# Department of Dermatology

## Chair of Skin and Venereal Diseases

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**Research focus**
- Cellular immune intervention
- RNA electroporation to improve DC vaccines and to generate antigen-specific T cells
- Functional role of DC subpopulations and antigen presentation
- Role of miRNA in cancer and immune-related diseases
- Composition, function, and clinical relevance of plasma extracellular vesicles (pEV)
- Characterization of the toponome of tissue and cells by multi-epitope ligand cartography (MELC)
- Pathomechanisms of chronic inflammatory skin diseases
- Identification of biomarkers in malignant melanoma
- Regulatory T cells for cell-based therapy in inflammatory bowel disease (IBD)

## Structure of the Chair

Professorships: 4
Personnel: 216
- Doctors (of Medicine): 43
- Scientists: 24 (thereof funded externally: 17)
- Graduate students: 12

**Clinical focus areas**
- Immunotherapy of melanoma and uveal melanoma (checkpoint blockade, DC vaccination)
- Treatment of psoriasis and autoimmune diseases
- Experimental treatment with regulatory T cells
- Recombinant allergens for diagnosis and therapy

## Research

The research activities of the Department of Dermatology focus primarily on malignant melanoma. In this research area, several directions developed, including studies to understand the pathogenesis of melanoma, the immunological response, the cellular immune therapy, and the identification of melanoma biomarkers. In detail, the Department of Dermatology is analyzing the biology and function of dendritic cells (DC), optimizing antigen-specific tumor vaccines using DC, developing a GMP compliant protocol for the use of CAR-T cells, analyzing the function of extracellular vesicles from plasma, and characterizing tissue sections with an improved automated immunofluorescence technology called MELC technology. Additional projects focus on the pathogenesis of HIV infection and autoimmune diseases. The Department established a broad interaction between basic molecular and immunological research and clinical application.

### Cellular immune intervention

PI: PD Dr. B. Schuler-Thurner
The aim of this working group, consisting of the GMP laboratory (manufacture of cellular therapeutics) and a clinical unit (patient application), is the production and clinical application of advanced therapy medicinal products (ATMPs). After seven phase I and II trials using DC vaccines, a multicenter phase III trial using tumor mRNA as vaccine antigen was started in July 2014. The goal of this trial is the prevention of tumor relapse in uveal melanoma by induction of tumor-specific T cells (200 patients planned, cooperation with the Department of Ophthalmology and seven German university eye hospitals). Since the start of the trial, 163 patients have been screened and 77 have been included.
Current improvements are the use of Next Generation Exon and RNA sequencing in conjunction with HLA-epitope prediction in order to improve the vaccination strategy as well as an optimized maturation of DC with the help of mRNA coding for NFkB. Such an optimized vaccine will be used within a Phase I clinical trial in metastatic uveal melanoma.
Based on preclinical work, also the adoptive transfer of T cells reprogrammed by RNA (CSPG4-CAR T cells) will start in late 2019 within a small Phase I trial. The GMP-quality team has successfully developed the implementation of all cellular therapies. Immunomonitoring is performed by the core unit FACS.
In 2019, a clinical trial (in cooperation with the Department of Medicine 1) will start to treat patients with colitis ulcerosa by the adoptive transfer of regulatory T cells produced in the GMP laboratory.

### RNA electroporation to improve DC vaccines and to generate antigen-specific T cells

PI: PD Dr. N. Schaft, PD Dr. J. Dörrie
This team examines the electroporation of mRNA for clinical application. With this technology, the DC-vaccine can be optimized and loaded with antigen and on the other hand, tumor-specific T cells can be generated. An activator of the NFkB pathway was mutated in such a way that it became constitutively active and generates DC, which induce long-living and more efficient tumor antigen-specific T cells and additionally activate NK cells. A clinical trial with these cells is in preparation. Using mRNA transfection, T cells can be reprogrammed to directly recognize tumor (or virus-infected) cells. For classical T cells, this technique was established previously and recently $\gamma/\delta$ T cells were added (in collaboration with the Children's Cancer Research Institute, Vienna).
Additionally, the transfection of patient T cells with a CSPG4-specific CAR was established under GMP conditions to treat cutaneous and uveal melanoma patients. This also is currently transferred to clinical application.
In view of future combination therapies, it was examined how modern targeted kinase inhibitors influence the functionality of T cells.

