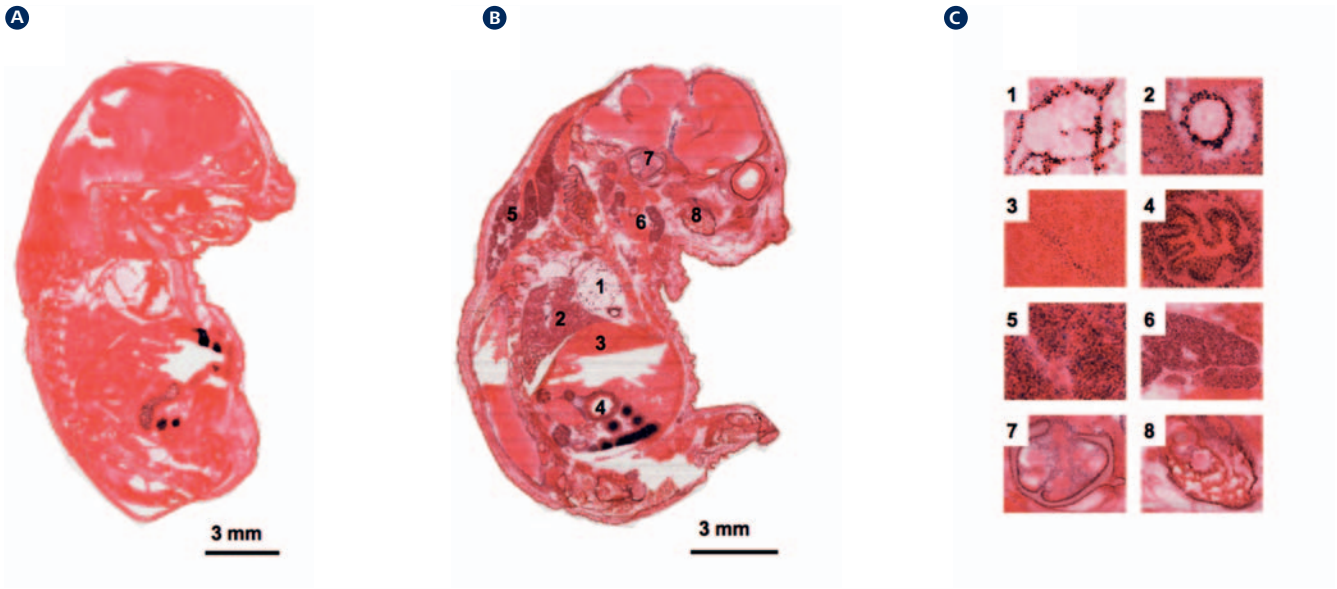

Figure 2.
Aven promoter activity in mouse embryos at day E17.5 of embryonic development.
Wildtype A and Aven+/- B embryos at day E17.5. The cryosections were stained with X-Gal to detect β-galactosidase expression under the control of the Aven promoter. C The inlets 1-8 show magnifications of Aven+/- tissues with significant X-Gal staining (1 = heart, 2 = lung with blood vessel, 3 = liver with a line of highly stained cells, 4 = intestine, 5 = brown fat tissue, 6 = mucous part of the salivary gland, 7 = cartilage primordium of cranial/facial bone, 8 = Meckel´s cartilage).

II

Tumor-Stroma Interaktionen und Tumorimmunologie

Tumor Cell-Stroma Interactions and Tumor Immunology

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Zellplastizität im Mikromilieu des Kolonkarzinoms

Cell Plasticity in the Intestinal Tumor Microenvironment

Cell-cell interaction is essential for tumorigenesis

Inflammation controls cell plasticity of tumor and stromal cells

Cancer associated fibroblasts in colon cancer

Colorectal cancer (CRC) is one of the most frequent malignancies and the second leading cause of cancer death in both men and women in Germany. While the vast majority of CRC are of sporadic origin, about 3-5% of develop in the context of chronic inflammation in patients suffering from inflammatory bowel disease (IBD). Although the spectrum of genetic alterations within tumor cells as well as the order of mutational events may differ between sporadic and inflammation-associated carcinogenesis, over the last decade it has become increasingly evident that both forms of cancer develop an inflammatory microenvironment that drives the different stages of carcinogenesis. Apart from the actual tumor cells the tumor microenvironment is comprised of cells of the innate and adaptive immune system as well as fibroblasts and endothelial cells. Tumor growth depends on the activation of these different cells, their polarization and the types of cytokines secreted into the microenvironment, which is responsible for the cellular interaction and ultimately controls signaling within tumor and stromal cells. Inflammation is an important driver of cell plasticity in both tumor cells as well

Der Fokus unserer Forschung liegt auf der funktionellen Analyse des Mikromilieus im Kolonkarzinom. Hierbei konzentrieren wir uns auf verschiedene Signalkaskaden, welche die Transkription von Genen regulieren, die für Zytokine, pro-und anti-apoptotische Proteine sowie Zellzyklusregulatoren kodieren. Mit Hilfe konditionaler Knockout-Mäuse, erreichen wir eine zelltypspezifische Inaktivierung verschiedener Signalwege in Darmepithelzellen wie auch in Immunzellen. Mit diesen Mäusen führen wir funktionelle Untersuchungen zur Rolle dieser Signalwege in den entsprechenden Zelltypen sowie deren Effekte auf benachbarte Zellen während der Tumorentstehung als auch während der Therapie von etablierten Tumoren durch. Entzündungsreaktionen repräsentieren einen starken Promoter von Zellplastizität sowohl in Tumorzellen als auch in lokalen und rekrutierten Stromazellen. Die Plastizität dieser verschiedenen Zellen spielt eine wichtige Rolle während aller Stadien der Tumorentwicklung: Initiation, Promotion und Progression (Invasion und Metastasierung). Seit vielen Jahren beschäftigen wir uns mit der systematischen Analyse des entzündlichen Tumormikromilieus im Kolonkarzinom und untersuchen insbesondere welche Rolle der IκB-kinase (IKK) Komplex für die Zellplastizität spielt. Es gelang uns eine essentielle Funktion der klassischen IKKβ-abhängigen NF-κB Aktivierung in Tumorzellen während der Tumorinitiation und Tumorprogression nachzuweisen. Nun konnten wir eine sehr überraschende neue Funktion dieses Signalwegs in Tumor-assoziierten Fibroblasten definieren.

as stromal cells. We use conditional mouse models to identify key signaling pathways that drive cell plasticity during the different phases of tumor development and which may represent novel therapeutic targets. Over the last years we have been specifically addressing how the inflammatory tumor microenvironment and particularly the IκB-kinase (IKK) complex affects plasticity of various cell types within the tumor microenvironment using mouse models of colorectal cancer. We were able to demonstrate an essential function of classical IKKβ-dependent NF-κB activation in tumor cells during tumor initiation, tumor promotion as well as tumor progression. During early tumor initiation NF-κB is involved in stem cell expansion and can contribute to re-programming of post-mitotic epithelial cells into tumor initiating stem cells. During tumor promotion NF-κB controls tumor cell survival and during tumor progression it contributes to invasion and metastasis.

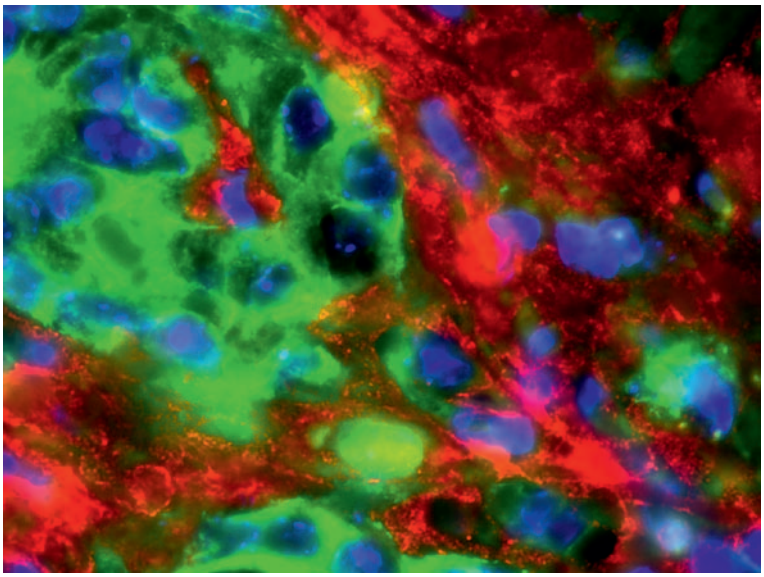
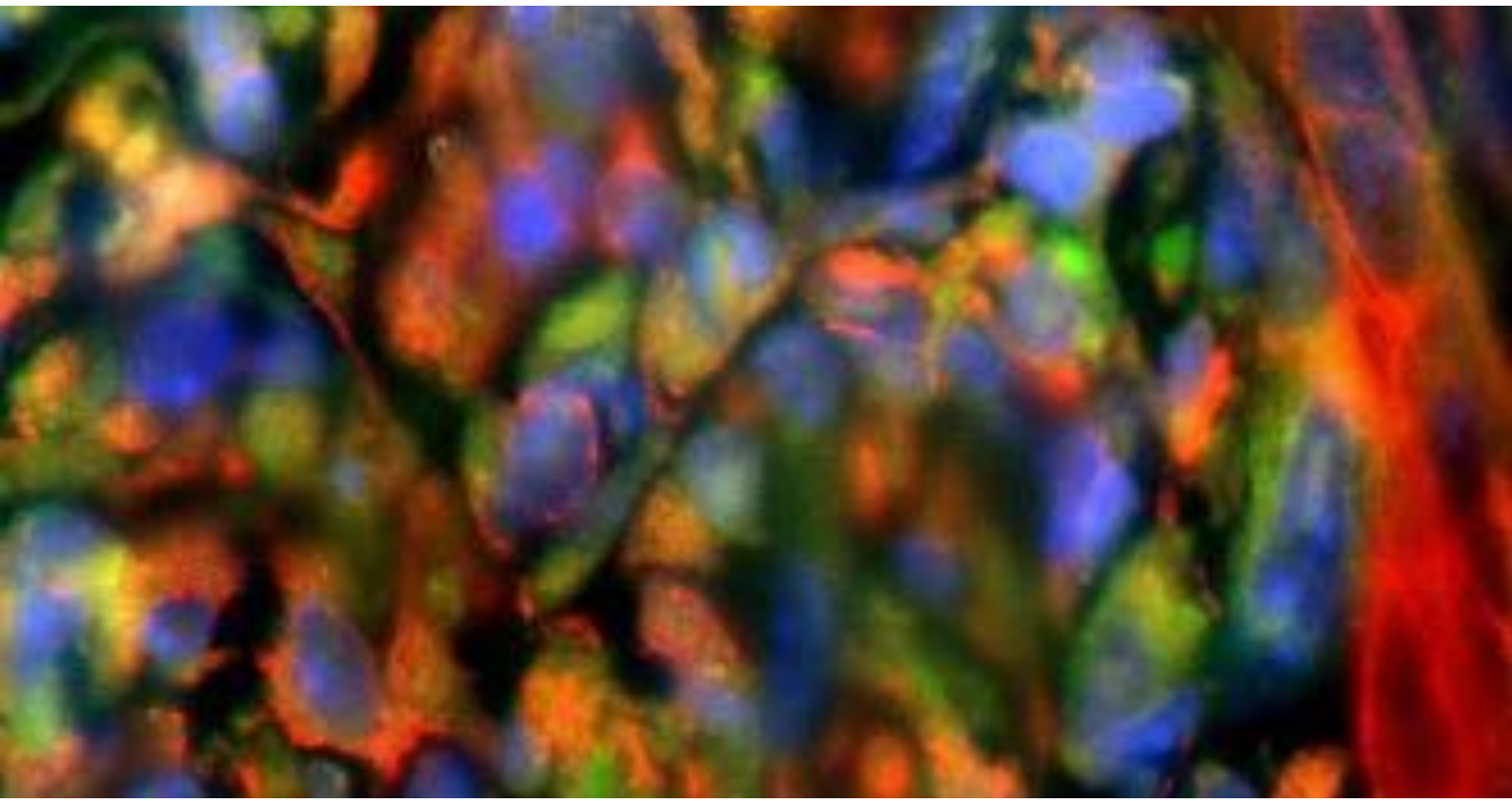
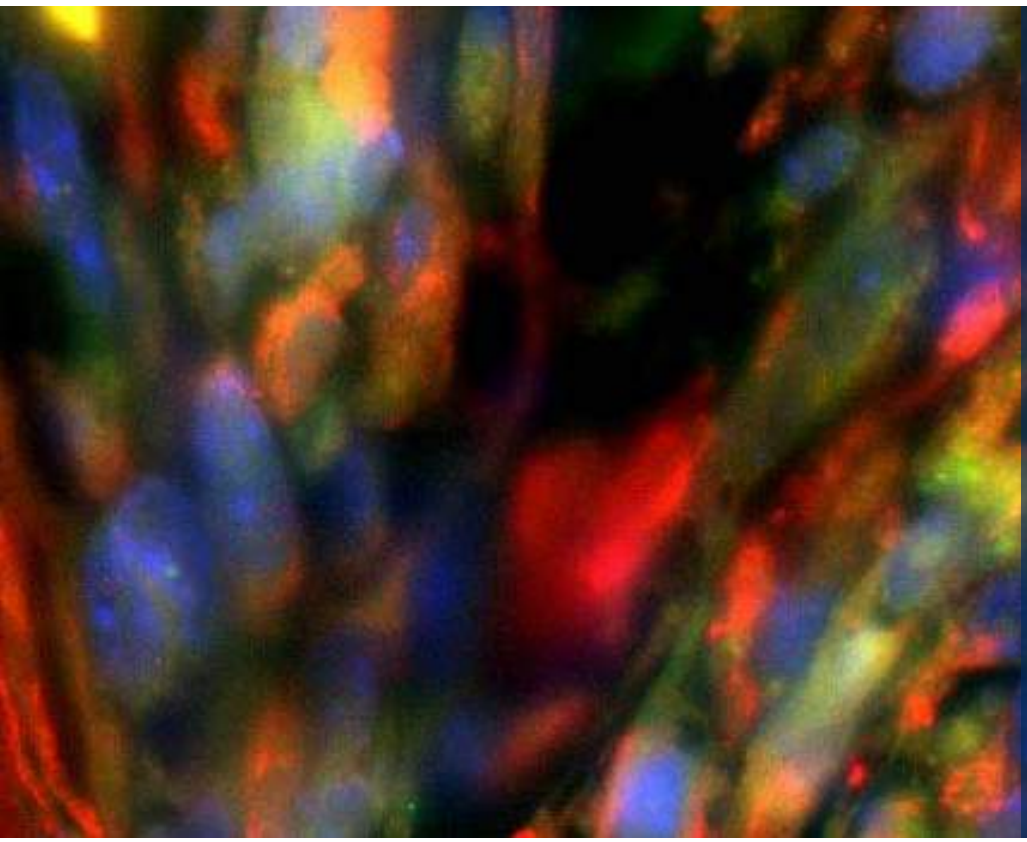


Figure 1.
Colon cancer cells (green) are surrounded by fibroblasts (red) which secrete factors that shape the different cells in the tumor microenvironment in a tumor promoting manner.



NF-κB confers anti-tumorigenic functions in cancer-associated fibroblasts

Besides immune cells or vascular cells, cancer associated fibroblasts (CAFs) comprise an essential component of the colonic tumor microenvironment and affect presumably every phase of colorectal carcinogenesis. Tumor-associated fibroblasts contribute to colorectal tumorigenesis not only by secreting factors that directly influence the tumor cells, but also by indirect mechanisms involving other cell types. Many factors that are released by the fibroblast into the tumor microenvironment, affect the innate as well as the adaptive immune system, both of which have an essential role in the development of colorectal malignancies. Importantly, CAFs were recently shown to have a pro-inflammatory NF-κB dependent signature in tumor models of skin, mammary and pancreatic cancer as well as their cognate human counterparts. In transplanted tumors recruitment of macrophages, neovascularization and tumor cell proliferation was dependent on NF-κB signaling in co-injected CAFs. Thus, the inflammatory infiltrates and proliferating mesenchymal cells in the tumor microenvironment presumably provide essential growth factors and signaling molecules in an NF-κB dependent manner that could further support proliferation and invasion of transformed cells. However, using a model of colitis-associated carcinogenesis we obtained surprising results that were in stark contrast to the previously published data that had suggested a pro-tumorigenic function of NF-κB in skin, mammary and pancreatic cancer. Fibroblast restricted inhibition of NF-κB signaling stimulated intestinal epithelial cell proliferation, suppressed tumor cell death, enhanced accumulation of CD4+Foxp3+ Treg cells and induced angiogenesis ultimately promoting colonic tumor growth. This was due to enhanced secretion of hepatocyte growth factor (HGF) by fibroblasts due to enhanced TGFβ signaling in these cells. Thus, inhibition of NF-κB signaling may be associated with unwarranted tumor promoting side effects. Our current studies aim to analyze these effects further.



