DRFZ BERLIN

Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

Leibniz Association

Annual Report 2017|2018

DRFZ BERLIN

Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

Leibniz Gemeinschaft

Annual Report 2017|2018

This Annual Report covers the research activities of the Deutsches Rheuma-Forschungszentrum Berlin (DRFZ), a Leibniz Institute, during the years 2017 and 2018.

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 Federal Ministry of Education and Research (BMBF), the Leibniz Association, the German Research Foundation (DFG), the European Commission, and through various other third parties, as mentioned in the text. Private foundations such as the Willy Robert Pitzer Foundation, the Rheumastiftung, the Dr. Rolf M. Schwiete Foundation and estates are an increasingly important pillar of research funding at the DRFZ. Thanks are due to all of them.

Photo: Werner E. Krätzig, the DRFZ laboratories

Content

About the DRFZ

Programme Area Pathophysiology of Rheumatic Inflammation

Programme Area Regenerative Rheumatology

Programme Area Epidemiology and Health Services Research

Technology Platforms, Shared Resource Labs and Support Services

Word of Welcome

Prof. Dr. med. Reinhold E. Schmidt,
President of Board of Trustees,
Hannover Medical University,
Department of Clinical Immunolgy and Rheumatology

Dear friends of the German Rheumatism Research Centre,

as the new President of the Board of Trustees of the DRFZ, a Leibniz Institute, it is my great pleasure to welcome and invite you to study the Annual Report for 2017/2018. I also like to congratulate the members of the DRFZ and its allied partners as well as its founding fathers, the Federal State of Berlin, the Immanuel Hospital, and last not least individuals like Jochen Kalden and Fritz Melchers on occasion of its 30th anniversary. I have followed this success story from its very beginning even as a reviewer long before it was established at its current place. Therefore I could observe over the decades when the DRFZ developed from a very small setting of scattered research groups into an internationally visible top rheumatology research institute. When in 2009 the DRFZ on recommendation of the German Research Council became a member of the Leibniz Association two program areas where created: Pathophysiology of Rheumatic Inflammation and Epidemiology of Rheumatic Diseases. This association with the continuous support of the Senate of Berlin and the Federal Ministry of Research has led to a highly dynamic and successful rheumatology research development at the DRFZ. In addition my predecessor Traudl Herrhausen managed also to obtain additional research support by the Willy Robert Pitzer Foundation for a new research group in the field of osteoarthritis, so that the third programme area Regenerative Rheumatology could be founded. The Dr. Rolf M. Schwiete Foundation is supporting the research for microbiota in inflammation, and the German Rheumatology Foundation funds the health care project for rheumatic diseases in children.

The Board of Trustees has the important task to ensure the quality of research. Since this responsibility is primarily with the directorate of the DRFZ and the leading scientists in the research areas the decisions about the permanent employment of scientists by the Board of Trustees is critical. This is of utmost importance in the coming years since the DRFZ as well as the Charité will see a generation change in the coming years. Therefore the Board of Trustees has appointed two years ago already a “Future Committee” with the task to develop future concepts for the Institute and prepare the search and appointments for Prof. Angela Zink, Prof. Andreas Radbruch as well as together with the Charité for Prof. Gerd Burmester. In regard to the succession in the program area Epidemiology and Health Care Research already last summer a workshop has taken place with national and leading European experts to discuss the future concept for this research area as well as later on collect suggestions for the position of the department head. Here meanwhile the appointment committee has already selected candidates from the application list. They will present their work and concepts in public in August 2019. For the succession of Andreas Radbruch and Gerd Burmester the DRFZ is involved in the “Future Immunology Committee”.

In addition the Leibniz Science Campus “Chronic Inflammation” is up for application for another extension period. Here Chiara Romagnani, an international recognized expert on the biology of innate lymphocytes and their role in inflammation, and Heisenberg-Professor at the Charité, has a central role. This Campus has led to other novel structural developments with the advancement of young scientists, a Graduate School of Chronic Inflammation (LeGCI), topic-oriented clubs, talks, seminars, a summer school as well as a translational aspect for patients like an outpatient clinics for inflammation. Last not least this Leibniz campus has led to even more intensive cooperation with other members of the Charité.

Most importantly in October 2018 the DRFZ was visited by an international evaluation committee from the Leibniz Association. I was very impressed by and the high quality research in rheumatology and the excellent preparation at the Leibniz evaluation. In July the Senate of the Leibniz Association and the GWK published the final evaluation of the institute: In this votum the research results of the DRFZ were described as of very high quality and the success of the institute for competitive grant money was acknowledged. And finally the institute was described as an international leading institution in the field of rheumatology research. This secures the basic funding for another 7 years period.

In the name of the Board of Trustees I like to thank all DRFZ staff for their education and enthusiasm presented in this annual report. Enjoy reading.

Yours

Reinhold E. Schmidt

Photos: Portrait: MHH; Campus: Kaiser/MHH

Word of Welcome

Professor Dr. med. Gerd-R. Burmester
Director of the Department of Rheumatology
and Clinical Immunology of the
Charité - Universitätsmedizin Berlin

Dear friends of the German Rheumatism Research Centre,

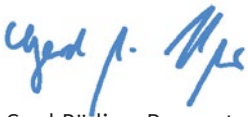
as a clinical and scientific partner of the German Rheumatism Research Centre (DRFZ), I would like to welcome all readers of the annual report.

Rheumatic and musculoskeletal diseases (RMDs), including systemic autoimmune diseases, lead to a great burden both for the affected patients and for society as a whole, with premature disability, loss of working hours and - if uncontrolled - a lower life expectancy. They are also one of the three main reasons why a patient visits a family doctor or specialist. Despite major advances in the diagnosis and treatment of RMDs, such as cytokine-oriented approaches and cell depleting/modulating therapies, there is still a great need for new treatment modalities. The Department of Rheumatology and Clinical Immunology of the Charité, and the Rheumatology Division of the Benjamin Franklin Campus, work closely together with the DRFZ to meet these challenges. This is reflected by a very fruitful interaction, both in the clinic and in the research laboratory.

What do we know about the current situation of people with arthritis? The epidemiological department of the DRFZ has gathered a great deal of knowledge. It carries out innovative and comprehensive studies and initiated the national database (core documentation), as well as the biologics register RABBIT, which are among the leading international databases. These not only analyse important clinical data, but will also provide important impetus for future clinical research, including studies initiated by investigators. In particular, important results have been achieved in the field of rheumatoid arthritis, especially in its early form, and spondyloarthritis. Several collaborative projects funded by the Federal Ministry for Education and Research (BMBF) and joint work in Collaborative Research Centres of the German Research Foundation (DFG) also bear witness to the successful cooperation between scientists at the Charité and the DRFZ.

What do people with arthritis want? Of course, pain relief and prevention of loss of function are very important. However, after a long conversation with the patient, the ultimate goal is healing. As with most internal diseases, this is difficult to achieve. However, is it impossible? Scientists from the DRFZ and the Charité are working hard to find new ways to put the disturbed immune system in a “fresh” state so that it no longer reacts to self-structures due to regained tolerance. Here, novel cell-oriented therapy approaches are carried out, ranging from rather mild methods to very complex autologous stem cell therapy.

What do we need to achieve our goals in the future? Of course, a close interaction between basic and clinical research, which leads to the implementation of the results from the laboratory bank into the clinic, is of utmost importance. The close cooperation between natural scientists and physicians from all areas of rheumatological research at the Charité and the DRFZ serves as a good example here. Fortunately, these units are also physically close to each other, which leads to an environment in which excellent research can pave the way for the best possible care of our patients.



Gerd-Rüdiger Burmester

Photos: Portrait: Charité; Campus: W.E. Krätzig

About the DRFZ

This section gives an overview of the DRFZ structure and its current performance data.

We report on important current developments, present the most important research networks in which the DRFZ either coordinates itself or is active as a partner and briefly explain a selection of outstanding current publications.

We report on outstanding prizes for our scientists, give insight into various scientific events, the promotion of young scientists at the DRFZ and show our activities in communicating our scientific tasks to the interested public.

In further chapters you can read the aims of the working groups sorted by programme areas and learn more about our Core Facilities and Technology Platforms.

www.drfz.de

Preface of the DRFZ Directors

30 Years Deutsches Rheuma-Forschungszentrum Berlin
10 Years member of the Leibniz Association

30 years ago in 1988, the federal state of Berlin together with the Immanuel Hospital, established an institute dedicated to rheumatic disease research: the German Rheumatism Research Centre (Deutsches Rheuma-Forschungszentrum Berlin, DRFZ). It started with a low budget and a few dedicated research groups dispersed all over the city of Berlin. In the year 2000, the DRFZ research groups moved into a modern building on the grounds of the campus of the Charité, in the centre of Berlin, a building shared with the Max Planck Institute for Infection Biology.

Today, the DRFZ is an internationally recognized comprehensive centre for research on rheumatic diseases, with currently 27 research groups and 5 technology platforms.

The Rheumatology and Clinical Immunology of the Charité - Universitätsmedizin Berlin, directed by Gerd-Rüdiger Burmester, is the major cooperation partner of the DRFZ, linked to it by a number of joint professorships and liaison research groups.

The DRFZ covers clinical, epidemiological and experimental aspects of rheumatology research.

*"Our mission is the development of improved, personalised, at best curative therapies for patients with rheumatic diseases and their rapid translation into clinical practice."**

In 2016, the DRFZ and the Charité established a joint "Leibniz ScienceCampus Chronic Inflammation", with the support of the Leibniz Association, as a comprehensive centre for integrated research on chronic inflammatory diseases.

"The Leibniz ScienceCampus Chronic Inflammation is a new cornerstone of the collaboration between Charité and DRFZ."

The Campus enables an exchange of concepts and therapeutic strategies among experts working on chronic inflammatory diseases, which can affect nearly any part of the body, but presumably share basic pathogenic mechanisms such as the ones described below, with research conducted at the DRFZ and other institutes in Berlin.

Member of the Leibniz Association

In 2009, following a recommendation of the German Science Council, the DRFZ became a member of the Leibniz Association, one of more than 90 research institutes jointly funded by the federal government and the states of Germany. To guarantee and maintain excellence of Leibniz research institutes, they are reviewed every seven years by an external review panel. The DRFZ just underwent this checkpoint evaluation again in 2018, an event that had required considerable preparation.

