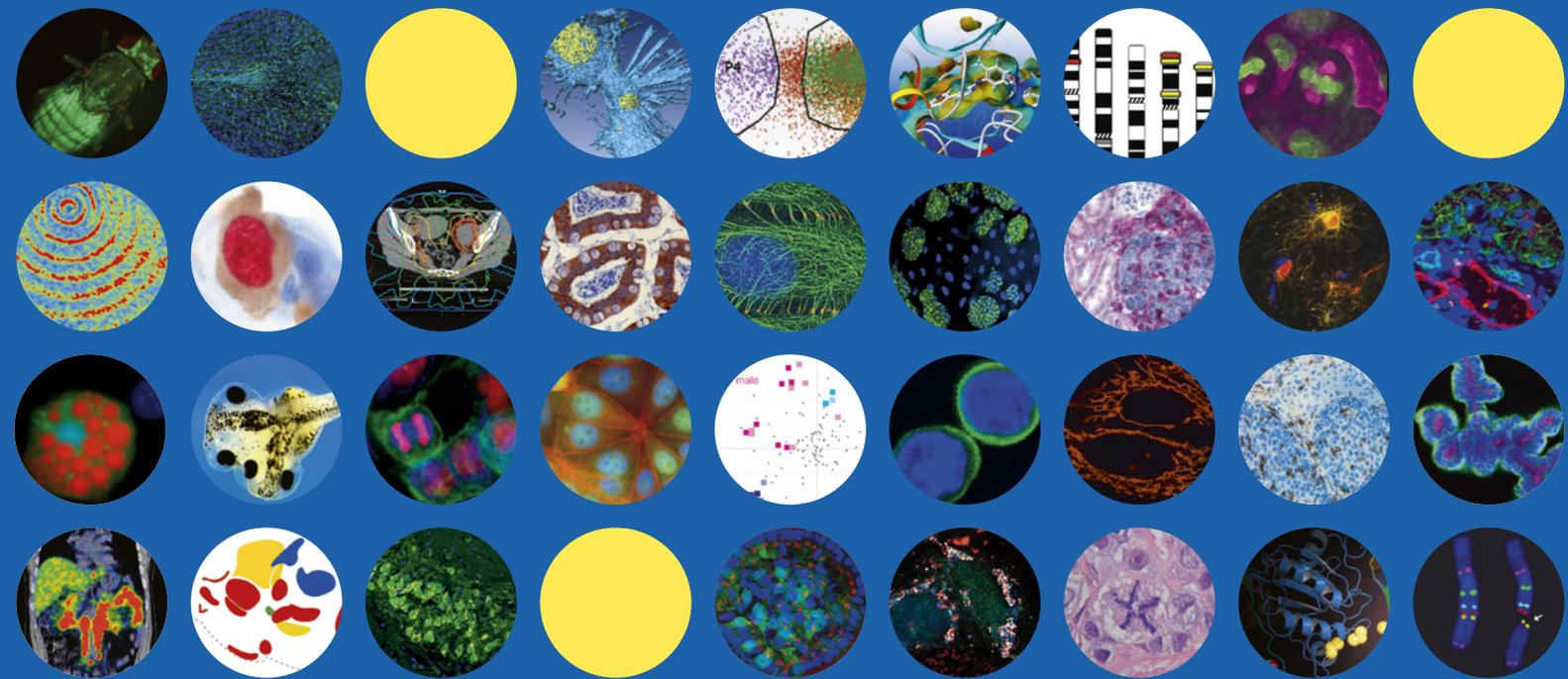


Cancer Research at DKFZ 2016



Research Program
TUMOR IMMUNOLOGY



RESEARCH PROGRAMS

The DKFZ covers the entire breadth of modern cancer research. Fields of research range from knowledge of the molecular basis of the development of cancer, distribution and risk factors within the population to diagnosis and treatment.