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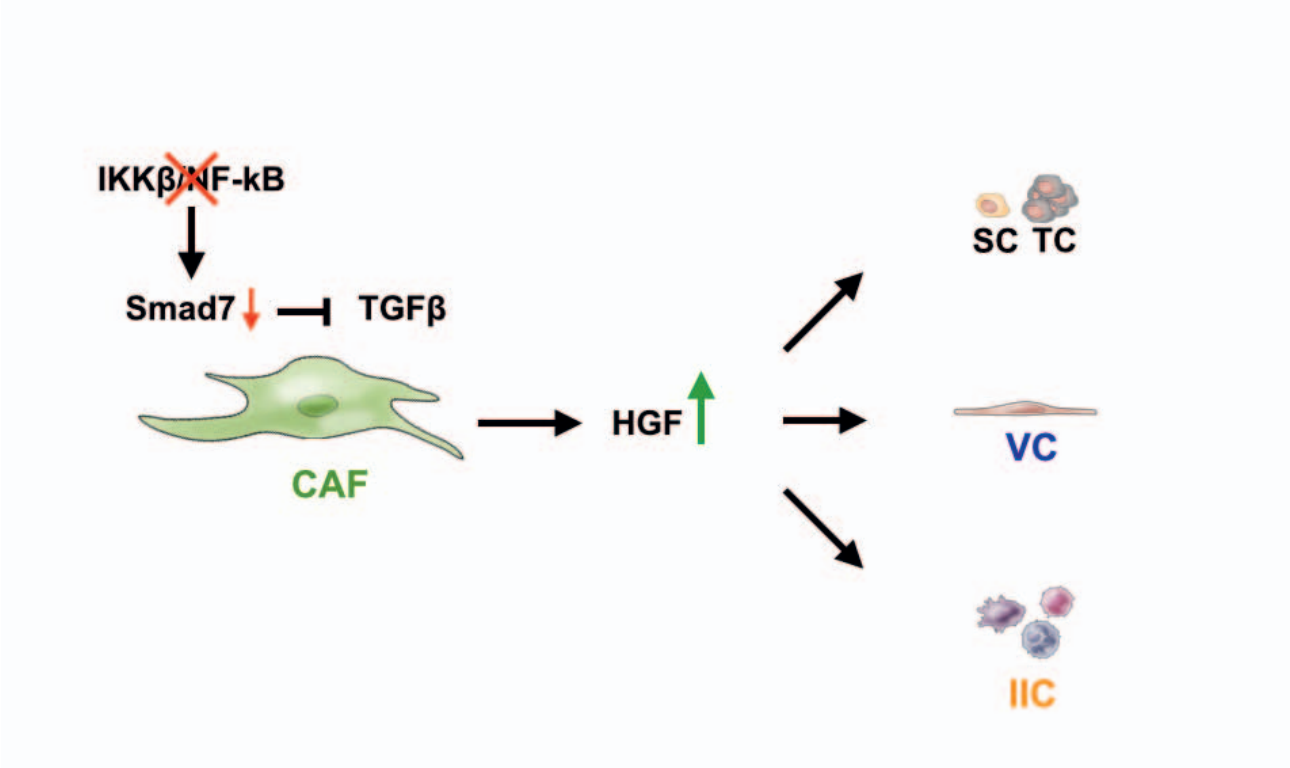

Figure 2.
Surprising tumor suppressive function of NF- B in cancer-associated fibroblasts (CAFs). In the absence of NF- B signaling, TGF signaling in CAFs is enhanced and leads to enhanced secretion of HGF, which acts on tumor and stem cells, vascular cells and T cells (Pallangyo et al., J Exp Med., 2015)

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Modulation der Ligand-Rezeptor-Interaktionen von Immunzellen

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Modulation of ligand-receptor interactions of immune cells

natural killer cells

receptor-ligand interaction

cancer immunotherapy

The immune system of vertebrates is comprised of two branches: the innate and the adaptive immune response. Components of the innate immune response, such as toxic peptides, macrophages, and natural killer (NK) cells, respond to pathogens within seconds or minutes in order to confine and defeat infections and cancer cells before their manifestation or while the adaptive immune response establishes. Consequently, patients with NK cell deficiency suffer from life-threatening systemic infections. Epidemiological studies showed that high activity of peripheral blood NK cells is associated with a 10% lower incidence of tumors for men and 4% for women. Moreover, NK cell infiltration into tumors is associated with better disease prognosis in non-small cell lung carcinoma, clear cell renal cell carcinoma and colorectal cancer. NK cell cytotoxicity is regulated by a dynamic balance of signals from several germ line-encoded inhibitory and activating surface receptors. Activation of NK cells to kill infected or tumor cells depends on the predominance of signals from the major activating NK cell receptors, NKG2D and the so called natural cytotoxicity

Die Komponenten des angeborenen Immunsystems, wie z. B. toxische Peptide, Makrophagen und natürliche Killerzellen (NK Zellen), reagieren auf Pathogene innerhalb von Sekunden bis Minuten, um Infektionen und Krebszellen einzudämmen bzw. zu bekämpfen, bevor sie sich manifestieren können, oder aber die erworbene Immunantwort sich etabliert hat. NK Zellen vermitteln durch Integration einer Vielzahl von Signalen ihrer inhibitorischen und aktivierenden Rezeptoren zwischen dem angeborenen und dem erworbenen Immunsystem.

Die Aktivierung von NK Zellen zur Zerstörung von virusinfizierten Zellen oder Tumorzellen hängt von der Vorherrschaft aktivierender Signale durch die zentralen humanen aktivierenden NK Zellrezeptoren, als Bestandteil einer komplexen immunologischen Synapse zwischen der NK Zelle und der entsprechenden Zielzelle, ab. Die molekularen Details der Wechselwirkung zwischen diesen aktivierenden NK Zellrezeptoren und ihren Liganden z. B. auf der Oberfläche von Tumorzellen sind weitestgehend unbekannt. Darüber hinaus haben Viren und Tumorzellen vielfältige Mechanismen entwickelt um einer Immunüberwachung und Zerstörung durch NK Zellen zu unterbinden. Unser Fokus liegt daher auf der biochemischen und zellbiologischen Analyse dieser Rezeptor-Ligand Systeme.

Ergebnisse aus diesen Studien leisten einen großen Beitrag zu unserem Verständnis der frühen angeborenen Immunantwort gegenüber Tumorzellen und virusinfizierten Zellen. Darüber hinaus bilden diese Erkenntnisse die Grundlage für eine zielgerichtete Modulation der Aktivität von NK Zellen und der Verbesserung der Effizienz von Zelltherapien durch die Überwindung der von Viren und Tumorzellen angewendeten Immune-Escape-Mechanismen.

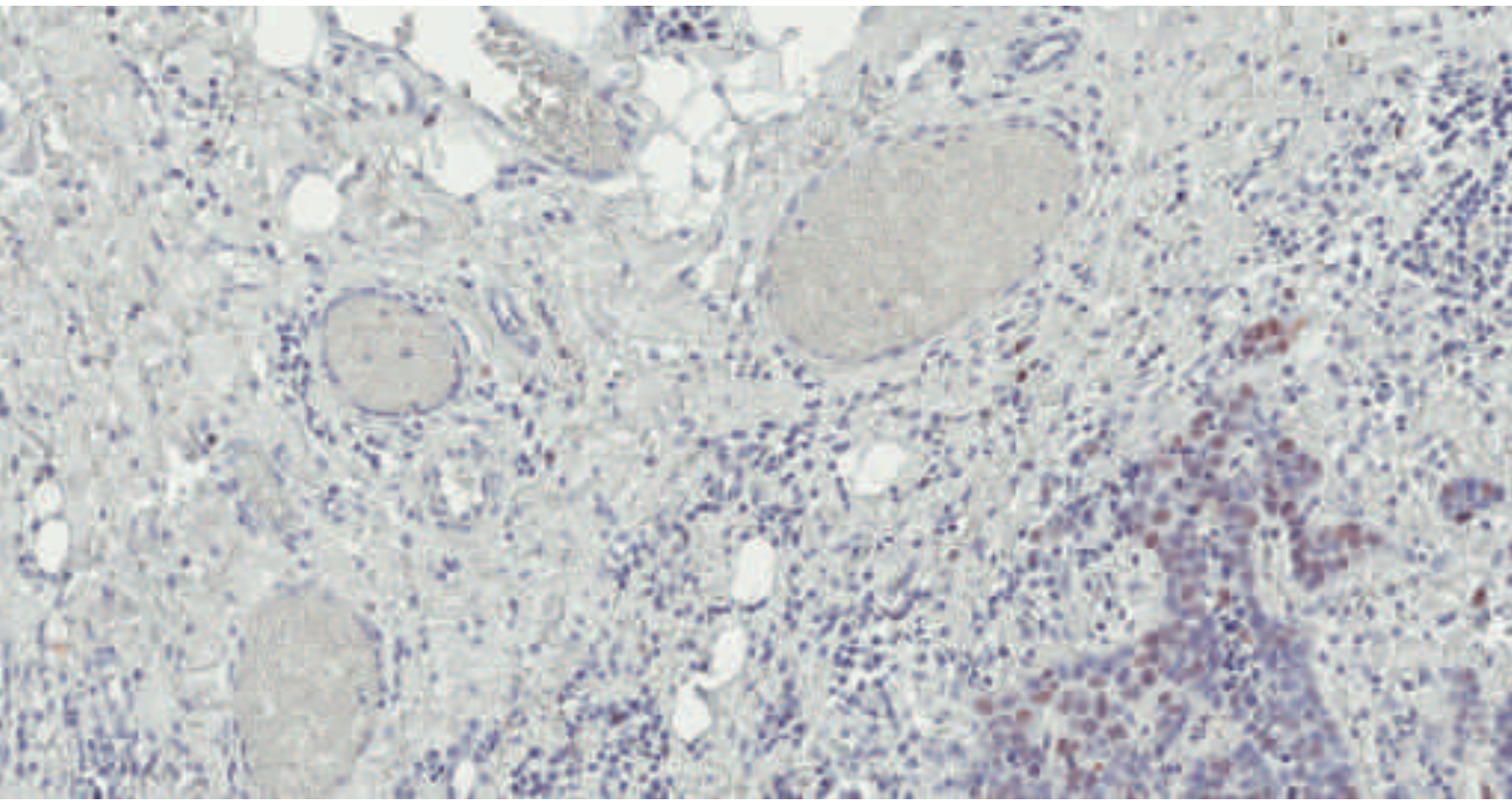
receptors (NCRs). Whereas eight different cellular ligands (MICA, MICB, ULBP1-6) have been described for NKG2D, only little is known about the cellular ligands of NCRs. Notably, these ligands can either be constitutively expressed or upregulated/induced upon virus infection or malignant transformation. By contrast, several viruses and tumors employ mechanisms to inhibit signaling of activating NK cell receptors and thus NK cell cytotoxicity in order to persist within the host. Therefore, we aim to understand how NK cells recognize virus-infected and especially tumor cells. Moreover, we are interested in the elucidation of immune escape strategies of viruses and tumor cells in order to develop strategies to interfere with these mechanisms and to support the host's immune response.

Restoration of tumor escape from immunosurveillance by NK cells

Head and neck squamous cell carcinoma (HNSCC) is a highly aggressive solid tumor originating from the epithelial lining of the upper aero-digestive tract with approximately 600,000 patients per year worldwide. Current therapeutic regimens for patients with HNSCC combine chemotherapy, radiotherapy and surgery with 5-year survival rates of 30–65% and 5–58% for the tumor stages T1–T4 and N0–N3, respectively. Prognosis remains poor due to (i) decreased leukocyte numbers, (ii) impaired proliferation of leukocytes, (iii) increased numbers of regulatory T cells, which are immunosuppressive to T cells, natural killer (NK) cells and NK-T cells, and iv) inhibition of cytotoxicity of immune cells such as NK cells by soluble inhibitors of activating receptors. Impaired immune cell function in HNSCC tumors is associated with establishment of an immunosuppressive tumor microenvironment.

We could show that the plasma of HNSCC patients contains high levels of soluble NKG2D ligands which accumulate after release from the surface of tumor cells by specific proteases (ligand shedding, FIGURE 1 A). Ligand shedding leads to multiple biological effects: i) a lower number of ligands is available on the tumor cell which could attract/activate NK cells, ii) soluble ligands bind to NKG2D on the NK cell surface and occupy its binding site without activation of the NK cell, thus preventing ligand recognition on the tumor cell surface, and iii) soluble ligands trigger the internalization and destruction of NKG2D/ligand complexes leading to a reduced number of NKG2D receptors on the NK cell surface and hence to decreased NK cell cytotoxicity.

Based on in vitro cytotoxicity experiments with primary human NK cells, we could show that depletion of soluble NKG2D ligands from patients' plasma restores NK cell cytotoxicity (FIGURE 1B).
In order to overcome this tumor immune escape mechanism in HNSCC patients, we currently develop a procedure to remove soluble NKG2D ligands from patients' plasma as a preconditioning prior to immunotherapy with cytotoxic lymphocytes such as donor NK cells or



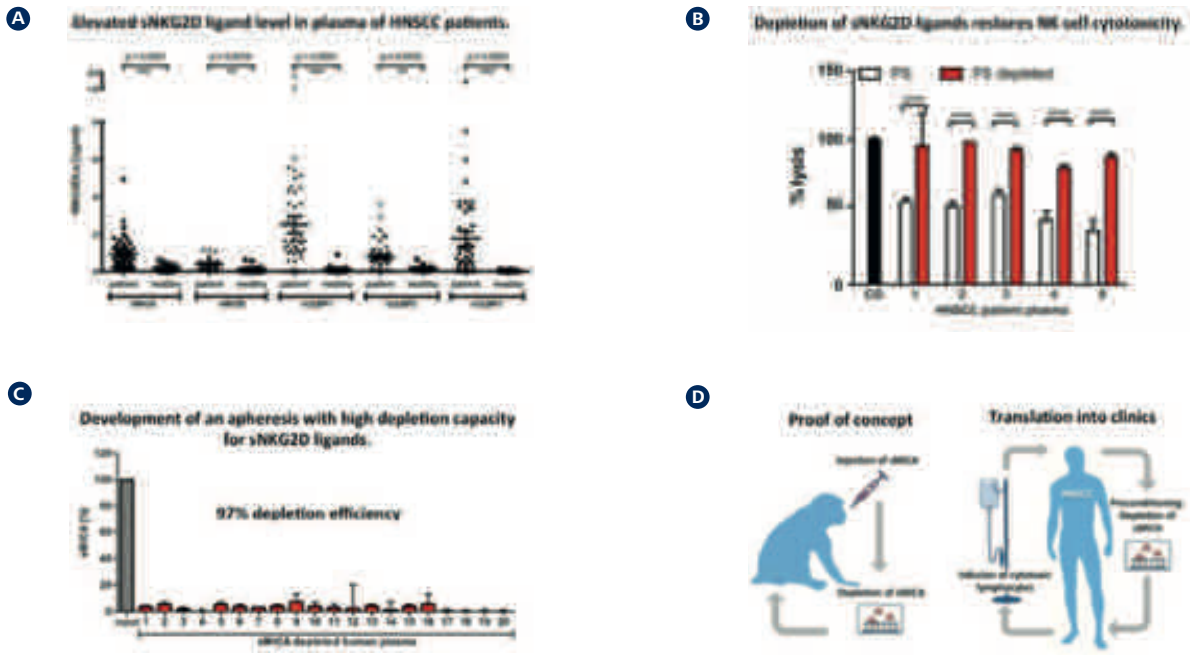
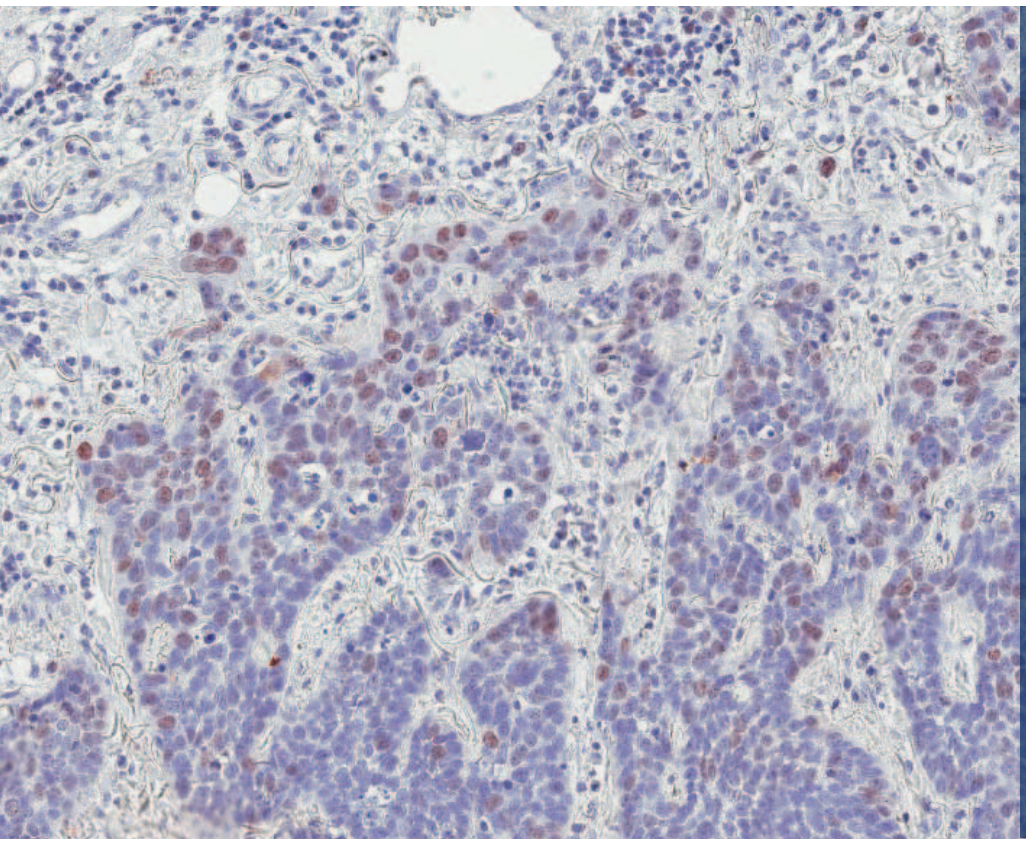


Figure 1.
Investigation and compensation of NKG2D-dependent tumor immune escape in HNSCC patients.
A Elevated plasma levels of sMICA, sMICB and sULBP1-3 were found in 44 HNSCC patients compared to plasma of 12 age-matched healthy controls.
B Cytotoxicity of primary human NK cells against tumor cells was inhibited by pre-incubation of NK cells with HNSCC patients' plasma containing high soluble NKG2D (sNKG2D) ligand levels (PS) compared to plasma of healthy controls (CO). Specific depletion of soluble NKG2D ligands from patients' plasma could restore NK cell cytotoxicity (PS depleted).
C Plasma of 20 healthy donors was supplemented with purified sMICA. Depletion of sMICA with an anti-MICA antibody coupled to magnetic beads showed an efficiency of 97%.
D Schematic overview of the pre-clinical validation of the adsoption apheresis in a rhesus macaque model (proof of concept) and the clinical setup combining the apheresis with immunotherapy in HNSCC patients (translation into clinics).