30 year anniversary

By the end of the year 2018, on the 20th of November, the DRFZ celebrated its 30 year anniversary in style. The Governing Mayor of Berlin, Michael Müller; the State-Secretary of the Federal Ministry for Research, Thomas Rachel; the President of the Leibniz Association, Matthias Kleiner; the Chair of the Charité, Karl Max Einhäupl; and the Chair of the Board of Trustees of the DRFZ, Reinhold Schmidt; emphasised the relevance of research at the DRFZ, its close cooperation with the Charité, and confirmed their continued support. Joachim Kalden and Fritz Melchers, who had been instrumental in founding the DRFZ, reviewed the development of the DRFZ since then, and Traudl Herrhausen, former president of the Board of Trustees of the DRFZ, discussed the pros and cons of private funding of research.

from left:
Michael Müller, Reinhold Schmidt, Andreas Radbruch, Matthias Kleiner, Karl Max Einhäupl

Photos: W.E. Krätzig, G. Breloer, G. Rottmann

**All quotes by Andreas Radbruch*

Prof. Dr. rer. nat. Andreas Radbruch
Scientific Director

Petra Starke
Adminstrative Director

Latest developments

Looking back at DRFZ research in the years 2017 and 2018, research groups leaving and new recruits joining the DRFZ have changed its profile considerably. Bimba Hoyer, principal investigator in the group of Falk Hiepe, became Chair of Rheumatology at the University of Kiel in 2017. Alexander Scheffold became Chair of Immunology at the University of Kiel in 2018. With these two departures, considerable expertise on plasma cells and T lymphocytes left the DRFZ. Julia Polansky-Biskup accepted a position at the Berlin Brandenburg Center for Regenerative Therapies, but remains connected to the DRFZ, as head of a liaison research group. Liaison research groups were also established for the new Chair of Microbiology at the Charité, Andreas Diefenbach; the new Charité Rheumatology recruited Antigoni Triantafyllopoulou and Tilman Kallinich, paediatric rheumatologist of the Charité. Ahmed Hegazy started his Lichtenberg Professorship for Translational Gastroenterology at the Charité. With Chiara Romagnani, Antigoni Triantafyllopoulou and Andreas Diefenbach, the DRFZ now hosts leading experts in the field of the innate immune system, specifically defining its role in inflammation. With Tilman Kallinich, juvenile idiopathic arthritis is now investigated with the tools available at the DRFZ, and Ahmed Hegazy adds back expertise on T cells in chronic inflammation, with a focus on a potential new target, the cytokine oncostatin.

Targeting pathogenic memory cells

The established research lines of the DRFZ continue to unravel the role of the adaptive immune system in driving chronic inflammation. Pathogenic memory plasma cells, originally described at the DRFZ, secrete antibodies that drive chronic inflammatory diseases and are refractory to conventional therapies, making them a new target deserving novel therapeutic strategies.

"Our aim is to find targets for novel therapies that specifically eliminate pathogenic memory cells and strengthen regulatory cells."

For the generic ablation of all plasma cells, both protective and pathogenic ones, several options have been developed and recently tested in clinical trials. Tobias Alexander and Falk Hiepe coordinated the participation of the Charité and the DRFZ in a nationwide clinical trial using the proteasome inhibitor *Bortezomib* "off-label", a drug approved for multiple myeloma, for therapy-refractory patients with Systemic Lupus Erythematosus. The trial was very successful in that the patients' disease activity dropped significantly and refraction to conventional therapy was broken. This was an important confirmation of the concept developed at the DRFZ; namely that pathogenic plasma cells can be a roadblock to successful therapy of rheumatic diseases.

More desirable therapeutic strategies would, however, be less generic and more selective, targeting only the pathogenic plasma cells, and not interfering with the acquired immune protection of the patients. Here the DRFZ has achieved two breakthroughs in the recent past. Firstly, the group of Koji Tokoyoda has identified laminin-β1 as a specific and required component of the survival niche for IgG secreting memory plasma cells in the bone marrow, presumably including the most pathogenic plasma cells. Laminin-β1 thus appears as the first candidate to target IgG secreting memory plasma cells selectively. Even more selective is an approach pioneered by Falk Hiepe and his group. They use conjugates of (auto)antigens and plasma cell-specific antibody fragments, to label plasma cells with a particular antigen. Plasma cells secreting antibodies binding to that (auto)antigen then mark these plasma cell for lysis by complement. This original concept has now for the first time been successfully validated in a preclinical mouse model.

In addition to pathogenic memory plasma cells, T lymphocytes can also induce chronic inflammations, a fact that has been known for a long time. However, it has been less clear whether they also are required to drive ongoing inflammation, that is, whether they are a relevant target in patients with an established disease. In the past years, the groups of Hyun-Dong Chang, Mir-Farzin Mashreghi and Andreas Radbruch had identified several genes, specifically Twist1, Hopx, and microRNAs, in particular miR-148a, exclusively expressed

The DRFZ on the campus of the Charité in Berlin Mitte, between main station and Reichstag

30th anniversary ceremony in the lobby of the DRFZ.

by T lymphocytes isolated from inflamed tissues of patients with intestinal or rheumatic inflammation. In 2017, they could demonstrate that these cells indeed control chronic inflammation once it is established, by eliminating them with antagomirs blocking miR148a in a murine model of chronic intestinal inflammation. This makes these cells another novel and essential target, requiring new therapeutic strategies, as these cells are also refractory to conventional therapies, like pathogenic memory plasma cells.

Regeneration

The programme area „Regenerative Rheumatology“ was established at the DRFZ in 2015, initially with two research groups. They are developing tools and models to study the most common rheumatic disease, osteoarthritis, on the level of single cells. The first research results are to be expected soon.

Improving quality and outcomes of care

The programme area “Epidemiology and Health Services Research” investigates the safety and effectiveness of new therapies in adults and children with rheumatic and musculoskeletal diseases (RMD), analyses the impact of biological, clinical and environmental factors on disease progression and outcome, and evaluates the quality and adequacy of health care. Research is based upon a network of more than 500 rheumatologists who contribute to the longitudinal observational cohort studies. The overall goal is to improve the lives of people with RMD by providing reliable data that inform clinical and political decision making.

Hwayoon Lee, Viola; Thomas Hoppe, Piano

Research funding

Research at the DRFZ is made possible by the core funding provided by the State of Berlin and the Federal Government. It is supported by the Leibniz Association, the German Research Foundation (DFG), the Federal Ministry of Education and Research (BMBF), the European Research Council (ERC) and the European Commission (EC), which support individual projects. It should be noted that in 2018, the liaison research groups of Antigoni Triantafyllopoulou and of Julia Polansky-Biskup both won an ERC starting grant, confirming the high quality of their research. Furthermore, we are grateful to the Rheumastiftung, the Willy Robert Pitzer Foundation and the Dr. Rolf M. Schwiete Foundation. Each of these private foundations most generously supports one outstanding research group at the DRFZ, and allows the DRFZ to explore health care, osteoarthritis and the contribution of microbiota to chronic inflammation.

We say thank you

A very special “thank you” goes to Traudl Herrhausen. She was president of the Board of Trustees of the DRFZ for six years and has now handed over to Reinhold Schmidt. The DRFZ has hugely benefited from her personal engagement and dedication.

We also say thank you to Helen Foster, Iain McInnes and Brigitta Stockinger for their outstanding job as long-term members of our Scientific Advisory Board, whose terms have ended in December 2017.

In this Annual Report 2017/2018 we present our research concept and the most important results of the last two years. For sustainability reasons, we have reduced the volume of the printed report. You can find more detailed information, such as publications, cooperation partners, or research networks on the DRFZ website.

Enjoy reading.

Andreas Radbruch and Petra Stark

Brief history of the DRFZ

in the 70s

In the beginning of the seventies the idea of „focused research on rheumatic diseases“ is born: The Robert Koch Institute in Berlin under the direction of Hans Kröger, Department of Biochemistry, launches a broad-based analysis of chronic diseases in Germany. One of the most important results is the high number of people affected by rheumatic diseases. Close cooperation begins with Raimund Frankl, Head of Internal Medicine at the Immanuel Krankenhaus.

December 1976. The “Information Colloquium on Rheumatism” takes place in Berlin. Rheumatologists from all over Germany are invited. The aim is to find out how rheumatism can be brought into focus in Germany.
First results are published in 1978 as a report by the Robert Koch Institute. It presents proposals for patient care, teaching and research and forms the basis for the discussion on the topic of rheumatic diseases in the German Parliament.

in the 80s

December 13th, 1988. The State of Berlin and the Immanuel Krankenhaus establish the German Rheumatism Research Centre Berlin, a foundation under civil law.

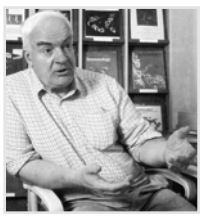
The founding fathers of the DRFZ are Hans Kröger, Robert Koch Institute; Elimar Brandt, Immanuel Krankenhaus, Fritz Melchers, then Director of the Basel Institute for Immunology; Joachim Kalden, then Director of the Rheumatological University Clinic in Erlangen, as well as Albrecht Hasinger (†1994), at the time State Secretary in the Senate Administration for Health of the State of Berlin.


Hans Kröger, Albrecht Hasinger

Fritz Melchers, Jochen Kalden

Elimar Brandt

1989. The founding Scientific Director Avrion Mitchison establishes the research field “Immunology of Rheumatic Diseases” with independent small research groups, following the concept of the Basel Institute of Immunology. The DRFZ is initially under the auspices of the Senate Administration for Health. Later, responsibility is transferred to the Senate Administration for Science.



Avrion Mitchison

in the 90s

1990. The first laboratories are spread all over the city, located at the Robert Koch Institute, the Immanuel Krankenhaus in Berlin Wannsee and the Freie Universität in Steglitz.

1991. The research area “Epidemiology” is established, headed by Angela Zink.

1996. Andreas Radbruch succeeds Avrion Mitchison as Scientific Director.

1998. The German Council of Science and Humanities (Wissenschaftsrat) positively evaluates the DRFZ.

The DRFZ at the Robert Koch Institute, 1995

in the 2000s

2000. Relocation of the DRFZ to the new building on the Campus Mitte of the Charité, shared with the Max Planck Institute for Infection Biology.

2003. The German Council of Science and Humanities again evaluates the DRFZ, rates it as an excellent research institute, and recommends it as a member of the Leibniz Association.

2007. Informal association to the Leibniz Association.

2008. Establishment of two programme areas: “Pathophysiology of Rheumatic Inflammation” and “Epidemiology of Rheumatic Diseases”, following the Leibniz Association bylaws.

2009. Petra Starke is appointed Administrative Director.

2009. Full membership of the Leibniz Association, joint funding by the Federal Government of Germany and the State of Berlin.

2011. Evaluation by the Leibniz Association, recommendation to continue and increase funding.

2015. The third programme area “Regenerative Rheumatology” is established.

2018. Regular evaluation by the Leibniz Association - the result will be announced soon.

The DRFZ today has more than 200 employees and a comprehensive scientific culture

Good to know

The DRFZ meets an urgent medical need

- More than 100 different rheumatic and musculoskeletal diseases are described.
- About 1.5 million adults and about 20.000 children and teenagers suffer from inflammatory rheumatic diseases in Germany.
- An additional 5 million patients suffer from osteoarthritis.
- Although available treatment has improved over the last years, there is still no cure for most rheumatic diseases. They continue to cause considerable morbidity and mortality. Most of the patients are on lifelong medication.
- Rheumatic diseases are on top of the expenditure of the health insurances and are the second most frequent cause for permanent work disability.

The mission of the DRFZ...

... is to investigate the long term outcomes of rheumatic diseases, including the impact of current treatment options, in order to inform clinical decision making, identify unmet needs and improve health care. Biomedical research identifies the cells initiating and those driving rheumatic diseases, and the underlying molecular mechanisms. Our aim is the development of improved, personalised, at best curative therapies for patients with rheumatic diseases, and their rapid translation into clinical practice.

