Annual Report 2015/2016

Deutsches Rheuma-Forschungszentrum Berlin
A Leibniz Institute

This Annual Report covers the research activities of the Deutsches Rheuma-Forschungszentrum Berlin (DRFZ) during the years 2015 and 2016.

The research activities of the DRFZ are made possible through financial support from the Senate Administration for Economy, Technology and Research of the Land Berlin, the Leibniz Association, the German Research Foundation (DFG), the Federal Ministry of Education and Research (BMBF), the European Commission, and through various other third parties, as mentioned in the text. Thanks are due to all of them.

Please visit our web site: www.drfz.de

Photographs: Poster session during the on-site visit of the Scientific Advisory Committee, 2016
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Organisational Chart

Programme Area

**Pathophysiology of Rheumatic Inflammation**
- Radbruch

**Regenerative Rheumatology**
- Radbruch (temporary)

**Epidemiology of Rheumatic Diseases**
- Zink

**Core Facilities and Technical Units**
- E. Flow Cytometry & Cell Sorting (FCCF)
- Chang, Kaiser
- Mass Cytometry (CyTOF)
- Mei, Grützkau
- Central Laboratory for Microscopy (Cinima)
- Hauser, Niesner
- Immune Monitoring Grützkau
- Ramin Labor for Molecular Rheumatology
- Grützkau, Häupl
- Animal Facility Schulz, Nöe
- Central Laboratory Hecker-Kia

Central Units

**DRFZ groups**
- Baumgrass
  - Signal Transduction
- Fillatreau (until 9.2015)
  - Immune Regulation
- Hamann
  - Experimental Rheumatology
- Kruglov (since 6.2016)
  - Chronic Inflammation
- Kubagawa
  - Humoral Immune Regulation
- Nedospasov
  - Inflammation Biology
- Radbruch
  - Cell Biology
- Tokoyoda
  - Osteoimmunology

**DRFZ group**
- Mashreghi (since 7.2016)
  - Therapeutic Gene Regulation

**Liaison group**
- Löhnig (since 9.2015)
  - Pfizer Laboratory of Osteoarthritis Research

**Liaison groups**
- Buttgereit
  - Glucocorticoids & Bioenergetics
- Diefenbach
  - Developmental Immunology
- Dörner
  - B Cell Memory
- Hauser
  - Immunodynamics
- Hiepe
  - Autoimmunology
- Hutloff
  - Chronic Immune Reactions
- Löhnig (until 6.2016)
  - Experimental Immunology
- Riemekasten (until 3.2015)
  - Cell Autoimmunity
- Niesner
  - Biophysical Analytics
- Romagnani
  - Innate immunity
- Scheffold
  - Cellular Immunology
- Sieper (until 3.2015)
  - Spondyloarthritis
- Worm
  - Allergology

**DRFZ groups**
- Listing (until 7.2017)
  - Statistics and clinical studies
- Minden
  - Paediatric Rheumatology
- Strangfeld
  - Pharmacoepidemiology
- Zink
  - Health Services Research

**Liaison group**
- Poddubnyy (since 4.2016)
  - Spondyloarthritides

**Liaison groups**
- Buttgereit
- Glucocorticoids & Bioenergetics
- Diefenbach
- Developmental Immunology
- Dörner
- B Cell Memory
- Hauser
- Immunodynamics
- Hiepe
- Autoimmunology
- Hutloff
- Chronic Immune Reactions
- Löhnig (until 6.2016)
- Experimental Immunology
- Riemekasten (until 3.2015)
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- Scheffold
- Cellular Immunology
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- Spondyloarthritis
- Worm
- Allergology

Cooperation Partners
- Charité - Rheumatology and Clinical Immunology, Burmester
- Charité - Gastroenterology, Infectiology and Rheumatology, Siegmund
- Charité - Dermatology, Venerology and Allergology, Blume-Peytavi (acting director)
- Charité - Institute of Microbiology and Hygiene, Diefenbach
- Charité - Cluster of Excellence NeuroCure, Schmitz
- Robert Koch Institute, Wieler

Infrastructute
- Administration, Scientific Coordination, IT Service, Public Relations, Lab Kitchen, Library, Reception Desk, Store

March 2017
as President of the Board of Trustees of the German Rheumatism Research Centre (Deutsches Rheuma-Forschungszentrum Berlin, DRFZ, a Leibniz Institute), it is a pleasure for me to welcome and to invite you to study the annual report for 2015/2016.

As laid down in the statutes of the DRFZ Foundation, one of the most important responsibilities of the Board of Trustees is to appoint the Scientific Director and the Administrative Director. I am delighted that both Andreas Radbruch and Petra Starke chose to extend their contracts beyond 2020. The recommendation by the Scientific Advisory Committee and the support of the responsible Senate Administration and the Charité-Universitätsmedizin Berlin were of substantial help in this matter. Maintaining continuity in the management of the DRFZ is a good basis for the upcoming evaluation by the Leibniz Association in 2018.

Another essential task of the Board of Trustees is to ensure the quality of the research. First and foremost, the directorate of the DRFZ bears this responsibility. The Board of Trustees must also approve decisions about permanent employment of the scientists. We thus guide and support our scientists in order to promote their careers.

Cutting-edge research on an international level is impossible without additional funding. We appreciate that the Federal German Government and the State Government of Berlin raised their financial support for the DRFZ by 2.2 million Euros per year, thus increasing the core budget to 9.5 million Euros. This allows us to attract private sponsors to support our basic research, in addition to the third-party funding from various public sources. Several private foundations have recently made possible new initiatives at the DRFZ. We are especially grateful for their trust and support.

In the past two years, three professorships orchestrated by the DRFZ have been established at the Charité: in 2015, Kirsten Minden was appointed endowed Professor for Health Service Research, supported by the Rheumastiftung. In Spring 2016, Max Löhning was appointed to an endowed Professorship for Osteoarthritis Research, funded by the Willy Robert Pitzer Foundation. Chiara Romagnani was appointed Professor for Innate Mechanisms of Chronic Inflammation at the Charité within the Heisenberg programme of the German Research Council (DFG) at the end of 2016. These joint professorships document the sound and close long-term cooperation between the DRFZ and the Charité. To this effect, the Board of Trustees is grateful to the authors of this cooperation: Andreas Radbruch, the Scientific Director of the DRFZ, and Gerd-Rüdiger Burmester, Director of the Medical Department, of Rheumatology and Clinical Immunology at the Charité. In establishing the concept of the Liaison Groups, they paved the way for the close integration of basic research and clinical applications.

In the name of the Board of Trustees, I thank all DRFZ staff for their dedication, shown in this annual report. Enjoy reading.

Yours, Traudl Herrhausen

Dear friends of the German Rheumatism Research Centre,
Dear friends of the German Rheumatism Research Centre,

as a clinical and scientific partner of the German Rheumatism Research Centre (DRFZ), I would like to express a warm welcome to all the readers of the Annual Report.

Rheumatic diseases comprise musculoskeletal and systemic autoimmune diseases (RMDs). These diseases are a massive burden for society; they are, to a high degree, responsible for work loss and premature invalidity. They are also one of the three leading reasons why a patient consults a general practitioner or a specialist. Despite major progress in the diagnosis and treatment of RMDs, such as cytokine directed approaches and cell depleting therapies, the need for new treatment is huge. The Department of Rheumatology and Clinical Immunology of the Charité, together with the Rheumatology Unit of the Campus Benjamin Franklin, joined forces with the DRFZ to meet these challenges. The collaboration among these institutions is based on the very successful interaction both in the clinic and the research laboratory.

Our primary focus lies on a patient centered approach for finding new strategies in innovative therapy. Molecular and cellular disease mechanisms lead to clinical manifestations that result in a comprehensive pattern of molecular and clinical profiles, which are essential for early diagnosis and the most appropriate treatment. Another important focus is the autoreactive immunological memory that drives chronic inflammation and maintains autoimmunity. This autoreactive memory is refractory to immunosuppressive therapies. So far, it can be only eliminated by unselective immunoablative regimens followed by autologous stem cell transplantation that may lead to long-term treatment-free remissions in refractory autoimmune diseases. Therefore, the research aims to identify targets for a selective depletion of autoreactive memory. Other fields of common research include bioenergetics of immune functions, glucocorticoid therapy, osteoporosis, and vasculitis.

What do we need to do to achieve our goals? Of course, the close collaboration between basic and clinical research must continue. The joint efforts of scientists and physicians, covering all aspects of rheumatology research at the Charité and the DRFZ, serve as an excellent model for such collaborations, working hard to achieve our common ultimate goal - research to benefit the patients.

Yours sincerely,

Gerd-Rüdiger Burmester
Our aim is simple: We want to cure rheumatic diseases

The DRFZ, a Leibniz Institute, is the only extra-academic research institution in Germany focusing on rheumatic diseases. It meets an urgent medical need. Although available treatment has improved over the last years, there is no cure for most of the rheumatic diseases yet. They still can cause considerable morbidity and mortality and most of the patients are on lifelong medication. Our aim is challenging: we want to develop curative therapies, to induce “therapy-free remission”. The last two years brought us a little bit closer to this aim, again.

17 of our research groups are working in the Programme Area Pathophysiology of Rheumatic Inflammation. They focus on the characteristic chronic inflammations that occur in joints, bones, muscles, tendons as well as in organs like the kidney, the skin and blood vessels. Most of the international research in rheumatology tries to understand how these inflammations develop and how they spread. We, in contrast, focus on the cells that are involved in driving the inflammation. These are mostly cells of the immune system that are actually supposed to fight pathogens. Apparently, in rheumatic diseases, some cells start to fight the own body and become pathogenic themselves, instead. Protective and pathogenic cells are constantly competing to gain control. Our goal is to identify the cell types involved and to describe their function in detail. This knowledge helps to develop new therapeutic approaches.

Here, we are pursuing two strategies at the same time: one is to strengthen the protective cells so that they are able to suppress the pathogenic ones. The other strategy is to target the pathogenic cells directly and selectively while sparing the protective cells. To date, such selective therapies are not available.

Lately, we have been able to identify major players. One is the pathogenic long-lived memory plasma cell which is targeted in new anti-rheumatic therapies. And even more recently, we have identified and characterised pathogenic innate lymphocytes and pathogenic T lymphocytes as targets of interest. The counterparts of these cells might also be an attractive starting point for novel therapies: Regulatory T and B cells which can keep pathogenic lymphocytes in check. Our studies show that, in order to survive, protective and pathogenic lymphocytes rely on support by cells of the surrounding tissue. We investigate these “survival niches” on the molecular level. Understanding the communication between lymphocytes and their environment gives us new options for therapies, not only for rheumatic diseases but also for other chronic inflammatory diseases like inflammation of the gut, the skin, or the nervous system.

We are pleased that two new research groups joined the Programme Area Pathophysiology of Rheumatic Inflammation in 2016: the group Chronic Inflammation, headed by junior scientist Andrey Kruglov, and a new liaison group Developmental and Mucosal Immunology, headed by Andreas Diefenbach who strengthens our research on innate immunology. This topic has so far been mainly addressed by Chiara Romagnani, who in 2016 was appointed to a professorship at the Charité within the Heisenberg programme of the German Research Council (DFG). Two group leaders left the DRFZ in 2015: Gabriela Riemekasten was appointed full professor and director of the Clinic for Rheumatology at the University Medicine in Lübeck. Simon Fillatreau was appointed to a professorship at the Institute Necker-Enfants Malades in Paris, France. Before he moved, he had been awarded a prestigious ERC Consolidator Grant, based on his research at the DRFZ.

Since 2015, the new Programme Area Regenerative Rheumatology complements our biomedical research in focusing on the chronic “wear and tear” joint disease osteoarthritis. This condition affects joint and bone tissue. However, what is happening on the molecular level is still enigmatic and no curative therapies are available. Furthermore, there are no therapeutic options to regenerate damaged or lost tissue. The research group Pitzer Lab Osteoarthritis Research headed by Max Löhning will meet the challenge to advance research on osteoarthritis and to improve treatments. This endowed professorship is supported by the Willy Robert Pitzer Foundation. Junior group leader Mir-Farzin Mashreghi
started a second research group in 2016 that will focus on therapeutic gene regulation.

The Programme Area Epidemiology of Rheumatic Diseases has the mission to discover determinants of the prognosis and outcome of rheumatic diseases, to understand the complex interaction of disease-related and treatment-related risks, to assess the adequacy of health care provision and to evaluate new therapeutic options. The overarching aim is to improve the quality and the outcomes of care and thus the quality of life of people with rheumatic diseases. One example of the clinical impact of our research is the RABBIT risk score calculator for infection which is available online. It helps physicians and patients to assess how different therapies impact on the risk of infection in order to make informed treatment decisions. Since 2015, the Rheumastiftung, a joint foundation of the German Society for Rheumatology and the patients’ organization Deutsche Rheuma-Liga, has been supporting an endowed professorship at the Charité. Kirsten Minden has been appointed to this position and head of the research group on Paediatric Rheumatology and Health Services Research. Since 2016, Denis Poddubnyy and his liaison group Spondyloarthritides complement the Programme Area, replacing the internationally reknown research group of Jochen Sieper, who retired. Together, four research groups cover the fields of pharmacoepidemiology, health services research in paediatric and adult rheumatology and spondyloarthritides. With the long-term cohort studies established over the years, the tremendous impact of disease activity on adverse outcomes such as growth retardation in children, anterior uveitis, myocardial infarction, stroke, infections, and mortality has been verified. Changes in patient profiles reflecting constantly improved outcomes over the last decades have been shown for adult and juvenile patients. However, the burden of disease is still high. The data are essential for health policy making and supply planning in Germany. This work would not be possible without the close collaboration with a network comprising more than 500 adult and paediatric rheumatologists all over Germany.

A hallmark of our work here at the DRFZ is the integration into the Charité medical campus. Not only do we share joint laboratories, we also have established 10 liaison research groups jointly supported by the Charité and the DRFZ. Clinical scientists of the Charité thus directly impact on the research at the DRFZ, and also translate new scientific concepts into novel diagnostic strategies and experimental therapies. Since July 2016, a new cornerstone of this collaboration is the Leibniz ScienceCampus for Chronic Inflammatory Diseases (C3ID). The Leibniz Association is funding this integrative research centre for 4 years, initially. We think that similar mechanisms drive inflammatory rheumatic diseases and chronic inflammatory diseases of the brain, the vasculature, the skin, the gut and other organs. Comparing the diseases and translating therapeutic concepts from one disease to another will offer unique chances to identify the drivers of inflammation in each disease and to tailor therapies to individual patients.

Our research would not be possible without the support of competitive research grants and private foundations, in particular the Willy Robert Pitzer Foundation and the Rheumastiftung. Our groups are part of national and international networks funded by the German Research Council (DFG), the Federal Ministry of Education and Research (BMBF), the Leibniz Association, the European Commission and the European Research Council.

In this annual report 2015/2016, we introduce some of these networks and we give insight into how research works at the DRFZ. And, needless to say, we describe our recent research highlights. Enjoy reading.

Andreas Radbruch and Petra Starke

Rheumatic and musculoskeletal diseases in Germany in a nutshell:
- More than 100 different rheumatic and musculoskeletal diseases are described.
- About 1.5 million adult persons and 20.000 children and young adolescents suffer from inflammatory rheumatic diseases such as rheumatoid arthritis, spondyloarthritides or vasculitis.
- An additional 5 million persons suffer from symptomatic, medically treated osteoarthritis.
- Biologic disease-modifying antirheumatic drugs that are used to treat inflammatory rheumatic diseases are on top of the health expenditures of the statutory health insurances.
- Rheumatic and musculoskeletal diseases are the main causes of permanent work disability and medical rehabilitation measures.
Research Highlights 2015-2016

How the immune system gains experience....

Memory CD8(+) T cells colocalize with IL-7(+) stromal cells in bone marrow and rest in terms of proliferation and transcription.


Research at the DRFZ has defined the bone marrow as the home of memory lymphocytes protecting us from systemic pathogens for a lifetime. Resting in terms of activation and proliferation, these memory lymphocytes are maintained individually in survival niches organized by mesenchymal stroma cells.

...and how a fatally experienced immune system drives chronic inflammation.

SIGLEC1 is a biomarker of disease activity and indicates extraglandular manifestation in primary Sjögren’s syndrome.


Siglec-1 as a surrogate marker for type I IFN responses in monocytes in a few microliters of peripheral blood outperforms gold standards in lupus diagnostics, such as autoantibody titres or the consumption of complement factors. Siglec-1 can be used for a longitudinal monitoring of disease activity to predict lupus flares. The quantitative measurement of Siglec-1 was included in the service portfolio of the common diagnostic lab “Labor Berlin” of the Charité.

The genes of memory T lymphocytes are epigenetically imprinted, reflecting their experiences and determining their functions in recall immune responses. The imprinting also shows that memory T cells from blood and bone keep different memories.

Individual T helper cells have a quantitative cytokine memory.


The transcription factor T-bet controls imprinting and expression of the gene for the proinflammatory cytokine interferon-g in memory T lymphocytes in a quantitative way, thus controlling the extent of inflammation.
T-bet expression by Th cells promotes type 1 inflammation but is dispensable for colitis.


In a murine model of inflammatory bowel disease, experienced T lymphocytes of the Th1 type are driving the chronic inflammation, mainly by expression of chemokines attracting proinflammatory M1 macrophages, which in turn attract more Th1 lymphocytes. The inflammation is initiated by bacteria of the microbiota. While some bacteria only can induce Th1 lymphocytes, others can activate all Th lymphocytes.

miR-148a is upregulated by Twist1 and T-bet and promotes Th1-cell survival by regulating the proapoptotic gene Bim.


The transcription factors T-bet and Twist1, the latter a hallmark of experienced T lymphocytes from chronically inflamed tissue, are essential for survival of these cells in inflammation. They induce expression of microRNA-148a, which downregulates expression of Bim, a critical death factor. The Twist1-microRNA-148a-Bim axis could be used to target selectively T lymphocytes driving chronic inflammation.

Therapeutic ablation of pathogenic cells driving chronic inflammation

The proteasome inhibitor bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus.


The multicentric clinical trial TAVAB (Therapy of Antibody-mediated Autoimmune Diseases by Bortezomib), reflects the collaboration of the DRFZ, the Charité and the University of Freiburg. It shows drastic efficacy of the drug Bortezomib in the treatment of SLE-patients. Bortezomib is a proteasome inhibitor, licensed for treatment of multiple myeloma, which targets plasma cells. In 12 SLE-patients, refractory to conventional treatment, and treated with Bortezomib, disease activity significantly declined and remained stable for 6 months on maintenance therapies. This trial defines autoantibody-secreting memory plasma cells as a novel, critical therapeutic target in rheumatic diseases driven by pathogenic autoantibodies, and proteasome inhibition as a therapy to eliminate plasma cells.

Selection and depletion of plasma cells based on the specificity of the secreted antibody.