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*corresponding author, Cover Illustration

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NK cells or T cells functionalized with tumor antigen-specific chimeric antigen receptors (CAR-NK or CAR-T cells). For this approach, we have developed a biofunctionalized surface, which allows for quantitative removal of soluble NKG2D ligands from human plasma (FIGURE 1C). As a proof of concept, the surface was coated with a MICA-specific antibody, for future therapeutic application, we have developed a pan-specific adsorber which is functionalized with the ectodomain of the NKG2D receptor. In in vitro experiments, both surfaces allowed for quantitative removal of either sMICA or all soluble NKG2D ligands at the same time. In order to validate our adsorber in a pre-clinical setting, we have initiated adsorbtion apheresis studies in rhesus macaques at the German Primate Center in Göttingen. In a first line of experiments, we have investigated the body distribution, plasma stability and immunocompatibility of human sMICA in rhesus macaques. Based on our results, human sMICA is well tolerated in the rhesus macaques without any adverse effects. In a next step, we will now employ adsorbtion apheresis in order to investigate the efficacy of plasma depletion of NKG2D ligands with our adsorbtion matrix (FIGURE 1D).

The research group of Prof. Dr. Joachim Koch is supported by grants from the Deutsche Forschungsgemeinschaft, the HIVERA program of the European Community, the Wilhelm-Sander Stiftung, the LOEWE excellence centre for Cell and Gene Therapy (LOEWE-CGT), the Robert Willy Pitzer Stiftung, the Alfons und Gertrud Kassel-Stiftung, the Research support Foundation (Vaduz), and the Hessische Vereinigung zur Förderung der Jugendgesundheitspflege e. V.. Moreover, we are grateful for the fruitful collaboration with Prof. Dr. Ulrike Köhl (MHH Hanover), Prof. Dr. Alexander Steinle (KGU Frankfurt), Prof. Dr. Michael von Bergwelt-Baildon (University Clinics, Cologne), Prof. Dr. Lutz Walter (DPZ Göttingen), and Miltenyi Biotec (Bergisch Gladbach).

Die Rolle des Knochenmarksmikromilieus bei den Leukämien

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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 against haematological malignancies. This is important, as the overall survival rate for all leukaemias in adults is only 44% and leukaemic stem cells are rarely eradicated. Eradication of cancer stem cells or leukaemia stem cells in leukaemia, however, is important for cure of a cancer.

In fact, we have previously shown that modification of the BMM by the naturally occurring hormone parathyroid hormone (PTH), the most potent regulator of bone, led to a 15 fold reduction of leukaemic stem cells in chronic myelogenous leukaemia (CML) and a differential effect on two myeloid leukaemias, CML and acute myeloid leukaemia (AML) (Krause DS et al., Nat Med, 2013). Based on this work we are in the process of initiating a clinical trial in collaboration with the Medical Clinic for Haematology/Oncology of the Goethe University in Frankfurt, the University Cancer Center, other German centers and pharmaceutical companies. In this trial we intend to augment the therapy of patients with CML who have

Trotz verbesserter Therapien, z.B. in Form von Tyrosinkinaseinhibitoren, 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.
Wie bereits von uns und anderen Gruppen publiziert, kann eine gezielte Modulation des Knochenmarksmikromilieus (KMMM), dem Ort, wo eine Leukämie entsteht und voranschreitet, eine Verringerung von leukämischen Stammzellen nach sich ziehen. Dies ist notwendig, denn leukämische Stammzellen können zu Therapieresistenz und Krankheitsrückfall führen. Das KMMM, welches leukämische Stammzellen vor der Chemotherapie „beschützen" kann, besteht aus verschiedenen Zelltypen wie Osteoblasten, Osteoklasten, mesenchymale Stammzellen, Endothelzellen, und der exrazellulären Matrix.

Wir testen experimentell, durch welchen Mechanismus eine Blockade eines auf Endothelzellen exprimierten Proteins, E-Selektin, das Überleben von leukämischen Stammzellen beeinträchtigt und wie die Lokalisation von leukämischen Stammzellen innerhalb des KMMMs und ihre spezifische Interaktion mit dem KMMM den Krankheitsverlauf einer Leukämie beeinflussen kann. In enger Kollaboration mit der Medizinischen Klinik für Hämatologie/Onkologie des Klinikums der Goethe Universität haben wir eine sich direkt aus den Ergebnissen der Laborforschung ergebende klinische Studie initiiert, die die Modulation des KMMMs bei der chronisch myeloischen Leukämie zum Ziel hat und, zumindest am Mausmodell, zu einer Verringerung der leukämischen Stammzellen geführt hat.

had a suboptimal response to a tyrosine kinase inhibitor with PTH, in order to test, if modification of bone can lead to a suppression of leukaemic stem cells in CML also in humans. Ancillary studies in which we will assess the effect of PTH treatment on bone turnover, normal haematopoiesis and signaling pathways in leukaemic stem cells will be performed in the laboratory. This work is very exciting to us, as it represents the translation of bench research into the clinic in a quest to develop new therapies – a path we also hope to go down for other new discoveries in our laboratory.

In other work in our group we are looking at how a leukaemia interacts with its BMM, how it modulates the BMM and how it is altered by the BMM itself. Once such intricate relationships are understood from different (patho-)physiological perspectives, we hope to find novel pathways to interfere with these specific interactions in order to impede leukaemic growth. One such perspective is to understand the interaction of leukaemia cells with the vascular niche, which consists of the rich sinusoidal structures in the BMM,

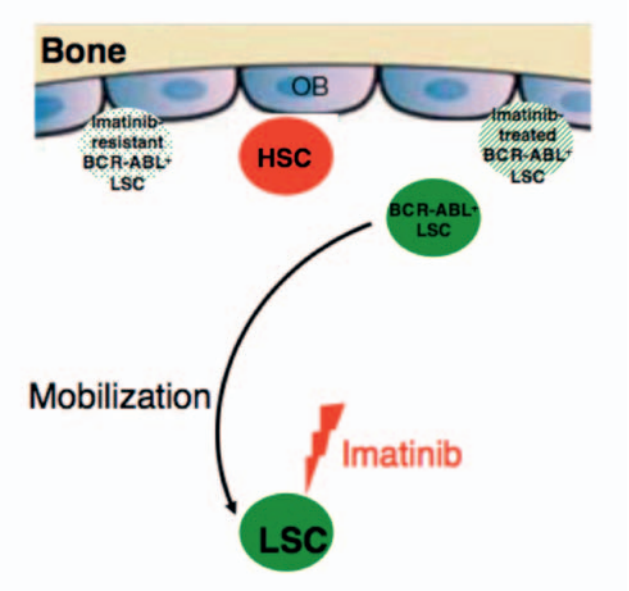
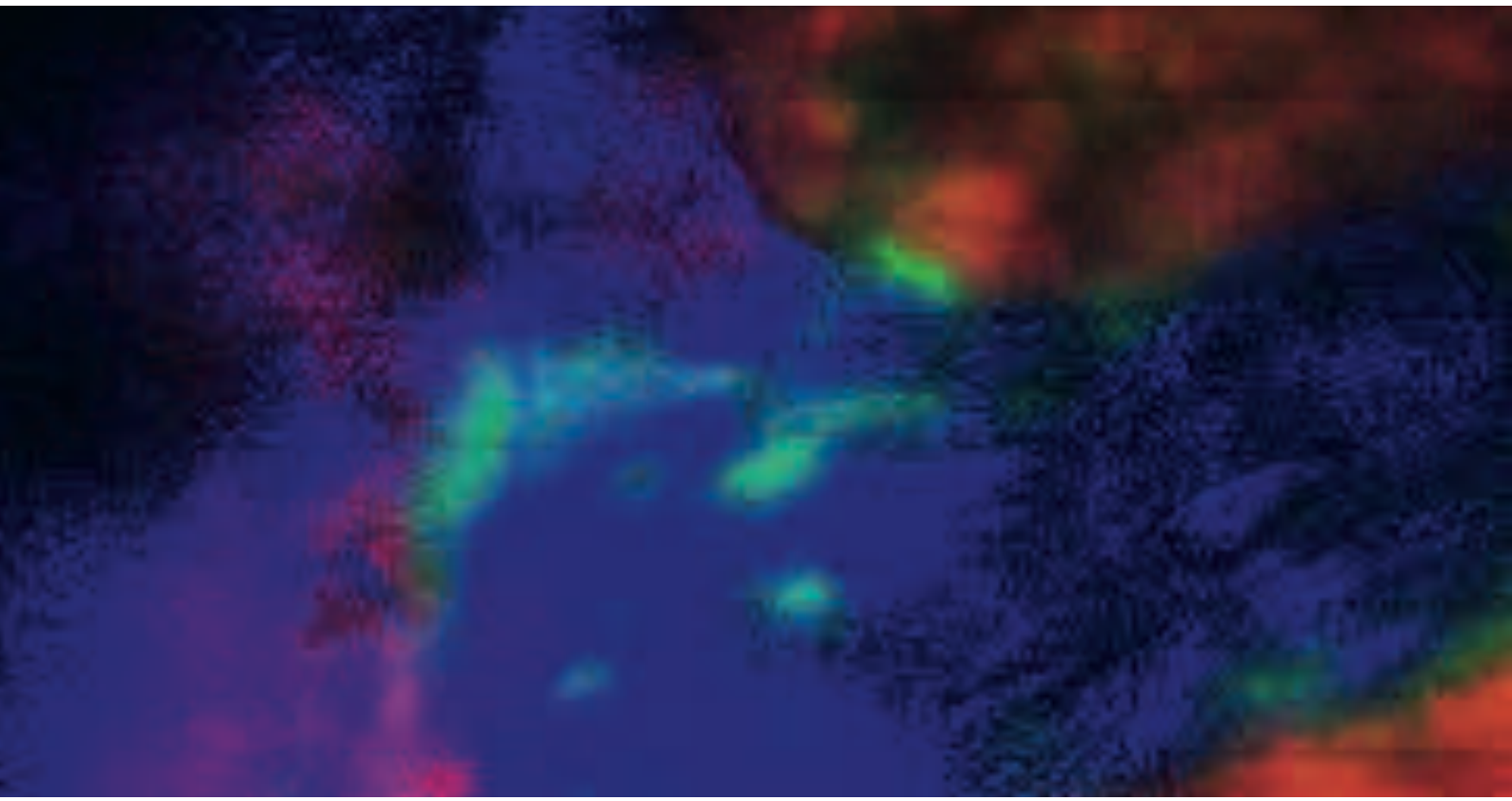


Figure 1.
Schematic showing the relation of distances of normal haematopoietic stem cells (HSC) (red), BCR-ABL1+ leukaemic stem cells (LSC) (green), imatinib-treated BCR-ABL1+ leukaemic stem cells (striped green) and an imatinib-resistant BCR-ABL1+ LSC (dotted green) to the endosteum. Mobilization of a BCR-ABL1+ leukaemic stem cell out of the niche by granulocyte colony stimulating factor led to more efficient eradication.

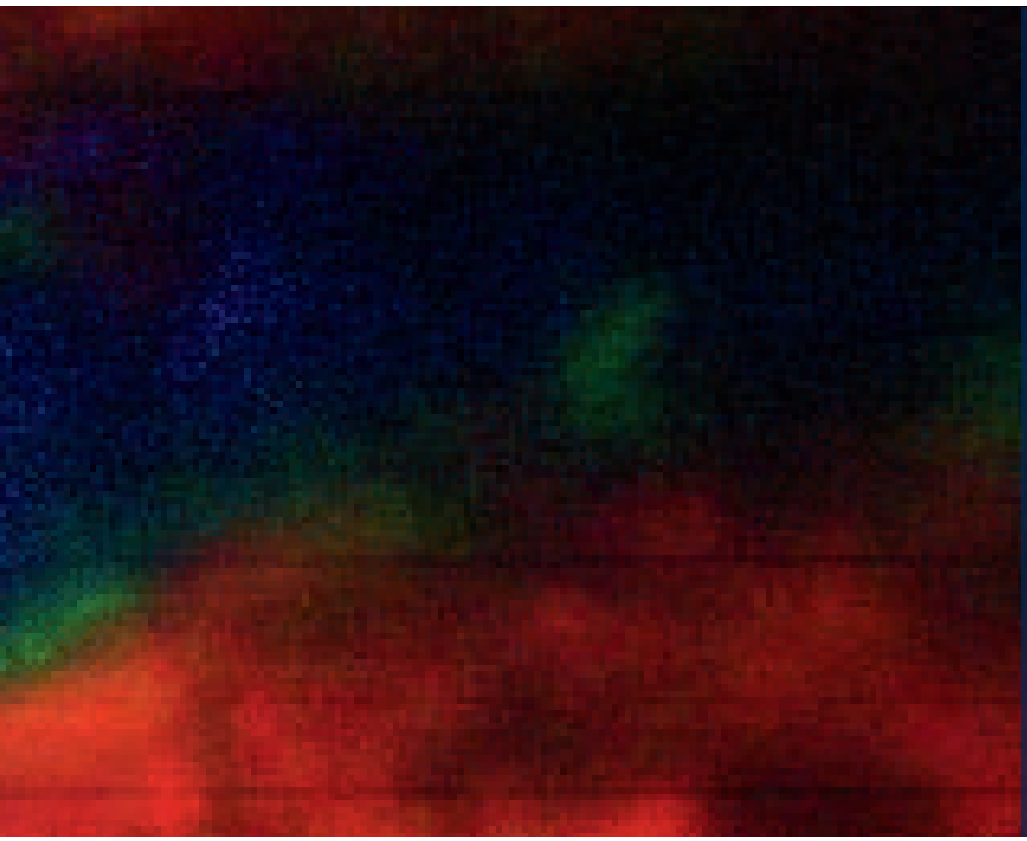


endothelial cells, pericytes and other accompanying cell types. We and others have shown for example that CD44, a type I transmembrane protein binding to hyaluronan, osteopontin and possibly E-selectin, and selectins and their ligands are mediators between leukaemic stem cells and their BMM in AML and CML (Krause DS et al, Nat Med, 2006, and Krause DS et al, Blood, 2014). These interactions establish contact points for leukaemia cells with their BMM. In collaboration with Glycomimetics Inc. and the Lausen group at the Georg-Speyer-Haus we are now testing the effect of inhibition of E-selectin on leukaemic growth in in-vitro and in-vivo assays, which is providing interesting and promising results.

Another focus of the laboratory is the analysis of the microanatomy of the leukaemic BMM by in-vivo 2-photon microscopy in collaboration with Prof. Stefanie Dimmeler. Preliminary data has shown that leukaemia-initiating cells in CML home to locations significantly further away from bone than normal haematopoietic stem cells. Interestingly, when these leukaemia-initiating cells are in-vitro treated by a tyrosine kinase inhibitor such as imatinib, this difference in location is reversed and the leukaemia-initiating cells are now found closer to bone. A point mutation in the kinase domain of the ABL protein, one of the fusion partners forming the oncogene BCR-ABL1, a hallmark of CML, leads to the leukaemia-initating cells being found close to the endosteum (Figure 1). As patients with such an imatinib-resistant mutation frequently experience a more aggressive clinical course of their CML, it is possible that these and other preliminary data we have may suggest that location in the niche may influence the clinical course of a leukaemia. We are currently aiming at deciphering the possible mechanism for this phenomenon.

We are very happy to be involved with the role of the transcriptional regulator Far upstream element-binding protein 1 (FUBP1) and its role in the development of leukaemia in a productive collaboration with the Zörnig Group, a project recently funded by the Sander Foundation.

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.



