UNIVERSITY HOSPITAL

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)
- Cellular motility and migration of NK cells and regulatory T cells

Structure of the Chair

Professorships: 4
Personnel: 212

- Physicians: 40
- Scientists: 24 (with external funding: 17)
- Graduate students: 10

Clinical focus areas

- Targeted and Immunotherapy of melanoma and uveal melanoma (checkpoint blockade, DC vaccination)
- Treatment of inflammatory and autoimmune skin diseases
- Experimental treatment with regulatory T cells
- Recombinant allergens for diagnosis and therapy
- Certified care of chronic wounds

Research

A major focus of research activities at the Department of Dermatology is melanoma. The studies deal with pathogenesis, immune defense, cellular immunotherapy, transcription factors and biomarkers of the tumor. A particular interest is in dendritic cells (DC), CAR T cells, extracellular vesicles in plasma, and MELC technology for tissue section analysis. There are also funded research projects on inflammatory skin diseases and autoimmune diseases. Across projects, we use the special expertise of network analyses and computer simulations.

Cellular Immunotherapy
PI: Prof. 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 vac- cines, a multicenter adjuvant phase III trial using tumor mRNA as vaccine antigen was started in July 2014 in cooperation with the Department of Ophthalmology in Erlangen and other major uveal melanoma centers, NCT01983748). Since the start of the trial, 226 patients have been screened and 115 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 is now used within a phase I clinical trial in metastatic uveal melanoma ((NCT04335890).
The GMP quality team (M. Kummer) has successfully developed the implementation of all cellular therapies.

RNA electroporation to generate antigen-specific T cells
PI: PD Dr. N. Schaft
This research focusses on the use of electroporation of T cell receptor- (TCR) and chimeric antigen receptor- (CAR) encoding mRNA to reprogram T cells to enable them to directly recognize tumor cells or virus-infected cells. For the clinical application of these cells to treat (uveal) melanoma patients, the clinical-scale production of CSPG4-specific CAR-T cells under full GMP compliance was developed. Moreover, preparations for the application to the Paul-Ehrlich-Institute for a phase I clinical trial authorization are running. Next to the classical format of a CAR (i.e. scFv antigen-binding moiety linked to intracellular co-stimulatory (e.g. CD28, 4-1BB) and T-cell-signaling (CD3ζ) domains), alternative CAR formats using non-canonical signaling domains (e.g. NKG2D, DAP-10, CD32A, CD16A) are preclinically developed and investigated. This also enables the functional testing of such new CARs in alternative cellular vessels like NK/NKT cells or myeloid cells, to broaden the possibilities of cellular therapy against cancer.

RNA electroporation to improve therapeutic DC vaccines
PI: PD Dr. J. Dörrie
This project aims to preclinically and translationally optimize DC as therapeutic vaccine against cancer, especially uveal melanoma and Merkel cell carcinoma. To this end, the DC are electroporated with mRNA to load them with tumor antigens and to activate them functionally. The latter is achieved with a mutated activator of the NFκB pathway that was rendered constitutively active and generates DC, which induce immune responses of higher potency. Additionally, in collaboration with Prof. J. Vera-González, innovative methods to analyze NGS data for identification of ideal tumor antigens are developed.

Functional role of DC subpopulations and antigen presentation
PI: Prof. Dr. D. Dudziak
This working group focuses on the functional characterization of primary DC subpopulations and their modulation of immune responses. Studies are being conducted on how the cytokine profile, surface profile, but also the migratory behavior of DCs can be controlled. The aim is to modify the DC subpopulations by different stimulators in such a way that the DCs generate an enhanced TH1, TH2 or TH17 CD4+ T cell response or cytotoxic CD8+ immune responses. The group works in both murine and human systems. So-called antigen-targeting antibodies are used, with which antigens are targeted to DC subsets, as well as cutting-edge technologies such as multi-color flow cytometry, multi-color confocal immunofluorescence and RNA sequencing. In cooperation with different clinical departments, human DC subpopulations are characterized. Since 2020, Prof. Dudziak is coordinator of the Bayresq.Net initiative IRIS to analyze new checkpoints to fight multidrug-resistant bacteria. Prof. Dudziak has also been recently appointed to be responsible for public relations in the German Society for Immunology and in the review board 'Cell Biology' of the DFG.

