immune cells for life

Regensburg Center for Interventional Immunology

Annual Report

2017-2019

Annual Report 2017-2019

This annual report describes the research activities of the Regensburg Center for Interventional Immunology (RCI), an extra-mural research institute of the Free State of Bavaria, during the years 2017 to 2019.

The research activities of the RCI are largely made possible by financial contributions from the Free State of Bavaria, the German Research Foundation (DFG), the European Commission, the German Cancer Aid, the German Federal Ministry of Education and Research (BMBF), and various other funding agencies.

We would like to thank them all.

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Welcome

Prof. Dr. Oliver Kölbl
Chairman and Medical Director
University Hospital Regensburg

With pride and joy, the University Hospital Regensburg looks back on ten years of RCI! Founded in 2010, the Regensburg Center for Interventional Immunology had the firm goal of developing immunology in Regensburg into a scientific and medical focus. Thus, a highly efficient network of physicians and scientists who dedicate themselves to different facets of modern immunology was created. From the very beginning, the focus was on the rapid translation of scientific findings into clinical application.

Embedded in the clinical infrastructure, the scientists at the RCI work in close cooperation with each other and with the needs of the patients. In this way, the RCI makes a significant contribution to advances in personalized medicine. The José Carreras Center for Somatic Cell Therapy (JCC), which was the only one of its kind at a university hospital when it opened in 2009, serves as the heart of the RCI.

This „cell factory“ enables the production of cell-based therapeutics for each patient individually. In conjunction with the clinical focus areas - oncology and transplantation medicine - the University Hospital Regensburg and the RCI are among the pioneers in the application of novel cancer therapies.

The University Hospital Regensburg will continue to accompany the RCI as a close partner. The cooperation that has grown successfully over the past ten years is the basis for further developing Regensburg as a medical and scientific center in immunology and cell therapy with excellence and international visibility. The integration of the RCI into the Leibniz Association will be an important milestone in this process - for the benefit of everyone involved, but above all, for the benefit of our patients.

Prof. Dr. Oliver Kölbl
Chairman and Medical Director
University Hospital Regensburg

Welcome

Prof. Dr. Udo Hebel
President of the University
of Regensburg

As President of the University of Regensburg, I am very pleased to address the readers of the Regensburg Center for Interventional Immunology's (RCI) annual report. The development of new immunotherapies is one of the scientific challenges of our time, it is lengthy, costi tensive, and subject to strict framework conditions. Accordingly, the University of Regensburg has long promoted a high level of scientific and medical competence in interventional immunology. Internationally renowned experts have been appointed to Regensburg, new research groups have been founded, and the infrastructure has been systematically expanded. The RCI was founded to find the mechanisms by which immune cell defects, tumors, autoimmune diseases, and transplant rejections can be cured. To this end, the function and interaction of the various immune cells and their mediators are examined and the knowledge generated is used to develop modern therapeutics. A particular focus is on the production of cell therapeutics and their testing in early clinical studies with the aim of developing improved therapeutic approaches.

Extra-mural research institutions have a very high strategic priority for the University of Regensburg. In this respect, it is particularly gratifying that the RCI was spun off on July 1, 2019 and is well on its way to being accepted into the Leibniz Association in the near future.

Established as one of the main research focuses of the University of Regensburg, the RCI participates in top international research. This fact not only makes Regensburg a well-known location for science far beyond national borders, it also enables numerous successful collaborations with other cancer treatment centers.

The history of the RCI so far reads as a success story and gives hope for the affected patients, which is not only due to the groundbreaking scientific progress, but above all to its highly committed scientists.

Prof. Dr. Udo Hebel
President of the University
of Regensburg

About the RCI

This section provides an overview of the objectives, history, and structure of the RCI and its current performance data. We introduce new “minds” that have been recruited over the past three years as well as a selection of outstanding scientific insights that RCI staff members have gained during this time. We give an overview of the press coverage of the RCI, report on current developments, present the most important research networks in which the RCI is involved, and give insight into scientific events and strategies to promote our young scientists. In further chapters we present the research groups and service platforms of the RCI sorted according to program areas.

Foreword by the RCI Board

The Regensburg Center for Interventional Immunology (RCI) has undergone rapid development over the last three years. Only twenty-eight months have passed between the laying of the foundation stone on March 8, 2017 and the move into the new research building at the beginning of July 2019. Not only was the building constructed in twenty-eight months, but also an administration under the new head of administration, Brigitte Herbst, was established and internationally renowned scientists were recruited. During this time, they began their work, established three new research divisions, and celebrated their first scientific and translational achievements - true to the RCI’s maxim of deriving medical innovation from strong basic research. Top-quality publications were published, new immune cell therapies were developed and put into clinical testing, the biotech company TriArm was founded with international investment capital from the RCI, international research alliances were newly forged and existing ones expanded, and the first therapeutic success with genetically manipulated immune cells was achieved. The RCI is now well positioned to pick up speed and make its contribution to the development of immune medicine in Germany and worldwide.

Looking forward to it!

Philipp Beckhove
Scientific Director

Brigitte Herbst
Head of Administration

Markus Feuerer
Deputy Scientific Director

Mission statement

Interventional Immunology: Medicine of the Future

The RCI is dedicated to the research, development, and accelerated application of improved therapeutic approaches against cancer, chronic inflammation, autoimmune diseases, and in organ and stem cell transplantation. Close networking between the University of Regensburg and the University Hospital Regensburg enables research efficiency.

The immune system

..... is responsible for the protection against pathogens, the fight against cancer cells, and the maintenance of organ and tissue function. Along with the nervous system, it is the most complex system in the human body.

Immune medicine helps patients to survive

Immunomodulation is common practice in today's medicine and can protect from diseases (e.g., by vaccination), alleviate incurable diseases (e.g., rheumatism), and increase the efficacy of specific therapies (e.g., transplantation or chemotherapy). For example, the survival rate of lymphoma has tremendously improved due to antibody therapy and survival rates after organ transplantation have also increased in recent years.

Immune medicine is the future of medicine

Medical research has shown that the immune system plays a major role in many more diseases than previously thought and deserves more consideration in therapy. One of the greatest challenges of modern medicine is to intervene in the immune system with a great deal of impact and minimal side effects, yet in line with the specific disease and the individual patient.

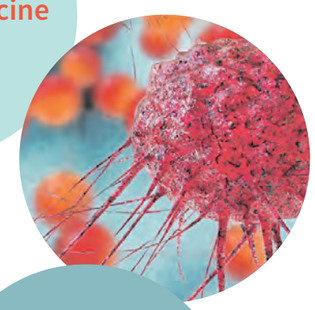
Research at the RCI

The aim of RCI scientists is to understand the mechanisms by which immune cells contribute to recovery from tumors, autoimmune diseases, and transplant rejections. To achieve this, the functions and interactions of the various immune cells and their messenger substances are examined and the knowledge generated is used to develop new therapeutics. Their production and testing in early clinical studies is a special focus of the RCI.

"A unique feature of the RCI is the combination of basic research and its translation to clinical application for the benefit of the patients."

The development of new immunotherapies is lengthy and takes at least ten years. In addition, it is expensive and is subject to strict legal regulations for clinical studies, cleanroom laboratories for production, etc.
To meet these requirements, the RCI brings together all relevant research areas, infrastructures and competencies, links them closely with each other and, through collaboration with partner clinics, uses them efficiently to develop innovative therapy formats for the benefit of patients.

Achievements in Immune Medicine



Cell Therapy as a Key Technology

Immune Cells as "Living Drugs"

The scientists at the RCI understand immune cells as input-output systems with multiple sensors and effector functions, which are linked by complex control algorithms and react to tissue damage with functional programs for cell repair and restoration of disturbed organ functions.

With the help of synthetic immunology, the scientists intervene in these processes, equipping immune cells with artificial sensors, functions, and control programs to generate „living drugs" with new capabilities for various therapeutic purposes.

To this end, the complementary expertise of all scientists is strategically interlinked in four program areas at the RCI. The research divisions, working groups, technology and service platforms, as well as the infrastructure are consistently working on a joint and translational development. Starting from basic immunological research in the fields of immune regulation, immunometabolism, and tissue homeostasis, the entire spectrum of therapy development is covered, including the development of new formats of genetic and pharmacological cell manipulation and GMP-compliant manufacturing up to clinical testing in early clinical trials.

A Brief History of the RCI

2008 BayImmuNet Funding
The Bavarian State Government supports the Bavarian Immunotherapy Network (BayImmuNet) under the direction of Prof. Dr. R. Andreesen with a total of 10 million euros in order to bring immunological research results quickly into clinical application.

BayImmuNet
Bayerisches Immuntherapie-Netzwerk

2009 Inauguration of José-Carreras-Center
José Carreras inaugurates the new laboratories for the drug-compliant production of immune cell therapeutics at the UKR.

Establishment of the RCI 2010
In November 2010, the University of Regensburg establishes the "Center for Interventional Immunology" supported by the Bavarian State Government.

Start of Funding 2011
The Free State of Bavaria decides on a start-up funding amount of one million euros with the prospect of increasing amounts in subsequent years.

Appointment of Scientific Board 2015
Prof. Dr. med. Philipp Beckhove is appointed director of the RCI at the University of Regensburg.

Topping Out Ceremony for the New Research Building 2018

Establishment of the RCI Foundation 2018
The Minister of Science, Prof. Dr. Marion Kiechle, signs the foundation deed and constitution of the Regensburg Center for Interventional Immunology (RCI) on October 10, 2018.

Extra-mural Institute 2019
The spin-off of the RCI as a legally independent research institute of the Free State of Bavaria takes place on July 1, 2019.

Organizational Chart

Foundation Board

Executive Board
Prof. Philipp Beckhove, Prof. Markus Feuerer, Brigitte Herbst

Board of Directors

Staff Council *

Administration
Brigitte Herbst

Program Area I Mechanisms and Targets	Program Area II Genetic Immunotherapy / Immune cell manipulation	Program Area III Cell production and Therapy	Program Area IV Strategic Development and Collaborations, Communication
Division of Immunology Prof. M. Feuerer	**Division of Genetic Immunotherapy** Prof. H. Abken	**JCC-José-Carreras-Center** Prof. M. Edinger	**Clinical Cooperation Groups** • Immunometabolomics Prof. M. Kreutz • Inflammation, Autoimmunity & Fibrosis Prof. M. Mack • Allogeneic HLA-DP specific TCRs PD Dr. S. Thomas • Organ Transplantation Prof. E. Geissler
Division of Interventional Immunology Prof. P. Beckhove	**Division of Functional Immune Cell Modulation** Prof. L. Gattinoni	**Core Facility "Good Clinical Practice - GCP- & Regulatory Affairs"** P. Schlosser	
Junior Group Epigenetic Immunooncology Dr. Ch.Schmidl	**Research Group Immunoregulation** PD Dr. P. Hoffmann Prof. M. Edinger	**Core Facility "Immunomonitoring"** Acting Head Prof. M. Edinger	
Core-Facility "Omics" Prof. M. Rehli	**W2 Professorship T Cell Therapy** Appointment: PD Dr. S. Thomas		**MAGIC** Prof. E. Holler
Core-Facility "FACS-Analytics and Cell Sorting" PD Dr. P. Hoffmann			**Communication, Strategic Collaborations and Development** N.N.
W2 Professorship for Algorithmic Bioinformatics Appointment: B. Kehr			**International Graduate Program** Dr. S. Stamova

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* not embodied in the statutes

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Theo Zellner, President of the Bavarian Red Cross

Recruitment from 2017-2019

2017

Prof. Dr. med. Markus Feuerer, Chair of Immunology at the University of Regensburg and Head of Division of Immunology at the RCI. M. Feuerer is a word-class scientist in immune tolerance and works on tissue-resident immune cells, inflammation, and organ function. Markus Feuerer is Deputy Scientific Director of the RCI.

Dr. rer. nat. Christian Schmidl was appointed Head of the RCI Junior Group Epigenetic Immunooncology. Previously, he worked at the Research Center for Molecular Medicine in Vienna and is a specialist in the field of regulation of immune cell function by epigenetic mechanisms. New impulses for immune medicine are expected from this innovative research field.

2018

Prof. Dr. med. Hinrich Abken, Chair of Genetic Immunotherapy at the University of Regensburg and Head of the Division of Genetic Immunotherapy at the RCI. Hinrich Abken is a pioneer in synthetic immunology and genetic modification of immune cells with chimeric antigen receptors. His gene constructs are used worldwide in clinical studies for cancer therapy.

2019

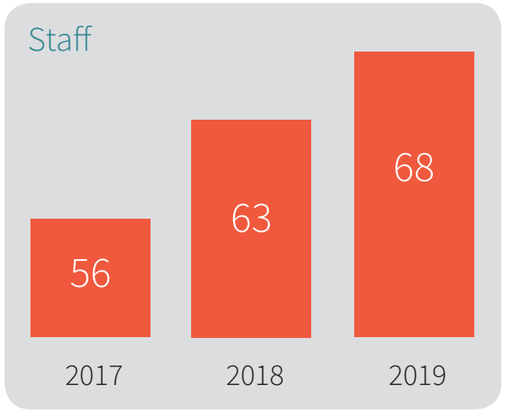
Prof. Dr. Luca Gattinoni, Chair of Functional Immune Cell Modulation at the University of Regensburg and Head of Division at the RCI. Previously, he worked at the National Cancer Institute in Washington and has become a worldclass leader in the therapeutic manipulation of immune cell function.

Priv. Doz. Dr. med. Simone Thomas
has been appointed to the W2 professorship for T cell therapy at the RCI. She is a specialist in the genetic alteration of T lymphocytes with tumor specific antigen receptors for the treatment of malignant diseases of the bone marrow and lymph nodes. In addition, she is very experienced in the planning and implementation of studies with genetically modified immune cells.

Performance Data

Funding

The core funding of the RCI is provided by the Free State of Bavaria. In addition, RCI scientists obtain funds from various national and international sources. A particular focus is laid on network projects to connect RCI scientists with scientists from the University of Regensburg and other important biomedical research centers in Germany, Europe, and worldwide.
From 2017 to 2019, several groups of the RCI participated in two Collaborative Research Centres (SFB-TRR221, SFB1350), one Clinical Research Unit (KFO262), three DFG Research Groups (FOR2127, FOR1961, FOR2858), several EU Consortia (Enacti2ng, TREGeneration, INsTRuCT, PAVE, The ONE Study), several German Aid Consortia (e.g. CD22 CAR, TECLA, TOSO CAR for CLL therapy), and BMBF Consortia (CD20 CAR-Time). Besides network projects, single project grants from various sources, especially the DFG, play an important role in RCI funding.



The people behind the research

- 68 employees are working at the RCI, 75% are women and 33% are from foreign countries.
- Scientists with a background in biology, chemistry and biochemistry, biotechnology and physics, as well as physicians collaborate at the RCI.
- Around 34 natural scientists currently work at the RCI, 15 of them are doctoral candidates who are organized in our Graduate Schools (page 26).

Budget

Budget (TEUR)

Third-party Funding (MEUR) Core Groups

Third-party Funding (MEUR) Clinical Cooperation Groups

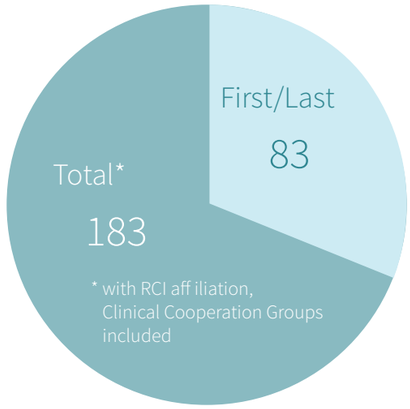
Qualifications

From 2017 to 2019, 28 doctorate, bachelor, and master students worked at the RCI.

Scientific Degrees Achieved 2017-2019

BSc, MSc	13
MD	2
PhD	14

Publications from 2017-2019



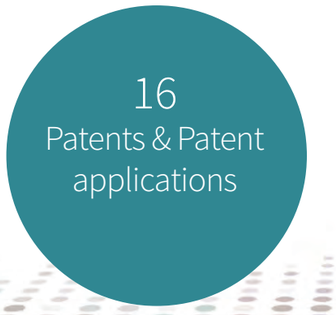
Scientific Productivity

The research results of the RCI are mainly published in international journals. An overview of all publications can be found on the RCI website. Patent applications also play an important role, as they are the prerequisite for the successful introduction of medical innovations into clinical use. Between 2017 and 2019, RCI scientists have obtained 16 patents or patent applications.

Scientific Communication

Current research results are regularly presented and discussed at numerous scientific conferences, e.g., the Annual Meeting of the German Society for Hematology and Medical Oncology e.V. (DGHO), the German Society for Immunology (DGfI), the CIMT Annual Meeting, the International Cellular Therapy Symposium (Erlangen), the International GvH/GvL Symposium, or the PEGS Europe Protein & Antibody Engineering Summit, as well as at the workshops and meetings of the network projects in which the RCI is involved.

The high number of lecture invitations at international conferences and the large number of third-party-funded national and international cooperation projects indicate the high level of recognition RCI scientists hold within the international scientific community.



Neue Waffe gegen KREBS

Mit gentechnisch hochgerüsteten Immunzellen feiern Mediziner derzeit Erfolge gegen Blutkrebs. Die Hoffnung ist groß, mit ihnen auch andere Tumore zu bekämpfen

VON JENS LUBBADEH

CAR-T-Zell- Therapie bei Krebs

Jährliche Todesfälle durch Krebserkrankungen in Deutschland in den Jahren 2000 bis 2017

Diagnose Krebs

Frauen

Männer

Welt am Sonntag, 9-15-2019

Killerzellen kämpfen gegen Krebs

MEDIZIN Professor Dr. Philipp Beckhove erklärte, wie man mit Immunzellen Krebs bekämpft.

VON ANGELIKA LUKESCH

Professor Dr. Philipp Beckhove
FOTO: LUKESCH

REGENSBURG. Die Universität und die Stadt Regensburg wollen den Bürgern in der neuen Vortragsreihe „Universität im Rathaus" mehr Teilhabe an den in der Stadt errungenen wissenschaftlichen Fortschritten gewähren. „Universität und Gesellschaft, vor allem die Stadtgesellschaft, sind eng verknüpft", sagte Gertrud Maltz-Schwarzfischer im Historischen Reichssaal. Die Regensburger Bürgermeisterin stellte den ersten Referenten dieser Reihe, Professor Dr. Philipp Beckhove, als einen der weltweit führenden Experten in der Entwicklung und schnelleren Anwendung verbesserter Therapieansätze gegen Krankheiten wie Krebs, Rheuma, Allergien oder Infektionen vor.

Der Präsident der Universität Regensburg, Professor Dr. Udo Hebel, hob ebenso die Bedeutung des Zusammenwirkens von Stadt und Wissenschaft hervor.

Staatsminister Bernd Sibler kam, um Beckhoves Ausführungen zu lauschen. „Synthetische Immunmedizin: Heilen mit ‚intelligenten Immunzellen'", lautete der Titel des Vortrags, den der Professor vom Regensburger Zentrum für Interventionelle Immunologie an diesem Abend vorstellte. Er stellte fest, dass erstmals „weit fortgeschrittene, therapieresistente Tumore bei vielen Patienten vollständig zurückgedrängt und langfristig kontrolliert werden können".

Dies geschehe mithilfe von Immunzellen. Das Besondere an den Immunzellen sei, dass sie nicht stationär im Körper vorhanden seien, sondern sich im Körper bewegten. Sogenannte „Killer-T-Zellen" suchen aktiv nach Tumorzellen. Dabei stellten diese Immunzellen quasi mobile Medikamentenfabriken dar, die viele unterschiedliche Aufgaben erfüllen können. Sie bekämpfen Krankheitserreger, kommunizieren mit allen Organen, reparieren Schäden und erhalten die Funktionen der Organe aufrecht.

Ein wichtiges Element bei diesem Thema sind die informationsverarbeitenden Input-Output Einheiten. Input hat mit den Sensoren der Zelle zu tun, Output mit den Werkzeugen, die der Immunzelle zur Verfügung stehen. Treten Störungen der Input-Output Funktion auf, dann ist das Resultat eine Krankheit. Manche Tumorzellen oder geschädigte Zellen besitzen einen Mechanismus, der reparierende Immunzellen abblockt. Auch hier gab es vor kurzem einen Durchbruch, indem es gelang, die sogenannten Stoppmoleküle der Krebszellen zu blockieren und dadurch die Tumorimmuntherapie zu verbessern. Auch die Heilung von metastasiertem Krebs sei damit möglich, sagte Beckhove. Der Professor berichtete auch darüber, dass eine neue Krebsimmuntherapie in der klinischen Testung sei. Die Zukunft in der Immunmedizin liege in der Gentherapie.

Mittelbayerische Zeitung, 5-24-2019

Einblick in die Welt der Immunologie

Neues Veranstaltungsformat Universität im Rathaus vermittelt Verständnis für Wissenschaft

Regensburg. (dp) Kaum eine Institution prägt das heutige Regensburg so stark wie die Universität, die vor über 50 Jahren ihren Vorlesungsbetrieb aufnahm. Mit Studierenden, Lehrenden, Forschenden und der Verwaltung sind es über 25 000 Menschen, die auf dem Campus aktiv sind, darunter rund 330 Professoren.

Mit dem neuen Veranstaltungsformat Universität im Rathaus laden die Stadt und die Uni alle Interessierten ein, sich einen Einblick in aktuelle Themen der Forschung und Wissenschaft zu verschaffen. „Neben Forschung und Lehre stellt der Wissens- und Innovationstransfer eine der zentralen Aufgaben einer Universität dar", erläutert Professor Dr. Udo Hebel, Präsident der Universität Regensburg.

Philipp Beckhove, Direktor des Regensburger Centrums für Interventionelle Immunologie Foto: Sarah Rohrer

„Es freut mich daher sehr, dass dieses neue Veranstaltungsformat die Universität und ihre Forschung näher an die Bürger heranbringt und so ein tieferes Verständnis für die Wissenschaft vermitteln kann."

Am Mittwoch, 22. Mai, um 20 Uhr wird im Historischen Reichsaal des Alten Rathauses Professor Dr. Philipp Beckhove seine Arbeit vorstellen. Die synthetische Immunologie, die Beckhove im Historischen Reichssaal den Bürgern vorstellen wird, analysiert, wie zur Entstehung der genannten Erkrankungen das Immunsystem Signale aus der Umgebung falsch verarbeitet. Dann „repariert" sie Immunzellen mit gentechnologischen Methoden und stattet sie so mit neuen Sensoren, „Softwareprogrammen" und Wirkstoffen für die Behandlung schwerer Erkrankungen aus.

Beckhove arbeitet an der Schaltstelle zwischen Forschung und Praxis. Er leitet das renommierte Regensburger Centrum für Interventionelle Immunologie (RCI), an dem alle relevanten Forschungsbereiche zusammengeführt und enger vernetzt werden. Zudem ist er auch Inhaber des Lehrstuhls für Interventionelle Immunologie an der Uni Regensburg. Durch die direkte Anbindung an das Universitätsklinikum können Ansätze der Grundlagenforschung direkt in die klinische Erprobung gehen.

Man weiß heute, dass das Immunsystem bei viel mehr Krankheitsbildern als bisher bekannt eine große Rolle spielt und in der Therapie daher mehr Berücksichtigung finden muss. Dabei ist eine der größten Herausforderungen, je nach Erkrankung in das Immunsystem möglichst wirkungsvoll einzugreifen und gleichzeitig wenig Nebenwirkung auszulösen. Ziel sind neue Diagnoseverfahren, Technologien und Medikamente.

Der Eintritt ist frei. Interessenten werden gebeten, sich bis zum 14. Mai unter E-Mail *einladungen.ur@uni-regensburg.de* oder per Fax an 0941/9434929 anzumelden.

Donau-Post, 5-10-2019

Erste Gentherapie gegen Krebs am UKR

In Regensburg darf ab 2019 eine neue Zelltherapie eingesetzt werden

Regensburg (rs). In Europa wurden jüngst die ersten Gentherapien zur Krebsbehandlung zugelassen. Das Universitätsklinikum Regensburg (UKR) wird als eine von wenigen Kliniken in Deutschland eine dieser in Israel, Europa und den USA entwickelten CAR-T-Zelltherapien bei Lymphompatienten einsetzen. Damit künftig für mehr Krebsarten solche vielversprechenden Therapien zur Verfügung stehen, hat zudem das am UKR angesiedelte Centrum für Interventionelle Immunologie (RCI) der Universität nun den Lehrstuhl für Gen-Immuntherapie geschaffen. In den USA gehört die Gentherapie, genauer die CAR-T-Zelltherapie, bereits seit Längerem zu den Behandlungsoptionen bei Lymphomen und anderen Krebsarten. Dabei werden dem Patienten Immunzellen entnommen, in einem Labor mit speziellen Rezeptoren zur Erkennung von Tumorzellen ausgestattet und dem Patienten als Transfusion zurückgegeben. Die so veränderten patienteneigenen Abwehrzellen sind nun dazu in der Lage, Krebszellen zu erkennen, anzugreifen und zu zerstören.

Oberärztin Dr. Simone Thomas Foto: UKR/Vincent Schmucker

„Die Zulassung der anti-CD19 CAR-T-Zellen für die Therapie von Lymphomen und Leukämien ist ein großer Fortschritt, denn die CAR-Therapie kann auch dann erfolgreich eingesetzt werden, wenn alle anderen Behandlungsmöglichkeiten bereits erschöpft sind. Sie birgt allerdings auch Risiken, sodass sie derzeit nur in spezialisierten Zentren durchgeführt werden sollte", beurteilt Professor Dr. Hinrich Abken, der seit Juni den neuen Lehrstuhl für Gen-Immuntherapie innehat, das Potenzial dieser Therapie.

Am UKR wird Privatdozentin Dr. Simone Thomas, Oberärztin der Klinik und Poliklinik für Innere Medizin III, Patienten mit der neuen Therapie behandeln. Erste Patienten sollen Anfang 2019 behandelt werden.

Rundschau, 9-19-2019

Prof. Dr. Hinrich Abken

Die CAR-T-Zelltherapie wird die Behandlung von Krebs revolutionieren

Professor Dr. Hinrich Abken, Inhaber des Lehrstuhls für Gen-Immuntherapie des Regensburger Centrums für Interventionelle Immunologie. © UKR/Domenika Golka

Ende August wurden die ersten beiden CAR-T-Zelltherapien aus den USA für Leukämie- und Lymphompatienten in Europa zugelassen. Angriffspunkt beider Therapeutika ist das CD19-Antigen auf B-Lymphozyten. Professor Dr. Hinrich Abken, Inhaber des neuen Lehrstuhls für Gen-Immuntherapie des Regensburger Centrums für Interventionelle Immunologie der Universität Regensburg, gilt als Pionier der CAR-T-Zelltherapie.

Im Interview bewertet er anlässlich des Weltlymphomtags am 15. September 2018 die Zulassung dieser Zelltherapeutika und gibt einen Ausblick in die Zukunft der Gen-Immuntherapie für Krebspatienten.

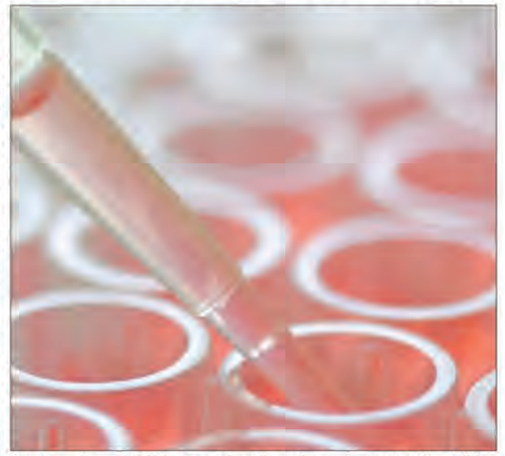
Krebs-Nachrichten, 9-15-2018

https://www.krebs-nachrichten.de/personalien-details/die-car-t-zelltherapie-wird-die-behandlung-von-krebs-revolutionieren.html

Erste Gentherapie gegen Krebs in Ostbayern

Uniklinikum wendet Zelltherapie aus den USA bei Lymphompatienten an

Regensburg. (dp) In Europa wurden jüngst die ersten Gentherapien zur Krebsbehandlung zugelassen. Das Universitätsklinikum Regensburg (UKR) wird als eine von wenigen Kliniken in Deutschland eine dieser in Israel, Europa und den USA entwickelten CAR-T-Zelltherapien bei Lymphompatienten einsetzen. Damit künftig für mehr Krebsarten solche vielversprechenden Therapien zur Verfügung stehen, hat das am UKR angesiedelte Regensburger Centrum für interventionelle Immunologie (RCI) der Universität nun den Lehrstuhl für Gen-Immuntherapie geschaffen und mit einem Pionier auf diesem Gebiet besetzt.