The DRFZ

- ...was founded in 1988 and has been a member of the Leibniz Association since 2009.
- ...has 27 research groups in three programme areas.
- ...is closely integrated into the Charité medical campus by joint laboratories, 14 liaison research groups, 6 joint professorships, joint applications for funding and the Leibniz ScienceCampus Chronic Inflammation.
- ... in collaboration with its partners from Charité and Max Planck Institute for Infection Biology, runs cutting edge technology platforms for the analyses of single immune cells, the cells of their environment and their interactions.
- ...cares about animal welfare of our laboratory animals in many respects *(page 84)*.

Joint professorships between DRFZ and ...

... the Charité

- Andreas Radbruch, "Experimental Rheumatology", since 1998
- Angela Zink, "Epidemiology of Rheumatic Diseases", since 2003
- Falk Hiepe, "Translational Rheumatology", since 1997
- Anja Hauser, "Intravital Microscopy and Immune Dynamics", since 2012
- Kirsten Minden, "Health Services Research in Rheumatology", funded by the Rheumastiftung, since 2015
- Max Löhning, "Osteoarthritis Research", funded by the Willy Robert Pitzer Foundation, since 2015

... the Freie Universität Berlin

- Raluca Niesner, „Dynamic and Functional *in vivo* Imaging", since 2018

Liaison Research Groups

This instrument developed by the DRFZ offers clinicians and basic scientists of partner institutions research opportunities at the DRFZ. The liaison groups are co-financed to varying degrees by the partner institutions and the DRFZ, their common denominator being research space, and access to the infrastructure and technology platforms at the DRFZ.

The people behind the research

- 205 employees work at the DRFZ, 67% of them are women.
- The proportion of foreign employees is currently 13%, from 19 nations.
- Scientists with backgrounds in biology, chemistry and biochemistry, biotechnology, mathematics, physics, sociology, statistics as well as physicians from various disciplines and veterinarians do research together.
- About 60 natural science and 30 medical doctoral students work at the DRFZ. Of these, one third is involved in graduate programmes *(page 23)*.
- Projects and developments are discussed in 13 different scientific clubs and seminars. Some lectures are available in the media library on the DRFZ website.

Funding

The core funding of the DRFZ is jointly financed by the Federal Government and the State of Berlin. In addition, the scientists apply for third party funding from various national and international funding sources. At present, 55 third-party-funded projects are being carried out

at the DRFZ, many of them being network projects.

Engagement of DRFZ scientists

DRFZ scientists are engaged in scientific societies, especially in the fields of rheumatology, immunology and flow cytometry and on the editorial boards of scientific journals and organising boards of "summer" schools for graduate and postgraduate students. They also actively engage in the dialogue with patients with rheumatic diseases.

The DRFZ enters the film world

The DRFZ has produced its first image film. The result can be watched on our website in the media centre.

Certificates of the DRFZ

Together with the Department of Rheumatology and Clinical Immunology of the Charité, the DRFZ is certified as one of the 31 EULAR Centre of Excellence.
www.eular.org

The DRFZ is a certified training centre of the German Society for Immunology (DGfI).
www.dgfi.org

For the third time, the DRFZ received the *Total E-Quality Award*, awarded by the Federal Ministry for Family Affairs, Senior Citizens, Women and Youth. The DRFZ received an excellent rating for handling family-related leaves, also for employees with non-permanent contracts, as well as for implementing virtual desktops for remote work.

DRFZ image film: making of

Visit the media centre for the first short image about the DRFZ

www.drfz.de

QR code leads directly to the movie

DRFZ image film: making of

The DRFZ in the Leibniz Association

Since 2009, the DRFZ is a member of the Leibniz Association and is active at various levels:

The DRFZ is engaged in two Research Alliances and one Research Network. In 2018, the DRFZ itself successfully applied for and coordinates the *Leibniz Network on Immune Mediated Diseases* The DRFZ has also been successful in applying for research grants in the Leibniz competition, such as a Junior Research Group (Kevin Thurley) and two network projects.

Since 2016, the *Leibniz ScienceCampus Chronic Inflammation* brings together experts of different disciplines to investigate underlying mechanisms of chronic diseases. As a comprehensive centre, it further strengthens the close collaboration with the Charité.

Andreas Radbruch has again been confirmed as spokesperson of Section C Life Sciences and thus as member of the Leibniz Executive Board. He also represents the Leibniz Association in the DEAL Commission of the German Research Alliance, negotiating the "publish and read" contracts with the major publishers and in the Forum Health Research, initiated by the Federal Ministry of Education and Research (BMBF). In 2018, Fritz Melchers, Senior Group Leader at the DRFZ, received a Leibniz Chair for Lifetime, acknowledging his personality and scientific achievements.

Postdocs and students of the DRFZ are involved in the respective Leibniz Doctoral Network and Leibniz Postdoc Network.

The individual activities are described on the following pages.

Leibniz about Leibniz

The Leibniz Association unites 95 institutions throughout Germany which are legally, scientifically and economically independent entities. They include both research institutes and facilities that mainly provide infrastructure for research and society.
Leibniz institutions collaborate intensively with universities...
..they are funded jointly by the German Federation and the countries, employing some 20,000 individuals, including 10,000 researchers. The entire budget of all the institutes is approximately 1.9 billion Euros.

Leibniz Association

www.leibniz-gemeinschaft.de

Organisational chart

Data Security, Animal Welfare, Job Safety, Ombudsperson, Equal Opportunities

Board of Trustees
Schmidt

Scientific Advisory Board
Meuer

Scientific Director
Radbruch

Administrative Director
Starke

Pathophysiology of Rheumatic Inflammation

Signal Transduction Baumgrass	**Glucocorticoids and Bioenergetics** Buttgereit (1a)	**Schwiete Lab for Microbiota and Inflammation** Chang	**Developemental and Mucosal Immunology** Diefenbach (1d)	**B Cell Memory** Dörner (1a)
Immunodynamics Hauser (1a)	**Inflammatory Mechanisms** Hegazy (1b)	**Autoimmunology** Hiepe (1a)	**Chronic Immune Reactions** Hutloff (2)	**Chronic Inflammatory Diseases of Childhood and Adolescence** Kallinich (1f)
Chronic Inflammation Kruglov	**Humoral Immune Regulation** Kubagawa	**Lymphocyte Development** Melchers	**Biophysical Anlaytics** Niesner (3)	**Immuno-Epigenetics** Polansky-Biskup (1e)
Cell Biology Radbruch	**Innate Immunity** Romagnani (1a)	**Systems Biology of Inflammation** Thurley	**Osteoimmunology** Tokoyoda	**Macrophages in Chronic Inflammation** Triantafyllopoulou (1a)
Allergology Worm (1c)		**Epidemiology and Health Services Research**		
Regenerative Rheumatology		**Pediatric Rheumatology and health services research** Minden	**Pharmacoepidemiology** Strangfeld	
Therapeutic Gene Regulation Mashreghi	**Pitzer Lab of Osteoarthritis Research** Löhning (1a)	**Health Services** Zink	**Spondyloarthritides** Poddubnyy (1b)	

Technology Platforms, Shared Resource Labs and Support Services

Flow Cytometry & Cell Sorting (FCCF) Chang, Kaiser	**Mass Cytometry (MCCF)** Mei, Grützkau	**Central Laboratory for Microscopy (CINIMA)** Hauser, Niesner	**Immune Monitoring** Grützkau	**Regine-von-Ramin Lab Molecular Rheumatology** Grützkau, Häupl, Mashreghi
Animal Facility and Embryotransfer Schulz, Pfeffer, Hutloff		**Central Laboratory** Lehmann	**Support Services** Administration, Scientific Coordination, IT-Service, Public Relations, Lab Kitchen, Library, Reception, Store	

Liaison-Cooperation Partners

(1) Charité – Universitätsmedizin Berlin
- (a) Rheumatology and Clinical Immunology, Burmester
- (b) Gastroenterology, Infectiology and Rheumatology, Siegmund
- (c) Dermatology, Venerology and Allergology, Ghoreschi
- (d) Institute of Microbiology, Infectious Diseases and Immunology, Diefenbach
- (e) Berlin-Brandenburg Center for Regenerative Therapies, BCRT, Volk
- (f) Charité - Pediatrics, Pneumonology and Immunology with intensive Medicine, Mall

(2) Robert Koch Institute until 9/18, then DRFZ

(3) Freie Universität Berlin, Faculty of Veterinary Medicine

as of June, 2019

DRFZ Boards

Board of Trustees

Permanent Members

Prof. Dr. Karl-Max Einhäupl
CEO Charité - Universitätsmedizin, Berlin, DE

Prof. Dr. Andreas Krause
Immanuel-Krankenhaus GmbH, Berlin, DE

Dr. Björn Maul
Senate of Berlin, DE

Dr. Christina Pesavento
Federal Ministry of Education and Research (BMBF), Berlin, DE

Elected Members

Prof. Dr. Reinhold E. Schmidt
President since 2018,
Hannover Medical University, DE

Traudl Herrhausen
President until 2017, Bad Homburg, DE

Prof. Dr. Erika Gromnica-Ihle
Honory president Deutsche Rheuma-Liga, Berlin. DE

Prof. Dr. Jörg Hacker
President Deutsche Akademie der Naturforscher Leopoldina, Halle/Berlin, DE

Dr. Helmut Häuser
Willy Robert Pitzer Foundation, Frankfurt/Main, DE

Prof. Dr. Elisabeth Märker-Hermann
Dr. Horst Schmidt Kliniken GmbH, Wiesbaden, DE

Botho von Portatius
Idstein, DE

Prof. Dr. Georg Stingl
Allgemeines Krankenhaus– Universitätskliniken, Wien, AT

from left: S. Finken, Ch. Pesavento, E. Gromnica-Ihle, E. Märker-Hermann, J. Hacker, R. Schmidt, G. Stingl, H. Häuser, A. Krause, B. von Portatius, G-R. Burmester

Scientific Advisory Board

Prof. Stefan Meuer
Chair, Ruprecht Karls University, Heidelberg, DE

Prof. Johan Askling
Karolinska Institute, Stockholm, SE

Prof. John Isaacs
Newcastle University, UK

Prof. Frank Luyten
(from 2018), Katholieke Universiteit, Leuven, BE

Prof. Vivianne Malmstroem
(from 2018), Karolinska Institute, Stockholm, SE

Prof. Katja Simon
(from 2018), University of Oxford, UK

Prof. Helen Foster
(until 2017), Newcastle University, UK

Prof. Iain McInnes
(until 2017), University of Glasgow, Scotland, UK

Prof. Brigitta Stockinger
(until 2017), The Francis Crick Institute, London, UK

from left: B. Stockinger, H. Foster, J. Askling, S. Meuer, October 2017

Administration, technical staff and officers

Administration

Assistant to the Administrative Director
Holger Schnurre

Travel costs / Secretary
Marion Nowak

Personnel Department
Sabine Wernhard

Finance Department
Norbert Adametz

Third-party money
Annette Bastigkeit, Alexander Hinz, Corinna Krüger, Manuela Ljunggren, Dirk Schlienz, Carsten Tressin

Purchasing Department
Alexander Hinz, Catja Wendt

Scientific Services

Scientific Director's Office
Tanja Durez, Christine Raulfs

Science Management
Dr. Ute Hoffmann, Dr. Eva-Juliane Kreiß, Dr. Elke Luger, Dr. Mairi McGrath, Dr. Katrin Moser

Public Relations
Hilmar Fünning, Jacqueline Hirscher

Library
Beate Löhr

Veterinarians
Anna Pfeffer, Dr. Anja Schulz

Technical Services

Animal Facilities/ET Lab
Sabine Gruczek, Maria Hoffmann, Christina Kasprzak, Manuela Ohde, Hong Minh Pham, David Schreiber, Paul Streckert, Vivien Theißig, Patrick Thiemann, Paolo Rosellini Tognetti

Animal Caretaker Trainee
Tobias Acosta-Ruediger

Store
Virginie Loze

Lab Kitchen
Birgit Füßel, Angela Lindner, Regina Schuck,

IT Services
Hilmar Frank, Hilmar Fünning, Antje Klauß, Christopher Lehmann, Falk Neumann

Reception Desk
Wolfgang Höhn

Officers

Job Safety Officer
Robert Günther

Biological Safety Officer
Dr. Imme Sakwa

Equal Opportunity Officer
Heike Hirseland, Dr. Elke Luger

Data Security Officer
Dina Schreckeis

Animal Welfare Officer
Anna Pfeffer

Ombudsperson
Prof. Dr. Peter-Michael Kloetzel

Photo: Bavaria Luftbild Verlags GmbH

Staff rotation

In 2017 and 2018, new groups have been added, group leaders have retired, existing groups have changed:

2017 The new Charité liaison groups „Developmental and Mucosal Immunology“ **Andreas Diefenbach** and ...

... **Antigoni Triantafyllopoulou** “Myeloid Cells and Granulocytes” strengthen research on the mechanisms of the innate immune system at the DRFZ.