Systems Medicine of skin diseases
PI: Prof. Dr. J. Vera-González
Multifactorial diseases are not controlled by single genes, but instead by dense networks of interacting genes, proteins and RNAs. We combine clinical data, molecular profiling of patient samples and computational modelling to detect the key gene networks controlling pathogenesis and therapy response in melanoma and autoimmune diseases (www.vcells.net/melanoma). We have algorithms for detecting and selecting tumor epitopes for anticancer therapy in melanoma (www.curatopes.com). Network and pharmacogenomics approaches are utilized to design miRNA-based anticancer therapies (www.synmirapy.net) and network analysis and computer simulations are used to engineer immune cells therapy for cancer.

Predictive diagnostics with biomarker patterns from plasma extracellular vesicles (pEV) using methods of artificial intelligence (AI)
PI: Prof. Dr. A. Baur
The group investigates the composition of plasma extracellular vesicles (pEV), in conjunction with AI algorithms, to establish predictive diagnostic tests, particularly for cancer patients. The project focuses on the assessment of protease activities and immune markers using novel and patented pEV isolation and analysis systems. The basis for this research were observations showing that the number of vesicles and the content of these factors increase significantly in the course of disease

development, as for example in cancer, infectious and neurodegenerative diseases. Conversely, healthy individuals lack these factors. Moreover, we obtained good evidence, that these factor and protease activity patterns discriminate different stages of a given disease. The project was selected by the BMBF in 2018 and was funded in 2020, including a partner specialized in technical development of novel test systems. Aim of the Corporation is the foundation of a startup company.

Characterization of the toponome of tissue and cells by multi-epitope ligand cartography (MELC)
PI: Prof. Dr. A. Baur, Dr. C. Ostalecki
The research group focuses on the tissue characterization using the innovative MELC (Multi-epitope ligand cartography) technology, which allows the staining of up to 100 antigens via antibodies on one tissue section or slide. Digital imaging of these tissue markers generates multiplexed datasets that provide an ideal basis for the application of data mining algorithms. Thus, the development of early melanoma has been analyzed, and novel expression patterns have been identified. In addition, clonal dedifferentiation of primary melanoma was revealed for the first time using these data mining algorithms, providing new insights into melanoma pathogenesis. New prognosis-determining parameters will be elaborated and provide new opportunities to conventional histological analysis.

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 immunohistochemical 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.

3D imaging of pigmented nevi and therapy-induced skin lesions during sytemic therapy of cutaneous malignancies
PI: Dr. M. Erdmann
Sequential high resolution 3D photography can exactly monitor initial changes in patients with many nevi. Additionally cutaneous effects of immune-oncologic as well as targeted therapies can be analyzed by this technique. We could demonstrate development and response of disseminated skin metastases under systemic therapy of melanoma.

Evidence-Based Dermato-Oncology and Health Services Research
PI: PD Markus Heppt, M.Sc., MHBA; Theresa Steeb, MPH
Projects on evidence-based dermato-oncology and health services research aim at contributing to better treatment decisions for both skin cancer patients and their treating physicians. Medical guideline projects with a focus on dermato-oncology (e.g. the evidence- and consensus-based ("S3") guideline on actinic keratosis and squamous cell carcinoma of the skin) are conducted as well as systematic reviews, meta-analyses, and network meta-analyses according to the principles of evidence-based medicine on topics of dermato-oncology, primarily on actinic keratosis. Additionally, the group deals with topics relevant to health care using both quantitative and qualitative research approaches, such as the evaluation of websites and videos on skin cancer. The projects are funded by the German Cancer Aid and the Skin Cancer Council Germany (Nationale Versorgungskonferenz Hautkrebs e.V.)

Transcription factors in melanoma
PI: PD Dr. med. Markus Heppt, M.Sc., MHBA; Anja Wessely, M.Sc.
This research group investigates how neural crest transcription factors contribute to the development and progression of cutaneous and uveal melanoma. Especially, the functional role of SOX10 is analyzed in uveal melanoma, which differs from cutaneous melanoma both clinically and genetically. Furthermore, the epigenetic regulation of the transcription factor Brn3a, which contributes to melanoma cell survival and promotes tumorigenesis, is investigated. The group generates uveal melanoma cell lines from fresh tumor tissue of primary tumors and metastases.