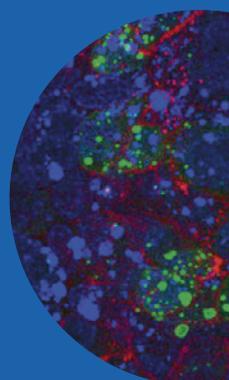
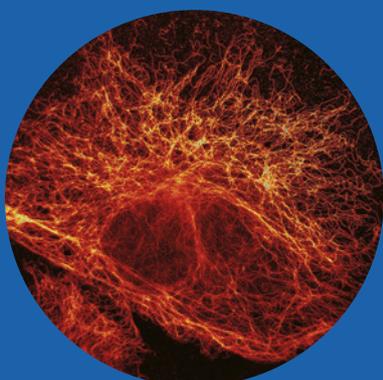
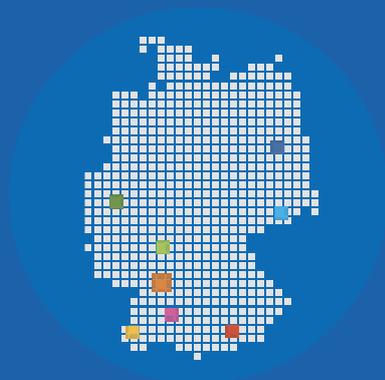
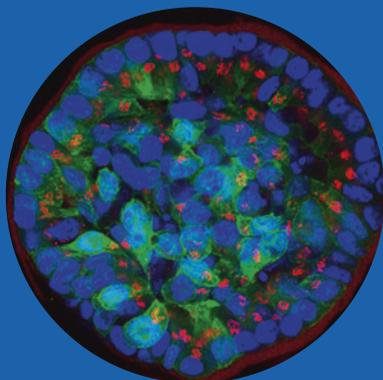
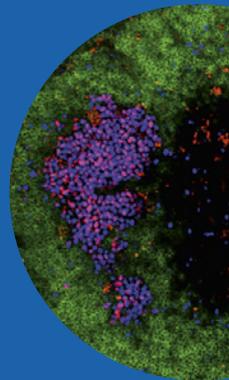
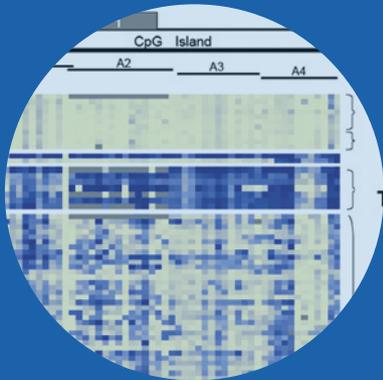
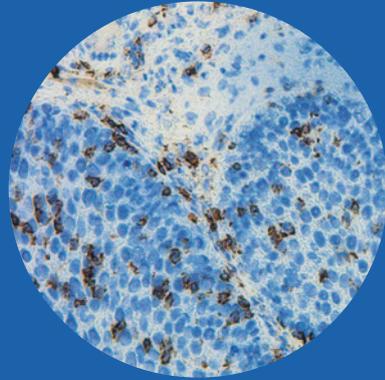
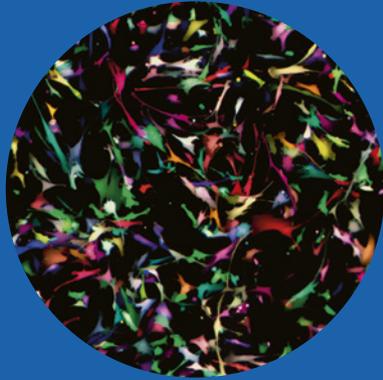
As an interdisciplinary environment, DKFZ employs scientists with qualifications in medicine, biology, biochemistry, physics, chemistry, mathematics, informatics or related issues. More than 100 division heads, group leaders and senior scientists, 200 postdocs and about 400 PhD students work together at the Center.

At the DKFZ, researchers benefit from intensive scientific exchange between research programs and individual groups, which serves as the basis for the internationally renowned research at the Center.

Research groups are organized into seven research programs:

- Cell Biology and Tumor Biology
- Functional and Structural Genomics
- Cancer Risk Factors and Prevention
- Tumor Immunology
- Imaging and Radiooncology
- Infection, Inflammation and Cancer and
- Translational Cancer Research.

In the German Cancer Consortium (DKTK), one of six German Centers for Health Research, the DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients (see also pages 150ff).



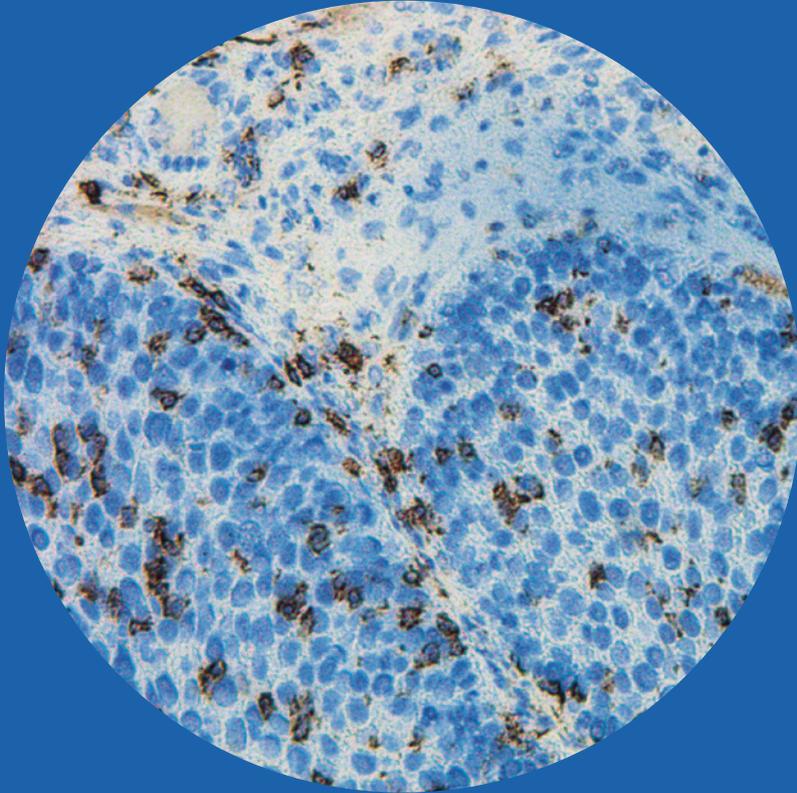


Coordinator
Prof. Dr. Hedda Wardemann

Tumor Immunology

The immune system is our body's most powerful weapon to combat pathogens and cancer cells. However, tumor cells have a repertoire of tricks to evade the immune response. The Divisions and Research Groups of the Tumor Immunology Program conduct basic and applied research in the field of immunology. We investigate the fundamental physiological and pathological processes of immune cell and organ development in the innate and adaptive immune system, as well as the mechanisms that regulate the function, activity and behavior of immune cells. To achieve this goal, the research groups develop and utilize sophisticated experimental model systems and technologies. Some of the central goals of the Research Program D are:

- Understanding the molecular and cellular signals that cause programmed cell death (apoptosis), how tumor cells resist apoptosis inducing signals and how this mechanism can be manipulated.
- Characterizing the functional role of the antibody repertoire at single cell level to measure the quality of B cell responses and to identify protective antibodies.
- Defining the mechanisms underlying self-tolerance, immunological tolerance towards tumors and the prevention of organ-specific autoimmunity.
- Determining physiological and pathological processes of cell and organ development in the immune system, as well as the maturation and plasticity of mature immune cells and the origins of tissue resident immune cells.
- Understanding regulatory immune cells and the molecular pathways that control their differentiation, function and role in organ homeostasis.
- Investigating the innate immune response to reveal possibilities to harness innate immune cells against tumors and the interaction between innate and adaptive cells during anti-tumor immune responses.
- Developing advanced methods to characterize tumor host interactions within the tumor microenvironment and tailored immunotherapeutic approaches that are translated into individual clinical treatments for cancer patients.
- Determining the regulatory effect of the cytokine TGF-beta on the immune system and tumorigenesis.



AWARDS
AND GRANTS

Dr. Katrin Busch:
Fritz and Ursula Melchers Postdoctoral Prize 2015

Dr. Markus Feuerer:
ERC Consolidator Grant 2015



Division Translational Immunology



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The immune system is characterized by its capability to recognize and eliminate malignant tumors. Immunotherapies exploit this unique ability and promise to become an efficient complement to standard tumor treatments in the future. The objective of the Division "Translational Immunology" is to gain new insights into the immune defense system of cancerous cells and to evolve the results from basic research through to clinical treatments. The pursuit of this is based on close interdisciplinary collaboration with the oncological departments of the university hospital. New therapeutic concepts developed by the Division are being "translated" into clinical application under the auspices of the National Center for Tumor Diseases (NCT) Heidelberg. Effective immune responses are based on a variety of active principles. The Division is looking for options to draw on the immune system's functions as a complementary treatment in the battle against cancer within the framework of synergistic projects.

We study and describe formative and regulative mechanisms of successful and unsuccessful T cell responses against cancer. We are particularly interested in understanding the generation of immune suppressive T cell subsets, recruitment of tumor specific T cells in tumors and the mechanisms of tumor cell eradication by the immune system.

FUTURE OUTLOOK:

Our findings are translated into new immunotherapeutic drugs (some of which are developed in a Joint Collaboration with Bayer Healthcare) and into innovative cellular therapy strategies such as adoptive T cell therapy.

SELECTED PUBLICATIONS:

- (1) Khandelwal N. et al. (2015). A high-throughput RNAi screen for detection of immune-checkpoint molecules that mediate tumor resistance to cytotoxic T lymphocytes. *EMBO Mol Med*, 7(4), 450-463.
- (2) Reissfelder C. et al. (2015). Tumor specific cytotoxic T lymphocyte activity determines colorectal cancer patient prognosis. *J Clin Invest*, 125(2), 739-751.
- (3) Klug F. et al. (2013). Low dose irradiation programs macrophage differentiation to an iNOS+/M1 phenotype that orchestrates effective T cell immunotherapy. *Cancer Cell*, 24(5), 589-602.
- (4) Witzens-Harig M. et al. (2013). Tumor cells in multiple myeloma patients inhibit myeloma-reactive T cells through carcinoembryonic antigen-related cell adhesion molecule-6. *Blood*, 121(22), 4493-4503.

Division Immunogenetics

The Division has made groundbreaking contributions to the field of programmed cell death (apoptosis). The group established that the CD95 receptor does not only act as a death receptor that induces apoptosis, but it also triggers the NF- κ B pathway involved in tumor proliferation, invasion and metastasis. Together with Apogenix, a company founded together with the DKFZ, the group has developed the biological, APG101, a soluble fusion protein consisting of two extracellular domains of the CD95 receptor and an antibody Fc fragment (CD95-Fc). APG101 has therapeutic effects in many diseases, e. g. in cancer.

Two TCM anti-cancer compounds, Wogonin and Rocaglamide, could be shown to preferentially induce apoptosis in tumor cells. Cyclin-dependent kinase 9 (CDK9) was identified as the direct molecular target of Wogonin, and Prohibitin 1 and 2

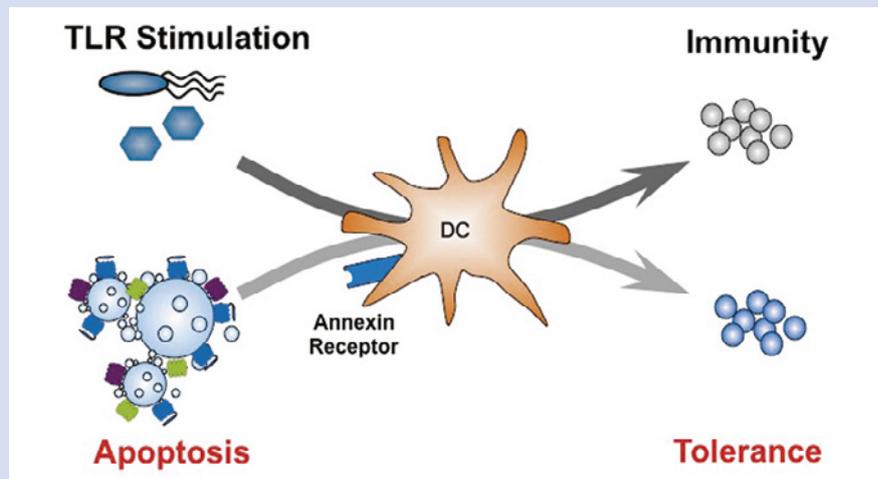
FUTURE OUTLOOK:

Future work will be directed at trying to block the CD95 death pathway. CD95 mediated non-death pathways will be addressed by re-sensitization towards apoptosis by drugs, and blocking of CD95 receptor signaling by drugs and/or soluble CD95 receptors. Further trials with the soluble CD95 receptor APG101 are planned. The molecular interactions of Wogonin and Rocaglamide to their targets will be elucidated, and will serve as a platform for further drug screening. The influence on cell death of tumor cells from novel NF- κ B regulating phosphatases will be characterized in order to find ways to manipulate them to treat patients. Annexins on the surface of apoptotic tumor cells suppress the anti-tumor immune response. Therefore, manipulation of the annexin system promises benefits for tumor therapy. The group will



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The annexin checkpoint system: In a dynamic process intracellular annexins are transferred to the surface of early apoptotic cells, bind to annexin receptors on dendritic cells (DC) and induce a tolerogenic phenotype in TLR (Toll-like-Receptor) activated DC. This process contributes to the regulation of peripheral immunological tolerance.

were identified as targets of Rocaglamide. Annexins were shown to be involved in induction of peripheral tolerance against antigens from apoptotic cells. They are transferred early upon induction of cell death to the surface of apoptotic cells. By inhibition of NF- κ B signaling, annexins suppress dendritic cell (DC) maturation.

A redox-regulating molecule, AF-1, was identified as being associated with aging of human cells. Knockdown of AF-1 can also substantially extend stress resistance and life span in *Drosophila*. AF-1 seems to be involved in a general aging mechanism.

focus on the identification of the annexin receptor and the molecular mechanism by which annexin treatment inhibits pro-inflammatory signaling. Future directions of the group's work will involve the investigation of the role of AF-1 as a putative master switch in aging. We will focus on AF-1's molecular mechanism, its druggability, and its role in age-related diseases.

SELECTED PUBLICATIONS:

- (1) Brechmann M. et al. (2012). A PP4 holoenzyme balances physiological and oncogenic nuclear factor-kappa B signaling in T lymphocytes. *Immunity*, 37(4), 697–708.
- (2) Kamiński M.M. et al. (2012). T cell activation is driven by an ADP-dependent glucokinase linking enhanced glycolysis with mitochondrial reactive oxygen species generation. *Cell Rep*, 2(5), 1300–1315.
- (3) Schleich K. et al. (2012). Stoichiometry of the CD95 death-inducing signaling complex: experimental and modeling evidence for a death effector domain chain model. *Mol Cell*, 47(2), 306–319.
- (4) Kiessling M.K. et al. (2011). High-throughput mutation profiling of CTCL samples reveals KRAS and NRAS mutations sensitizing tumors toward inhibition of the RAS/RAF/MEK signaling cascade. *Blood*, 117(8), 2433–2440.



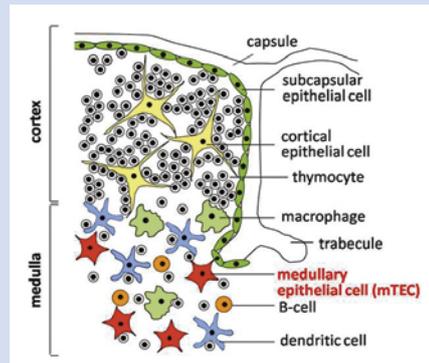
Division Developmental Immunology



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Self/non-self discrimination is a hallmark of the immune system of multi-cellular organisms. The thymus of vertebrates plays a central role in the induction of T cell tolerance (“central tolerance”). During self-tolerance induction, the highly diverse T cell receptor repertoire is probed against the “immunological self” of the body to get rid of auto-reactive T cells. Our discovery of promiscuous gene expression (pGE) and its essential function in preventing organ-specific autoimmunity has led to a reappraisal of the role of central tolerance in self/non-self discrimination. pGE signifies that tissue-restricted self-antigens are ectopically expressed in medullary thymic epithelial cells (mTECs). This gene pool encompasses >85 percent of all known genes and represents all tissues of the body. pGE allows self-antigens to become continuously accessible to developing T cells, thus rendering them tolerant. Specific failure of pGE of even a single self-antigen can lead to severe organ-specific autoimmune diseases like type 1 diabetes mellitus. This gene pool also includes tumor-associated antigens, thus imposing immunological tolerance towards tumors, a fact to be considered in the selection of tumor antigens for clinical vaccination trials.



The thymus is the site where central T cell tolerance is imposed. It consists of an outer cortex and a central medulla. The medulla is densely packed with various antigen-presenting cells, which present a plethora of self-antigens to developing T cells and thus induce self-tolerance. Medullary thymic epithelial cells (shown in red) have the unique property of expressing numerous tissue-restricted self-antigens in a promiscuous fashion and are thus essential for the prevention of autoimmunity.