### Functional role of DC subpopulations and antigen presentation

PI: Prof. Dr. D. Dudziak
This research focuses on the characterization of murine and human primary DC subsets. Recently, the group could show that antigen targeting induces protective immune responses in a murine mouse melanoma model which were independent of a specific DC subpopulation. Besides, in close collaboration with various clinical institutions, DC subpopulations and other antigen presenting cells from human tissues are characterized by multicolor confocal immunofluorescence analysis and 18-color flow cytometry and human antigen targeting antibodies are generated. Prof. Dr. D. Dudziak is the coordinator of the Emerging Fields Initiative 'BIG-THERA', which correlates tumor immune cell infiltration in breast cancer via big-data radiogenomic approaches depending on checkpoint therapy (compare own report).

### Role of miRNA in cancer and immune-related diseases

PI: Prof. Dr. J. Vera-González
MicroRNAs are non-coding RNA involved in complex regulatory biochemical networks. Our aim is to combine patient data, quantitative ex-

perimental data, computational biology tools, and mathematical modeling to elucidate the role played by miRNA in cancer and other immune-related diseases. In collaboration with Prof. A. Baur, we are working on a systems-biology-oriented diagnostic tool for assessing the probability of tumor relapse in melanoma based on miRNA profiling of plasma-derived extracellular vesicles. In association with Prof. Dr. B. Schmeck (university hospital Giessen and Marburg), we are working on the reconstruction of miRNA networks involved in lung infection and inflammation.

### Composition, function, and clinical relevance of plasma extracellular vesicles (pEV)

PI: Prof. Dr. A. Baur

The research group investigates the molecular mechanisms leading to the generation of extracellular vesicles (EV) and analyzes their content and function. The group focuses on the assessment of factors and biomarkers contained in plasma EV (pEV) and their prognostic value with respect to the development of disease. An important discovery was made when circulating pEV were measured in the periphery and found to be significantly elevated in tumor patients and in individuals with chronic infections and neurodegenerative diseases. The pEV biomarker profile seems particularly distinct and therefore promising in operated tumor patients (melanoma) with a different risk for relapse. In 2016, biomarker profiles were established that could be used for the early detection of melanoma and cancer in general. In 2018, the project was selected and further funded by the BMBF in preparation for a potential follow-up grant aiming at the founding of a startup company. Initial discussions with industrial partners were very promising.

### Characterization of the toponome of tissue and cells by multi-epitope ligand cartography (MELC)

PI: Prof. Dr. A. Baur, Dr. C. Ostalecki

This research team aims at correctly rising human tissue and cells, using the innovative multi-epitope ligand cartography (MELC)-technology which allows the staining of up to 100 antigens via antibodies on one tissue section or slide. In the last year, the technology has been used very successfully in several projects, analyzing human tissue and PBMC (peripheral blood mononuclear cells). For example, the early development of cutaneous melanoma was analyzed thoroughly and new factors were identified that lead to early tumor formation. The results from this study are currently used to discriminate early melanomas from dysplastic nevi. Through cooperation with industrial partners, we currently establish a new software for the analysis of our multi-antigen stained tissue slides. The project is funded by Bayern Innovativ and is meant to foster the interaction between a recently established start-up out of the Department of Dermatology (Tissomatic GmbH).

### Pathomechanisms of chronic inflammatory skin diseases

PI: Prof. Dr. M. Sticherling

Chronic inflammatory diseases make up a major part of skin diseases. Apart from e.g. psoriasis, atopic eczema, and granulomatous diseases, autoimmune mediated diseases restricted to the skin, like bullous autoimmune skin disorders, as well as specific skin involvement among multi-organ diseases, like collagenous skin diseases (inflammatory connective tissue diseases), may be addressed. Scientifically, the involvement of B-cells is addressed ex vivo and *in vitro* by molecular biological and immune-histochemical methods in the inflammatory process of psoriasis and cutaneous lupus erythematosus as model diseases. In addition, the differential involvement of Toll-like receptors (TLR) and their modulation in cutaneous inflammatory processes is examined.

