Hannover Biomedical Research School

Lab Descriptions

Medizinische Hochschule Hannover

TWINCORE

Fraunhofer ITEM

MHH
Department of Dermatology, Allergy and Venereology

Heads: **Prof. Dr. Alexander Kapp (Head of Department); Prof. Dr. Thomas A. Werfel (Head of Research)**

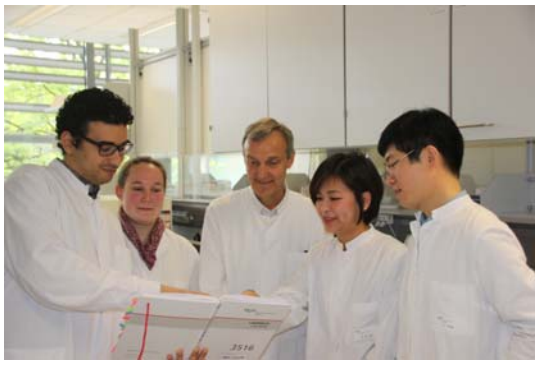
Location: Dermatology Department
MHH, Carl Neuberg Str 1, 30625 Hannover
(**Experimental Lab is at MHH Campus Building I3**)

Homepage: http://www.mh-hannover.de/dermatologie.html

PhD Supervisor: Prof. Dr. Ralf Gutzmer / **Prof. Dr. Thomas Werfel**
PhDs of the group: Dr. Susanne Mommert / Dr. Lennart Rösner / Dr. Katrin Schaper-Gerhardt / Dr. Jana Zeitvogel

Prof. Dr. Thomas Werfel

Members of the group



Prof. Dr. Thomas Werfel (supervisor, center) with PhD students (from left: Ahmed Farag, Jessica Grünewald, Chen Wen Hui, Yang Xiaoliang), in the middle Prof. Dr. Thomas Werfel

Research Projects

- Adaptive immune responses
- Role of antimicrobial peptides in the skin
- The role of the histamine H4 receptor in allergic inflammation in the skin.
- Functions of keratinocytes in allergic and in skin diseases
- The role of the anaphylatoxin C3a in chronic inflammatory skin diseases

The scientific focus of the Department of Dermatology, Allergy and Venereology lies on allergic, chronic inflammatory, autoimmune skin diseases and on skin cancer. This is accomplished in basic research projects, mostly funded by the Deutsche Forschungsgemeinschaft. A number of clinical studies are funded by other institutions.
Particulary eczematous skin diseases (atopic dermatitis, allergic contact dermatitis) in addition to urticaria, psoriasis and bullous autoimmune diseases and respiratory diseases (which are sometimes studied as control diseases to skin diseases) are investigated. In April 2008, the research division “Immunodermatology and Allergy Research” (Head: Prof. Dr. Thomas Werfel) was founded within the Department of Dermatology, Allergy and Venereology. The current projects are closely connected to clinical and basic studies from the whole department. Malignant melanoma is the major disease which is studied in the field of dermato-oncology.

Publications

- Kopfnagel V, Wagenknecht S, Brand L, Zeitvogel J, Harder J, Hofmann K, Kleine M, Werfel T. RNase 7 downregulates TH2 cytokine production by activated human T cells. Allergy. 2017 Apr 4. doi: 10.1111/all.13173. [Epub ahead of print]
- Schaper K, Rossbach K, Köther B, Stark H, Kietzmann M, Werfel T, Gutzmer R. Stimulation of the histamine 4 receptor upregulates thymic stromal lymphopoietin (TSLP) in human and murine keratinocytes. Pharmacol Res. 2016 Nov;113:209-215.
- Mommert S, Kleiner S, Gehring M, Eiz-Vesper B, Stark H, Gutzmer R, Werfel T, Raap U. Human basophil chemotaxis and activation are regulated via the histamine H4 receptor. Allergy. 2016 Sep;71(9):1264-73.
- Roesner LM, Heratizadeh A, Wieschowski S, Mittermann I, Valenta R, Eiz-Vesper B, Hennig C, Hansen G, Falk CS, Werfel T. α-NAC-Specific Autoreactive CD8+ T Cells in Atopic Dermatitis Are of an Effector Memory Type and Secrete IL-4 and IFN-γ. J Immunol. 2016 Apr 15;196(8):3245-52.
- Rossbach K, Schaper K, Kloth Ch, Gutzmer R, Werfel T, Kietzmann M, Bäumer W. Histamine H4 receptor knockout mice display reduced inflammation in a chronic model of atopic dermatitis. Allergy. 2016 Feb;71(2):189-97.
- Hradetzky S, Roesner LM, Heratizadeh A, Crameri R, Garbani M, Scheynius A, Werfel T. Differential cytokine induction by the human skin-associated autoallergen thioredoxin in sensitized patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol. 2015 May;135(5):1378-80.