FUTURE OUTLOOK:

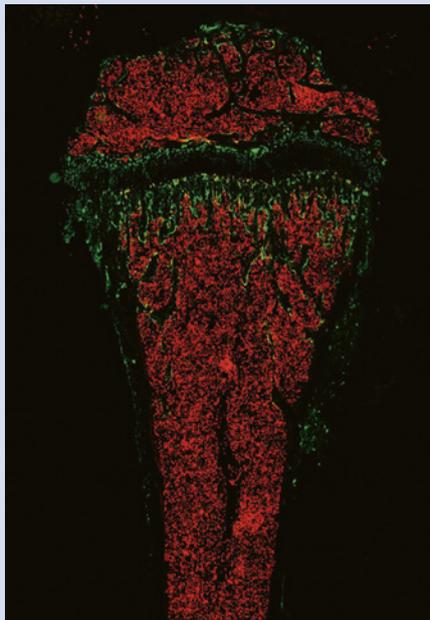
We aim to understand how the expression patterns of individual mTECs faithfully add up to the full complement of self-antigens at the population level. We found the mouse and human mTEC compartment to be a composite of numerous distinct co-expressed gene clusters with single mTECs displaying recurrent gene co-expression patterns. We expect a more comprehensive understanding of the functional organization of the thymic microenvironment in the context of self-tolerance, and new insights into gene (co)-regulation in pGE and beyond. We will continue to apply our findings to human disorders, i. e. autoimmune diseases and identify underlying molecular mechanisms controlling the intra-thymic expression (or lack thereof) of prominent auto-antigens. We also study the developmental biology of thymic epithelial cells, with the future aim of following their full course of differentiation *in vitro* and *in vivo* from tissue-resident bi-potent stem cells. Using a sphere assay we successfully identified and characterized a bi-potent TEC stem cell candidate of the embryonic and adult mouse thymus, and we currently extend these findings to human TEC stem cells and their malignant counterparts, i. e. cancer stem cells in human thymomas. Finally, we aim to develop new diagnostic tools for human thymoma subtypes.

SELECTED PUBLICATIONS:

- (1) Brennecke P. et al. (2015). Single-cell transcriptome analysis reveals coordinated ectopic gene expression patterns in medullary thymic epithelial cells. *Nat Immunol*, 16(9), 933-941.
- (2) Ucar A. et al. (2014). Adult thymus contains FoxN1- epithelial stem cells that are bi-potent for medullary and cortical thymic epithelial lineages. *Immunity*, 41(2), 257-259.
- (3) Pinto S. et al. (2013). Overlapping gene co-expression patterns in human medullary thymic epithelial cells generate self-antigen diversity. *Proc Natl Acad Sci U S A*, 110(37), E3497-E3505.
- (4) Kyewski B. and Klein L. (2006). A central role for central tolerance. *Annu Rev Immunol*, 24, 571-606.

Division Cellular Immunology

The Division of Cellular Immunology is investigating the physiological and pathological processes of cell and organ development in the immune system as well as their immunological functions. We generated reporter knock-in mice to demonstrate that T cells and myeloid cells (e. g. dendritic cells and granulocytes) arise in the thymus from distinct progenitors under physiological conditions. Moreover, a genetic block of Notch1 signals in T cell progenitors leads to their developmental deviation to dendritic cells instead of T cells. T cell development and maturation occur in a discrete primary immunological organ, the thymus. Previous projects focused on thymus organogenesis, while in current projects we investigate functions of the transcription factor FoxN1 in thymic epithelial cells (TECs). A central area of our research is the investigation of the roles of mast cells



Immunofluorescence staining of lymphocytes (red) and osteoclasts (green) in the bone marrow of a mouse femur.

in the immune system. Different knockout mice enabled us to characterize an enzyme of the heparin biosynthesis pathway and to elucidate the mechanism by which mast cell proteases can degrade endothelin, a blood pressure regulating factor, and detoxify structurally related snake toxins.

FUTURE OUTLOOK:

Members of our team study the dynamic processes of stem cell differentiation and the plasticity of the development of mature immune cells. To this end, we develop mouse models in which stem cells and their progeny are inducibly labeled at a certain time point. Furthermore, we have generated 'universal stem cell recipient' mice which can be transplanted with bone marrow stem cells without the need for myeloablation, e. g. by irradiation. In another fate mapping project, we are investigating the origins of different tissue resident macrophages like osteoclasts, Kupffer cells in the liver, and microglia in the central nervous system. We are extending our thymus research toward unravelling mechanisms of acute T cell leukemia (T-ALL) development. We discovered that thymocytes undergo transformation if they non-physiologically persist in the thymus. This occurs with surprisingly high incidence if the influx of fresh progenitors into the thymus is interrupted. We hope that this new T-ALL model shall enable us to investigate the cellular and molecular mechanisms of T-ALL formation in the thymus.

Comprehensive investigations of mast cell functions remain a central area of our research. We have generated a mouse mutant that is completely mast cell deficient but has an otherwise normal immune system. This new mouse represents an excellent model to clarify the question which infections or diseases beyond allergy mast cells play immunological roles. Specifically, we will test the roles of mast cells in wound healing, asthma, responses to infection and in tumor models.



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SELECTED PUBLICATIONS:

- (1) Busch K. et al. (2015). Fundamental properties of unperturbed haematopoiesis from stem cells in vivo. *Nature*, 518(7540), 542-546.
- (2) Gomez Perdiguero E. et al. (2015). Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature*, 518(7540), 547-551.
- (3) Gutierrez D.A. et al. (2015). Hematopoietic Kit Deficiency, rather than Lack of Mast Cells, Protects Mice from Obesity and Insulin Resistance. *Cell Metab.* 21(5), 678-691.
- (4) Martins V.C. et al. (2014). Cell competition is a tumour suppressor mechanism in the thymus. *Nature*, 509(7501), 465-470.