2017 **Chiara Romagnani**, group leader at the DRFZ since 2009, wins a Heisenberg Professorship at the Charité, enabled by the DRFZ. Her research group “Innate Immunity” continues as a liaison group.

2017 **Julia Polansky-Biskup**, senior scientist in the group of Alf Hamann, is appointed to the Berlin-Brandenburg Center for Regenerative Therapies, and starts the liaison research group “Immuno-Epigenetics” at the DRFZ.

2017 **Alf Hamann**, head of the senior research group “Experimental Rheumatology” at the DRFZ, retires.

2018 **Raluca Niesner**, group leader at the DRFZ since 2010, becomes Professor for “Dynamic and Functional *in vivo* Imaging” at the Freie Universität Berlin, Department of Veterinarian Medicine; her group “Biophysical Analytics” becomes a liaison group

2018 **Petra Bacher**, postdoc in the group of Alexander Scheffold, becomes Junior Professor for Immunology and Immunogenetics at the University of Kiel.

2018 **Sergei Nedospasov**, head of the research group “Inflammation Biology”, retires. The scientific theme is continued in the group Andrey Kruglov.

2018 **Alexander Scheffold** becomes Professor for Immunology and Director at the Institute for Immunology, University of Kiel.

2017 **Ahmed Hegazy** returns from the Kennedy Institute for Rheumatology in Oxford and starts the Charité liaison group “Inflammatory Mechanisms”. In 2018 he wins a Lichtenberg Professorship.

2018 **Bimba Hoyer,** senior scientist in the group of Falk Hiepe, becomes Professor for Rheumatology at the University of Kiel.

2017 **Hyun-Dong Chang,** senior scientist in Andreas Radbruch’s group and Scientific Head of the Flow Cytometry Core Facility, starts his own research group “Schwiete Lab for Microbiota and Inflammation”, funded by the Dr. Rolf M. Schwiete Foundation.

2018 **Kevin Thurley** starts the Leib-niz junior research group “Systems Biology of Inflammation”. The DRFZ had recruited him from the University of California, USA.

2017 **Fritz Melchers**, founding father of the DRFZ and former senior scientist at the Max Planck Institute for Infection Biology, starts as senior research group leader at the DRFZ.

2019 **Tilmann Kallinich,** paediatric rheumatologist at the Charité, starts his liaison group “Chronic Inflammatory Diseases of Childhood and Adolescence“.

Performance data

Funding

The core funding of the DRFZ is jointly financed by the Federal Government and the State of Berlin.

In addition, scientists of the DRFZ apply for funding from various national and international sources. Many research grants are network projects, linking the DRFZ to scientists from the Charité and other major competence centres of biomedical research. Currently, several DRFZ groups are involved in two Collaborative Research Centres (TRR130, TRR 241), one Priority Programme (1937), one Clinical Research Unit (2165), one Shared Resource Laboratory and the NeuroCure Cluster of Excellence of the German Research Foundation (DFG). The DRFZ is also engaged in several networks for musculoskeletal diseases of the Federal Ministry for Education and Research (BMBF) and in network projects of the Leibniz Association. On the European level, the DRFZ is part of the European Innovative Medicines Initiative (IMI) RTCure.

In addition to network projects, individual project grants from various sources are an important part of research funding. In 2018, two liaison group leaders have won a prestigious Starting Grant of the European Research Council (ERC).

Furthermore, private foundations have enabled the DRFZ to start new research groups in the last years.

Epidemiological registers as well as the national databases for children and adults are enabled by unconditional funding of consortia of pharmacological companies.

Selected network projects, registers and projects funded by private foundations are introduced on pages XXff.

Qualification

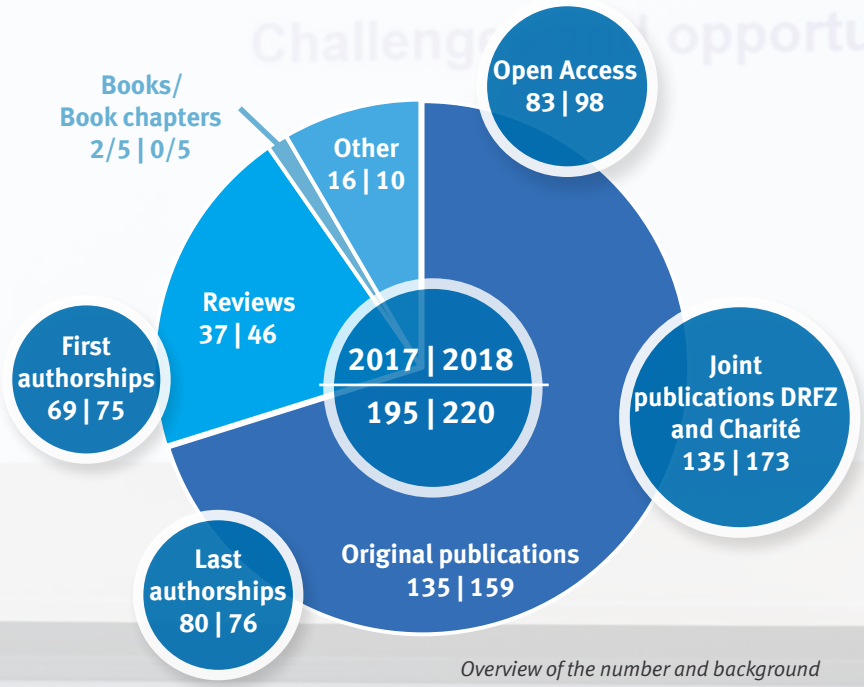
More than 100 PhD, MD, master and bachelor students are working at the DRFZ. Each year about 35 of them graduate.

Qualifications	2017	2018
Bachelor, Magister, Diplom, Master	27	11
Dr. rer. nat./PhD, Dr. Ing, Dr. rer. medic.	10	14
Dr. med.	3	10
Habilitations	1	1

Scientific output

The research results of the DRFZ are mainly published in international journals. An overview of all publications can be found on the DRFZ website.

www.drfz.de



Overview of the number and background of publications at the DRFZ

Scientific communication

Recent research results are regularly presented and discussed at numerous scientific conferences like the annual meetings of...

- the German Society for Rheumatology (DGRh)
- the German Society of Immunology (DGfI)
- the Conference of the German Society for Cytometry (DGfZ)
- the Conference of the European League against Rheumatism (EULAR)
- the CYTO Congress of the International Society for Advancement of Cytometry (ISAC)
- the Meeting of the American College of Rheumatology (ACR)
- the European Congress of Immunology (ECI)

...or at various workshops and meetings of the network projects the DRFZ is engaged in.

The expertise of the DRFZ scientists is also reflected in the number of invited lectures they give at regional, national and worldwide meetings.

Invited talks	2017	2018
International and national talks	137	182

Background picture: Andreas Radbruch, incoming president of the European Federation of Immunological Societies (EFIS), at the European Congress for Immunology (ECI) in Amsterdam, 2018

Leibniz ScienceCampus Chronic Inflammation

CHRONIC INFLAMMATION
Leibniz ScienceCampus Berlin

The Campus-Concept: research, training and treatment across disciplines

The ScienceCampus Chronic Inflammation is a platform for basic researchers and clinicians which enables the comparative analysis of chronic inflammatory diseases of the joints, the gastrointestinal system, the skin, the vasculature, the pancreas, kidneys and the nervous system. It aims to translate therapeutic concepts from one disease to others, based on the scientific understanding that similar mechanisms drive inflammatory diseases independent of the organ affected.

Beyond the scientific perspective, the Campus raises public awareness of chronic inflammation as a major unmet medical challenge.

Established in 2016, the Campus is jointly funded by the Leibniz Association, the Charité and the DRFZ for initially four years.

Bringing together players of different disciplines is the major aim of the ScienceCampus. Seven departments of the Charité and the Max Planck Institute for Infection Biology are partners. We strongly benefit from the combination of expertise in different fields: Together, we investigate underlying mechanisms of chronic inflammations and use this knowledge to further develop tailored therapies for patients.

Campus Talk, DRFZ

Scientific communication: the Chronic Inflammation Forum (CIF)

The CIF bundles the scientific discussion measures and educational programmes for young researchers of the ScienceCampus. A central element for communication are the **Scientific Discussion Clubs** on the various scientific foci of the ScienceCampus. They provide a platform for regular discussion and quality control of projects, as well as for initiation of cooperation and networking. International experts are regularly invited to present their research and to discuss their concepts in the **Campus Talk Series**.

In the **Inflammation Lecture**, a basic scientist and a clinician give a joint lecture on a certain chronic inflammatory disease. These "tandem talks" are the first ones of their kind in Berlin; they provide information about state-of-the art treatment, as well as about the current state of research. The Inflammation Lectures illustrate how basic research affects therapies and vice versa.

In 2017 and 2018, seven Inflammation Lectures and ten Campus Talks took place. Most of these talks can be watched online in the **media centre.**

www.drfz.de

The Inflammation Network for patients - an assembly of clinical experts

Often, patients are treated according to their long-standing medical history, meaning that e.g. patients with chronic nephritis are usually seen by their nephrologists only, even if their chronic inflammation also affects organs other than the kidneys. Patients with complex inflammations difficult to treat are enrolled in the **"Entzündungssprechstunde"** (clinical access point), and benefit from the broad expertise of the Clinical Inflammation Network: An interdisciplinary team of specialists, who together assess the patients and develop tailored, personalised therapies.

Transfer to the public

Raising the public awareness of chronic inflammatory diseases and informing patients about our research is a central part of the ScienceCampus. For the third time, it participated in the annual Long Night of Science at the DRFZ: experts from Berlin rheumatological clinics and researchers from the DRFZ inform the visitors in the new **Public Lecture Series** about new therapies and research approaches for various chronic inflammatory diseases.

www.drfz.de

The lectures are available in the **media centre**.

