Department of Medicine 5 – Hematology and Oncology

Chair of Hematology and Oncology

Address
Ulmenweg 18
91054 Erlangen
Phone: +49 9131 8535955
Fax: +49 9131 8535958
www.medizin5.uk-erlangen.de

Director
Prof. Dr. med. Andreas Mackensen

Contact
Prof. Dr. med. Andreas Mackensen
Phone: +49 9131 8535955
Fax: +49 9131 8535958
andreas.mackensen@uk-erlangen.de

Research focus
- Immune regulation by DN T cells
- Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)
- T cells between immunotherapy and autoimmunity
- Immunometabolism
- Tumor associated macrophages and posttranscriptional regulation by Hoxa9
- Communication of tumor cells and microenvironment
- Molecular immunotherapy
- T cell-based immunotherapy of ocular melanoma
- Tumor microenvironment
- Tumor immune escape
- Cellular immunotherapy
- HLA-laboratory

Structure of the Department

Professorships: 2
Personnel: 131
- Doctors (of Medicine): 38
- Scientists: 9 (thereof funded externally: 7)
- Graduate students: 13

Clinical focus areas
- In-patient and out-patient care of patients with leukemia, lymphoma, and non-malignant hematologic diseases
- Allogeneic and autologous stem cell transplantation
- Out-patient stem cell transplant unit
- In-patient and out-patient care of patients with urological tumors, bone and soft tissue sarcoma, head and neck tumors, lung tumors and other solid tumors
- Out-patient unit for urologicial tumors (AURONTE)
- Hematological diagnostics

Research

The main research focus of the Department of Medicine 5 concentrates on tumor immunology. Several research groups examine basic immunological mechanisms of tumor formation, tumor defense, and tumors escape. We have a special research focus on the characterization and blockade of graft-versus-host reactions after allogeneic stem cell transplantation and the improvement of graft-versus-leukemia responses. The long-term goal is to translate these concepts into innovative cell-based therapies.

Immune regulation by DN T cells

PI: Prof. Dr. A. Mackensen, Dr. S. Völkl
The population of human TCRα/β+ CD4/CD8 double-negative (DN) T cells plays a special role in the regulation of immune responses. In this project, the group investigates the immunoregulatory function of human DN T cells. In addition, the role of DN T cells under pathologic conditions as autoimmunity and transplant rejection is currently determined. The long-term goal is to develop a clinical strategy for using DN T cells to treat graft-versus-host disease (GvHD) after allogeneic stem cell transplantation.
Funding: DFG, IZKF

Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)

PI: Dr. J. Winkler, Prof. Dr. T. Winkler, Prof. Dr. M. Mach
The aim of our project is the preclinical development of a new, first-in-man cell based therapy for the improvement of humoral immune responses in patients after alloSCT. We developed a study protocol for a phase I/IIa clinical trial for the adoptive transfer of allogeneic donor B-lymphocytes for patients four months after alloSCT according to GCP. The application of allogeneic B lymphocytes is intended for 15 patients in escalating cell dosages. So far, 13 patients received the B-cell product and no severe adverse events were observed.
Funding: DFG

T cells between immunotherapy and autoimmunity

PI: PD Dr. Dr. A.N. Kremer
The main focus of this group is the separation of beneficial graft-versus-leukemia (GvL) effect after alloSCT from detrimental GvHD by characterization of the intracellular processing pathways of HLA class II restricted antigens as well as the identification of tumor-specific T-cell targets in breast cancer.
Further we analyze the role of these antigens in the pathogenesis of autoimmune diseases and the CD4+ T cell mediated eradication of HLA class II negative tumors via indirect antigen presentation.
Funding: DFG, Else Kröner Fresenius Foundation, Ernst Jung-Foundation, IZKF

Immunometabolism

PI: Prof. Dr. D. Mougiakakos
We focus on alterations of the metabolism and the immune system in cancer and after stem cell transplantation. An understanding regarding tumor-associated (metabolic) strategies contributing to an immunosuppression will support development of therapeutic strategies. Furthermore, we aim at "learning" how tumors weaken immune responses in order to translate these findings into potential experimental approaches for the treatment of GvHD following SCT.
Funding: Deutsche Krebshilfe (Max-Eder Junior Research Group), José Carreras Leukemia Foundation, Else Kröner Fresenius Foundation, European Hematology Association, Elitenetzwerk Bavaria, ELAN, IZKF, Marohn Foundation, industry