Am Regensburger Uniklinikum wird weiter an der sogenannten CAR-T-Zelltherapie geforscht. Foto: UKR

Professor Dr. Hinrich Abken

Krebs ohne Tumor – der Weltlymphomtag am heutigen Samstag rückt eine vergleichsweise seltene Krebserkrankung des blutbildenden Systems in den Fokus der Öffentlichkeit. Gegen ein Lymphom, das umgangssprachlich auch als Lymphdrüsenkrebs bezeichnet wird, kann das Skalpell nichts ausrichten.

Patienten profitieren von Expertenwissen aus USA

Bei malignen Lymphomen wirken sich bösartige Tumorzellen zerstörerisch auf einen Teil des Immunsystems aus. Über 20000 Menschen erkranken daran pro Jahr in Deutschland. In der Regel werden Lymphome hierzulande mit einer Chemotherapie behandelt, auch eine Stammzelltransplantation kann nötig sein. Anders in den USA: Hier gehört die Gentherapie, genauer die Chimeric-Antigen-Receptor-T-Zelltherapie, bereits seit längerem zu den Behandlungsoptionen bei Lymphomen und anderen Krebsarten. Etwa ein Jahr nach der Zulassung von zwei CAR-T-Zelltherapien für Leukämie- und Lymphompatienten in den USA sind diese Behandlungen seit Ende August auch in Europa zugelassen. Eines dieser Zelltherapeutika wird in Kürze im UKR zum Einsatz kommen.

Bei der CAR-T-Zelltherapie werden dem Patienten Immunzellen, sogenannte T-Zellen, entnommen, in einem Labor mit speziellen Rezeptoren zur Erkennung von Tumorzellen ausgestattet und dem Patienten dann als Transfusion zurückgegeben. Die so veränderten patienteneigenen Abwehrzellen sind nun dazu in der Lage, Krebszellen zu erkennen, anzugreifen und zu zerstören.

Therapie nur in spezialisierten Zentren

„Die Zulassung der CAR-T-Zellen für die Therapie von Lymphomen und Leukämien ist ein großer Fortschritt, denn die CAR-Therapie kann auch dann erfolgreich eingesetzt werden, wenn alle anderen Behandlungsmöglichkeiten bereits erschöpft sind. Sie birgt allerdings auch Risiken, sodass sie derzeit nur in spezialisierten Zentren durchgeführt werden sollte“, beurteilt Professor Dr. Hinrich Abken, der seit Juni den neuen Lehrstuhl für Gen-Immuntherapie des RCI innehat, das Potenzial dieser Therapie. Am UKR wird die Privatdozentin Dr. Simone Thomas, Oberärztin der Klinik und Poliklinik für innere Medizin III, Patienten mit der neuen Therapie behandeln.

Professor Dr. Wolfgang Herr, Direktor der Klinik und Poliklinik für innere Medizin III ist sehr zuversichtlich, dass „voraussichtlich Anfang 2019 Patienten, die an einem mehrfach vorbehandelten, diffus großzelligen oder einem primär mediastinalen B-Zell-Lymphom leiden, im UKR mit der neuen CAR-T-Zelltherapie aus den USA behandelt werden können – verbunden mit der Hoffnung, dass ein solches Zelltherapeutikum zukünftig auch für weitere Krebsarten verfügbar sein wird“.

Behnadlung wird am RCI weiter verbessert

„Bei soliden Tumoren ist die Wirksamkeit der CAR-T-Zelltherapie aus unterschiedlichen Gründen derzeit noch sehr begrenzt. Wir wollen diese Hürden überwinden, indem wir die Herstellung der CAR-T-Zellen optimieren, das Wirkprinzip analysieren und ihre therapeutische Anwendung auch für weitere Krebserkrankungen und solide Tumoren ermöglichen.

Das würde unsere derzeitigen Behandlungsmöglichkeiten revolutionieren“, fasst Professor Dr. Abken seine Forschungsziele zusammen. Er arbeitet nun daran, die Krebstherapie der Zukunft schonender und wirksamer zu machen.

Donau-Post, 9-15-2018

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Mittelbayerische Zeitung, 3-9-2017

Mit Hammerschlägen untermauerten sie die Grundsteinlegung: (von links) Bürgermeisterin Gertrud Maltz-Schwarzfischer, Forschungs-Dekan Medizinprofessor André Gessner, Medizinprofessor Torsten E. Reichert, Medizinprofessor Philipp Beckhove (Direktor des neuen Zentrums), Staatssekretär Bernd Sibler, Claudia Zirra (Staatliches Bauamt), Rektor Dr. Udo Hebel und Medizinprofessor Reinhard Andreesen. Foto: Tino Lex

Spitzenmediziner bekommen neues Forschungszentrum

GESUNDHEIT In der Einrichtung des Uniklinikums sollen Wissenschaftler Immuntherapien entwickeln. 2020 soll das Gebäude stehen.

VON TINO LEX, MZ

REGENSBURG. Gestern war ein guter Tag für die medizinische Spitzenforschung in Regensburg: Am Mittwochmittag ist der Grundstein für das Regensburger Centrum für Interventionelle Immunologie (RCI) am Uniklinikum gelegt worden. Der Freistaat Bayern stellt rund 15,6 Millionen Euro für den Forschungsneubau zur Verfügung. „Das ist eine hervorragende Investition in den Medizin- und Wissenschaftsstandort Regensburg", erklärte Unipräsident Dr. Udo Hebel dazu.

Das Gebäude im Westen des Geländes des Uniklinikums wird mehr als 1500 Quadratmeter Nutzfläche für Labore und Arbeitsräume bieten und soll bis 2019/2020 fertiggestellt sein. Das RCI wurde 2010 an der Universität Regensburg gegründet und bündelt Forschungsbereiche, die an der Entwicklung von Immuntherapien beteiligt sind. Ziel ist, dass sich das RCI zu einem Leibniz-Institut weiterentwickelt. „Dies unterstützen wir vom Freistaat jährlich mit rund 4,5 Millionen Euro", sagte Staatssekretär Bernd Sibler. Er würdigte wie auch seine Vorredner die hohen Verdienste von Medizinprofessor Reinhard Andreesen um das Zentrum. Als einen „Wegbereiter der Immunmedizin in Regensburg, ja in ganz Bayern" würdigte Sibler den Mediziner Andreesen. „Er war immer zuerst Arzt und Mensch – daran richtete er stets auch seine wissenschaftliche Arbeit und sein außergewöhnliches Engagement in Forschung und Lehre aus", sagte Unipräsident Hebel.

Andreesen erforschte von 1977 bis 1979 am Max-Planck-Institut für Immunbiologie und später am Universitätsklinikum Freiburg den Einsatz von Immunzellen gegen Krebs. Diese Arbeit setzte er seit 1991 mit verschiedenen Forschungsprojekten am Universitätsklinikum Regensburg fort, wo er mit der Errichtung des José-Carreras-Centrums für Somatische Zelltherapie 2008 auch den Weg für die erste „Zellfabrik" an einer deutschen Universität ebnete. Heute gelten regulierende Eingriffe in das menschliche Immunsystem als einer der zukunftsträchtigsten Bereiche der Medizin bei der Behandlung zahlreicher Erkrankungen.

Wie wichtig es ist, grundlagenwissenschaftliche Erkenntnisse frühzeitig in die klinische Anwendung am Patienten zu bringen, erläuterte Chemieprofessor Ernst Rietschel, ehemaliger Präsident der Leibniz-Gesellschaft und Gründungsdirektor des Berlin Institute of Health in seinem Festvortrag. „Professor Andreesen hat es immer eindrucksvoll vorgelebt, in der Forschung, speziell in der Immunwissenschaft, nicht aufzugeben."

Die Regensburger Bürgermeisterin Gertrud Maltz-Schwarzfischer verwies darauf, dass Andreesen „hochspezialisiertes medizinisches Wissen und Können mit Empathie und praktischer Hilfe für seine Patientinnen und Patienten und deren Angehörige verbindet".

Andreesen indes war sichtlich gerührt von derart viel Lob für seine Person. „Das war nicht ich allein. So etwas schafft man nur in Teamarbeit."

SO ENTSTAND DAS ZENTRUM

› **Netzwerk:** „BayImmuNet" koordinierte von Regensburg aus die Entwicklung von Immuntherapien an den fünf bayerischen Universitätskliniken.

› **RCI:** Darauf aufbauend wurde 2010 das Regensburger Centrum für Interventionelle Immunologie (RCI) als zentrale Einrichtung der Universität Regensburg gegründet. *(xtl)*

Der Immunmedizin verschrieben

Grundstein für Forschungsgebäude und Festakt für Professor Dr. Reinhard Andreesen

Regensburg. „Reinhard Andreesen zählt zu den profiliertesten und weitsichtigsten Professoren unserer Universität. Er war immer zuerst Arzt und Mensch – daran richtete er stets auch seine wissenschaftliche Arbeit und sein außergewöhnliches Engagement in Forschung und Lehre aus." Mit diesen Worten beschreibt Professor Dr. Udo Hebel, Präsident der Universität Regensburg, das langjährige Wirken von Professor Dr. med. Reinhard Andreesen.

Professor Dr. Reinhard Andreesen (l.) mit seiner Frau Brigitte (m.) und Festredner Professor Dr. Dr. Ernst Rietschel. (Foto: UKR)

Andreesen, der von 1969 bis 1975 Medizin in Freiburg, Heidelberg und Südafrika studiert hatte, wurde 1991 auf eine Professur nach Regensburg berufen. Als Leiter der Abteilung für Hämatologie und internistische Onkologie war er am Aufbau des Universitätsklinikums Regensburg maßgeblich beteiligt. Für Patienten mit Tumoren und Erkrankungen des blutbildenden Systems wurden hier Behandlungsmethoden nach neuesten internationalen Standards etabliert, unter anderem mit der Einrichtung der Stammzelltransplantationseinheit. Andreesen leitete die Abteilung bis zum Beginn seines Ruhestands im März 2013. Bis 2015 stand er als Seniorprofessor und Direktor dem Regensburger Centrum für interventionelle Immunologie (RCI) vor, das er maßgeblich mit initiierte und aufbaute.

Wegbereiter der Immunmedizin

Als einen „Wegbereiter der Immunmedizin in Regensburg, ja in ganz Bayern" würdigte Wissenschaftsstaatssekretär Bernd Sibler das erfolgreiche Engagement Professor Andreesens: „Professor Andreesen hat einen ganz wesentlichen Beitrag zum Aufbau des RCI geleistet: Er war einer der Initiatoren und wesentlich daran beteiligt, dass aus einer Idee Wirklichkeit wurde", so Sibler.

Bereits zu Beginn seiner wissenschaftlichen Laufbahn war Andreesen von den Wirkmechanismen immunmedizinischer Eingriffe überzeugt. Von 1977 bis 1979 erforschte er am Max-Planck-Institut für Immunbiologie und später am Universitätsklinikum Freiburg den Einsatz von Immunzellen gegen Krebs. Diese Arbeit setzte er seit 1991 mit verschiedenen Forschungsprojekten am Universitätsklinikum Regensburg fort, wo er mit der Errichtung des José-Carreras-Centrums für somatische Zelltherapie 2008 auch den Weg für die erste „Zellfabrik" an einer deutschen Universität ebnete. Heute gelten regulierende Eingriffe in das menschliche Immunsystem als einer der zukunftsträchtigsten Bereiche der Medizin bei der Behandlung zahlreicher Erkrankungen.

Wie wichtig es ist, grundlagenwissenschaftliche Erkenntnisse frühzeitig in die klinische Anwendung am Patienten zu bringen, erläuterte Professor Dr. Dr. h.c. mult. Ernst Rietschel, Präsident der Leibniz-Gemeinschaft a.D. und Gründungsdirektor des Berlin Institute of Health, in seinem Festvortrag. „Wenn wir die Medizin nachhaltig voranbringen wollen, brauchen wir abseits aller industriellen Therapieentwicklung die unabhängigen Wissenschaftler mit guten Ideen und Leidenschaft. Professor Andreesen hat es immer eindrucksvoll vorgelebt, in der Forschung, speziell in der Immunwissenschaft, nicht aufzugeben. Und diese Haltung hat er an viele Nachwuchswissenschaftler weitergegeben", so Rietschel.

Gertrud Maltz-Schwarzfischer, Bürgermeisterin der Stadt Regensburg, wies darauf hin, dass Professor Andreesen „hoch spezialisiertes medizinisches Wissen und Können mit Empathie und praktischer Hilfe für seine Patienten und deren Angehörige verbindet. Nach wie vor wirbt er unermüdlich um Spenden für Projekte, die dazu beitragen, den Alltag der Patienten und ihrer Angehörigen zu erleichtern", sagte Maltz-Schwarzfischer. Zudem habe Andreesen mit der Gründung des Bayerischen Immuntherapie-Netzwerks 2008 diesen Forschungsbereich für Regensburg deutlich sichtbar werden lassen.

Das Netzwerk „Bay-Immu-Net" wurde vom Freistaat Bayern mit 14 Millionen Euro gefördert und koordinierte von Regensburg aus die Entwicklung neuer Immuntherapien an allen fünf bayerischen Universitätskliniken. Darauf aufbauend wurde 2010 das RCI als zentrale Einrichtung der Universität Regensburg gegründet. Hier wird die immunmedizinische Forschung von Fakultät und Universitätsklinikum unter einem Dach vereint und soll zu einem außeruniversitären Institut weiterentwickelt werden. „Professor Andreesen stellte der Fakultät schon vor mehr als zehn Jahren seine Ideen eines außeruniversitären Instituts zur Immunmedizin vor. Heute gibt es das RCI, das mit internationaler Sichtbarkeit äußerst erfolgreich arbeitet und mit großer Unterstützung des Freistaates Bayern sowie von Universität und Fakultät in die Leibniz-Gemeinschaft überführt werden soll", so Professor Dr. Dr. Torsten Reichert, Dekan der Fakultät für Medizin der Universität Regensburg.

Doch auch in anderer Hinsicht prägte Andreesen die Universität. Als Prorektor der Universität Regensburg engagierte er sich von 2007 bis 2009 besonders für den internationalen Austausch. „Aus eigener Erfahrung war er immer ein Verfechter der Internationalisierung und des kooperativen Miteinanders über alle Kontinente hinweg", so Universitätspräsident Hebel. So initiierte Andreesen unter anderem mit der Universität von Lusaka (Sambia) eine Kooperation zum Austausch von Studenten, Ärzten und Wissenschaftlern.

2014 wurde Andreesen in Anerkennung seiner Leistungen als Arzt, Wissenschaftler und Gründer der Leukämiehilfe Ostbayern e.V. das Verdienstkreuz am Bande des Verdienstordens der Bundesrepublik Deutschland verliehen.

Die Immunmedizin ist heute – neben der Tumorforschung und der Transplantationsmedizin – einer der drei wissenschaftlichen Schwerpunkte der Fakultät für Medizin der Universität Regensburg. Doch die immunmedizinische Therapieentwicklung ist aufwendig – sie braucht Zeit und Geld, denn die Anwendung innovativer Eingriffe ins menschliche Immunsystem ist streng reguliert und erfordert eine spezielle Forschungsinfrastruktur.

Immunmedizinischer Leuchtturm

„Der Freistaat Bayern stellt für das RCI laufende Stellen und Mittel von jährlich 4,6 Millionen Euro zur Verfügung. Darüber hinaus errichten wir auf dem Campus des Universitätsklinikums Regensburg einen Forschungsneubau für rund 15,6 Millionen Euro und legen hierfür heute den Grundstein.", betonte Staatssekretär Bernd Sibler. „Gerade die Einflussnahme auf das Immunsystem ist eine der großen Errungenschaften moderner Medizin und einer ihrer zukunftsträchtigsten Bereiche", freute sich der Staatssekretär über den Baubeginn.

Der Forschungsbau – im Ensemble des Universitätsklinikums Regensburg als „Bauteil D5" bezeichnet – entsteht unter der Projektleitung des staatlichen Bauamts Regensburg in Fortsetzung der schon bestehenden Forschungsgebäude und schließt den Campus des Klinikums nach Westen hin ab. Das Gebäude wird mehr als 1500 Quadratmeter Nutzfläche für Labors und Arbeitsräume bieten und soll bis 2019/20 fertiggestellt sein. „Die Besonderheit des Projekts ist bautechnisch, aber auch funktional die Platzierung", erläuterte Claudia Zirra, Bereichsleiterin Hochschulbau des staatlichen Bauamts Regensburg. „Das Raumprogramm wird als Aufstockung auf dem Sockelgeschoss des Vorgängergebäudes D4 umgesetzt. Dies ermöglicht eine enge Vernetzung der Forschungsflächen in beiden Gebäuden und ist mit Blick auf den Grundstücksflächenverbrauch extrem ressourcenschonend. Als angenehmer Nebeneffekt entsteht ein gemeinsamer Innenhof mit hoher Aufenthaltsqualität, der den Forschern beider Gebäude zur Verfügung steht", so Claudia Zirra. Beherbergen wird das neue Forschungsgebäude künftig das RCI sowie weitere Forschergruppen der Fakultät für Medizin.

Donau-Post, 3-15-2017

Leuchtturm Immunologie

Grundstein für 15-Millionen-Forschungsbau

Regensburg. (web) Mit der Grundsteinlegung für das über 15 Millionen Euro teure Forschungsgebäude im Regensburger Centrum für Interventionelle Immunologie (RCI) haben das Universitätsklinikum und die Universität Regensburg nun auch die räumlichen Voraussetzungen einer zentralen Forschungseinrichtung geschaffen, in der Forschung neben der Patientenbetreuung am Uniklinikum direkt zur Entwicklung neuer Medikamente und neuer Therapien geführt wird.

Das RCI gilt jetzt schon über Deutschland hinaus als Leuchtturm der Spitzenforschung. Der Freistaat stellt hierfür rund 15,6 Millionen Euro bereit. „Damit investieren wir in den medizinischen Fortschritt und in die Zukunft des Wissenschaftsstandorts Bayern“, betonte Staatssekretär Bernd Sibler am Mittwoch bei der Grundsteinlegung für den Forschungsneubau.

„Eine besondere Rolle beim Aufbau des RCI nahm Professor Dr. Reinhard Andreesen ein: „Er gehört zu den engagierten Initiatoren und war maßgeblich daran beteiligt, diese Idee Wirklichkeit werden zu lassen“, so der Staatssekretär weiter. Andreesen wurde vor der Grundsteinlegung mit einem Festakt geehrt. Bereits zu Beginn seiner wissenschaftlichen Laufbahn war Professor Andreesen von den Wirkmechanismen immunmedizinischer Eingriffe überzeugt. Von 1977 bis 1979 erforschte er am Max-Planck-Institut für Immunbiologie und später am Universitätsklinikum Freiburg den Einsatz von Immunzellen gegen Krebs. Diese Arbeit setzte er seit 1991 mit verschiedenen Forschungsprojekten am Universitätsklinikum Regensburg fort, wo er mit der Errichtung des José-Carreras-Centrums für somatische Zelltherapie 2008 auch den Weg für die erste „Zellfabrik“ an einer deutschen Universität ebnete.

Heute gelten regulierende Eingriffe in das menschliche Immunsystem als einer der zukunftsträchtigsten Bereiche der Medizin bei der Behandlung zahlreicher Erkrankungen.

Das Regensburger Centrum für Interventionelle Immunologie wurde 2010 an der Universität Regensburg gegründet. Es bündelt die Forschungsbereiche der Universität und des Universitätsklinikums, die an der Entwicklung von Immuntherapien beteiligt sind. Ziel ist es, das Centrum zu einem außeruniversitären Institut der Leibniz-Gemeinschaft zu entwickeln. Der Freistaat unterstützt das RCI jährlich mit rund 4,5 Millionen Euro. Das Uniklinikum Regensburg versorgt jährlich etwa 33000 Patienten stationär sowie rund 137000 ambulant.

Donau Post, 3-9-2017

Graduate Programs

Christina Fischer
Speaker PhD Council

All RCI doctoral students in the natural sciences are integrated into the structured graduate programs of the University (**Regensburg International Graduate School of Life Sciences; RIGeL**) or the Medical Faculty (**Biomedical International Graduate School; BioMediGS**) while medical students are supervised in the **Regensburg Medical Graduate School, MedReGS.** In addition, bachelor and master students are trained at the RCI within the framework of the "Molecular Medicine" program and related courses of studies.

21 Students
PhD/MD
6 Nationalities

Central elements of the graduate training are:

- structured graduate programs with compulsory modules (good scientific practice, biostatistics, etc.)
- mentoring and regular progress reports
- supervision, laboratory and literature seminars
- regular research retreats
- continuous evaluation of the training programs

Doctural students discussing with senior scientist at the RCI

The PhD students of the RCI are members of the **PhD Council** and send two stakeholders to the regular staff meetings of the RCI Board of Directors.

The RCI supports PhD students through:

- funding of speakers for doctoral seminars
- career promotion measures (job fairs, mentoring programs, etc.)
- soft skills courses
- laboratory exchange programs
- international recruitment of doctoral candidates

RIGeL Regensburg International Graduate School of Life Sciences

BIOMEDIGS BIOMEDICAL INTERNATIONAL GRADUATE SCHOOL

G>H G>L sfb transregio 221 Integrated Graduate School

Research Highlights

Discovery of immune cell precursors for tissue repair and regeneration

An RCI team of immunologists, led by **Prof. Dr. Markus Feuerer, Dr. Michael Delacher**, and **Dr. Christian Schmidl**, investigates an immune cell population (regulatory T cells) specialized in tissue repair and regeneration.

To use these cells for therapy, the anatomical site and steps of differentiation have to be known. The research team could show that precursor cells learn some of their new tasks and fix them in their genome (DNA) while they are still in lymphatic organs such as the spleen or lymph nodes. This two-step process is regulated by transcription factors, which lead to a remodeling of the genetic landscape and the stepwise implementation of new properties, e.g., the migration into tissues such as the skin, fat, or intestine, as well as the secretion of tissue-repair factors or anti-inflammatory cytokines. The transcription factor BATF (Basic leucine zipper transcription factor) is a key factor in this reprogramming.

The scientists could also show that cells without BATF expression cannot mature and, therefore, cannot support tissue regeneration. Those results will contribute to the development of a specific therapy for the regeneration of damaged tissue or organs, e.g., after bone marrow transplantation (stem cell transplantation) in leukemia treatment.

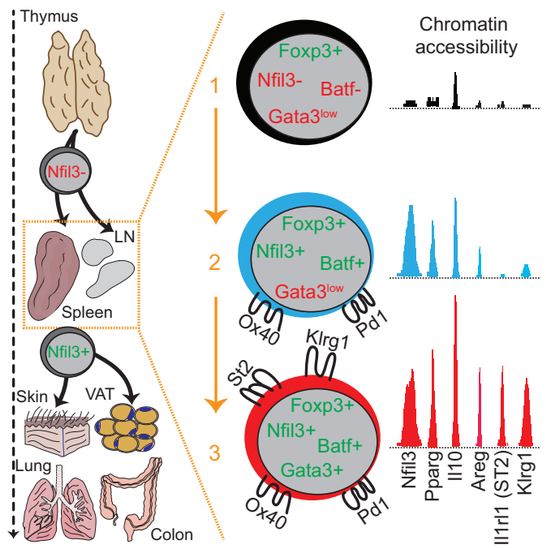


Fig.: Differentiation program in the lymphatic system

Original publication:
Delacher M et al., Precursors for Nonlymphoid-Tissue Treg Cells Reside in Secondary Lymphoid Organs and Are Programmed by the Transcription Factor BATF. *Immunity* 2020 52 (2), 295-312.e11

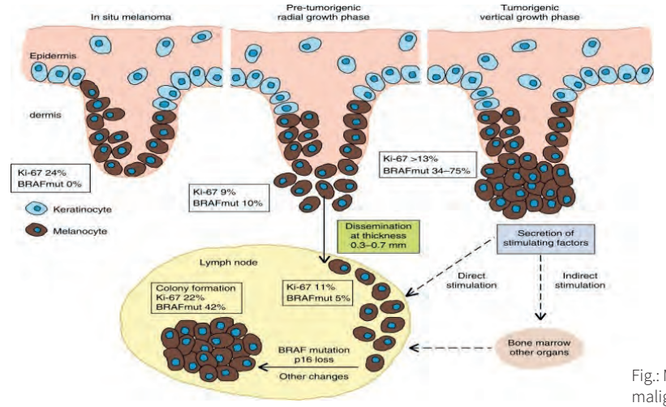


Fig.: Metastatic cascade in malignant melanoma

When does metastatic dissemination start?

A team led by **Dr. Melanie Werner-Klein** at the RCI Division of Immunology has investigated samples of more than 1,000 melanoma patients and could show that the dissemination of melanoma cells to the sentinel lymph node occurs very early, already at a tumor thickness of 0.5 mm. Melanoma cells show only a few mutations at this early stage. Mutations that are decisive for metastatic growth, such as those in the oncogenes BRAF or MET, are generally acquired within the target organs, e.g., in the lymph nodes. The finding that dissemination of melanoma cells starts early and that melanoma cells genetically alter within the target organ is important for the development of adjuvant therapies, e.g., targeted immunotherapies against metastasis.

Original publication:
Werner-Klein M et al., Genetic alterations driving metastatic colony formation are acquired outside of the primary tumour in melanoma. *Nat Commun* 2018; 9; 595

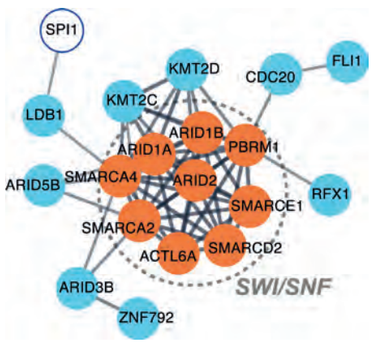


Fig.: Network of PU.1-associated proteins

Which is the right switch in the genome – looking for a needle in the haystack ...

The information stored in our genetic material (genome) is behind everything in our cells. The various cell types can only function properly, if the access to this genetic information is carefully regulated. This “reading” of the information is regulated by genomic switches, which are turned on and off by so-called transcription factors. However, there are millions of possible binding sites for transcription factors in the genome and it is not yet fully understood how transcription factors can find exactly those switches that are important for the specific cell type. The team led by **Prof. Dr. Michael Rehli**, head of the “Omics” Core Facility, could show for the first time that the transcription factor PU.1 needs to cooperate with a so-called remodeling machine in order to occupy its binding sites in the genome and redistribute other transcription factors properly, e.g., in blood cells.

Original publication:
Minderjahn J et al., Mechanisms Governing the Pioneering and Redistribution Capabilities of the Non-Classical Pioneer PU.1. *Nat Commun* 2020, 11 (1), 402

Gene therapy with artificial antigen receptors to overcome immune blockade in the tumor

Scientists of the Division of Genetic Immunotherapy at the RCI tested and described a new therapeutic approach for particularly therapy-resistant tumors. The team of **Prof. Dr. Hinrich Abken** developed a new generation of chimeric antigen receptors ("next-generation CAR") to achieve an improved and long-lasting activation of T cells after antigen contact. The next-generation CAR differs from the current four generations as it intervenes in the multi-step activation process of the T cell after binding to the target cell (tumor cell). This prolongs the activation state of the CAR T cell and thus increases its efficiency. After binding to the target structure by the TCR or CAR, the T cell is activated stepwise, whereby, among other things, CD30 ligand (CD30L, CD153) and a little later also CD30 is expressed on the surface of the T cell.

The CD30L-CD30 interaction initiates, among other things, the subsequent suppression of T cell activation to limit the T cell response. The new CAR is designed to prevent this limitation by blocking the CD30L-CD30 interaction. Therefore, the extracellular part of the CAR carries the CD30-blocking domain in addition to the tumor-detecting domain. This anti-tumor anti-CD30 CAR has an improved and prolonged activity against various target cells, especially solid tumors in animal models. This "next-generation" CAR is of particular relevance for the treatment of solid tumors that have so far been difficult to treat.