This is the first approach to target plasma cells according to the specificity of the (auto)antibodies they secrete. Plasma cells are stained in vitro or in vivo with a conjugate of an anti-plasma cell antibody fragment and an antigen of interest. Plasma cells secreting antibodies specific for the antigen decorate themselves with their antibodies, and they are killed by complement-mediated lysis or antibody-dependent cellular cytotoxicity (ADCC).
Can we regenerate immunoregulation in chronic inflammation and allergy?

**Regulatory T Cell Specificity Directs Tolerance versus Allergy against Aeroantigens in Humans.**

With a new technology developed at the DRFZ, regulatory and effector T lymphocytes reacting to a given antigen can efficiently be isolated together from tissue or blood. In healthy persons regulatory and effector T lymphocytes see the same proteins of airborne antigens, in allergic persons they see different ones, allowing the effector T lymphocytes to trigger allergy.

**Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus.**

Based on the observation that effector T lymphocytes driving chronic inflammation do not express Interleukin-2, and thus do not activate regulatory T lymphocytes, subcutaneous low-dose IL-2 therapy was tried for patients with Systemic Lupus Erythematosus. 10 patients refractory to conventional treatment were included in the phase I/IIa study PRO-IMMUN. A remarkable expansion and activation of the Treg population was observed and disease activity decreased.
The impact of state-of-the-art therapies


Disease severity and burden of illness in systemic juvenile idiopathic arthritis have improved significantly between the years 2000 to 2013. The median disease activity (JADAS-10) declined from 7 in 2000 to 2 in 2013, while the proportion of patients with inactive disease increased from 19% to 41%. At 3-year follow-up, 72% of patients with systemic JIA had inactive disease, and 77% had no functional limitations.


Patients who experience a serious infection have a significantly lower risk to develop a subsequent sepsis or to die from the infection if they are exposed to biologic DMARDs at the time of the infection. This has the potential to change clinical practice.


The risk of lower gastrointestinal perforations is significantly increased in patients treated with the IL-6 inhibitor tocilizumab. Further, clinical presentation of this rare but dangerous complication is altered, making diagnosis difficult.


Current and even past use of oral contraceptives moderated patient-reported outcomes in inflammatory arthritis. Protective effects may be induced via central nervous pathways rather than through the suppression of peripheral inflammation.


Patients with Sjogren's syndrome who often have problems with their teeth can safely use dental implants.
Research Projects and Networks

**ERC Advanced Grant Protective and pathogenic immunological memory and its organisation by stroma cells (IMMEMO)**

Hidden in the bone marrow: Longlived memory cells are driving chronic inflammation. We found new targets to eliminate them. Immunological memory protects us from recurrent infections and provides the basis for the use of vaccines. But the dark side is its ability to drive chronic inflammatory diseases and allergies, some of which are refractory to conventional immunosuppressive therapies. Despite its relevance, little is known about how immunological memory is generated and maintained.

In the ERC-IMMEMO project, we investigated the organization and role of immunological memory both in protective immunity and in diseases mediated by the immune system.

We had originally described antibody-secreting memory plasma cells that reside and rest in “survival niches” in the bone marrow for very long times. We now extended this concept to memory T helper lymphocytes, cytotoxic memory lymphocytes and memory B lymphocytes. We identified prominent populations of bone marrow resident resting memory lymphocytes that most likely maintain lifelong memory to systemic antigens, like measles and mumps. We identified signals involved in homing of memory cell precursors to the bone marrow, their differentiation into memory cells and their survival as resting cells. This led to the entirely novel concept of maintenance of immunological memory by persistence of memory cells in dedicated stromal niches, resting in terms of activation, proliferation and mobility, and surviving as long as they receive survival signals from their environment.

The results of IMMEMO have thus fundamentally challenged the previous dogma that immunological memory is maintained by homeostatic proliferation of circulating memory lymphocytes and by memory lymphocytes residing in the epithelial tissues.

We have identified molecular adaptations of memory-effector T helper cells (Th1) to chronic antigen-exposure and inflammation that qualify as original and novel targets for the selective therapeutic ablation of proinflammatory Th1 cells.

Above all, we have identified autoreactive memory plasma cells as the driving force and unmet therapeutic challenge of refractory inflammatory autoimmune and allergic diseases. We have developed and translated into the clinics novel concepts for the selective depletion of these plasma cells. This has already resulted in experimental clinical trials breaking the refractoriness of therapy-refractory SLE patients. Our results have considerable clinical impact for the treatment of immune-diseases like allergies and chronic inflammatory diseases, most of which are still not curable today.

Output: 5 PhDs complete, 1 patent, >30 publications

Most relevant publications:
- Okhrimenko et al., 2014
- Sercan Alp et al., 2015
- Westendorf et al., 2014
- Haftmann et al., 2015
- Zehentmeier et al., 2014
- Taddeo et al., 2015

**ERC Advanced Grant IMMEO**

| PI’s at DRFZ | Radbruch, Chang |
| Funded by | European Research Council |
| Funding period | 2011-2016 |
| www.drfz.de/en/forschung/netzwerke/erc-advanced-grant-immemo/ |

**Be the Cure for Rheumatoid Arthritis (BTCure)**

BTCure is the largest European program aiming at the development of new therapies against RA. It brings together pharmaceutical and academic rheumatology research. A better understanding of the molecular mechanisms causing RA will help to develop new diagnostic tools. The goal is to identify new targets and biomarkers that will benefit patients in the future.

Our scientists focus on the exploration of the mechanisms responsible for the “pathogenic memory” of T- and B-cell subsets, most probably driving the chronicity of autoinflammatory rheumatic diseases. The main goal is to identify and characterize particular cell subsets responsible for a pathogenic immunological memory and those involved in the chronicification of rheumatic diseases by global molecular approaches. New biomarkers for monitoring and therapeutical targeting of these cell subsets will be identified, aiming to reset the dysregulated immunological tolerance. The DRFZ also plays an important role in the development of new techniques and “standard operating procedures” for cellular and translational medicine.

So far, major achievements of the DRFZ within BTCure are:
• Identification of an inhibitory micro RNA (miR-148a) that is involved in the longevity of pathological T helper lymphocytes (Haftmann et al., 2015)

• Development of a strategy to deplete autoantibody-secreting plasma cells (Taddeo et al., 2015)

• Development of a standardized procedure for a genome-wide characterization of effector T cell subsets (Westendorf et al., 2014)

• Identification of protective and pathogenic type I interferon gene signatures in viral infection and autoimmunity (Kyogoku et al., 2013)

• Characterization of a new biomarker (SIGLEC-1) for monitoring disease activity in SLE (Rose et al., 2013)

• Identification of disease-associated gene signatures in monocytes of RA and SLE patients that are potential biomarkers (Smiljanovic et al., 2012)

• Establishment of mass cytometry (CyTOF) to identify cellular biosensors for therapy monitoring and diagnostics in blood, synovial fluid and urine samples (Baumgart et al., 2017; Schulz et al., 2017).

BT Cure will be completed in March 2017, but a new successor IMI consortium has already been formed, called RTCure (Rheuma Tolerance for Cure), which focuses on the development of immune tolerance therapies for the treatment of rheumatic diseases. The RTCure application has been already successfully evaluated and will be probably start in May 2017. The DRFZ is heading a work package aiming to elucidate critical immune reactions driving chronic rheumatic inflammation. This knowledge will be used to define novel targets and pathways that can be addressed therapeutically to achieve immune tolerance. In addition, we will be responsible for the development of new tools, which will allow immune monitoring of tolerance therapies and identifying cellular signatures for companion prognostics.

B cells: Immunity and Autoimmunity – Collaborative Research Center 130

Since 2013 the German Research Council (DFG)-funded Transregional Collaborative Research Center (TRR) 130 "B cells: Immunity and Autoimmunity" brings together experts in the field of B cell immunology from 5 different places in Germany (Erlangen – Nuremberg, Berlin, Freiburg, Götttingen, Ulm). Research within this program focuses on a better understanding of the role of B lymphocytes during physiologic immune responses as well as chronic inflammatory pathologies.

The DRFZ contributes to this consortium with its expertise in the field of memory B lymphocytes, especially memory plasma cells, in biomedical and clinical context. Furthermore, it provides optical technology development, i.e. flow cytometry and intravital microscopy. The main achievements of the DRFZ groups are summarized below:

• In the project “Selective plasma cell targeting” an affinity matrix to selectively target pathogenic (auto) antigen-specific plasma cells was developed. The method has potential relevance in the treatment of systemic lupus erythematosus since in contrast to existing therapies such as bortezomib protective humoral memory remains unaffected (Taddeo et al 2016).

• In the project “Analysis of B cell dynamics in chronic neuroinflammation” we for the first time described that memory plasma cells are maintained in the central nervous system of mice suffering from Experimental Autoimmune Encephalo-myelitis, a mouse model of chronic multiple sclerosis. Moreover, the concept of tissue oxidative stress memory was defined, i.e. tissue oxidative stress persisting even in the recovery phase of the disease (Radbruch et al, 2015). Currently the link between possibly pathogenic long-lived plasma cells and oxidative distress in chronic neuroinflammation is investigated.

• In the project “Deciphering the role of cytokines produced by B lymphocytes” the effector role of cytokines produced by B lymphocytes was elucidated in various autoimmune pathologies.
• A key role of vitamin D in triggering distinct differentiation pathways of B lymphocytes determining pathogenic or regulatory functions in chronic inflammatory diseases was determined in the project “Regulation of B cell differentiation by vitamin A and D” (Hallau et al 2016 and Heine et al 2014).

• The central project “Dynamic multi-photon microscopy and microendoscopy – quantifying communication and function of B lymphocytes in vivo” develops new techniques and provides expertise in intravital microscopy. This allows the consortium to better study the role of B lymphocytes in their natural environment – the living organism (Mossakowski et al 2015 and Keller et al 2017).

Currently, the application for a second funding period is under review.

Molecular adaptations of pathogenic memory T helper cells in chronic inflammation - Ideenwettbewerb Rheumastiftung

The Rheumastiftung, funded by the German Society for Rheumatology and the patient organization Deutsche Rheuma-Liga, supports innovative scientific projects aiming at the development of novel therapeutical approaches for rheumatic diseases.

In this project we are investigating effector/memory T helper (Th) cells in the context of chronic inflammatory diseases. Th cells control and enhance immune reactions through the production of interleukins and chemokines, the molecules by which cells of the immune system communicate with each other and with cells of the tissue. They are essential for protective immunity but can also initiate and maintain chronic inflammation. Clinical trials aiming at the depletion of all Th cells in chronic inflammatory diseases were unsuccessful so far, as they did not distinguish between anti- and pro-inflammatory Th cells and were also accompanied by loss of protective immunity.

We want to understand how protective and anti-inflammatory memory T helper cells can be distinguished from memory T helper cells that are driving rheumatic diseases with the ultimate goal to selectively deplete pathogenic T helper memory cells. Previous studies from our group have indicated that Th cells involved in chronic inflammation, i.e. cells which have a history of chronic reactivation, undergo changes in gene expression, which promote their persistence and function in the inflamed tissue. In order to find biomarkers that are specifically expressed by pro-inflammatory and pathogenic memory Th cells, we are comparing the gene expression profiles of memory Th cells isolated directly from inflamed joints of patients with rheumatic diseases to those of protective memory Th cells isolated from the blood of healthy individuals. Candidate biomarkers identified in this comparison will be tested whether they qualify as targets to selectively deplete pro-inflammatory memory Th cells in preclinical models of chronic inflammation. By this approach we hope to develop new drugs to treat rheumatic diseases.
DEEP: The German epigenome programme

DEEP is the German contribution to the “International Human Epigenome Consortium” which aims at generating genome-wide epigenetic maps for numerous cell types. Although all cells in the human body share the identical genome, the cells differentiate into an array of diverse cell types expressing a distinct and characteristic set of genes.

Epigenetic signatures - based on modifications of the DNA and of DNA-binding proteins - structure the genome and license or restrict the transcriptional activity of genes. Analyzing the epigenetic landscape of a cell population reveals substantial information on its life-style and functional capabilities and highlights essential genes characteristic for a given phenotype. This allows insights into cellular physiology of unprecedented depth.

DEEP aims at supplying and interpreting up to 100 epigenomes of primary human cells relevant in metabolic and in inflammatory diseases. It brings together experts on the generation of epigenomic data, on bioinformatic analysis of large and complex data-sets and scientists and clinicians investigating metabolic diseases and inflammatory diseases. At the DRFZ, we focus on the epigenetic regulation of memory T helper (Th) lymphocytes under healthy conditions as well as in rheumatoid arthritis (RA).

The project has 3 main goals:

• How do epigenetics shape the development of CD4+ T memory cells under healthy conditions? What are critical regulators?
• How do effector/memory T cells alter to chronically activated cells in inflammatory diseases? What is the role of epigenetic imprinting?

• Which critical regulators under epigenetic control might identify novel therapeutic targets?

Together with partners at the Charité, we have developed standardized workflows for sample acquisition, cell sorting and sample processing and have delivered highly purified T cell populations from healthy individuals and rheumatic patients for the generation of the epigenomic datasets. We completed the analyses of the T memory fractions from healthy donors and made several exciting findings which we published in a recent study in IMMUNITY (Durek et al, IMMUNITY, 2016):

• CD4+ T memory circulating subsets are generated in a consecutive order TN-TCM-TEM-TEMRA while tissue-resident subsets branch-off early and display a specific epigenomic imprint
• Several known molecular players involved in memory differentiation are under epigenetic expression control
• The comparative analyses of the epigenomic signatures revealed new candidate genes which might be controlling T memory formation
• A progressive heterochromatin-associated loss of DNA methylation accompanies memory T cell formation, which might qualify as a cellular senescence marker.

In addition to this comprehensive study, we also utilized our datasets for the analysis of molecules which are involved in guiding the migration behavior of T cells (Pink et al, J. Immunol, 2016) and contributed to a DEEP-study analyzing the interesting class of bivalent promoters (Kinkley et al, Nature Communications, 2016).

Currently, we are analyzing the datasets of T cells from rheumatic patients, to find mechanisms and molecular players which might be involved in the alternative differentiation of memory T cells under chronic inflammatory conditions.

DEEP

PI's at DRFZ
Polansky, Hamann

Partners at DRFZ/Charité
Chang, Dong, Radbruch, Sawitzki, Siegmund, Sieper, Syrbe

Coordinator
Jörn Walter, Saarland University, Saarbrücken, Germany

Partner
19 academic and 3 industrial partners

Funded by
Federal Ministry of Education and Research (BMBF)

Funding period
2012 - 2017

www.deutsches-epigenom-programm.de
Sysinflame - A Systems Approach to Chronic Inflammatory Diseases

SysINFLAME is a national research network and part of the program “e:med”, founded to accelerate the system-oriented research of diseases and preventive measures by linking life and information sciences. SysINFLAME is focusing on chronic inflammatory disorders (CID), which comprise a group of indications with fast growing expenses due to rising incidence and large unmet need.

The exploration process for a systems-based medicine in CID has three main directions:

- **Disease manifestation:** The mechanism by which disease susceptibility precipitates health into a particular phenotype at a particular time point is unclear. Following high risk populations into manifestation events and describing molecular network events associated with the shift from sub-clinical to overt disease, will enable the design of early health maintenance or pre-emptive therapeutic interventions on an individual level.

- **Disease progression and comorbidities:** Multidimensional molecular data, biospecimen and high-resolution phenotype data will lead to a better understanding of regulatory networks and events that drive complicated disease behavior and comorbidities – and enable the clinicians to develop a better use of existing drugs.

- **Therapy Response:** In a time-resolved study the response to targeted anti-cytokine therapies will be analyzed. Understanding kinetics of transcriptional network changes associated with response and non-response to different biologics will generate insights into pathways that are modulated by the different compounds and define the quality of a molecular remission as an important future target. This will also provide a good starting point for developing sound biomarkers that may predict therapy response and steer clinical therapy.

The main contribution of the DRFZ is to provide high dimensional immuno-phenotyping data generated by multiparametric flow and mass cytometry (CyTOF) technologies on peripheral leukocytes responding to targeted therapies in chronic inflammatory conditions. This approach will provide an exceptional opportunity to provide new immunophenotypic data on anti-TNF-studies in rheumatoid arthritis, ankylosing spondylitis and Crohn’s disease, which offer a new dimension in systems-oriented clinical research.

The main achievements of the first funding period were (1) identification of a NK-cell subpopulation that correlates with responsiveness to TNF-α blockers in ankylosing spondylitis; (2) establishment of a mass cytometry antibody panel (CyTOF – OMIP) to analyze peripheral blood cells by 30 cellular parameters, (3) introduction of silver nanoparticles as high sensitivity probes in mass cytometry and (4) establishment of a protocol to stabilize whole blood samples for long-term storage at -80°C.

The first funding period of sysINFLAME has been finished at the end of 2016. Fortunately, the BMBF has agreed to support a second funding period, sysINFLAME phase 2, which has started in February of 2017.

### sysINFLAME

<table>
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<tr>
<th>PI’s at DRFZ</th>
<th>Radbruch, Grützkau</th>
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<tr>
<td>Coordinator</td>
<td>Stefan Schreiber, University Hospital Kiel</td>
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<td>Partner</td>
<td>7 academic partners</td>
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<td>Funded by</td>
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Systems biology of T helper cells: immunomodulation – not just immunosuppression

T cells are key mediators of immunity and tolerance. Dysregulation of T cell development and functions can lead to autoimmune diseases and allergies affecting a large part of the world’s population. A comprehensive understanding of T cell processes by applying a systems biology approach will help to develop more sophisticated pharmacological intervention strategies.

Our network developed out of an already existing nucleus for systems biology of immune cells and focuses on identification of decision-making processes in Th cells. Our aim is to identify hubs, autoregulatory loops, and limiting processes in Th cell activation and cell fate decision to discover potential sensitive targets for effective and specific manipulation of Th cells. We concentrate not only on immunosuppression, but also on immunomodulation of Th cells. This could provide an opportunity not only to block the immune system but in addition to interfere with its dysregulation in diseases. The ultimate goal of such interference will be to balance the homeostasis of the immune system.

In close cooperation four interdisciplinary work packages, containing at least one experimental work group and one theoretical work group each, examine transcription factor networks, digital decision making, microRNA (miRNA) pro-files and functional imprinting of gene expression during Th cell activation as well as differentiation.

So far we have obtained the following main results:

- Identification of T helper cell subtype-specific enhancers and super-enhancers (Fang et al. 2015)
- Discovery that miR-148a controls survival of Th1 cells by regulating Bim expression (Haftmann et al. EJI 2015). Identification of a quantitative IFN-γ memory in individual Th1 cells (Helmstetter et al. 2015)
- Development of a protocol for delivery of antagomirs into primary B and T-lymphocytes (Haftmann C et al. JIM 2015)
- Construction of a STAT6-associated Th2 network (Jargosch et al. 2016)
- Identification of T cell-mediated vascular rejection after kidney transplantation by the combined measurement of 5 specific microRNAs as biomarkers in blood of patients. (Matz et al. 2016)
- Discovery that binary IL-2 expression ensures a wide linear antigen response range in vivo (Fuhrmann et al. 2016)

Targeting neuromodulators expressed in proinflammatory

Musculoskeletal disorders are debilitating diseases drastically reducing the quality of life of affected patients. The pain these pathologies are causing can often not be managed adequately. The Neuroimmunology and Pain consortium (short: NEUROIMPA), being part of the “Forschungsnetz Musculoskeletale Erkrankungen”, aims at an understanding of how the interaction of cells of the immune system and the nervous system regulates the generation and maintenance of inflammation associated pain.