### Identification of biomarkers in malignant melanoma

PI: Prof. Dr. L. Heinzerling

This research group focuses on predictive and therapeutic biomarkers in melanoma to optimize selection of therapeutic options. With a semi-automated mRNA extraction from formalin fixed paraffin-embedded (FFPE) sections of primary melanomas and melanoma metastases, a set of 20 indicator genes, previously identified by array analyses, was evaluated. The comparison of responders and non-responders for different immunotherapy options (DC-vaccination, checkpoint blockade antibodies) resulted in differential gene expression signatures. Furthermore, a large biobank of melanoma patients (including tumor mutations) is established (in collaboration with the Institute of Pathology).

### Regulatory T cells for cell-based therapy in inflammatory bowel disease (IBD)

PI: Dr. C. Bosch-Voskens

The focus of this project, funded by KFO 257 and since July 2018 via SFB/Trans Regio 241 (compare own reports), is on regulatory T cells (Treg). In IBD, it is postulated that insufficient numbers of regulatory T cells (Treg) that attenuate local proliferation of effector T cells in the gut can be corrected by infusion of autologous Tregs. An authority-approved Treg cell protocol has been established for the optimized *in vitro* expansion of Treg cells of colitis ulcerosa patients. Such cells will be intravenously administered in an upcoming clinical trial to mitigate disease activity (collaboration with the Department of Medicine 1).

## Teaching

The Chair of Skin and Venereal Diseases teaches students of Medicine, Dentistry, Molecular Medicine, integrated immunology, integrated life sciences, and cell and molecular biology in dermatology, molecular and cellular immunology in combination with translational applications (GMP-laboratory). The educational program is organized in seminars, practical training courses in the clinic and laboratories, lectures, as well as Bachelor's, Master's, and MD theses. The Department of Dermatology is responsible for the organization of dermatological advanced training courses for physicians.

### Selected publications


Gross S, Erdmann M, Haendle I, Voland S, Berger T, Schultz E, Strasser E, Dankerl P, Janka R, Schliep S, Heinzerling L, Sotlar K, Coulie P, Schuler G, Schuler-Thurner B. Twelve-year survival and immune correlates in dendritic cell-vaccinated melanoma patients. JCI Insight. 2017 Apr 20;2(8). pii: 91438

Khan FM, Marquardt S, Gupta SK, Knoll S, Schmitz U, Spitschak A, Engelmann D, Vera J, Wolkenhauer O, Pützer BM. Unraveling a tumor type-specific regulatory core underlying E2F1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. Nat Commun. 2017 Aug 4;8(1):198

Lehmann CHK, Baranska A, Heidkamp GF, Heger L, Neubert K, Lühr JJ, Hoffmann A, Reimer KC, Brückner C, Beck S, Seeling M, Kießling M, Soulat D, Krug AB, Ravetch JV, Leusen JHW, Nimmerjahn F, Dudziak D. DC subset-specific induction of T cell responses upon antigen uptake via Fcγ receptors in vivo. J Exp Med. 2017 May 1;214(5):1509-1528

Ostalecki C, Lee JH, Dindorf J, Collenburg L, Schierer S, Simon B, Schliep S, Kremmer E, Schuler G, Baur AS. Multi-epitope tissue analysis reveals SPPL3-mediated ADAM10 activation as a key step in the transformation of melanocytes. Sci Signal, 2017;10 (470): pii: eaai8288

Voskens CJ, Fischer A, Roessner S, Lorenz C, Hirschmann S, Atreya R, Neufert C, Atreya I, Neurath MF, Schuler G. Characterization and Expansion of Autologous GMP-ready Regulatory T Cells for TREG-based Cell Therapy in Patients with Ulcerative Colitis. Inflammatory Bowel Disease 2017 Aug;23(8):1348-1359

Hecht M et al. Clinical outcome of concomitant vs interrupted BRAF inhibitor therapy during radiotherapy in melanoma patients. Br J Cancer, 2018,118(6):785-92


### International cooperations

Prof. K. Saksela, Department of Virology, University of Helsinki, Helsinki: Finland

Prof. Dr. P. Coulie, de Duve Institute and the Université catholique de Louvain, Brussels: Belgium

Prof. Dr. J. Ravetch, Rockefeller University, New York: USA

Prof. Dr. H. Schmidt, Department of Pharmacology and Personalized Medicine, Maastricht University, Maastricht: The Netherlands