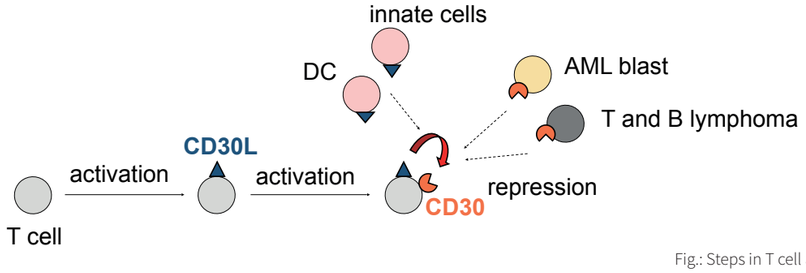


Fig.: Steps in T cell activation

Original publication:
Hombach, A et al., Blocking CD30 on T cells by a dual specific CAR for CD30 and colon cancer antigens improves the CAR T cell response against CD30 negative tumors. *Mol Ther* 2019; 27, 1825
Patent application: Hombach, A., Abken, H. "CD30 chimeric antigen receptor and its use." WO2016008973 A1, PCT/EP2015/066252, EP3169703A1, US20170145095, licensed to: HumOrigin, Taipeh

HLA-DP antigens as target structures for leukemia-specific immunotherapy

The effect of allogeneic hematopoietic stem cell transplantation (HSCT) relies on lymphocytes that are transferred into the patient to destroy leukemic cells. If this graft versus leukemia (GvL) effect is insufficient, it can be strengthened by the transfer of leukemia specific T cells. For this purpose, suitable T cell target structures have to be identified. The research group led by **PH Dr. Simone Thomas** could identify HLA-DP antigens as GvL target structures for the production of leukemia-specific T cells. HLA-DP antigens offer the advantage that they are non-identical in up to 80% of donor/patient pairs and preferentially expressed by leukemia cells.

The researchers were able to reliably produce HLADP- reactive T cells in stimulation systems for the first time. The cells selectively recognized leukemia cells from different patients and could eliminate those cells in a mouse model. No side effects against healthy tissue cells were detected under normal conditions. Based on this study, HLA-DP-specific T cells will be further developed as a leukemia-specific immunotherapy after allogeneic HSCT.

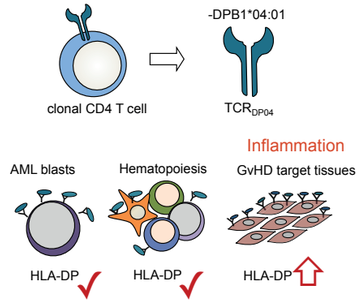


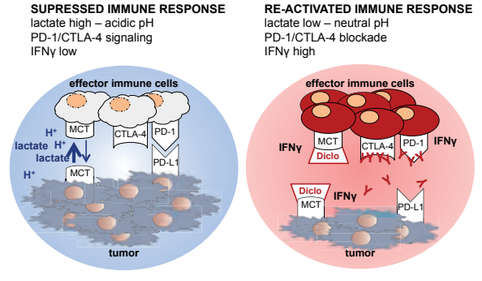
Fig.: HLA-DP-specific T cell receptors and HLA-DP expression patterns on target cells

Original publication:
Herr W et al., HLA-DPB1 mismatch alleles represent powerful leukemia rejection antigens in CD4 T-cell immunotherapy after allogeneic stem-cell transplantation. *Leukemia* 2017; Feb;31(2): 434

Glycolysis inhibition as an adjuvant therapy for checkpoint blockade

The elevated conversion of glucose into lactate (glycolysis) is characteristic for cancer cells. Lactate is usually exported in cotransport with a proton. This results in lactate accumulation and concomitant acidification of the tumor microenvironment, which impairs T and NK cell function. Besides this, the stimulation of inhibitory molecules on immune cells, so-called checkpoints, protects the tumor from an immune response. These molecules are blocked in a so-called checkpoint therapy. Researchers of the Clinical Cooperation Group Immunometabolomics led by **Prof. Dr. Marina Kreutz** and **PD Dr. Kathrin Renner** showed a negative correlation between a high glycolytic index in biopsies of melanoma patients and their response to checkpoint inhibition.

In accordance, the genetic knockout of the lactate-producing enzyme led to an increased response to checkpoint blockade in a murine melanoma model. What is more, the nonsteroidal anti-inflammatory drug diclofenac, which inhibits lactate secretion and thereby acidification by blocking the main transporters, augmented the response to checkpoint inhibition. Therefore, the administration of anti-glycolytic agents may strengthen the response to immunotherapy in patients.

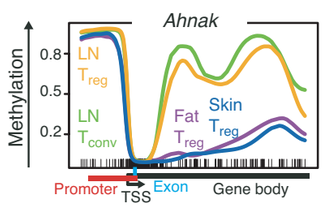


Original publication:
Renner K et al., Restricting Glycolysis Preserves T Cell Effector Functions and Augments Checkpoint Therapy. *Cell Rep* 2019; Oct 1;29(1):135

Molecular characteristics of immune cells involved in tissue repair

How are damaged tissues repaired? Many research groups worldwide are interested in this question and several independent studies could already identify a population of tissue resident T cells that are involved in the regeneration of damaged organs. These special immune cells, called regulatory T cells, migrate into damaged tissue and promote its regeneration by the secretion of wound-healing factors. However, many details have been unclear until recently: What are the characteristics of these immune cells and what molecular mechanisms determine their development? How can this cell population be distinguished from other regulatory T cells with other functions? The research group led by **Prof. Dr. Markus Feuerer** has now made an important step forward in the characterization and precise modeling of this new cell population. The scientists are interested in the question, which genes are switched on, which are switched off, and which are regulated by epigenetics.

Using whole genome methylation data, they have already detected a „signature“ of these immune cells involved in tissue repair, which allows their precise description and definition via surface molecules. Furthermore, it was shown that this population of regulatory T cells requires a specific transcription factor to develop. If this transcription factor is deleted, this cell population is not developed. The results of the project will help researchers all over the world to better understand the role of immune cells in tissue repair and regeneration. At some point in the future, we may be able to promote tissue regeneration by stimulating immune cell migration into damaged tissue.



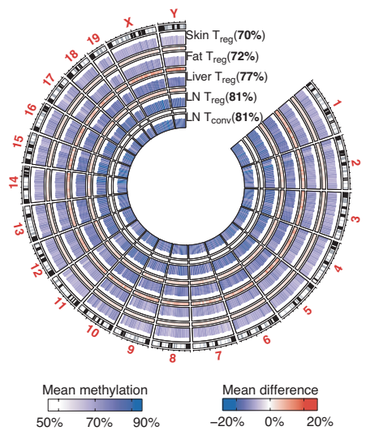


Fig.: DNA methylation analyis of regulatory T cells from different organs

Original publication:
Delacher M et al., Genome-wide DNA-methylation landscape defines specialization of regulatory T cells in tissues. *Nature Immunology* 2017; 18(10):1160

Regulatory T cells: self-regulation of the immune system

If the immune system gets out of control, life-threatening effects ranging from allergy to the self-destruction of the body's own tissue (autoimmunity) may occur. In general, the regulation of the immune system is mediated by specialized immune cells, such as regulatory T cells (Tregs). These can monitor and reduce the activity of other immune cells and contribute to the repair of damaged tissue. **Prof. Dr. Markus Feuerer** and **Dr. Michael Delacher** at the Division of Immunology could now show that Rbpj (recombination signal binding protein for immunoglobulin kappa J region), a gene regulating factor, plays an important role in the functional control of regulatory T cells. Upon genomic deletion of Rbpj, up to 50% of all Treg cells in lymphoid organs developed into regeneration-promoting cells, which usually comprise less than 5%. But Rbpj deleted Treg cells were also unable to control otherwise harmless TH2-polarized immune reactions. These results are an important step towards molecular approaches for the therapeutic control of regulatory cell functions and the targeted use of these important cells for the treatment of immune diseases.

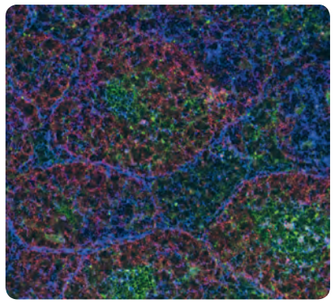


Fig.: Histology of reactive lymph node

Original publication:
Delacher M et al., RBPJ expression in regulatory T cells is critical for restraining TH2 responses. *Nature Communications* 2019

Regulatory T lymphocytes used for the treatment of transplant complications

The aim oft the research group „Immunoregulation“, led by **PD Dr. Petra Hoffmann** and **Prof. Dr. Matthias Edinger**, is to increase the safety and efficiency of allogeneic stem cell transplantation (SCT) for the treatment of patients with leukemia and lymphoma. Graft-versus-Host Disease (GvHD) is a severe and sometimes life-threatening complication after allogeneic SCT caused by donor T cells that attack solid organs of transplanted patients such as the skin, liver and gut.
The research group previously showed that the prophylactic administration of a specific donor T cell subpopulation, called Foxp3+ regulatory T cell (Treg), can prevent this complication after allogeneic SCT. In a recent paper published in the scientific journal „Leukemia“, the researchers significantly extended their initial findings and now demonstrate that donor Treg are also therapeutically effective in ongoing acute GvHD.

These results from experimental SCT models are currently tested in first clinical phase I/II studies in cooperation with the University Hospital Regensburg.

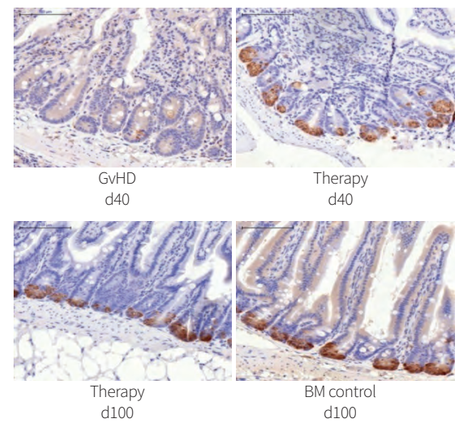


Fig.: Intestine histology of GvHD animals with or without Treg treatment

Original publication:
Riegel C et al., Efficient treatment of murine acute GvHD by in vitro expanded donor regulatory T cells. *Leukemia* 2019; Nov 12

News

Move to New Research Building

In June 2019, the new D5 research building at the University Hospital Regensburg was completed. The first RCI research groups have already moved into the new premises.

Fig.: New RCI research building D5

Anti-CD30 CAR successful in Phase I Study

At the Baylor College of Medicine in Houston, Texas, the phase I study with anti-CD30 CAR T cells for the treatment of Hodgkin's lymphoma and anaplastic large cell lymphoma has been successfully completed (NCT01316146). The CD30 CAR was developed by **Prof. H. Abken**. A commercial phase II study with this CAR is under negotiation.

From left to right:
Prof. Dr. B. Weber (Vice President of UR), Franziska Durst, Stefan Ebner, Dr. Dario Vidojković (Chairman ESdUR e. V.)

Graduation award for Franziska Durst

At this year's Dies Academicus at the University of Regensburg, **Franziska Durst** received the Graduation Award "Prof. Dr. Reinhard-Wirth-Studienabschlusspreis" for her extraordinary achievements and successes to date. In particular, her final thesis in the Master's program "Molecular Medicine" at the RCI achieved the highest grade of 1.0. Since March 2019, Franziska Durst has been continuing her research in the Division of Interventional Immunology as part of a doctoral thesis. The award presented by the Alumni Association at the University of Regensburg (ESdUR e.V.) is endowed with EUR 1,000 and serves to recognize outstanding academic achievements.

m4-Award 2017 for Clinical Cooperation Group

Award winner Prof. M. Mack (2nd from the right)

ImmuCon - Depletion of pro-inflammatory monocytes for the treatment of acute exacerbations of multiple sclerosis (MS)

About 2.5 million people worldwide live with multiple sclerosis. Up to 90% of patients suffer from a form of the autoimmune disease with acute exacerbations. **Prof. Mack** and **Dr. Renner** (Clinical Cooperation Group "Inflammation, Autoimmunity & Fibrosis") have developed a therapeutic approach based on a combination of steroids and a new humanized antibody.

The antibody is directed against so-called monocytes that carry the surface protein CCR2. These immune cells, which are responsible for tissue destruction, will temporarily be removed by antibody therapy to keep brain damage during MS exacerbations to a minimum. With the help of the funding, the team will investigate the synergistic effect of steroids and CCR2 antibodies in greater detail.

Clinical Advisory Board implemented

A Clinical Advisory Board (CAB) with internationally renowned clinical experts has been appointed to advise the RCI in the fields of solid tumor oncology, autoimmune diseases, and chronic inflammation with respect to therapeutic needs, ethical aspects, feasibility, and significance of planned clinical studies at an early stage. **Members of the CAB include Prof. M. Maus, Prof. G. Schett, Prof. R. Thimme, Prof. H. Wiendl, Prof. W. Herr, Prof. H.J. Schlitt, Prof. R. Linker, and Prof. T. Wekerle among others.**

First Patient treated with First-in-class Checkpoint Inhibitor (BAY 1834942) (06/2018)

In cooperation with **Prof. P. Beckhove** and the German Cancer Research Center (DKFZ), Bayer has developed a therapeutic antibody against an immune checkpoint molecule (CEACAM-6) discovered by Prof. P. Beckhove. This antibody has been tested in an international clinical study for the treatment of advanced tumors since 2018. *https://adisinsight.springer.com/drugs/800035873*

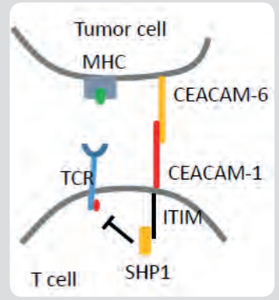


Fig.: Signaling in CEACAM-6-mediated immunosuppression

New Foundation: TriArm Therapeutics

TriArm Therapeutics, based in Shanghai, Taipei, and Regensburg, was co-founded by **Prof. H. Abken** in July 2019 and received US$ 20 million from Series A VC funding. The goal of TriArm is the development and production of CAR T cells for the treatment of malignant tumors and autoimmune diseases. The development of new CAR formats will be performed in the company's laboratories in Regensburg. In Shanghai, production facilities with 35 production units are currently being set up. The focus of the business operation is particularly on the Asia-Pacific region.

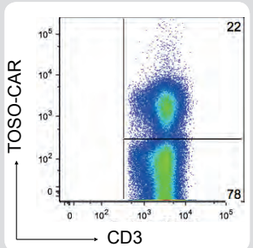
News

Cell therapy manufacturing at the CliniMACS (above) with a transduction efficiency of 20% (right)

Successful TOSO CAR Production

The **research group lead by Prof. H. Abken** identified TOSO (IgM receptor) as a target structure for a CAR T cell therapy of chronic lymphocytic leukemia (CLL). In contrast to the anti-CD19 CAR that is currently in use, the healthy B cells of the patients will not be adversely affected, which is a potential advantage of this therapeutic approach.

On track for testing in a phase I study, the first trial run of the production of anti-TOSO CAR T cells using an automated process has been successfully completed on a clinical scale.



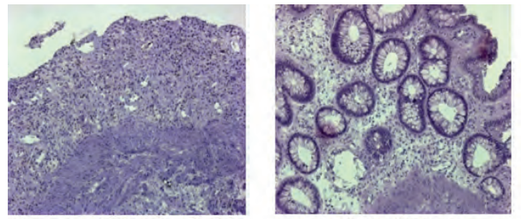
Prof. T. Wekerle

New Cell Therapy against Kidney Transplant Rejection

A phase I-II study on tolerance induction to prevent organ rejection after living donor kidney transplantation was initiated in cooperation with the University Hospital Vienna (**Prof. Dr. T. Wekerle**) (EudraCT 2018-003142-16). The approach combines donor bone marrow and recipient Treg transplantation. The RCI acts as the manufacturer of the Treg preparations and **Prof. M. Edinger** cooperates with his colleagues in Vienna regarding study planning and implementation. One of the first patients of the study was recently treated successfully.

Clinical Studies on Cell Therapy for Graft-versus-Host Disease: The RCI supports new treatment approaches

For the treatment of complications after allogeneic stem cell transplantation, **Prof. Dr. M. Edinger** initiated two clinical studies that investigate the use of donor Treg cells for the treatment of graft-versus-host disease (GvHD). Within the scope of the multicenter study (Regensburg, Mainz, Würzburg) for the treatment of acute GvHD (EudraCT 2012-002685-12), which was initially funded by the Bavarian Immunotherapy Network, 16 patients with life-threatening intestinal GvHD have been treated to date. The safety of this therapeutic procedure has been proven and an encouraging efficacy was detected in some patients.



Intestinal damage in a GvHD patient: before Treg therapy and six weeks after therapy

The chronic form of transplantation complications is investigated in an EU-funded joint project (TREGeneration, www.tregeneration.eu) (EudraCT 2016-003947-12). Here, Treg-based forms of therapy are compared at international sites. In Regensburg, 16 cGvHD patients have already been treated with *in vitro* expanded donor Treg cells and the safety of this therapeutic procedure has been proven for the first time. Efficacy analyses and data on cell distribution and survival (using T cell receptor sequencing) are expected in 2020. The Treg cell preparations for this study have been manufactured by the GMP team at the José-Carreras-Center of the RCI.

TREGeneration

Clinical partners of the EU-funded Horizon 2020 research project *TREGeneration*

Joao MF Lacerda
iMM Lisboa
Lisboa
Portugal

> single infusion of MACS separated Treg

Mario Arpinati
University Hospital S. Orsola
Bologna
Italy

> multiple infusions of cyropreserved MACS-separated Treg

Frederic Baron
Centre Hospitalier Universitaire Sart-Tilman
Liège, Belgium

> single infusion of MACS separated Treg followed by IL-2 treatment

Jerome Ritz
Harvard Medical School
Boston
USA

> single infusion of MACS separated Treg followed by IL-2 treatment

Matthias Edinger
University Hospital Regensburg
Germany

> single infusion of FACS sorted & in-vitro expanded Treg

News

PD Dr. S. Thomas

RCI Support for new Gene Therapy Studies at UKR

With help from its GCP (good clinical practice) and Immuno-monitoring facilities and its biobanking-team, the RCI supports cell therapy studies in cooperation with the UKR, at present, predominantly together with the Dept. of Internal Medicine III (Director: Prof. Dr. W. Herr).

PD Dr. S. Thomas is the principal investigator of the phase I-II study initiated by Medigene® to test PRAME-specific T cell receptor transduced cells for the treatment of patients with acute myeloid leukemia, myelodysplastic syndrome, or multiple myeloma. The first patients have already been enrolled and treated in this first-in-human study.

In cooperation with Novartis®, the so-called BELINDA study was initiated (local clinical investigators: PD Dr. S. Thomas, Prof. Dr. D. Wolff, and Prof. Dr. M. Edinger), in which the efficacy of CAR T cell therapy is tested in comparison to autologous stem cell transplantation for early recurrence of highly malignant lymphoma.

BELINDA: CD20-targeting CAR in r/r hg-NHL, recruiting

Blood-cancer clinical-trial CD-TCR-001 investigates TCR-T-Immunotherapy with MDG1011

Research Collaborations & Consortia

Joint research projects play an important strategic role at the RCI. The RCI and its scientists have been involved in many research collaborations over the past three years; the most formative ones include:

Comprehensive Cancer Center Ostbayern (CCCO)

The CCCO establishes and ensures the highest medical standards of diagnosis and treatment for cancer patients in Eastern Bavaria. In cooperation with national partners (Research Alliance for Immune Medicine, CCC Mainfranken), the CCCO promotes the development of new diagnostic and therapeutic approaches in order to efficiently and promptly translate research results into clinical practice. The RCI is a founding partner of the CCCO and plays a crucial role in the coordination of the CCCO's translational research.

Research Alliance on Immune Medicine

In recent years, the Universities of Erlangen-Nuremberg, Regensburg, and Würzburg have built up internationally recognized expertise in immune medicine. They have also invested in state-of-the-art infrastructure for the development of cellular immunotherapeutics, e.g., at the RCI. This expertise is crosslinked with that of other groups in the Research Alliance on Immune Medicine to develop improved therapeutic approaches against cancer, infection, and autoimmune diseases, as well as in organ and stem cell therapy, and to bring those approaches into clinical use quickly. The Research Alliance for Immune Medicine combines all competencies to enable a closer interaction between basic science and applied research. Hence, new therapeutic approaches can be applied to patients more quickly and research groups can better compete with others on the international level. The development of new therapies takes on average 10 to 20 years, it is very expensive, and very difficult for single universities to realize. With its research departments, technology platforms, and the JCC, the RCI is a central component of the Research Alliance on Immune Medicine and supports, within the framework of SFB-TRR 221 or FOR 2127 for example, the development of immunotherapeutics at partner sites.

Bavarian Center for Cancer Research, BZKF

The Bavarian State Government has established a Bavaria-wide, decentralized cancer research center with the participation of the Bavarian University Hospitals of Augsburg, Erlangen-Nuremberg, Regensburg, Würzburg, and the two Universities of Munich, i.e., Ludwig-Maximilians-University and Technical University of Munich. This center is intended to improve access to top-level medicine in oncology for patients in Bavaria, with new diagnostic and therapeutic procedures and innovative clinical studies. The center will pool the competences and expertise of the six Bavarian cancer clinics to promote and improve cancer research. The RCI is a central partner of the BZKF and will be, in particular, responsible for the development and production of innovative cell therapeutics and immunomonitoring in early clinical trials using the latest analytical technologies.

RCI participation in German Research Foundation projects

The RCI has successfully participated in numerous German Research Foundation (DFG) collaborations to better understand immunological processes of tumor progression on the genetic/transcriptional level, to develop cellular strategies to improve the graft-versus-leukemia effect, and to prevent the rejection in allogeneic stem cell transplantation.

SFB-Transregio 221

The RCI participates in the SFB-Transregio 221 (Modulation of graft-versus-host and graft-versus-leukemia immune responses after allogeneic stem cell transplantation; first funding period 2018-2021; www.gvhgvl.de) and is involved in the integrated graduate school of the SFB-TRR 221. RCI scientists play a pivotal role in this SFB-TRR. Their research focuses on the blocking of new immune checkpoint molecules in multiple myeloma and acute myeloid leukemia to improve allogeneic stem cell transplantation (Prof. P. Beckhove). To enhance the graft-versus-leukemia effect, donor T cells are equipped with allo-HLA-DPB1- specific T cell receptors (TCR-DP) (PD Dr. S. Thomas, Prof. Dr. W. Herr). For the therapy of graft-versus-host disease (GvHD), *in vitro* expanded donor Treg cells will be investigated with respect to their migration, function, and T cell receptor repertoires (PD Dr. P. Hoffmann, Prof. M. Rehli, Prof. M. Edinger) and the efficacy of tissue-resident Treg cells will be evaluated. The researchers will make use of the tissue repair function of these cells for the prevention and therapy of GvHD (Prof. M. Feuerer).

FOR 1961 „Mature T cell lymphomas"

The aim of the RCI research group and its seven partners is to understand the molecular mechanisms of the development of T cell lymphoma and to analyze the interaction of TCR/CAR with TCL1, a transcription factor that is overexpressed in T cell prolymphocytic leukemia (T-PLL). Mouse models for the induction of T cell leukemia by TCL1 and CAR overexpression have been developed to understand the influence of a tonic CAR/TCR signal in the development of T cell lymphoma.

Research Collaborations & Consortia

FOR 2127 “Selection and adaptation during metastatic cancer progression”

The RCI is involved in the elucidation of genetic and epigenetic aberrations in malignant breast cancer progression, the influence of the tumor milieu (Prof. M. Rehli), as well as local and systemic immune tolerance against metastatic tumor cells by ectopic gene expression in antigen-presenting cells of the bone marrow (Prof. P. Beckhove).

FOR 2858 „Role of translocator protein (18 kDa) (TSPO) as a diagnostic and therapeutic target in the nervous system”

TSPO is a protein with numerous functions, especially in the nervous system. RCI scientists (Prof. P. Beckhove) participate in this research group and analyze the role of TSPO in the regulation of immune responses in the brain, e.g., during the progression of brain tumors or in autoimmune reactions.

EU-Programs

The RCI participates in several EU cooperative research programs and training networks within the framework of the Innovative Training Network (ITN) set up for the structured training of young scientists (PhD students) in Europe. The RCI plays a central role as a training center with particular expertise in specialized technologies of immune cell engineering and adoptive T cell therapy for the strengthening or suppression of specific immune reactions.

The RCI has participated in the following collaboration projects (2017-2019):

Enacti²ng (Horizon 2020)

Using high resolution microscopy, the research association of academic and commercial partners will study the formation of an immunological synapse of T cells with their respective target structures in order to understand the T cell anti-tumor response at the molecular level. The RCI (Prof. H. Abken) studies the temporal-spatial kinetics of synapse formation in the CAR-mediated T cell response against solid tumors.

TREGeneration (Horizon 2020)

In this consortium, adoptively transferred donor Treg cells for the therapy of chronic graft-versus-host disease after allogeneic stem cell transplantation are tested in clinical studies for the first time (Prof. M. Edinger).

The One Study (Horizon 2018-2020)

A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation Integrating basic research ideas for improved health care

The ONE Study applies the novel concept of cell therapy to human clinical organ transplantation. This cooperative project aims at developing and testing various immunoregulatory cell products in organ transplantation recipients, allowing a direct comparison of the safety, clinical practicality, and therapeutic efficacy of each cell type.

The central focus of the ONE Study project is to:

- produce and manufacture distinct populations of hematopoietic immunoregulatory cells
- comparatively study the tolerogenic characteristics of these regulatory cell types
- test these cell therapy products side by side in a clinical trial with living donor renal transplant recipients

INsTRuCT (Innovative Training Network, EU-Horizon 2020)

The INsTRuCT consortium is a research network of leading European scientists from academia and industry, dedicated to basic research and clinical translation of immunotherapies based on myeloid regulatory cells (MRC). RCI scientists (Prof. E. Geissler, Prof. M. Rehli) focus on the characterization, classification, and development of myeloid regulatory cells.

PAVE (Marie-Curie-EU Training Network)

The PAVE consortium focuses on the interdisciplinary development of new nanotechnology approaches for the combined immunotherapy of pancreatic cancer using nanovaccines, cellular immunotherapies, personalized nanomedical approaches, image-guided surgery and molecular imaging. Scientists at the RCI (Prof. P. Beckhove) investigate tumor-specific T cell responses and immune resistance mechanisms of pancreatic tumors.

Research Collaborations & Consortia

COST-Consortia

RCI scientists participate in several consortia for the exchange of information and research date about immune cell therapy in Europe, e.g.:

CA17138 - Integrated European Network on Chronic Graft-versus-Host Disease (cGvHD)

A FACTT- Action to Focus and Accelerate Cell-based Tolerance-inducing Therapies

ERC-Consolidator Grant REGiREG

(Prof. M. Feuerer, 2015-2020): Regulatory T cells (Tregs) play a central role in the suppression of immune reactions against the body's own tissue. Unfortunately, they also prevent desired immune reactions against tumor cells. The aim of the ERC grant is to search for new ways and drugs to keep Tregs cells and their function in check and to help the immune system to effectively fight against cancer cells. In addition, Prof. Feuerer is interested in another field that is still largely unexplored, i.e., the tissue specific development of Treg cells. It is already known that certain groups of Treg cells specialize within organs and take over organ-supporting functions in the absence of a classical immune response.

German Aid Consortia

The RCI participates in academic/clinical consortia of the German Cancer Aid to evaluate innovative products and new strategies of adoptive T cell therapy in academic phase I studies ("investigator initiated trials"), i.e., CAR T-cell development with completed preclinical evaluations.

TOSO CAR for CLL therapy

The consortium includes four partners for the development of a CAR T cell therapy of CLL. The concept is based on research of Prof. H. Abken, i.e., TOSO as an alternative target with potentially reduced side effects compared to the currently used CD19 CAR. The RCI researchers developed the TOSO CAR, are currently setting up the manufacturing process for TOSO CAR T cells and will act as manufacturer for the related clinical trial within the JCC.

TECLA – T cells engineered for CD30+ cutaneous lymphoma attack

TECLA is a funded phase I study for the therapy of CD30+ cutaneous lymphoma with CD30 CAR T cells. The GMP-compliant virus for the transduction of CAR has been produced; the preparation of the manufacturing process for CAR T cells is ongoing.

CD22 CAR

The aim of the consortium is to develop an optimized anti-CD22 CAR for clinical use in the treatment of B-cell lymphoma and leukemia. The RCI (Prof. H. Abken) is involved in work on the optimization of the CD22 CAR and its function.

From CARs to TRUCKs

The consortium with nine partners is developing vectors and procedures for the production of TRUCKs, i.e., CAR T cells with an induced release of transgenic cytokines for the treatment of GD2+ pediatric tumors. The RCI (Prof. H. Abken) has developed, optimized, and tested the GD2 CAR with induced IL-12 release *in vitro*. Mouse models at partner sites will demonstrate the efficacy and safety of the developed procedures to prepare for their clinical evaluation.

T-Lock

The consortium is working on the breakdown of T cell resistance of tumors in the therapy with immune-checkpoint-blocking antibodies. The participating scientists at the RCI (Prof. P. Beckhove) are using genome-wide screening methods for the systematic identification of common resistance mechanisms of different tumor types to immune checkpoint therapies. The aim is to develop personalized approaches for the prediction and breaking of immune resistance in tumors.