At the DRFZ, we are particularly focussing on the role of effector/memory Th lymphocytes in the generation and maintenance of pain in chronic inflammation. We have already collected evidence which demonstrate that different types of Th lymphocytes differ in their capacity to induce inflammatory pain. Based on transcriptome analyses we have identified several candidate molecules which could mediate the sensitisation of sensory neurons in inflammation. It is the aim of this project to better understand on a molecular level the interaction of Th lymphocytes with neurons in the inflamed tissue. We do this by interfering with the expression or action of candidate molecules and testing the consequence on pain. The results of this project and the consortium as a whole will lead to a better understanding of the mechanisms of inflammatory pain generation and the development of therapeutic strategies for pain management in inflammatory rheumatic diseases.
Proclair and Metarthros

The Federal Ministry of Education and Research has been funding eight research networks in Germany since 2015. The epidemiologists coordinate the research network PROCLAIR (linking patient-reported outcomes with claims data for health services research in rheumatology) and participate in METARTHROS (metabolic impact on joint and bone diseases). In PROCLAIR, persons insured in the BARMER GEK health insurance with claims diagnoses of rheumatoid arthritis, ankylosing spondylitis or osteoarthritis of the hips, knees or hands answered written questionnaires pertaining to burden of illness, health behaviour and current treatment. The questionnaire reports were linked to the claims data on treatment, co-morbidity, and health care utilization. First results show significant discrepancies in access to rheumatological care and in preventive measures such as vaccination depending on the region of residence and sociodemographic factors, as well as a high burden of disease. With collaborators from the universities of Oldenburg, Dresden and Berlin, socioeconomic aspects of ankylosing spondylitis and outcomes of joint surgery in osteoarthritis are currently investigated. In METARTHROS the impact of overweight and diabetes on the outcome of juvenile idiopathic arthritis and rheumatoid arthritis has been investigated with data from five different cohort studies.

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<th>PROCLAIR</th>
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<td>PI’s at DRFZ</td>
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<td>Coordinator</td>
<td>Angela Zink, DRFZ</td>
<td>Coordinator</td>
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<td>Partner</td>
<td>University Oldenburg, BARMER GEK, Charité, University Dresden</td>
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Leibniz Research Alliance “Bioactive compounds and Biotechnology”

Bioactive compounds are the basis of everyday medical treatments based on pharmaceuticals. While part of them are designed by chemists, the majority was rather designed by nature in the evolution of organisms that interact with their living environment. Thus, microbes or even higher organisms might be a rich source of bioactive compounds with effects on physiology, metabolism, the immune system, or with antibiotic action. The alliance strives to exploit this treasure for application in a variety of biomedical fields.

The research alliance bundles activities within the Leibniz Association focusing on:

- the collection of strains and biological materials as potential sources of novel compounds,
- the isolation, analysis, and chemical modification of bioactive compounds,
- the testing of potential fields of application as anti-infectives, anti-inflammatory or other medical uses, or application in health products, nutrition and agriculture.

Two groups of the DRFZ participate in the activities of the research alliance: AG Experimental Rheumatology (Hamann) and AG Immune Regulation (Fillatreau). Their aim is to find novel compounds that might modulate the immune system, notably those that down-regulate inflammation and up-regulate inhibitory pathways involving e.g. suppressive cytokines such as IL-10, IL-27, IL-35 or suppressive cells such as Tregs or Bregs.

The alliance will be instrumental both, in finding novel sources of potential immunomodulators and in developing first hits for potential drug candidates.

By this, the alliance is strengthening the translational activities within the DRFZ that aim at converting the cutting edge knowledge in immune regulation into novel tools for therapy of chronic inflammatory and autoimmune diseases.

Leibniz Research Alliance “Healthy Ageing”

Healthy ageing – living free of disease, functional decline, and disability as long as possible while remaining active until late in life – should be an achievable goal for most older people in modern industrialized societies. Nonetheless advanced age still means an increased likelihood of serious illness. Only very few enjoy full health and independence in the later phases of their lives. The increased percentage of senior citizens in the population also presents its own social and economic challenges. That is why we are searching for new, effective, and practical approaches to make the life of seniors as healthy as possible.

Who is the Alliance “Healthy Ageing”

To address the multiple challenges of healthy ageing and demographic change, the LRA Healthy Ageing was formed in 2013. The LRA consists of 20 Leibniz Institutes with scientists from many different disciplines: Biology, medicine, psychology, education science, sociology, and economics. The goal of the LRA is to illuminate the biological and social factors behind the ageing process and its effects in order to develop novel strategies for prevention and adaption capable of sustainable promoting healthy ageing. It sees itself as a competent contact for politics and media concerning all biomedical and social-economic questions of ageing and demographic change.

Research

The main topics are: Characterizing the biological basics of ageing, understanding intrinsic and extrinsic ageing, molecular understanding of age related diseases, cognitive dysfunctions in ageing and its social impacts, interdependency between socio-economic and psycho-social life circumstances and its impact on biological ageing.

Within the LRA, the DRFZ initiated the focus group “Immunology and Ageing”, bringing together all member institutes working in the field of immunology.

Leibniz Research Alliance “Healthy Ageing”

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<th>PI’s at DRFZ:</th>
<th>Gritzkau, Radbruch</th>
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<tr>
<td>Speakers</td>
<td>Prof. Dr. Jean Krutmann, Leibniz Research Institute for Environmental Medicine (IUF) and Prof. Dr. K. Lenhard Rudolph, Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI)</td>
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It is Friday noon and the seminar room at the DRFZ is filled to the very last seat. The last attendees rush through the door and grab their lunchboxes. Right on time the newly established interdisciplinary “Campus Inflammation Lecture” starts. The innovation of the new lecture format is, that a physician and a basic researcher give the lecture together by addressing chronic inflammatory diseases (CID) from a clinical and an experimental point of view. Physicians can register for CME points of the Berliner Ärztekammer. “We will come again!” the researchers note on the evaluation form which is collected at the end of the Campus Inflammation Lecture.

For nearly 30 years, the Leibniz-Institute DRFZ and the Charité–Universitätsmedizin Berlin have established an intimate cooperation for basic research on rheumatic diseases and its translation into clinical reality. This successful cooperation set the ground for the comprehensive center for Chronic Inflammatory Diseases, the Leibniz ScienceCampus Berlin.

**Scientific Challenge**
The ScienceCampus started in Summer 2016 and is based on the scientific understanding that highly similar cellular mechanisms drive inflammatory rheumatic diseases and CID of the brain, the vasculature, the skin, the gut, the pancreas, and other organs. Today, for most of these diseases no cure is available. In the ScienceCampus we compare these diseases in one integrative research center. We aim to translate therapeutic concepts from one disease to another and monitor their efficacy with cutting-edge biomedical technology. This offers unique chances to identify the drivers of inflammation in each disease, and define innovative ways to block them.

**Milestones**
Milestones of research are the identification of the cells and mechanisms controlling the chronicity of inflammation in inflammatory diseases of the gut and the skin, neuroinflammation, and inflammatory rheumatic diseases. Further goals are the development of biomarkers and biosignatures identifying the key players, and predicting the response to therapy for a tailored, individualized treatment based on a precision medicine approach. Beyond the scientific perspective, the ScienceCampus raises public awareness of CID as a major unmet medical entity and challenge of utmost public relevance, inflicting morbidity and mortality on 5 - 10% of the population.

**Structural Elements**
The Inflammation Lecture is only one of the many structural elements of the ScienceCampus. Others are e.g. the joint governance shared by the DRFZ and the Charité and joint appointments of principal investigators in Liaison Research Groups - a unique tool originally developed by the DRFZ and the Charité. Furthermore, joint grant-based research networks, joint educational programs, like the Leibniz Graduate School on Chronic Inflammatory Diseases and the Leibniz Postdoc College strengthen the scientific cooperation. Cutting-edge biomedical technology platforms and epidemiological expertise is located at the DRFZ. Several weekly scientific discussion clubs are organized under the umbrella of the Chronic Inflammation Forum.

The first international symposium of the ScienceCampus *Chronic Inflammation - one Disease, a thousand Manifestations* will take place on November 20-21, 2017 in Berlin.

**Comprehensive consultation hour of CID patients for their individualized treatment**
For physicians in practice and their patients the “Entzündungs-sprechstunde”, an original consultation platform for joint patient management by specialists from the Departments of Rheumatology, Gastroenterology, Neurology and Dermatology, was installed. Patients suffering from CID, especially those with multiple organ manifestations, are counseled jointly by clinical specialists of inflammatory diseases of the different organs, who on the background of the ScienceCampus, have developed a comprehensive scientific and clinical understanding of CID.

First general assembly of the Leibniz ScienceCampus Chronic Inflammation, September 2016, Berlin, DRFZ
**Introduction**

Scientists & Clinicians
- scientific discussion clubs
- education, lectures, talks
- access to core facilities
- gain of knowledge
- joint publications
- investigator driven trials
- access to patients’ material

Patients
- access to the comprehensive consultation hour „Entzündungssprechstunde“
- access to state of the art knowledge
- access to an interdisciplinary pool of experts
- increased chance of cure

Physicians in private practice
- discussion of problematic cases
- training in quality circles
- CME points
- contact to basic scientists and state of the art science
- gain of knowledge
- increased chance of a cure
- access to a pool of experts

Students, Graduates, PostDocs
- scientific discussion clubs
- work in a translational environment
- soft skills
- credit points for graduates
- graduate school for chronic inflammation
- PostDoc mentoring

**The strength of the ScienceCampus**
The benefit of the ScienceCampus is multi-layered: scientists and clinicians, students, graduates and PostDocs as well as patients and physicians profit from the tight interaction.

**We team up with our local partners**

Charité—Universitätsmedizin Berlin:
- Medizinische Klinik I, Medizinische Klinik für Gastroenterologie, Infektiologie, Rheumatologie
- Experimental and Clinical Research Center (ECRC) and Exzellenzcluster Neurocure
- Institut für Neuropathologie
- Charité Centrum Innere Medizin und Dermatologie, Klinik für Dermatologie, Venerologie und Allergologie
- Charité Centrum Innere Medizin mit Gastroenterologie und Nephrologie, Medizinische Klinik mit Schwerpunkt Nephrologie u. Internist. Intensivmedizin, CVK
- Charité Centrum Audiologie/Phoniatrie, Augen- und HNO-Heilkunde, CVK

Max Planck Institute for Infection Biology
2015-2016 at a Glance

2015

February
Simon Fillatreau is awarded an ERC consolidator grant

March
Gabriela Riemekasten is appointed director of the Clinic for Rheumatology in Lübeck
Joachim Sieper enters retirement

April
Habilitation Hildrun Haibel from the Sieper group

May
Kirsten Minden is appointed endowed Professor for “Health Services Research”

June
Retreat of the Leibniz Graduate School for Rheumatology
The Long Night of Science attracts more than 1,000 visitors

July
4th EULAR Advanced Epidemiology Course
Simon Fillatreau is awarded a research award of the GlaxoSmithKline Foundation
Habilitation Bimba Hoyer from the Hiepe group
Joachim Listing enters retirement

September
Andreas Radbruch is elected incoming president of the European Federation of Immunological Societies (EFIS, 2016-2018 and president 2019-2021)
Max Löhning is appointed endowed Professor for “Osteoarthritis Research”
Opening of the Program Area Regenerative Rheumatology
Simon Fillatreau is appointed group leader at the Institut Necker Enfants Malades, Paris
Bimba Hoyer is awarded the Rudolf-Schön-Preis of the German Society for Rheumatology
Advanced Cytometry Course at the 4th European Congress of Immunology, Vienna, Austria, H.-D. Chang, A. Grützkau, A. Scheffold

October
25th Annual Meeting of the German Society for Cytometry at the DRFZ and Charité, Hyun-Dong Chang, president
2nd Symposium of the German-Chinese Association of Molecular Medicine and Molecular Pharmacology

November
Andreas Radbruch is elected spokesman of the Leibniz Section C (Life Sciences)
Tobias Alexander and Bimba Hoyer win the „Ideenwettbewerb Rheumastiftung“

December
Albrecht Hasinger Lecture by Michael L. Dustin (Oxford, UK) and Award of Avrion Mitchison Prize for Immunology to Caroline von Spee-Mayer and Christian Neumann (both DRFZ)
Andreas Radbruch is appointed member of the Advisory Board of the Research Institute for Biomedical Sciences, Tokyo University, Japan

2016

January
Habilitation Paula Hoff from the Buttgereit group

February
International Meeting “Immunology and Microbiology - building a bridge between Paris and Berlin", organized by P. van Endert, S. Fillatreau (both Paris, FR), S.H.E. Kaufmann (MPI-IB Berlin) and A. Radbruch (DRFZ)
April
Denis Poddubnyy, appointed director of the Rheumatology Department at the Campus Benjamin Franklin, Charité, starts his liaison group "Spondyloarthritis"
Andrey Kruglov starts his junior research group "Chronic Inflammation" at the DRFZ
Opening of the Pitzer Lab "Osteoarthritis Research"

May
Chiara Romagnani appointed to a professorship at the Charité within the Heisenberg programme of the DFG

June
The Long Night of Science attracts 1,200 visitors

July
Mir-Farzin Mashreghi starts his junior research group "Therapeutic Gene-regulation"
The Leibniz Association funds the Leibniz Science Campus for Chronic Inflammation
Angela Zink awarded the Carol-Nachman-Medaille for Rheumatology of Wiesbaden, Germany
Retreat of the Leibniz Graduate School for Rheumatology

September
Visit of 22 international Postdocs "Postdoc-NeT 2016", organized by the German Academic Exchange Service (DAAD)

October
26th Annual Meeting of the German Society for Cytometry at the DRFZ and Charité, Hyun-Dong Chang, president
Annual on-site visit of the Scientific Advisory Board

November
Andreas Diefenbach starts his liaison group "Developmental and Mucosal Immunology"
International Symposium: "New Scales: Immune and Neuronal Diversity and Disease" with 200 participants

December
Albrecht Hasinger Lecture by Mary Goldring (New York, US) and Award of Avrion Mitchison Prize for Rheumatology to Corinna Wehmeyer (Birmingham, UK)
2015/2016 at a Glance

- 224 publications in total
  - 165 peer reviewed
  - 6 book chapters
  - 36 reviews
  - 82 open access
  - 174 joint publications with Charité
  - 56 first authorships
  - 63 last authorships

Qualifications 2015 vs 2016:

- Bachelor
  - 2015: 5
  - 2016: 4
- Magister/Diploma/Master
  - 2015: 11
  - 2016: 10
- Dr. med. (MD)
  - 2015: 8
  - 2016: 6
- Dr. rer. med.
  - 2015: 0
  - 2016: 1
- Dr. rer. nat. (PhD)
  - 2015: 17
  - 2016: 10
- Habilitation
  - 2015: 2
  - 2016: 1
Publications 2016

- 48 reviews
- 167 peer reviewed
- 20 others
- 68 open access
- 3 book chapters

First authorships: 51
Last authorships: 62

Presentations

Basic funding (in million €)
- 2015: 9.1
- 2016: 9.4

Third party funds DRFZ groups (in million €)
- 2015: 7.8
- 2016: 8.0

Third party funds Liaison groups (in million €)
- 2015: 3.1
- 2016: 3.9
Working at the DRFZ

We are...

...international:
About 15% of the scientists come from abroad, from 18 different countries.

...interdisciplinary:
Physicians, biologists, chemists, physicists, veterinarians, sociologists, bioinformaticians and mathematicians join their expertise at the DRFZ.

...interactive:
In 13 different scientific discussion clubs and seminar series the scientists discuss their work.

Promotion of Young Researchers
Since 2013, we run the Leibniz Graduate School on Rheumatology (LGRh), offering translational training for MD and PhD students.

Excellent work life balance
- flexible working hours
- virtual desktops for home office
- support of parental leave
- streams of selected talks available online
- 3 places in the nearby INA. Kindergarten
- in 2016, the DRFZ has received the Total E-Quality award for the third time

Networking with the German Society of Immunology
The DRFZ is a certified training center of the German Society for Immunology (DGfI). It is involved in organizing the DGfI Academy on Immunology with its Spring School, Autumn School and Translational Immunology School. (See: www.dgfi.org)

Networking with the European League against Rheumatism
eular
Together with the Division of Rheumatology and Clinical Immunology of the Charité, the DRFZ is one out of 25 European Centers of Excellence in Rheumatology. DRFZ group leaders participate in 8 Task Forces of EULAR and two FOREUM calls.

Photograph: U. Hoffmann, LGRh Retreat 2016
Public Outreach

Public events
Regularly, the DRFZ organizes events for the public, in particular for patients. During the Berlin “Long Night of Science”, taking place every year in Summer, about 1,000 guests visit the DRFZ and communicate with the researchers. With hands-on experiments and a guided tour they get an insight into the research at the DRFZ. Our partners from the Charité and rheumatology departments of other local clinics as well as patient organisations also contribute with information and activities on rheumatic diseases. About 80 different scientific institutions all over Berlin participate in this event.

Every year in Autumn, the DRFZ opens its doors to patients on the “World Arthritis Day”. This event is jointly organised with the Charité and the Rheuma-Liga Berlin.

On the “Day of Immunology” in April, we invite school classes to our labs. The children get insight in the world of science and are doing some hands-on experiments themselves.

Publishing in journals for physicians and patients
For many years, Andreas Radbruch has been a co-editor of the Zeitschrift für Rheumatologie, a journal for physicians. The section Forschung aktuell updates on new findings in basic and clinical research.

In addition, Andreas Radbruch edits a section in Mobil, a journal for patients published by the Deutsche Rheuma-Liga. Since 2014, this section has been informing more than 200,000 readers about research highlights and new therapeutic concepts.

Media Coverage
Activities and research results of the DRFZ are frequently covered in the media, with a recorded average of about 300 hits a year.
Organisation

The DRFZ

- was founded 1988 as a foundation of the civil law
- is a member of the Leibniz Association since 2009 (www.leibniz-gemeinschaft.de)
- has 207 employees (163 scientists and 44 infrastructure staff)
- has 6 endowed professorships with the Charité:
  - Andreas Radbruch, Experimental Rheumatology (1998)
  - Angela Zink, Epidemiology of Rheumatic Diseases (2003)
  - Falk Hiepe, Rheumatology (1997)
  - Anja Hauser, In Vivo Imaging and Immuno Dynamics (2012)
  - Kirsten Minden, Health Services Research (2015), funded by the Rheumastiftung
  - Max Löhning, Osteoarthritis Research (2015), funded by the Willy Robert Pitzer Foundation

DRFZ Bodies

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The Board of Trustees supervises the management of the DRFZ and ensures the maintenance of research quality. It determines the framework concerning the realisation of the foundation’s purpose.