MHH
Institute of Experimental Hematology

Head: **Prof. Dr. med. Axel Schambach, PhD**

Location: Hannover Medical School (MHH), *Hans-Borst-Center*
Carl-Neuberg-Straße 1, 30625 Hannover
Homepage: http://www.mh-hannover.de/experimentalhematology.html

PhD Supervisors: Prof. Dr. med. Axel Schambach, PhD / Prof. Dr. Hildegard Büning / Prof. Dr. med. Thomas Moritz / PD Dr. Michael Morgan / Dr. Melanie Galla / Dr. Johann Meyer / Dr. Olga Kustikova / Dr. Tobias Mätzig / Dr. Nico Lachmann / Dr. Dirk Hoffmann / Dr. Michael Rothe / Dr. Dr. Adrian Schwarzer

For lab rotation info contact: morgan.michael@mh-hannover.de

Members of the institute.

Prof. Dr. Schambach

Research Projects

- Tailoring viral vectors for gene therapy, regenerative medicine and vaccine development
- Development of novel vector-based strategies for transient or permanent modification of somatic cells
- Toxicological screenings of advanced gene-modified cell products
- Studies on host-vector-interactions including cell autonomous immune responses
- Analysis of clonal competition in hematopoiesis and its underlying mechanisms to decipher general principles of regeneration and transformation
- Controlled induction and differentiation of pluripotent cells
- Gene editing

The Institute of Experimental Hematology is composed of several research groups and operates at the intersection of basic and clinical research. Our work focuses on the development of molecularly defined therapeutic approaches in acquired and inherited gene-related diseases. To this end, we combine seven major scientific goals. Firstly, we focus on improving current vector systems regarding efficiency of gene transfer and cell type specificity as well as their applicability as vaccines; we analyse the mechanism of action of vectors based on lenti-/retroviruses and on adeno-associated viruses for transient or permanent modification of somatic cells; we determine safety profiles of gene transfer methods and develop strategies to prevent associated risks. Secondly, we operate in the context of national and international consortia to develop clinical trials to treat severe inherited or acquired diseases, for which currently existing approaches offer only limited perspectives. Thirdly, we investigate vector-host interactions and aim to discover pathways that support the competitive fitness and self-renewal of normal and malignant hematopoietic stem cells. Finally, we develop novel approaches to induce pluripotent cells and to differentiate them into hematopoietic stem cells as a cellular resource for regenerative medicine.

Publications

- Viereck J, Kumarswamy R, Foinquinos A, Xiao K, Avramopoulos P, Kunz M, Dittrich M, Maetzig T, Zimmer K, Remke J, Just A, Fendrich J, Scherf K, Bolesani E, Schambach A, Weidemann F, Zweigerdt R, de Windt LJ, Engelhardt S, Dandekar T, Batkai S, Thum T. Long noncoding RNA Chast promotes cardiac remodeling. Sci Transl Med. 2016; 8(326):326ra22.
- Karpinski J, Hauber I, Chemnitz J, Schäfer C, Paszkowski-Rogacz M, Chakraborty D, Beschorner N, Hofmann-Sieber H, Lange UC, Grundhoff A, Hackmann K, Schrock E, Abi-Ghanem J, Pisabarro MT, Surendranath V, Schambach A, Lindner C, van Lunzen J, Hauber J, Buchholz F. Directed evolution of a recombinase that excises the provirus of most HIV-1 primary isolates with high specificity. Nat Biotechnol. 2016; 34(4):401-409.