Tumor associated macrophages and post-transcriptional regulation by Hoxa9

PI: PD Dr. H. Bruns, Dr. C. Bach
Macrophages are the main component of the tumor microenvironment in the most malignancies. Although macrophages can, in principle, target neoplastic cells and mediate antibody-dependent cytotoxicity, tumor-associated macrophages (TAM) regularly fail to exert direct cytotoxic functions. However, TAM are thought to be protumorigenic because they promote angiogenesis and metastasis. The underlying mechanisms responsible for this observation remain unclear. Our research is focused on the functional and molecular analysis of the tumor microenvironment and aims at identifying and modulating potential therapeutic target structures. A further project is the post-transcriptional regulation by Hoxa9. The oncogene Hoxa9 contributes to post-transcriptional regulation by interaction with the RNA export and protein synthesis regulator eIF4e. To date, target genes of this interaction have not been identified. Therefore, we aim to identify posttranscriptional targets of Hoxa9 and eIF4e by RNA immunoprecipitation. Moreover, analyses of altered RNA-export will be performed as functional validation. In summary, this study will

help to clarify the contribution of Hoxa9 to leukemogenesis and provide a solid basis to uncover novel therapeutically relevant targets.
Funding: DFG, Wilhelm Sander Foundation, IZKF, Johannes and Frieda Marohn Foundation

Communication of tumor cells and microenvironment

PI: Dr. G. Lutzny-Geier
Our group is interested in the communication of tumor cells with their microenvironment. Understanding how different signaling pathways get activated through intrinsic signals of the tumor cell itself and extrinsic signals of the microenvironment is one aim of our studies. Therefore, we investigate how the microenvironment is modulated by tumor cells and if interference with this modulation can be used as new therapeutic approach for lymphoma patients.
Funding: ELAN, Trunk Foundation, industry, DFG

Molecular immunotherapy

PI: Dr. F. Müller
The young research group exploits antibody-targeted recombinant immunotoxins to kill cancer cells specifically. The immunotoxins induce a highly immunogenic cell death which changes the immunosuppressive milieu within a tumor thereby inducing anti-cancer immunity. Central to the group's research are (i) the development of innovative immunotoxins and of (ii) understanding and augmenting the immunotoxin-induced anti-cancer immune response. The mechanism of immune modulation by immunotoxins in combination with checkpoint inhibitors and toll-like receptor agonists is studied in animal models.
Funding: DFG, IZKF, Research Foundation of Medicine, industry

T cell-based immunotherapy of ocular melanoma

PI: Dr. J. Bosch
The main focus of our research group is to develop a T cell-based immunotherapy specifically designed for treatment of ocular melanoma. We focus on analysis of immune cell infiltration in the primary tumor originating in the immune-privileged eye. In addition, we determine if uveal melanoma vaccines or bi-specific antibodies activate different subpopulations of CD4+ T cells and which cytokines activated T cells secrete. Furthermore, we test if chimeric antigen receptor modified (CAR) T cells are reactive and cytotoxic against uveal melanoma cells.
Funding: DFG

Tumor-microenvironment and transendothelial migration

PI: Dr. Y. Resheq
Our group analyses the impact of H_2O_2-depletion on dendritic cells in the tumor microenvironment in order to understand the significance of this mechanism. Additionally, we focus study the transendothelial migration of immune-cells in various diseases (including GvHD and RCC due to its immunogenic properties). Herein, we use so called flow-based adhesion assays allowing a precise visualizing of the transmigration-cascade and thus the identification of innovative therapeutical targets.
Funding: ELAN, Staedtler Foundation, Roggenbuck Foundation, Research Foundation of Medicine

Tumor immune escape

PI: Prof. Dr. A. Mackensen, Dr. M. Aigner
By modulation of their metabolism, tumors are able to generate advantages for growth and proliferation for themselves. Our group focuses on the functions of 5'-Deoxy-5'methylthioadenosine (MTA) and its degrading enzyme MTAP as it is known that these molecules play a role in many malignancies. The influence of MTA produced by tumors on the activation, proliferation, and various effector functions of cytotoxic T cells are studied in cooperation with the university of Regensburg.
Funding: DFG