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*co-first authorship

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Die Rolle der Knochenmarksnische bei Myelodysplastischen Syndromen und myeloider Leukämie

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Role of the Bone Marrow Microenvironment in Human Myelodysplasia and Acute Leukemia

Bone marrow niche

Cellular crosstalk

Patient-derived xenografts

Our research interrogates the complex biology of hematologic malignancies by investigating both intrinsic and extrinsic mechanisms that control the fate of the stem cells responsible for disease propagation. Increasing evidence suggests that genetically altered "leukemic stem cells" (LSCs) actively engage in crosstalk with niche cells present in the bone marrow microenvironment and often are responsible for primary resistance to treatment and/or subsequent relapse. In addition, we and others, have also shown that diseased hematopoietic cells are able to provide instructive signals that "hijack" the microenvironment and convert it into a "self-reinforcing" one (Figure 1) (Schepers, Cell Stem Cell, 2013; Medyouf, Cell Stem Cell, 2014).

This implies that identifying and targeting the signals involved in this bi-directional crosstalk between niche and LSCs could possibly represent an attractive novel therapeutic option to limit this niche support and subsequently hamper the growth of the malignant stem cells, thereby improving patient outcome.

Myelodysplastische Syndrome (MDS) bilden eine heterogene Gruppe hämatologischer Erkrankungen, die von blutbildenden Stammzellen des Knochenmarks ausgehen, und die durch eine unzureichende Bildung reifer Blutzellen charakterisiert sind. Vor allem ältere Menschen sind betroffen. MDS können sich fortschreitend verschlechtern und zum Versagen des Knochenmarks führen. Etwa 30% der Betroffenen entwickeln eine sekundäre akute myeloische Leukämie (sAML), die besonders schwierig zu behandeln ist. Die aktuellen Therapiemöglichkeiten sind sehr begrenzt und beeinflussen nicht den Verlauf der Krankheit. Neue therapeutische Strategien werden daher dringend benötigt, um der wachsenden Herausforderung durch MDS in unserer alternden Gesellschaft zu begegnen.

Meine Arbeiten haben kürzlich gezeigt, dass die zelluläre Mikroumgebung im Knochenmark, die so genannte Knochenmarksnische, eine entscheidende Rolle bei der Pathogenese von MDS spielt. Mesenchymale Nischenzellen bilden ein Gerüst, in dem sich die blutbildenden Zellen entwickeln können. Unsere Arbeiten ergaben, dass ein komplexer Signalaustausch zwischen den erkrankten hämatopoietischen Zellen und ihren benachbarten Nischenzellen stattfindet. Mesenchymale Nischenzellen von MDS Patienten zeigen eine Reihe von molekularen Veränderungen, die wahrscheinlich zum Krankheitsbild beitragen. Andererseits können prä-leukämische MDS Zellen ihrerseits ihre Nische verändern und eine MDS Stammzellnische etablieren, die nun statt der normalen Blutbildung das Fortschreiten der Krankheit fördert.

Eines der Hauptziele unserer Nachwuchsgruppe ist es, die Moleküle zu identifizieren, die diesen Signalaustausch vermitteln. Potenzielle Möglichkeiten, in die Interaktion zwischen Nische und hämatopoietischen Zellen einzugreifen, sind bisher kaum untersucht. Sie stellen eine sehr attraktive und neuartige Möglichkeit dar, die Nischenfunktion insbesondere bei MDS therapeutisch zu beeinflussen.

To achieve these goals, we carry out integrative "omics" approaches, using primary patient-derived samples, and subsequently evaluate the functional relevance of our findings using in vitro co-culture systems, as well as our extensive expertise in in vivo modeling of human diseases using syngeneic models (Medyouf, Nat. Med, 2007; Medyouf, Blood, 2010; Medyouf, JEM, 2011) and patient-derived xenografts (Gerby, Leukemia, 2010; Medyouf, Cell Stem Cell, 2014). This highly translational work partially relies on clinically well-characterized primary samples, which are readily available through our well-established collaborations with several local, national and international clinical experts.

Background on the disease entities studied in our group

In terms of disease entities, our group primarily focuses on myelodysplastic syndromes (MDS) and related acute myeloid leukemia (AML). However, we also have a long-standing interest in an aggressive type of lymphoid disease, which accounts for 15% of all newly diagnosed cases of childhood acute lymphoblastic leukemia (ALL), namely T-cell ALL. MDS are frequent malignant bone marrow

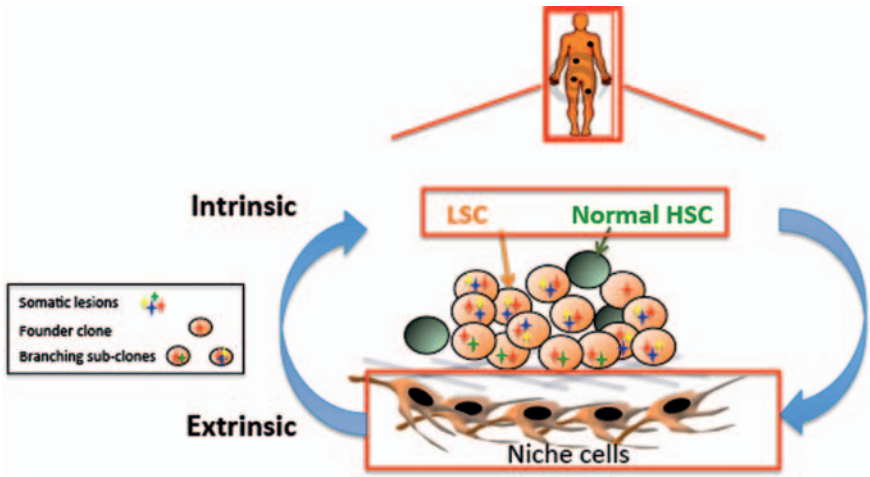
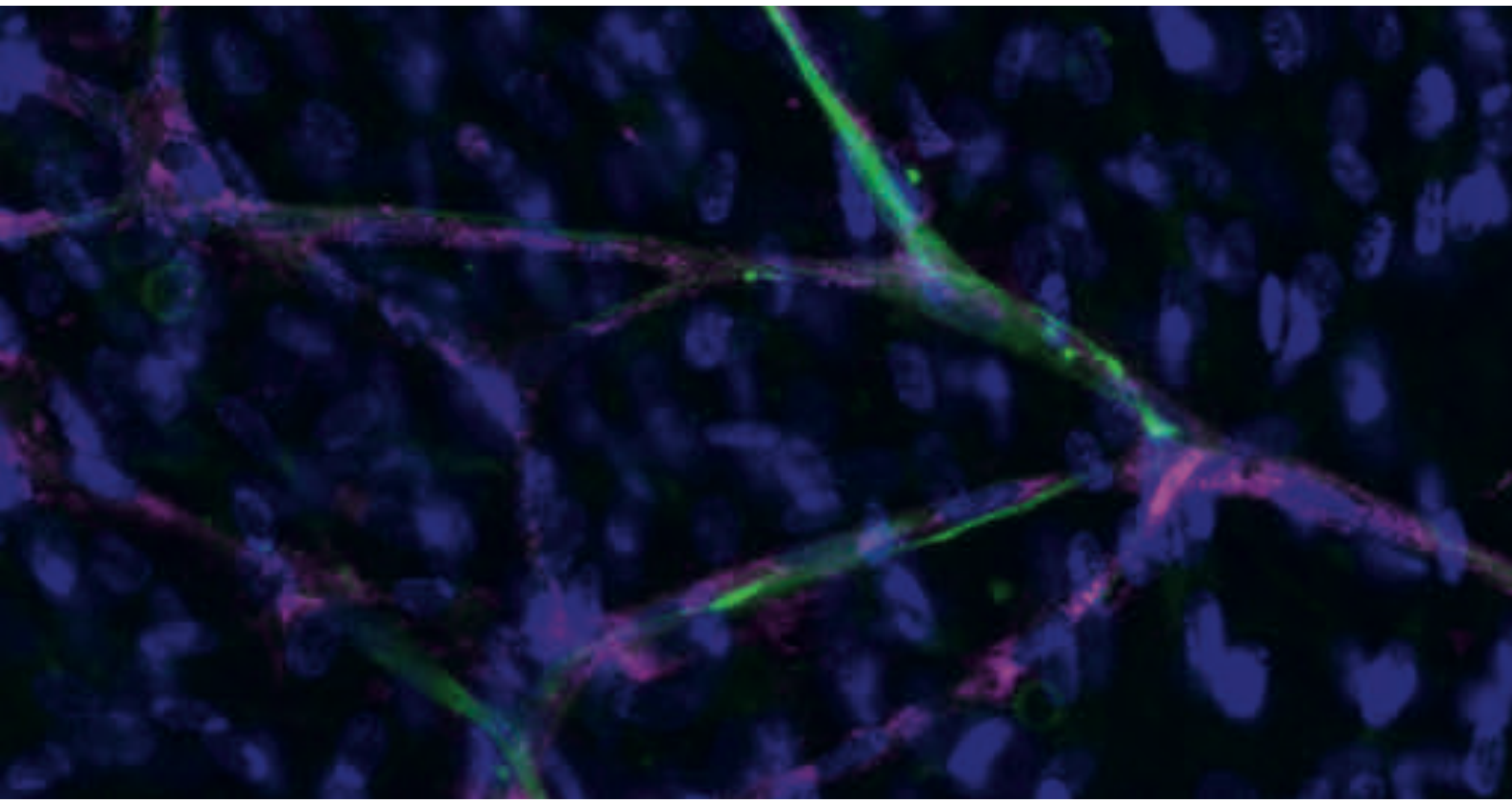


Figure 1.
Schematic view of the research program



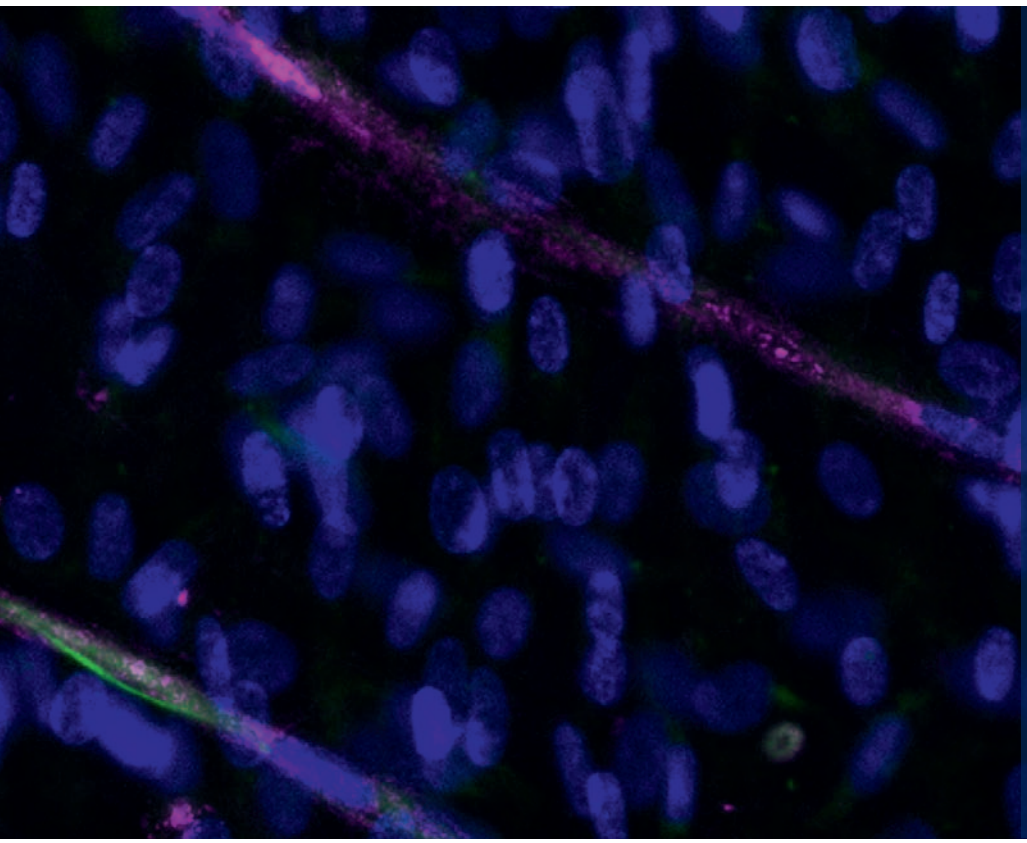
disorders of the elderly with limited treatment options and a high risk of progression to acute myeloid leukemia that are characterized by an aggressive course. These syndromes are characterized by the ineffective production of mature blood cells. As such, most MDS patients rely on frequent blood transfusions. Beyond hematopoietic stem cell transplantation, no treatment is able to alter the natural course of this disease. Likewise, T-ALL treatment is primarily based on highly toxic intensive chemotherapy, with limited options for children with primary resistance or relapse. Of note, relapse occurs in one quarter of childhood T-ALL patients within 5 years of treatment and the prognosis is dismal. Importantly, niche-derived signals have been proposed to contribute to the emergence and/or maintenance of these disease entities (Pitt, Cancer Cell, 2015; Medyouf, Nat. Med, 2007; Medyouf, JEM, 2011; Medyouf, Cell Stem Cell, 2014; Raaijmakers, Nature, 2010), thereby suggesting that niche targeting strategies could bear the potential of improving patient outcome.

Exploring the importance of niche-derived factors in human MDS

Our current work in MDS is interrogating several niche-derived factors, involved in inter-cellular crosstalk, which we have previously identified to be recurrently deregulated in patient-derived mesenchymal niche cells (Medyouf et al., Cell Stem Cell, 2014). Our preliminary data indicate that targeting some of these niche-derived factors in our established co-culture model system indeed has an impact on the growth of primary MDS cells, in particular when looking at the CD34+ stem cell enriched fraction. We are currently following up on these promising inhibitor studies using state-of-the-art genetic tools (CRISPR/CAS) combined with in vivo experiments using both newly generated mouse models (collaboration with Omar Abdel-Wahab, MSKCC) and our previously described niche-dependent xenograft models of MDS. Our overarching goal is to carry out pre-clinical studies using highly relevant in vivo models that could subsequently pave the way to the design of new clinical trials.

Exploring the importance of somatic mutations in human MDS

It is well-known that the clinical course and phenotypic manifestations of MDS are highly variable. In addition to the role of the microenvironment, this diversity is likely to be contributed to by the complex genetic make-up observed in each individual patient. Indeed, MDS patients have been shown to carry a plethora of somatically acquired mutations that occur in diverse combinations and recurrently affect genes involved in important cellular processes (Haferlach, Leukemia, 2014). In particular, our recent collaborative effort with the group of Prof. W-K Hofmann (Mannheim University Hospital, Germany) has allowed us to precisely define patient-specific mutational trajectories leading to MDS development, thereby highlighting the existence of both linear and branching paths leading to clonal evolution. These events further enhance the over-all patient specific clonal heterogeneity and likely contribute to the tremendous variation observed in terms of clinical manifestations. Most importantly, this work also demonstrated that therapeutic resistance is frequently due to the incom-



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plete clearance of specific subclones, which acquire additional abnormalities that further drive disease progression (Mossner and Medyouf, submitted).

Follow-up work on this topic is now focusing on experimentaly defining the relationship between specific genotypes and phenotypic manifestations, as well as using our patient-derived insight into mutational trajectories to build up mouse models that more faithfully recapitulate different stages of the human disease, which will be invaluable to study the cell intrinsic and extrinsic events leading to MDS progression. Importantly, our data on therapeutic resistance also raise the possibility of a cell-extrinsic contribution through a niche-mediated selective protection of specific MDS subclones, which will be investigated in the future work of my group.

Role of IGF signaling in normal and leukemic stem cells

In addition to our ongoing studies on MDS, my previous work on T-ALL revealed that the insulin-like growth factor pathway plays an essential role in the activity of T-ALL LSCs, and that its therapeutic targeting could be beneficial for T-ALL patients (Medyouf, JEM 2011). This key longevity pathway has also been involved in AML pathogenesis and is currently being interrogated by our group as a potential therapeutic target in MDS. There is, however, only a limited amount of literature directly addressing the role of this signaling axis in normal hematopoiesis. In particular, no study has evaluated the consequences of lowering IGF signaling on primitive self-renewing hematopoietic stem cells in particular in the context of exposure to other therapeutic agents such as chemotherapy. Indirect evidence obtained in the context of dietary restriction settings seem to suggest that lowering systemic IGF levels may increase the fitness of normal HSCs, while other reports rather point to an essential role of the IGF axis in the maintenance of self-renewal potential, both in ES cells and human hematopoietic stem cells.

Our group is currently using well-defined genetic mouse models (collaboration Martin Holzenberger, Paris, France) as well as transplantation assays and in vivo drug combination therapies to evaluate the impact IGF1R targeting would have on normal versus leukemic stem cells.

Conclusion

Because of the pivotal role of niche cells and niche-derived factors in the control of stem cell function, as well as the possible similarities between LSCs and normal HSCs, we believe that deciphering the complex interplay between niche and hematopoietic cells in normal and disease contexts will allow us to propose new strategies to specifically dampen the niche support towards malignant cells while possibly improving the support towards normal HSCs.

Our work is currently supported by a starting grant from the European Research Council and a José Carerras Career Award.