Research Collaborations & Consortia

Restore

The pan-European research initiative RESTORE, coordinated by the BIH Center for Regenerative Therapies and the Charité Berlin, is dedicated to the development of cell and gene therapies (Advanced Therapies) to combat diseases in a holistic way. The aim of the initiative is to establish Europe as a leader of Advanced Therapies promoting successful collaborations between research institutes, hospitals, patient associations, and pharmaceutical companies. The RCI is an active partner in this initiative, and the European Commission has already pledged start-up funding. RESTORE is currently participating in the European Commission's FET Flagship Competition.

MAGIC

The RCI coordinates the central immunomonitoring for the international research project "Mt Sinai Acute GvHD International Consortium" on a European level in close collaboration with the Department of Internal Medicine III, the Institute for Medical Microbiology and Hygiene, and the Institute of Functional Genomics of the Medical Faculty of the University of Regensburg. MAGIC's goal is to test biomarkers of GvHD in patients of the leading transplantation centers worldwide (in Germany the University Medical Centers of Hamburg, Freiburg, Würzburg, Erlangen, Frankfurt a.M., Dresden, Cologne, Münster, and the Charité in Berlin, among others). Serum samples for biomarker determination and data on GvHD will be collected weekly and in compliance with international standards. The aim of the consortium is to validate already known and new biomarkers for the determination of GvHD prognosis in the future. Based on this, clinical treatment concepts for risk-adapted early therapies will be developed.

FANTOM

The Functional ANnoTation Of the Mammalian genome project is a worldwide cooperation project to identify all functional elements of the mammalian genome. The goal of the 6th edition of the FANTOM project (FANTOM6) is to elucidate the function of long non-coding RNAs (lncRNAs) in the human genome. Prof. M. Rehli (RCI) focuses on lncRNAs in macrophages and regulatory T cells.

Vienna Science and Technology Fund (WWTF)

Prof. M. Edinger (RCI) cooperates with Prof. Dr. T. Wekerle (University of Vienna) in a clinical study funded by the Vienna Science and Technology Fund (WWTF). The study investigates the induction of tolerance after living donor kidney transplantation by adoptive transfer of *in vitro* expanded Treg cells.

BMBF Joint Programs

RCI scientists participate in BMBF joint programs in order to develop central processes for the production of cells as pharmaceutical products and to bring them to clinical use in cooperation with pharmaceutical/biotech companies.

BMBF CD20 CAR-Time

With the industrial partner Miltenyi Biotec and two academic partners, the consortium is developing a CD20 CAR for the elimination of melanoma stem cells destined for clinical testing. Prof. H. Abken has developed the scientific concept and an optimized CD20 CAR for further clinical development. The RCI is also interested in elucidating the mechanisms of growth control by the few CD20+ stem cells in established melanomas. The respective phase I study with CD20 CAR T cells is open for patient recruitment.

Collaborations with pharmaceutical and biotech companies

TriArm Therapeutics

This new spin-off (Series A funding July 19, 2019) based in Shanghai, Taipei, and Regensburg will develop, produce and (together with partners) clinically test CAR T cells and TCR T cells for the treatment of malignant tumors. Innovative manufacturing procedures with short production times, non-viral gene transfer, and modified intracellular signaling pathways will be used.

iOmx AG

In 2016, iOmx AG (based in Munich, Germany) was founded by RCI scientists, with the help of international venture capital, in order to transfer discoveries on new immune checkpoint molecules and immune resistance mechanisms in various tumors into clinical application in a timely manner. Currently, therapeutics (blocking antibodies and small compounds) against several oncological targets are in preclinical development.

In addition, further collaborations with the following pharmaceutical and biotech companies facilitate the clinical translation of discoveries made by RCI scientists:

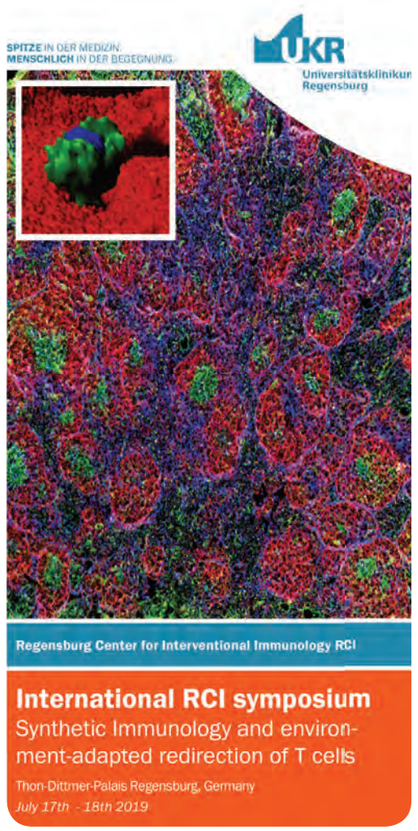
- BioNTech
- Celegene
- Celyad
- Gilead
- Medigene
- Miltenyi Biotec
- Novartis
- Pharis

Conferences & Seminars

On July 17-18, 2019, 170 international participants met at the

International RCI Symposium
„Synthetic immunology and environment-adapted redirection of T cells“.

Find more information on our website:
rcisymposium2019.jimdofree.com



International RCI Seminars

Since 2018, RCI has organized monthly lectures on RCI-relevant topics. They are very popular beyond the RCI and give young scientists the opportunity to discuss their research results with international scientists.

RCI – International Lecture Series 2018/2019

14.11.2018 Prof. Kathrin Schumann, Munich
19.12.2018 Prof. Christina Zielinski, Munich
09.01.2019 Prof. Dietmar Zaiss, Edinburgh
27.02.2019 Prof. Sine Reker Hadrup, Copenhagen
13.03.2019 Prof. Nicole Joller, Zurich
10.04.2019 Dr. Valerie Zimmermann, Montpellier
08.05.2019 Dr. Mirijam Heemskerk, Leiden
05.06.2019 Prof. Adelheid Cerwenka, Mannheim
10.07.2019 Dr. Carolin Daniel, Munich

RCI Lecture Series 2019/2020

11.12.2019 Prof. Bertram Bengsch, Freiburg
15.01.2020 Prof. Wolfgang Kastenmüller, Würzburg
12.02.2020 Prof. Wolfgang Schamel, Susana Minguet, Freiburg
25.03.2020 Prof. Georg Gasteiger, Würzburg
22.04.2020 Prof. Gabriele Niedermann, Freiburg
13.05.2020 Dr. Dominguez Conde, London
17.06.2020 Dr. Mirjana Efremova, London
15.07.2020 PD Annette Künkele, Berlin

Program Areas

Program Area I

Mechanisms and Targets

Program Area I investigates the highly complex interactions of different immune cells with each other and with the other cells of the organism.
The goal is to understand how the immune system ensures the organism's health.
Dysfunctions can lead to severe diseases such as cancer, chronic inflammation, and autoimmunity or to undesirable, potentially fatal rejection reactions after organ transplantation.
Program Area I is located at the interface between basic research and translational research with the aim of discovering starting points and targets for new immunotherapeutic approaches and exploring their relevance for targeted immunotherapeutic intervention.
Over the course of the year 2020, this program area will be supplemented by a W2 professorship for algorithmic bioinformatics. All scientific groups of Program Area I work closely together in translational projects with the scientists of Program Area II.

Prof. Dr. Markus Feuerer

1

Division of Immunology

Division of Immunology Staff

Central Question:

How is tissue repair regulated by immune cells and how can this be modulated?

Main Research Focus

The Division of Immunology focuses on mechanisms involved in the induction of peripheral immune tolerance, immune regulation, and organ homeostasis which are induced and regulated by specialized immune cells such as regulatory T cells (Treg) or macrophages. The goal is to elucidate their basic molecular mechanisms, differentiation and tissue specialization, as well as their function and interaction with tissue cells. Targeted therapeutic manipulation of immune cell functions in tissue regeneration might, in the future, enable the develpment of specialized immunotherapies for individual tissues and organs to improve treatment of chronic inflammation, autoimmune diseases, and transplant rejection, as well as breaking immune cell blockade in the context of cancer. Considering the central question of how regulatory mechanisms can be exploited for immunotherapy, we are dedicated to the development of new artificial immune networks. Not only would these strengthen immunotherapeutic approaches in cancer therapy, but they could also support immune cells which are controlling inflammatory reactions.

Current Projects

The group is working on the following topics:

A. **Regulatory T cells in regeneration**
B. **Functional characterization of fibroblast - immune cell interaction**
C. **Immunological tolerance mechanisms of the skin**
D. **Influence of microbial diversity on immune reactions**
E. **Regulatory T cells and cardiac diseases**
F. **Synthetic sensors for regulatory T cells**
G. **Synthetic immunology**

The understanding of tissue regeneration and organ homeostasis by immune cells is still in its infancy. Important molecular mechanisms and interaction partners are yet unknown. Therefore, the Division of Immunology focuses on these questions. We will use this knowledge for the development of new immune cell therapies using techniques of synthetic immunology.

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
1.324	22	5
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

DELACHER M, et al. Precursors for Nonlymphoid-Tissue Treg Cells Reside in Secondary Lymphoid Organs and Are Programmed by the Transcription Factor BATF. *Immunity* 2020; 18:295

CHENG HW, et al. Origin and differentiation trajectories of fibroblastic reticular cells in the splenic white pulp. *Nat Commun* 2019; 15:1739

DELACHER M, et al. Rbpj expression in regulatory T cells is critical for restraining TH2 responses. *Nat Commun* 2019; 8:1621

DELACHER M, et al. Genome-wide DNA-methylation landscape defines specialization of regulatory T cells in tissues. *Nat Immunol* 2017;18(10):1160

Third-party Funding (Selected)

EU ERC-Co Grant #648145 RegiReg
DFG SFB/Transregio 221
DFG HE3116/9-1

Collaborators (Selected)

Prof. B. Brors, DKFZ, Heidelberg
Prof. J. Abramson, Weizmann institute of Science, Israel
Prof. B. Ludewig, Kantonsspital St. Gallen, Switzerland

Staff

Scientists

Prof. Dr. Markus Feuerer
Prof. Dr. Thomas Hehlgans
Prof. Dr. Uwe Ritter
Dr. Bernd Echtenacher
Dr. Michael Delacher
Dr. Sebastian Bittner
Dr. Lisa Schmidleithner

Doctoral Students

Christina Fischer
Lieke Sanderink
Asmita Pant

Technicians

Brigitte Ruhland
Dorothea Weber-Steffens
Marina Wuttke
Kathrin Schambeck
Veronika Hofmann
Luise Eder (office)

Project 1.1

Tissue regeneration by immune cells

How could we support and use the immune system to treat tissue damage?

Staff:
Dr. Michael Delacher
Dr. Sebastian Bittner
Dr. Bernd Echtenachter
Dr. Lisa Schmidleithner
Lieke Sanderink
Asmita Pant
Marina Wuttke
Veronika Hofmann
Kathrin Schambeck
Prof. Dr. Markus Feuerer

The immune system is able to fight against pathogens and can help repair damaged tissues and organs. This project examines how we could use the self-healing function of the immune system in therapeutic approaches.

The self-regulation of the immune system is one of its most important features and is mediated by a specialized immune cell population called regulatory T cells. These cells are able to monitor other immune cells and to reduce their activity. In addition, highly specialized, tissue resident regulatory T-cells can contribute to the repair of injured tissues by releasing helpful molecules.

Self-healing or regulation

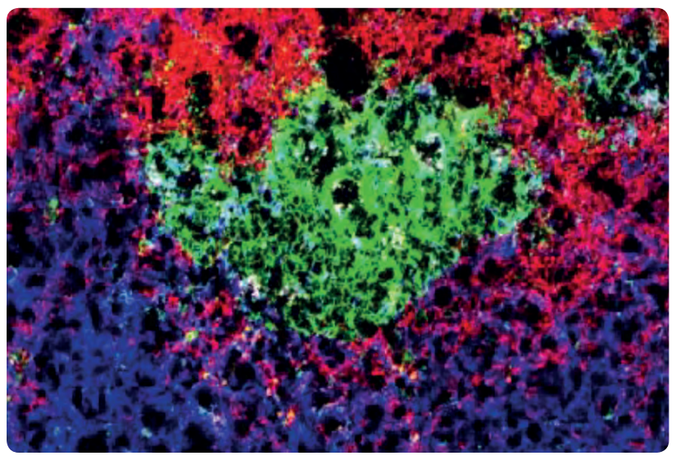
We are interested in the difference between self-healing and regulation of the immune system. We already know some details about the function of regulatory T cells: On the one hand they contribute to tissue repair and are, therefore, primarily found in damaged tissue.

On the other hand, they control the immune system in order to protect the body from excessive inflammation.

In our ongoing research, we are investigating the development of cells that contribute to tissue repair and how we can use these cells in therapy, for example for the regeneration of injured tissue after bone marrow transplantation (stem cell transplantation) in leukemia patients.

We are also investigating how we can specifically weaken regulatory T cells in malignancies in order to allow an increased immune cell reactivity against the tumor.

Fig.: Reactive germinal center



Project 1.2

Immune cells in the heart

Regulatory T cells and cardiac diseases

Staff:
Dr. Sebastian Bittner
Veronika Hofmann
Marina Wuttke
Prof. Dr. Markus Feuerer

The development of cardiac failure can be accompanied by inflammatory processes in the heart. Therefore, this project will investigate the contribution of regulatory immune cells to heart function and whether these cells are a possible target for future immunotherapies.

Cardiac insufficiency is a serious functional disorder of the heart showing a deficient pumping function. The body is no longer supplied with sufficient blood and thus the organs with enough oxygen and energy. Cardiac failure is one of the main causes of cardiovascular morbidity and mortality. In addition, the hospitalization of cardiac patients is an enormous economic factor. To develop new possibilities for therapeutic intervention, there is a crucial need for a detailed analysis of the pathological mechanisms of this disease.

Can Tregs protect the heart?

In recent years, various studies showed a protective effect of so called regulatory T cells (Tregs).

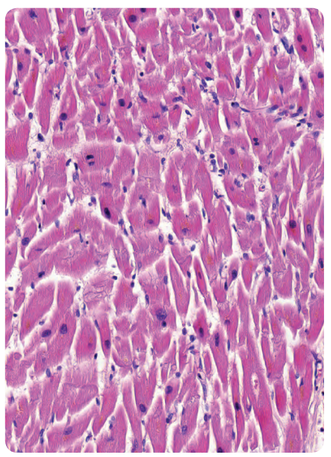
These immune cells play a decisive role in self-tolerance and prevention of eventual misdirected immune reaction against the body's own structures.

They modulate the function of other immune cells such as effector T cells and, therefore, also play an important role in autoimmune diseases and cancer. It is known that Treg cells can have a protective effect against cardiovascular diseases, especially atherosclerosis, heart attack, and dilated cardiomyopathy (disease of the heart muscle). However, the involved features of Treg cells are still largely unknown.

Our special focus is on molecules that promote wound healing and regeneration of damaged muscle tissue.

A better understanding of the role of Treg cells in the pathophysiology of cardiac failure will help to develop new approaches for future therapies and investigate the organ-specific functions of these cells.

Fig.: Heart muscle



Staff:
Dr. Sebastian Bittner
Veronika Hofmann
Brigitte Ruhland
Prof. Dr. Thomas Hehlgans
Prof. Dr. Markus Feuerer

Project 1.3
Synthetic sensors for Tregs

Artificial environment scanner – a new concept for Treg cell-based therapies of chronic inflammation and autoimmune diseases

In this project, we will design artificial sensors for regulatory immune cells to better detect and control inflammation. Using the latest technologies, immune cells will be reprogrammed and equipped with new functions to be applied as completely new and innovative therapeutic approaches for the treatment of inflammatory diseases.

The immune system provides effective defense and protection against pathogens. It has to distinguish between the body's own and foreign structures such as potentially dangerous bacteria, viruses and fungi, and it has to be strictly controlled.
Misdirected immune reactions against the body due to a lack of tolerance are summarized as autoimmune diseases. One of the most important control mechanisms is provided by so called regulatory T cells (Tregs).

They modulate the function of other immune cells and thus prevent autoimmune diseases and allergies. Numerous research projects in recent years have demonstrated that Treg cells are promising cells for innovative therapeutic approaches for patients with rheumatoid arthritis, type 1 diabetes, and chronic inflammatory bowel diseases.

In addition, their application in organ and stem cell transplantation can reduce the rejection of foreign tissue and cells. In recent years, various new synthetic methods have been developed to modify immune cells and provide them with new functions.

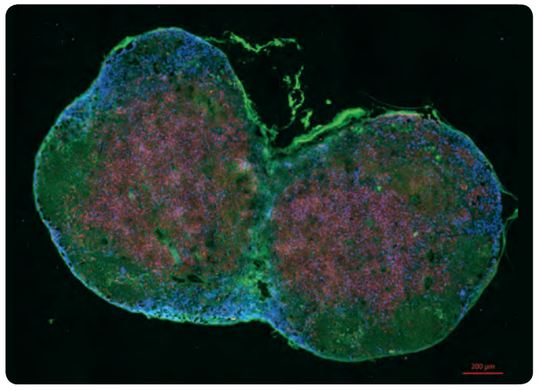


Fig.: Immnofluo-rescence image of a reactive lymph node

High-tech Treg cells

At the RCI, we are now using these new high-tech methods to reprogram and improve Treg cells for therapeutic purposes. We want to developed synthetic sensors for the detection of inflamed tissue. Treg cells armed with these artificial sensors will be able to detect various inflammatory molecules in their environment and induce regenerative and protective effects directly within the inflamed tissue. These improved and reprogrammed high-tech cells could, in the future, be used in the therapy of various inflammatory (auto-immune) diseases.

Project 1.4
Fibroblasts and the immune system

Functional characterization of the interaction of fibroblasts and immune cells for therapeutic intervention

Fibroblasts are part of the connective tissue and play an important role during wound healing. Their deregulation can cause errant wound healing processes and even the spread of cancer. We want to investigate the involvement of the immune system as well as possibilities for therapeutic intervention.

Staff:
Dr. Lisa Schmidleithner
Marina Wuttke
Veronika Hofmann
Kathrin Schambeck
Prof. Dr. Thomas Hehlgans
Prof. Dr. Markus Feuerer

The structure of different tissues is defined by their extracellular matrix which is produced by fibroblasts and regulates cell-cell communication, cell adhesion and cell differentiation.
Fibroblasts, therefore, play a central role in the maintenance of organ homeostasis. During wound healing, fibroblasts can be activated by the immune reaction accompanying the injury. This activation can promp the production of a variety of different proteins further promoting the regeneration process. Moreover, fibroblasts themselves can produce cytokines which, in turn, activate the immune system after an injury and support a more effective immune response.
Fibroblasts play another important role in immune reactions: They generate structures that enable the interaction of immune cells and thus promote an immune response.

Therefore, fibroblasts are not only necessary for general homeostasis, but also for fast and targeted immune reactions.
However, if fibroblasts are deregulated, this balance can be disturbed and may lead to various diseases, e.g. uncontrolled wound healing can cause fibrotic diseases and deregulated immune responses.
Furthermore, so-called tumor-associated fibroblasts support tumor growth by generating an environment which is conducive to the spread of cancer cells while inhibiting the anti-tumor activity of immune cells.

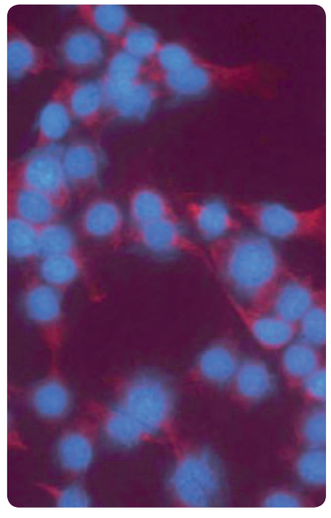


Fig.: Fibroblasts

Fibroblast – immune cell interaction as a therapeutic target

We are interested in the interactions between immune cells and fibroblasts.

How do fibroblasts modulate the immune response? How does the immune system activate fibroblasts? What role do immune cells play during the development, differentiation and function of fibroblasts? And where can we intervene to prevent excessive reactions on the part of the fibroblasts?

Staff:
Christina Fischer
Dorothea Weber-Steffens
Prof. Dr. Thomas Hehlgans

Project 1.5
Influence of microbial diversity on immune reactions

We want to analyze the influence of the microbiome and its metabolites on immune reactions in homeostasis and immune cell activation. Our aim is to support cellular immunotherapies on the one hand and modulate immune functions on the other hand to control inflammation, autoimmune reactions, and transplant rejection.

The surface of the human body is populated by innumerable microorganisms, which as a whole are called microbiome. These complex communities of bacteria live in a symbiotic relationship with the host. The host can profit from the colonization of symbiotic bacteria, which prevents the colonization of pathogenic bacteria on the skin, the lungs, the gastrointestinal tract, and other body surfaces. In addition, bacteria allow the metabolization of otherwise indigestible food components, providing the body with essential nutrients and energy.

Furthermore, it has been shown that alterations in microbial diversity are associated with changes of microbial metabolites that influence immune cell effector functions. In our established model systems, we investigate which bacterial metabolites contribute to the regulation of these effector functions during homeostasis as well as during disease-related immune activation and which molecular control mechanisms they are based on.

We want to identify immune cell effector mechanisms that are controlled by microbial diversity and find possibilities for the translation into personalized immunotherapy.

Fig.: Illustration of a bacteria - immune cell - interaction

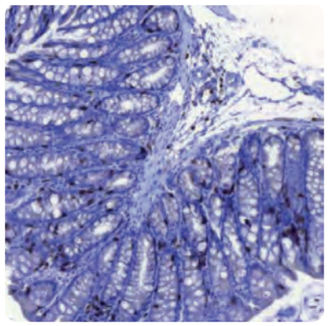


Fig.: Hematoxylin-Eosin-staining of a colon section

Staff:
Prof. Dr. Uwe Ritter
Prof. Dr. Markus Feuerer

Project 1.6
Immunological tolerance mechanisms of the skin

The integration of the skin-associated lymphoid tissue for therapeutic intervention

We are interested in the immune system of the skin. In particular on the question of how long-term contact with the environment can influence the skin-associated immune response. We try to understand the molecular switches in the immune system which contribute to the maintenance of the immunological balance and tolerance. Our goal is to correct deregulated immune responses by modulation of these molecular switches.

With a surface area of 2 sq m, the skin is one of the largest organs in our body. The direct exposure to the environment results in damage, ranging from microscopic wounds to large injuries. Although these processes take place on the surface of our skin, they are still recognized by the immune system. Our skin is equipped with special communication systems (lymph), which transmit necessary information directly to the control centers of the immune system. This skin-associated lymphatic system represents a network, reaching the complexity of our brain. It connects the skin to the lymph nodes, where regeneration programs are initiated to restore and maintain skin functionality. This has to be strictly controlled by innumerable control mechanisms to prevent immune pathological responses against our own tissue.

Misleaded immune reactions can lead to autoimmune diseases

However, our immune system does not always function properly. Thus, misdirected immune reactions can be generated, resulting in autoimmune diseases like rheumatoid arthritis and multiple sclerosis. A disturbed immunological balance is also discussed to be causal in cancer and transplant rejection. We want to decrypt so far unknown checkpoints of the immune system, that are involved in the correct coordination of immune cells. Our focus is on the immune system of the skin, where the immunological balance and tolerance must be constantly readjusted in response to new environmental factors.

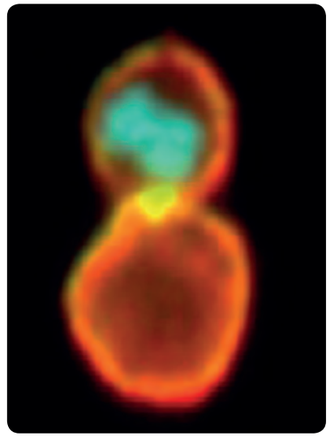


Fig. 1: The picture shows the interaction of two immune cells. At the yellow spot, information is exchanged that determines the type of immune response.

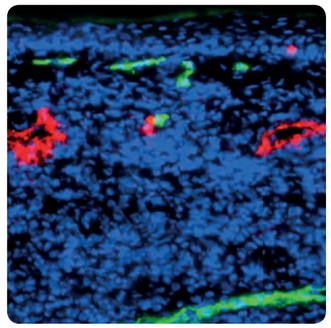


Fig. 2: The picture shows blood vessels (red) and lymphatic vessels (green).

Prof. Dr. Philipp Beckhove

2

Division of Interventional Immunology

Central Question:

How do tumor cells communicate with immune cells and how can we break the immune resistance of tumors?

Main Research Focus

The Division of Interventional Immunology investigates the cellular and molecular mechanisms of immune cells used to fight and control tumor growth. From this, new immunotherapeutic approaches are developed and tested in early clinical trials at the RCI and together with external partners. Special emphasis is put on the characterization of determinants of successful and failing T lymphocyte reactions against tumors, as well as the identification and clarification of immune regulatory genes and signaling pathways in tumor cells. The researchers of the division characterize tumor-specific T cell responses in the human blood, bone marrow and tumor tissue. Examples of the successful translation of this research include the adoptive transfer of tumor-reactive memory T cells derived from bone marrow, the recruitment of tumor specific T cells into tumor tissue using low-dose irradiation, and the collaboration with pharmaceutical and biotech companies that are using our findings on immune checkpoint molecules to develop new therapeutics for cancer immunotherapy. The Division of Interventional Immunology is directly linked to the Department of Internal Medicine III (Hematology/Oncology) at the UKR and thus offers excellent conditions for a patient-oriented immunological research and its clinical translation.

Current Projects

The division is currently working on the following projects:

A. **Systematic identification of immune checkpoint and immune resistance genes in tumor cells using single cell deep sequencing techniques/ RNAi-based high-throughput screening platform**
B. **Investigations on mechanisms and signaling pathways of selected immune checkpoint/immune resistance genes using molecular genetic manipulation of immune cells and tumor cells; initiation of drug development programs for therapeutic inhibition, in some cases in partnerships with pharmaceutical companies**
C. **Development of new TRUCK concepts for genetically manipulated T cell therapies for the local inhibition of immunoregulatory genes**
D. **Investigations on the induction and conversion of regulatory T cells derived from tumor-specific Tconv cells in the bone marrow and tumor microenvironment using siRNA-based high-throughput screening methods**
E. **Studies on spontaneously and therapeutically induced tumor-specific T cell responses in tumor patients and their clinical relevance**

Division of Interventional Immunology Staff

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
1.568	15	9
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

GE Y, et al., Tumor-Specific Regulatory T Cells from the Bone Marrow Orchestrate Antitumor Immunity in Breast Cancer. *Cancer Immunol Res* 2019; 12:1998-2012

F. SCHMITZ-WINNENTHAL, et al., A phase 1 trial extension to assess immunologic efficacy and safety of prime-boost vaccination with VXM01, an oral T cell vaccine against VEGFR2, in patients with advanced pancreatic cancer. *Oncoimmunology* 2018; Jan 16;7(4):e1303584

RAPP C, et al., Identification of T cell target antigens in glioblastoma stem-like cells using an integrated proteomics-based approach in patient specimens. *Acta Neuropathol* 2017; Aug;134(2):297-316

DETTLING S, et al. Identification of CRKII, CFL1, CNTN1, NME2, and TKT as Novel and Frequent T-Cell Targets in Human IDH-Mutant Glioma. *Clin Cancer Res* 2018;24(12):2951–2962.

Third-party Funding (Selected)

EU-PAVE A Nanovaccine Approach for the Treatment of Pancreatic Cancer (2019-2023)
DKH Consortium T-Lock - TP4 Unravelling immune resistance mechanisms in melanoma cells via RNAi screening (2019-2022)
FOR 2127 Selection and adaptation during metastatic cancer progression, 02/2018-01/2021
SFB-TRR-221 Modulation of graft-versus-host and graft-versus leukemia immune responses after allogeneic stem cell transplantation (2018-2022)
FOR 2858 The role of TSPO in immune control of glioblastoma (2019-2022)

Cooperations (Selected)

Prof. L. Klein, LMU, Munich
Prof. B. Brors, DKFZ, Heidelberg
Prof. P. Hau, University of Regensburg
Prof. C. Herold-Mende, University of Heidelberg

Staff

Scientists
Prof. Dr. Philipp Beckhove
Dr. Slava Stamova
Dr. Valentina Volpin
Dr. Anchana Rathinasamy
Dr. Maria Xydia

Doctoral Students
Franziska Durst
Julian Sax
Ayse Nur Menevse

Technicians
Birgitta Ott-Rötzer
Karin Holz
Jasmin Mühlbauer
Heiko Smetak
Sabine Termer (office)

Dr. Maria Xydia

Project 2.1

The origin of tumor-promoting regulatory T cells in cancer patients

How to block a tumor accomplice

Suppressor Tregs inhibit tumor destruction. They are found in increased numbers in cancer patients and reduce patient survival. Dr. Xydia investigates mechanisms of Treg formation and aims to discover factors that drive Treg generation and function in cancers. Such factors could be targeted by drugs, antibodies, or engineered killer T-cells to generate an efficient cancer immunotherapy.