Cellular immunotherapy

PI: Prof. Dr. A. Mackensen, Dr. R. Gary, Dr. M. Aigner
The focus of this group lies on adoptive T cell therapy. Within the scope of a clinical trial phase I/IIa, CMV- and EBV-specific T cells are manufactured for patients after allogeneic stem cell transplantation to mediate protection against CMV and EBV infection. The T cell reconstitution after alloSCT is analyzed by Next Generation Sequencing of T cell receptors in cooperation with Charité Berlin.
In addition, we are establishing the GMP compliant manufacturing of CARs (chimeric antigen receptor T cells) and TRUCKS (cytokine producing CARs) and their translation to the clinic.
Funding: Deutsche Krebshilfe

HLA-laboratory

PI: Prof. Dr. B. Spriewald
In recent years, the laboratory has been interested in new methods for the detection of various subclasses of anti-HLA antibodies in solid organ transplantation. Our immunogenetic studies look into polymorphisms of several cytokines and T cell regulatory genes and their association with rheumatic and malignant disorders. Another focus is on experimental studies for the induction of transplantation tolerance and reduction of chronic rejection. These studies are performed in close collaboration with the working group of experimental heart surgery.

Teaching

The Department of Medicine 5 takes part in the curricular teaching for Medicine and Dentistry. Bachelor's and Master's theses as well as MD and PhD theses are offered and supervised regularly.

Selected publications

Tittlbach H, Schneider A, Strobel J, Zimmermann R, Maas S, Gebhardt B, Rauser G, Mach M, Mackensen A, Winkler TH, Winkler J. GMP-production of purified human B lymphocytes for the adoptive transfer in patients after allogeneic hematopoietic stem cell transplantation. J Transl Med. 2017 Nov 7;15(1):228

Resheq YJ, Menzner AK, Bosch J, Tickle J, Li KK, Wilhelm A, Hepburn E, Murihead G, Ward ST, Curbishley SM, Zimmermann HW, Bruns T, Gilbert DF, Tripal P, Mackensen A, Adams DH, Weston CJ. Impaired Transmigration of Myeloid-Derived Suppressor Cells across Human Sinusoidal Endothelium Is Associated with Decreased Expression of CD13. J Immunol. 2017 Sep 1;199(5):1672-1681

Bruns H, Böttcher M, Qorraj M, Fabri M, Jitschin S, Dindorf J, Busch L, Jitschin R, Mackensen A, Mougiakakos D. CLL-cell-mediated MDSC induction by exosomal miR-155 transfer is disrupted by vitamin D. Leukemia. 2017 Apr;31(4):985-988

Jitschin R, Saul D, Braun M, Tohumeken S, Völkl S, Kischel R, Lutteropp M, Dos Santos C, Mackensen A, Mougiakakos D. CD33/CD3-bispecific T-cell engaging (BiTE®) antibody construct targets monocytic AML myeloid-derived suppressor cells. J Immunother Cancer. 2018 Nov 5;6(1):116

Spriewald BM, Bach C, Zingsem J, Strobel J, Winkler J, Mackensen A, Roesler W. Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions. Bone Marrow Transplant. 2018 Jun;53(6):791-794

Gary R, Aigner M, Moi S, Schaffer S, Gottmann A, Maas S, Zimmermann R, Zingsem J, Strobel J, Mackensen A, Mautner J, Moosmann A, Gerbitz A. Clinical-grade generation of peptide-stimulated CMV/EBV-specific T cells from G-CSF mobilized stem cell grafts. J Transl Med. 2018 May 9;16(1):124

International cooperations

M. Miano, MD, Department of Pediatric Haematology-Oncology, IRCCS Istituto Giannina Gaslini, Genoa: Italy

Prof. F. Falkenburg, Leiden University: The Netherlands

Dr. T. Graf, Centre for Genomic Regulation, University of Barcelona: Spain

Dr. I. Pastan, NCI, NIH, Bethesda: USA

Prof. R. Kiessling, Karolinska Institut, Stockholm: Sweden