Immuntherapie maligner Erkrankungen

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Immunotherapy of malignancies

chimeric antigen receptors

natural killer cells

adoptive cancer immunotherapy

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 Fv (scFv) antibody fragment connected via a flexible spacer and a transmembrane domain to intracellular signaling domains such as CD3ζ chain (first-generation CARs) or CD3ζ together with one or more costimulatory protein domains (second- and third-generation CARs). Optimized CARs combined with improved retro- and lentiviral vectors for gene transfer have yielded genetically modified effector cells with potent antitumoral activity and the ability to persist in vivo. This has been successfully demonstrated in recent years by different groups for CD19-specific CAR-modified T cells that induced durable remissions in patients with malignancies of B-cell origin. Natural killer (NK) cells represent another valuable effector cell population for adoptive cancer immunotherapy, but experience with CAR-engineered NK cells is still limited. NK cells are part of the innate immune system and play an important role in

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 virusinfizierter und maligner Zellen spielen. Durch Expression sogenannter chimärer Antigenrezeptoren (CAR) generieren wir mittels lentiviralem Gentransfer genmodifizierte NK-Zellen, die Tumorzellen selektiv abtöten. Chimäre Antigenrezeptoren 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. Zielantigene sind hierbei tumorassoziierte Oberflächenantigene wie zum Beispiel der epidermale Wachstumsfaktor-Rezeptor EGFR und das verwandte ErbB2/HER2 Protein, das Adhäsionsmolekül EpCAM, das Gangliosid GD2 und Differenzierungsantigene wie CD19 und CD20. Gegenwärtig entwickeln wir in enger Kooperation mit akademischen Partnern am Standort Frankfurt eine ErbB2/HER2-spezifische Variante der klinisch einsetzbaren humanen NK-Zelllinie NK-92 für klinische Anwendungen. Daneben verfolgen wir ähnliche Ansätze basierend auf ex vivo expandierten, genmodifizierten primären Lymphozyten aus dem peripheren Blut, sogenannten Zytokin-induzierten Killerzellen.

cancer immunosurveillance. Unlike T cells, they do not require prior sensitization and recognition of peptide antigens presented in complex with MHC molecules. Instead, their cytotoxicity is triggered rapidly upon appropriate stimulation through germline-encoded cell surface receptors. In cancer patients NK cells, like other immune cells, are often functionally compromised due to the immunosuppressive activity of the tumor. Hence, for adoptive cancer immunotherapy donor-derived allogeneic NK cells are being preferred since they do not recognize tumor cells as 'self', thereby bypassing inhibitory signals.

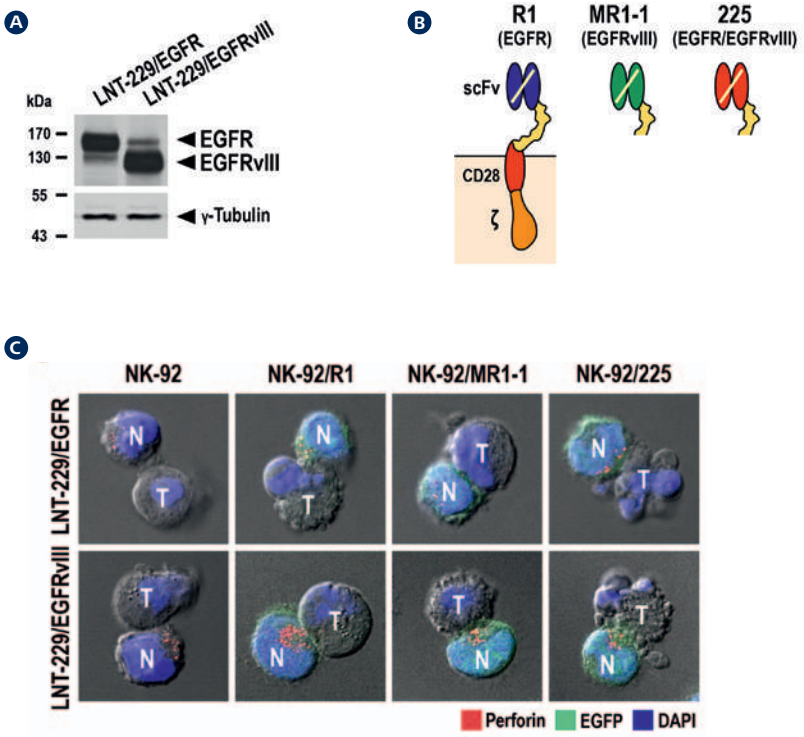
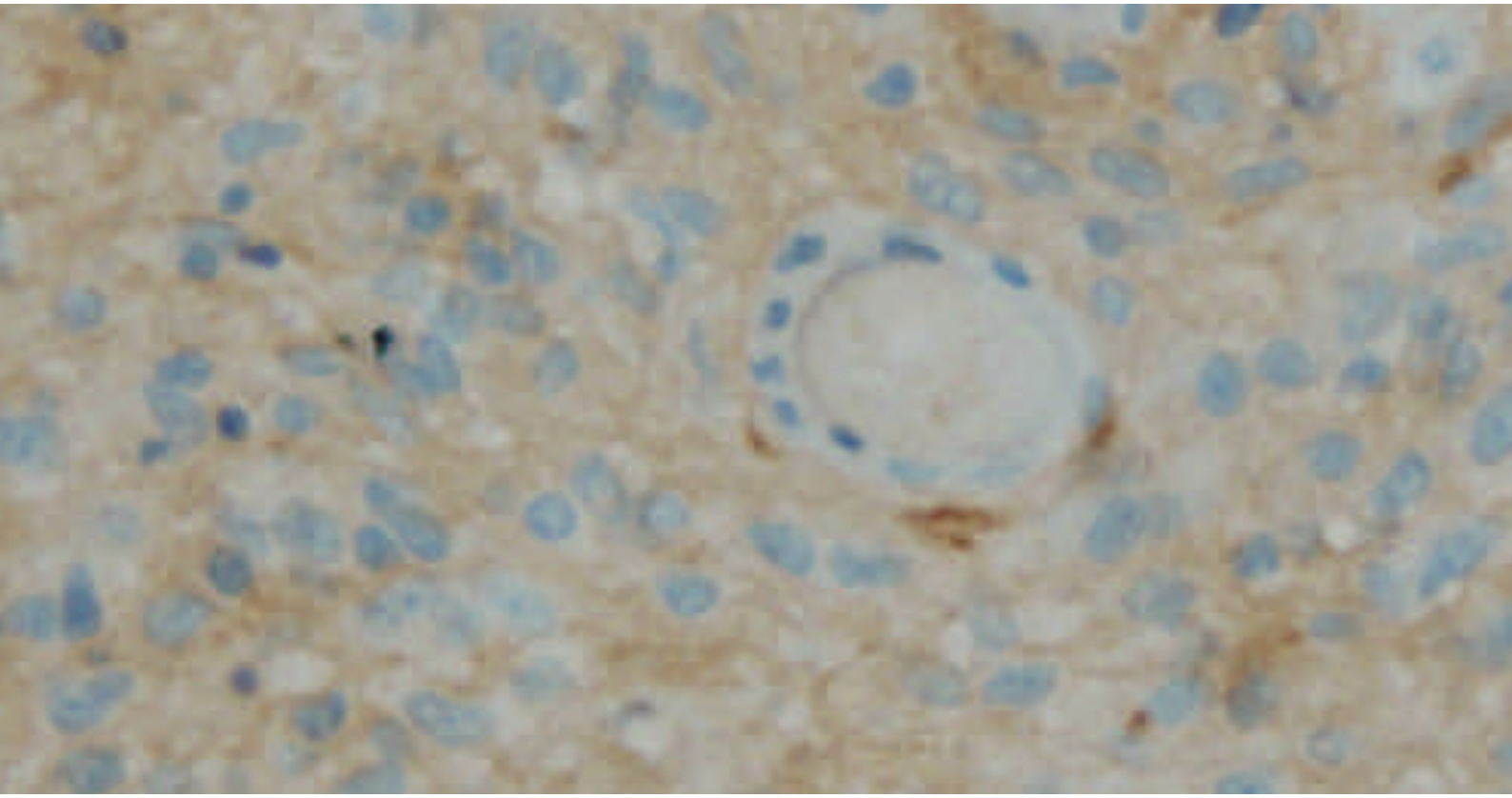


Figure 1.
Targeted cytotoxicity of CAR-engineered natural killer cells.

A Expression of the tumor-associated antigen EGFR and its mutant form EGFRvIII in LNT-229/EGFR and LNT-229/EGFRvIII glioblastoma cells.

B NK-92 cells specifically recognizing EGFR, EGFRvIII or both antigens were derived by transduction with lentiviral vectors encoding chimeric antigen receptors that harbor scFv antibody fragments binding to epitopes unique to EGFR (R1) or EGFRvIII (MR1-1), or an epitope present in both target receptors (225), in each case fused to CD28 and CD3ζ signaling domains.

C After contact of the CAR-expressing NK cells (N) with target tumor cells (T), cytotoxic granules that contain perforin and granzymes are oriented towards the immunological synapse and release their content into the synaptic cleft. This results in target cell death by apoptosis indicated by membrane blebbing and disintegration of the nucleus. While parental NK-92 cells were unable to induce tumor cell death, CAR NK cells targeted to EGFR and/or EGFRvIII rapidly triggered lysis of glioblastoma cells expressing the respective tumor antigens.



Tumor-specific natural killer cells

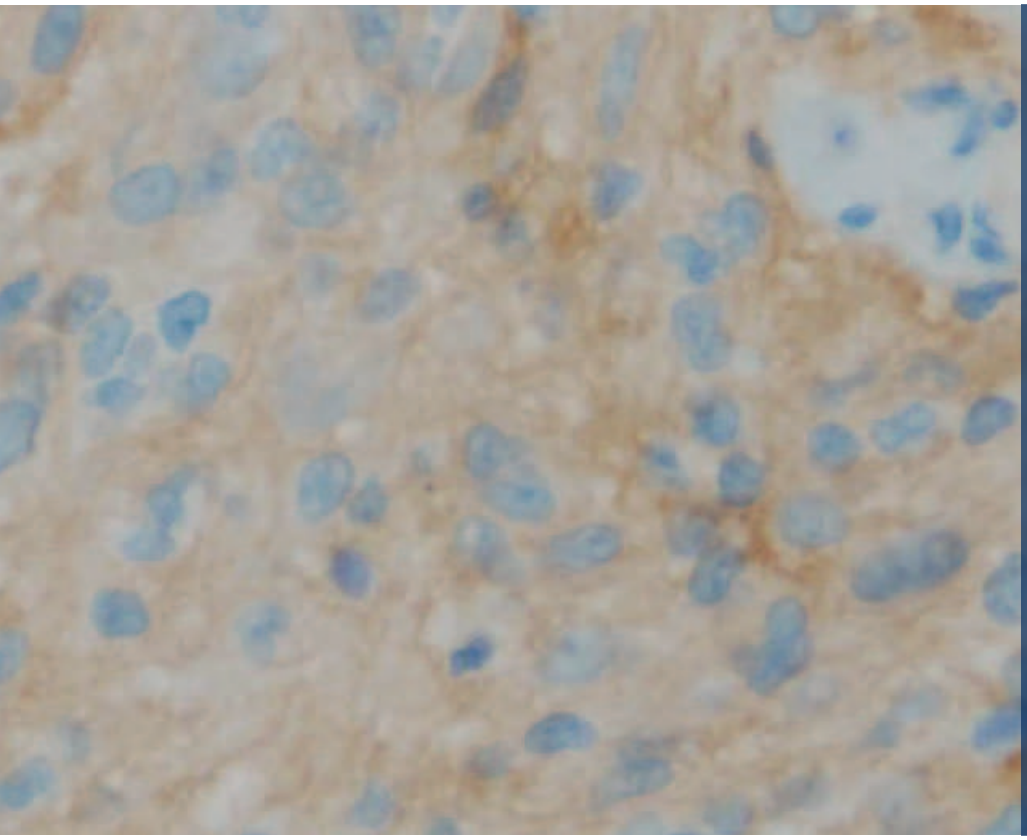
Similar to donor-derived primary NK cells, the continuously expanding human NK cell line NK-92 has been safely applied as an allogeneic cell therapeutic in clinical trials, with responses observed in some of the cancer patients treated. To enhance their therapeutic utility, in earlier work we generated genetically modified variants of NK-92 by transduction with retroviral or lentiviral vectors encoding first- and second-generation CARs specific for the differentiation antigens CD19 and CD20 expressed by B-cell malignancies, or antigens such as the receptor tyrosine kinase ErbB2 (HER2), the pancarcinoma antigen EpCAM or the glyco¬sphingolipid GD2, which are present on cancer cells from many solid tumors. In ongoing work we are extending this approach to epidermal growth factor receptor (EGFR), which is highly expressed by many tumors of epithelial origin, and the tumor-specific EGFR mutant EGFRvIII as target antigens. Like primary NK cells, NK-92 express natural cytotoxicity receptors (NCRs) which in part signal through CD3ζ. Hence, CD3ζ-containing CARs can readily link to endogenous signaling pathways and trigger potent and antigen-specific cytotoxicity of NK-92 cells against otherwise NK-resistant tumor cells (Figure 1).

Genetic modification of primary lymphocytes

In addition to our work with clinically usable NK-92 cells we are developing improved CAR vectors and optimized transduction protocols suitable for primary NK cells. Thereby NK-specific promoter sequences are being used to restrict CAR expression to differentiated natural killer cells. In a collaborative project together with the Department of Stem Cell Transplantation and Immunology, Clinic for Pediatric and Adolescent Medicine at the University of Frankfurt, we are investigating tumor-specific cytokine-induced killer (CIK) cells as a potential pre-emptive immunotherapy to prevent relapse of acute leukemia and other childhood malignancies. CIK cells consist mainly of T cells and NK-T cells, and are being expanded ex vivo from peripheral blood mononuclear cells. We could demonstrate potent and selective cytotoxicity of CD19-specific CAR CIK cells against cancer cell lines and primary pre-B-ALL blasts in vitro and in animal models in vivo (Figure 2).

CAR-NK cells for clinical applications

Following GMP-compliant procedures, we generated in close collaboration with the Blood Donation Service in Frankfurt a clonal ErbB2-specific NK-92 cell line that may become useful as an off-the-shelf cell therapeutic for cancer immunotherapy. These CAR NK cells selectively recognized ErbB2-expressing cells of different tumor origins, thereby exhibiting rapid and serial target cell killing in vitro as well as potent antitumor activity in an experimental metastasis model in vivo. As a prereq-uisite for a planned phase I clinical trial, together with colleagues from the Institute of Neurooncology at the University of Frankfurt we are currently investigating the activity of the ErbB2-specific NK-92 cells in experimental model systems for glioblastoma. Elevated levels of ErbB2 have been found in a large proportion of glioblastoma tumors and have been correlated with increased mortality.



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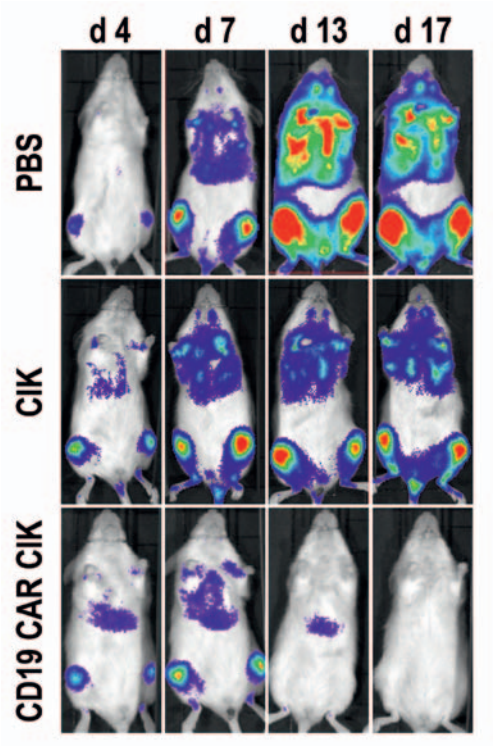

Figure 2.
Remission of pre-B-ALL upon treatment with CD19-targeted CAR CIK cells. Immunodeficient NSG mice were intravenously injected with luciferase-expressing primary human pre-B-ALL blasts and either treated with unmodified cytokine-induced killer cells (CIK) or CIK cells transduced with a lentiviral vector that encodes a CD19-specific chimeric antigen receptor (CD19 CAR CIK). Control animals were injected with PBS. Leukemia development was monitored by in vivo bioluminescence imaging. While unmodified CIK cells slowed down disease progression, treatment with CD19 CAR CIK cells resulted in complete elimination of leukemia.