Our immune system is armed with T cells that can distinguish between foreign bodies and our own tissues with the help of T cell receptors (TCR). Each T cell is equipped with a unique TCR-fingerprint, which recognizes and binds only particular antigens, resulting in T cell activation.

While killer T cells recognize and destroy tumors, suppressor regulatory T cells (Treg) calm down the killers to protect healthy tissue from damage but simultaneously inhibit tumor eradication.

Cancer patients show increased Treg numbers which reduce their life expectancy. However, the mechanisms behind this phenomenon are not yet clear. According to animal experiments, tumor factors induce Treg proliferation but also get killers to change their identity into suppressors. As modern immunotherapy aims to increase killers in the tumor, Dr. Maria Xydia investigates whether killers keep their destructive power or convert to tumor-promoting suppressors in cancer patients. Using laser beams, she isolated single T cells from tumors and blood of breast cancer patients and sequenced the genetic material of each cell separately to identify its TCR fingerprint and functional identity. She discovered that killers but not suppressors share common fingerprints between blood and tumor, and, therefore, have common ancestors that enter the tumor. In tumors, killers and suppressors shared many common fingerprints, showing that they had differentiated from the same T cell.

When Dr. Xydia looked deeper into single cell gene expression, she could identify common ancestors among activated T cells, which had only recently met their antigen but not yet developed any killer or suppressor identity. Bioinformatic analysis predicted that activated T cells can develop either to powerful killers or to strong tumor supporters with 1662 genes possibly involved in this decision. Selected cytokine genes are further investigated by Franziska Durst with respect to their role in the generation of tumor-specific suppressors, and may act as potential targets for efficient cancer immunotherapy.

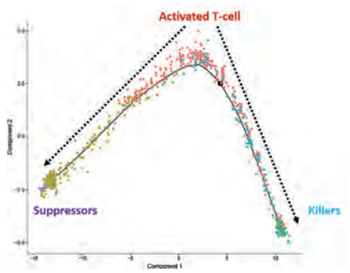


Fig.: Activated single T cells developing into tumor killers or tumor-promoting suppressors

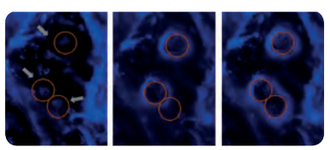


Fig.: Isolation of single T cells (blue) from breast tumors using laser beams

Project 2.2

Regulatory T cell migration to the tumor

The journey of regulatory T cells from the bone marrow to the tumor

The aim of this project is to identify specific migratory cues that guide the preferential migration of regulatory T cells (Tregs) to the tumor. Identifying such migratory mechanisms is important for the design of therapeutic strategies that restrict the entry of Tregs into the tumor thereby enhancing anti-tumor immunity. This project fits into the major focus of the RCI to understand the role of Tregs in the tumor.

Regulatory T cell (Tregs) are a special cell type that supports the growth of a tumor by suppressing immune cells and anti-tumor immune reactions. This results in poor clinical outcome and reduced patient survival.

The bone marrow (BM), which is the primary lymphoid organ, is another preferred location during regulatory T cell (Treg) recirculation and contributes to peripheral tolerance against self antigens and potential tumor antigens in cancer patients. The research of Dr. Rathinasamy is focused on the understanding of the compartmentalization of tumor antigen-specific Tregs in BM, blood, and tumor. In addition she will identify mechanisms that specifically mobilize tumor specific Tregs from the bone marrow to the tumor.

Mammoglobin is an antigen that is overexpressed in breast tumors. Dr. Rathinasamy detected reduced frequencies of mammoglobin specific Tregs in the BM of breast cancer patients that corresponded with an increased frequency in the blood and tumor. This suggests that tumor antigen-specific Tregs are mobilized from the BM to the tumor via the blood.

Migration marker S1P1 and CCR2 correlate with Treg accumulation in the tumor

The scientist identified two major migratory markers (S1P1 and CCR2) highly expressed by tumor antigen-specific Tregs in BM. The ligands of these markers (S1P and CCL2) showed a concentration gradient from the BM (low ligand concentration) to the blood (high ligand concentration) which suggests a preferential migration of tumor antigen-specific Tregs from the BM to the blood.

Dr. Anchana Rathinasamy

The expression of CCR2 ligand (CCL2) in breast tumor tissue resulted in the accumulation of Tregs. This preferential mobilization of antigen-specific Tregs from the BM contributes to poor clinical responses in cancer patients. Therefore, disrupting increased S1P levels in the blood or using monoclonal antibodies to block CCR2 may represent a therapeutic strategy to restrain Tregs within the BM and reduce Treg infiltration into the tumor.

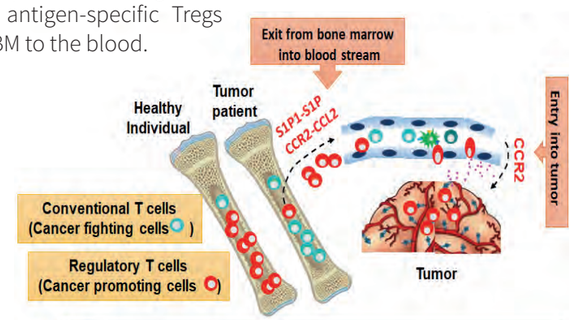


Fig. Illustration of the migration of regulatory T cells from bone marrow to tumor tissue

Dr. Valentina Volpin

Project 2.3

New molecules for the fight against cancer

CAM kinase leads to resistance to immunotherapy. CAM kinase inhibitors could improve cancer treatment.

Despite the enormous progress in cancer immunotherapy, a large number of patients with hematological malignancies, such as multiple myeloma, are resistant to currently available therapeutic strategies. Our goal is to identify new tumor-associated molecules (so-called immune checkpoint molecules) that contribute to the resistance of tumor cells against the immune system. Switching off identified candidate molecules could offer new therapeutic options.

The expression of immune checkpoint molecules on tumor cells promotes their resistance to immune attacks and limits the function of immune cells. About 3,000 candidate molecules have been investigated so far and one of them, CAMK1D, was selected by the RCI scientists for further analysis. The CAM kinase CAMK1D is expressed in various hematological and solid tumors and the scientists could show that it plays an important role in tumor entities that are resistant to currently available immunotherapies. In addition, they could show that tumor resistance is mediated by an intrinsic mechanism that interferes with the cell death signaling cascade. Our group managed to switch CAMK1D off in tumor cells using molecular scissors and could show that this leads to an increased susceptibility of tumor cells to immune cells (T cells). The depletion of the molecule in tumor cells enables T cells armed with killer receptors to kill the tumor cells. This raises hopes for therapeutic options for a large number of cancer patients.

The group works with several mouse models to investigate the immunosuppressive role of CAMK1D. In these models, tumor cells without CAMK1D expression showed an increased sensitivity to immune cells and tumor growth was significantly reduced compared to tumors with CAMK1D expression.

Development of a CAMK1D inhibitor to kill tumor cells

In collaboration with a pharmaceutical company, we developed a small molecule that led to the inhibition of the immune checkpoint molecule on protein level and increased tumor cell death.

The results were found for hematological and solid tumors (such as melanoma), underlining the role of CAMK1D in different tumor entities. The identified molecule therefore opens new options for the use of immunotherapies together with standard therapies in oncology.

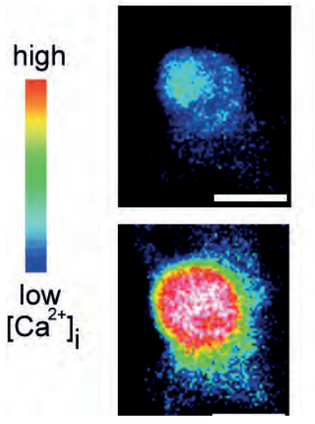


Fig.: Tumor cells before (top) and after (bottom) the addition of T cells. T cells armed with killer receptors induce signals (red) that lead to tumor cell death.

Project 2.4

On the way to an individualized immunotherapy

Bioinformatics provide a deeper insight into the challenges of a successful immunotherapy

Bioinformatics is used to identify individual co-expression clusters of immune checkpoint molecules, which are jointly regulated and used by cancer cells to face multiple attacks of the immune system. This heterogeneity highlights the complex challenges of a successful cancer immunotherapy. Bioinformatics analysis at the RCI contributes to a deeper understanding of cancer and contributes to the development of a personalized and targeted immunotherapy - not only of cancer.

The development of immunotherapeutic approaches in the fight against cancer has become one of the major priorities of tumor research in recent years. Unfortunately, only a minority of patients respond to current therapies. The goal of so-called immune checkpoint therapies is to block molecules by antibodies or inhibitors that make tumor cells resistant to immune cells. The inhibition of these molecules is intended to strengthen the immune system in order to eliminate malignant cells.

We investigate why many patients do not respond to immunotherapy and which molecular mechanisms are used by cancer cells to become resistant. So far, several hundred potential immune checkpoint molecules have been identified by scientists at the Division of Interventional Immunology and some of them have been investigated with respect to their function in cancer. Using bioinformatic approaches, the aim is to find out to what extent the different molecules are jointly regulated and interact functionally with each other.

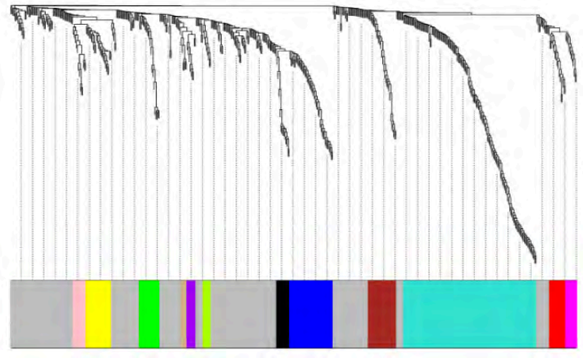


Fig.: Gene tree from data on brain tumors. The individual colors represent clusters of molecules that correlate with each other. Together they can undertake biological functions and can be used by tumors to circumvent the attacks of the immune system.

Julian Sax

Several co-expressed gene clusters have already been identified, i.e., groups of molecules that are jointly up- or down-regulated and thus correlate with each other. These clusters are very heterogeneous as some of them seem to occur in only one type of cancer, while others are found in many different cancer types. At the same time, there are great differences between individual patients. While a certain cluster is very active in one patient, it may be inactive in another one. In addition, yet another cluster seems to be up-regulated in the second patient.

This heterogeneity shows the challenges in finding an effective therapy for as many patients as possible. Therefore, research will (have to) head towards an individualized therapy to combine the best possible outcome with few side effect in the future.

Dr. Slava Stamova

Project 2.5

Using synthetic immunology approaches to generate TRUCK T cells secreting immune checkpoint blocking molecules

Arming immune cells for a more efficient fight against cancer

Understanding how cancer evades the immune system is pivotal for the development of novel therapies and strategies for immunotherapy in oncology. A novel strategy that is being developed at the RCI is to genetically modify immune cells, i.e., provide them with new receptors and the ability to secrete blocking molecules that interfere with escape mechanisms utilized by the tumors. This could make them superior in eradicating cancer cells.

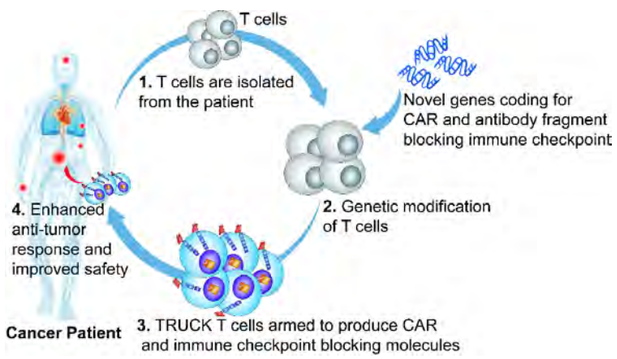
The sentinels of the immune system - the T cells - have the ability to recognize and eradicate cancer cells. However, malignant cells evade T cells. They "hide" from the immune cells by "deleting" from their surface the molecules that would help T cells recognize them. Furthermore, cancer cells can "hijack" normal regulatory pathways used by the immune system to control immune responses, i.e., the expression of ligands that interact with inhibitory receptors (immune checkpoint receptors) on T cells which can dampen T cell functionality. Blocking antibodies targeting immune checkpoints, such as PD-1, CTLA-4 etc., have already been used with success in the clinic, but systemic application of these antibodies can lead to severe side effects.

A novel immune checkpoint with great potential in immunotherapy is CEACAM6.

It has been shown that this molecule is expressed on many tumor entities, promotes tumor progression, and has a role in T cell inhibition. Dr. Stamova has generated a fragment of a blocking antibody targeting CEACAM6, which has the ability to interfere with the interaction of CEACAM6 and its counterpart CEACAM1 (expressed on T cells) that mediates inhibition of T cell function. A way to avoid immune checkpoint blockade induced side effects is to deliver the blocking antibodies locally in the tumor microenvironment.

Using synthetic immunology approaches in collaboration with the group of Prof. Abken, Dr. Stamova generates so-called TRUCK T cells by bringing in the gene coding for a chimeric antigen receptor (CAR), that recognizes tumor antigens on the surface of the tumor cells, together with the gene coding for the CEACAM6 blocking antibody fragment. The newly generated TRUCK T cells utilize the CAR to find and destroy cancer cells that would otherwise be "invisible" to the immune system.

T cell activation via this CAR induces the secretion of the blocking antibody fragment that interferes with the interaction between CEACAM6 and CEACAM1 and thus hinders the inhibitory effect of the immune checkpoint signaling. In this way, T cells functionality is restored and T cell killing efficiency is markedly improved. This novel synthetic immunology approach can improve the efficiency of the existing adoptive T cell therapies and the safety of immune checkpoint blockade.



Project 2.6

Detection of new immune drugs for the brain

New approach for the treatment of brain tumors and multiple sclerosis

Brain cells and immune cells communicate via signals (messages). If these are deficient or too frequently sent, glioblastoma or multiple sclerosis may develop. The scientists are working on the discovery of new proteins that are important for the communication between brain cells and immune cells. The aim is to improve cell-cell communication and enhance the treatment of multiple sclerosis and glioblastoma patients by blocking or activating relevant proteins.

Our immune cells can distinguish between healthy body cells and tumor cells by scanning their cell surface proteins. When they recognize tumor cells, they are expected to attack and kill them. However, many tumor cells develop resistance mechanisms, e.g., glioblastoma cells (brain tumor cells) can present proteins on their surface that block the activity of immune cells. The tumor, thereby, escapes the attack of the immune cells and continuously grows. Autoimmune diseases in turn arise when our immune system attacks healthy body cells. In multiple sclerosis, for example, brain cells (oligodendrocytes) are attacked by immune cells due to altered surface proteins leading to the damage of neurons. The goal of our project is to identify proteins on the cell surface of human brain cells that are important for the development of glioblastoma or multiple sclerosis.

Identification of glioma cell proteins that influence immune cells

So far, we have analyzed 4,160 proteins and found 126 proteins that might be important for brain cell interaction (communication) with immune cells. We selected two protein candidates that could alter the function of immune cells when activated or blocked in brain cells. Blocking these two proteins in multiple sclerosis patients might stop cytotoxic immune cells from attacking brain cells. In glioblastoma patients, in turn, activation of the proteins might lead to an improved immune cell function against tumor cells. We are currently investigating the role of these proteins in detail.

Ayse Nur Menevse

Brain cells send harmful messages to immune cells in multiple sclerosis and glioblastoma patients.

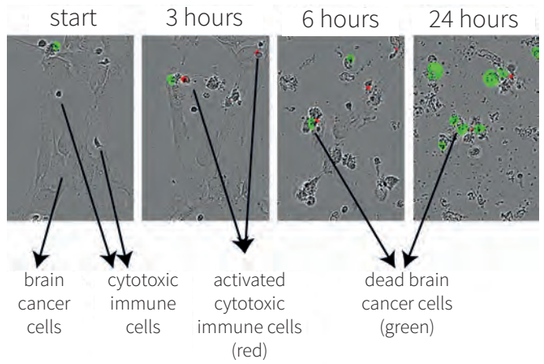


Fig.: Real-time live imaging of a coculture of immune cells and brain tumor cells

Dr. Anchana Rathinasamy

Project 2.7

Autologous Tumor-TIL culture platform

On the road towards a personalized cancer treatment

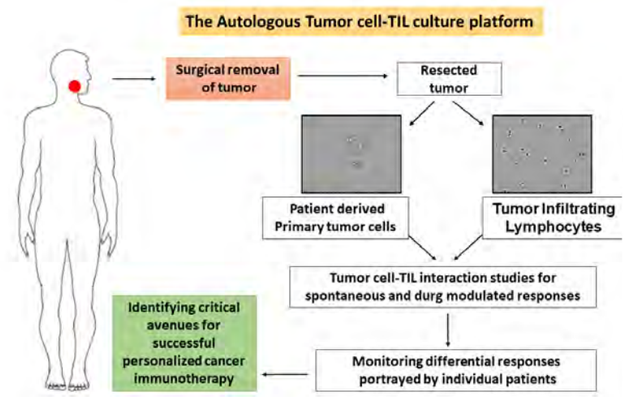
To better understand, predict and achieve tumor regression after immune intervention, in-depth analysis of spontaneous and drug-modulated interactions between tumor infiltrating lymphocytes (TIL) and the corresponding primary autologous tumor cells from individual patients are required. Hence, we established an autologous tumor cell – T cell culture system *in vitro*. This project fits in with one of the RCI's objectives to extend the findings of basic research into translational aspects towards a personalized cancer treatment.

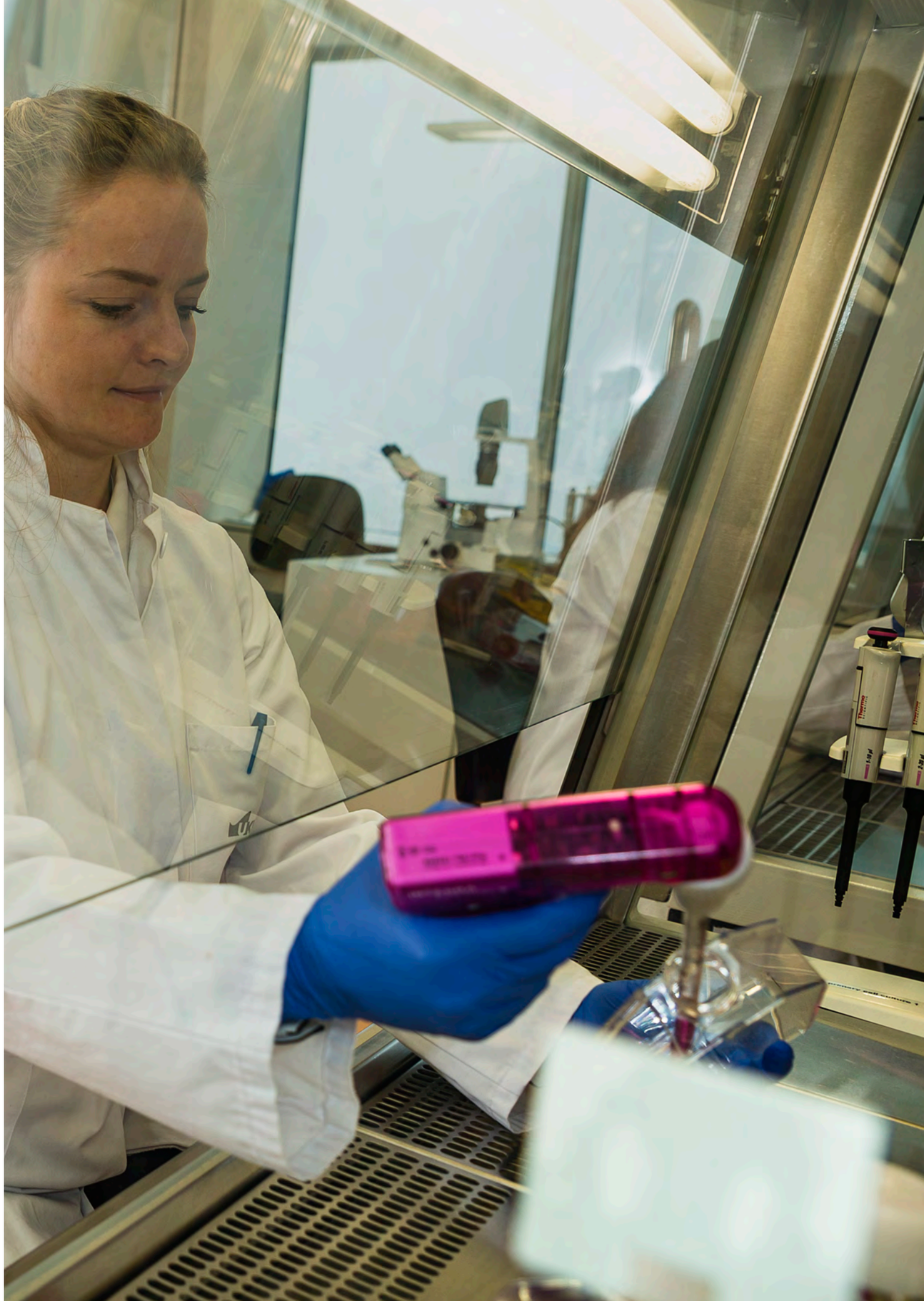
Although immunotherapy holds considerable promise in cancer treatment, many patients still remain refractive or become resistant to their treatment, which inhibits a successful clinical outcome. This could be mainly attributed to differing immune responses in individual patients. Therefore, monitoring individual patient responses is required to design patient specific treatment regimens.

Immune cell - tumor cell interaction *in vitro*

Our aim is to establish an autologous cell culture system *in vitro* facilitating growth and expansion of primary tumor cells and TILs derived from resected patient tumors. Using this coculture system, tumor cell - TIL interaction could be analyzed to monitor T cell responses or tumor cell killing at individual patient level. Based on these assessments, it will be possible to identify critical aspects in the development of successful personalized cancer immunotherapy regimens.

The autologous tumor cell - TIL platform is a joint venture that is established at the RCI to integrate the clinic and promote new collaborative projects between the clinic and the RCI. The Comprehensive Cancer Center Ostbayern (CCCO) and the RCI intend to further develop this platform into a biobank. Upon individual patient consent, we isolate, culture and store patient-derived autologous tumor cells and TILs in addition to serum, peripheral blood mononuclear cells, frozen tumor sections, etc. that could be assessed for individual patient responses for the benefit of the patients. This platform could help the scientific community to enhance investigations and knowledge about immunotherapy with the possibility of extending the findings towards a personalized cancer therapy.





Dr. Christian Schmidl

3

Junior Group Epigenetic Immunooncology

Central Question:
What prevents immune cells from fighting cancer?

Main Research Focus

In 2018, the Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo for the discovery of inhibitory signaling pathways (so-called immune checkpoints) that impede the activity of T cells. This phenomenon also limits T cell function in cancer and hampers the rejection of a tumor by immune cells. Immune checkpoint inhibitors used in cancer therapy can reactivate T cells by blocking these inhibitory signalling pathways.

However, many patients do not respond to immunotherapy with checkpoint inhibitors, which is partly due to epigenetic alterations in the patients' immune cells. Epigenetic alterations have a lasting effect on gene expression without changing the DNA sequence itself. Our research group wants to decipher such alterations in T cells of tumor patients. The analyses should allow conclusions about the driving molecular factors of T cell dysfunction and provide starting points for the reactivation of T cells.

Current Projects

The research group works on the following topics:

A. **Epigenetic regulation of T cell function in the tumor environment**
B. **Manipulation of T cell function by CRISPR/Cas9**

We want to understand epigenetic mechanisms that affect T cell functions in the tumor. Therefore, we focus on the chromatin structure that provides important information on the activity of immunologically relevant genes. Using genome manipulation, we want to switch off recently discovered key factors that limit T cell function in order to improve the anti-tumor immune response. To achieve our goal, we are establishing the CRISPR/Cas9 system in our laboratory to be able to modify the genome of immune cells.

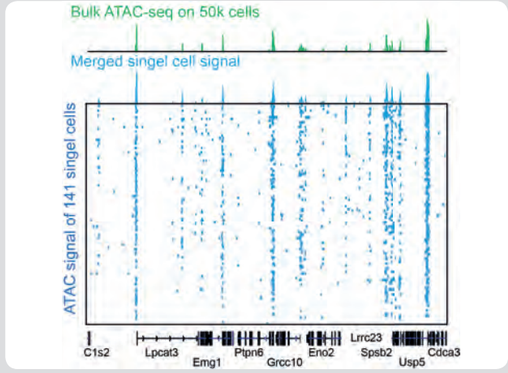


Fig.: Single cell chromatin analysis of T cells

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
0.285	11	N/A
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

SCHMIDL C* et al., Combined chemosensitivity and chromatin profiling prioritizes drug combinations in CLL. *Nature Chemical Biology* 2019; 15(3):232-240

SCHMIDL C et al., Epigenetic mechanisms regulating T-cell responses. *Journal of Allergy and Clinical Immunology* 2018; 142: 728-743

DELACHER M et al., Rbpj expression in regulatory T cells is critical for restraining TH2 responses. *Nature Communications* 2019; 10: 1621

DATLINGER P et al., Pooled CRISPR screening with single-cell transcriptome readout. *Nature Methods* 2017; 14: 297-301

Third-party Funding (Selected)

2019-2022 German Research Foundation (DFG) grant: Tumor microenvironment-directed epigenome remodeling of tumor infiltrating T cells.

Collaborators (Selected)

RCI: Markus Feuerer, Philipp Beckhove, Hinrich Abken, Michael Rehli, Marina Kreutz, Christina Zielinski (TU Munich), Thomas Brabletz (FAU Erlangen)

Staff

Scientists
Dr. Christian Schmidl

Doctoral Students
Dania Riegel
Elena Romero Fernández

Technicians
Manuela Kovács-Sautter
Brigitte Wild

Dania Riegel

Project 3.1

Epigenetic regulation of T cells in the tumor

Molecular characterization of immune cells to improve anticancer immuno-therapies

Immune cells can recognize and kill tumor cells. However, many tumor cells use a trick to prevent their death: they strongly impair the function of immune cells. For this purpose, tumor cells carry immunosuppressive molecules on their surface, such as PD-L1 (Programmed cell death ligand 1), which binds to PD-1 (Programmed cell death 1) on immune cells. These interactions render immune cells dysfunctional and prevent them from killing tumor cells.

In 2014, a so-called immune checkpoint inhibitor for blocking PD-1 was approved as a drug that significantly improves the survival rate of melanoma patients and is successful in other cancer types as well.
Therefore, cancer therapy using immune checkpoint inhibitors has been considered one of the most important developments in oncology. Unfortunately, not all cancer patients benefit from a treatment with immune checkpoint inhibitors.

Epigenetic mechanisms lead to immune cell dysfunction

Recent studies show the involvement of special gene regulatory programs in immune cells. These programs are stabilized by epigenetic mechanisms such as the modification and packaging of DNA in the nucleus of the immune cells, which could reduce or even prevent the effect of immune checkpoint inhibitors.

Therefore, our goal is to better understand the molecular processes leading to the dysfunction of immune cells in order to find ways for new immunotherapeutic approaches. For this purpose, we isolate specific immune cells (T cells) from human tumor samples and analyze their phenotype, functionality, and underlying molecular programs.

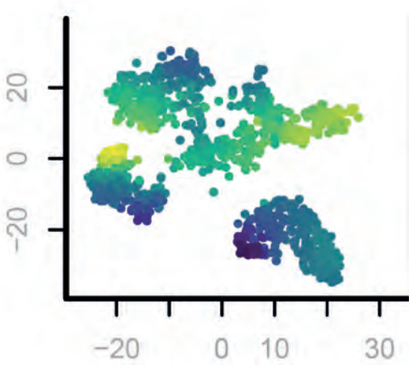


Fig.: Bioanalytic analysis of immune cells from a tumor

Project 3.2

Genome Editing in immune cells

CRISPR/Cas9

Lukas Wöhrl

Modern genetic engineering was revolutionized by the discovery of the “molecular gene scissors” CRISPR/ Cas9, a technology to specifically modify genes within cells. We want to use this method to investigate the function of individual immune-related genes and to specifically deactivate those genes in immune cells that prevent anti-tumor activity.

The discovery of the CRISPR/Cas9 system fundamentally revolutionized the world of science in 2012. If scientists previously wanted to change the genetic make-up of an organism, they had to use a random editing system, which could lead to undesirable and also harmful side effects. This is largely prevented by the application of the CRISPR/ Cas9 system as theses molecular scissors are specifically directed to their DNA target and only cut at this specific genomic site. Therefore, the method offers innumerable possibilities to switch on, switch off, and alter target genes.