Spokespersons
Dean of the Charité
Axel R. Pries (right)
Scientific Director of the DRFZ
Andreas Radbruch (left)

Scientific Advisory Board
Burkhard Becher, CH; Lorenzo Moretta, IT; Reinhold E. Schmidt, DE; Stefan Ehlers, DE; Fiona Powrie, UK (missing on the picture).

Photos: Arne Sattler

Summer School „Connecting Concepts of Chronic Inflammation“

In May 2018, the first annual Leibniz-Summer School was held in Berlin. Young researchers with basic science or medical background were introduced to real patient cases. They were introduced to the disease from the patients‘ point of view. The aim was to understand and combine the approaches of clinicians on the one hand and basic researchers on the other hand in developing optimal diagnostic and treatment concepts. The second Summer School was held in May 2019.

LeGCI Graduate School

LeGCI

Leibniz Graduate School Chronic Inflammation

In 2017, the graduate forum „From Basics to Clinic“, organised by the PhD students, kicked off the Leibniz Graduate School on Chronic Inflammation (LeGCI). The programme is tailored to the research focus of the DRFZ and the ScienceCampus. In an interdisciplinary approach, it offers training and consulting for scientific and medical doctoral students of the DRFZ and our partners of the ScienceCampus.

1st International Symposium

In March 2018, the ScienceCampus held its **1st International Symposium on Chronic Inflammation - One Disease, a Thousand Manifestations**. 15 speakers from Germany, Sweden, Great Britain, France and the USA started a lively debate on various topics.

Leibniz Network Immune Mediated Diseases

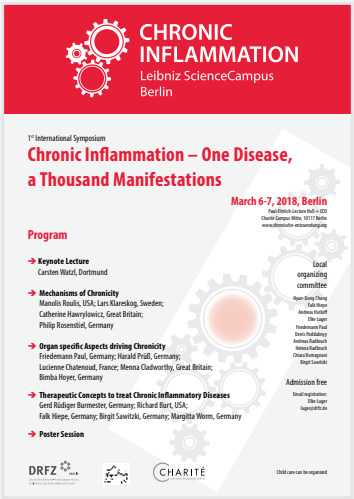
In 2018, the ScienceCampus initiated a **Network on Immune Mediated Diseases** within the Leibniz Association *(page 13)*.

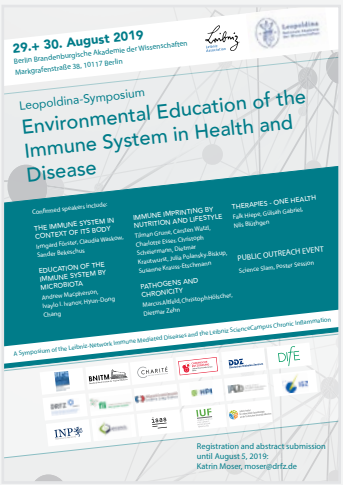
Together with this network, the ScienceCampus is organizing its first symposium - the **Leopoldina-Symposium Environmental Education of the Immune System in Health and Disease**, to be held at the Berlin-Brandenburg Academy of Sciences and Humanities in Berlin, DE, August 29-30, 2019.

Major aims of the Leibniz ScienceCampus Chronic Inflammation

- Comparative analyses to unravel common and individual mechanisms
- Translation of therapeutic strategies between diseases sharing therapeutic targets
- Identification of biosignatures and biomarkers as therapeutic targets
- Comprehensive training of researchers and clinicians
- Public recognition of chronic inflammatory diseases as a medical, societal and economic challenge
- Establishment of a clinical inflammation network (board of clinical specialists)
- Clinical access point for patients with chronic inflammatory diseases (Entzündungssprechstunde)

Participants of the first Leibniz Summer School, 2018





Helena Radbruch in discussion with participants of the Summer School.

Promoting junior staff

PostDoc College on Chronic Inflammation

For postdocs, the Leibniz ScienceCampus has set up its own forum, the **Leibniz PostDoc College on Chronic Inflammation**. The focus is on networking, but also on advice and the coordination of teaching activities in preparation for habilitation. Workshops, e.g. on leadership competence and communication, are organised by the postdocs themselves.

The DRFZ postdoctoral representatives: Gitta Heinz and Randall Lindquist

Leibniz Postdoc Network

The postdoc representative Gitta Heinz is also one of the two spokesperson of the Leibniz PostDoc Network which connects postdocs from all Leibniz Institutes.

Photo: private, Spokespersons and officers of the Leibniz Postdoc Network

"Being spokesperson of the Leibniz Postdoc Network allows me to interact and exchange ideas with researchers from all disciplines. I also get an insight in the organizational structure and strategical topics of the Leibniz Association. The PostDoc Network helps us to increase the visibility of postdoctoral researchers as interest group within the Leibniz Association and to place our perspective on topics like working conditions and career paths."

Lecture Series on Chronic Inflammatory Diseases

In 2018, the PostDoc College fellows newly established the **Lecture Series on Chronic Inflammation Diseases** for students and doctoral researchers of the DRFZ and the ScienceCampus. The postdocs present their research areas and perspectives spanning state-of-the-art experimental methods, cellular mechanisms of chronic inflammation, novel therapeutic approaches and drug discovery. In 2018, 13 lectures took place.

Campus-Lecture Series on Chronic Inflammatory Diseases

Chronic Inflammatory Diseases are a major health issue without satisfactory treatment despite decades of research. In this lecture series, postdoctoral researchers associated with the Leibniz WissenschaftsCampus Berlin, will present their research areas and perspectives spanning state-of-the-art experimental methods, cellular mechanisms of chronic inflammation, novel therapeutic approaches and drug discovery. The aim is to share experiences, ideas and concepts thereby increasing interest in the complex field of chronic inflammatory diseases among advanced Master's students and PhD students in all related subjects.

Date	Speaker	Topic
18.10.18	Andreas Hutloff	Introduction to chronic inflammation and DRFZ/Leibniz ScienceCampus
25.10.18	Daniel Schulz	The role of stromal niches in chronic inflammation
01.11.18	Randy Lindquist	Imaging of inflammation
08.11.18	Gitta Heinz	RNA-based gene regulation in chronic inflammation
15.11.18	Laleh Khodadadi	The maintenance of memory plasma cells
22.11.18	Axel Schulz	High-Parametric Mass Cytometry: A single-cell, system-level technology for deciphering chronic inflammatory diseases
29.11.18	Yvette Meißner	Inflammation, rheumatoid arthritis and cardiovascular disease
06.12.18	Asylkhan Rakhymzhan	Optical methods
13.12.18	Randy Lindquist	Chronic inflammation and cancer
20.12.18	Shintaro Hoyjo	Helper T cells in chronic inflammation
2019		
10.01.19	Stefan Frischbutter	Drug Discovery in academia
17.01.19	Patrick Maschmeyer	Functions of microRNAs in chronic inflammatory diseases
24.01.19	Marina Babic	Immune checkpoints as therapeutic targets in inflammation
31.01.19	Shintaro Hoyjo	Helper T cells in chronic inflammation
07.02.19	Alexander Beller	Microbiota analysis in health and disease
14.02.19	Randy Lindquist	Chronic inflammation at ectopic sites

DRFZ Leibniz CHARITÉ

Schedule of the Lecture Series

Doctoral student network

In the course of the development of the Postdoc Network, the doctoral researchers decided to take up on the networking idea: they regularly organise networking events and biannual doctoral researcher assemblies where they elect representatives and discuss ideas and wishes for their education and graduate programmes (LeGCI, ZIBI), enrolments at universities or career perspectives.

The DRFZ PhD student representatives, left side: Marie Urbicht and Jonathan Stefanowski (till 2018), Lukas Heiberger and Rebecca Cornelis (since 2018)

Leibniz PhD Network

The doctoral student representative Jonathan Stefanowski is also engaged in the Leibniz PhD Network:

"When I first got involved in the PhD Network during the General Assembly in 2017, I was impressed by the interdisciplinary of the member institutes and museums within the Leibniz Association and the huge differences of working conditions for doctoral researchers (DRs).

Leibniz PhD Network

The Network wants to improve this and aims to develop standards for all DRs. As an elected spokesperson, I am happy to be able to contribute to the general situation, specifically developing goals in order to prevent power abuse and to improve supervision."

Photo: private, Steering group of the Leibniz PhD Network

Graduate Programmes

In addition to the LeGCI, the DRFZ students are members of other graduate programmes:

- Interdisciplinary Centre of Infection Biology and Immunity (ZIBI)
- Berlin School for Regenerative Therapies (BSRT)
- Dahlem Research School (DRS) of the Freie Universität Berlin
- Integrated Research Training Group of the CRC TRR 130 "B cells and beyond"
- Integrated Research Training Group of the CRC TRR 241 "Immune-Epithelial Communication in Inflammatory Bowel Diseases"
- Graduate School "Computational Systems Biology" (GRK 1772), Humboldt University Berlin

Certified Education

Together with the Department of Rheumatology and Clinical Immunology of the Charité, the DRFZ is certified as one of the 31 EULAR Centre of Excellence.
www.eular.org

Furthermore, the DRFZ is a certified training centre of the German Society for Immunology (DGfI).
www.dgfi.org

Guest Scientist Stipends

In order to facilitate the recruitment of talented external postdocs, the DRFZ has budgeted two stipends for postdoctoral fellows.

Training Courses

Scientists of the DRFZ are involved in the organisation of various offers for young scientists. There are national educational offers like the Summer School of the Leibniz ScienceCampus, the EULAR Epidemiology Course, the DGfI Spring, Autumn and Translation Schools for Immunology, the joint Summer School of the European Network of Immunology Institutes (ENII) and the European Federation of Immunological Societies (EFIS) as well as the B Cell Winter School of the CRC TRR130 IRTG.

The DRFZ regularly offers Technology Courses like EMBO courses for Cytometry and Microscopy or the Advanced Cytometry course at the triennial European Congress of Immunology (ECI).

Background picture: Poster session at the evaluation of the DRFZ by the Senate of the Leibniz Association, October 2018

Selected research networks

Leibniz Research Alliances and Networks

Research Alliance „Bioactive Compounds and Biotechnology“

Biologically active substances are the basis of most drugs. The aim of this research alliance with currently 17 institutes is to track down biological active substances, to investigate their effects and finally to use them therapeutically.

The focus is on

- Collection of organisms and biological materials as potential sources for new active substances
- Isolation, analysis and chemical modification of active substances
- Research into potential applications for biological agents:
  - for example as antibiotics, anti-inflammatory drugs or with other therapeutic effects
  - Application in health products, nutrition and agriculture

Spokesperson:
Ludger Wesjohann, Leibniz Institute of Plant Biochemistry (IPB), Halle, DE

PI at the DRFZ:
Mir-Farzin Mashreghi *(page 69)*

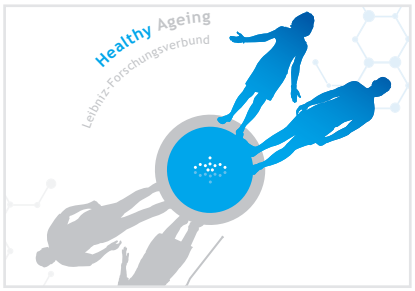
www.leibniz-wirkstoffe.de

Research Alliance „Healthy Ageing“

Healthy ageing - living an active life as long as possible free from disease and physical impairment - is an achievable goal for most elderly people in industrialised societies.