- Song G, Pacher M, Balakrishnan A, Yuan Q, Tsay HC, Yang D, Reetz J, Brandes S, Dai Z, Pützer BM, Araúzo-Bravo MJ, Steinemann D, Luedde T, Schwabe RF, Manns MP, Schöler HR, Schambach A, Cantz T, Ott M, Sharma AD. Direct Reprogramming of Hepatic Myofibroblasts into Hepatocytes In Vivo Attenuates Liver Fibrosis. Cell Stem Cell. 2016; 18(6):797-808.
- Hoffmann D, Göhring G, Heuser M, Ganser A, Schambach A, Morgan MA. Letter to the Editor: Production of Mature Healthy Hematopoietic Cells from Induced Pluripotent Stem Cells Derived from an AML Diagnostic Sample Containing the t(8;21) Translocation. Stem Cells. 2016; 34(3):797-799.
- Münch RC, Muth A, Muik A, Friedel T, Schmatz J, Dreier B, Trkola A, Plückthun A, Büning H, Buchholz CJ. Off-target-free gene delivery by affinity-purified receptor-targeted viral vectors. Nat Commun. 2015;6:6246.
- Lachmann N, Ackermann M, Frenzel E, Liebhaber S, Brennig S, Happle C, Hoffmann D, Klimenkova O, Lüttge D, Buchegger T, Kühnel MP, Schambach A, Janciauskiene S, Figueiredo C, Hansen G, Skokowa J, Moritz T. Large-scale hematopoietic differentiation of human induced pluripotent stem cells provides granulocytes or macrophages for cell replacement therapies. Stem Cell Reports. 2015;4(2):282-296.
- Sallach J, Di Pasquale G, Larcher F, Niehoff N, Rübsam M, Huber A, Chiorini J, Almarza D, Eming SA, Ulus H, Nishimura S, Hacker UT, Hallek M, Niessen CM, Büning H. Tropism-modified AAV vectors overcome barriers to successful cutaneous therapy. Mol Ther. 2014;22(5):929-939.
- Happle C, Lachmann N, Škuljec J, Wetzke M, Ackermann M, Brennig S, Mucci A, Jirmo AC, Groos S, Mirenska A, Hennig C, Rodt T, Bankstahl JP, Schwerk N, Moritz T, Hansen G. Pulmonary transplantation of macrophage progenitors as effective and long-lasting therapy for hereditary pulmonary alveolar proteinosis. Sci Transl Med. 2014;6(250):250ra113.
- Münch RC, Janicki H, Völker I, Rasbach A, Hallek M, Büning H, Buchholz CJ. Displaying high-affinity ligands on adeno-associated viral vectors enables tumor cell-specific and safe gene transfer. Mol Ther. 2013;21(1):109-118.
- Rybniker J, Nowag A, Janicki H, Demant K, Hartmann P, Büning H. Incorporation of antigens into viral capsids augments immunogenicity of adeno-associated virus vector-based vaccines. J Virol. 2012;86(24):13800-13804.
- Hösel M, Broxtermann M, Janicki H, Esser K, Arzberger S, Hartmann P, Gillen S, Kleeff J, Stabenow D, Odenthal M, Knolle P, Hallek M, Protzer U, Büning H. Toll-like receptor 2-mediated innate immune response in human nonparenchymal liver cells toward adeno-associated viral vectors. Hepatology. 2012;55(1):287-297.
- Meyer J, Rhein M, Schiedlmeier B, et al. Remarkable leukemogenic potency and quality of a constitutively active neurotrophin receptor, deltaTrkA. Leukemia. 2007;21:2171-2180.
- Suerth J, Galla M, Maetzig T, Baum C, Schambach A. Self-inactivating alpharetroviral vectors with a split-packaging design. J Virol. 2010;84(13):6626-6635.
- Schiedlmeier B, Santos AC, Ribeiro A, et al. HOXB4's roadmap to stem cell expansion. Proc Natl Acad Sci USA. 2007; 104:16952-16957.
- Kustikova O, Fehse B, Modlich U, Düllmann J, Kamino K, von Neuhoff N, Yang M, Schlegelberger B, Li Z, Baum C. Clonal dominance of hematopoietic stem cells triggered by retroviral gene marking. Science. 2005; 308: 1171-1174.

MHH
Institute of Immunology

Head: **Prof. Dr. Reinhold Förster**
Location: MHH, Carl Neuberg Str 1, 30625 Hannover, Building I11, Level 02
Homepage: http://www.mh-hannover.de/immunologie.html

PhD Supervisors: Prof. Dr. Reinhold Förster, Dr. Günter Bernhardt, Prof. Dr. Immo Prinz



From left to right: Reinhold Förster, Günter Bernhardt, and Immo Prinz

Research Projects and selected Publications

Förster Lab:
Lymphoid organs such as lymph node and spleen, but also ectopic lymphoid tissue, such as bronchus-associated lymphoid tissue (BALT), play an important role in initiating protective as well as regulatory immune responses. Using molecular as well as imaging approaches, including 2-photon microscopy we aim to better understand the dynamics of how the different immune cells present in lymphoid organs interact with each other and how effector cells such as NK cells or cytotoxic T lymphocytes mediate their function in vivo. Furthermore we aim to decipher the molecules and mechanisms that allow homing of immune cells arriving at lymph nodes via afferent lymphatics.

- Halle S. et al. 2016. In Vivo Killing Capacity of Cytotoxic T Cells Is Limited and Involves Dynamic Interactions and T Cell Cooperativity. *Immunity*. 44:233.
- Fleige H, et al. 2014. IL-17-induced CXCL12 recruits B cells and induces follicle formation in BALT in the absence of differentiated FDCs. *J Exp Med*. 211:643.
- Ulvmar, M.H., et al. 2014. The atypical chemokine receptor CCRL1 shapes functional CCL21 gradients in lymph nodes. *Nature Immunol*ogy15:623-630.

Bernhardt Lab:
We discovered that CD155 plays a non-redundant role in modulating gut humoral immune response in mice. Since then, it was shown that the CD155/ligand-system is involved in many immunologically relevant processes such as cytotoxic T cell mediated killing of target cells, CD4 T cell activation, or manipulation of NK cell activity. In our group, we currently investigate how CD155 and its ligand impact on development and function of follicular helper T and NKT cells.

- Georgiev H, et al. 2016. Distinct gene expression patterns correlate with developmental and functional traits of iNKT subsets. *Nature Communications*, 7:13116.
- Georgiev H et al. 2016, CD155/CD226-interaction impacts on the generation of innate CD8(+) thymocytes by regulating iNKT-cell differentiation. *Eur J Immunol*. 46:993.
- Danisch, S. et al. 2013. CD226 interaction with CD155 impacts on retention and negative selection of CD8 positive thymocytes as well as T cell differentiation to follicular helper cells in Peyer's Patches, *Immunobiology* 218:152.

Prinz Lab:
We are exploring the development, homeostasis, and function of innate lymphocytes such as NK cells and γδ T cells. These cells likely play an important role in immediate immune responses against invading pathogens. The focus of our group is clearly the investigation of γδ T cells, in particular of the mechanisms that lead to their differentiation into interferon-γ or interleukin-17 producing effector cells. Thereby, we are very interested in the role of the γδ TCR and the relation of TCR specificity and γδ T cell function. To this end, we established protocols for high-throughput TCR sequencing. Furthermore, we investigate dynamic immune responses of γδ T cells using two-photon laser scanning microscopy.