Genome editing for the targeted modification of immune cells

We want to use targeted genetic manipulation to better understand the role of certain genes in the immune system and to specifically manipulate immune cell functions.
We have so far established this genome editing method in T cells, which are particularly important in the fight against cancer. We found that the CRISPR/Cas9 system perfectly works in T cells isolated from volunteer blood samples. The targeted inactivation of a selected gene was achieved with a very good efficiency of 80%. We were also able to modify tumor infiltrating lymphocytes (TIL, T-cells obtained from patient tumor samples) with an efficiency of up to 70%.

The targeted modification of TILs that are often unable to fight the tumor could provide information about the specific role of TILs in progressive cancer.

In addition, the working group would like to modify genes in so-called CAR T cells, that are already approved for cancer therapy. Here, he patient’s own T cells are specifically provided with a receptor to recognize and destroy the cancer cells. With the help of the CRISPR/Cas9 system, we aim to specifically modify genes and further improve this therapeutic approach.

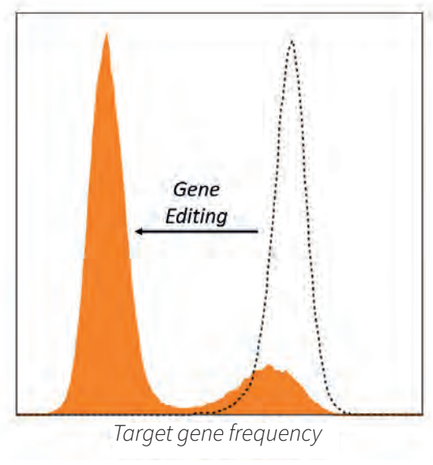


Fig.: Efficiency of switching off a gene in human T cells by CRISPR/Cas9

Core Facility “Omics” (NGS Core Unit) Staff
Head: Prof. Dr. Michael Rehli

4

Core Facility “Omics” (NGS Core Unit)

The Technology and Service Platform “Omics” (NGS Core Unit) helps RCI researchers to read the genotypes and wirings of human cells that cause diseases or may contribute to their treatment. We are collecting billions of data points, which we analyze and transform into findings about the cells and their functions.

In 1990, one of the most exciting research missions in history was completed. After 13 years of sequencing work, the human genome, which is the blueprint of all our cells, was decoded for the first time. However, it soon became clear that the blueprint alone was not the answer to everything.

The human body consists of more than 400 cell types (skin cells, blood cells, brain cells, etc.), which use the same blueprint, but differ significantly in their form and function. The genomic switches controlling specific cellular functions and reactions are regulated by so-called epigenetic mechanisms. Today, modern sequencing technologies allow us to collect much more information about a cell than just the genome sequence. This includes the mapping of its epigenetic characteristics, the accessibility of the genome, the activity of individual and characteristic genetic regions, and even the spatial arrangement of the genome in the cell nucleus. Nowadays, we only need days - not years like in the 1990s - to gather such data.

The Core Facility “Omics” (NGS Core Unit) is a Technology and Service Platform at the RCI. Our task is to support RCI researchers in (epi-) genetic studies as well as transcriptome and chromatin analyses. We help them to plan their experiments, prepare their samples for sequencing, if necessary, and we perform the sequencing.

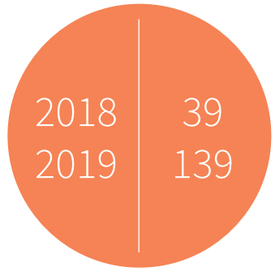
In addition, we transform the huge data sets into an “understandable” form and support the scientists in interpreting the sequencing data and answering their scientific questions.

Sequencing technologies are becoming increasingly important in basic and clinical research. Hence, our technical expertise is also appreciated and employed by researchers outside the RCI.

NGS CORE

Selected switch sequences

2017-2019 Numbers



Sequencing Runs

Collaboration Projects

Selected Publications

DELACHER et al., Precursors for Nonlymphoid-Tissue Treg Cells Reside in Secondary Lymphoid Organs and Are Programmed by the Transcription Factor BATF. *Immunity* 2020

MINDERJAHN et al., Mechanisms governing the pioneering and redistribution capabilities of the non-classical pioneer (2020). *Nat Commun* 2020

DELACHER M et al., Rbpj expression in regulatory T cells is critical for restraining TH2 responses. *Nat Commun* 2019

GEBHARD et al., Profiling of aberrant DNA methylation in acute myeloid leukemia reveals subclasses of CG-rich regions with epigenetic or genetic association. *Leukemia* 2019

KAPPELMANN-FENZL et al., C-Jun drives melanoma progression in PTEN wild type melanoma cells. *Cell Death Dis* 2019

Vatter et al., In-vitro blockade of the CD4 receptor co-signal in antigen-specific T-cell stimulation cultures induces the outgrowth of potent CD4 independent T-cell effectors. J *Immunol Methods* 2018

Staff

Scientists

Prof. Dr. Michael Rehli
Dr. Claudia Gebhard
Dr. Nicholas Strieder

Technicians

Johanna Raithel

PD Dr. Petra Hoffmann
Irina Fink
Rüdiger Eder

5

Core-Facility “FACS-Analytics and Cell Sorting”

The Technology and Service Platform “FACS-Analytics and Cell Sorting” (FACS Core Unit) provides several state-of-art flow cytometers and high-speed cell sorters. The knowledge gained this way contributes to a better understanding of basic immune processes in the body and thus significantly supports the development of new and personalized therapeutic concepts.

The Technology and Service Platform “FACS-Analytics and Cell Sorting” (FACS Core Unit) was set up in 2004 by P. Hoffmann & M. Edinger from the Department of Internal Medicine III (Hematology/Oncology) at the University Hospital Regensburg (UKR) and was integrated into the RCI in 2017. It was developed from a joint project of several clinics and institutes at the UKR, supported by the José-Carreras Foundation, and offers researchers at the RCI, the University of Regensburg (UR), and the University Hospital Regensburg (UKR) comprehensive access to state-of-the-art flow cytometric cell analysis and sorting technologies.

Flow cytometry is a cell analysis method that allows the determination of a large number of different cell parameters, such as size and granularity, as well as the expression of specific surface and/or intracellular marker molecules in a qualitative and quantitative way.

Functional changes can thus be revealed during the course of cell development or disease as well as after therapeutic intervention. In addition, cell type-specific marker profiles can be used for the targeted isolation of specific, highly-purified cell populations for further downstream analyses.

The The FACS Core Unit has several state-of-art flow cytometers and high-speed cell sorters at its disposal. Furthermore, highly competent service personnel is available to answer all questions concerning flow cytometry.

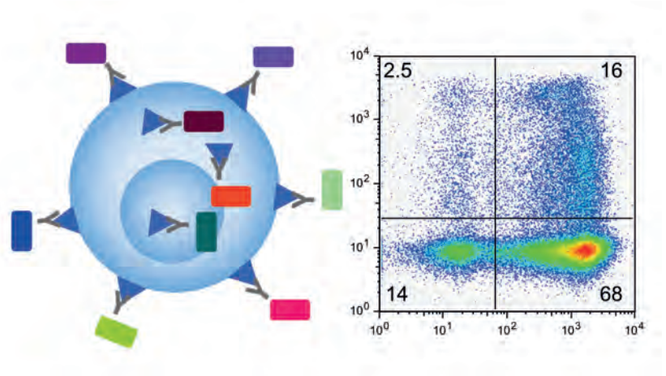
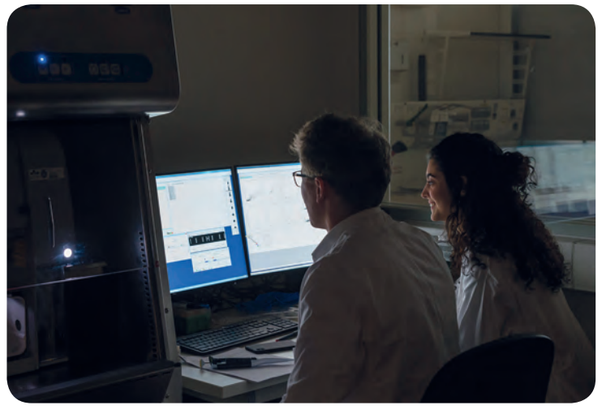


Fig.: Schematic representation of a cell after multi-color staining with fluorescence labeled antibodies (left) and original results of an immune cell staining (right)



FACS Core Unit staff during data analysis

2017-2019 Numbers

2017 - 2019
1.140

Number of performed cell sortings

RCI 11
UKR UR 20

Number of working groups using the technology platform

Selected Publications

DELACHER et al., Precursors for Nonlymphoid-Tissue Treg Cells Reside in Secondary Lymphoid Organs and Are Programmed by the Transcription Factor BATF. *Immunity* 2020

COSSARIZZA et al., Guidelines for the use of flow cytometry and cell sorting in immunological studies (second edition). *Eur J Immunol* 2019

MINDERJAHN et al., Mechanisms governing the pioneering and redistribution capabilities of the non-classical pioneer PU.1. *Nat Commun* 2019

HOFFMEISTER et al., Elucidation of the functional roles of the Q and I motifs in the human chromatin-remodeling enzyme BRG1. *J Biol Chem* 2019

RIEGEL et al., Efficient treatment of murine acute GvHD by in vitro expanded donor regulatory T cells. *Leukemia* 2019

Staff

Scientists
PD Dr. Petra Hoffmann

Technicians
Rüdiger Eder
Irina Fink
Jaqueline Dirmeier (parental leave)

Program Area II

Genetic Immunotherapy / Functional Immune Cell Manipulation

Program Area II focuses on the preclinical development of immune-cell therapeutics. This includes the identification, differentiation, expansion, and preclinical testing of therapeutically relevant immune cell populations, as well as their functional manipulation and optimization through genetic, epigenetic, or pharmacological intervention.

Program Area II integrates and transfers findings on immunoregulatory mechanisms and targets from Program Area I into therapeutically applicable cell therapies. Well-engineered and sound development projects are transferred to Program Area III to be prepared for their clinical testing. Program Area II will be supplemented by a W2 professorship for T Cell Therapy in 2020.

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1 Division of Genetic Immunotherapy

1.1 How do CAR T cells detect tumor cells?
1.2. How can we improve CAR T cell persistence during the immune response?
1.3. How can we suppress chronic inflammation?
1.4. TRUCKS: Transforming specific T cells into living factories
1.5. Adaptation of CAR T cells to drug production and clinical trials
1.6 How can we strengthen the CAR T cell immune response in the tumor?

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2 Division of Functional Immune Cell Modulation

2.1 Reprogramming T cell fate for therapeutic approaches
2.2 Reprogramming T cell fate and anti-tumor immunity by modulating T cell metabolism
2.3 CAR-modified CD8+ T memory stem cells for the treatment of human B cell malignancies

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3 Research Group Immunoregulation

3.1 Prophylaxis & therapy of transplantation complications by physiological immunoregulatory mechanisms

1

Division of Genetic Immunotherapy

Division of Genetic Immunotherapy
Head: Prof. Dr. Hinrich Abken

?

Central Question:
Which tools are important for immune cells to effectively fight cancer and autoimmune diseases?

Main Research Focus

Recent research has shown the important role of the immune system in the successful treatment of serious diseases such as cancer and autoimmune diseases. We would like to use this knowledge to direct immune cells specifically against tumors (cancer) as well as to regulate chronic inflammation (autoimmune diseases) to improve these conditions.

„Living Drugs“ - Modified immune cells to effectively fight cancer and autoimmune diseases

Our central strategy is based on CAR (Chimeric Antigen Receptor)-modified immune cells. T lymphocytes taken from the patient are genetically modified to carry specific recombinant receptors (CARs), which enable them to recognize defined target structures on tumor cells. The CAR T cells produced in the laboratory will then be returned to the patient in large numbers by transfusion. They will be able to detect and eliminate the tumor and activate further immune cells on site to generate an effective defense reaction.

Current Projects

We work on the development of suitable CARs and CAR T cells. Our three main goals are:

A. to learn about the mechanism of action of CAR T cells and
B. to improve their effect on solid tumors in particular
C. to generate a lasting immune control

The research group of Prof. H. Abken (previously at the University of Cologne) has been one of the pioneers in the young research field of CAR-modified immune cells and has contributed to the development of the standard design of several generations of CARs, which are now tested in clinical trials worldwide. These include the “4th-generation CARs” (“TRUCKs”), which are “living factories” that produce therapeutically effective substances in tumors and initiate a comprehensive immune defense. A further focus is on the translation of CAR T cells developed in experimental models into clinical trials. To this aim, we collaborate with numerous partners, both locally with the José-Carreras-Center as a manufacturing center, as well as with other research groups and hospitals around the world.

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
2.760	33	4
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

HOMBACH et al., Blocking CD30 on T cells by a dual specific CAR for CD30 and colon cancer antigens improves the CAR T cell response against CD30 negative tumors. *Mol Ther* 2019; 27, 1825 - 183

BLUHM et al., CAR T cells with enhanced sensitivity to B cell maturation antigen for the targeting of cell non-Hodgkin’s lymphoma and multiple myeloma. *Mol Ther* 2018; 26, 1906 – 1920

GOLUMBA-NAGY et al., T cells with CD28-ζ CAR resist TGF-β repression through IL-2 signaling which can be mimicked by an engineered IL-7/IL-2Rβ autocrine loop. *Mol Ther* 2018; 26, 2218 – 2230

CHMIELEWSKI & ABKEN, CAR T cells releasing IL-18 convert to T-bethigh FoxO1low effectors which exhibit augmented activity against advanced solid tumors. *Cell Reports* 2017; 12, 3205 – 3219

Third-party Funding (Selected)

EU Horizon2020: Enacti2ng
German Cancer Aid: From CARS to TRUCKs
German Cancer Aid:TECLA study
German Cancer Aid: CD22 CAR
German Cancer Aid: TOSO CAR
German Research Foundation (DFG): Control-T;
Oncogene Collaboration: CTL1 and TCR in T-PLL

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Valerie Bezler
Jordan Hartley
Marcell Kaljanac

Technicians
Linda Otzelberger
Anja Pavlica
Sandra Schantz (office)

Markus Barden
Jordan Hartley
Marcell Kaljanac

Project 1.1

How do CAR T cells detect tumor cells?

Chimeric antigen receptors (CARs) are synthetic receptors on the surface of immune cells and have the ability to activate immune cell after binding to a defined target structure. Whereas T cell activation by a natural T cell receptor is well understood, the temporal and spatial sequence of target recognition by a CAR T cell is still unclear. Our aim is to understand this procedure with respect to time and space to make immunotherapy with CAR T cells more effective.

In contrast to natural T cell receptors (TCR), CARs consist of only one polypeptide chain and bind their target structures by means of an antibody. However, the CAR uses signaling molecules of the TCR to activate the T cell. As a “single chain” TCR, the CAR behaves differently in many respects to the TCR and requires different prerequisites to activate the T cell effectively. To further improve the design and effectiveness of CARs, we have to understand the first steps during the contact between the CAR on the T cell and the target structure on the tumor cell.

A better understanding of the mechanisms during CAR - tumor cell contact will lead to further optimization of the therapeutic efficiency of CAR T cell therapy.

The first and crucial contact between the CARs and the tumor cell occurs in the few seconds after binding. If a contact zone with several hundred CARs is formed, an effective signal can be generated and the T cell can be activated to destroy the tumor cell. However, if the contact zone is not formed, the T cell and tumor cell come apart and the tumor cell is not eliminated. So far, the prerequisites for a successful formation of a contact zone are unknown.

As a productive CAR T cell – tumor cell contact is crucial for the therapeutic success, among other things, our investigations will significantly influence further development of adoptive cell therapy with CAR T cells.

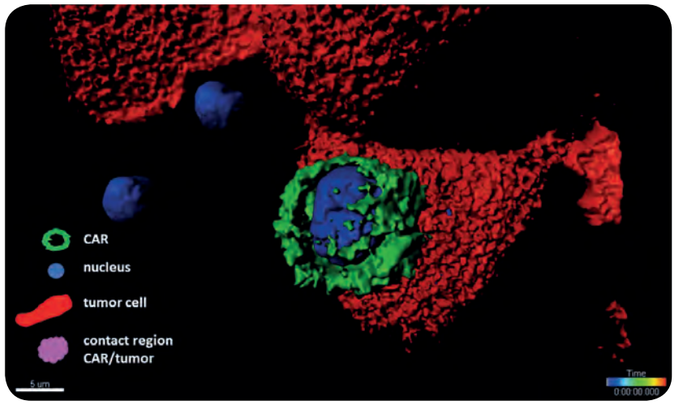

Fig.: Contact of a CAR T cell and a tumor cell (Source: Markus Barden)

Project 1.2

How can we improve CAR T cell persistence during the immune response?

Dr. Andreas Hombach

CAR T cells are activated at their target site, such as a tumor, where they initiate an immune response. Afterwards, the T cells switch off their activity to avoid exhaustion. However, switching off the immune response is not desired in the fight against cancer as long as the tumor has not been completely eliminated. In our project we develop strategies to make T cell activation last longer and be more effective.

The natural T cell activation is accompanied by a precisely timed expression of the two molecules CD30L and CD30, among others, which recognize each other and initiate the termination of the T cell response. Our aim is to block CD30 with an antibody to rule out the binding and signaling of CD30L in a way that the immune response is not stopped. If this CD30 blockade will be integrated in the CAR, it is only the CAR that will benefit from a prolonged activation, while other T cells will not.

We already succeeded in designing a CAR that continues to recognize the tumor and triggers an anti-tumor reaction.

T cells with such a “next-generation CAR” show better anti-tumor activity compared to conventional CAR T cells leading to a more sustained immune response. This is an essential step towards a lasting and more effective cellular tumor therapy.

In the future, our aim is to further develop this strategy towards a clinical phase I study for the treatment of gastrointestinal tumors.

“Next-generation CARs” prolong T cell activation by CD30 blockade.

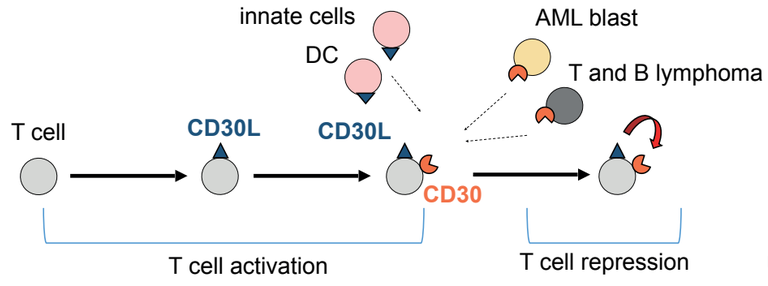

Fig.: T cell activation steps

Marcell Kaljanac

Project 1.3

How can we suppress chronic inflammation?

Autoimmune diseases are often accompanied by a chronic inflammation, which further fuels the disease. Presumably, this is caused by a defective or inefficient suppression of the immune response. Since suppressor T cells (regulatory T cells, Tregs) are naturally involved in this process, our strategy is to provide Treg cells with a specificity for their target cells by means of a CAR, which than can be activated on site to slow down the immune response.

Regulatory T cells (Tregs) play an essential role in the modulation of immune reactions and are ideal partners for the targeted limitation of inflammatory reactions. By the introduction of CARs into regulatory T cells, Treg activity could be directed to the inflammatory site to suppress the inflammatory reaction. The CAR technology has successfully been applied to effector T cells to induce immune responses, so far. Some years ago, we succeeded in using CARs to induce immune cell suppression by Tregs. Currently, we are investigating how Treg cells can best be controlled by CARs in order to increase their suppressive activity.

CAR Tregs may have a great potential in the treatment of chronic inflammatory diseases.

So far, we could already show the control of Treg cells by a CAR, e.g., in a preclinical model of allergen-induced bronchial asthma. If bronchial asthma is triggered by inhalation of an allergen, inflammatory and stress reactions are induced in a predictable manner, i.e., first locally in the lungs and later in the entire body.

If we provide Treg cells with a CAR directing them to the lungs, the reaction to the allergen can be suppressed in an effective and lasting manner. The potential of a CAR Treg therapy will be analyzed in some autoimmune diseases in the future.

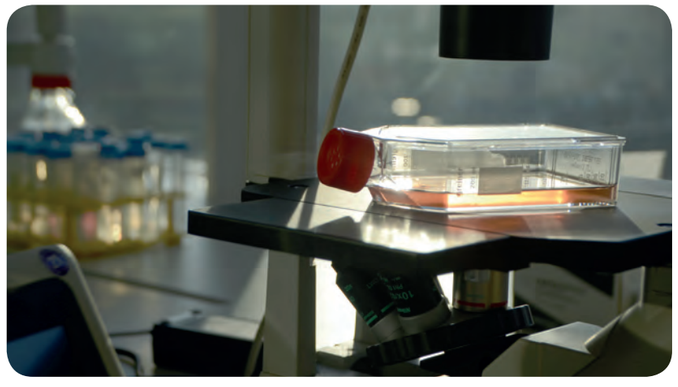

Fig.: Cell flask at the microscope

Project 1.4

TRUCKS: Transforming specific T cells into living factories

Staff
of Prof. Hinrich Abken
Dr. Astrid Holzinger, Marcell Kaljanac,
Jordan Hartley, Valerie Bezler,
Markus Barden, Linda Otzelberger,
Anja Pavlica, Sandra Schantz

CAR T cells can migrate to the tumor, proliferate and initiate an immune response. Our aim is to make use of these properties and make CAR T cells act as “living factories” to produce specific drugs directly at the tumor site. So-called TRUCKs (the “4th generation” CAR T cells) carry and produce their “cargo” that is specifically released at its destination.

Some drugs are toxic to such an extent that they can cause serious side effects when administered systemically in the body. It may be difficult to achieve a sufficiently high concentration of these therapeutic agents in the tissue to have an effect without hurting healthy organs.

TRUCKs are “intelligent factories” for therapeutically active substances with broad application potential in cell therapy

In our approach, CAR T cells are modified to only produce the active substance when they are located in a defined target tissue (e.g. a tumor). We developed TRUCKs (T cells redirected for unrestricted cytokine initiated killing) as a basic technology for a targeted and locally induced release of transgenic, biologically active mediators in a target tissue. The modified CAR T cells have an on-off switch which controls the production depending on the location of the cell.

As soon as it reaches the target tissue, a CAR signal is generated and the drug is produced. If the cell circulates in the body and has not yet reached the target site, or is leaving the target site, the CAR signal is missing and the drug is not produced.

In addition, the drug is constantly produced by the T cell as soon as the cell is at its destination, which is another advantage over classical drug therapies.

Currently, our research group is investigating the application of a locally induced release of biologically active mediators for adoptive immunotherapy.

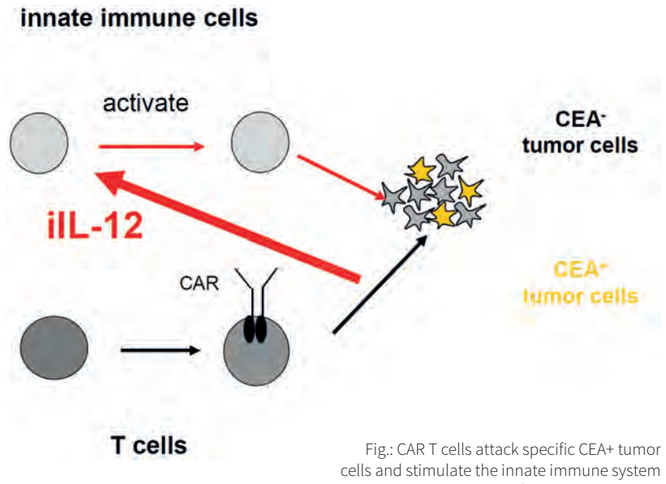

Fig.: CAR T cells attack specific CEA+ tumor cells and stimulate the innate immune system to extend anti-tumor activity.

Dr. Astrid Holzinger

Dr. Tina Böld

Project 1.5

Adaptation of CAR T cells to drug production and clinical trials

Adoptive cell therapy with CAR T cells has shown great promise for the treatment of several tumors in experimental and clinical studies. To be tested in clinical studies, CAR T cells have to be produced according to the rules of "good manufacturing practice" (GMP) and have to undergo extensive quality controls. In this project, we are working in close collaboration with the José-Carreras-Center (JCC) on the GMP-compliant production of CAR T cells for clinical trials.

CAR T cells are individually produced for each patient. This requires the translation of a laboratory process into a drug manufacturing process.

We are collaborating with the José-Carreras-Center (JCC) to translate the laboratory process into a GMP-compliant process which is suitable for the production of CAR T cells for clinical testing.

Most of the manufacturing will be carried out in a fully automated, monitored, controlled and reproducible process in a clean room designed for the production of therapeutics located in the José-Carreras-Center (JCC). The manufacturing requires a large number of production and quality assurance steps, which are currently being set up and validated in detail.

The production of therapeutics, particularly of genetically modified immune cells, is subject to strict controls of the manufacturing process and extensive quality controls of the final cell product. Although the manufacturing process is based on the procedures in an experimental research laboratory, it is subject to a multitude of other process and quality controls before the product can be used for clinical trials in patients.

Fig.: Cell production at the CliniMACS Prodigy

Project 1.6

How can we strengthen the CAR T cell immune response in the tumor?

Jordan Hartley

In many tumors, the immune response is actively suppressed. The immune defense is, therefore, ineffective and the tumor cannot be successfully controlled. Our goal is to provide T cells with specific mechanisms to resist their suppression and to successfully eliminate the tumor. Our aim is to transfer this strategy to other immune cells to develop further options for the generation of a long-term immune control of cancer.

In many tumors, T-cell-mediated anti-tumor reaction is suppressed by a high local concentration of tumor growth factor-ß1 (TGF-ß), especially in common cancers such as gastrointestinal, lung, breast, ovarian, and prostate cancer. Even if a specific anti-tumor immune response is developed in these patients and T-cells migrate specifically to the tumor tissue, immune cell function is suppressed and the immune defense is ineffective. As a result, T cell immunotherapy fails and the tumor continues to grow, even though an immune response is developed.

Conquering TGF-ß mediated immunosuppression in the tumor could lead to an improved efficiency of CAR T cell therapy.

Our goal is to counteract immunosuppression to make CAR T cells resistant to TGF-ß. Recently, we could demonstrate that TGF-ß resistance of CAR T cells can be induced by CD28 costimulation and IL-2 receptor signaling. We are now using this knowledge to equip CAR T cells with these signals to make CAR T cell therapy for tumors more persistent and robust.

This work is of considerable importance for the application of CAR T cell therapy in tumors with particularly strong immunosuppression. Furthermore, we are investigating the possibility of using TGF-ß resistance in other, so far less successful CAR T cell therapies as well.

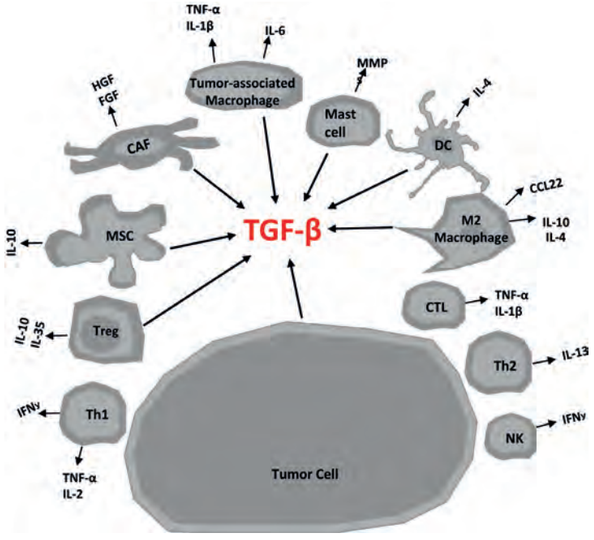

Fig.: The multifaceted role of TGF-ß in the tumor environment (Hartley & Abken, Clinical & *Translational Immunology, Therapy* 2019)

Prof. Dr. Luca Gattinoni

2

Division of Functional Immune Cell Modulation

Central Question:
What are the molecular and metabolic pathways governing stem cell-like behavior in T cells? How can we leverage this knowledge to augment the effectiveness of T cell-based immunotherapies?

Main Research Focus

„Be fire with fire; threaten the threatener … shall they seek the lion in his den."

W. Shakespeare, The Life and Death of King John, c. 1595

Tumor growth and heterogeneity is thought to be sustained by a small population of cancer stem cells that, similar to normal stem cells, are able to regenerate themselves while giving rise to more differentiated cancer cell types.

As with "fighting fire with fire" we aim to confer stem cell-like properties to anti-tumor T cells to enable them to endure long-lasting battles against tumors sustained by cancer stem cells. To this end we are developing new pharmacological and genetic approaches to reprogram T cell fate through the modulation of key molecular and metabolic switches that control self-renewal and differentiation programs.