The aim of this research alliance is to investigate the biological and social factors of the ageing process and its effects. From this, new intervention strategies will be developed to promote healthy ageing in a sustainable way. The network also sees itself as a competent partner for politics and media in all biomedical and socio-economic questions related to ageing and demographic change.

In the research alliance, scientists from biology, medicine, psychology, educational research, sociology, spatial planning and economics from 21 Leibniz Institutes are collaborating.



Cover image of a brochure about the research alliance

Spokespersons:
Jean Krutman, Leibniz Research Institute for Environmental Medicine (IUF), Düsseldorf, DE; Helen Morrison, Leibniz Institute on Aging (FLI), Jena, DE

PIs at the DRFZ:
Andreas Grützkau *(page 83)*
Andreas Radbruch *(page 59)*

www.leibniz-gesundes-altern.de

Leibniz Network „Immune Mediated Diseases“

In 2018, the DRFZ successfully applied for a Leibniz network on immune mediated diseases, coordinated by the DRFZ.

An intact immune system protects us from infections and cancer. Malfunctions of the immune system can therefore cause numerous diseases. In Germany, about ten percent of the population suffers from one of more than 100 different immune-mediated diseases. These include allergies, neurological inflammatory diseases, intestinal inflammation, rheumatic diseases and diabetes. They not only are a burden to patients and their relatives, but also cause considerable economic costs. Many of these diseases are still incurable today - partly because we do not understand them well enough. The aim of the Leibniz Network Immune Mediated Diseases is to elucidate the underlying mechanisms and to develop therapies. 16 Leibniz Institutes from various disciplines are involved.

In August 2019, the first meeting will take place in Berlin as a Symposium of the Leopoldina National Academy of Sciences.

Coordinator at the DRFZ:
Andreas Radbruch *(page 59)*
Elke Luger

www.leibniz-gemeinschaft.de/forschung/leibniz-netzwerke/immun-vermittelte-erkrankungen.html

Leibniz Network „Mathematical Modeling and Simulation“

Socially relevant topics such as climate change, energy and health issues challenge the international research community to develop interdisciplinary and integrated approaches combining natural, life and social sciences. High information and data volumes as well as the growing importance of simulation and optimization of technological and social processes create the need for adequate and up-to-date methods for analysis and information generation. As a connecting element, modern methods of mathematical modelling and simulation (short: MMS) have proven to be a fundamental resource. For instance, they enable reliable extraction of information from large data sets, avoidance of expensive experiments, the prediction of experiments, the analysis of stochastic events and the shortening of development cycles.

The main objective of this network of 32 Leibniz Institutes of all sections is to systematically use this potential for synergies. To make the most sustainable and effective use of hard- and software resources, questions of the most suitable, fastest and most error-resistant methods are discussed.

Contact at the DRFZ:
Kevin Thurley *(page 61)*

www.wias-berlin.de/research/Leibniz-MMS/

Leibniz Netzwerk Mathematische Modellierung und Simulation

Leibniz - Collaborative Excellence „Epigenetic regulation of ImmuneAging: Heterochromatic DNA methylation as a regulator of T cell senescence “

The functional decline of the immune system with aging (ImmuneAging) is a major burden for elderly individuals leading to multiple age-associated diseases including chronic inflammation. T lymphocytes contribute to ImmuneAging by acquiring a senescent phenotype, which seems to result from cumulative proliferation stress over the life-time of a human being.

We recently discovered a progressive, heterochromatin-restricted loss of DNA methylation, which correlated to the proliferation history of the cells. We now hypothesize that this ‚proliferation-induced heterochromatic de-methylation‘ (PIHD) is functionally involved in the senescence process in T cells.

In this collaborative project, we want: i) to define the molecular mechanism and the cellular consequences of PIHD, ii) to compare the extent of PIHD in T cells during healthy conditions and during disease, iii) to identify substances able to prevent or revert PIHD and hence, T cell senescence.

Coordinator:
Julia Polansky-Biskup*(page 58)*

Partners:
Leibniz Institut für Altersforschung -Fritz-Lipmann-Institut (FLI), Jena, DE; Leibniz-Institut für Zoo-und Wildtierforschung (IZW), Berlin, DE; Leibniz Institut für Molekulare Pharmakologie (FMP), Berlin, DE; Charité - Universitätsmedizin Berlin, DE; Universität des Saarlandes, DE

Leibniz - Collaborative Excellence „Chronic quiescence - maintenance of hematopoiesis and immunological memory in health and latent infection, and its disruption in chronic inflammation“

Since 2019, the DRFZ is coordinating this Leibniz Research Network, funded by the Leibniz Competition Programme. The project aims to investigate the molecular mechanism underlying the quiescence of hematopoietic stem cells (HSC) and memory lymphocytes in bone marrow niches. Quiescence of these cells is fundamental for hematological and immunological memory, which maintains chronic inflammatory diseases during their dormant states.

An international and interdisciplinary network of experts in stromal cell biology, haematology, and molecular cell biology, in particular RNA biology, will complement the expertise of the Leibniz institutes DRFZ and Forschungszentrum Borstel. The consortium combines experimental *in vivo* and *ex vivo* approaches to define the signals inducing, maintaining or terminating quiescence, the integration of signalling pathways in the hematopoietic and immune cells, and the targets of signalling, which confer long-lasting quiescence.

Coordinator:
Fritz Melchers *(page 56)*

Partners:
University of Leeds, UK; Max-Planck-Institute for Infection Biology, Berlin, DE; Forschungszentrum Borstel, DE; Allgemeines Krankenhaus Wien, AT; Julius-Maximilians-Universität Würzburg, DE; Helmholtz-Zentrum für Infektionsforschung, Braunschweig, DE

Backround picture: Thurley K, Gerecht D, Friedmann E, Höfer T (2015). PLoS Comput Biol 11(4): e1004206.

Research networks funded by the German Research Foundation (DFG)

CRC TRR 130
B cells: Immunity and Autoimmunity

The aim of this collaborative research centre is to gain a better understanding of the role of B lymphocytes in physiological immune reactions and chronic inflammatory diseases.
The DRFZ contributes with its expertise in the field of memory B lymphocytes, in particular of memory plasma cells. In addition, it provides important technologies for the analysis of single cells and cells in tissue, i.e. flow cytometry and intravital microscopy.

Participants of the review meeting at the DRFZ, January 2017

Spokespersons:
Lars Nitschke, University Clinic Erlangen, DE; Andreas Radbruch, DRFZ, DE; Michael Reth, University of Freiburg, DE

PIs at the DRFZ:
Andreas Radbruch, Ria Baumgrass, Hyun-Dong Chang, Thomas Dörner, Andreas Grützkau, Anja Hauser, Guido Heine, Falk Hiepe, Max Löhning, Mir-Farzin Mashreghi, Raluca Niesner, Chiara Romagnani, Margitta Worm

www.trr130.forschung.uni-erlangen.de

CRC TRR 241
Immune-Epithelial Communication in Inflammatory Bowel Diseases

The etiological background of Inflammatory Bowel Diseases (IBD: Crohn's disease, ulcerative colitis) is still poorly understood, in particular the local cell-cell interactions. The driving hypothesis behind this new joint initiative is that a dysregulated signal exchange between the epithelium and immune cells and the consequences thereof contribute to the pathogenesis of IBD.
The DRFZ focuses on how the crosstalk of intestinal microbiota and immune cells can affect intestinal barrier functions and on how mechanisms of the innate immune system can initiate inflammation or, in contrast, lead to epithelial protection and barrier repair.

Spokespersons:
Christoph Becker, University Clinic Erlangen, DE; Britta Siegmund, Charité, Berlin, DE

PIs at the DRFZ:
Hyun-Dong Chang, Andreas Diefenbach, Ahmed Hegazy, Andrey Kruglov, Andreas Radbruch, Chiara Romagnani, Antigoni Triantafyllopoulou

www.transregio241.de

Priority Programme SPP 1937 Innate Lymphoid Cells

Innate Lymphoid Cells (ILCs) are important effector cells in the immune defence of infections and tumors. It is now known that they are also involved in the pathogenesis of various inflammatory diseases such as chronic inflammatory bowel diseases or rheumatoid arthritis. More recently, it became clear that ILCs are also tissue-bound cells that are deeply linked to the biology of different organs and tissues.

The three research groups of the DRFZ involved in this initiative are investigating the interaction between ILCs and the surrounding tissue in order to gain an understanding of the development of inflammation-driven diseases.

Spokesperson:
Andreas Diefenbach, Charité and DRFZ, Berlin, DE *(page 47)*

PIs at the DRFZ:
Chiara Romagnani *(page 60)*
Anja Hauser *(page 49)*

http://spp-innatelymphoidcells.de

GerMaNet

The newly developed mass cytometry (CyTOF technology) captures the complexity of cellular systems in unprecedented detail and promises significant contributions in biomedical diagnostics and research. The German Mass Cytometry Network (GerMaNet), coordinated by the DRFZ, pools the expertise of all German mass cytometry centres to:

- create common quality standards that can be used at each facility to normalize the instrumentation and data;
- establish a Bioinformatics Contact office to assist in data analysis and interpretation;
- form a common training package for operators and users of mass cytometry in Germany;
- create a user and education network so that mass cytometry can be exposed to other areas of basic, translational, and medical research that may be unaware of its usefulness;
- organise annual meetings for exchange of experiences and to present and discuss new technological developments.

The GerMaNet annual meetings have been organised by the DRFZ in 2018 and 2019 and enjoy popularity beyond the borders of Germany with more than 100 international participants in 2019.

Coordinator
Henrik Mei *(page 79)*

PIs at the DRFZ:
Henrik Mei *(page 79)*
Andreas Grützkau *(page 83)*

www.drfz.de/aktuelles/veranstaltungen

Networks funded by the Federal Ministry for Education and Research (BMBF)

Neuroimpa – Neuroimmunology and pain

Musculoskeletal diseases, such as rheumatic diseases but also osteoporosis, restrict mobility and quality of life. The severe and chronic pain is often inadequately treated. The NEUROIMPA research network is investigating the interaction between the nervous system and the immune system in chronic inflammation and osteoporosis in order to find out how this interaction triggers and maintains inflammation-associated pain. The aim is to develop new therapies for the treatment of pain.

Coordinator:
Hans-Georg Schaible, University Clinic Jena, DE

PIs at the DRFZ:
Hyun-Dong Chang *(page 46)*
Andreas Radbruch *(page 59)*

www.gesundheitsforschung-bmbf.de

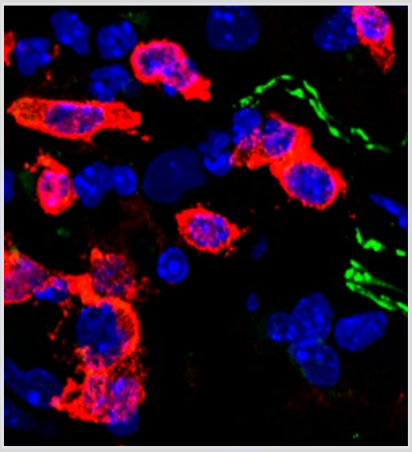


Figure Neuroimpa:
Knee joint in ovalbumin-induced arthritis (OIA) in a mouse model: Immigrated CD4-T lymphocytes (red) and pain-sensitive (Calcitonin gene-related peptide) nerve fibers (green) colocalize in the inflamed joint. The DNA of the cell nuclei is stained blue.