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The principal task of the Scientific Advisory Committee (SAC) is to advise the Board of Trustees regarding scientific questions. The SAC is made up of internationally renowned scientists acknowledged for their research in the field of rheumatism and in the related basic research.

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Regulation of cytokine expression in different T cell subsets

T lymphocytes are a crucial part of the adaptive immune system and play an important role in pathogen defense. However, their malfunction is related to various autoimmune and allergic disorders.

Our group is investigating molecular mechanisms of lymphocyte activation and activation-induced cell fate decisions to understand the role of T cells in chronic inflammatory diseases (such as Rheumatoid Arthritis and Systemic Lupus Erythematosus). We focus on the regulation of cytokine expression in different T cell subsets, digital (all-or-none responses as opposed to analog/graded) decision-making, and transcription factor networks under physiological and pathological conditions.

In order to identify so far unknown or to characterize already known hubs playing a role in chronic inflammation we
- characterized IL-2 action in vivo,
- identified NFAT-associated proteins by SILAC-based mass spectrometry,
- created STAT6- and STAT4-associated TF-networks,
- discovered T helper cell subtype-specific enhancers and super-enhancers, and
- analyzed the interplay of cytokine expression in disease-associated Th cell subpopulations.

Furthermore, we are working on novel approaches for analysis and visualization of multi-parametric flow cytometry data.

Our findings will contribute to a better understanding of physiological and pathophysiological processes of Th cell subsets. Moreover, the characterization of decisive steps and identification of critical molecules during Th cell activation as well as discovery of certain T cell subsets with a specific cytokine pattern are of potential value for diagnostic/ prognostic purposes and therapeutic manipulations in autoimmune and allergic diseases.
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SELECTED PUBLICATIONS


How do cells adapt to oxygen deficiency and a lack of nutrients in the inflamed tissue?

Glucocorticoids and Bioenergetics

The bioenergetic balance of cellular systems determines their survival, development and functionality. In acute and chronic inflammation (e.g. rheumatoid arthritis: RA), as well as in injuries to the blood vessel system (e.g. fractures), the cellular need for nutrient and oxygen may exceed the supply. This results in local nutrient and oxygen deficiency (hypoxia).

To maintain their functions, immune cells, mesenchymal stem cells (MSC) and endothelial cells that accumulate in inflammatory regions or in the fracture hematoma must own appropriate adaptation mechanisms. Important elements of cellular adaptation to hypoxia are the isoforms of the transcription factor hypoxia-inducible factor (HIF). HIF regulates cellular functionality and differentiation and plays a critical role in inflammatory and regenerative processes.

Our research focuses on cellular adaptation mechanisms during inflammation. We aim to investigate the influence of hypoxia as a key factor in acute and chronic inflammation. Furthermore, we are interested in the cellular mechanisms of the inflammatory phase of tissue regeneration and their potential manipulation by therapeutics such as glucocorticoids and DMARDs (disease-modifying anti-rheumatic drugs).

We demonstrated that growth and energy state of human CD4+ T helper cells are influenced differently depending on the degree of hypoxia. Physiological O2-deficiency does not influence the growth of T helper cells. However, pathophysiological hypoxia leads to a disruption of IL2-mediated signaling and the intracellular signaling pathways mediated by oxygen radicals.

In addition, we demonstrated that IL-6 receptor blockade in human neutrophils causes different cellular responses depending on the availability of cellular oxygen. Neutrophils show a significantly higher activity in the uptake of pathogens under pathophysiological hypoxia than under optimal oxygen availability. A blockade of the IL-6 receptor inhibits this activity under hypoxia but not under normal levels of oxygen. This demonstrates that (I) blocking the IL-6 receptor is especially efficient in chronic inflammation which is usually characterized by hypoxia and (II) the mode of action of anti-inflammatory drugs depends on the cellular microenvironment.

Adaptation mechanisms of immune cells to a change in the inflammatory microenvironment differ from species to species. In particular, animal models do not reflect the exact mechanisms of inflammatory joint disease and of fracture healing in humans. Thus, an extrapolation of data from animal models to the human is hardly possible. We are developing human in vitro 3D models for musculoskeletal research. This allows us to better understand the pathogenesis of inflammatory joint disease. Replacing research on animal models with human in vitro models avoids painful interventions and stress on animals and may even lead to a better understanding of the mechanism of disease in humans.
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SELECTED PUBLICATIONS


Innovative insights into B Cell Memory with impact on protective and autoreactive immunity

Our group has a focus on basic principles of the induction and maintenance of human memory B cells (BC) and plasma cells (PC). In particular, the humoral memory plays an important role in long-term protection against pathogens, but unfortunately also in the pathology of autoimmune diseases. We believe that the autoimmune BC memory represents a key challenge for successful therapeutic immunotargeting. Understanding the differential processes that ultimately lead to the induction and maintenance of protective versus autoreactive immunoglobulins is a central topic of our research. Therefore we address three main areas:

1) basic mechanisms in the induction and maintenance of protective, antigen-specific memory BC upon primary and secondary vaccination,
2) maintenance of distinct memory PC subsets in human bone marrow and
3) specific characteristics of memory BC in different autoimmune disorders, such as rheumatoid arthritis, primary Sjögren’s syndrome and systemic lupus erythematosus.

First, kinetics and characteristics of memory BC differentiation into PC in human are studied during active disease, upon immunotherapy and immunizations. In these studies we apply antigen-specific detection systems using tetanus toxoid as well as autoantigens. The identification and isolation of specific BC permit comprehensive phenotypic, molecular and functional studies. A second line of research comprises studies of various PC subsets residing in the bone marrow and extending previous findings of CD19 positive and negative human bone marrow PC.

On preclinical grounds (in vitro activity and mechanism of action) and during phase 1-3 of clinical development, we study a number of monoclonal antibodies considered for therapeutic use. We analyze in detail the impact of certain therapeutics on the B cell receptor (BCR) signaling network as well as the general differences of BCR related kinases in health and disease with a special focus on the equilibrium of kinases and phosphatases. Our current hypothesis is that disturbances of signaling pathways and interrelated survival mechanisms are key to understand abnormalities in autoimmunity. The modulation of BCR responses will help us to better understand how memory BC are regulated during steady state or after activation.

We aim to get further insights into the differential regulation and development of protective versus autoimmune memory BC and PC to clear the way for the development of innovative and selective therapeutics targeting BC functions.

Keywords
- antigen-specific memory B cells,
- human plasma cells,
- bone marrow,
- immunization,
- autoimmunity,
- SLE,
- BCR signaling

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Selected publications


Epigenetics, molecular regulation of T cell differentiation, and novel concepts for the therapy of autoimmune/chronic inflammatory diseases

Our group is focusing on two areas: I) epigenetics and II) immune regulation/translation.

I) Here we study the epigenetic impact on CD4+ T cell differentiation in health and under chronic inflammatory conditions, to understand how long-term shifts in the phenotype and functional profile of T cells are maintained on the molecular level.

Our work has documented the impact of epigenetic regulation for the stable expression of the master transcription factor Foxp3 in regulatory T cells and for several homing-related molecules. More recently, as members of the DEEP consortium, we established full epigenomes of human T cells and studied the role of epigenetics for T memory cell differentiation. This work:

• unravelled a major loss of genome-wide DNA methylation with memory development;
• supported a linear model of differentiation in circulating T cells in the order naïve -> Tcm (T central memory cells) -> Tem (T effector memory re-expressing cells) -> Temra (T effector memory re-expressing CD45RA cells),
• highlighted various known or novel transcription factors regulating the memory differentiation process and which are under epigenetic expression control.

We expect that this research will help to better understand the features of T cells fuelling chronic inflammation. Moreover, it might lead to the identification of novel targets and tools for the therapeutic modulation of T cells in inflammatory diseases.

II) Here we tested several approaches to strengthen self-tolerance: a) by vaccination with chemically modified peptides and, b) by vaccination with peptides coupled to a transporter module targeting it into the (tolerogenic) compartment of mucosal tissues. In addition, we searched by high throughput screening for novel compounds able to induce inhibitory cytokines of the immune system such as IL-27, IL-35, IL-10, or to induce Foxp3.

Ad a) We found that coupling of peptides to synthetic carriers (PEG) or nanobeads is enhancing their tolerogenic effect and is able to inhibit the development of experimental autoimmune encephalomyelitis, a murine model for Multiple Sclerosis; yet application at the peak of disease was so far not effective.

Ad b) Use of a transporter peptide improved the tolerogenic effect of local vaccination, but in total, the mucosal pathway was not as tolerogenic as predicted.

Our screenings for compounds targeting inhibitory pathways delivered a number of candidates that increase EB13 (a component of the inhibitory cytokines IL-27 and IL-35) and simultaneously down-regulated effector cytokines. In addition, one substance was found that induces Foxp3 in mouse T cells. In cooperation with S. Fillatreau, several hits were found that induced IL-10 in B cells.

Thus, exploiting the portfolio of natural tolerance and inhibitory mechanisms of the immune system might provide novel approaches for the therapy of autoimmunity and chronic inflammation in diseases such as rheumatoid arthritis.
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SELECTED PUBLICATIONS

We are interested in determining how immune cells behave in the tissue context, how they interact with other immune cells as well as with various cell types in the tissues they reside in, and how that shapes immune responses. We aim to dissect how the behavior of various immune cell subsets in various tissues affects processes such as chronic inflammation, which occurs in the course of rheumatic diseases. One focus of our lab is analyzing the biology of long lived plasma cells. As the producers of antibodies, they play a crucial role in immunological memory, securing life-long protective immune responses. The longevity of plasma cells depends on their microenvironment, which provides survival factors in tissue niches of the bone marrow. We could identify bone marrow stromal cells acting as stable components of these niches. They attract plasma cells to the bone marrow niches by secretion of CXCL12. The numbers of these stromal niche organizers remain stable during the course of an immune response, thereby limiting the number of available niches to the plasma cells, which migrate from secondary lymphoid organs to the bone marrow to become long lived. In contrast, eosinophils, which provide the survival factor APRIL to plasma cells, are transient niche inhabitants. In order to further characterize the cellular dynamics in the bone marrow niches, we have recently developed a microendoscopic implant which allows us to analyze cellular migration and interactions in the bone marrow over months by intravital microscopy.

Furthermore, we could show that plasma cells in the small intestine can also become long lived, and that the microenvironment of the gut provides similar survival signals to them as the bone marrow, although the cell types that produce these factors differ between tissues. Interestingly, plasma blasts generated in mucosal immune responses can also contribute to the long-lived plasma cell pool in the bone marrow.

Besides their crucial functions in protective immunity, long lived plasma cells also contribute to autoimmune diseases by secreting autoreactive antibodies that can mediate tissue destruction and the perpetuation of chronic inflammation. Using experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis, we recently demonstrated that the chronically inflamed central nervous system also provides niches for long lived plasma cells. In line with that, non-proliferative plasma cells could be found in biopsies derived from the CNS of multiple sclerosis patients. Hence, under the conditions of chronic inflammation, niches for immune memory can form even in organs that are void of immune cells in healthy individuals. A better understanding of the mechanisms underlying the formation and maintenance of those niches is crucial to therapeutically target pathogenic plasma cells.
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SELECTED PUBLICATIONS


Our research group is fundamentally involved in analyzing the mechanisms which contribute to and help maintain severe autoimmune diseases, in order to develop new therapeutic concepts.

Our main focus is on the role of long-lived autoreactive plasma cells in autoimmune diseases. Long-lived plasma cells reside in niches in the bone marrow and inflamed tissues, where they are resistant to immunosuppressive/cytotoxic drugs or therapies targeting B cells. In collaboration with the research group from Andreas Radbruch, we look for new therapeutic strategies targeting the autoreactive memory. We introduced the proteasome inhibitor bortezomib that depletes plasma cells in the treatment of refractory autoimmune diseases. We also learned that selective plasma cell depletion has to be combined with a therapy targeting the plasma cell precursors. Since all these therapies unselectively deplete plasma cells regardless whether they secrete protective or pathogenic antibodies, we developed an affinity matrix technology for antigen-specific plasma cell depletion. Very recently, we could show for the first time that long-lived memory plasma cells can be depleted in an antigen-specific manner using this technology in a murine model.

Together with the Unit for Bone Marrow Transplantation (Renate Arnold) at the Charité – Universitätsmedizin Berlin and the research group of Andreas Thiel (BCRT), we demonstrated that the autoreactive memory could be eliminated by immunoaablation followed by autologous hematopoietic stem cell transplantation, in patients with severe autoimmune diseases that are refractory to conventional immunosuppression. In most cases this provided the fundament for the subsequent regeneration of an intact immune system. In some patients, however, the disease relapsed or secondary autoimmune disorders occurred. We investigate the reasons for this in a controlled clinical trial in systemic lupus erythematosus (SLE).

In another project, we study the role of dendritic cells in SLE. These cells, in their function as antigen-presenting cells and producers of cytokines, play a significant role in the pathogenesis of SLE. As they are a potential target in the development of new therapies, their characterization is of major relevance.

Several cytokines are involved in the pathogenesis of SLE and other systemic autoimmune diseases. In past and future clinical trials, we have studied biologics selectively targeting different cytokines or cells (e.g. BAFF/BLys, APRIL, type I interferon, IL-10, B cells, PDC, co-stimulatory molecules) . We expect that these different therapeutic approaches will allow us to develop personalized therapies. To identify the optimal therapeutic target and/or characterize disease activity adequate biomarkers are required. We have already identified several serologic and cellular biomarkers (autoantibodies, Siglec1 expression on monocytes, B and T cell subpopulations). Their relevance for the aforementioned aims is being studied in the clinic.
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SELECTED PUBLICATIONS


Successful interaction of antigen-specific T and B cells is the key for an effective adaptive immune response. T follicular helper (Tfh) cells are the T cell subset providing help for B cells during the germinal center reaction. They are the prerequisite for the generation of high affinity memory B cells and long-lived plasma cells. Therefore, manipulation of the Tfh response is of particular clinical interest to either promote the generation of protective antibodies during vaccination or to eliminate harmful antibodies in autoimmune diseases or allergy.

Our group is interested in the generation of Tfh cells, their maintenance, and dysregulated germinal center responses resulting in autoimmunity. One focus of our group are costimulatory receptors which are important for fine-tuning of the immune response. Absence of costimulation can result in severe immunodeficiency, whereas an overexpression of costimulatory receptors is often associated with exaggerated immune responses, resulting in autoimmunity or allergy (Grimbacher et al, Nat Immunol 2003; Hutloff et al, Arthr Rheum 2004). Consequently, costimulatory receptors are an attractive target for therapeutic intervention. Blocking reagents against various costimulatory receptors are currently in clinical trials or already in use.

We recently demonstrated that the costimulatory molecule ICOS, which was originally identified in our group (Hutloff et al, Nature 1999), has a very specific role for maintenance of Tfh cells in late phases of the germinal center response. Blockade of ICOS signaling leads to upregulation of the transcription factor KLF2 in Tfh cells. Via regulation of several migratory receptors, this results in relocation of Tfh cells from the B cell back to the T cell zone and subsequent loss of the Tfh phenotype (Weber et al, J Exp Med 2015). This mechanism exemplifies the importance of migratory receptors and illustrates that location can dictate cell fate.

Another focus of our group is T/B interaction outside lymphoid tissues. Lymphocytic infiltrates are frequently found in inflamed tissues where they substantially contribute to tissue destruction. Using a mouse airway inflammation model we showed that a population of tissue-resident Tfh-like cells drives the differentiation of antigen-specific B cells into germinal center like cells and plasma cells, thereby contributing to the local generation of pathogenic antibodies (Vu Van et al, Nat Commun 2016). Our findings that the majority of antigen-specific T and B cells does not reside in secondary lymphoid organs but the inflamed tissue and that active T/B cooperation can also take place in non-organized tissue infiltrates has important implications for the treatment of autoimmune diseases.
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**SELECTED PUBLICATIONS**


Interaction of immune system and microbiota in chronic inflammation

Dr. rer. nat. Andrey Kruglov

Chronic inflammation in humans is strongly associated with dramatic changes in microbiota in various compartments. There is a clear indication that rheumatic diseases, such as rheumatoid arthritis and autoimmune colitis, can be quantitatively and qualitatively influenced by commensal microorganisms, but mechanistic aspects of microbiota contribution to the disease development, pathogenesis and chronicity remain to be determined. We are dissecting interactions of microbiota and the immune system in the development of chronic rheumatic diseases.

Tissue repair during chronic immune reactions is one of the key aspects of successful recovery from disease. We have uncovered that TNF, one of the key proinflammatory mediators, blocks tissue repair via enhancement of IL-22BP expression by epithelial cells during autoimmune colitis. Increase in IL-22BP expression by TNF downregulates IL-22 biological activity and, thereby, dampens epithelial cell proliferation, microbial peptide synthesis and alters microbiota composition during chronic intestinal inflammation.

One of the mechanisms of immune-mediated control of microbiota composition is the production of microbiota-specific IgA antibodies by intestinal plasma B cells.

The population of IgA producing plasma cells in the intestine is heterogeneous with respect to the expression of surface molecule. However, there is lack of data describing the relation of these cell subsets to each other and their specificity. We took advantage of the differential expression of CD11b, Ly6C and Ly6G molecules on IgA producing B cells in the lamina propria. We have found that these molecules are upregulated after homing to the gut. Subsequent *in vivo* and *in vitro* analysis revealed that Ly6C-expressing IgA cells seemed to represent a terminal stage of CD45+IgA+ plasma cells in the small intestine. Finally, IgA antibodies produced by Ly6C- and Ly6C+ plasma cell subsets showed distinct recognition pattern of Gram-positive and Gram-negative commensal bacteria. Altogether, our data suggest the presence of distinct stages of IgA producing cells in the lamina propria, their developmental pathways and specificity towards various microbial species.

Moreover, we have generated a set of microbiota-specific IgA antibodies specific to distinct microbiota species. These antibodies can be further used for selective targeting of single microbiota species during rheumatic diseases. As an example, we have tested IgA antibody against Lachnospiraceae, bacteria that are increased in the intestine during chronic rheumatic diseases. We showed that administration of these antibodies during colitis ameliorated disease, suggesting that targeting distinct microbes can modulate chronic inflammation.

Altogether, our data reveal new pathways in tissue repair during chronic inflammation and dissect the mechanisms of microbiota control by immune system and suggest new ways of treating rheumatic diseases by modulating intestinal microbiota.
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**SELECTED PUBLICATIONS**


What is the functional composition of IgM Fc receptor (FcµR) and how does FcµR function in lymphocytes.

Humoral Immune Regulation

Antibody, a key player in humoral immunity, has dual binding activities: to antigens via its amino terminal variable regions, called Fab, and to effector molecules via its carboxyl terminal constant region, called Fc. One of the effector molecules is a family of Fc receptors (FcRs). FcRs for switched antibodies (i.e., IgG, IgE, IgA) are expressed by many different immune cells and are extensively characterized as central mediators coupling innate and adaptive immune responses. Much of the gained knowledge from these studies has been translated to clinical fields. By contrast, FcR for IgM, the first antibody appearing in phylogeny, ontogeny and immune responses, has defied genetic identification until our successful cloning eight years ago.