- Ravens S. et al. 2017. Human γδ T cells are quickly reconstituted after stem-cell transplantation and show adaptive clonal expansion in response to viral infection. *Nature Immunol*ogy 18:393.
- Reinhardt A. et al. 2016. IL-23-dependent γδ T cells produce IL-17 and accumulate in enthesis, aortic valve, and ciliary body. *Arthritis & Rheumatology*, 68:2476.
- Kashani E et al. 2015. A clonotypic Vγ4Jγ1/Vδ5Dδ2Jδ1 innate γδ T-cell population restricted to the CCR6+CD27− subset. *Nature Communications*, 6:6477.

MHH
Institute of Virology

Head: **Prof. Dr. Thomas F. Schulz**

Location: Medical University Hannover (MHH)
Carl-Neuberg-Straße 1, 30625 Hannover
Homepage: http://www.mh-hannover.de/virologie.html

PhD supervisors (from left to right): Prof. Dr. Schulz, Dr. Bohne, PD Dr. Heim, Prof. Dr. Krey, Prof. Dr. Messerle, Prof. Dr. Sodeik, Prof. Dr. Viejo-Borbolla, . Dr. Kay-Fedorov (no photo)

Research Projects

- Kaposi Sarcoma Herpesvirus. DFG SFB 566, SPP 1230, IRTG 1273, EU IP INCA, SFB 900
- Human and murine cytomegalovirus. SFB 900, DFG SFB 587, DZIF
- Cell Biology of Herpes simplex virus. DFG SPP 1175, project grant, REBIRTH, EU, SFB 900
- Envelope proteins of influenza virus, corona viruses, HIV. BMBF, SFB 900
- Enteroviruses and inflammatory signalling
- Evolution and assembly of hepatitis C virus replication complexes. SFB 900
- Pathomechanisms of immunodeficiencies
- Immune and neuromodulation mediated by herpesviruses. SFB 900, N-RENNT, Marie Curie CIG

Basic Research in the Institute of Virology is geared towards the understanding of the pathogenesis caused by viral infections. Several groups work on aspects of cellular entry, establishment of latency, gene expression, assembly, structural virology, pathogenesis, immune and neuromodulation of large DNA viruses, such as different members of the herpesvirus and adenovirus families as well as the family of retro- and enteroviruses, hepatitis C and influenza, filo- and Coronaviruses. Herpesviruses and adenoviruses are of particular concern in immunosuppressed patients, such as transplant recipients, who make up an important part of the patient clientele at Medical University Hannover, one of the leading transplant centres in the country. The importance of newly emergent RNA viruses for public health has been highlighted recently by the 2009 H1N1v ‘swine flu’ pandemic and influenza viruses are therefore an important research topic at the Institute of Virology. Research groups at the Institute of Virology receive substantial peer-reviewed grant funding from the German Research Council (DFG), the European Union, the Federal Ministry for Research and several charities. Prof. Thomas F. Schulz coordinates a large EU integrated Project (INCA) funded under the European Union Framework 6. Programme as well as a DFG-funded Collaborative Research Centre “Chronic Infections” and the COALITION initiative.

Publications

- Glass M, Busche A, Wagner K, Messerle M, Borst EM. Conditional and reversible disruption of essential herpesvirus proteins. Nat Methods. 2009; 6(8):577-9.
- Zhang G, Chan B, Samarina N, Abere B, Weidner-Glunde M, Buch A, Pich A, Brinkmann MM, Schulz TF. Cytoplasmic isoforms of Kaposi sarcoma herpesvirus LANA recruit and antagonize the innate immune DNA sensor cGAS. Proc Natl Acad Sci U S A. 2016 Feb 23;113(8):E1034-43.
- Gramolelli S, Weidner-Glunde M, Abere B, Viejo-Borbolla A, Bala K, Rückert J, Kremmer E, Schulz TF. Inhibiting the Recruitment of PLCγ1 to Kaposi's Sarcoma Herpesvirus K15 Protein Reduces the Invasiveness and Angiogenesis of Infected Endothelial Cells. PLoS Pathog. 2015 Aug 21;11(8):e1005105.
- Vogt C, Hackmann C, Rabner A, Koste L, Santag S, Kati S, Mandel-Gutfreund Y, Schulz TF, Bohne J. ORF57 overcomes the detrimental sequence bias of Kaposi’s sarcoma-associated herpesvirus lytic genes. J Virol. 2015; May;89(9):5097-109.
- González-Motos, V., Jürgens, C., Ritter, B., Kropp, K.A., Durán, V., Larsen, O., Binz, A., Ouwendijk, W.J.D., Rovis, T.L., Jonjic, S., Verjans, G.M.G.M., Sodeik, B., Krey, T., Bauerfeind, R., Schulz, T.F., Kaufer, B.B., Kalinke, U., Proudfoot, A.E.I., Rosenkilde, M.M., and Viejo-Borbolla, A. Varicella zoster virus glycoprotein C increases chemokine-mediated leukocyte migration. PLoS Pathogens, *in press*.