Clinical Cooperation Unit Applied Tumor Immunity

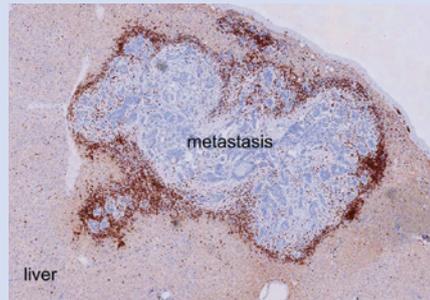


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The research team of the Clinical Cooperation Unit Applied Tumor Immunity focuses on the development of advanced analytical methods to characterize tumor host interactions in the immunological tumor microenvironment and the periphery. In particular, whole-slide imaging of histological sections coupled with automatic image processing, laser microdissection and multiplex protein quantification technologies as well as multiplex serological assays have been established. The goal is a comprehensive mechanistic analysis of immunological pathomechanisms in the tumor microenvironment and to develop individualized immunological therapy approaches that are then translated into clinical care of

T cell friendly environment, with redistribution of T cells, repolarization of M2 macrophages towards M1 macrophages and regression of metastatic lesions in chemotherapy refractory CRC patients (Halama et al., *Cancer Cell* 2015). In order to further support these developments of individualized immunological therapies the platforms Digital Tumor Tissue Computation (DTC) and Intratumoral Immunomonitoring have been established at NCT in close cooperation with Dirk Jäger's group. As the Department of Medical Oncology is the main unit for cancer patient care at the NCT, the direct link between research in the Clinical Cooperation Unit and translation into clinical trials and care is highly efficient.



CD3 staining showing intense T cell infiltration at the invasive margin in metastatic CRC.

FUTURE OUTLOOK:

The future goal of this Clinical Cooperation Unit is to develop and apply powerful tools to better stratify patients, analyze the microenvironment, and offer tailored treatments for individual patients. Further development of advanced technologies will allow an unparalleled insight into the makeup of the immunological pathomechanisms in serum samples, archival and fresh cancer specimens, as well as in new non-rodent explant models from patients. Extending immunological data sets by analyzing the mutational repertoire of tumors will improve our understanding of cancer at different levels.

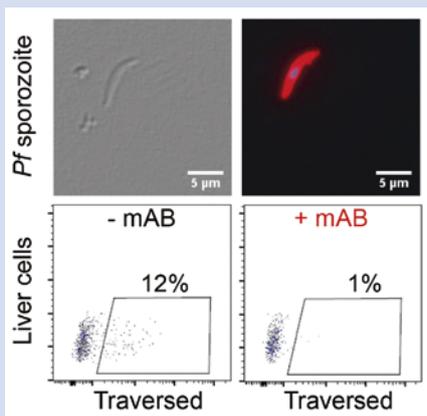
individual patients. Recently, Dirk Jäger's group could show in metastatic colorectal cancer, initially in preclinical human tissue models as well as a phase I clinical trial that CCR5 inhibition induced a dramatic change of the environment towards a more

SELECTED PUBLICATIONS:

- (1) Halama, N. et al. (2015). Tumoral immune cell exploitation in colorectal cancer liver metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. *Cancer Cell*, 29(4), 587-601.
- (2) Zörnig, I. et al. (2015). Prognostic Significance of Spontaneous Antibody Responses against Tumor-Associated Antigens in Malignant Melanoma Patients. *Int J Cancer*, 136(1), 138-151.
- (3) Klug, F. et al. (2013). Low-dose irradiation programs macrophage differentiation to an iNOS⁺/M1 phenotype that orchestrates effective T cell immunotherapy. *Cancer Cell*, 24(5), 589-602.
- (4) Halama, N. et al. (2011). Localization and density of immune cells in the invasive margin of human colorectal cancer liver metastases are prognostic for response to chemotherapy. *Cancer Res*, 71(17), 5670-5677.

Division B Cell Immunology

Antibodies are soluble B cell antigen receptors that efficiently help the immune system to combat invading pathogens. The majority of available vaccines rely on the induction of highly specific antibody responses. Antibodies are also widely used as biological therapeutics in the treatment of non-infectious diseases, including cancer. However, not all natural antibody responses are protective, and numerous attempts to develop antibody-based vaccines or therapies have been unsuccessful. Due to the enormous diversity of the B cell repertoire, antibody responses can be generated against nearly any structure, but our understanding of the cellular and molecular mechanisms underlying the



Qualitative assessment of a recombinant antibody (mAB) cloned from a primary human B cell to recognize sporozoites of the malaria parasite *Plasmodium falciparum* (Pf) (top) and to inhibit Pf traversal of human liver cells (bottom).

induction of protective vs. non-protective antibody responses is still limited. The Division of B Cell Immunology studies an-

tibody responses in health and disease. Direct measurements of the composition of the antigen receptor repertoire have long been limited due to the high degree of antibody gene diversity. In order to be able to perform in-depth analyses of the antibody repertoire, we have developed a platform for the high-throughput amplification and sequencing of antibody genes from single cells. The approach is fully compatible with the direct cloning and generation of recombinant monoclonal antibodies. The lab combines experimental tools and bioinformatics to perform molecular and functional analyses of antibody repertoires at the single cell level in mice and humans.