Current Projects

The Division of Functional Immune Cell Modulation is engaged in the development of T cell-based immunotherapies for the treatment of patients with advanced tumors.
Our research focuses on the reporgramming of T cell fate. Specifically, we are interested in elucidating the molecular networks orchestrating T cell differentiation and stemness, as well as in developing new approaches to modulate these pathways in anti-tumor T cells to improve their therapeutic effectiveness. Our strategies encompass the manipulation of:

A. Transcription factors
B. Epigenetic regulators
C. microRNAs
D. Metabolic pathways

The most promising approaches emerging from these studies are then translated from bench to bedside in close collaboration with the José-Carreras-Center (JCC).
A major area of current investigation is the development of immunotherapies based on the adoptive transfer of T memory stem (T SCM) cells. A clinical-grade process for the manufacturing of CAR-modified TSCM has been successfully developed. This innovative platform will serve as a launching pad for the next wave of adoptive TSCM- based immunotherapies.

Staff of Prof. Gattinoni

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
N/A	13	N/A
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

GATTINONI L et al., T memory stem cells in health and disease. *Nature Med* 2017; *23:18–27*

GAUTAM S et al., The transcription factor c-Myb regulates CD8+ T cell stemness and antitumor immunity. *Nature Immunol* 2019; 20:337–349

YAO C et al., Single-Cell RNA-Seq Reveals TOX as a key regulator of CD8+ T cell persistence in chronic Infection. *Nature Immunol* 2019; 20:890–901

JI Y et al.; miR-155 harnesses Phf19 to potentiate cancer immunotherapy through epigenetic reprogramming of T cell fate. *Nature Commun* 2019; 10:2157

YAMAMOTO TN et., A T cells genetically engineered to overcome death signaling enhance adoptive cancer immunotherapy. *J Clin Invest* 2019; 129:1551–1565

Collaborators (Selected)

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Dragana Slavkovic Ph.D

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Technicians
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Katrin Zehenter (office)

Dr. Jessica Fioravanti

Project 2.1

Reprogramming T cell fate for therapeutic approaches

T cell senescence and exhaustion are major barriers to successful cancer immunotherapy. With this project we aim to enhance CD8+ T cell stemness and anti-tumor function by restraining T cell senescence and functional exhaustion through epigenetic modulation of key factors driving terminal differentiation.

Adoptive immunotherapies based on the transfer of naturally occurring and genetically engineered tumor-reactive T lymphocytes are rapidly becoming a real therapeutic option for cancer patients. Although these regimens can induce complete and durable tumor regression, current response rates remain inappropriate, especially in patients with solid tumors. This demonstrates the need for further improvements. There is now some evidence that long-term remissions are associated with an elevated frequencies of stem cell-like memory T lymphocytes and the preferential expression of gene networks regulating less differentiated memory T cells. On the other hand, T cells from non-responders upregulate programs involved in terminal effector differentiation, exhaustion and apoptosis. Extensive effort has been devoted to boosting T cell fitness by either preventing or reverting these dysfunctional cellular states through gene engineering and pharmacologic approaches. It is known that transcription factors dynamically cooperate with epigenetic regulators to establish and maintain cellular identity or to guide differentiation towards a defined cell fate.

Their central role in the regulation of cell differentiation and lineage specification makes them attractive targets for the development of more effective T cells for adoptive immuno-therapy. Our aim is to increase our understanding of the epigenetic programs regulating CD8+ T cell self-renewal, multipotency and antitumor function by investigating the role of common subunits that participate in the activity of several chromatin remodeling complexes, including the polycomb repressor complex 2 (PRC2) and the nucleosome remodeling and histone deacetylase (NuRD) complex. We found that these epigenetic factors are profoundly induced in CD8+ T cells that are refractory to terminal differentiation and that show an enhanced anti-tumor function, suggesting their potential critical role in regulating T cell stemness and anti-tumor immunity.

Modulating these epigenetic regulators for therapeutic purposes is particularly appealing as they potentially could have broad epigenetic effects given that they are subunits of several chromatin remodeling complexes.

The aims of this project are:
1) To understand the role of various epigenetic regulators in the formation and maintenance of stem cell-like CD8+ T cells and
2) To improve the effectiveness of adoptive immunotherapy by conferring stemness to tumor-specific CD8+ T cells by modulating the expression of various epigenetic factors. This project will involve genetic manipulation of numerous epigenetic regulators to precisely pinpoint their functions, downstream mechanisms of action, and therapeutic potential.

Project 2.2

Reprogramming T cell fate and anti-tumor immunity by modulating T cell metabolism

The regulation of nutrient uptake and utilization in T cells is critically important for the control of their differentiation and fate decisions. Pharmacologic manipulation of key metabolic pathways in tumor-reactive T cells is a promising new avenue to reprogram their function, longevity, and therapeutic efficacy.

Dr. Jeremy Baldwin

In the past few years, it has become increasingly clear that T cell function and fate commitment are tightly linked to their metabolic activity, attracting considerable interest around the possibility of targeting metabolism for novel immunotherapeutic interventions. We have previously revealed that glycolysis is a major metabolic pathway that limits the formation of long-lived memory CD8+ T cells by driving cells toward a terminally differentiated effector state. We further demonstrated that 2-deoxyglucose (2-DG), an inhibitor of glycolysis under clinical evaluation because of its direct negative impact on glycolytic tumor cells, might be repurposed to enhance CD8+ T cell stemness and their therapeutic fitness for adoptive T cell therapy.
This early work, however, did not investigate the fate of glucose-generated pyruvate. Specifically, it remained unclear the relative role of lactic acid fermentation versus pyruvate decarboxylation and entry into the tricarboxylic acid (TCA) cycle.
To address this question, we use pharmacologically and genetically manipulated lactate dehydrogenase (LDH), which catalyzes the conversion of pyruvate to lactate. We found that LDH is a pivotal metabolic checkpoint regulating CD8+ T cell fate decision towards effector cells. Ldha deletion or blockade of LDH rewired CD8+ T cell metabolism promoting pyruvate oxidation into TCA cycle and mitochondrial respiration, resulting in reduced frequencies and number of effector cells. More importantly, these maneuvers promoted the formation and maintenance of CD8+ memory stem (TSCM) cells. By combining LDH inhibition with different common gamma-chain cytokines we have found unanticipated cooperative effects with IL-21.

LDH inhibition combined with IL-21 maximize the generation of TSCM cells and their therapeutic efficacy in a preclinical model of adoptive immuno-therapy.

Surprisingly, LDH inhibition did not significantly affect IL-21–induced metabolism but caused major transcriptomic changes, including the suppression of IL-21–induced exhaustion markers LAG3, PD1, 2B4, and TIM3. The basis for the transcriptomic changes is not known, but emerging evidence indicate that LDH can have profound influences on the epigenetic state of a cell. The impact of LDH inhibition on cytokine-stimulated transcription represents an exciting area of future investigation.

Dr. Dragana Slavkovic Lukic

Project 2.3

CAR-modified CD8+ T memory stem cells for the treatment of human B cell malignancies

T memory stem (TSCM) cells are a rare subset of memory lymphocytes endowed with the stem cell–like ability to self-renew and the multipotent capacity to reconstitute the entire spectrum of memory and effector T cell subsets. These cells have the potential to overcome the limitations of current adoptive T cell therapies, including inefficient T cell engraftment, persistence, and ability to mediate a prolonged immune attack against tumors.

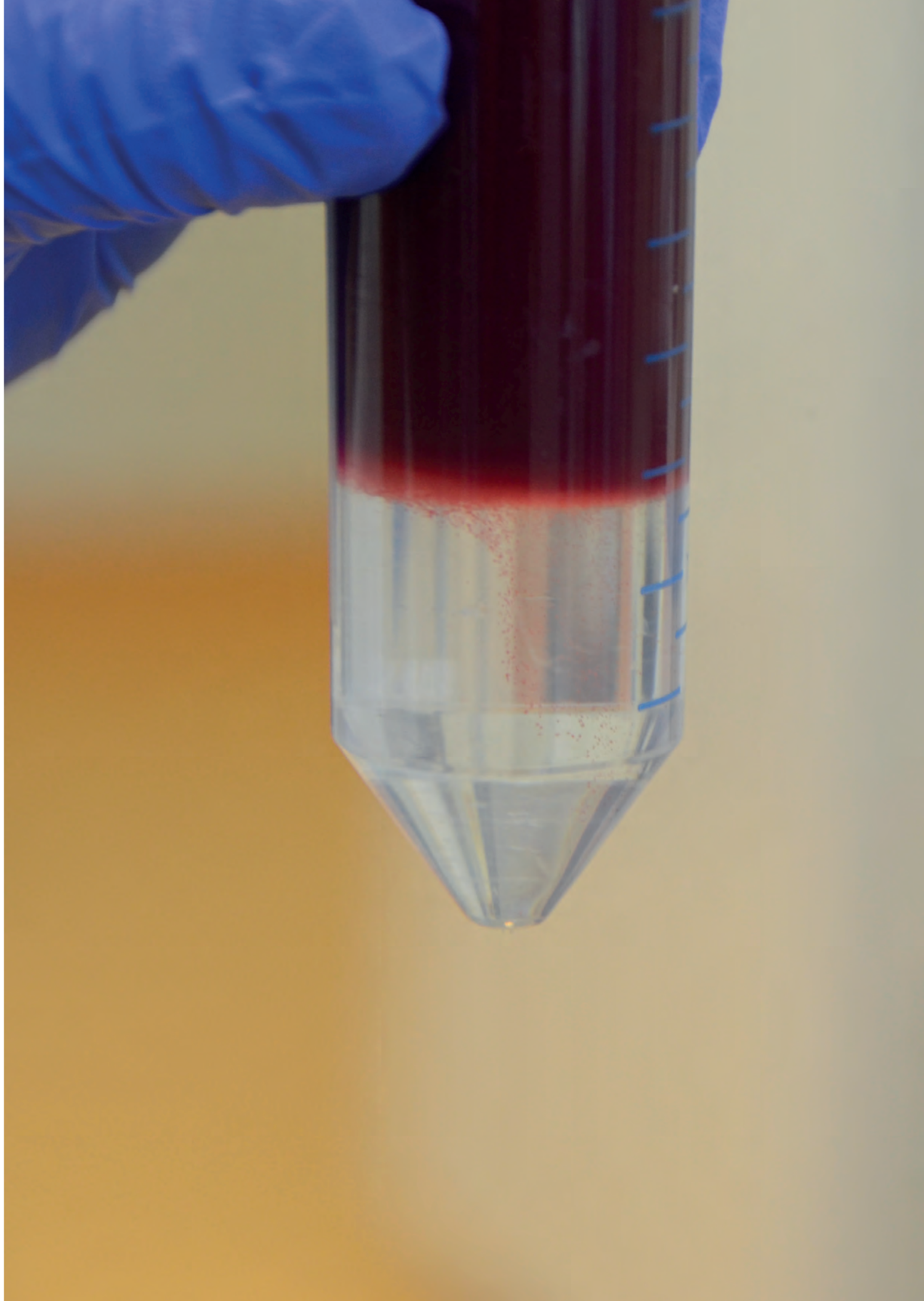
T memory stem (TSCM) cells are a rare subset at the apex of the hierarchical system of memory T lymphocytes. Owing to their extreme longevity, robust proliferative potential and the capacity to reconstitute a wide-ranging diversity of the T cell compartment, TSCM cells are emerging as an ideal cell population for adoptive immunotherapy.

Seminal work by our group in preclinical animal models has formally demonstrated that TSCM cells mediate more potent anti-tumor responses than conventional central memory and effector memory T subsets, which are the main cell populations currently employed in the clinic.

Thus far, the clinical exploitation of TSCM cells has been hindered by their relative paucity in the circulation and the lack of robust, clinical-grade manufacturing protocols that are capable of generating and maintaining this cell type *in vitro*. We have recently established a clinical-grade manufacturing strategy for the generation of large numbers of CAR-modified TSCM cells starting from naive CD8+ T cell precursors.

Briefly, CD8+, CD62L+, CD45RA+ naive T cells enriched by streptamer-based serial-positive selection are activated by CD3/CD28 engagement in the presence of interleukin-7 (IL-7), IL-21, and the glycogen synthase-3ß inhibitor TWS119, and genetically engineered to express a CD19-specific chimeric antigen receptor (CD19-CAR). These conditions enable the generation of CD19-CAR-modified CD8+ TSCM that are equivalent to their naturally occurring counterpart. This clinical-grade platform provides the basis for an ongoing phase 1 study evaluating the activity of allogeneic CD19-CAR-modified CD8+ TSCM in patients with B-cell malignancies refractory to prior allogeneic hematopoietic stem cell transplantation that is conducted at the U.S. National Cancer Institute in collaboration with Dr. James Kochenderfer. To facilitate the widespread adoption of CAR-modified TSCM cells, we are currently developing a closed and automated platform using the clinical sorter MacsQuant Tyto® and the CliniMacs Prodigy® platform.

This novel manufacturing process will serve to produce autologous TSCM cells modified with a CD19/CD22 bispecific CAR that will be tested in a new phase 1 clinical trial at the University Hospital Regensburg.



3

Staff of
Prof. Dr. M. Edinger
& PD Dr. rer. nat. P. Hoffmann

Research Group Immunoregulation

Central Question:
Immunobiology of allogeneic stem cell transplantation

Main Research Focus

Allogeneic stem cell transplantation (aSCT) is a curative treatment option for patients with congenital or acquired hematologic diseases and most frequently applied for the treatment of otherwise incurable leukemia or lymphoma. The success of this treatment modality relies on immunotherapeutic mechanisms, as lymphocytes in the graft recognize patient's blood cells as foreign and destroy them, thereby contributing to the elimination of leukemia/ lymphoma. Furthermore, they support the engraftment of donor stem cells for hematopoietic reconstitution. However, such immune responses may spread to solid organs (primarily to skin, gut, and liver) and thereby cause graft-versus-host disease (GvHD), an immune-mediated transplant complication. The Research Group Immunoregulation investigates the basic mechanisms of donor – recipient immune reactions after aSCT to improve the safety and efficacy of this life-saving treatment modality.

Current Projects

The research group works on the following topics:

A. **Basic research on immunobiology allogeneic stem cell transplantation**
B. **Research on physiological immunoregulatory mechanisms for the prophylaxis & therapy of transplantation complications (focused on tolerance induction by regulatory T cells)**
C. **The exploration of new cell therapeutic treatment options in GvHD in early clinical studies (translational research)**

The research group covers the entire spectrum of preclinical and translational research and investigates fundamental immunobiological questions in experimental models, verifies findings in human cells (from healthy donors or SCT patients) using cellular and molecular biology methods, and develops new methods and technologies for testing innovative cell therapies in early clinical studies. The group collaborates with many experts and scientists worldwide on this research field.

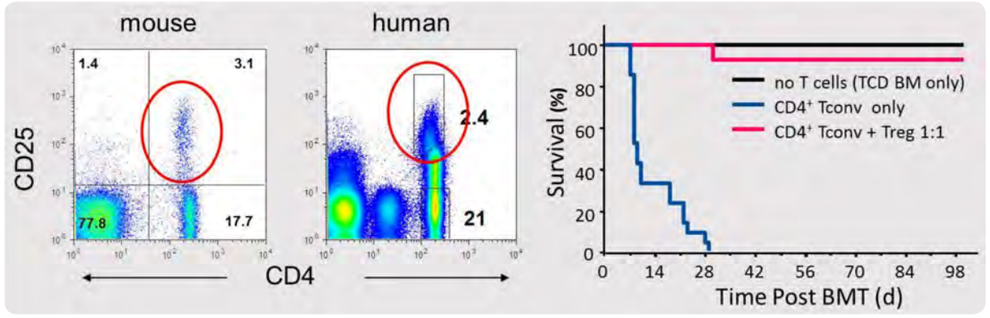


Fig.: Phenotype of mouse and human regulatory T cells (Treg) and survival after experimental bone marrow transplantation with and without the transfer of donor Tregs (Edinger et al., Nat Med 2003).

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
1.764	11	3
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

RIEGEL C ET AL., Efficient treatment of murine acute GvHD by in vitro expanded donor regulatory T cells. *Leukemia* 2019

MINDERJAHN J et al., Mechanisms governing the pioneering and redistribution capabilities of the non-classical pioneer PU.1. *Nat Commun* 2019; 11(1):402

NOGUCHI S et al., FANTOM5 CAGE profiles of human and mouse samples. *Sci Data* 2017; Aug 29; 4:170112

COSSARIZZA A et al., Guidelines for the use of flow cytometry and cell sorting in immunological studies (second edition). *Eur J Immunol* 2019; Oct;49(10):1457-1973

FOELL J et al., Haploidentical CD3 or α/ß T-cell depleted HSCT in advanced stage sickle cell disease. *Bone Marrow Transplant* 2019;54(11):1859-1867

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Dr. Christin Albrecht
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Claudia Weber
Verena Woller
Irina Fink
Niklas Wenzl
Rüdiger Eder
Jaqueline Dirmeier (parental leave)

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& PD Dr. rer. nat. P. Hoffmann

Project 3.1

Prophylaxis & therapy of transplantation complications through physiologic immune regulatory mechanisms

Graft-versus-Host-Disease (GvHD) after allogeneic stem cell or bone marrow transplantation (SCT/BMT) is induced by conventional donor T cells (Tconv) contained in the stem cell graft and is a main cause of treatment-related morbidity and mortality. The research group „Immunoregulation“ previously showed that Foxp3+ donor regulatory T cells (Tregs) do not cause GvHD, but prevent or ameliorate acute GvHD caused by co-transplanted Tconv cells. Based on these previous findings, the following research questions are currently investigated in experimental models:

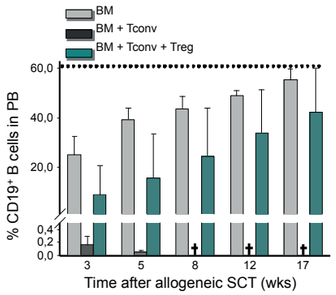

Figure: Peripheral B-cell reconstitution after GvHD-free SCT (BM) in patients with GvHD (BM+Tconv) or prophylactic Treg-treatment

How does the transfer of immunosuppressive Tregs affect immune reconstitution?

In thus far unpublished experiments we found that GvHD leads to severe disturbances of immune reconstitution, in particular to quantitative and functional impairments of the B cell compartment. Inhibition of GvHD through donor Treg transfer improves rather than impairs immune reconstitution, as they promote lymphoid progenitor cell survival and function via direct and indirect protective mechanisms.

Role of donor Treg for long-term tolerance after allogeneic SCT?

To investigate the impact of donor Treg on long-term tolerance development after allogeneic BMT, Treg subpopulations in GvHD-free transplant recipients are depleted at serial time points. These ongoing experiments already revealed the pivotal importance of donor Treg-mediated suppression for the development and maintenance of peripheral tolerance after allogeneic SCT.

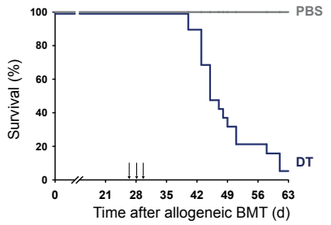

Fig.: Survival of GvHD free SCT recipients after Treg depletion in a MHC-mismatched GvHD model

Therapeutic efficacy of donor Treg in acute GvHD?

To investigate whether donor Tregs are therapeutically effective, they were applied 10-12 days after GvHD onset. It was shown that their transfusion rescued 66% of animals from otherwise lethal acute GvHD.

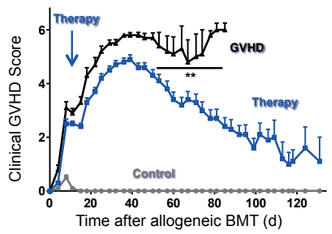

Fig.: GvHD score in MHC-mismatched transplant recipients with and without Treg therapy (Riegel et al., *Leukemia* 2019)

Program Area III

Cell Production and Therapy

The clinical translation of scientific findings is an important goal of the RCI; therefore, particular emphasis is laid on the development and implementation of clinical studies. Program Area III is used for the translation of the results and therapeutic approaches developed in Program Areas I and II into clinical use. This is done in close collaboration with clinical development partners. The GMP-compliant production unit of new cell therapeutics at the José-Carreras-Center serves as a core area and prerequisite for clinical testing and clinical application of cell therapies developed at the RCI which are to be tested at cooperating clinical trial centers. The manufacturing of therapeutics is complemented by the platforms for regulatory affairs (Core Facility GCP & Regulatory Affairs) and for the evaluation of the efficacy and safety of our approaches (Core Facility Immunomonitoring).

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1 José-Carreras-Center for Somatic Cell Therapy (JCC)

GMP Facility for the manufacturing of innovative cell therapeutics

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2 Core Facility “Good Clinical Practice - GCP- & Regulatory Affairs”

Clinical studies for innovative therapeutic approaches

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3 Core Facility “Immunomonitoring”

Monitoring of the immune status in patients

José-Carreras-Center
Regensburg

1

José-Carreras-Center for Somatic Cell Therapy (JCC)

GMP Facility for the manufacturing of innovative cell therapeutics

JCC illumination

The José-Carreras-Center for Somatic Cell Therapy (JCC) is a central componant of the RCI: It is a separate research building with a total floor area of 193 m^2 harboring several cleanroom laboratories. Headed by Prof. Dr. M. Edinger, the JCC is specialized in the pharmaceutical development and GMP (good manufacturing practice)-compliant production of cell therapeutics, including advanced therapy medicinal products (ATMP) and genetically modified cells. In its 70 m^2 cleanroom area (class A to D) and several laboratories for cellular analysis, the JCC focuses on the generation of cell products for early clinical trials in an academic environment. The JCC is the first center capable of performing GMP-approved cell sorting using FACS technology, what permits the production of cell products with an exceptional degree of purity. Furthermore, cell populations can be enriched or depleted by means of different magnetic separation methods (e.g. Clini-MACS® and CliniMACS-Prodigy®).

Focus

The JCC currently focuses on the GMP-compliant production of *in vitro* expanded regulatory T cells (Tregs) using combined MACS and FACS technologies for the treatment of patients with transplantation complications (acute and chronic GvHD after allogeneic stem cell transplantation, EudraCT 2012-002685-12 & 2016-003947-12) and for tolerance induction after kidney transplantation (in collaboration with the University Hospital Vienna, EudraCT 2018-003142-16).

GMP-compliant FACS sorting at the JCC

Our next steps

The testing, validation and clinical trial application for the approval of combined T and B cell depletions of stem cell products for haploidentical transplant patients with hemoglobinopathies (in collaboration with the Pediatric Hemato-/Oncology Department at the UKR as part of a multicenter international SCT-study) as well as the genetic modification of T cells with chimeric antigen receptors (CAR) and T cell receptors (TCR) for the treatment of patients with hematologic and solid tumors (in collaboration with the Division of Genetic Immunotherapy [Prof. Abken] and the Division of Functional Immune Cell Modulation [Prof. Gattinoni]) are currently main research efforts. The JCC is registered and approved as a genetic engineering facility and fulfils all technical, regulatory and personnel requirements for the production of innovative cell therapeutics.

JCC Staff in cleanroom clothing

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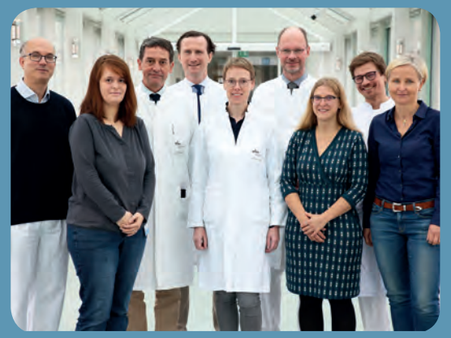

CAR T cell Therapy Team at the RCI/UKR

2

Core Facility “Good Clinical Practice - GCP & Regulatory Affairs”

Clinical studies for innovative therapeutic approaches

RCI scientists are dedicated to develop and investigate new immune cell therapies for frequent and aggressive diseases such as cancer, autoimmune and chronic inflammatory diseases.
Promising therapeutic concepts are tested in early clinical trials. The Core Facility “GCP & Regulatory Affairs” was established to support RCI scientists to develop and investigate new immune cell therapies for frequent and aggressive diseases such as cancer, autoimmune and chronic inflammatory diseases.

What is a clinical study?

Clinical studies are necessary to determine the safety, tolerability, and efficacy of new drugs and therapies before they can be used in routine patient treatment.

Who are we?

RCI scientists, project leaders, medical professionals and physicians work together in our interdisciplinary team.

What do we do?

We work in close collaboration with the Trial Center and the Early Clinical Trial Unit (ECTU) of the Department Internal Medicine III, the Center for Clinical Trials Regensburg (ZKS) of the UKR and the José-Carreras-Center (JCC) to maintain the infrastructure and expertise for the implementation of phase I-IV clinical trials. The GCP & Regulatory Affairs Facility acts at the interface between physicians, patients, scientists, manufacturers, academic study groups, and pharmaceutical companies.

All clinical studies at the RCI are subject to strict international guidelines (ICH-GCP) and quality standards, as well as the respective legal national laws and standards (AMG, GCP-V).

Focus on innovative cell therapies

About 20,000 people in Eastern Bavaria are diagnosed with cancer each year. Despite the continuous medical progress there is still no cure for many patients. Immune therapeutic approaches recently advanced cancer treatment, including innovative immune cell therapies employing genetically modified lymphocytes (CAR T cells). RCI researchers work extensively on the development of new cellular therapy formats that have to be tested in clinical trials. The close cooperation of the RCI and its cell manufacturing facility José-Carreras-Center (JCC) with the UKR permits the rapid exploration of new cell therapies in early clinical trials.

Benefit for the patients

Novel cell therapies offer new treatment options for otherwise incurable diseases. Beyond the clinical benefit for individual patients, clinical trials are pivotal for the advancement of medical research and treatment and thereby they also improve the life of future patients.

GCP-Team at the RCI: PD Dr. S. Thomas, Prof. M. Edinger, P. Schlosser, U. Fehn

Clinical Studies

Trex001
Treg002
Treg003
MAGIC
CD-TCR-001
Belinda
BAY18650

Publications supported by the GCP Team (Selected)

KATTNER AS et al., IL6-receptor antibody tocilizumab as salvage therapy in severe chronic graft versus-host disease after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. *Annals of Hematology* 2020 (epub ahead of print).

ILLERHAUS G et al., High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. *The Lancet Haematology* 2016;3(8):e388-97.

STEIN-THOERINGER CK et al., Lactose drives Enterococcus expansion to promote graft versus-host disease. *Science* 2019;366(6469):1143-9.

MICHEL C et al., Imatinib dose reduction in major molecular response of chronic myeloid leukemia: results from the German Chronic Myeloid Leukemia-Study IV. *Haematologica* 2019;104(5):955-62.

HARTWELL MJ et al., An early biomarker algorithm predicts lethal graft-versus-host disease and survival. *JCI insight* 2017;2(3):e89798.

HEHLMANN R et al., Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia* 2017;31(11):2398-406.

Third-party Funding (Selected)

EU Horizon 2020 program
José-Carreras-Leukaemia Foundation
Free State of Bavaria
Vienna Science, Research and Technology Fund (WWTF)
Bayer AG

Collaborators (Selected)

University Hospital of Regensburg (UKR)
Internal Medicine III
Early Clinical Trial Unit (ECTU)
José-Carreras-Center (JCC)
Center for Clinical Trials Regensburg (ZKS)
Comprehensive Cancer Center Ostbayern (CCCO)
coTrials

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Scientists
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PD Dr. Simone Thomas

Technicians
Pavla Schlosser
Ute Fehn
Karin Meissner

Dr. T. Böld, Head of test laboratory

3

Core Facility “Immunomonitoring”

Monitoring of the immune status in patients

Numerous immunomonitoring methods have been established to serve clinical research at the RCI. These include the determination of the immune status in tumor patients, the examination of tumor infiltrating leukocytes/ lymphocytes, and the examination of immune reconstitution after transplantation or after cell therapy. The tests are carried out at the testing laboratory of the José-Carreras-Center (JCC) headed by Dr. Tina Böld and in close collaboration with all RCI Core Facilities and research groups.