III

Experimentelle Therapie
Experimental Therapy

Molekulare Therapie viraler Infektionen

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Molecular therapy of viral infections

HIV neutralizing antibodies and their epitopes

HIV-1 Env immunogens

Influenzavirus HA variants with increased human receptor usage

Our research activities focus on the development of new experimental strategies for therapeutic and prophylactic interventions against viral infections, in particular against HIV-1. A research priority is the identification of HIV neutralizing antibodies and their epitopes starting from polyclonal patient sera in view of therapeutic and prophylactic applications. We select these antibodies based on antigen-specific single B cell sorting or via the phage display technology using soluble native-like trimeric envelope (Env) constructs. We generate these from clinical strains including viruses from recently infected persons and CXCR4 using viruses associated with faster disease progression and potentially the capacity to infect human stem and progenitor cells. The recombinant Env trimers are also being used as experimental immunogens, i.e. in dromedaries, to select broadly neutralizing “nanobodies” with favourable properties for therapeutic applications. We recently succeeded to identify a set of nanobodies with broad neutralizing activity targeting the CD4 binding site in HIV-1 Env. These are promising candidates for further development with regard to

Unsere Forschungsaktivitäten konzentrieren sich auf die Entwicklung neuer experimenteller Ansätze zur therapeutischen und prophylaktischen Behandlung viraler Infektionen, insbesondere HIV. Wir fokussieren uns auf die Identifizierung HIV-neutralisierender Antikörper in Patientenseren sowie ihrer Epitope im viralen Hüllprotein (Env). Über die „Phage display" Technologie oder Env-spezifische B-Zellsortierung selektionieren wir mit klinisch relevanten rekombinanten Env-Konstrukten Antikörper aus polyklonalen Seren, die dann hinsichtlich ihrer Neutralisationsfähigkeit verschiedener HIV-Subtypen in vitro untersucht werden. Für die Selektionen sowie als experimentelle Immunogene exprimieren wir lösliche Env-Trimere, die dem nativen Env-„spike" auf dem Virus ähneln. Damit konnten wir nach Immunisierung von Dromedaren kürzlich breit neutralisierende Antikörperfragmente, sog. „nanobodies", selektionieren, die sich aufgrund ihrer charakteristischen Eigenschaften besonders für therapeutische Zwecke eignen.

Im Fokus unserer Charakterisierung von Env-Immunogenen stehen aktuell, aufgrund der beobachteten Zunahme unter den Primärinfektionen, Hüllproteine sogenannter X4 Viren, die über den CXCR4-Rezeptor infizieren. Diese sind mit einer schnelleren Krankheitsprogression assoziiert und können möglicherweise auch hämatopoietische Stammzellen infizieren. Auch für Influenzaviren gelang es uns kürzlich, Hüllproteine zirkulierender Varianten zu charakterisieren, die sich durch eine verbesserte Nutzung humaner gegenüber aviären Rezeptoren in vitro auszeichnen und somit möglicherweise pandemisches Potential besitzen.

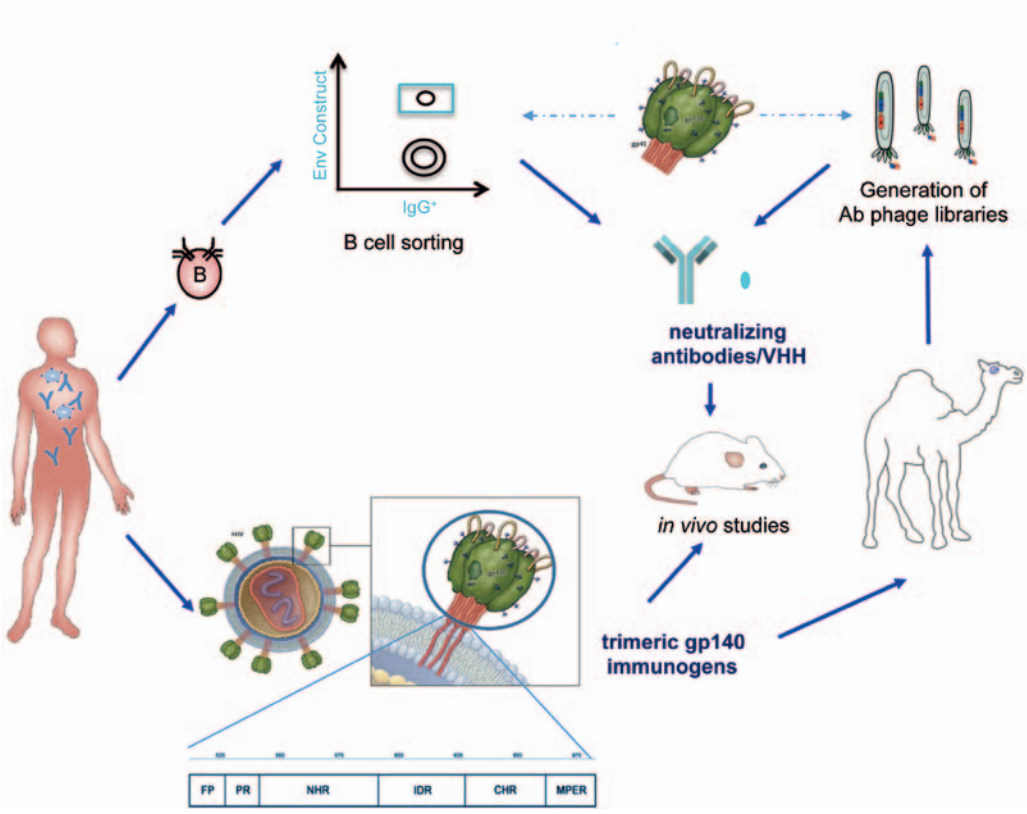
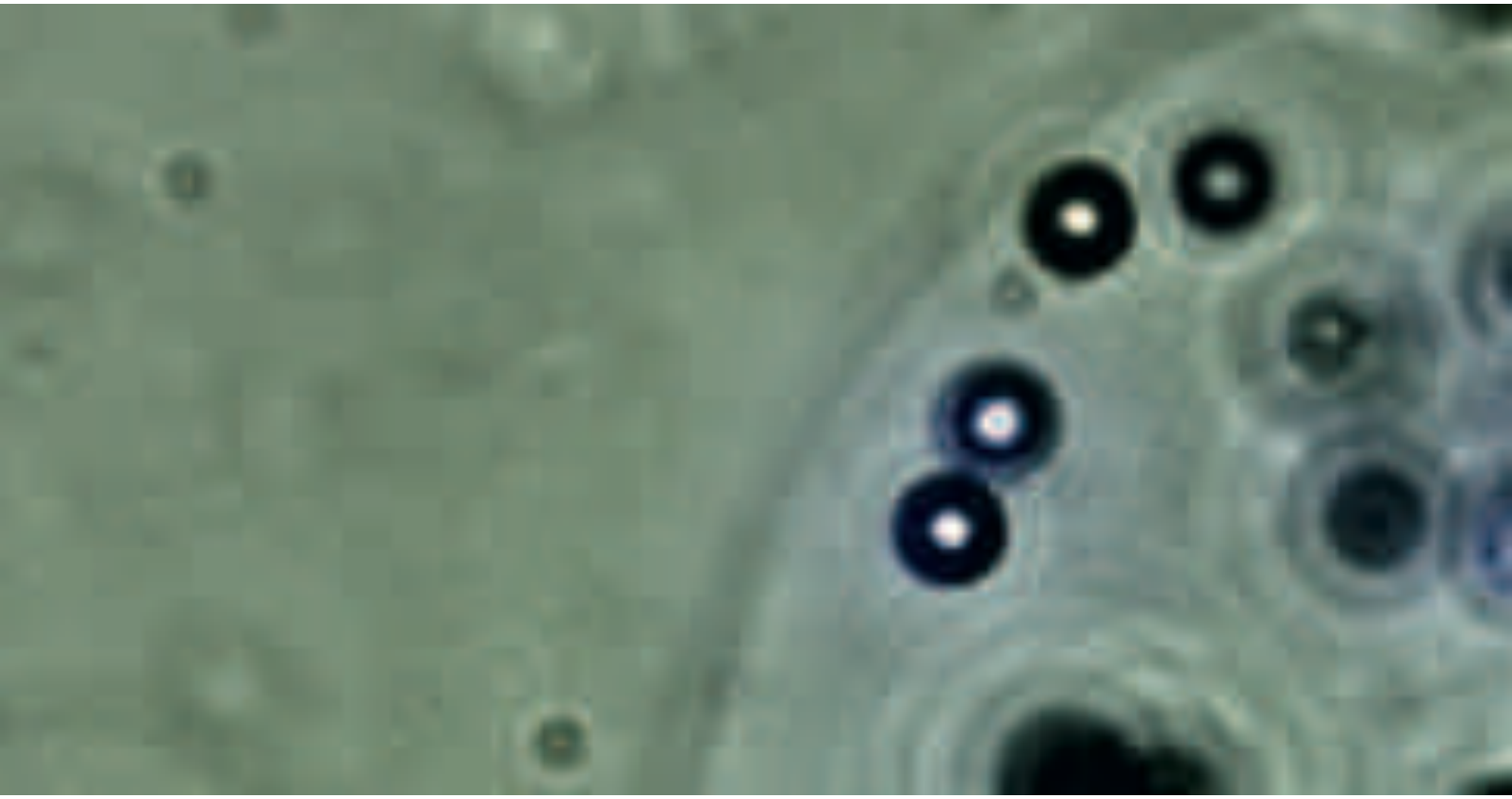


Figure 1.
Identification of HIV neutralizing antibodies from patients and immunized animals. Soluble trimeric gp140 Env complexes derived from clinical isolates serve for immunizations and for the selection of Env-specific antibodies. Selections are being performed by antigen-specific single B cell sorting from patients or from nanobody phage libraries generated from immunized dromedaries. After in vitro neutralization studies, neutralizing antibodies will be evaluated in humanized mice for therapeutic/prophylactic efficiency.



therapeutic applications due to the favourable intrinsic properties of nanobodies. In a further project we characterized the hemagglutinin (HA) proteins from H5N1 Influenza viruses circulating in some human populations with respect to human receptor usage. We could functionally prove in vitro a shift from bird to human receptor usage concerning the infectivity of virus particles pseudotyped with these HA glycoproteins.

Identification of virus neutralizing antibodies and their epitopes from HIV controllers

Starting from a group of HIV positive persons able to control viremia over years in the absence of antiviral therapy (elite

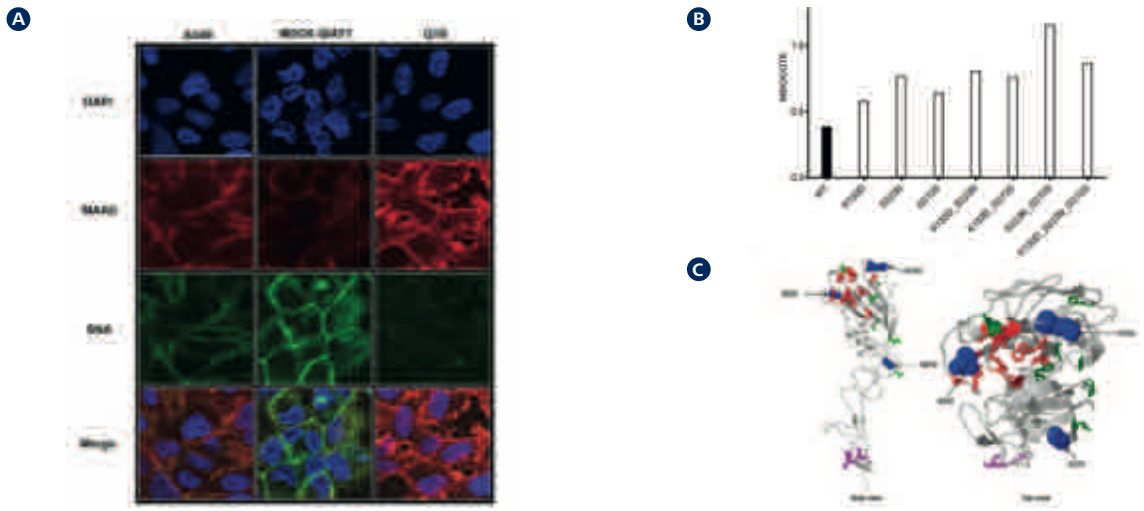
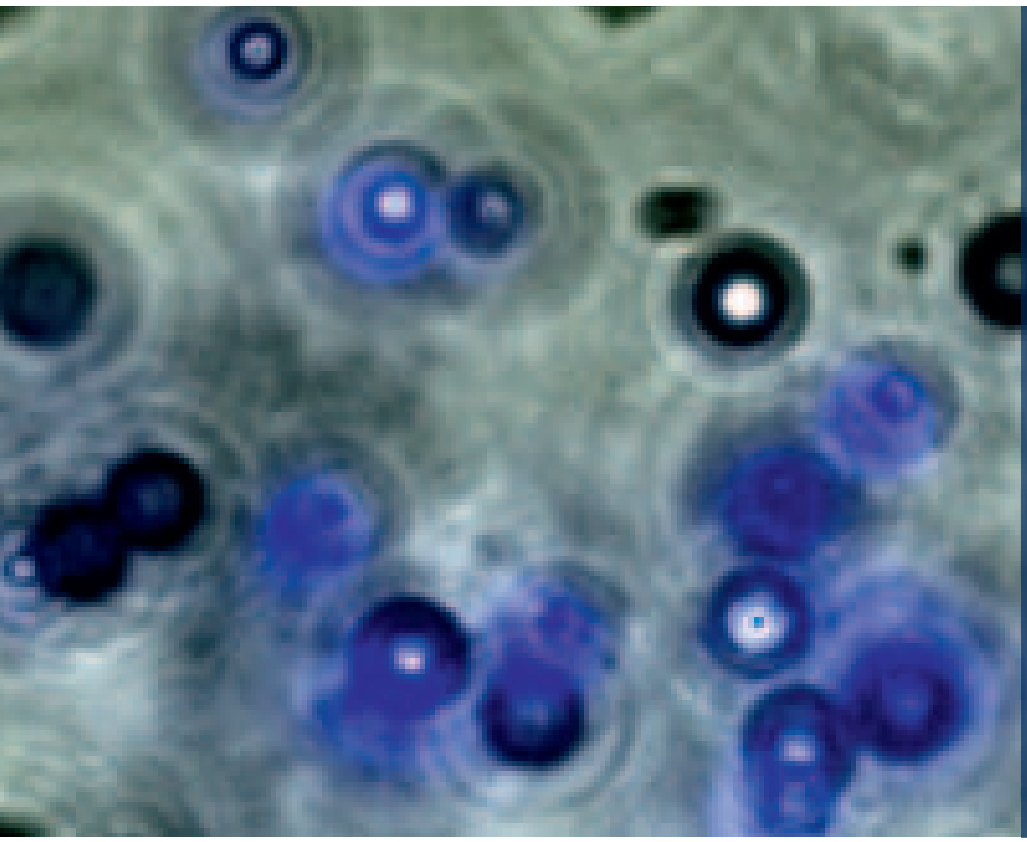


Figure 2.
Experimental confirmation of in silico predicted mutations in H5 HA conferring enhanced entry via human α2,6 sialic acid receptors.
A Whereas A549 cells express human receptors (stained with biotinylated lectin SNA) and bird receptors (stained with biotinylated lectin MAAII), MDCK-SIAT1 cells strongly overexpress human receptors and QT6 cells only express bird receptors.
B Quantitation of infection of MDCK and QT6 cells (shown is the ratio of transduced GFP positive cells MDCK/QT6) with wildtype (WT) and mutant H5 HA pseudotyped retroviral particles confirms enhanced entry of virus particles with the predicted mutations into MDCK cells.
C Location of the predicted mutations (blue) in HA1 close to the receptor binding side chains (red) in side (left) and top (right) view.



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controllers) we could detect broadly neutralizing antibodies in their plasma by in vitro neutralization assays. We identify these antibodies based on the phage display technology and direct antigen-specific B cell sorting. Vice versa, we identify the epitopes of neutralizing antibodies by screening phage displayed peptide libraries with the corresponding monoclonal antibodies. Using an Env-tailored phage library we could identify a new epitope in the membrane proximal external region (MPER) from the transmembrane protein gp41, which is currently being further optimized within the European project HIVERA in conjunction with a second MPER epitope as immunogen for vaccination studies. In a second project, using soluble trimeric gp140 Env proteins from the most prevalent HIV-1 subtype C as immunogens for the vaccination of dromedaries in collaboration with Dr. U. Wernery (Dubai), we could recently select a set of broadly neutralizing "nanobodies" targeting the CD4 binding site in Env from the generated phage immune libraries. These will be further optimized and tested in animal models for in vivo efficacy.

Characterization of Env immunogens from CXCR4 using (X4) HIV-1

Recent studies indicated increased numbers of primary infections with X4 HIV-1. This raises some concern, as usually primary infections are established via the CCR5 receptor (R5 viruses) and X4 viruses, which are associated with faster disease progression, occur several years after infection in about 50% of the patients. Hardly anything is known about X4 Envs concerning antigenicity, immunogenicity and structural aspects, and if so, the information is derived from lab adapted X4 strains (Arnold et al., Retrovirology 2013), as primary X4 Envs were not available. Therefore, we are currently generating a set of primary X4 Env from different HIV-1 subtypes in collaboration with our partners at the NYU Medical School (Dürr, Nyambi, Zolla-Pazner) to analyse the neutralization behaviour, immunogenicity and structural aspects of the corresponding virus particles. Preliminary neutralization data indicate that primary X4 Env differ considerably from lab adapted X4 known so far.

Identification of H5N1 hemaglutinins (HA) with increased usage of human receptors

H5N1 viruses currently only infect humans sporadically but if so mortality rates are about 60%. In order to predict potential pandemic H5N1 viruses our collaboration partner V. Veljkovic (Belgrade) developed a computer algorithm able to predict amino acids within HA, which potentially shift the receptor usage from bird receptors to human receptors. We could experimentally validate the predictions by showing that the introduction of the predicted amino acid exchanges into functional HA on pseudoviruses indeed resulted in increased infection of target cells with human receptors, whereas infection of cells with bird receptors was reduced. Thus, by combining bioinformatical and experimental approaches we could develop a method to preict the pandemic risk of bird Influenza viruses (Schmier et al., 2015). Interestingly, the predicted mutations are found in sporadic H5N1 infections of humans observed in Egypt and increase in recent years.