IgM FcR (FcµR) is only expressed by adaptive immune lymphocytes: B, T, and, to a lesser extent, NK cells in humans and only B cells in mice, suggesting the distinct function of FcµR compared to other FcRs as well as the species difference in cellular distribution. FcµR-bearing cells bind secreted IgM antibody with strikingly high avidity of ~10 nM (trans interaction). In our recent analyses, however, FcµR binds more efficiently the Fc portion of IgM antibody when it is attached to a membrane component via its Fab region on the same lymphocyte surface (cis interaction). This preferential cis engagement of FcµR implies that FcµR can modulate the functional activity of lymphocyte surface receptors or components recognized by either natural or immune IgM antibody.

Based on mutational analyses, we have defined several key residues in the transmembrane and cytoplasmic tail of the human FcµR molecule that involve in the receptor function: (i) the transmembrane His residue anchors the receptor in the plasma membrane; (ii) the membrane-proximal cytoplasmic Tyr residue mediates protection from apoptosis when the cis engagement occurs between Fas death receptor and FcµR; and (iii) two membrane-distal cytoplasmic Tyr residues involve the receptor-mediated endocytosis.

Cell surface levels of FcµR are sensitive to the extracellular IgM concentration, tissue milieu and cellular activation status. Since the serum IgM concentration in humans is ~1 µM, 100-fold above the FcµR avidity for IgM ligands, FcµR on lymphocytes must be occupied with IgM in vivo and the IgM-bound FcµR should be internalized, rapidly retrieved from early endosomes and returned to the cell surface. Brief pre-incubation of freshly-prepared lymphocytes in IgM-free media is thus required for the assessment of the full cell surface expression of FcµR by flow cytometry using either IgM ligands or receptor-specific monoclonal antibodies. Given these findings, we predict that cell surface FcµR is not vulnerable in patients with selective IgM immunodeficiency. Contrary to this assumption, surface FcµR levels on blood B cells, especially marginal zone-like B cells, in these patients are significantly diminished irrespective of pre-incubation, as compared to those in healthy controls. This suggests a different, not yet found, mechanism for reduced FcµR expression in this immunodeficiency.

The existing nomenclature issue of Toso, Fas apoptosis inhibitory molecule 3 (FAIM3) versus FcµR now reaches a general consensus that Toso/FAIM3 is an authentic IgM Fc-binding protein and that the initial designated FAIM3 (for
humans) and Faim3 (for mice) genes are thus officially renamed to FCMR and Fcmr, respectively.

The outcomes from these investigations are expected to confirm the importance of IgM and FcµR in immune protection and regulation in rheumatic diseases. We are currently exploring another membrane protein non-covalently associating with FcµR.

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**SELECTED PUBLICATIONS**


Cytokines in inflammation and anti-cytokine therapy

The main focus of the group is to develop optical technologies and methodologies allowing to visualize and quantify dynamic processes at cellular and sub-cellular level in the living organism in order to provide new insights into pathophysiologic phenomena relevant in chronic inflammation. In tight cooperation with clinicians (Dr. Helena Radbruch, Prof. Dr. Friedemann Paul and Prof. Dr. Frank Heppner) and immunologists (Prof. Dr. Anja Hauser), we set a special focus on developing methods for better understanding chronic neuroinflammation. Thereby, we designed and used NADH and NADPH fluorescence lifetime imaging (FLIM) applied to intravital as well as to live cell imaging to identify over-activated NADPH oxidases (NOX1-4, DUOX1,2), which is the source of massive O2– production – the initiator of reactive oxygen species. If this process is controlled, it represents the oxidative burst and thus oxidative eustress (e.g. in phagocytosis), but if it is random, it leads to oxidative stress. We found in both the brain stem tissue of a mouse model of Multiple Sclerosis (MS) and in blood-derived monocytes of MS patients a persisting over-activation of NADPH oxidases and defined the concept of oxidative stress memory (Mossakowski et al, 2015, Acta Neuropath.).

By combining our technology with fluorescent reporter mice we were further able to identify astrocytes and microglia as main contributors of tissue oxidative stress especially in the recovery phase of the disease (Radbruch et al, 2016, Front. Immunol.). Currently, we are translating NAD(P) H-FLIM to imaging in mouse lupus models as well as to SLE patients, to characterize the oxidative stress behavior in the kidney as compared to blood-derived cells. In order to better understand inflammatory processes in chronic neuroinflammation models, we developed an intravital imaging approach of the retina which allowed us to longitudinally monitor immune infiltration of this part of the central nervous system and to correlate this with the degeneration of its microglial network in one and the same animal (Bremer et al, 2016, Front. Immunol.).

To further develop our intravital imaging, we designed a microendoscopic implant to longitudinally image femoral marrow both during bone healing and homeostasis. Moreover, we developed a combined imaging strategy for multiplexed imaging in living organisms allowing for dynamic visualization of complex phenomena involving up to 8 cellular and tissue compartments.
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■ SELECTED PUBLICATIONS


We develop technologies for intravital imaging and live cell imaging to achieve new insights into chronic inflammatory processes

Biophysical Analytics

The main focus of the group is to develop optical technologies and methodologies allowing to visualize and quantify dynamic processes at cellular and sub-cellular level in the living organism in order to provide new insights into pathophysiologic phenomena relevant in chronic inflammation. In tight cooperation with clinicians (Dr. Helena Radbruch, Prof. Dr. Friedemann Paul and Prof. Dr. Frank Heppner) and immunologists (Prof. Dr. Anja Hauser), we set a special focus on developing methods for better understanding chronic neuroinflammation.

Thereby, we designed and used NADH and NADPH fluorescence lifetime imaging (FLIM) applied to intravital as well as to live cell imaging to identify over-activated NADPH oxidases (NOX1-4, DUOX1,2), which is the source of massive O2– production – the initiator of reactive oxygen species. If this process is controlled, it represents the oxidative burst and thus oxidative eustress (e.g. in phagocytosis), but if it is random, it leads to oxidative stress. We found in both the brain stem tissue of a mouse model of Multiple Sclerosis (MS) and in blood-derived monocytes of MS patients a persisting over-activation of NADPH oxidases and defined the concept of oxidative stress memory (Mossakowski et al, 2015, Acta Neuropath.).

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By combining our technology with fluorescent reporter mice we were further able to identify astrocytes and microglia as main contributors of tissue oxidative stress especially in the recovery phase of the disease (Radbruch et al, 2016, Front. Immunol.). Currently, we are translating NAD(P) H-FLIM to imaging in mouse lupus models as well as to SLE patients, to characterize the oxidative stress behavior in the kidney as compared to blood-derived cells. In order to better understand inflammatory processes in chronic neuroinflammation models, we developed an intravital imaging approach of the retina which allowed us to longitudinally monitor immune infiltration of this part of the central nervous system and to correlate this with the degeneration of its microglial network in one and the same animal (Bremer et al, 2016, Front. Immunol.).
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**SELECTED PUBLICATIONS**


Chronic immune reactions are a key feature of inflammatory rheumatic diseases. Current state-of-the-art immunosuppressive therapies are able to stop disease progression and maintain remission. However these therapies do not induce a therapy-free remission, i.e. discontinuation of treatment leads to relapse of disease.

From the experimental therapy of immunoablation and regeneration of a patient’s immune system from their own progenitor cells, also termed “autologous stem cell transplantation”, with about 20 years of experience at the Charité and DRFZ, we know that most if not all patients have an immunological memory driving the rheumatic inflammation, and this memory is refractory to conventional therapy. It is the aim of our group to identify the cells impersonating this pathogenic immunological memory, understand their development, their persistence, and their resistance to current therapies. From such an understanding new options should emerge for their selective therapeutic targeting and the induction of therapy-free remission.

In a basic approach, we have revisited the current concepts on how immunological memory is organized. We have developed the novel concept of a compartmentalized immunological memory in which the long-term memory to systemic antigens is maintained in the bone marrow, while the memory cells found in circulation are rather short-lived. We have identified a new type of memory cell, the memory plasma cell, secreting protective or pathogenic antibodies. We could show that reticular mesenchymal stromal cells of the bone marrow organize dedicated survival niches in which antigen-experienced lymphocytes differentiate into memory cells and persist as cells resting in terms of activation, proliferation, and mobility, as long as they are provided with survival signals. In such niches, memory cells are also protected from conventional therapies targeting activated immune cells. We are identifying the specific survival signals for different types of memory cells. Such signals and their receptors qualify as novel and selective therapeutic targets. At present we are collaborating with the group of Falk Hiepe to identify and target (pathogenic) memory plasma cells.

How can we distinguish pathogenic from protective memory cells? For memory T helper (Th) lymphocytes we could show that pathogenic memory Th lymphocytes initiate and drive inflammation through chemokines recruiting inflammatory effector cells, like macrophages and granulocytes. In chronic inflammation, pathogenic memory Th lymphocytes adapt to repeated reactivation. We have identified such molecular adaptations, e.g. expression of the genes Hopx, Twist1 and the microRNA miR-148a. Together with the group of Mir-Farzin Mashreghi we are now testing synthetic, membrane-permeable oligonucleotides for the inhibition of these vital adaptations, and thus the selective targeting of pathogenic memory Th lymphocytes.
COOPERATION PARTNERS

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SELECTED PUBLICATIONS


www.drfz.de/en/zellbiologie
Chronic inflammatory disorders, especially rheumatic diseases, are triggered and maintained by effector mediators produced by the adaptive immune system, such as T cells and B cells. The adaptive immune system employs three major effector modules, namely type 1 (IFN-γ and TNF), type 2 (IL-4, IL-5 and IL-13) and type 3 or type 17 (IL-17, IL-22), which give rise to distinct inflammatory tissue responses. In T cells, such inflammatory programs are induced by the T cell receptor (TCR) in conjunction with distinct cytokines and/or environmental signals and can be epigenetically imprinted and memorized. While the imprinting of inflammatory signatures enables a faster and stronger response during secondary infection, it facilitates on the other hand the induction and perpetuation of chronic inflammation, a hallmark of rheumatic diseases.

Recently, it appeared evident that emerging innate cell subsets lacking the TCR and collectively known as innate lymphoid cells (ILCs), exhibit a similar heterogeneity of effector modules, which can be activated in the course of inflammation. The ILC family includes three main groups of cells: group 1 ILCs, including cytotoxic Natural Killer (NK) cells and the IFN-γ producing ILC1; ILC2 producing IL-13/IL-5, and ILC3 secreting IL-22/IL-17. The signals and innate receptors instructing the different effector programs and their execution in ILCs remain largely unknown. Such innate sensors could also enhance effector functions in T cells, thus promoting inflammation in a TCR-independent fashion. Moreover, it is still unclear whether these inflammatory programs can be also memorized and imprinted in ILCs, thus possibly sustaining chronic inflammation.

Therefore, our main research focus is devoted to study the innate modules and triggers employed by ILCs and T cells to initiate and maintain inflammation in a TCR-independent fashion and to understand whether distinct inflammatory programs can be imprinted in ILCs to promote rheumatic diseases. The identification of alternative triggering and perpetuators of inflammation will provide us with new potential targets for the treatment of chronic rheumatic diseases.
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**SELECTED PUBLICATIONS**

Immune-mediated diseases such as Rheumatoid Arthritis, Diabetes or Multiple Sclerosis, but also inflammatory bowel diseases or allergies are thought to be initiated and maintained by T and B lymphocytes, which react against own body components (self-antigens) or harmless foreign substances (allergens, commensal microbiota). Current therapeutic approaches focus on general immune suppression instead of targeting those few disease-relevant lymphocytes. In contrast to murine models, major roadblocks towards specific therapies in humans are technical difficulties A) to identify and characterize the antigen-specific T cells and their target antigens in patients and B) to specifically approach them therapeutically.

Our group has established sensitive technologies to study antigen-specific T cells involved in immunopathology directly from patients. We characterize T cells contributing to “pathologic” or “healthy” immune reactions against auto-antigens or harmless foreign substances and describe the alterations in immunopathology. Understanding antigen-specific T cells as the drivers of disease and how these T cells can control or prevent autoimmunity or allergy has both diagnostic and therapeutic relevance. For development of therapeutic approaches, we are trying to utilize the physiological population of regulatory T cells (Treg), known to prevent autoimmunity. We are trying to identify their physiologic target antigens and to specifically modify their suppressive potential in vitro, i.e. by genetic engineering.

Besides professional immune-suppressive Treg, we are also interested which mechanisms of self-control inflammatory T cells employ to limit overt inflammation. Amplifying these autoregulatory circuits would be a valuable therapeutic strategy, building on re-establishment of the body’s physiological control mechanisms. Here we are focusing on the regulation of the anti-inflammatory or tissue-protective cytokines IL-10 and IL-22. Using gene expression profiling and functional in vitro and in vivo assays, we are studying the inducing signals and the transcriptional network regulating their expression. We have identified Notch as a switch to activate IL-10 as well as IL-22 in inflammatory T cells and defined additional critical transcription factors. We are also trying to define the physiological niche for T cell modulation by Notch and additional environmental signals, which shall be translated into in vitro T cell modulation strategies.

Suppression and self-control: How T cells fight autoimmunity.
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**SELECTED PUBLICATIONS**


Memory T helper (Th) cells are critical for long-lasting immune memory to infectious pathogens and autoantigens. Despite their central role, the generation, maintenance and reactivation of memory Th cells in the body still remained unclear. Recently, we have found and further described the microenvironment ‘niches’ for survival of memory Th cells in the bone marrow (BM). We have also reported that CD69 and CD49b (integrin alpha2) are required as homing receptors for the generation and maintenance of memory Th cells in the BM. These molecules can be target molecules to block the generation and maintenance of pathogenic memory Th cells in autoimmune diseases.

We have identified the precursors of BM memory Th cells as CD49b+ T-bet+ CD4 T cells, generated during the primary immune response. It has been previously reported that B cells contribute to the generation of effector Th cells (Tfh cells). However, we determined that the generation of the precursors of BM memory Th cells was negatively controlled by B cells. These findings suggest that B cells play a role in the bifurcation of activated effector and resting memory Th cell lineages. This finding alerts that, if only inflammation is blocked, pathogenic memory can be inversely enhanced. We should consider blocking both effector and memory T cells to treat autoimmune diseases.

We have identified a novel functional ligand of CD69, myosin light chain (Myl) 9 and 12. Myl9/12 is expressed in megakaryocytes and platelets. The migratory precursors of BM memory Th cells adhere to BM sinusoidal endothelial cells via the interaction of CD69 and most likely Myl9/12. In the pathogenesis of allergic airway inflammation, the interaction also functions to recruit inflammatory T cells into inflamed tissues. The role of the interaction of CD69 and Myl9/12 in autoimmune diseases will be investigated.

There is still much to discover about the reactivation of memory Th cells, i.e. the recall response. To determine how memory Th cells reactivate memory B cells, we currently study the cellular and molecular mechanisms of humoral memory response in the body, focusing on memory Th cells. Based on the knowledge of the protective antigen-specific memory Th cells in vivo, we now compare the localization and dynamics of protective and auto-reactive memory Th cells and then will determine how auto-reactive memory Th cells are generated, maintained and reactivated in the body, finding out the cellular and molecular targets to treat autoimmune diseases.
**COOPERATION PARTNERS**

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**SELECTED PUBLICATIONS**


Dong J, Chang HD, Tokoyoda K, Radbruch A. Immunological memory of the bone marrow. Z. Rheumatol. 74:527-8, 2015

Novel therapeutic approaches of type I-allergy by immunomodulation

The “Allergology” group is focused on immunomodulation of IgE-dependent type I allergies. Currently, approx. 20% of the German population are affected by hay fever, allergic asthma or atopic dermatitis. Our research is focused on the understanding of molecular and cellular key events for the development and maintenance of IgE production. Special interests among our group include immunomodulatory functions of nuclear receptor ligands, mechanisms of specific immunotherapy, anaphylaxis, and regulation of skin homeostasis.

Nuclear receptor ligands include molecules like vitamin D and retinoids. We have shown that vitamin D modulates profoundly B cell activation and hampers the IgE response. Currently, we study in detail molecular and cellular signalling and also initiated a clinical translation program. In these studies, we target vitamin D receptors in immune cells in vivo and determine the impact on specific allergic symptoms. Our overall aim is to achieve long-term tolerance to allergens.

The overall perspective of our research is to develop novel strategies for innovative treatment protocols in allergy. We transfer our experimental data into clinical trials (ad hoc translation).
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**SELECTED PUBLICATIONS**

Moinzadeh P; Aberer E; Ahnadi-Simab K; Blank N; Distler JH; Fierlbeck G; Genth E; Gaenther C; Hein R; Hese S; Herich L; Herrgott I; Ketto J; Kreuter A; Kriif T; Kuhl K; Lorenz HM; Meier F; Melchers I; Mensing H; Mueller-Ladner U; Pfeiffer C; Riemekasten G; Sardi M; Schmalzing M; Sunderkötter C; Susel L; Turner HH; Vaith P; Worm M; Wozel G; Zeidler G; Hunzelmann N; and all participating DNSS centers (2015). Disease progression in systemic sclerosis-overlap syndrome is significantly different from limited and diffuse cutaneous systemic sclerosis. Ann Rheum Dis. 74(4):730-7.


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Programme Area

Regenerative Rheumatology

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Biological regeneration of cartilage by reprogramming of chondrocytes

The Pitzer Laboratory of Osteoarthritis Research investigates the cellular and molecular mechanisms leading to the development of osteoarthritis (OA). Our goal is biological regeneration of cartilage in affected joints.

OA is the most frequently occurring joint disease among adults worldwide and the most important cause of disability among elderly people in Germany. This chronic degenerative disease leads to progressive cartilage loss and is often accompanied by inflammatory processes. Recent studies indicate dysfunctional molecular signaling within the cartilage-producing cells of the joints, the chondrocytes. This applies particularly to differentiation and apoptosis programs of these cells. So far, the chondrocytes’ in situ biology is understood only to some degree. Here, the biggest obstacles for further advancement in the research of these rare cells are (1.) their difficult accessibility and (2.) the limited possibilities to isolate and culture them without changing their phenotypes.

Chondrocytes reside in the joint cartilage layers in different arrangements and with varying types of metabolism. It is not clear yet whether this points to a homogenous population or to differentiated subtypes. It is known that central transcription factors like SOX9 and RUNX2 regulate the chondrocytes’ development right up to hypertrophic and/or degenerative stages. Comparable processes take place in the immune system that can be regarded as a prototypical model of cell differentiation in a complex network responding to its environment. Here, our group’s accumulated knowledge on the (re-)programming of T cells will be transferred to chondrocytes and the field of OA research.