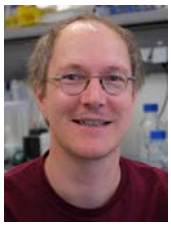
MHH

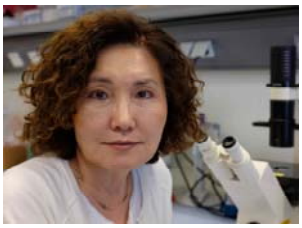
Institute of Clinical Chemistry / Inflammation Research

Head: **Prof. Dr. Kyeong-Hee Lee**

Location: MHH, Carl Neuberg Str 1, 30625 Hannover
Homepage: https://www.mh-hannover.de/36049.html

PhD Supervisor: Dr. Föger / Prof. Dr. Lee


Dr. Föger


Prof. Dr. Lee

Research Projects

- Immune modulation during influenza A-induced lung inflammation
- Physiological functions of receptor internalization
- Immunoregulation in gammaherpesvirus-mediated chronic infection
- The role of actin cytoskeletal regulation in immune cell function and signalling
- Diagnostic and therapeutic potential of novel immune regulatory reagents in inflammatory disease

The Research Unit for Inflammation Research at the Institute of Clinical Chemistry investigates novel regulatory themes of inflammatory responses from the vantage point of immune control against infection. The overall research goal is to identify molecular and cellular key mechanisms of inflammation and to develop novel perspectives for clinical interventions. To pursue our studies, we follow a multidisciplinary approach, in which we combine cell biological, immunological and genetic methods with the use of animal disease models. The specific interest of Prof. Lee is the modulation of effector and memory T and B cell-mediated protective immune responses. Ongoing projects focus on the role of regulatory B cells in adaptive immunity during viral infection with the aim of uncovering novel pathogenetic mechanisms of virus induced lung inflammation. In addition, Dr. Föger, who is an independent research group leader, explores how actin cytoskeletal dynamics and membrane trafficking processes contribute to normal and pathophysiological processes in the immune system and affect inflammatory signal transduction.

Selected Publications

- J. Yu, V.H.H. Duong, K. Westphal, A. Westphal, A. Suwandi, G. Grassl, K. Brand, A.C. Chan, N. Föger, K-H. Lee. Surface receptor Toso controls B cell-mediated regulation of T cell immunity. **J. Clin Investigation.** 2018. May 1;128(5):1820-1836
- A. Westphal, W. Cheng, J. Yu, G. Grassl, M. Krautkrämer, O. Holst, N. Föger and K-H. Lee. Lysosomal trafficking regulator Lyst links membrane trafficking to TLR-mediated inflammatory responses. **J Exp Med**. 2017. Jan 214(1):227-244
- K.S. Lang, P.A. Lang, A. Meryk, L-M Boucher, J. Haight, P. Funkner, A. Wakeham, N. Honke, M. Recher, A. A. Navarini, N. Honke, P. S. Ohashi, D. Häussinger, K-H Lee* and T. W. Mak* (* shared senior authorship). Involvement of Toso in activation of monocytes, macrophages, and granulocytes. **Proc Natl Acad Sci USA**. 2013. Feb 12;110(7):2593-8
- Föger N, Jenckel A, Orinska Z, Lee KH, Chan AC, Bulfone-Paus S. Differential regulation of mast cell degranulation versus cytokine secretion by the actin regulatory proteins Coronin1a and Coronin1b. **J Exp Med**. 2011. Aug 29;208(9):1777-87
- X-H Nguyen, P. Lang, K. Lang, G Fattakhova, D Adam, N Föger, A. Kamal, P Prilla, S Mathieu, C Wagner, TW Mak, AC Chan and K-H Lee. Toso regulates the balance between apoptotic and non-apoptotic death receptor signaling by facilitating RIP1 ubiquitination. **Blood**. 2011
- Föger N. et al., Requirement for coronin 1 in T lymphocyte trafficking and cellular homeostasis. **Science**. 2006
- Lee, K-H. et al., The role of receptor internalization in CD95 signaling. **EMBO J**. 2006
- Lee, K-H. et al., The immunological synapse balances TCR signaling and degradation. **Science**. 2004.
- Lee, K-H. et al., T cell receptor signaling precedes formation of the immunological synapse. **Science**. 2002.

MHH

Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO), Research Area “Molecular Biotechnology and Stem Cell Research”

Head: **Prof. Dr. Ulrich Martin**
Location: MHH, HBZ, building J11, Carl-Neuberg-Str.1, 30625 Hannover

Homepage http://www.lebao.eu/

PhD Supervisors: PD Dr. Ina Gruh / Prof. Dr. Ulrich Martin / Dr. Ruth Olmer / Dr. Robert Zweigerdt

Members of the LEBAO

Research Projects

- Reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) and establishment of iPSC-derived patient- or disease-specific cell lines
- Differentiation of embryonic stem cells (ESCs) and iPSCs into airway and alveolar epithelial cells as well as vascular cell types
- Examination of genetic abnormalities of iPSCs
- Targeted genetic modification of iPSCs
- HLA-Knockout iPSC lines as potential universal cell source for cellular therapies
- Trophoblast-based induction of peripheral immunological tolerance towards pluripotent stem cells derivatives
- Establishment and characterization of bio-artificial cardiac tissues
- Establishment of human pluripotent stem cell (hPSC) culture (including hiPSCs and hESCs) in clinical scale and grade
- Establishment of efficient cardiomyogenic differentiation of hPSCs and preparation of cardiomyocytes for tissue engineering and heart repair in pre-clinical animal model

