UNIVERSITY HOSPITAL

# Department of Medicine 5 – Hematology and Oncology

## Chair of Hematology and Oncology

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**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: 127
- Doctors (of Medicine): 37
- Scientists: 12 (thereof funded externally:6)
- Graduate students: 12

**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.

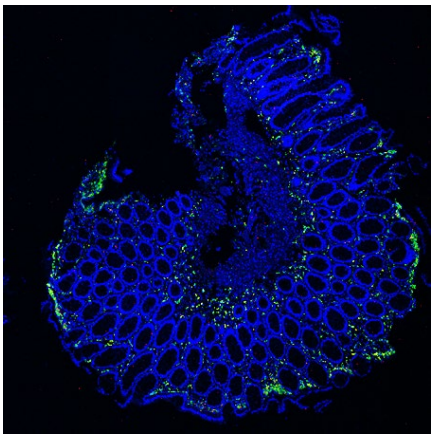

*Figure 1. Tissue section from the colon of a GvHD patient. Macrophages were stained by anti-CD68 (green) and anti-PD-L1 (red). Cells were counterstained with DAPI (nucleus, blue).*

**Immune regulation by DN T cells**
PI: Prof. Dr. A. Mackensen, Dr. S. Völkl
The population of human TCR$\alpha/\beta$+ 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, Forschungsstiftung Medizin

**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, Wilhelm-Sander-Stiftung, Bavarian Ministry for Science and Arts

**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: DFG (Einzelanträge, TRR221, TR305, GRK2599, FOR2866), IZKF, Elitenetzwerk Bayern, Industrie

**Tumor associated macrophages and therapeutic antibodies**
PI: PD Dr. H. Bruns
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.
Funding: DFG, Wilhelm Sander Foundation, Volkswagen 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: German Cancer Aid (Max-Eder Junior Research Group), 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 immuneprivileged eye. In addition, we determine if uveal melanoma vaccines or bi-specific antibodies activate different sub-populations 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

**Modulation of T cell responses in graft-versus-host disease**
PI: PD Dr. S. Spoerl
Our research aims at therapeutically targeting T cell responses after allogeneic stem cell transplantation. In this context, we want to avoid a severe immune reaction mediated by the graft-versus-host effect (GvHD), by at the same time maintaining the graft-versus-leukemia effect in order to prevent a relapse of the underlying disease.
Our studies do not only target GvHD-specific medication but also focus on the involvement of special T cell subtypes as for example T follicular helper cells or regulatory T follicular cells the pathogenesis of GvHD.
Funding: ELAN, Forschungsstiftung Medizin, Manfred-Roth-Stiftung

**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 cells (T cells, NK cells) are studied.
Funding: DFG

**Cellular immunotherapy**
PI: Prof. Dr. A. Mackensen, Dr. M. Aigner, Dr. R. Gary,
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. We are expanding the application of this cellular therapeutics against other viruses like SARS-CoV-2 and BKV
In addition, we have established manufacturing of CARs (chimeric antigen receptor T cells) and TRUCKS (cytokine producing CARs) and their translation to the clinic.
Funding: Deutsche Krebshilfe, Bayerisches Ministerium für Wissenschaft und Kunst, Wilhelm-Sander Stiftung

**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**

Bruns H, Jitschin S, Gamali S, Saul D, Böttcher M, Mackensen A, Jitschin R, Mougiakakos D. A novel immunoregulatory function of beta-2-microglobulin as a promoter of myeloid derived suppressor cell induction. Leukemia. 2019 May;33(5):1282-1287.

Kretschmann S, Herda S, Bruns H, Russ J, van der Meijden ED, Schlötzer-Schrehardt U, Griffioen M, Na IK, Mackensen A, Kremer AN. Chaperone protein HSC70 regulates intercellular transfer of Y chromosome antigen DBY. J Clin Invest. 2019 Jun 17;129(7):2952-2963.

Jitschin R, Böttcher M, Saul D, Lukassen S, Bruns H, Loschinski R, Ekici AB, Reis A, Mackensen A, Mougiakakos D. Inflammation-induced glycolytic switch controls suppressivity of mesenchymal stem cells via STAT1 glycosylation. Leukemia. 2019 Jul;33(7):1783-1796.

Haug T, Aigner M, Peuser MM, Strobl CD, Hildner K, Mougiakakos D, Bruns H, Mackensen A, Völkl S. Human Double-Negative Regulatory T-Cells Induce a Metabolic and Functional S witch in Effector T-Cells by Suppressing mTOR Activity. Front Immunol. 2019 Apr 26;10:883.

Strobl CD, Schaffer S, Haug T, Völkl S, Peter K, Singer K, Böttcher M, Mougiakakos D, Mackensen A, Aigner M. Selective PRMT5 Inhibitors Suppress Human CD8 + T Cells by Upregulation of p53 and Impairment of the AKT Pathway Similar to the Tumor Metabolite MTA. Mol Cancer Ther. 2020 Feb;19(2):409-419.


**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