In previous studies, we identified central cytokines and key transcription factors controlling the differentiation of T cells into subtypes (Bonilla et al., Science 2012; Peine et al., PLoS Biol. 2013; Baumann et al., PNAS 2015; Peine et al., Trends Immunol. 2016). In addition, we used this understanding of molecular processes to reprogram mature T cells into new stable phenotypes with additional functions (Hegazy et al., Immunity 2010). More recently, we showed a quantitative cytokine memory in individual cells. This means that a cell memorizes and stably maintains its individual production amount of a given cytokine (Helmstetter et al., Immunity 2015). We suggest that chondrocytes feature similar subtypes, differentiation programs, and possibilities of reprogramming. Ultimately, we want to reprogram the chondrocyte phenotypes that lead to the development of OA in patients in such a way as to achieve a long-lasting cartilage build-up.
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SELECTED PUBLICATIONS


Chronic inflammation is not only a key feature of autoimmune disorders including rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis, but is currently discussed to be a trigger for the initiation and propagation of osteoarthritis (OA), formerly considered as a non-inflammatory arthritis. Many immune cell types contribute to the persistence of chronic inflammation, either by promoting proinflammatory responses or by interfering with biological processes that allow the regeneration of destroyed tissues. In order to skew the balance in favor of regeneration as opposed to immunopathology, we want to acquire a profound knowledge of the molecular mechanisms that mediate such biological responses. Our aim is to identify genes and regulatory RNAs and their underlying functions by which they control the activity and survival of cells that contribute to chronic inflammation or help to regenerate destroyed tissues. For the global identification of such genes and regulatory RNAs, we have established a next generation sequencing platform. This technology allows us to obtain the expression patterns of mRNA and regulatory RNAs even from rare cells or from limited sample material that we obtain from patients with rheumatic diseases as well as OA. Furthermore, we want to interfere with the cellular functions by using therapeutic oligonucleotides targeting the identified mRNA and regulatory RNAs in preclinical models of inflammation and osteoarthritis. So far, we have identified the microRNA, miR-148a, which is upregulated in memory T helper (Th) cells isolated from inflamed tissues of patients with rheumatic joint diseases. We could show that miR-148a directly promotes the survival of repeatedly activated Th1 cells. By using a class of cholesterol-tagged inhibitory oligonucleotides against microRNAs, so called antagonirs, we achieved a significant knock-down of miR-148a in repeatedly activated Th1 cells. This knock-down in turn resulted in an upregulation of the mRNA coding for the proapoptotic protein Bim, which is a target of miR-148a. The consequence of Bim upregulation was enhanced apoptosis of repeatedly activated Th1 cells. Thus, miR-148a qualifies as a therapeutic target in order to deplete proinflammatory Th1 cells by systemic application of antagonirs in chronic inflammatory diseases. Our results demonstrate that therapeutic oligonucleotides are a suitable tool to reduce the expression of cell intrinsic target RNAs driving chronic inflammation and thus, to selectively modulate or ablate pathogenic cells. In the future we are going to further investigate the potential of therapeutic oligonucleotides including siRNAs and antagonirs in targeting relevant genes and regulatory RNAs that are important in maintaining chronic inflammation and help to achieve remission in degenerative diseases such as OA.
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DRFZ groups

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Programme Area

Epidemiology of rheumatic diseases

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The focus of our research is on juvenile idiopathic arthritis (JIA), the most common chronic inflammatory rheumatic disease in childhood and adolescence. Three large prospective observational cohort studies allow us to address various research questions with regard to phenotypes, outcome and its determinants, cost and adequacy of health care provision in JIA: 1) the national paediatric rheumatologic database (NPRD), in which more than 8,000 children and adolescents with JIA from 61 paediatric rheumatology sites in Germany are recorded per year, 2) the biologic register JuMBO (Juvenile arthritis Methotrexate/Biologics long-term Observation) for young adults with JIA that follows about 1,200 patients into adulthood, 3) the Inception Cohort Of Newly diagnosed children with JIA (ICON), in which about 950 JIA patients and 480 healthy controls are observed.

During the last year, our group has specifically examined:

- risk factors, frequency and outcomes of uveitis in patients with recent onset of JIA,
- how JIA affects the quality of life of children and adolescents and whether current routine care reduces the burden of illness,
- the cost of early JIA from the societal perspective and the main cost drivers in the first two years of paediatric rheumatology care,
- predictors of a successful stop of methotrexate in JIA patients who achieved remission on drug and were recorded in the JIA biologic registers BiKeR and JuMBO,
- the health care situation of young people in the period of transfer from child-centred to adult-oriented health care services by claims data.

Risk factors of uveitis, such as disease onset before the 4th birthday, the JIA category oligoarthritis, the presence of antinuclear antibodies and a high disease activity were identified. They may help in identifying a patient group that could benefit from early treatment with methotrexate, since we could demonstrate that this drug prevents uveitis. Current routine care improves the quality of life of JIA patients, approximating that of healthy peers after three years of care. During this time, most JIA patients attain inactive disease at least once. We found that the likelihood of experiencing recurrence of active disease is a function of time in inactive disease prior to drug discontinuation. Thus, patients in inactive disease should remain on treatment for at least 12 months before drug discontinuation.

All projects are based on close cooperation with the paediatric rheumatology sites in Germany, the national uveitis study group, and other national and international research groups.
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**SELECTED PUBLICATIONS**


In our clinical research work, we are interested in the epidemiology of spondyloarthritis as well as in improving diagnosis and therapy of the disease. In basic research work, we focus on elucidating the pathogenesis, including mechanisms of inflammation and bone formation in spondyloarthritis (SpA).

In the PROCLAIR study we investigate the disease burden, standards of care and disease-related costs in ankylosing spondylitis in Germany.

Regarding early diagnosis of SpA, we developed and tested screening parameters for identification of patients with possible SpA, which is critical for an early diagnosis of the disease. These data together with published results from other research groups resulted recently in the development of an international recommendation for the early referral of patients with a suspicion of axial spondyloarthritis by non-rheumatology specialists dealing with patients with back pain (orthopaedists, general practitioners). Further studies exploring possibilities of self-referral and developing referral strategies for other specialists (i.e., ophthalmologists, dermatologists, gastroenterologists) are ongoing.

Apart from this, we initiated a prospective cohort of patients with axial spondyloarthritis, the German Early Spondyloarthritis Inception Cohort – GESPIC (the project is still ongoing). In this cohort we study the natural course of the disease, predictors of a long-term outcome and of structural damage development in the sacroiliac joints and in the spine, including various biomarkers (ArthroMark project) and metabolic factors (METARTHROS project). Most recently we extended GESPIC to patients with early Crohn’s disease in order to study factors (including microbiome) associated with the development of arthritis phenotype.

Moreover, we performed a number of clinical trials analyzing the effect of different treatment options like glucocorticoids, TNF blockers and other biologics, such as ustekinumab, in the treatment of axial spondyloarthritis. The ESTHER study is the first study worldwide to investigate a long-term (10 years) follow-up in patients with early axial SpA treated with TNF blockers. In 2016 we initiated a large multicenter study CONSUL aimed at investigation of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of Structural damage in the spine over two years in patients with ankylosing spondylitis. In the ongoing NEUROIMPA project we investigate intraarticular treatment options in patients with arthritis of the knee joint.
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SELECTED PUBLICATIONS


The main interest of our group is to investigate long-term outcomes of rheumatic diseases including the effects of drug treatment in daily routine care.

In 2001 we established the longitudinal observational cohort study RABBIT (Rheumatoid Arthritis: Observation of Biologics Therapy) to closely monitor patients with rheumatoid arthritis (RA) treated with newly approved drugs and to compare the outcomes with an internal control group of patients under conventional synthetic treatment. Until December 2016, more than 15,400 patients starting a treatment were enrolled by about 300 rheumatologists all over Germany. Patients are observed for at least 5 and up to 10 years, regardless of any treatment changes. Every 6 months details about treatment course and adverse events are collected. We are continuously expanding the observed therapies by newly approved drugs. In 2015 and 2016, the first three biosimilars were incorporated in the observation.

Serious infections are common adverse events in patients with RA. A great concern is the development of sepsis where case fatality reach rates up to 50%. With data of the RABBIT cohort, we could confirm that older patients and those with a chronic renal disease are more likely to develop sepsis after a serious infection. The highlight of the analysis was a significantly lower risk for sepsis in patients treated with a biologic drug at the time of the serious infection compared to patients on conventional synthetic DMARD treatment. This result, for the first time and with striking effect size, confirmed observations from animal studies with epidemiologic data. This had not been possible in humans before.

With Rhekiss, started in 2015, we run a prospective cohort study dedicated to investigate the safety of therapies in pregnancy and lactation. We aim to add substantial evidence to the limited knowledge about the course and outcome of pregnancies in patients with various inflammatory rheumatic diseases and the influence of drug treatment. Women wishing for a child or at the beginning of pregnancy can be enrolled. The course of pregnancy including treatments and complications, the outcome and the first two years of child development are reported from rheumatologists and patients. One hundred rheumatologic units enrolled more than 400 pregnant patients until December 2016. The first results were reported at EULAR and ACR. In contrast to RABBIT, Rhekiss is a web-based system.

A new project currently under development in our research group is RABBIT-SpA, a web-based observational cohort study to observe patients with axial spondyloarthritis and psoriatic arthritis.

The results of our projects are highly relevant for clinicians and are directly transferred into daily clinical practice. The identification of prognostic factors or better treatment strategies for specific groups of patients, but as well the detection of risk factors for specific adverse events help clinicians to individualize treatments and to find the most suitable therapy for each patient. One example is the widely used calculator for the risk of serious infection (RABBIT Risk Score Calculator) which is available on our website.
### Cooperation Partners

- 300 rheumatologists in Germany
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Research Networks: EULAR Working Group RODS (Register and Observational Drugs Studies), ENCePP (European Network of Centers of Pharmacovigilance and Pharmacoepidemiology), EuNeP (European Network of Pregnancy Registers)

### Selected Publications


Improving health care provision by continuous outcome monitoring

Health Services Research in Adult Rheumatology

Our research focuses on the systematic and long-term evaluation of the quality and outcomes of health care for patients with rheumatic and musculoskeletal diseases in Germany. We investigate changes in health care provision, in clinical and patient-reported outcomes and deficits in health care within rheumatology as well as on the population level. We regularly give feedback to the treating rheumatologists and inform decision makers on the current state and gaps in health care. Our data are used to plan future health care provision and to improve the quality of care.

The National Database of the German Collaborative Arthritis Centres which is now in its 25th year, with 17,000 patients observed annually, is a tool not only used for our research but also for the work of several stakeholders such as rheumatologists, patient representatives, politicians and health authorities. It describes changes in health care, patient profiles and outcomes as well as their economic consequences. Over the years, the data show continuous improvements in clinical and patient-reported outcomes, increasing costs of treatment and decreasing societal costs due to work disability, and the importance of social and psychological factors. One of our most recent observations is a continuously increasing age at onset as well as increasing current age in all patient groups, reflecting longer life expectancy as well as changes in risk factors.

The group is involved in two nation-wide research networks funded by the Federal Minister of Health. In the METARTHROS network (Metabolic impact on joint and bone disease) we investigate the impact of obesity, diabetes and metabolic syndrome on juvenile idiopathic arthritis and rheumatoid arthritis, using all cohorts available in the Unit, supporting the idea of obesity as contributor to the development of inflammatory arthritis. In the PROCLAIR network (Combining Patient-Reported Outcomes with CLAims data) we found significant regional differences in health care, a strong influence of social status on disease burden and undersupply of specialized care in particular in old, disabled persons with rheumatoid arthritis. Our next studies in PROCLAIR will focus on spondyloarthritides and osteoarthritis.

Data from the early inception cohort Course And Prognosis of Early Arthritis (CAPEA) are currently used for the collaborative investigation of poor prognostic markers in rheumatoid arthritis and for the investigation of biomarkers in early RA in cooperation with the universities of Duesseldorf and Granada.

Keywords
Health services research, Trends in treatment, Long-term observation, Cost of illness, Predictors of outcome

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Due to the successful combination of intrinsic molecular specificity with high spatial resolution, fluorescence microscopy is a versatile technique largely employed in both routine and high-end research applications of biosciences and biomedicine. Currently, these applications reach from the investigation of fixed biopsies, living cell cultures, vital organ models or even living organisms on a molecular basis and down to electron-microscope-like spatial resolution, i.e. supra-resolution techniques (like STED microscopy, PALM, STORM or SSIM/SPEM).

The expertise at the Core facility for innovative imaging und analysis (CINIMA) at the DRFZ covers standard fluorescence techniques like wide-field and confocal fluorescence microscopy to the newest developments in vital organ explants and intravital multi-photon microscopy.

Confocal laser-scanning microscopy and wide-field fluorescence microscopy

For fast screening of histology samples of different organs, the DRFZ research groups employ the fully automated wide-field fluorescence microscope (Keyence). In order to achieve three-dimensional images at high resolution the Zeiss LSM710 confocal microscope is used. Both whole field images reaching to a few mm² (when tile scans are made) and images depicting cellular interaction/co-localization at sub-cellular level using the 63x oil-immersion lens (NA = 1.3, i.e. resolution at 488 nm excitation wavelength of 229 nm laterally and 577 nm axially) can be acquired. A central feature of the confocal microscope at the DRFZ is the possibility of live cell visualization and monitoring in a temperature- and CO2-regulated incubation chamber. With this system, spectral resolution of up to five colors can be acquired.

In order to achieve multiplexing in histology, we a Toponome imaging cycler is used. This system allows to detect more than 100 markers in one histological section, by sequentially staining and bleaching the sample, a process termed Multi-epitope Ligand Cartography (MELC). We are developing customized algorithms to analyze the data generated using this system, in the sense of multiplexed histocytometry.

Multi-photon laser-scanning microscopy for deep-tissue and intravital microscopy

While the standard wide-field and confocal microscopy based on single-photon excitation intrinsically allows for high resolution due to UV/visible illumination, they do not allow for high imaging depths in intact, living organs. Due to the benefits of ultra-short pulsed near infrared (NIR) and infrared (IR) illumination, multi-photon microscopy counteracts exactly this shortcoming of standard fluorescence microscopy. The intrinsic 3D resolution and the excitation within the tissue optical window, i.e. at wavelengths where neither water nor hemoglobin absorb radiation, makes multiphoton microscopy an ideal tool for the visualization of cellular motility and communication deep in vital organ models or in organs within living organisms at low endogenous fluorescence and sub-cellular resolution.

The DRFZ and its partners at the Charité already have a wide expertise concerning multi-photon imaging within explanted organs, e.g. hippocampal brain slices (Dr. Jan Leo Rinnenthal, Dr. Helena Radbruch, Prof. Frank Heppner, Institute for Neuropathology, Charité) and spleen slices (Prof. A.E. Hauser, Dr. R. Niesner), and even more, within living organisms in intestine
(group of Prof. A.E. Hauser), lymph node (group of Prof. A.E. Hauser), bone-marrow (group of Prof. A.E. Hauser) and organs of the central nervous system, i.e. brain stem (Dr. Helena Radbruch), brain cortex (Dr. Jan Leo Rinnenthal, Prof. Frank Heppner, Simon Bayerl, Prof. Vajozy) and neuronal retina (Dr. R. Niesner, Prof. Paul). Currently, we focus our attention in extending this expertise to intravital spleen and kidney imaging, to longitudinal bone marrow endoscopy and to the use of optical coherence tomography in the mouse eye.

While extending the expertise in the field of deep-tissue and intravital multi-photon imaging with applications especially in immunology plays a central part in the work at the DRFZ imaging core-facility CINIMA, tight collaborations with other imaging facilities in Berlin as well as with systems biology groups ensure the access of DRFZ scientists to a broad palette of fluorescence imaging techniques and data evaluation. In 2011 JIMI (Joint network for Intravital MIcroscopy) was founded in order to bundle the expertise of Multi-Photon intravital imaging present at the DRFZ, Berlin (Dr. R. Niesner und Prof. Dr. A. Hauser) with the expert knowledge of microscopy at the MDC (Dr. A. Sporbert) and image analysis present at the HKI in Jena (Prof. M.T. Figge). The goal of JIMI is to make intravital microscopy accessible for researchers from different fields in life science. We provide help in planning and performing intravital microscopy experiments as well as in the analysis of the data. This is completed by consulting and assistance through regular seminars of the JIMI members and of invited experts of the field of optical imaging in biosciences and biomedicine. Between 2012 and 2016, JIMI has been granted funding by the DFG. In this time period, JIMI supported 38 projects out of 8 national and international institutions and published 27 scientific articles (www.jimi-network.de). Furthermore, JIMI is majorly involved in leading national and international imaging networks like CTLS (headed by Prof. Spencer Shorte, Imagopole, Institute Pasteur, Paris) or German BioImaging (led by Prof. Elisa May, University of Konstanz) and closely cooperates with leading microscopy core-facilities as well as microscopy companies in Germany, France and UK. To further increase the access of the JIMI users to information and to enhance scientific exchange, we organized yearly work-shops dedicated to live and intravital microscopy: the Imaging cytometry meetings at the annual meeting of the DGfZ (German Society for Cytometry), in October 2015 and October 2016, both in Berlin.

Technical equipment

- 1 Lavision TrimScope1 (equipped with Ti:sa Laser)
- 1 Lavision TrimScope 2 (equipped with Ti:sa Laser and optoparametric oscillator. Detection with PMTs or time-correlated single photon counting device)
- 1 Double header Lavision TrimScope 2 (equipped with Ti:sa Laser and optoparametric oscillator. Detection with PMTs or time-correlated single photon counting device).
- 1 Zeiss LSM710 confocal microscope
- 1 Keyence Biorevo fluorescent microscope
- 1 Zeiss Axiovert fluorescent microscope
- 1 Leica fluorescent microscope for multiplex imaging
- 1 Amnis Imaging flow cytometer
The central laboratory facility of the DRFZ was founded in the year 2000. The lab managers provide services for all research groups, the main focus being on the supply with antibodies and their conjugates. Apart from this central task, the lab managers are also responsible for infrastructural aspects concerning the DRFZ, such as: the estimation and acquisition of financial contributions of the liaison groups to the DRFZ infrastructure, the ordering system regarding the supply with cell culture and general materials, management of general scientific equipment, including acquisition, calculation and service, in collaboration with the administration of the DRFZ and the supply of groups with basic materials, chemicals and chemical solutions for working with cell cultures.

**Antibodies**
Specific antibodies and their fluorochrome derivatives are of central importance for doing experimental cell-biological research. Therefore, the team of lab managers working in the central laboratory particularly focuses on the production and supply of more than 1,000 substances. More than 250 antibody-producing hybridomas are cultivated. Specific antibodies are isolated from cell culture supernatants, purified and, if necessary, conjugated with various fluorochromes. Thus, the lab managers provide the basic supply with all relevant biological tools necessary for doing FACS analysis, cell sorting, histology, ELISA, and other immunological techniques. (Fig.1)

The huge variety of antibodies and conjugates is accessible to scientists working at the DRFZ, the Max Planck Institute for Infection Biology, the Charité-Universitätsmedizin Berlin, and in other collaborating groups. The intranet folder “OnlineAntibodiesManagement” offers information on the current quantity of samples available in the stock. Users are also provided with background information such as, for instance, the name of clone, concentration, and titer, or with other data regarding the samples.