The LEBAO, being one of the central pillars of the Cluster of Excellence "REBIRTH", is part of the Department of Cardiothoracic, Transplantation and Vascular Surgery of the MHH. The close alignment between basic research and the clinic allows focused approaches in research and development, and promotes an accelerated translation of innovative therapeutic concepts into clinical practice. Within the LEBAO different aspects of regenerative medicine and organ transplantation are investigated. Projects in all areas of research aim at the development of new therapies for the treatment of cardiovascular and respiratory diseases.
“Molecular biotechnology and stem cell research” is one of the research areas in the LEBAO. The groundwork for the development of novel cell-based therapies for the treatment of cardiac and pulmonary diseases is laid through investigations on a molecular and cellular level. Our research not only focuses on adult resident stem cells and ES cells, but also on iPS cells as an emerging tool for disease modeling, drug screening and patient-specific therapies.

Publications (selection)

- Harrison, P. T., Hoppe, N., and **Martin, U.** 2018. Gene editing & stem cells. *J Cyst Fibros* 17, no. 1:10.
- Jara Avaca, M., and **Gruh, I.** 2018. Bioengineered cardiac tissue based on human stem cells for clinical application. *Adv Biochem Eng Biotechnol* 163:117.
- **Martin, U.** 2017. Genome stability of programmed stem cell products. *Advanced Drug Delivery Reviews* 120:108.

- **Martin, U.** 2017. Therapeutic Application of Pluripotent Stem Cells: Challenges and Risks. *Front Med* 4:229.
- Kempf, H., and **Zweigerdt, R.** 2018. Scalable Cardiac Differentiation of Pluripotent Stem Cells Using Specific Growth Factors and Small Molecules. *Adv Biochem Eng Biotechnol* 163:39.
- Merkert, S., and **Martin, U.** 2018. Targeted Gene Editing in Human Pluripotent Stem Cells Using Site-Specific Nucleases. *Adv Biochem Eng Biotechnol* 163:169.
- **Olmer, R.***, Engels, L.*, Usman, A., Menke, S., Malik, M. N. H., Pessler, F., Goehring, G., Bornhorst, D., Bolten, S., Abdelilah-Seyfried, S., Scheper, T., Kempf, H., **Zweigerdt, R.**, and **Martin, U.** Differentiation of human pluripotent stem cells into functional endothelial cells in scalable suspension culture. Stem Cell Reports 10, no. 5:1657.
- Merkert, S., Bednarski, C, Göhring, G., Cathomen, T., and **Martin, U.** 2017. Generation of a gene-corrected isogenic control iPSC line from Cystic Fibrosis-patient specific iPSCs homozygous for p.Phe508del mutation mediated by TALENs and ssODN. *Stem Cell Research* 23:95.
- Haase, A., Göhring, G, and **Martin, U.** 2017. Generation of non-transgenic iPS cells from human cord blood CD34+ cells under animal component-free conditions. *Stem Cell Research*. In press.
- Jara-Avaca, M.*, Kempf, H.*, Ruckert, M., Robles-Diaz, D., Franke, A., de la Roche, J., Fischer, M., Malan, D., Sasse, P., Solodenko, W., Drager, G., Kirschning, A., **Martin, U.#**, and **Zweigerdt, R.#**. 2017. EBIO Does Not Induce Cardiomyogenesis in Human Pluripotent Stem Cells but Modulates Cardiac Subtype Enrichment by Lineage-Selective Survival. *Stem Cell Reports* 8, no. 2:305.
- Konze, S. A., Werneburg, S., Oberbeck, A., **Olmer, R.,** Kempf, H., Jara-Avaca, M., Pich, A., **Zweigerdt, R.,** and Buettner, F. F. 2017. Proteomic Analysis of Human Pluripotent Stem Cell Cardiomyogenesis Revealed Altered Expression of Metabolic Enzymes and PDLIM5 Isoforms. *J Proteome Res* 16, no. 3:1133.
- Rojas, S. V., Kensah, G., Rotaermel, A., Baraki, H., Kutschka, I., **Zweigerdt, R.**, **Martin, U.**, Haverich, A., **Gruh, I.#**, and Martens, A.**#**. 2017. Transplantation of purified iPSC-derived cardiomyocytes in myocardial infarction. *PLoS One* 12, no. 5:e0173222.
- Borger, A. K., Eicke, D., Wolf, C., Gras, C., Aufderbeck, S., Schulze, K., Engels, L., Eiz-Vesper, B., Schambach, A., Guzman, C. A., Lachmann, N., Moritz, T., **Martin, U**., Blasczyk, R., and Figueiredo, C. 2016. Generation of HLA-universal iPSCs-derived megakaryocytes and platelets for survival under refractoriness conditions. *Mol Med* 22:274.
- Kempf, H., Andree, B., and **Zweigerdt, R.** 2016. Large-scale production of human pluripotent stem cell derived cardiomyocytes. *Adv Drug Deliv Rev* 96:18.
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Rainer Blasczyk