FUTURE OUTLOOK:

The B Cell Immunology Division studies the clonal evolution of B cell responses to controlled infection and vaccination in humans and murine animal models, respectively. The long-term goal of the Division is to determine how differences in the antibody repertoire are associated with protective vs. nonprotective antibody responses. Specifically, the research aims at

- (I) understanding how the antibody repertoire is shaped on a molecular and functional level by antigen-driven selection,
- (II) defining qualitative differences in the antibody repertoire in health and disease,
- (III) identifying protective antibodies and exploring their therapeutic potential in cancer and infectious diseases, and at
- (IV) developing strategies for the targeted manipulation of the B cell system in order to induce protective antibody responses.



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SELECTED PUBLICATIONS:

- (1) Imkeller K. et al. (2015). sciReptor: Analysis of single-cell level immunoglobulin repertoires. *BMC Bioinformatics*, 4; 17:67.
- (2) Murugan R. et al. (2015). Direct high-throughput amplification and sequencing of immunoglobulin genes from single human B cells. *Eur J Immunol*, 45(9), 2698-2700.
- (3) Muellenbeck M.F. et al. (2013). Atypical and classical memory B cells produce *Plasmodium falciparum* neutralizing antibodies. *J Exp Med*, 210(2), 389-399.
- (4) Benckert J. et al. (2011). The majority of intestinal IgA+ and IgG+ plasmablasts in the human gut are antigen-specific. *J Clin Invest*, 121(5), 1946-1955.



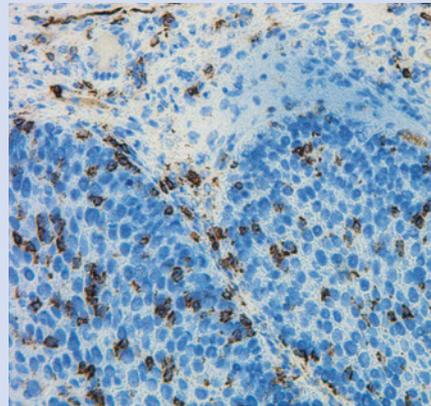
Boveri Junior Research Group Innate Immunity



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The innate immune response serves as the first line of immune defense against cancer and does not only directly lead to tumor cell destruction, but also to efficient subsequent activation of the adaptive immune system. The Boveri Group “Innate Immunity” investigates Natural Killer (NK) cells in cancer, with the goal of improving therapeutic anti-tumor strategies. NK cells not only kill tumor cells, but can also produce inflammatory cytokines and activate cells of the adaptive immune system. Their



CD56-positive NK cells (brown) infiltrating cervical carcinoma.

activation is determined by a delicate balance between signals delivered by activating and inhibitory receptors, most of which are specific for self-MHC class I. Many tumors lose expression of MHC class I molecules and escape from direct recognition by CD8+ T cells, but at the same time become highly susceptible to NK cell-mediated killing. In cancer patients, however, NK cell function is frequently severely impaired. To harness NK cells against tumors we are currently focused on I.) amplifying NK cell recognition of tumor cells by enhancing signals via activating receptors, II.) identifying and exploiting checkpoints of NK cell activation in tumor beds, III.) guiding high numbers of highly active NK cells into the tumor tissue, and IV.) generating long-lived NK cell populations with a sustained competence of effector function for NK cell adoptive transfer.

FUTURE OUTLOOK:

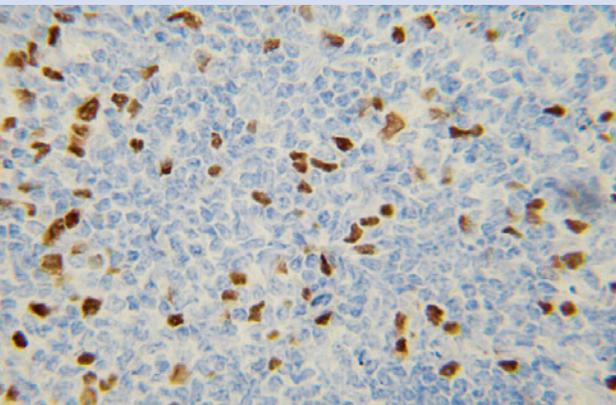
Our future projects will continue to develop strategies to harness NK cells against tumors. In particular, we will aim at identifying and targeting factors in the tumor microenvironment that counteract NK cell activation and cause NK cell exhaustion. In addition to NK cells, tissue resident NK related populations of innate lymphoid cells will be studied. These studies will potentially result in a novel class of NK cell checkpoint inhibitors. We will also explore the interaction of NK cells with adaptive cells during anti-tumor immune responses. Moreover, very recent evidence indicates that NK cells can remember previous exposure to antigens and cytokines, and the first evidence of NK cell memory formation in viral infection has been presented. Accordingly, in future projects we aim to exploit NK cell memory function for cancer therapy. Together, we will focus on gaining novel insight into mouse and human NK cell biology and the tumor microenvironment, building the basis for innovative strategies of immunotherapy against cancer.

SELECTED PUBLICATIONS:

- (1) Cerwenka A. et al. (2015). Natural killer cell memory in infection, inflammation and cancer. *Nat Rev Immunol*, 16(2), 112-123.
- (2) Rölle A. et al. (2014). IL-12 producing monocytes and HLA-E drive NKG2C+ NK cell expansion in HCMV infection. *J Clin Invest*, 124(12), 5305-5316.
- (3) Fiegler N. et al. (2013). Downregulation of the activating Nkp30 ligand B7-H6 by HDAC inhibitors impairs tumor cell recognition by NK cells. *Blood*, 122(5), 684-693.
- (4) Ni J. et al. (2012). Sustained effector function of IL-12/15/18 preactivated NK cells against established tumors. *J Exp Med*, 209(13), 2351-2365.