**Service**
On request, the lab managers also offer their advice and assistance in case of technical problems, for instance concerning the isolation and purification of proteins, derivatisation, fusion or fragmentation of antibodies and other proteins, production of specific affinity matrices for chromatographic purposes and for the establishment of ELISAs. All preparations go hand in hand with specific quality controls. (Fig.2+3)

The field of activity of the central laboratory also includes the introduction and establishment of new methods and techniques, in particular, regarding new fluorochromatic markers.

**Perspectives**
The acquisition of further hybridomas for new scientific questions is essential. The fight against mycoplasma or endotoxin contamination has to be adapted continuously to state-of-the-art technology. The increasing use of multicolor techniques in FACS requires a continuous increase in the number of available fluorochromes, to provide enough substances with sufficient brightness, photo stability and narrow emission spectra in different combinations. Beyond that the introduction of the CyTOF technology in the
DRFZ implies new fields of responsibility, e.g. the establishment of antibody conjugation with heavy metals.

The growing number of groups and scientists working at the DRFZ makes the adaption of infrastructural aspects of the central laboratory necessary and represents another great challenge for the lab management. The main aim is to guarantee the availability of necessary equipment and facilities at all times.
Flow Cytometry & Cell Sorting (FCCF)

The Flow Cytometry Core Facility (FCCF) provides a comprehensive range of services and proprietary technological innovations to ensure state-of-the-art analysis and sorting of cells. The Central Laboratory, operated by the DRFZ, was established in 2000 and is equipped with a broad spectrum of machines. It is used by more than 300 scientists and clinicians from the DRFZ, the Charité, the Max Planck Institute for Infection Biology and other research facilities.

Flow cytometry is an analytical method used for the quantitative measurement of physical, biochemical/cell biological and immunogenetic parameters of single cells by optoelectronical means. On the basis of these parameters various cell features, such as viability, quantification of antigens, phenotype, function, and cell cycle can be determined.

In a flow cytometer, up to 20,000 cells per second can be analyzed for more than 15 parameters simultaneously and quantitatively using light scattering and combinations of antibodies labelled with different fluorescent dyes. The high sensitivity of the cell analyzer allows the detection of as few as 50 molecules per cell. This technology allow us to monitor patients with rheumatic diseases before and during therapy on a cellular level, aiding us not only in the identification of cellular signature of different rheumatic diseases, prediction of therapy response, and monitoring of therapy response, but may also help to understand the cellular processes underlying rheumatic diseases.

By cell sorting cells of interest can be isolated from complex mixtures and collected for further biochemical or functional analyses. For this, cells are measured (as in the cell analyzer) and subsequently packaged into individual droplets. The droplets are then given an electrical charge according to their staining pattern and then deflected by charged electrodes into waiting sample tubes.

In combination with suitable preenrichment methods, such as magnetic cell sorting, also rare cells, such as antigen-specific T cells can be analysed and isolated with high purity for subsequent molecular analyses. For the isolation of sensitive cells, such as plasma cells or stroma cells from the bone marrow, the FCCF utilizes a BD Influx™ sorter with adapted high-speed sorting protocols that ensure high viability and purity of the cells.

To improve the sensitivity of multiparameter flow cytometry we are, in cooperation with the company APE, working on the hardware development for a new multispectral Flow Cytometer. A spectral flow cytometer detects the entire spectra of an individual fluorescence labelled cell, instead of only detecting a specific peak of a certain fluorochrome which has passed
through an optical band-pass filters, and thus collects more light increasing the detection sensitivity (Feher et al., 2016).

In cooperation with APE we have also developed a LED based calibration tool (quantiflash”) which enables us to perform quality control of our machines with respect to the dynamic detection range as well as the signal-to-noise ratio (Giesecke et al., 2017). It also allows us to calibrate the measured light intensities of a flow cytometer to absolute values. By this we are now for the first time able to quantify absolute numbers of proteins expressed by a cell.

To train our users, we offer a two hour basic course on the proper use of the techniques used in flow cytometry every month. The course is open for all who are interested. Together with various groups working at the DRFZ, the FCCF offered workshops for users from around the world. Every year the FCCF opens its doors for the “Long Night of Sciences” for making cell sorting and cellular immunology more perceptible for public visitors, such as rheumatic patients, students or pupils.

Our service offers for scientists are accessible via internet. After the registration, the users get access to the online-scheduler located on: http://fccf.drfz.de

There, the use of equipment, the documentation of experiments, and billing can be managed. Users also have access to the central data server in order to view their flow cytometry data.

■ COOPERATION PARTNERS
Max Planck Institute for Infection Biology, Berlin
Charité - Universitätsmedizin Berlin
(Campus Mitte, Campus Steglitz, Campus Virchow)
Technische Universität Berlin
Angewandte Physik und Elektronik GmbH (A•P•E), Berlin
European development fond „EFRE“ 10158448

■ SELECTED PUBLICATIONS


Comparison study of various flow cytometers using a novel ultra stable calibration light source.


Immune Monitoring

Dr. rer. nat. Andreas Grützkau

Immune monitoring includes the combination of various procedures of diagnosis, which provide information about the immune state of a patient. Depending on the clinical discipline, humoral factors, like cytokines, antibody titres or complement factors, the cellular composition of peripheral blood, functional-cellular parameters or rather a combination of them all, can be determined. Immune monitoring programmes already assist in the diagnosis and treatment of many complex clinical manifestations. For example, physicians use immune monitoring in transplantation medicine, in cases of sepsis, in the course of immune modulatory therapies, and in vaccine strategies to evaluate specific immune responses. The immune monitoring core facility aims to identify immunophenotypic signatures as biomarkers for monitoring disease activity and prediction of treatment responses.

**Siglec-1 a new biomarker in lupus diagnostics**

Siglec-1 is an adhesion molecule specifically expressed in peripheral monocytes that was originally identified by cell-specific transcriptomic studies as a type I interferon surrogate marker. Interestingly, in cooperation with our clinical liaison partners it could be shown that an increased expression of Siglec-1 correlates with disease activity in patients suffering in SLE and Sjögren’s syndrome (Biesen et al., 2008; Rose et al., 2016). Based on these promising results, Siglec-1 has been extensively investigated as a new biomarker in recent years and has been validated in various clinical studies (Rose et al. 2013; Rose et al. 2016; Rose et al. 2017), so that it could be shown to have a higher diagnostic potential than other gold standards in lupus diagnostics, e.g. autoantibody titres or the consumption of complement factors. Meanwhile, this biomarker has been successfully translated from bench to routine diagnostics and the quantitative measurement of this parameter is offered in the portfolio of the diagnostic laboratory of the Charité (“Labor Berlin”). Therefore, this is a paradigm of how modern high-throughput technologies can be used to identify promising, new molecular biomarkers, which will be successfully validated in well-designed clinical trials. This is all the more remarkable because similar to the development of drugs, only very few biomarker candidates overcome hurdles of further validation studies. In the context of Siglec-1 as type I interferon surrogate marker, it was also investigated in detail why up to now no other blood-based biomarkers, such as the interferon signature, i.e. a specific pattern of genes regulated by IFN-α/β in blood cells, has been reached diagnostic routine in rheumatology. Here, we could show by a comprehensive study comparing own gene expression data and those published by other groups, that interferon signatures are strongly influenced by the cellular composition of white blood cells. Each type of immune cell type responds with another set of interferon-associated genes and it could be concluded that only interferon signatures generated in a cell-specific manner are useful for diagnostic purposes (Strauss et al., 2017).

**NK cells as predictors for a successful anti-TNF-α therapy response**

Unfortunately, at this stage it is not possible to predict whether a patient will respond to a specific therapy or not before starting of therapy. However, this is exactly the goal of the so-called personalized or individualized medicine aiming
to match the best possible therapy to the individual patient. This minimizes the risk of adverse side effects and can save enormous health care costs, since on average only 50%-60% of rheumatoid patients treated with expensive biologics benefit from a noticeable improvement in their disease symptoms. In collaboration with Prof. Jochen Sieper, Prof. Dennis Poddubny and Dr. Uta Syrbe at the Charité campus Benjamin Franklin, we conducted an extensive immune monitoring study on ankylosing spondylitis patients treated with TNF-α blocking drugs. It could be shown that in blood of these patients, the frequency of certain natural killer cell subpopulations allows a prediction of the treatment success with TNF-α blockers even before starting therapy. These results have just been submitted for publication in "Scientific Reports".

**Bioinformatics**

Multidimensional data sets generated especially by mass cytometry requires new algorithms which automatically recognize and quantify relevant cell populations. For this purpose, a software (“immunoClust”, Sörensen et al., 2015) has been developed by bioinformaticians and mathematicians of the DRFZ and the department for medical bioinformatics of the rheumatology at the Campus Charité Mitte.

**Perspectives**

The complex immune monitoring approach described is used to accompany therapy studies to identify predictors of therapy responses. Furthermore, attempts are currently being made to develop algorithms which allow automation of the primary data analysis. Ultimately, it is necessary to look for ways to adjust and optimize immune monitoring of larger sample quantities with regard to a high-throughput method.

**SELECTED PUBLICATIONS**


**Mass Cytometry**

Mass cytometry permits deep cellular phenotyping in clinical immunology and basic research, with more than 50 parameters that can be measured simultaneously in a single assay. This is achieved by combining principles of flow cytometry and inductively coupled plasma mass spectrometry (ICP-MS), a technology that has been developed for trace metal analysis.

Using mass cytometry, we perform biomarker discovery studies in several cohorts of patients with different chronic inflammatory diseases such as rheumatoid arthritis, SLE, and inflammatory bowel diseases. We follow the idea that the blood cytome contains important yet covered information about the patient's condition and response to future therapy. We pursue cytomics to achieve precision medicine in the treatment of chronic inflammation and aim at developing a diagnostic that can be used to select only effective treatments - individually for each patient.

In basic research, we use mass cytometry to capture the diversity of different cell types implicated in chronic inflammatory processes such as T and B lymphocytes, plasma cells and myeloid immune cells. Such diversity relates to e.g. states of cell differentiation and activation, migration and adhesion, apoptosis and survival. Understanding the complexity of cellular systems and provides new insight into the homeostasis and dynamics of immunity, which are of particular interest in cases of specialized lymphocytes bearing protective vs. autoreactive immune memory, and of immune cells that fuel acute inflammation such as monocytes.

To serve these aims at maximum quality, we strive for improving mass cytometry endeavours by developing and improving cell sample barcoding, expanding the measurement capacity by generating new probes and by developing and validating accessory techniques to minimize experimental variations such as cell preservation and antibody cocktail lyophilisation. Implementing these features helps to improve the accuracy of measurements and the interpretation of highly complex multi-dimensional datasets by downstream computational analyses.

The DRFZ mass cytometry unit serves a variety of internal and external collaborations and is an active part of the worldwide mass cytometry community. The DRFZ spearheads the German Mass Cytometry Network that will be established in 2017.


**COOPERATION PARTNERS**

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**SELECTED PUBLICATIONS**

Regine von Ramin-Laboratory for Molecular Rheumatology

Through the generous bequest from Mrs. Regine von Ramin and further financing by the Berlin senate-administration WiFoku, the Regine-von-Ramin Laboratory for Molecular Rheumatology (RvR-Laboratory) was founded in December of 2004. This facility will be used jointly by research groups of the DRFZ and the affiliated groups of the Charité for the purposes of genome-wide gene expression analysis using Affymetrix-Technology. In addition to global transcription analysis, it will also be possible to carry out microarray-based miRNA expression analysis.

Technical equipment belonging to the Regine von Ramin Laboratory

The RvR-Laboratory contains an Affymetrix-station, which is equipped with the the Scanner 3000 7G and the Fluidics FS450. For the purposes of RNA-sample quality control, a Bioanalyzer (Agilent) and Nanodrop ND-1000 spectral photometer are available in addition to standard instruments. Additionally, the aHybTM-Hybridisation station (Milenyi Biotec) allows for processing of array formats that are spotted on slides, and thereby processes like a miRNA expression profiling using the miRXplore Array (Milenyi Biotec).

An ideal supplement to this facility is a Laser Capture Microdissection machine (LCM) from Fa. Arcturus, which allows a cutting out of morphologically and immune-histologically characterized tissue samples for molecular analysis without enzymatically digesting them. Both systems are primarily used for molecular analysis of cells at the level of their DNA, RNA and proteins. Through the integration of LCM-technology in the RvR-Laboratory, it is possible to perform global gene expression analysis on tissue samples that are morphologically and immuno-histologically identifiable (Figure 1).

Bioinformatic Analysis

A close cooperation with the Department of Bioinformatics (Joachim Grün, DRFZ; Thomas Häupl, Charité) and the Charité spin-off company "BioRetis", allowed the establishment of a comprehensive mouse- and disease-relevant human transcriptome database. The data-warehousing of these data by the BioRetis-analysis platform allows for comfortable and precise group comparative analysis that can be implemented worldwide by existing national and international research organizations within the framework of a defined rights allocation system. An overview of the basic analysis strategies can be found in the following chapter on “Bioinformatics” by Joachim Grün.

Generating disease-, cell- and cytokine-specific gene expression profiles

One research focus at the DRFZ is the analysis of disease- and cell-specific global gene expression profiles. It has been shown that peripheral monocytes isolated from RA, SLE and Bechterew’s disease-patients show disease-specific gene signatures that could be successfully used for disease-classification. The large number of differentially expressed genes reflects the complexity of chronic-inflammatory rheumatic diseases. The central pathophysiological role of pro-inflammatory cytokines, such as TNF-α or INF-α/γ, in the inflammatory-processes could be shown clearly with the clinical success of cytokine-specific biologicals. However, there is currently no reliable molecular biomarker that would allow for a targeted and thereby individualized therapy. Therefore, cytokine-
specific gene signatures have been generated and analyzed ex-vivo in two EU-supported research-projects (Autocure and IMI JU BTCure).

Through a comparison of these expression profiles with the disease-specific profile, Biljana Smiljanovic was able to show, in the course of the research conducted for her dissertation, that peripheral monocytes are highly-sensitive biomarkers that express disease-dependent, qualitative and quantitative variability in their cytokine signature. While monocytes from Lupus-patients are characterized primarily by an IFN-α/γ-induced immune-response, RA-patients were characterized by a dominance of TNF-α in this process. This knowledge will be used in further investigations to clarify if these molecular cytokine-response signatures can be used to predict a positive response to therapy.

## REFERENCES


Although the list of methods replacing animals in experimental research is constantly growing, for some scientific questions the use of animal models is still necessary. Especially for the understanding of multifactorial diseases like autoimmune disorders, in which different organs and cell types are involved, the complexity of a living organism is required.

Therefore, the DRFZ runs a state of the art animal facility. This facility is divided into an experimental area in Berlin-Mitte and a separate breeding area in Berlin-Marienfelde, where numerous mouse strains are kept. Trained animal caretakers and veterinarians ensure best husbandry conditions and a seamless monitoring of the animals in favor of animal welfare.

All mice are bred and held under so called SPF (specific pathogen free) conditions to ensure that animals are free from pathogens that could interfere with animal experimental studies. For this purpose, the facility is equipped with personnel airlocks, and all material is thoroughly autoclaved before entering the facility. Moreover, mice undergo a microbiological check-up on a regular basis in order to detect potentially pathogenic microorganisms.

As a part of the Leibniz-Gemeinschaft the DRFZ intends to communicate openly about animal experiments. Scientists working with mice at the DRFZ put the principles of the 3Rs (Replacement, Reduction and Refinement) into practice to minimize suffering and improve animal welfare.

The DRFZ provides a training program on animal experimental work according to EU and German animal welfare legislation, consisting of a theoretical and practical part. Successful participation is officially certified.
The Embryo Technology Laboratory is a joint core facility together with the Robert Koch Institute. It is located within the animal facility in Berlin-Marienfelde and provides state of the art technologies for modern mouse colony management like in vitro fertilization (IVF) and cryopreservation.

The following services are offered (Fig. 1):

1) Embryotransfer. To guarantee a defined health status in the SPF breeding area, new transgenic mouse lines have to be imported via embryotransfer. Two cell embryos (generated by IVF or classical mating) are washed extensively to remove any pathogens (Fig. 2) and implanted into pseudopregnant foster mice.

2) Cryopreservation of mouse sperm and embryos. Mouse strains which are temporarily not needed can be stored as 2-cell embryos or sperm in liquid nitrogen. Frozen material is also an option for world-wide shipping of transgenic mouse lines.

3) In vitro fertilization. IVF is used to recover mouse lines from frozen sperm and is generally a very efficient method to generate mouse embryos.

---

**Scientist**

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Technical staff: Paolo Rosellini Tognetti

Additional assistance: Janni Breinl

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Ronald Naumann, Transgenic Core Facility, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden

Frank Zimmermann, Biotechnology Laboratory, University Heidelberg

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![Embryo Technology Laboratory](image)

**Fig. 1:** Workflow for services offered by the ET-Lab.

**Fig. 2:** Washing of embryos. The fertilized oocyte is protected by the zona pelucida which is impermeable for pathogens. Residual sperm is still sticking to the zona.