Standard of care for patients with chronic wounds
PI: PD Dr. C. Erfurt-Berge, Prof. R. Renner
This research group investigates diagnostic and therapeutic approaches in the care of patients with chronic wounds. The main focus is on rare dermatoses as cause of chronic wounds such as pyoderma gangrenosum or necrobiosis lipoidica. In addition to the care situation within but also beyond specified wound centers, the group investigates factors influencing wound healing such as mobility, quality of life and develops new concepts for patient education. Cooperations exist with the study course Medical Process Management at FAU, as well as the University of Coburg (Master study course Health Promotion). Currently, two projects are funded by the Initiative chronische Wunde e.V. on the topics of patient information and education, as well as recording mobility and sleep in patients with chronic wounds. In cooperation with the University of Applied Sciences Osnabrück (Research Group Informatics in Health Care), a grant was recently approved within the BMBF task "Adaptive Technologies for Society - Intelligent Interaction of Humans and Artificial Intelligence". The group is also involved in teaching and has been able to implement and scientifically evaluate both new practical teaching concepts and digital learning opportunities on the subject of wound management in teaching at FAU.

Regulatory T cells for cell-based therapy in inflammatory bowel disease (IBD) and cellular motility in a three-dimensional network
PI: PD Dr. C.J. Bosch-Voskens, PhD
The focus of this project, funded by KFO 257 and since July 2018 by SFB/Trans Regio 241, is on regulatory T cells (Treg). In inflammatory bowel disease, 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. Together with the Medical Department 1, a phase I fast-track dose-escalation clinical trial was initiated late 2020 (NCT04691232) and is currently actively enrolling patients. In another project, we study motility and migration of NK cells and regulatory T cells in 3-D collagen gels and were able to show that NK cell motility is dramatically impaired after cryopreservation, which leads to a significant reduction of the cytotoxic function.

Mechanisms to improve CAR T cell therapy in solid tumors
PI: Dr. med. U. Uslu
After the success of chimeric antigen receptor (CAR) T cells in hematological malignancies, its efficacy is currently evaluated in different solid tumors. However, first results were not as compelling as for hematological malignancies, due to the fact that CAR T cells need to cope with several challenges, e.g., the insufficient engineered T cell migration and the unfavorable tumor microenvironment. Thus, this group has worked on mechanisms to improve CAR T cell therapy. In addition, stable DNA based receptor transfer for permanent receptor expression on T cells with tumor antigen-specific receptors was established in-house by this group, which will be crucial for moving this therapy towards a clinical use.

Teaching

The Chair of Skin and Venereal Diseases teaches students of medicine, dentistry, molecular medicine, integrated immunology, integrated life sciences, and cellular 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 clinics 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

Mark C, Czerwinski T, Roessner S, Mainka A, Hörsch F, Heublein L, Winterl A, Sanokowski S, Richter S, Bauer N, Angelini TE, Schuler G, Fabry B, Voskens CJ. Cryopreservation impairs 3-D migration and cytotoxicity of natural killer cells. Nat Commun. 2020 Oct 16;11(1):5224. doi: 10.1038/s41467-020-19094-0. PMID: 33067467; PMCID: PMC7568558.

Lühr JJ, Alex N, Amon L, Kräter M, Kubánková M, Sezgin E, Lehmann CHK, Heger L, Heidkamp GF, Smith AS, Zaburdaev V, Böckmann RA, Levental I, Dustin ML, Eggeling C, Guck J, Dudziak D. Maturation of Monocyte-Derived DCs Leads to Increased Cellular Stiffness, Higher Membrane Fluidity, and Changed Lipid Composition. Front Immunol. 2020 Nov 27;11:590121. doi: 10.3389/fimmu.2020.590121. eCollection 2020. PMID: 33329576.

Lee JH, Eberhardt M, Blume K, Vera J, Baur AS. Evidence for liver and peripheral immune cells secreting tumor-suppressive extracellular vesicles in melanoma patients. EBioMedicine. 2020 Dec;62:103119. doi: 10.1016/j.ebiom.2020.103119. Epub 2020 Nov 23. PMID: 33242827;PMCID: PMC7695971.

Schaft N. The Landscape of CAR-T Cell Clinical Trials against Solid Tumors-A Comprehensive Overview. Cancers (Basel). 2020 Sep 9;12(9):2567. doi: 10.3390/cancers12092567.Cancers (Basel). 2020.PMID: 32916883.

Steeb T, Wessely A, Schmitz L, Heppt F, Kirchberger MC, Berking C, Heppt MV. Interventions for Actinic Keratosis in Nonscalp and Nonface Localizations: Results from a Systematic Review with Network Meta-Analysis. J Invest Dermatol. 2021 Feb;141(2):345-354.e8. doi: 10.1016/j.jid.2020.06.021. Epub 2020 Jul 6.PMID: 32645365.