Britta Eiz-Vesper

Members of the group "Molecular Immunotherapy"

Research Projects

- Generation of chimeric antigen receptors (CARs) of monoclonal antibodies with unique T-cell-like properties to control Epstein-Barr virus-associated tumors (BMBF)
- alloCELL: Monitoring of antigen-specific T cells in patients and donors, selection of suitable T-cell donors, GMP-compliant manufacturing of specific T cells and application
- Effects of G-CSF mobilization on antiviral T-cell characteristic (Jose Carreras Foundation)
- Dynamics of antigen presentation during infection with human adenovirus (ADV): Evaluation of ADV-specific T-cell responses to newly identified target antigens (Deutsche Kinderkrebsstiftung, BMBF)

The research interests of the "Molecular Immunotherapy" work group at the Institute for Transfusion Medicine include antigen-specific adaptive and innate immunity, functional studies of peptide binding, the identification of antitumor and antiviral T-cell epitopes and the characterization and expansion of major histocompatibility complex (MHC)/ligand-specific T cells. The mechanism of antigen cross-presentation via heat shock proteins (HSPs) and the role of suppressors of cytokine signaling (SOCS) and micro (mi)RNAs involved in differentiation and function of T cells is a major focus of our research. Our studies are mainly related to adoptive T-cell immunotherapy, especially to methods to safely and effectively reduce or prevent clinical manifestation of cytomegalovirus (CMV), Epstein-Barr virus (EBV), or adenovirus (ADV) infection or reactivation in immunocompromised patients after transplantation.

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MHH

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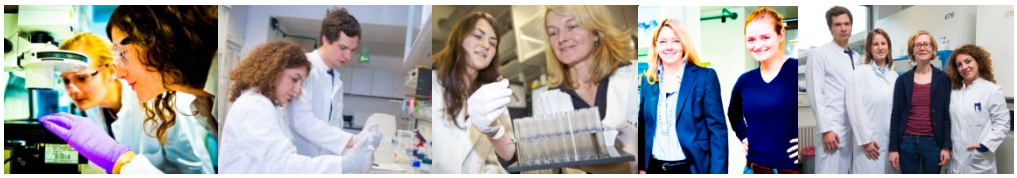

From left to right: work impressions from the Hansen and Dittrich lab, PD Dr. Viemann (right), Prof. Dr. G. Hansen (left), and PD Dr. Anna-Maria Dittrich (without lab coat)

Research Projects

- Immunological determinants of allergic and inflammatory diseases in childhood (AG Hansen&AG Dittrich).
- Novel cell-based therapeutic approaches to rare lung diseases (AG Hansen)
- Cystic fibrosis Pseudomonas aeruginosa-microbiology, CFTR-genetics and CF-related immune phenotypes (AG Tümmler&AG Dittrich).
- Neonatal tolerance and sepsis (AG Viemann).

The department for Pediatric pneumology, allergology and neonatology consists of three working groups, all located in the pediatric research center of Hannover Medical University. We are funded by the German Science Foundation, the German Ministry of Health and Education and various other, non-profit organizations. We are part of the German Lung Center, a multi-center structure to enhance patient-orientated research in the field of lung diseases throughout Germany.

Our research focuses on allergies and asthma, cystic fibrosis, rare pediatric lung and the development of the neonatal immune system. Our unifying aim is to understand the causes and course of these diseases in order to develop preventive or therapeutic measures. Our research has a common backbone in our query to understand inflammatory and immunological mechanisms in different pediatric diseases.

For example, in neonatology, we are interested in understanding the development of the neonatal immune system including pathologies such as neonatal sepsis, unique to the developing child. For asthma and allergic diseases, we strive to understand the development of allergic diseases vs. tolerance as a basis for the development of pro-tolerogenic therapeutic approaches. For rare lung diseases, we develop novel cell-based therapeutic to correct rare inborn pulmonary diseases. For cystic fibrosis, immunological host factors associated with different disease courses form a central core of attempts to further our understanding of this deleterious genetic diseases.

Publications

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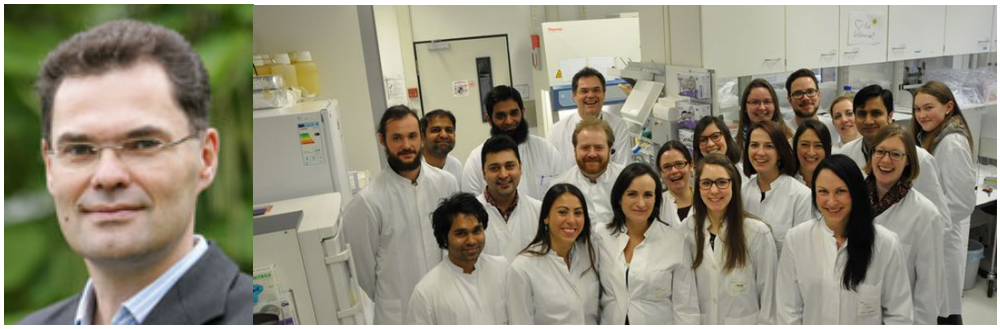