Helmholtz Junior Research Group Immune Tolerance

The immune system has evolved over time to defeat external threats such as bacteria and viruses as well as internal threats like cancer. The ability of the immune system to destroy such a diverse number of foreign invaders is a tribute to its flexibility. However, this comes at a price and the complexity could lead to severe autoimmune diseases. In addition, misguided or deregulated immune responses have recently been implicated in non-classical immune disorders such as



Treg distribution in a lymph node (brown: nuclear Foxp3 staining).

obesity. To minimize such collateral damage, powerful mechanisms of immune tolerance have evolved to keep unwanted immune responses at bay. Unfortunately, these mechanisms also inhibit immune responses against a growing tumor. Peripheral immune regulation, including tissue-specific immune control, is maintained by specialized regulatory cells (T lymphoid and myeloid). This includes regulatory T cells (Tregs) and tissue macrophages, both being key-players in the regulatory network.

It is now well accepted that deficiency or dysfunction of Tregs causes various severe immune disorders due to immune hyper-activation. Conversely, an increased number of Tregs in tumor-bearing individuals suppresses efficient anti-tumor immunity and is, thereby, often associated with poor prognosis. Cancer immunology is now one of the most exciting and prom-

ising frontiers in cancer research, and recent clinical trials have proven that immunotherapies driving to activate T cells can induce durable responses. In this sense, harnessing the potential of immune regulation is one of the most promising new approaches to control immune function and to treat cancer.

We are interested in fundamentally understanding and modulating regulatory immune cells. In this respect, future strategies to bring Treg- or macrophage-based therapies into clinical application will rely on a better understanding of the molecular pathways that control the differentiation and function of these cells. We have a special focus on tissue-resident Treg cells. We want to principally understand the unique features of Treg specialization in tissues and their function in organ homeostasis, a phenomenon that is hardly understood, but holds great promise for local, tissue-specific immunotherapies.



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SELECTED PUBLICATIONS:

- (1) Hettinger J. et al. (2013). Origin of monocytes and macrophages from a committed progenitor. *Nat Immunol*, 14(8), 821–830.
- (2) Cipolletta D. et al. (2012). PPAR- γ is a major driver of the accumulation and phenotype of adipose tissue Treg cells. *Nature*, 486(7404): 549–53.
- (3) Feuerer M. et al. (2009). How punctual ablation of Foxp3+ T cells unleashes an autoimmune lesion within the pancreas islets. *Immunity*, 31(4), 654–664.
- (4) Feuerer M. et al. (2009). Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med*, 15(8), 930–939.





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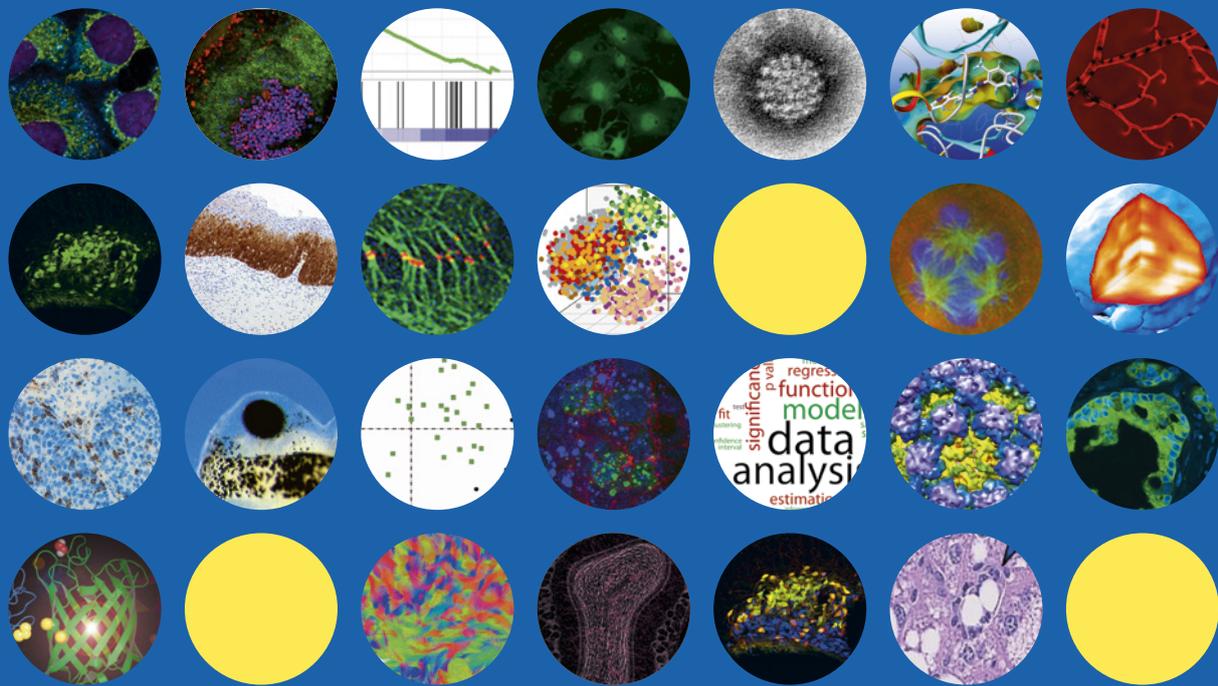
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