Gen- und Zelltherapie monogener Erkrankungen des Blutsystems

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Hyperinflammation and the Hematopoietic Stem Cell Pool in Chronic Granulomatous Disease (CGD)

Chronic Granulomatous Disease (CGD) is a rare inherited primary immunodeficiency characterized by defective antimicrobicidal activity of phagocytes, resulting in increased susceptibility to recurrent and life-threatening infections. In addition, CGD patients often display augmented inflammatory responses, even in the absence of infectious agents (sterile inflammation), leading to granuloma formation and inflammatory bowel disease. Inflammation is known to promote proliferation of hematopoietic stem and progenitor cells (HSCs/HPCs) and to orchestrate their egress to the blood stream via a variety of mechanisms. Inflammatory signals lead to augmented NF-κB activity, transcription of proinflammatory cytokines and activation of the inflammasome resulting in caspase-1-dependent secretion of the proinflammatory cytokines IL-1β and IL-18. In CGD patients, increased activity of caspase-1 and elevated release of IL-1β and other proinflammatory cytokines by activated mononuclear cells contributes to dysregulated inflammatory responses, even in the absence of clinical infection. In view of the compelling evidence linking inflammation

1. Veränderungen der Blutstammzellen bei der Septischen Granulomatose
Für schwer erkrankte Patienten mit Septischer Granulomatose, für die kein passender Knochenmarkspender zur Verfügung steht, entwickelten wir die Gentherapie als Behandlungsalternative. Vorangegangene Gentherapiestudien zeigten aber nur temporäre Erfolge und den raschen Verlust der genkorrigierten Zellen. Wir untersuchten, ob bei Septischer Granulomatose ein krankheitsintrinsischer Defekt in den blutbildenden Stammzellen vorliegt. Es zeigte sich, dass im Mausmodell der Septischen Granulomatose die Stammzellen stärker aktiviert sind und dass die Anzahl der daraus gebildeten Vorläuferzellen vergrößert war. Funktionelle Analysen ergaben zudem einen Defekt der blutbildenden Stammzellen, die verschiedenen reifen Blutzelltypen über lange Zeiträume hinweg zu generieren. Wir stellten erhöhte Zytokin- und Chemokinkonzentrationen in den Knochen dieser Mäuse fest. Dabei kristallisierte sich Interleukin-1β als einer der entscheidenden Faktoren heraus. Derzeit untersuchen wir, inwieweit eine pharmakologische Hemmung von Interleukin-1β und anderen Zytokinen das Anwachsen der Stammzellen bei der Gentherapie der Septischen Granulomatose verbessern kann.

2. Hemmung der AML1/ETO Tetramerisierung als therapeutische Alternative für akute myeloische Leukämien mit der t(8;21) Translokation.
Die Bildung von Tetrameren ist essentiell für die Transformationseigenschaften des AML1/ETO Proteins, einem Produkt der chromosomalen Translokation t(8;21). Mittels einer Struktur-basierten in silico Analyse der Oligomerisierungsoberfläche von AML1/ETO, haben wir chemische Substanzen identifiziert, welche mit der Bildung der Tetramere von AML1/ETO interferieren könnten. Aus dieser Substanzenbank haben wir 7.44 als wirksame Verbindung identifiziert (Abbildung 2). Wir haben zeigen können, dass 7.44 die Proliferation von AML1/ETO-abhängigen Zellen hemmt, während die myeloische Differenzierung der Zellen stimuliert wird. Diese Effekte konnten wir auch in AML1/ETO transformierten primären Blutstammzellen belegen. In vivo Versuche zeigten zudem, dass 7.44 in der Lage ist, die Proliferation von AML1/ETO Zellen nach Transplantation in humanisierte Mausmodelle zu hemmen. Basierend auf unseren Beobachtungen wird 7.44 als Modelstruktur für die Synthese und Isolierung neuer niedermolekularer Substanzen mit höherer Affinität und besseren pharmakokinetischen Eigenschaften dienen, welche letztendlich als wirksame Mittel gegen AML1/ETO-abhängige Leukämien eingesetzt werden können.

to defects in HSCs, we investigated the effect of inflammation on the HSC composition in the bone marrow of X-CGD patients and mice. We found a profound functional defect in the hematopoietic stem cell pool in CGD. HSCs from X-CGD animals were impaired in their long-term engraftment capacity and were outcompeted by wild-type HSCs in competitive repopulation assays. Similarly, the bone marrow of CGD patients contained less HSCs and increased numbers of progenitors when compared to healthy controls. This imbalance was attributed to increased levels of pro-inflammatory cytokines (in particular IL-1β) in the bone marrow of X-CGD patients and mice. IL-1β is a pleiotropic proinflammatory modulator of other cytokines, adhesion molecules, and enzymes and it also influences hematopoietic cell differentiation. We found that IL-1β activates HSCs, which are known to express IL-1 receptors, and induces HSCs to exit from quiescence. We propose a model, in which a functional defect in X-CGD HSCs develops over time due to persistent exposure of HSCs/HPCs to inflammatory cytokines and chemokines. Thus, persistent hyperinflammation in CGD triggers proliferative stress leading to exhaustion of repopulating HSCs (Figure 1). Our results may explain the failure of long term engraftment observed by us and others in CGD patients undergoing gene therapy with gene modified, autologous hematopoietic stem cells. Consequently proactive treatment of CGD patients with anti-inflammatory drugs might reduce chronic sterile inflammation and could also have an impact on the quantity and quality of HSCs available for autologous gene therapy. In terms of

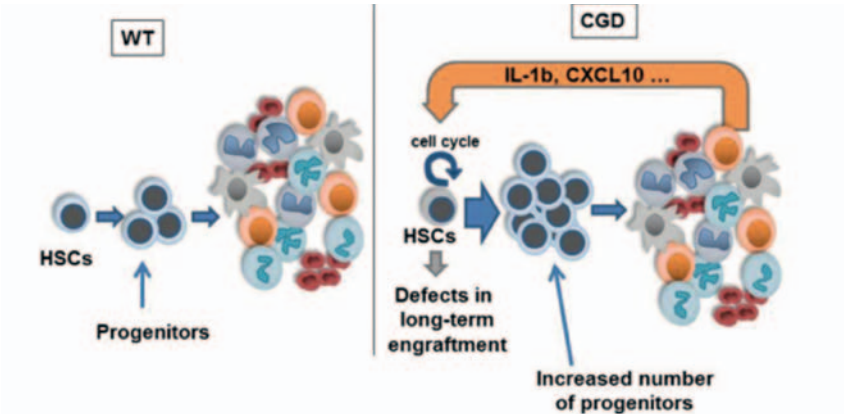
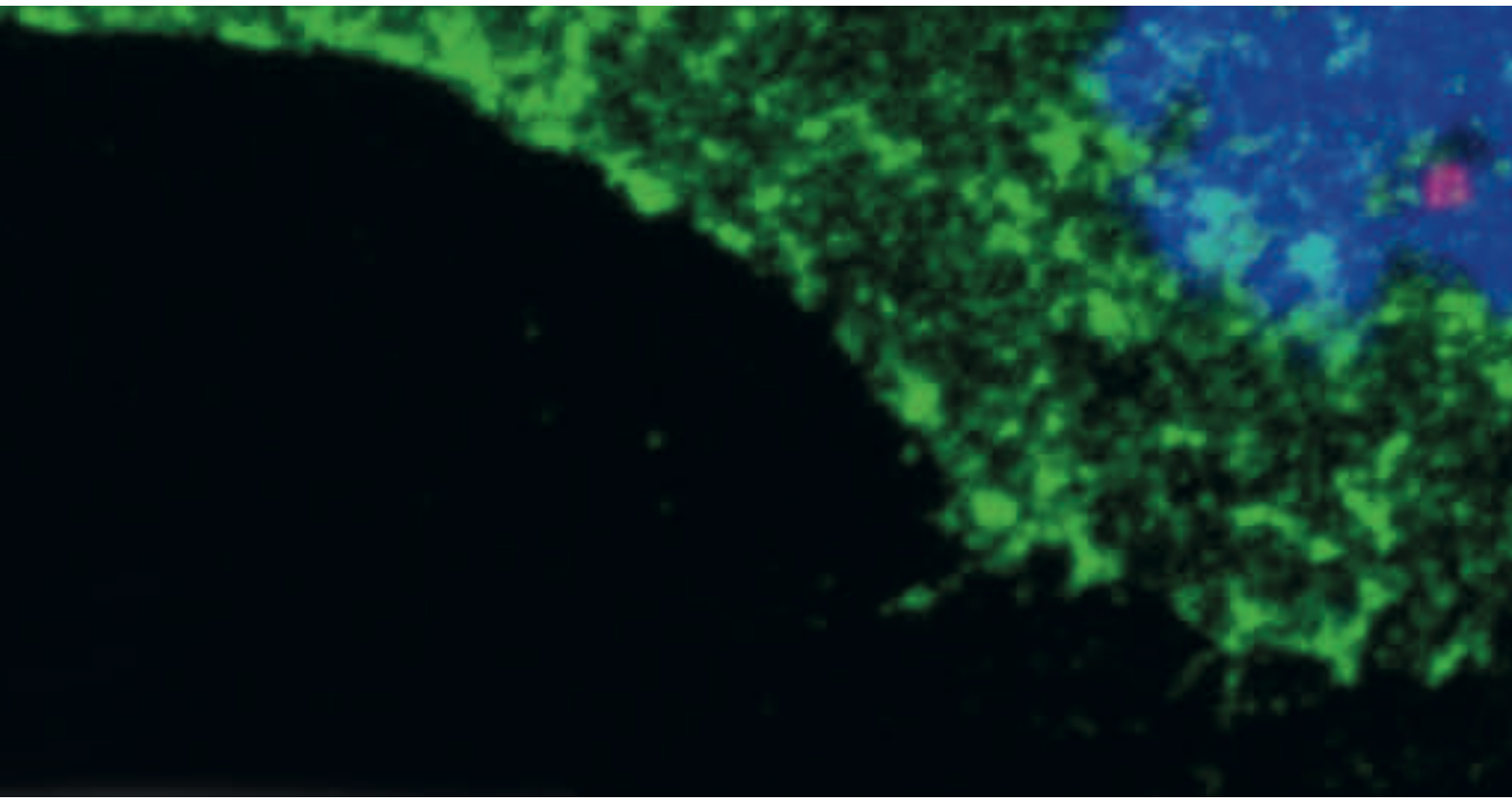


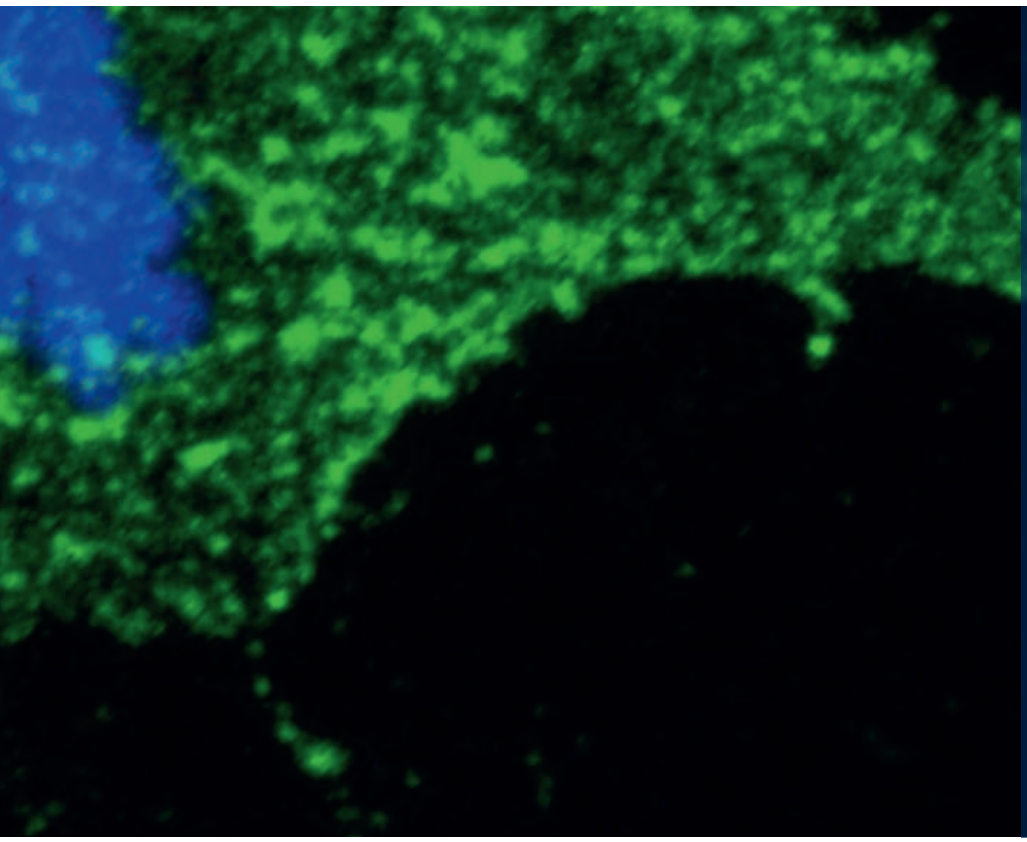
Figure 1.
Proposed model of HSC exhaustion in bone marrow of X-CGD mice. Cytokines like IL-1β and CXCL10 are increased in X-CGD bone marrow and induce HSC cycling, thereby leading to an expansion of hematopoietic progenitors and exhaustion of functional stem cells. This results in a reduced potential of X-CGD cells to support long-term engraftment.



clinical practice, enforced reduction of the inflammatory burden should be considered in those patients with pre-existing inflammatory disease, and also as part of preparative regimens for gene therapy prior to HSC harvest. This could not only facilitate the collection of larger numbers of functional HSCs/HPCs, but also may create an improved microenvironment for successful engraftment of transduced cells in the bone marrow stem cell niche. (This work is under revision in Journal of Allergy and Clinical Immunology)

Molecular approaches for the treatment of t(8;21) AML

Oligomerization is a key feature of many transcription factors involved in malignant transformation and contributes to aberrant protein functions by affecting alternative DNA-binding site selection and co-factor recruitment. AML1/ETO, the product of the t(8;21) chromosomal translocation, is required for the onset and maintenance of one of the most common forms of acute myeloid leukemia (AML). AML1/ETO acts primarily as a transcriptional repressor of AML1 target genes leading to an epigenetic-driven block of myeloid differentiation. Tetramerization of AML1/ETO through the NHR2 domain not only endows the protein with a new DNA binding specificity for duplicated AML1 sites, but also creates new docking sites for cofactor recruitment. Thus, tetramerization of AML1/ETO triggers the formation of a stable high molecular weight transcription factor complex, which is essential for AML1/ETO-dependent leukemogenesis. Destabilization of the AML1/ETO complex either by NHR2-derived polypeptides, deletion of the NHR2 domain or disruption of oligomerization-dependent interaction partners abrogates the oncogenic properties of AML1/ETO. Previously, we ana-



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lyzed the NHR2 tetramerization interface employing a structure-based computational strategy. This study revealed the existence of five amino acid (hot spot) critical for the dimer-tetramer transition. Three of these five amino acids addressed a druggable pocket of 269 A3 volume in the dimer counterpart. This pocket was used by us for the identification of small molecules mimicking these three amino acids in a structure-based virtual screening. Based on this screen, 78 compounds were selected and further analyzed in a tetramerization assay for their ability to inhibit the NHR2 dimer-tetramer transition in vitro. One of the analyzed compounds, 7.44, was active at an IC50 of 630 ± 24 µM. We have shown that compound 7.44 acts as an inhibitor of AML1/ETO-dependent hematopoietic cell transformation. Compound 7.44 inhibits the proliferation of the human AML1/ETO-expressing SKNO-1 and Kasumi-1 cells, while the proliferation of K562 cells, which are independent of AML1/ETO function, remains unaffected. Upon 7.44 treatment, SKNO-1 and Kasumi-1 cells undergo partial granulocytic differentiation and show a reduced ability to form colonies in semisolid media. In addition, the compound reverses the AML1/ETO-dependent deregulation of gene expression and induces growth arrest, granulocytic differentiation, and a reduction in the ability of AML1/ETO transformed human CD34+ primary hematopoietic progenitor cells to form colonies in semi-solid media. Treatment of SKNO-1 and Kasumi-1 cells with compound 7.44 reduces tumor formation in transplanted humanized mouse models. In summary, compound 7.44 triggers a loss of leukemic properties in AML1/ETO-dependent human leukemia cells. Compound 7.44 belongs to the still rare class of drugs targeting α-helix-mediated protein-protein interactions and could serve as a lead structure to guide the development of structurally related agents with increased binding affinity, improved bioavailability, and enhanced anti-leukemic effects. (This work is under revision in Molecular Cancer Therapeutics)

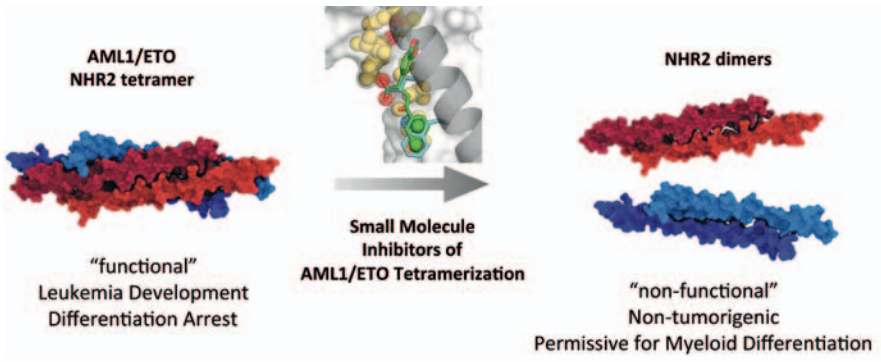

Figure 2.
Schematic diagram of the strategy used to inactivate the oncogenic potential of AML1/ETO. AML1/ETO forms tetramers which are essential for leukemia development. Disruption of tetramerization with small molecular weight compounds reverts AML1/ETO oncogenic activity.