Members of the group and Prof. Dr. Kalinke (left)

Research Projects

- Analysis of the impact of the constant antibody moiety on monoclonal antibody-mediated effects. Industry
- Virus-induced type I interferon responses by human/murine antigen presenting cells. ZIB, VISTRIE
- Analysis of local anti-viral type I interferon responses in liver and brain. ZIB, IRTG
- Establishment of new model systems for basic research and preclinical analysis of new pharmaceuticals that is superior to animal experiments. BMBF
- Cell-directed drug delivery by nano-spheres. ZIM
- Development of novel vaccination strategies for immune compromised patients. HAI

The Institute of Experimental Infection Research is mainly working on new therapies for infectious diseases together with researchers and medical doctors of the Helmholtz Centre for Infection Research and the Medical University Hannover. One important focus of our work is to find out how different types of viruses induced type I interferon (IFN) and how the viruses evade the early antiviral host defense. Here we focus on vesicular stomatitis virus (VSV), different herpes viruses and viruses belonging to the group of poxviruses. In various different viral infections IFN responses are induced within hours. This secures the survival of the host until the adaptive immunity eliminates the virus. We showed that upon VSV infection plasmacytoid dendritic cells (pDC) were activated to produce high quantities of protective IFN. All closer studied viruses developed IFN evasion mechanisms. We analyze how different viruses such as VSV, herpes viruses, poxviruses and others induce and / or inhibit IFN. Furthermore, we study the impact of virus-induced IFN on adaptive immunity. In this work local conditions within the central nervous system play an important role. Virus neutralizing antibodies are an integral part of adaptive immunity. We study how the constant antibody moiety contributes to antibody function and how this portion interacts with receptors of the immune system. These studies help to predict therapeutic monoclonal antibody function in the human body.

Publications

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Members of the group, Dr. Lochner (right)

Research Projects

- Mechanisms of tolerance and immunity during mycobacterial infection. DFG SFB 900
- Epigenetic markers for quantification of inflammatory and regulatory T cells. DFG KFO 250
- Role of regulatory immune cells in the allergic immune response of the lung. DFG SFB 587
- DC-SIGN as therapeutic target structure in allergic airway inflammation. DFG
- Dendritic cells for novel immunotherapies. DC-Thera. EU
- Development of BAC transgenic mouse models for the functional analysis of DCs. Boehringer Ingelheim Fonds
- Role of TLR signalling in dendritic cell and macrophage-mediated host defence against pneumococcal infection. DFG
- A Glycomics approach for the treatment of cancer: Role of human DC-SIGN in humanized mouse models. EUREKA, EU

The main goal of our work lies in the development of novel, improved vaccination strategies and treatments of infectious diseases. Although vaccines against many pathogens are available, each year millions of people die from respiratory and gastrointestinal infections, tuberculosis, malaria and AIDS. One of the focuses of our research is on dendritic cells (DC). DC recognize pathogens via so called pattern recognition receptors (TLRs, CLRs) and play a central role in the induction of specific immune responses. In our laboratory we are not only interested in the function of highly specialized subtypes of dendritic cells, but we also explore the significance of pattern recognition receptors as targets for vaccination strategies and as new therapeutic and prophylactic measures. Beside dendritic cells, T cells are important mediators of an effective immune response. Here, our research concentrates on the role of inflammatory T-helper 17 cells in intestinal infections. We are also interested in the function of regulatory T cells, which play a key role in regulating the immune responses, thereby preventing unrestrained immune reactions.

Publications

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Helmholtz Centre for Infection Research

Research Group Model Systems for Infection and Immunity

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Members of the group and Prof. Dr. Wirth (left)

Research Projects

Both, pathogen specific evasion strategies and impairment of defense mechanisms of the host contribute to the persistence of infections. Development of novel strategies for prevention and treatment of chronic infections requires understanding of the mechanisms underlying persistence of pathogens. The research group **Model Systems for Infection and Immunity** at **the Helmholtz Centre for Infection Research** focuses on developing strategies for elucidating adaptive and innate defense mechanisms as well as viral mechanisms that contribute to persistent infection. To generate the respective model systems, (epi)genetic engineering of cells and mice is being pursued.

Particular research foci are

- understanding the mechanisms of T cell tolerance during infections and identifying options for overcoming T cell impairment in therapeutic settings
- developing of predictive cell and mouse models for human herpes viruses and liver viruses
- validation of novel compounds against chronic viral infections
- investigating Interferon I and III based antiviral defense in chronic infection

Publications

- Lipps, C., Klein, F., Wahlicht, T., Seiffert, V., Butueva, M., Zauers, J., Truschel, T., Luckner, M., Köster, M., MacLeod, R., Pezoldt, J., Hühn, J., Yuan, Q., Müller, P.P., Kempf, H., Zweigerdt, R., Dittrich-Breiholz, O., Pufe, T., Beckmann, R., Drescher, W., Riancho, J., Sañudo, C., Korff, T., Opalka, B., Rebmann, V., Göthert, J.R., Alves, P.M., Ott, M., Schucht, R., Hauser, H., Wirth, D., May, T., 2018. Expansion of functional personalized cells with specific transgene combinations. Nature Communications 9, 994.
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