PROCLAIR

PROCLAIR (Linking Patient-Reported Outcomes with CLAims data for health services research in Rheumatology), coordinated by the DRFZ, provides reliable data on the health care of people with inflammatory rheumatic diseases and osteoarthritis. Around 20,000 persons insured with BARMER health insurance company who had been diagnosed with rheumatoid arthritis, axial spondyloarthritis or osteoarthritis of the hip, knee or finger joints (according to their claims data) were interviewed on the burden of their illness and its symptoms by means of written questionnaires. The data from the questionnaire were linked with the claims data. This allows for a detailed analysis of disease burden and health care situation.

Coordinator:
Angela Zink, DRFZ, Berlin, DE *(page 75)*

Partners:
University of Bremen, DE; Charité, DE; University of Dresden, DE; Barmer Health Insurance

www.drfz.de/forschung/projekte-netzwerke/

Sysinflame - A Systems Approach to Chronic Inflammatory Disease

This e:Med consortium bundles different expertises and scientific fields in order to create a systems medicine understanding of Chronic Inflammatory Diseases (CID). The focus is on molecular mechanisms of manifestation, therapeutic response and disease progression integrating several layers of dynamic molecular information. Both the thorough examination of individual patients under targeted therapy, as well as the analysis of large longitudinal studies will provide a good starting point for developing sound biomarkers to predict disease courses and to guide precision therapies. The main contribution of the DRFZ is to provide high-dimensional immunophenotyping data generated by multiparametric flow and mass cytometry (CyTOF) technologies on peripheral leukocytes responding to targeted therapies in chronic inflammatory conditions.

Coordinator:
Stefan Schreiber, University Hospital Kiel, DE

Contact at the DRFZ:
Andreas Grützkau *(page 83)*

www.sys-med.de/en/consortia/sysinflame/

Networks funded by the European Commission (EC) and the European Research Council (ERC)

DNA Damage Response-instructed Macrophage Differentiation in Granulomatous Diseases (DDRMac)

ERC Starting Grant

Granulomas are a typical histological finding of several chronic inflammatory diseases. They develop as a reaction to a persistent inflammatory stimulus and consist of macrophages that differentiate into multinucleated giant cells and epithelial cells. These structures of organised inflammation replace healthy tissue causing organ dysfunction.

We revealed that macrophage precursors in granulomas experience a replication block and trigger the DNA Damage Response (DDR), a fundamental cellular process activated in response to genotoxic stress. This leads to the formation of multinucleated macrophages with tissue-remodelling signatures. We hypothesize that the DDR promotes macrophage reprogramming to inflammation-maintaining modules. Our goal is to unravel the macrophage-specific response to genotoxic stress as an essential regulator of chronic inflammation-induced pathologies such as sarcoidosis, inflammatory bowel diseases and rheumatoid arthritis. We postulate that the interruption of signalling cascades leading to granuloma formation may be a new therapeutic strategy for chronic inflammatory diseases.

PI at the DRFZ:
Antigoni Triantafyllopoulou *(page 63)*

Epigenetic fine-tuning of T cells for improved adoptive cell therapy (EpiTune)

ERC Starting Grant

Adoptive T cell therapy is a promising approach in various clinical settings, from target-specific immune reconstitution fighting cancer and chronic infections to combating undesired immune reactivity during auto-immunity and after organ transplantation. However, its clinical application is currently hampered by a limited survival and fitness of the T cells after transfer to the patient and the functional plasticity of T cells resulting in possible functional switches (e.g. from immunosuppressive to pro-inflammatory).

We showed earlier that epigenetic players such as DNA methylation essentially contribute to T cell differentiation and harbour the unique prospect to imprint a stable developmental and functional state in the genomic structure of a cell.

This project aims to utilise the profound impact of epigenetic mechanisms on the senescence process as well as on the functional imprinting of T cells. Using epigenetic manipulations (e.g. CRISPR/Cas9) during *in vitro* expansion, we aim to equip the cells with the required properties for their successful and safe therapeutic application.

PI at the DRFZ:
Julia Polansky-Biskup *(page 58)*

Rheuma Tolerance for Cure - RTCure

The aim of this European consortium of the Innovative Medicines Initiative (IMI) is to develop therapies for patients in the earliest stages of rheumatoid arthritis (RA) and for people with a high probability of developing this disease. The network of 12 universities and research organisations, 6 EFPIA partners and 2 companies is developing new methods for biomonitoring the course of the disease and therapy response. The network will also validate methods to monitor immune tolerance treatments; highly-targeted medicines that stop the immune system's attacks on the joints while ensuring the immune system remains able to fight off infections. The long-term goal is finding treatments which prevent or reverse the onset of RA and cure patients in early stages of the disease.

Coordinator:
Lars Klareskog, Karolinska Institutet, SE

PIs at the DRFZ:
Andreas Radbruch *(page 59)*
Hyun-Dong Chang (work package coordinator) *(page 46)*
Andreas Grützkau *(page 83)*

https://www.rtcure.com/
www.imi.europa.eu/projects-results/project-factsheets/rtcure

Selected epidemiological registers

Rhekiss - Rheumatic diseases and pregnancy – enhancing our knowledge

Women with inflammatory rheumatic diseases have fewer children compared to other women. If this is due to an increased proportion of unsuccessful pregnancies or if they are less likely to conceive is not known. Insufficient knowledge about the course and risks of pregnancy in women with inflammatory rheumatic diseases and about the risks or benefits of drug treatment during pregnancy and child wish makes it difficult for the rheumatologist to give advice to women with the desire for a child.

To gain more information we started the pregnancy register Rhekiss in 2015. It is a prospective cohort study dedicated to investigate the safety of therapies during child wish, in pregnancy and lactation. We aim to add substantial evidence to the limited knowledge about the chances to conceive and the course and outcome of pregnancies in patients with various inflammatory rheumatic diseases. Rhekiss is a web based system in which rheumatologists and patients enter information on the course of disease and pregnancy, drug treatments, outcome of pregnancy and development of the child. Up to now, more than 1,400 women are enrolled.

With the information collected, Rhekiss will contribute to greater safety in the care for pregnant women with inflammatory rheumatic diseases. Furthermore, it facilitates to inform patients about planning pregnancies or the risk of unintended pregnancies.

Coordinator:
Anja Strangfeld *(page 74)*, DRFZ Berlin, DE; Rebecca Fischer-Betz, Universität Düsseldorf, DE

https://rhekiss.de/

European network of pregnancy registers in rheumatology (EuNeP)

The information about outcomes of pregnancies in women with inflammatory rheumatic diseases (IRD) and on the safety of drugs when used before or during pregnancy should be as robust as possible. To gather enough data in one individual data source to adjust for all the possible influences is nearly impossible for rare risk factors, rare diseases or rare events. Therefore, collaborations of several databases is needed to overcome this limitation. The aim of EuNeP is to combine existing data from different pregnancy registers and to improve future pregnancy counselling by using better information on pregnancy outcomes and drug safety. Experts from France, Germany, Norway and Switzerland who already run prospective pregnancy registers in women with IRD were brought together. Since the start of EuNeP in 2017, major efforts have been made to develop a standardized core data set including data from the existing registers, from literature and from surveys among patient representatives

Lead:
Anja Strangfeld *(page 74)*, DRFZ Berlin, DE; Rebecca Fischer-Betz, Universität Düsseldorf, DE

Coordination:
Yvette Meißner, DRFZ Berlin, DE

Partners:
Université Paris-Descartes, FR; Groupe Hospitalier Cochin-Saint Vincent de Paul, Paris, FR; University of Trondheim, NO; University Hospital and University of Bern, CH

Funded by:
FOREUM Foundation for Research in Rheumatology

http://www.foreum.org/prg_14_eunep_pregnancy_registers.cfm

Rhekiss

FOREUM
Foundation for Research in Rheumatology

Private foundations supporting research

Dr. Rolf M. Schwiete Foundation

Schwiete Laboratory for Microbiota and Inflammation

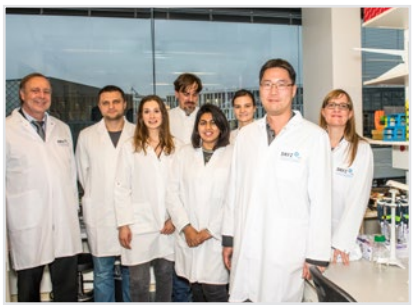
Patients with chronic inflammatory diseases such as rheumatoid arthritis often have an altered gastrointestinal microbiota compared to healthy people. The research group "Microbiota and Inflammation" of Hyun-Dong Chang is dedicated to the analysis of the dialogue between microbiota and the immune system with respect to preventing or driving chronic inflammation. The aim is to develop an innovative approach for the prevention and therapy of chronic inflammatory diseases and associated cancers. Since 2017, this group has been substantially supported by the Dr. Rolf M. Schwiete Foundation.

Contact at the DRFZ:
Hyun-Dong Chang *(page 46)*

The foundation

The Dr. Rolf M. Schwiete Foundation is a non-profit foundation based in Mannheim promoting, amongst others, research in medicine and chemistry. Its founder, the entrepreneur Rolf M. Schwiete, left all his assets to the foundation.

https://schwiete-stiftung.com



Visit of Dr. Jürgen Staiger, chairman of the Dr. Rolf M. Schwiete Foundation

Willy Robert Pitzer Foundation

Pitzer Laboratory for Osteoarthritis Research

Around five million people in Germany are affected by osteoarthritis, a degenerative joint disease that often requires artificial joint replacement in late stages. Little is known about the causes of osteoarthritis, and there is no efficacious therapy available to date. In order to better understand this disease, Max Löhning's research group is investigating the molecular processes occurring in cartilage tissue. The long-term goal is to find ways to restore the natural regenerative capacity of cartilage cells (chondrocytes). Since 2015, the Willy Robert Pitzer Foundation has supported the Pitzer Laboratory for Osteoarthritis Research at the DRFZ and the Charité - Universitätsmedizin Berlin.

Contact at the DRFZ:
Max Löhning *(page 68)*

The foundation

The Willy Robert Pitzer Foundation is a non-profit foundation based in Frankfurt am Main. It is supporting numerous projects in the fields of science, health and social affairs. Its founder, the architect Willy Robert Pitzer, left most of his assets to the foundation.
www.pitzer-stiftung.de

Visit of the board of the Willy Robert Pitzer Foundation

German Rheumatism Foundation

Joint Professorship for Health Services Research

In 2015, Kirsten Minden was appointed professor for Health Services Research. This joint professorship of the DRFZ and the Charité is the first major funding project of the Rheumastiftung and has contributed to strengthening health services research at the DRFZ. Using new approaches, the group analyses health care and disease burden of patients and their families and identifies deficits. Furthermore, new treatment strategies are evaluated. The aim is to improve health care and quality of life of patients suffering from rheumatic diseases.