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Maren Weisser: „Analyse hämatopoetischer Stamm- und Vorläuferzellen bei NADPH-Oxidase 2-Defekt."
Dissertation am Fachbereich 15: Biowissenschaften der Goethe Universität Frankfurt am Main, 20.05.2015

Finanzen und Administration

Die Abteilung Finanzen/Administration setzt jährlich ein durchschnittliches Finanzvolumen von 8,5 Millionen Euro um und betreut dabei rund 100 Mitarbeiterinnen und Mitarbeiter. Sie wird geführt von Robert Dornberger, der dabei von Christof Kaiser unterstützt wird.

Christiane Strack im Personalbüro erledigt sämtliche Personalfragen. Gabriele Heckl erstellt die Bilanz, bearbeitet alle Ausgangsrechnungen, die Reisekostenabrechnungen und ist für die Abrechnung internationaler Drittmittel zuständig. Emilia Seibert zeichnet verantwortlich für die Drittmittelverwaltung für die Bereiche der DFG, der DLR und der LOEWE-Förderungen. Marion Czech betreut die Kreditorenrechnungen sowie die Drittmittel nationaler Stiftungen.

Ansprechpartner in der Telefonzentrale und am Empfang ist Bernd Würdemann. Adrian Gresik ist verantwortlich für die vielfältigen Aufgaben des Innendienstes. Er, Michael Paul und Heinrich Krompietz kümmern sich um die haustechnischen Ausstattungen und Installationen und arrangieren alle Arten von wissenschaftlichen Tagungen und Veranstaltungen. Dabei werden sie von Volker Hopf unterstützt.

Yoseph Alazar, Maria Fernandes und Yasemin Piskin reinigen die Laboratorien, entsorgen die anfallenden Abfälle und kümmern sich um die Bereitstellung von Laborbedarf. Sie werden dabei von Neriman Sarac unterstützt.

Our administration and services department is led by Robert Dornberger who over-sees a yearly budget of approximately 8.5 million Euros. He also takes care of the administrative needs of about 100 staff members and is supported by Christof Kaiser.

He is assisted by Christiane Strack who heads the personnel department. Gabriele Heckl prepares the balance sheets, is responsible for all outgoing invoices, all claims of travel expenses and is in charge of accounting of international grants. Emilia Seibert is responsible for grants from the DFG, DLR and LOEWE. Marion Czech handles grants from nationwide foundations and takes care of all incoming invoices.

Bernd Würdemann is our receptionist and the first contact with the Institute. Adrian Gresik is responsible for the internal service tasks. He, Michael Paul and Heinrich Krompietz take care of the technical equipment and the installations and arrange all kinds of scientific meetings and events. They are supported by Volker Hopf. Yoseph Alazar, Maria Fernandes and Yasemin Piskin clean the laboratories, dispose of the waste and restock the supplies. They are supported by Neriman Sarac.

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Wissenschaftlicher Service

Zentrale Einheit FACS
Die zentrale FACS-Einrichtung besteht aus vier Durchflusszytometern zur Zellanalyse (BD LSRFortessa, FACSCantoII, FACSCalibur, FACScan) und zwei Zellsortern (BD FACSAria). 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. Tefik Merovci führt die anfallenden Hochgeschwindigkeits-Zellsortierungen durch und ist für den einwandfreien Zustand aller FACS-Geräte am Institut verantwortlich. In einigen Fällen fungiert Thorsten Geyer als zusätzlicher Operator an den Zellsortern. Die Sortiereinheit steht primär den Arbeitsgruppen des Georg-Speyer-Hauses, aber auch externen Forschergruppen zur Verfügung.

Zentrale Einheit Histologie
Zur Anfertigung von histologischen Präparaten betreibt das Georg-Speyer-Haus eine Histologie-Serviceeinheit unter der Leitung von Dr. Boris Brill. 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. Das Labor stellt seine Leistungen den Arbeitsgruppen des Georg-Speyer-Hauses sowie externen Forschergruppen zur Verfügung.

Core Facility FACS
The FACS core facility consists of four FACS instruments (BD LSRFortessa, FACSCantoII, FACSCalibur, FACScan) and two sorters (BD FACSAria). Dr. Stefan Stein oversees the performance of the FACS facility and is available for scientific questions regarding flow cytometry in general and the establishment of new FACS based assays. Tefik Merovci is responsible for high-speed cell sorting as operator in this central service unit for all research groups of the GSH as well as for external researchers. Tefik also takes care of the maintenance and functionality of the flow cytometers in the institute. Occasionally, Thorsten Geyer serves as an additional FACSorting operator.

Core Facility Histology
The Georg-Speyer-Haus operates a histology core facility. It is supervised by Dr. Boris Brill. 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. The services of the histology core facility are available to all scientists of the Georg-Speyer-Haus as well as to external research partners in collaboration.

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Tierhaltung
Das Georg-Speyer-Haus betreibt eine Tierhaltung, um den Forschungsgruppen die Zucht von Mäusen und Experimente zu ermöglichen. Die Tierhaltung stellt in vivo Imaging Systeme, wie Endoskopie (Storz Coloview Set), in vivo konfokale Mikroskopie (Cellvizio) und ein Detektionssystem für Fluoreszenz und Luciferase in vivo (IVIS Lumina II) zur Verfügung.

IT
Dr. Klaus Lehmen und Steffen Luft sind zuständig für das EDV-Netzwerk, die Integration und Administrierung der wissenschaftlichen Datenbanken und Auswertungsgeräte, die Beratung und Unterstützung bei allen Fragen zu den eingesetzten Hardware- und Softwarekomponenten sowie für den Einkauf und die Instandhaltung der EDV-Systeme. Dr. Klaus Lehmen betreut darüber hinaus die Homepage und ist zuständig für die digitale Datensicherheit / Datenschutz des Hauses.

Arbeitssicherheit und Genehmigungen
Dr. Herbert Kühnel gewährleistet die Funktionsfähigkeit der Laboratorien, versorgt die Arbeitsgruppen mit der nötigen Ausstattung, holt behördliche Genehmigungen ein, kümmert sich um die Arbeitssicherheit und regelt die Entsorgung.

Animal Husbandry
The Georg-Speyer-Haus has an animal facility which provides capacity for our research groups for mouse breeding and experiments. Included in the animal facility are imaging techniques like endoscopy (Storz Coloview Set), in vivo confocal microscopy (Cellvizio) and a detection system for fluorescence and luciferase in vivo (IVIS Lumina II).

IT
Dr. Klaus Lehmen and Steffen Luft are in charge of the IT network and the integration and administration of scientific databases and analysis equipment. They advice and support the Georg-Speyer-Haus members in all matters of hard and software, and purchase and maintain the IT equipment. Dr. Klaus Lehmen also maintains the website and is in charge of data security.

Occupational safety and permissions
Dr. Herbert Kühnel attends for equipment and supply, permissions, occupational safety and disposal.

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Veranstaltungen

22.11.2015
Paul Ehrlich – 100. Todestag
Anlässlich des 100. Todestages des Nobelpreisträgers Paul Ehrlich werden die Leistungen des großen Medizinforschers in drei Veranstaltungen in Frankfurt gewürdigt.

22.11.2015
Festakt Paulskirche

23. – 24.11.2015
Wissenschaftliches Symposium im Paul Ehrlich-Institut

29.10. – 03.04.2015
Ausstellung „Arsen und Spitzenforschung" im Historischen Museum, Frankfurt

19.11.2015
Dr. Nabil Djouder
CNIO Madrid
„Growth factors, Nutrients and Cancer"

12.11.2015
Prof. Dr. Burkhard Becher
Universität Zürich
„T cell:myeloid cell interactions in autoimmunity"

03.11.2015
Bürgervorlesung
„Lungenkrebs – Auswege durch die Immuntherapie?"

22.10.2015
Dr. Sine Reker Hadrup
Technical University of Denmark
„Novel technologies for mapping of immune reactivity against cancer"

15.10.2015
Dr. Kyung Hyun Ryu
National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Bethesda, USA
„Fences make good neighbors: staying out of your neighbors genetic yard"

02.10.2015
Dr. Thomas Oellerich
Universitätsklinikum Frankfurt
„Mass spectrometry-based proteomics: Current status and future perspective"

01.10.2015
Dr. Maher Hanoun
Klinik für Hämatologie,
Universitätsklinik Essen
„Neural regulation of the leukemic stem cell niche"

25.09.2015
Dr. Oliver Renner
Spanish National Cancer Research Centre (CNIO), Madrid
„Pim-1 kinase activity as drug target for cancer therapy"

14.09.2015
Auswahlsymposium zum "Paul Ehrlich- und Ludwig Darmstaedter-Nachwuchspreis"

Cynthia Sharma
Julius Maximilian University of Würzburg Research Center for Infectious Diseases
„Transcriptome complexity and regulatory RNAs in bacterial pathogens"

Claus-Dieter Kuhn
Elite Network of Bavaria and University of Bayreuth
„How non-coding RNA regulates our genes"

Gerhard Kroenke
University Hospital Erlangen, Department of Internal Medicine 3, Rheumatology and Immunology
„Enzymatic lipid oxidation as regulatory checkpoint during inflammation and immunity"

Benjamin Judkewitz
Exzellenzcluster NeuroCure, Charité Berlin
„Deep tissue imaging with time-reversed light"

Marc Aurel Busche
Technische Universität München, Klinikum rechts der Isar, Department of Psychiatry and Psychotherapy & Institute of Neuroscience
„Pathophysiological mechanisms of Alzheimer's disease: from neurons to networks in vivo"

03.09.2015
Dr. Claudia Günther
Friedrich-Alexander-Universität, Erlangen
„Programmed cell death in the intestinal epithelium and liver"

27.08.2015
Dr. Fatih Ceteci
Beatson Institute, Glasgow
„Metabolic Profiling of Colorectal Cancer Reveals Glutamic-Pyruvate Transaminases as Novel Potential Therapeutic Targets"

17.08.2015
Dr. Leonie Quinn
University of Melbourne
„Unraveling pathways fundamental to cancer using flies: the ssDNA binding protein Psi/FUBP is essential for overgrowth in Drosophila EGFR/RAS-driven glioma models"

25.06.2015
Dr. Christina Scheel
Helmholtz-Zentrum München
„Priming for stem cell like traits and epithelial plasticity by transient activation of Twist1"

29.05.2015
Dr. med. Cyrus Khandanpour
Universitätsklinikum Essen
„Role of Gfi1 in leukemia

28.05.2015
Prof. Dr. Ingo Röder
Faculty of Medicine Carl Gustav Carus, TU Dresden
„A systems biological perspective on the organization of hematopoietic stem cells"

13.05.2015
Bürgervorlesung
„Krebs – Was kann ich selbst tun?"

30.04.2015
Dr. Stefan Knapp
Goethe-Universität,
Institut für Pharmazeutische Chemie
„Targeting epigenetic effector domains of the bromodomain family in cancer"

16.04.2015
Dr. Michal Bassani-Sternberg
Max-Planck-Institute of Biochemistry, Martinsried
„Mass spectrometry based immunopeptidomics – from discoveries to therapies"

09.04.2015
„Targeting HOX Gene Expression in Acute Myeloid Leukemia"
Dr. Michael Kühn
Memorial Sloan Kettering Cancer Center, New York

13.03.2015
Prof. Dr. James P. Allison
The University of Texas Anderson Cancer Center, Houston, USA
„Immune checkpoint blockade in cancer therapy: New insights, opportunities and prospects for a cure"

12.03.2015
Prof. Dr. Michael Bachmann
Helmholtz Zentrum Dresden Rossendorf and University Cancer Center (UCC) TU Dresden
„Modular strategies for redirecting immune effector cells"

03.03.2015
Various Speakers
„Net4CGD, 2nd Annual Meeting"

02.03.2015
Schülervorlesungsreihe

12.02.2015
Dr. Michael Milson
HI-STEM gGmbH im Deutschen
Krebsforschungszentrum (DKFZ),
Heidelberg
„A rude awakening: exit from dormancy drives hematopoietic stem cell attrition and eventual bone marrow failure"

11.02.2015
Dr. Annika Böttcher
Helmholtz-Zentrum München
„Wnt/PCP activated intestinal stem cells are primed for the secretory lineage and retain multi-lineage potential"

05.02.2015
Dr. Ralf Kühn
Max-Delbrück-Centrum
für Molekulare Medizin
„Direct production of mouse mutants using ZFNs, TALENs or Crispr/Cas in one-cell embryos"

29.01.2015
Prof. Dr. med. Arthur Kaser
University of Cambridge
„Genes, environment & microbiota: Does ER stress convert autophagy defects into Crohn's disease?"

23.01.2015
Dr. Nabil M. Ahmed
Baylor College of Medicine, Houston
„Broad Spectrum CAR T cells for Solid Tumor Immunotherapy"

22.01.2015
Dr. Francois Ghiringhelli
INSERM U866 and Centre
Georges-Francois Leclerc, Dijon
„IRF1 dictates the IL-21 dependent anticancer functions of Th9 cells"

20.01.2015
Dr. Jörg Hildmann
BD Biosciences
„Introduction of the BD LSRFortessa FACS instrument: New insights into multicolor flow cytometry"

15.01.2015
Prof. Dr. Ritva Tikkanen
Universität Gießen
„Function of flotillins in cellular signaling and membrane trafficking"

Lehrveranstaltungen

WS 2014|15, SS 2015, WS 2015|16
Anleitung zum wissenschaftlichen Arbeiten für Diplomanden und Doktoranden
Greten F, Groner B, Wels W, Zörnig M, Koch J, Grez M, Dietrich U, Lausen J, Medyouf H, Sevenich L, Farin H, Krause D

WS 2014|15, SS 2015, WS 2015|16
Individuelle 6-wöchige Laborpraktika in Zusammenarbeit mit der Goethe Universität
Greten F, Groner B, Wels W, Zörnig M, Grez M, Dietrich U, Lausen J, Koch J, Medyouf H, Sevenich L, Farin H, Krause D und Mitarbeiter

WS 2014|15, WS 2015|16
Biochemie-Praktikum II für Studierende der Goethe-Universität
Zörnig M, Greten F, Groner B, Wels W, Grez M, Dietrich U, Lausen J, Koch J, Medyouf H, Sevenich L, Farin H, Krause D und Mitarbeiter

SS 2015, WS 2015|16
Ringvorlesung „Molekulare Onkologie und Tumoronkologie" im Rahmen des Studiengangs „Molekulare Medizin" an der Goethe-Universität
Greten F, Wels W, Koch J, Lausen J, Stein S, Zörnig M, Farin H, and others

WS 2014|15, WS 2015|16
Lecture series „Tumor Biology/Biochemistry of oncogenic signaling pathways", Biochemistry Department, University Frankfurt
Koch J, Zörnig M

04.03.2015
GRK 1172 Winter School

17.10. – 18.10.2015
Crash Course Basics of Molecular and Clinical Immunology
Dietrich U, Radeke H, Waibler Z, Anzaghe M, Schütz C, Miller L, Schülke S, Bönig H, Weigert A

26.01. – 02.03.2015
Schülervorlesung und -praktikum
Lecture series and practical course for high school students
Organisation: Dr. Ursula Dietrich
Prof. Dr. Florian Greten
"Krebsentstehung: genetische Grundlagen, Diagnostik und neue Therapieansätze"

Prof. Dr. Joachim Koch
„Immunkontrolle von Krebs und Infektionen"

Prof. Dr. Daniela Krause
„Stammzellen und Krebsstammzellen"

Prof. Dr. Theo Dingermann
„Gentechnologie: Grundlagen und Konsequenzen"

Dr. Ursula Dietrich
„HIV/AIDS - ein Immundefizienzvirus erobert die Welt"

30.03. – 02.04.2015
Schülerpraktikum in den Laborgruppen des GSH

03.12.2015
Veranstaltung zum Welt-AIDS-Tag in Zusammenarbeit mit der Goethe Universität, Vorträge, Laborbesichtigungen, Posterwalks
AG Dietrich

08. – 09.10.2015
Summer School des LOEWE Zentrums
Lausen J, Lehmen K, Stein S

Every Friday
Research Meeting: Recent results, advances and problems of individual research projects are presented and discussed in English

Der Verein »Freunde und Förderer des Georg-Speyer-Hauses«

Innovative Forschung und wissenschaftlicher Fortschritt in unserer Gesellschaft sind nur möglich durch das Engagement der Wissenschaftler 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 Krebs-, Aids- und Genforschung 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) und der Forschermitgliedschaft (Wissenschaftler, Studenten) 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.

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5000,– €

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www.georg-speyer-haus.de/friends/index.htm

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„Keine Schätzungen,
exakte Messungen.
Tatsachen haben bei
mir immer gestimmt.“
Paul Ehrlich