Our portfolio includes:

- Multicolor flow cytometry for relative and quantitative determination of leukocyte/ lymphocyte subpopulations in the course of disease or therapy
- Lymphocyte function tests for the intracellular determination of cytokine secretion as well as Cytokine Capture Assay, Cytokine Bead Array, Cytokine ELISA, and ELISPOT methods
- Intranuclear determination of transcription factor expression
- Cytotoxicity tests
- Cell sorting for the determination of lineage-specific chimerism after transplantation (in collaboration with the FACS Core Facility)
- Single cell sorting for RNA sequencing (in collaboration with the FACS Core and Omics Core Facilities) and single cell cloning of tumor infiltrating lymphocytes
- HLA peptide multimer analysis using flow cytometry for the detection of antigen-specific T cells
- T cell receptor sequencing for the determination of Treg cell expansion after therapeutic application (in collaboration with the Omics Core Facility)
- *In vitro* live cell imaging methods for real-time analysis of cell survival, migration, and cytotoxic mechanisms

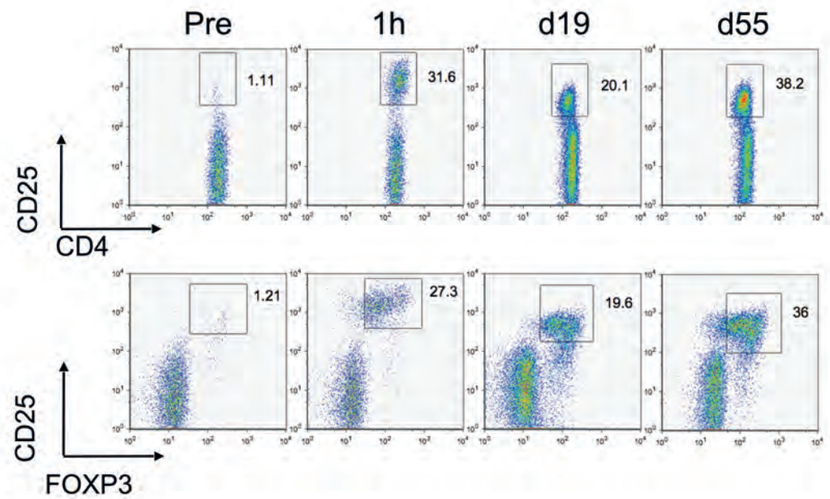

Fig.: Immunomonitoring of regulatory T cells

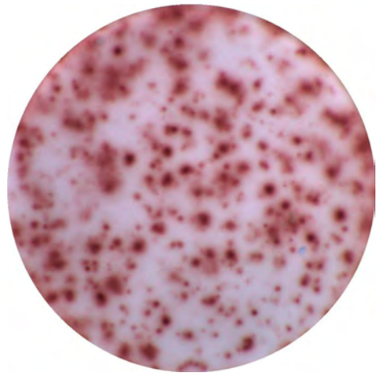

Fig.: ELISPOT for the determination of cytokine producing T cells

Staff

Scientists

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Yvonne Hader (UKR)
Kristina Kolodova (UKR)

Program Area IV

Strategic Development and Collaborations, Communication

Program Area IV comprises measures that serve the strategic development of the RCI and that could be assigned to one of the other Program Areas at an advanced stage of development.
In addition, Program Area IV includes public relations and strategic networking with relevant partner institutions.

Prof. Dr. Marina Kreutz

1

Clinical Cooperation Group Immunometabolomics

Central Question:
Why do immune cells fail in the defense against tumors? What can we do about it?

Main Research Focus

„Tell me what you eat, and I'll tell you what you are" - this old saying definitely applies to tumor cells. Tumor cells feed mainly on sugar.

This characteristic of tumor cells was described by the Nobel Prize winner Otto Heinrich Warburg and is, therefore, also called "Warburg effect". While most normal body cells cover their energy requirements mainly through oxidative phosphorylation, the majority of tumor cells use aerobic glycolysis, in which sugar is broken down to lactate. The Warburg effect is accompanied by an increased glucose uptake and an increased production of lactate by the tumor cells, which is released into the tumor environment via special transporters leading to lactate accumulation and acidification of the tumor tissue. Previous analyses have shown that lactate and acid released by the tumor lead to the inhibition of the immune response and can weaken immunotherapeutic approaches. Therefore, it is necessary to find possibilities to counteract the immunosuppression by lactate and acid, as well as to identify further factors that impede immune cells in their antitumor activity.

Current Projects

The Clinical Cooperation Group works on the following topics:

A. **Characterization of "metabolic checkpoints" of the tumor that suppress immune cells (T cells)**
B. **Analysis of immune cell metabolism during the interaction of immune cells and tumor cells**
C. **Genetic and pharmacological modulation of cell metabolism to strengthen the anti-tumor defense**

The aim of our group is to characterize tumor-associated metabolic changes that inhibit immune cells. Furthermore, underlying mechanisms of immunosuppression will be deciphered to develop possibilities to strengthen T cell function in the tumor environment.
First investigations in animal models have already shown that the genetic blockade of lactate release by tumor cells leads to a significantly improved immune response against the tumor. We assume that, in addition to the suppression of tumor metabolism, the adaptation of immune cell metabolism to the tumor milieu also leads to an improved anti-tumor response. Therefore, we will genetically modify tumor-infiltrating immune cells to make them resistant to lactate and acid. Pilot experiments showed that T cells overexpressing certain enzymes are unable to take up and degrade lactate. This "doping of T cells" might be able to break the immune blockade in the tumor.

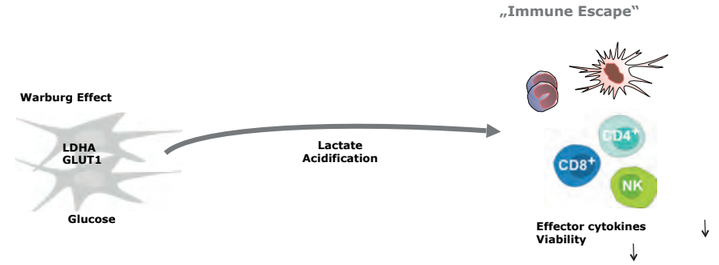

Fig.: The increased glycolytic activity of tumor cells, the so-called Warburg effect, leads to the secretion of lactate as well as the acidification of the tumor milieu. This in turn contributes to the suppression of an immune response directed against the tumor. On the one hand, the expression of important effector cytokines is suppressed, on the other hand, the viability of T cells and NK cells is impaired (Brand et al., *Cell Metabolism* 2016).

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
1.952	15+3 Reviews	4
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

BOHN T et al., Tumor immunoevasion via acidosis dependent induction of regulatory tumor-associated macrophages. *Nat Immunol* 2018; 19(12):1319-1329

RENNER K et al., Restricting Glycolysis Preserves T Cell Effector Functions and Augments Checkpoint Therapy. *Cell Reports* 2019; 29 (1)

BRUMMER C et al., Metabolic targeting synergizes with MAPK inhibition and delays drug resistance in melanoma. *Cancer Lett* 2018; 24; 442:453-463

RENNER K et al., Metabolic Hallmarks of Tumor and Immune Cells in the Tumor Microenvironment., *Front Immunol* 2017 Mar 8; 8:248.

Third-party Funding (Selected)

2014 – 2018	Clinical Research Unit KFO 262 (together with P. Oefner): Tumor metabolism as modulator of immune response and tumor progression
2017 – 2019	International Immuno-Oncology Network BMS (together with T. Pukrop, C. Blank): Impact of NSAIDs on the response to checkpoint therapy
2018 – 2022	SFB Transregio (together with K. Peter, H. Bruns): Modulation of GvH and GvL immune response after allogeneic stem cell transplantation

Collaborators (Selected)

DR. JACQUES POUYSSÉGUR, Institute of Research on Cancer and Aging (IRCAN), University of Nice-CNRS-Inserm, Nice, France
DR. CHRISTIAN BLANK, The Netherlands Cancer Institute, Dept. Medical Oncology and Division of Molecular Oncology & Immunology, Amsterdam, The Netherlands
PROF. DR. JOHN CLEVELAND, Department of Tumor Biology, Moffitt Cancer Center & Research Institute, Tampa, FL, USA

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Prof. Dr. Marina Kreutz
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PD Dr. Kathrin Renner-Sattler

Project 1.1

Doping of immune cells

Strengthening the function of human T cells in their fight against tumor cells

The function of immune cells in the tumor is often limited due to the tumor environment. The aim of this project is to make immune cells resistant to their suppression in the tumor environment by overexpression of certain genes. Thereby, T cells will survive and be functionally active even in a lactate-rich and acidic tumor environment. This is particularly important with regard to immunotherapeutic approaches that are developed at the RCI.

Tumor cells have a sweet tooth and feed mainly on sugar. In tumor patients, the increased sugar consumption has been used for many years for the diagnosis of primary tumors and metastases. The sweet life of tumor cells leads to the release of the waste product lactate and to the acidification of the environment of the tumor.

T cells can attack and kill tumor cells

T cells can potentially kill tumor cells. However, the activity of T cells in the tumor is disturbed by lactate, the degradation product of sugar and acid. When T cells take up lactate and acid they can no longer fulfill their task, i.e., the recognition and destruction of tumor cells. This also applies to T cells, which are designed for immunotherapy to combat tumors in patients. Therefore, the aim of this project is to make immune cells in the tumor fit and resistant to accumulating lactate.

For this purpose, T cells will be equipped with an enzyme that breaks down lactate. This enzyme is already present in immune cell, but not in sufficient quantity. Through genetic manipulation, the T cells will be forced to increase their production of this endogenous protein. First experiments *in vitro* showed that genetically modified immune cells still absorb lactate, but this lactate is then used for energy production. This leads to an increased anti-tumor activity of theses “strengthened” immune cells.

In further studies, these genetically modified T cells will be tested in mouse tumor models with the support of other groups at the RCI. In addition, further approaches to strengthen T cell function will be tested. Here, we will learn from other immune cells, so-called macrophages, that are used to get along with lactate.

The close interdisciplinary networking within the RCI as well as the available core facilities allow genetic analyses of macrophages to identify genes that may contribute to a further strengthening of T cell functions.

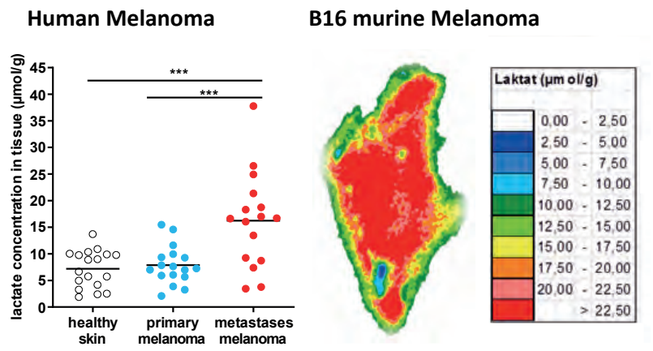

Fig.: Human melanoma metastases show significantly increased lactate levels, comparable to the murine B16 melanoma model. Lactate concentration was determined by “induced metabolic bioluminescence imaging” (Brand et al., *Cell Metabolism* 2016).

Prof. Dr. Matthias Mack

2

Clinical Cooperation Group Inflammation, Autoimmunity & Fibrosis

Central Question:
Why do autoimmune reactions lead to fibrosis and organ failure?

Main Research Focus

Inflammatory diseases and autoimmunity are found in many areas of medicine. In most cases they not only lead to pain, but also to scarring (fibrosis) of the tissue with functional limitations and even organ loss over a long period of time. Treatments are usually lengthy and poorly tolerated. The aim of our research group is to better understand the underlying immune reactions and scarring, and to develop more specific, effective and tolerable therapies. The focus of our interest is on inflammatory diseases of the kidney (e.g. systemic lupus erythematosus), the central nervous system (e.g. multiple sclerosis), and the locomotor system (e.g. rheumatoid arthritis). Our methods range from elaborate single cell analysis to translational examination of patient samples.

Current Projects

The group is currently working on the following main topics:

A. **Importance of interleukin-3 for inflammation and fibrosis**
B. **Regulatory B cells in autoimmune diseases**
C. **Mechanisms of fibrosis formation in kidney diseases**

The research group combines animal models of different autoimmune diseases with the analysis of clinical material from healthy donors and patients with autoimmune diseases using the latest technologies for immunological analysis. Thereby, important discoveries have been made, such as the central role of interleukin-3 in the development of autoimmunity and renal fibrosis. In addition, new drugs have been developed, such as blocking antibodies against Interleukin-3, which are currently in preclinical development for the therapy of inflammatory diseases.

Research group of Prof. Dr. M. Mack

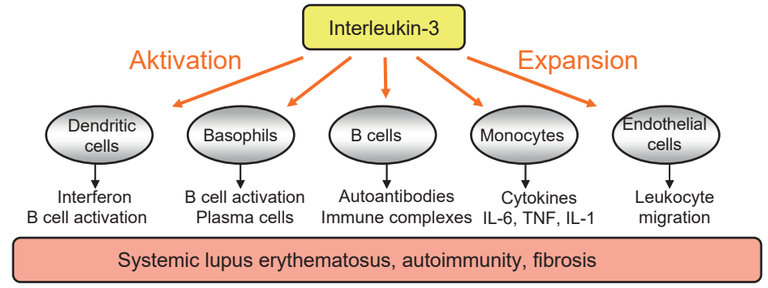

Fig.: Effect of interleukin-3 on several cells that are crucial for the development of systemic lupus erythematosus, autoimmunity, and fibrosis

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
2.800	31	5
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Ausgewählte Publikationen

LAGUMERSINDEZ-DENIS N et al., Differential contribution of immune effector mechanisms to cortical demyelination in multiple sclerosis. *Acta Neuropathol* 2017; 134: 15-34

BALAM, S et al., IL-3 Triggers Chronic Rejection of Cardiac Allografts by Activation of Infiltrating Basophils. *J Immunol* 2019; 202: 3514-3523

BUCHTLER, S et al., Cellular Origin and Functional Relevance of Collagen I Production in the Kidney. *J Am Soc Nephrol* 2018; 29: 1859-1873

Selected Publications

2019-2021	DFG Material Aid (MA2198/9-1), Chronic allograft fibrosis
2018-2021	SFB 1540 (Project Mack), Renal fibrosis
2017-2021	VIP+ Program (BMBF), Preclinical development of IL-3 antibodies
2018-2020	M4 Award (Bavarian State Ministry of Economic Affairs), Monocyte depletion

Collaborators (Selected)

PROF. MICHAEL DIAMOND, Washington University School of Medicine, Dept of Internal Medicine, U. S.
PROF. DR. M. PRINZ, University Medical Center Freiburg, Dept. of Neuropathology, Germany
PROF. FALK NIMMERJAHN, University of Erlangen, Chair of Genetics, Germany

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Prof. Dr. Matthias Mack

Project 2.1
The role of IL-3 in chronic transplant rejection

The chronic rejection of transplants is still a problem. The process is characterized by an increasing transplant scarring and the narrowing of vessels. As there are no specific treatment possibilities, investigation of the underlying mechanisms and the development of effective therapies are required.

Interleukin-3 (IL-3) is a mediator of the immune system, which is released by specialized cells (T cells) after their activation. IL-3 acts on cells that are important for the development of inflammation and cause scarring via secondary mediators. Therefore, IL-3 plays an important role in inflammatory and fibrotic diseases. Besides fundamental questions about IL-3, we are also investigating in which diseases IL-3 is overexpressed in the patient.

IL-3 plays a decisive role in the chronic rejection of heart transplants

In the model of heart transplantation in mice, we studied the involvement of IL-3 in chronic rejection and the development of fibrosis. Initially, we found that IL-3 is strongly overexpressed in chronically rejected transplants and CD4+ and CD8+ T cells were identified as the source of IL-3. Switching off IL-3 in transplant recipients led to a significantly lower development of fibrosis and thus to a significantly longer functioning of the transplanted heart.

The mechanisms by which IL-3 contributes to fibrosis and rejection have been unknown until recently. We could show now that basophilic granulocytes in the graft are activated by IL-3 to release IL-4 and IL-6 and thus contribute significantly to the development of chronic rejection. Selective depletion of basophilic granulocytes as well as switching off IL-3, IL-4 or IL-6 led to a significant weakening of fibrosis and a reduced release of the highly profibrotic cytokine TGF-beta.

In further analyses, we will investigate which cells contribute directly to the production of collagen and, thereby, the development of fibrosis, focusing on hematopoietic cells. By investigating mice with a collagen I deficiency especially in their hematopoietic cells, we will investigate how these cells contribute to the chronic rejection of transplants and which factors are involved. Finally, the results will be validated by the analysis of patient material after transplantation.

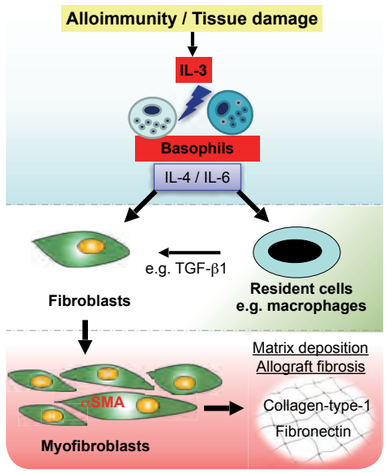

Fig.: Schematic representation of IL-3-dependent signaling pathways during chronic rejection of heart transplants

Head: PD Dr. Simone Thomas

3

Clinical Cooperation Group Allogeneic HLA-DP specific TCRs

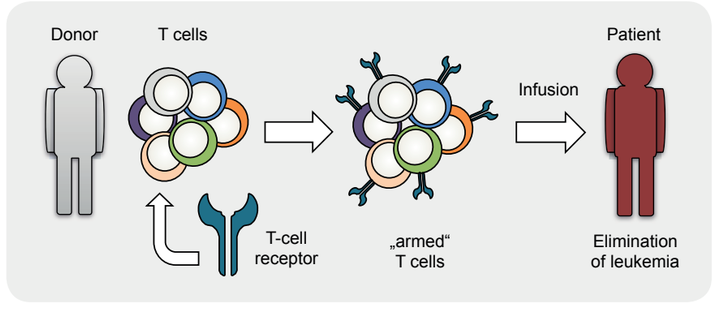

Fig.: Reprogramming of T cells with T cell receptors

Central Question:
How can we arm T lymphocytes to fight leukemia?
And how safe is it?

Main Research Focus

Cancer immunotherapies are on the rise - How can we strengthen the body's immune defense against leukemia?

In recent years, immunotherapies have become increasingly important in the treatment of leukemia and lymphoma. The most important immunotherapy to date is haematopoietic stem cell transplantation (HSCT). However, the regenerating immune system of the donor (especially T lymphocytes) is often unable to eliminate remaining leukemia cells in the patient to prevent leukemia relapse. The aim of our research is to modify donor T lymphocytes in such a way that they can specifically recognize and destroy leukemia cells in the patient. This is achieved with the help of so-called T cell receptors which recognize specific protein components (antigens) on leukemia cells.

In our studies, we use patient-specific tissue characteristics (HLA-DP antigens) as target antigens. In addition, we develop safety mechanisms, such as switches, to make this therapy as safe as possible.

Current Projects

The research group works on the following topics:

A. **Generation and characterization of HLADP specific T cell receptors**
B. **Development of safety mechanisms for the targeted control of T cell receptor-modified T lymphocytes**
C. **Implementation of clinical studies for the translation of new T cell therapies to the clinic**

The aim of the group is to isolate and characterize leukemia-specific T cell receptors in order to reprogram T cells from a healthy donor to leukemia-reactive T cells. A special focus is on the development of safety or switch mechanisms that allow switching on and off the reprogrammed T cells.

This issue is of clinical relevance, as the HLA-DP target antigens we are using can also occur on healthy tissue under certain circumstances, which might harm healthy tissue.

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
0.63	10	2
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

MATHEW NR, … Thomas S, … Zeiser R. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells. *Nat Med* 2018; 24:282

JETANI H, … Thomas S, … Hudecek M. CAR T-cells targeting FLT3 have potent activity against FLT3-ITD+ AML and act synergistically with the FLT3-inhibitor crenolanib. *Leukemia* 2018; 32:1168

HERR W, … Thomas S. HLA-DPB1 mismatch alleles represent powerful leukemia rejection antigens in CD4 T-cell immunotherapy after allogeneic stem-cell transplantation. *Leukemia* 2017; 31:434

Third-party Funding (Selected)

2018 – 2021	SFB Transregio 221: Modulation of graft-versus-host and graft-versus leukemia immune responses after allogeneic stem cell transplantation; Project A02: Efficacy and safety of HLA-DPB1 specific T cell receptors as mediators of transplant-versus-leukemia effects (together with W. Herr)
2016 – 2019	HLA-DPB1 specific T cell receptors for adoptive immunotherapy, Wilhelm Sander Foundation
2014 – 2018	Clinical Research Unit KFO 262: Tumor metabolism as modulator of immune response and tumor progression, Project 9: IDH mutations in metabolism and anti-leukemia immune responses (together with M. Kreutz und W. Herr)

Collaborators (Selected)

PROF. DR. KATHARINA FLEISCHHAUER, Institute for Experimental Cellular Therapy, University Hospital Essen
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Staff

Scientists	Doctoral Students	Technicians
Dr. Kathrin Hammon		Carina Mirbeth

Scientists and technicians of the research group headed by PD Dr. Simone Thomas

Project 3.1

T cell receptor modified T cells

Strengthening T lymphocytes against leukemia

Cancer immunotherapies have been on the rise in leukemia and lymphoma treatment for some years now. The RCI also focuses on the development of novel immunotherapies. The aim of our project is to strengthen immune cells in the fight against leukemia. To do this, we transfer leukemia-recognizing T cell receptors into T lymphocytes and develop mechanisms that make this therapy as safe as possible.

Today, allogeneic hematopoietic stem cell transplantation (HSCT) is the most successful immunotherapy mainly used in acute leukemia patients. Here, the donor's regenerating immune system contributes to the fight against leukemia. So-called T lymphocytes (also called T cells) play a crucial role in this approach as they recognize and destroy the residual leukemia cells in the patient after chemotherapy. However, this effect is often too weak to prevent the relaps of leukemia.

T lymphocytes can specifically be strengthened against leukemia

To specifically strengthen T cells to fight leukemia cells, we equip them with so-called T cell receptors. These receptors act as keys or sensors that recognize specific proteins (antigens) on leukemia cells. Once the antigen is bound, the receptor can initiate leukemia cell destruction by the T cell.

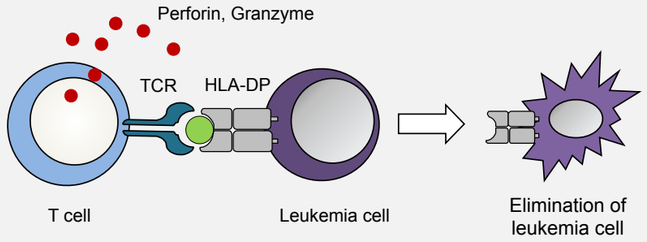

Fig.: Recognition of leukemia cells by T cells

The identification of antigens that are specifically present on leukemia cells, but not on healthy tissue cells is challenging. However, this is important to prevent healthy tissue from being recognized and destroyed by the activated T cells.

HLA-DP antigens as T cell target structures

In our preliminary work, we could show that certain tissue characteristics of the patient (so-called HLA-DP antigens) can serve as target structures for a leukemia-specific immunotherapy with T cells.

As the patient's T cells normally do not recognize these endogenous antigens, we will equip the donor's T cells with HLA-DP specific T cell receptors to allow the specific recognition and destruction of leukemia cells.

However, it cannot be completely excluded that this therapy, which is directed against HLA-DP antigens, also attacks healthy tissue. Therefore, another goal of our project is to develop safety mechanisms for this approach. One focus is on the development of switches to specifically switch T cell activity on and off.

Prof. Edward K. Geissler, PhD

4

Clinical Cooperation Group Organ Transplantation

Central Question:

How can we expand the donor pool for liver transplantation and increase long-term outcome of patients?

Main Research Focus

If the liver fails, there is acute danger to life! If the liver is seriously and irreversibly damaged, it can no longer perform its vital functions in our metabolism (e.g. detoxification, blood clotting, absorption of nutrients).

The most common reason for a liver transplantation is an advanced cirrhosis of the liver, which can result from numerous chronic diseases. Other possible reasons are acute liver failure (e.g. due to poisoning or infection) and certain cases of hepatic cancer.
The following crucial questions are currently being asked In the research field of liver transplantation:

- How can the quality of donor livers be improved to have as many organs as possible available for transplantation?
- How can cell damage in liver tissue (caused by insufficient perfusion) be reduced?
- Which is the optimal way to suppress the immune system to prevent rejection of the transplanted organ without increasing susceptibility to infection?

In addition to these questions, the research group is dedicated to fundamental questions of immunology in the context of transplantation of solid organs, especially the development of tolerance and transplant rejection.

Current Projects

The research group works on the following topics:

A. Mregs
We are investigating the therapeutic potential of a new population of regulatory macrophages that are able to induce regulatory T cells.

B. Immunomonitoring (The One Study)
We are working on the standardization and validation of immunomonitoring methods for the risk assessment of transplant rejection after kidney transplantation in collaboration with partners within the EU consortium “The One Study”.

C. Invariant Natural Killer T cells (iNKT cells) as a target for improving the outcome of liver transplantation. The aim of this research project is to find out how iNKT cells are activated in fatty liver and how this can be prevented. The final goal is to find possibilities for the transplantation of increasing numbers of fatty livers.

Transplantation Immunology and Experimental Surgery Staff

2017-2019 Numbers

2017 - 2019	2017 - 2019	2017 - 2019
2.803	35	3
Third-party Funding (MEUR)	Publications	Scientific Degrees Achieved

Selected Publications

SAWITZKI B et al., The ONE Study: Evaluation of Regulatory Cell Therapy in Kidney Transplantation Using a Harmonized Trial Design. *Lancet* (in press).

HUTCHINSON JA et al., Predicting early viral control under direct-acting antiviral therapy for chronic Hepatitis C virus using pretreatment immunological markers. *Front Immunol* 2018; 9:146.

HAEGER A, et al., Collective cancer invasion forms an integrin-dependent radioresistant niche. *J Exp Med* 2020; 6;217(1):1-18

RIQUELME P et al., TIGIT+ iTregs elicited by human regulatory macrophages control T cell immunity. *Nat Commun* 2018; Jul 20;9(1):2858

Third-party Funding (Selected)

2019 – 2022	SFB 1350, Project B06, Role of immigrating B-lymphocytes and their functional properties in the development of graft nephropathy
2014 – 2021	FOR2127, TP B2, Innate immunosurveillance of metastatic disease
2010 – 2018	European Union FP7 Programme, Collaborative Project, The ONE Study: A unified approach to evaluating cellular immunotherapy in solid organ transplantation

Collaborators (Selected)

AURELIE MOREAU (Université de Nantes) | BIRGIT SAWITZKI (Charité, Berlin) | FADI ISSA/PAUL HARDEN (Oxford University, UK)

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Stephanie Blaimer

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Joachim Schweimer
Anke Hofmann
Erika Ostermeier

PD Dr. med. Jens M. Werner

Project 4.1

Invariant Natural Killer T cells (iNKT cells) as a target to improve the outcome of liver transplantation

The prevalent shortage of donor organs is aggravated by the fact that the frequency of fatty liver disease is increasing in the Western world. Invariant Natural Killer T cells (iNKT cells) are specialized immune cells that are important for the recognition of lipids. The aim of our research project is to find out how iNKT cells are activated in the context of fatty liver and how this can be prevented to allow the transplantation of fatty livers in the future.

The liver is the central organ for the detoxification of the body. If its function is disturbed, the body is flooded with toxins and many vital factors are no longer produced, e.g., factors involved in blood clotting. In many cases, liver transplantation is the only treatment option for patients with liver failure. Unfortunately, there is a severe shortage of donor organs and approximately 3,000 patients are waiting for a new liver in the Euro-Transplant area alone. It is, therefore, important to find new ways for the transplantation of as many donor livers as possible. The lack of suitable donor organs is further aggravated by the fact that the frequency of fatty liver disease is increasing in the Western world. This has a considerable impact on the function of potential donor organs.

Activation of iNKT cells in fatty liver disease

We previously found in a cell culture model that a certain immune cell population is specialized in the recognition of lipids. Invariant Natural Killer T cells (iNKT cells) are activated in the context of fatty liver disease and secrete increased amounts of pro-inflammatory mediators (cytokines).

The goal of our research project is to find out how iNKT cells are activated in the context of fatty liver disease. We established a cell culture model to simulate a fatty liver disease using expanded iNKT cells and lipid-loaded HepaRG cells (terminally differentiated hepatoma cells).

Preliminary results of this *in vitro* model suggest that hepatocytes can suppress IL-4 production of iNKT cells by contact-dependent mechanisms; however, this activity is inhibited when hepatocytes are loaded with lipids.

In the future, we will compare lipid-loaded and unloaded HepaRG cells by means of proteome analysis (protein analysis). We are expecting some information about potentially important ligands for iNKT cells.

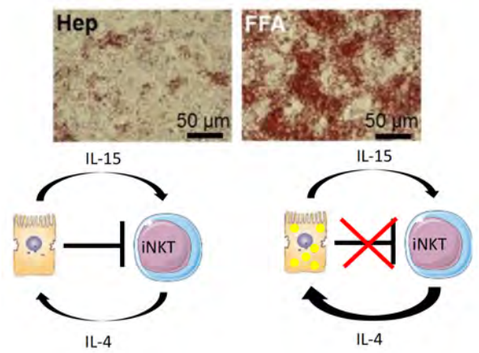

Fig.: The role of fat loading (FPA) in monocyte-mediated secretion of IL-4 by iNKT cells in liver cells

Imprint

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