**Fig. 3:** Developmental stages of mouse embryos.

a) Sperm and oocytes (hidden in the cumulus cells) 5 min after IVF.

b) 45 min after IVF. The sperm almost completely dissolved the cumulus cells.

c) 2-cell embryos.

d) 4- and 8-cell embryos.

e) Morula stage.

f) Blastocysts.
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<td>An integrated high-resolution immunophenotyping and computational biomarker discovery approach for monitoring clinical trials</td>
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<td>Engineering resting B cells for the suppression of unwanted immunity</td>
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<td>NEU² IL-27-35</td>
<td>Identification and functional analysis of new small molecules inducing anti-inflammatory IL-27 and IL-35</td>
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<td>EPILYZE</td>
<td>DNA Methylierungs-Signaturen als innovative Biomarker für die quantitative und qualitative Analyse von Immunzellen, Teilprojekt E</td>
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<td>OATREAT</td>
<td>Prospektive randomisierte, doppel-blinde und placebo-kontrollierte klinische Studie mit Hydroxychloroquin (HCQ) bei Patienten mit einer entzündlichen Osteoarthritis (OA) der Hände</td>
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<td>Technology Transfer</td>
<td>Verstetigung der Verwertungskonzepte in den lebens- und umweltwissenschaftlichen Instituten der Leibniz-Gemeinschaft - Deutsches Rheuma-Forschungszentrum Berlin</td>
<td>BMBF</td>
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<td>NEUROIMPA - Neuroimmunologie und Schmerz</td>
<td>Neuromodulation in entzündungsfördernden T Zellen</td>
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<td>DEEP Deutsches Epigenom Programm</td>
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<td>e:Bio T-Sys</td>
<td>Modulation of transcriptional regulation of Th cells</td>
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<td>MicroRNAs and genes regulating the transition of protective into pathogenic memory T helper cells in chronic inflammatory diseases</td>
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<td>METARTHROS</td>
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<td>ICON - Frühkohorte</td>
<td>Frühkohorte juvenile idiopathische Arthritis-Arbeitspaket Studienprotokoll</td>
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<td>PROCLAIR</td>
<td>Gesundheitsversorgung und Krankheitslast bei Personen mit rheumatoider Arthritis (RA)</td>
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<td>ZIMA-RETI-IM</td>
<td>Retina-Bildungsverfahren zur Frühdiagnose neurodegenerativer und neuroimmunologischer Erkrankungen (RETI-IM); Entwicklung der Gesamtintegration eines murinen Retina-Mikroskopiesystems mit der Erarbeitung von Anwendungsszenarien</td>
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<td>Entwicklung einer RNA-Sequenzierungs-Pipeline für Dienstleistungen im Bereich der Forschung, Klinik und Industrie; Optimierung und Validierung der speziellen RNA-Aufreinigung für RNA-Seq aus histo-pathologischen Proben</td>
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<td>Unraveling the interactions between the immune system and bone (OSTEIMMUNE)</td>
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<td>Protective and pathogenic immunological memory and its organisation by stroma cells (ERC Grant)</td>
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<td>BeTheCure (IMI Inflammation - Translational Research and Adaptive Immunity)</td>
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<td>Infect-ERA ABIR</td>
<td>Identifying DC subsets that induce protective effector and memory T cells during Listeria and Salmonella infection</td>
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<td>Investigating the role of cytokine-producing B cells in the pathogenesis of autoimmune diseases of the central nervous system</td>
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<td>RABBIT</td>
<td>Langzeitbeobachtung der Therapie mit Biologika bei rheumaoider Arthritis</td>
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<td>Irc-p B-Cells</td>
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<td>EINSTEIN</td>
<td>The role of dendritic cells in presenting tumor and autoimmune epitopes produced by proteasomal peptide splicing</td>
<td>Foundation - Einstein Stiftung Berlin</td>
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<td>NPRD</td>
<td>The Indicible T cell Co-Stimulator ICOS as target for elimination of tissue-resident follicular helper-like T cells</td>
<td>Foundation - Fritz Thyssen Stiftung</td>
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<td>Ideenwettbewerb “1st Rheuma heilbar”</td>
<td>Molecular Adaption pathogenic Gedächtnis T Helperzellen bei rheumatischen Entzündungen</td>
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<td>Kinderkern- dokumentation</td>
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<td>VPSS</td>
<td>Mundgesundheitliche Probleme und Implantat-Versorgung bei Patienten mit primärem Sjögren-Syndrom</td>
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<td>Others - Chiba University</td>
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<td>RITUXIMAB in RA</td>
<td>Combined cellular and serological biomarkers for the prediction of responsiveness to B cell depleting therapy with rituximab in patients with RA</td>
<td>Others - Deutsche Gesellschaft für Rheumatologie e.V. (DGRh)</td>
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<td>DGRh Start-Up 2014</td>
<td>Functional stabilization of clinically suitable Treg populations by RNA mediated “epigenetic editing”.</td>
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<td>ZMV Transition</td>
<td>Transition – Empowering young people with rheumatic diseases for transition to adult care</td>
<td>Others - Deutsche Rheuma-Liga Bundesverband e.V.</td>
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<td>UOS</td>
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<td>Others - Hamburger Elterninitiative rheumakranker Kinder e.V.</td>
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As of December 31, 2016
## Third party funding projects - Liaison Groups

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<td>Longitudinal intravital imaging of dynamics of osteo-immunological interactions during bone healing</td>
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<td>DFG SPP 1937: Innate Lymphoid Cells</td>
<td>Analysing the heterogeneity of innate lymphoid cells and relationship with their microenvironmants in situ and in vivo</td>
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<td>IMMUNOBONE</td>
<td>Delineation of human plasma cell subsets and their bone marrow niche</td>
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<td>SFB 613 Induction and Modulation of T-cell-Mediated Immune Reactions in the Gastrointestinal Tract</td>
<td>Characterization of human peripheral and intestinal T cell responses after mucosal antigen exposition: Induction of tolerance vs. immunity</td>
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<td>Analysis of the presentation of orally applied antigens and the specific T-cell reaction: tolerance versus immunity</td>
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<td>SFB 650 Cellular approaches to the suppression of unwanted immune reactions - from bench to bedside</td>
<td>New generation anti-B cell therapy</td>
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<td>Induction of tolerance by immunoablation followed by autologous stem cell transplantation in refractory autoimmune diseases</td>
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<td>Targeting of pathogenic T helper cells in chronic rheumatic inflammation</td>
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<td>Redirecting the antigen-specificity of polyclonal regulatory T cells to optimize their therapeutic efficacy and safety</td>
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<td>Immune modulation of allergic diseases by nuclear hormone receptor ligands</td>
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<td>Characteristics and regulation of human, antigen-specific B cell memory</td>
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<td>Nutzen des Placeboeffektes bei atopischer Dermatitis – Steigerung der pharmakologischen Wirkung bei Juckreiz durch Konditionierungs- und Erwartungsprozesse</td>
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<td>Cyclooxygenasen als Modulatoren allergischer Reaktionen, mechanistische Hintergründe und therapeutisches Potential</td>
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<td>Entwicklung eines 3D-Modells zur Simulation der initialen Frakturheilungsphase in vitro - Effektive Reduzierung von Tierversuchen in der Frakturheilungsforschung</td>
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<td>In vitro und in silico Modellierung der Immunopathogenese von Arthritiden zur effektiven Reduzierung der Zahl von Versuchstieren im Bereich der Therapieforschung</td>
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<td>ArthroMark</td>
<td>Biomarker und Bildgebung zur Diagnose und Stratifikation der Rheumatoiden Arthritis und Spondyloarthritis</td>
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<td>CONSUL</td>
<td>Comparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of Structural damage in the spine over two years in patients with ankylosing spondylitis: a randomized controlled multicentre trial</td>
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<td>e:Bio T-Sys</td>
<td>Interplay of epigenetic and transcriptional imprinting of T helper cell fate</td>
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<td>METARTHROS</td>
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<td>NEUROIMPA - Neuromimmunologie und Schmerz</td>
<td>Metabolic Impact on Joint and Bone Diseases*, TP 6 &quot;(Soluble markers of energy and glucose homeostasis in arthritis</td>
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<td>PROCLAIR</td>
<td>Linking Patient-Reported Outcomes with CLAims data for health services research in Rheumatology</td>
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<td>GLORIA</td>
<td>Comparing the effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for elderly patients with rheumatoid arthritis</td>
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<td>RAPID</td>
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<td>IMI PRECISESADS</td>
<td>PRECISESADS Molecular reclassification to find clinically useful biomarkers for systemic autoimmune diseases</td>
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<td>ESTHER</td>
<td>Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI: a randomised controlled trial</td>
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<td>Effects of glucocorticoids on the expression of Thioredoxin in human CD4+ T cells under hypoxic conditions</td>
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<td>Effects of glucocorticoids on membrane-bound glucocorticoid receptor (mGCR) expression in human monocytes under hypoxic conditions</td>
<td>Industry</td>
<td>Buttgereit</td>
<td>07/2012</td>
<td>10/2018</td>
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<td>PreTheraX</td>
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<td>Industry</td>
<td>Buttgereit</td>
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<td>RhGIO</td>
<td>Glucocorticoid-Induced Osteoporosis in Patients With Chronic Inflammatory Rheumatic Diseases or Psoriasis</td>
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<td>Buttgereit</td>
<td>10/2015</td>
<td>09/2018</td>
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<td>Compliance und Lebensqualität (CELL) bei PSS-Patienten - Entwicklung eines strukturierten Schulungsprogramms</td>
<td>Industry</td>
<td>Worm</td>
<td>2016</td>
<td>ongoing</td>
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<td>Einfluss von LC-PUFA auf die Ausprägung der allergischen Immunantwort im Mausmodell</td>
<td>Industry</td>
<td>Worm</td>
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<tr>
<td>Project Title/ Acronym</td>
<td>(sub)-Project</td>
<td>Funding Source</td>
<td>Scientist(s) in Charge</td>
<td>Start</td>
<td>End</td>
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<td></td>
<td>Pathogen-specific T helper cells as diagnostic sensors in CF patients</td>
<td>Foundation - Cystic Fibrosis Foundation (USA)</td>
<td>Scheffold</td>
<td>07/2015</td>
<td>ongoing</td>
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<tr>
<td>ArthroMo</td>
<td>Etablierung und Validierung eines humanen 3D in vitro Arthrose-Modells</td>
<td>Foundation - Wolfgang-Schulze-Stiftung</td>
<td>Buttgereit</td>
<td>10/2016</td>
<td>09/2017</td>
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<td>SNF: Sinergia</td>
<td>The alarmin interleukin-33 in infection, immunity and autoimmunity</td>
<td>Others - Schweizerischer Nationalfonds</td>
<td>Löhning</td>
<td>01/2016</td>
<td>12/2018</td>
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<td>BIH, SPARK</td>
<td>Affinity matrix for the depletion of plasma cells secreting pathogenic autoantibodies</td>
<td>Others - Berlin Institute of Health</td>
<td>Hiepe</td>
<td>07/2016</td>
<td>06/2018</td>
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<td>RefineMOMo</td>
<td>Optimierung des Schmerzmanagements im Maus-Osteotomie-Modell – Integration von Refinement-Untersuchungen in einer grundlagenwissenschaftlichen Studie</td>
<td>Others - BfR Bundesinstitut für Risikobewertung</td>
<td>Buttgereit</td>
<td>01/2016</td>
<td>12/2017</td>
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<td>EULAR Task Force Project on Glucocorticoids</td>
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<td>Others - EULAR</td>
<td>Buttgereit</td>
<td>05/2014</td>
<td>04/2017</td>
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<td>Antigen-spezifische T-Zellen als diagnostische Sensoren von latenter vs. aktiver Tuberkulose</td>
<td>Others - Labor Berlin – Charité Vivantes Services GmbH</td>
<td>Scheffold</td>
<td>04/2015</td>
<td>ongoing</td>
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as of December 31, 2016

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### Third party funds

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<th>DRFZ Groups</th>
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<td>DFG-SFB/TR</td>
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<td>Further DFG projects</td>
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<td>Government (BMBF</td>
<td>BMWI)</td>
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<td>EC/ FP-7/ Horizon 2020/ERC</td>
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<td>Industry</td>
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<td>Leibniz Competition</td>
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<td>Foundations</td>
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<td>557</td>
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<td>Others</td>
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<td>536</td>
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<td><strong>Total</strong></td>
<td>7,822</td>
<td>8,001</td>
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**Liaison Groups (Charité)**

<table>
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<tr>
<th>2015</th>
<th>2016</th>
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<tr>
<td>DFG-SFB/TR</td>
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<tr>
<td>Further DFG projects</td>
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<tr>
<td>Government (BMBF</td>
<td>BMWI)</td>
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<tr>
<td>EC/ FP-7/ Horizon 2020</td>
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<tr>
<td>Industry</td>
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<tr>
<td>Leibniz Competition</td>
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<td>Foundations</td>
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<tr>
<td>Others</td>
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<td><strong>Total</strong></td>
<td>3,104</td>
</tr>
</tbody>
</table>

as of December 31, 2016

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as of March 22, 2017
Qualifications

2015

Bachelor theses


Ruth Leben, 2015. Asymmetrische Zwei-Photon-Anregung zur Erweiterung der simultan detektierbaren Chromophoren intravitalmikroskopie, Beuth Hochschule für Technik Berlin

Franziska I. Szelinski, 2015. Assessment of SIGLEC-a (CD169) as possible biomarker for IFN-a in patients with primary Sjögren’s syndrome, TU-Berlin

Master theses/Diploma theses
Stefanie Gryzik, 2015. Funktionelle Charakterisierung Autoimmunerkrankungen-assozierter SNPs in nicht-kodierenden Regionen des humanen STAT4-Gens, Uni Potsdam


Julia Bluhm, 2015. The Role of Epigenetics in Foxp1 Gene Regulation in CD4+ T Lymphocytes, Biologisch-Pharmazeutischen Fakultät der Friedrich-Schiller-Universität Jena

Lisa Deichgräber, 2015. Untersuchungen zur HIF-Expression in T-Helferzellsubpopulationen, Beuth Hochschule für Technik Berlin

Maxim Nosenko, 2015. Engineering of artificial lymph nodes, Lomonosov Moscow University

Florian Padberg, 2015. The role of the Transcription factor Cax2 in Th17 Cell Development and Function, Technische Universität Braunschweig, Fakultät Maschinenbau

Roman Rauch, 2015. Einfluss von superparamagnetischen Nanopartikeln (SPIONs) auf die Differenzierung von humanen Monozyten zu Makrophagen, TU-Berlin

Kerstin Schönbeck, 2015. Expression und Funktion von Zytotoxischem T-Lymphozyten Antigen-4 (CTLA-4) in humanen mesenchymalen Stromazellen (hMSC), TU-Berlin

Erik Schröter, 2015. Impact of the fracture hematoma on MSC activation, Beuth Hochschule für Technik Berlin

Mario Simonetti, 2015. Tolerogene Wirksamkeit PEGylierter Peptide, TU-Berlin

Caroline Spee-Mayer, 2015. Role of Treg and IL-2 in the pathogenesis and treatment of SLE, HU Berlin

MD theses


Franziska Rauhut, 2015. Untersuchung der Relevanz von Interleukin-17 bei Patienten mit systemischem Lupus erythematoses, Charité

Meike Storms, 2015. Krankheitskosten der frühen juvenilen idiopathischen Arthritis, Charité


Katharina Wylon, 2015. Immunologische Wirkung einer Einmalgabe von 100.000 I.E. Cholecalciferol (Vitamin D), HU Berlin

PhD theses

Qingyu Cheng, 2015. Autoantibodies from long-lived ‘memory’ plasma cells of NZB/W mice drive immune complex nephritis, Charité

Kristina Conrad, 2015. Quantifizierung löslicher und zellulärer Biomarker bei Patienten mit Spondyloarthritiden, HU Berlin

Duc van Dang, 2015. Novel molecular mechanisms involved in the suppressive function in B cells, HU Berlin


Sarah Fleischer, 2015. Dysbalanced BCR signaling in B cells of patients with SLE, HU Berlin

Claudia Giesicke, 2015. Molecular and phenotypic studies of human antigen-specific effector- and memory B cells, HU Berlin

Vandana Kumari, 2015. Mechanisms underlying the regulatory function of tumor necrosis factor-α in skin inflammation, HU Berlin
Patrick Maschmeyer, 2015. Hepatic stellate cells induce gut tropism of CD8+ T lymphocytes, TU-Berlin

Maria Nassiri, 2015. Herz-Kreislauß-Medikamente als Kofaktoren der Anaphylaxie, HU Berlin

Anna Okhrimenko, 2015. Human bone marrow hosts resting polyfunctional long-term memory T cells, HU Berlin

René Riedel, 2015. Localization and Characterization of Murine Memory B Lymphocytes, FU Berlin

Stefanie Ries, 2015. New insights into pathways controlling B cell fate and IL-6 expression, TU-Berlin

Angelika Rose, 2015. Mechanisms of IL-2 therapy in murine models of systemic lupus erythematosus (SLE), TU-Berlin

Caroline Winsauer, 2015. The contribution of TNF from distinct cellular sources to autoimmune colitis, FU Berlin

Ina Wirries, 2015. Phänotypische und funktionelle Charakterisierung von CD19-Plasmazellen im humanen Knochenmark, HU Berlin

Jakob Zimmermann, 2015. The Role of Th1, Th17, and Th17+1 Cells for the Initiation and Perpetuation of Inflammatory Bowel Disease, HU Berlin

Hildrun Haibel, 2015. Therapie der axialen Spondyloarthritis, Charité

Bimba Hoyer, 2015. Die Rolle von Plasmazellen bei Autoimmunerkrankungen, Charité

Christopher Skopnik, 2016. Structure and function relationship of the IgM Fc receptor (FcµR), TU-Berlin

Olga Trupp, 2016. Tropheryma whippelii as potential source for novel immunoregulatory agents, Technische Universität Braunschweig

Siska Wilantri, 2016. Immuno-modulation by inhibitory cytokines coupled to antigenic peptide and carrier peptide, Charité


Pascal Klaus, 2016. Modulation of the humoral immune response by antithymocyte globulin (ATG), Charité - Universitätsmedizin Berlin

Marie Lettau, 2016. Etablierung immunohistochemischer Multifluoreszenzfärbungen für Gedächtnis-B-Zell-Lokalisationsstudien in humanen lymphatischen Geweben, Charité - Universitätsmedizin Berlin


Magdalena Kraft, 2016. Lebensdauer der im Rahmen einer mukosalen Immunantwort generierten Plasmazellen, Charité – Universitätsmedizin Berlin

Adrian Richter, 2016. Vergleich von Therapien der rheumatoiden Arthritis in Langzeitbeobachtungsfeldstudien unter besonderer Berücksichtigung fehlender Daten, Charité – Universitätsmedizin Berlin
<table>
<thead>
<tr>
<th><strong>PhD theses</strong></th>
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<tbody>
<tr>
<td>Jannike Bayat Sarmadi, 2016. <em>In vivo</em></td>
<td>analysis of CD3-specific antibody treatment-induced cellular changes in the small intestine, FU Berlin</td>
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<tr>
<td>Elisabeth Kenngott, 2016. Analysis and</td>
<td>characterization of the 13C carrier peptide, Humboldt-Universität</td>
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<tr>
<td>Maybritt Mardahl, 2016. Molecular</td>
<td>regulation of P-selectin ligand in Th1 and Th2 cells <em>in vitro</em>, Freie Universität Berlin</td>
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<tr>
<td>Anna Pascual-Reguant, 2016. Deciphering</td>
<td>tissue-specific signals and molecular mechanisms in control of TH17 cells, FU Berlin</td>
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<tr>
<td>Jennifer Pfeil, 2016. Induction of</td>
<td>antigen-specific tolerance by carrier-conjugated peptides, Humboldt-Universität</td>
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<tr>
<td>Laura Tech, 2016. Analysing the</td>
<td>effectors contributing to germinal center dynamics: proliferation, migration and differentiation of B cells <em>in vivo</em>, FU Berlin</td>
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<td><strong>Habilitation</strong></td>
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<tr>
<td>Paula Hoff, 2016. Osteoimmunologische</td>
<td>Prozesse in der initialen inflammatorischen Phase der Frakturheilung, Charité - Universitätsmedizin Berlin</td>
</tr>
</tbody>
</table>
Sitemap

Approach with local traffic

- approx. 10 min walking distance from Berlin Central Station "Hauptbahnhof" (yellow)
- Bus TXL, Stop "Charité - Campus Mitte"
- Bus 147, Stop "Schumannstraße"
- from Airport Berlin-Schönefeld: Train RE7 or RB14 to „S+U Hauptbahnhof“ (approx. 30 min.)
Title:
Intestinal microbiota has crucial functions in chronic inflammatory diseases. One of the immune-mediated mechanisms is the production of immunoglobulin A (IgA) at mucosal surfaces. Here we show the localization of IgA producing B cells in the small intestine.

Picture taken by Andrey Kruglov and Sandra Prepens