Contact at the DRFZ:
Kirsten Minden *(page 72)*

The foundation

The Rheumastiftung, a joint endeavour of the Deutsche Rheuma-Liga e.V., the largest patient organisation in Germany, and the German Society for Rheumatology (DGRh), was established in 2008. The non profit foundation supports basic and clinical research projects that aim to improve the treatment of rheumatic diseases and to increase the chances of cure.
www.rheumastiftung.org

Ideenwettbewerb - ist Rheuma heilbar? /Competition for ideas - is rheumatism curable?

In addition, the Rheumastiftung is funding the Project "Deleting the memory for rheumatism" since 2011, now in the second funding period)

Contact at the DRFZ:
Hyun-Dong Chang *(page 46)*

Research highlights

Training, imprinting and maintenance of (pathogenic) immunological memories

For many years, the prevalent concept of immunological memory had been that it is maintained by antigen-experienced lymphocytes circulating through the body. This concept has been challenged recently by research from the DRFZ and other groups. Researchers at the DRFZ have shown that CD4+ and CD8+T memory lymphocytes and memory plasma cells survive as long-lived cells in the bone marrow and in inflamed joints. Here, memory lymphocytes persist individually in distinct niches organised by mesenchymal stromal cells.

CD8+ and CD4 + memory T lymphocytes are found in the spleen and bone marrow. While the cells in the spleen proliferate to maintain the memory pool, the CD8+ memory T lymphocytes in the bone marrow are resting in terms of proliferation and maintain exclusive long-term memory. This underlines the special role of the bone marrow for immunological memory. The long-lived bone marrow memory cells are independent of the circulating memory cells, and at least one subset of them – CD69+ memory cells – in both mice and humans express signature genes reported for resident memory cells from other tissues, again highlighting the resident status of these cells.

Maintenance of CD8+ memory T lymphocytes in the spleen but not in the bone marrow is dependent on proliferation. *Siracusa F, Alp ÖS, Maschmeyer P, McGrath M, Mashreghi MF, Hojyo S, Chang HD, Tokoyoda K, Radbruch A. Eur J Immunol. 2017 Nov;47(11):1900-1905. Epub 2017 Oct 11.*

Nonfollicular reactivation of bone marrow resident memory CD4 T cells in immune clusters of the bone marrow. *Siracusa F, McGrath MA, Maschmeyer P, Bardua M, Lehmann K, Heinz G, Durek P, Heinrich FF, Mashreghi MF, Chang HD, Tokoyoda K, Radbruch A. Proc Natl Acad Sci U S A. 2018 Feb 6;115(6):1334-1339. Epub 2018 Jan 22.*

CD69+ memory T lymphocytes of the bone marrow and spleen express the signature transcripts of tissue-resident memory T lymphocytes. *Siracusa F, Durek P, McGrath MA, Sercan-Alp Ö, Rao A, Du W, Cendón C, Chang HD, Heinz GA, Mashreghi MF, Radbruch A, Dong J. Eur J Immunol. 2019 Jan 23. doi: 10.1002/eji.201847982*

Stromal cells organise survival niches for long-lived plasma cells in the bone marrow. We have found that they express the chemokine CXCL12. To investigate the impact of CXCL12 and its ligand CXCR4 on the homing and survival of antibody secreting cells we analysed bone marrow stroma cells from lupus mice. We could provide the definitive proof that plasmablasts are recruited to the bone marrow by CXCR4, by blocking their immigration by AMD3100 (Plerixafor). This work provides us with a molecular understanding of the lifestyle of (pathogenic) memory plasma cells, required to target them as selectively as possible and to prevent their regeneration.

We could further show that the microRNA 221 (miR-221) retains B cell and hematopoietic precursors in the bone marrow by amplifying their PI3K signalling in response to the chemokine CXCL12. This leads to increased survival and increased adhesion in their niches in the bone marrow.

CXCR4-CXCL12 interaction is important for plasma cell homing and survival in NZB/W mice. *Cheng Q, Khodadadi L, Taddeo A, Klotsche J, F Hoyer B, Radbruch A, Hiepe F. Eur J Immunol. 2018;48(6):1020-1029.*

MiR221 promotes precursor B-cell retention in the bone marrow by amplifying the PI3K-signaling pathway in mice. *Petkau G, Kawano Y, Wolf I, Knoll M, Melchers F. Eur J Immunol. 2018;48(6):975-989.*

Plasma cells in the bone marrow not only secrete protective IgG antibodies, but also pathogenic antibodies maintaining autoimmune diseases. We exploited a strategy used by *Salmonella (S.) typhimurium* to selectively ablate IgG secreting plasma cells from the bone marrow which could be used as a potentially new therapeutic strategy for ablating IgG plasma cells. *S. typhimurium* uses a protein with partial homology to laminin-β to evade effective immune responses. We recently discovered that laminin-β is exclusively provided by bone marrow stroma cells supporting IgG-secreting memory plasma cells. Since in many chronic inflammatory diseases, the pathogenic antibodies are IgG antibodies, interference with the obviously vital laminin-β signal of the bone marrow niche for IgG-secreting plasma cells may allow the selective ablation of those plasma cells, sparing protective plasma cells secreting IgA and IgM.

Salmonella SiiE prevents an efficient humoral immune memory by interfering with IgG+ plasma cell persistence in the bone marrow. *Männe C, Takaya A, Yamasaki Y, Mursell M, Hojyo S, Wu TY, Sarkander J, McGrath MA, Cornelis R, Hahne S, Cheng Q, Kawamoto T, Hiepe F, Kaufmann SHE, Yamamoto T, Radbruch A, Tokoyoda K. . Proc Natl Acad Sci U S A. 2019 Apr 9;116(15):7425-7430. doi: 10.1073/pnas.1818242116. Epub 2019 Mar 25.*

To visualize interactions of lymphocytes with their environment in the bone marrow researchers of the DRFZ developed microendoscopic devices for repeated intravital microscopy of the bone marrow over extended time periods, i.e. weeks to months. The latest studies revealed an unexpected dynamic of the vascular bed in this organ, probably unique among mammalian tissues. We expect this insight will decisively change our understanding of essential processes occurring within the bone marrow.

Longitudinal intravital imaging of the femoral bone marrow reveals plasticity within marrow vasculature. *Reismann D, Stefanowski J, Günther R, Rakhymzhan A, Matthys R, Nützi R, Zehentmeier S, Schmidt-Bleek K, Petkau G, Chang HD, Naundorf S, Winter Y, Melchers F, Duda G, Hauser AE, Niesner RA. Nat Commun. 2017 Dec 18;8(1):2153.*

Translating basic research into the clinic: Therapeutic targeting of pathogenic memory plasma cells and B cells in rheumatic diseases

After the original discovery of long-lived memory plasma cells, research at the DRFZ had also described long-lived plasma cells secreting pathogenic antibodies in a murine model of systemic lupus erythematosus (SLE). These cells, as obvious drivers of chronic inflammation, were refractory to conventional therapies. In humans, they manifest as cells secreting pathogenic antibodies, even if the precursors of plasma cells (B lymphocytes) are depleted, e.g. by Rituximab. The DRFZ had thus defined pathogenic memory plasma cells as a novel therapeutic challenge and prime roadblock to regeneration of tolerance in antibody-driven diseases. While the treatment of SLE patients with the proteasome inhibitor Bortezomib has shown good success, it is however accompanied by strong side effects. Therefore, we are now working on optimizing the anti-plasma cell therapy and on new strategies targeting B cells.

With Bortezomib treatment, the (auto) antibody titres decrease by approx. 30 %. At the same time, there is a 50% decrease in both short-lived and long-lived plasma cells in blood and bone marrow. The precursor cells of the plasma cells, the B cells, are not affected. After Bortezomib is discontinued, these cells rapidly build up the pool of short-lived plasma cells, which is associated with an increase in autoantibody titres. The successful treatment of SLE patients with Bortezomib therefore requires a combination therapy that simultaneously eliminates B cells.

Proteasome inhibition with bortezomib induces a therapeutically relevant depletion of plasma cells in SLE but does not target their precursors. *Alexander T, Cheng Q, Klotsche J, Khodadadi L, Waka A, Biesen R, Hoyer BF, Burmester GR, Radbruch A, Hiepe F. Eur J Immunol. 2018 Jul 6. [Epub ahead of print]*

In collaboration with our partners from the Charité, the Bortezomib treatment has already been successfully transferred to a small group of patients with anti-NMDA encephalitis. Here, too, autoantibodies play a key role in the disease (1). At the same time, we could demonstrate in an animal model that survival niches for long-lived plasma cells are indeed found in the inflamed brain (2).

(1) Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. Scheibe F, Prüss H, Mengel AM, Kohler S, Nümann A, Köhnlein M, Ruprecht K2, Alexander T, Hiepe F, Meisel A. Neurology. 2017 Jan 24;88(4):366-370. Epub 2016 Dec 21.

(2) The chronically inflamed central nervous system provides niches for long-lived plasma cells. Pollok K, Mothes R, Ulbricht C, Liebheit A, Gerken JD, Uhlmann S, Paul F, *Niesner R, Radbruch H, Hauser AE. Acta Neuropathol Commun. 2017 Nov 25;5(1):88. doi: 10.1186/s40478-017-0487-8.*

In rheumatoid arthritis (RA), cytokines produced by B cells are well-known drivers of pathogenesis. In comparison to B- cells from healthy donors, B cells from RA patients display an altered cytokine production. Amongst others, this leads to a loss of expression of the protective factor TRAIL. These defects were partly erased after treatment with the IL-6-signalling inhibitor tocilizumab, indicating that abnormal IL-6 signalling contributes to these abnormalities. This highlights the potential of abnormal B cell function in RA for new treatment strategies.

Anti-interleukin-6 signalling therapy rebalances the disrupted cytokine production of B cells from patients with active rheumatoid arthritis. Fleischer S, Ries S, Shen P, Lheritier A, Cazals F, Burmester GR, Dörner T, Fillatreau S. Eur J Immunol. 2018;48(1):194-203.

from left: Thomas Häupl (Charité), Andreas Grützkau and Andreas Hutloff (DRFZ).Networking during the advisory board review of the ScienceCampus Chronic Inflammation, 2017
Photo: Arne Sattler

Microbiota, and how a misguided immune system controls chronic inflammation

The microbiota, in particular the microbiota of the gut, play a key role in preventing or licensing chronic inflammatory diseases such as inflammatory bowel diseases and rheumatic diseases. Identifying the microbial players involved in this may offer entirely new options to prevent and treat such diseases, and to predict disease progression and response to therapy in a non invasive way by analysing the dynamic heterogeneity of the microbiota. The DRFZ has developed a unique tool for the unbiased visualisation of the heterogeneity of human and murine microbiota, and the isolation of defined microbial species, namely high-resolution microbiota cytometry and cell sorting. Microbiota protecting, or licensing, of chronic inflammation have already been identified based on these methods.

Hyun-Dong Chang,DRFZ, Photo: Arne Sattler

Bacteria of the microbiota determine whether certain T cells can trigger intestinal inflammation or not. These results underline the importance of the interaction between intestinal bacteria and cells of the immune system in healthy organisms and in chronic inflammation.

The intestinal microbiota determines the colitis-inducing potential of T-bet-deficient Th cells in mice. *Zimmermann J, Durek P, Kühl AA, Schattenberg F, Maschmeyer P, Siracusa F, Lehmann K, Westendorf K, Weber M, Riedel R, Müller S, Radbruch A, Chang HD. Eur J Immunol. 2018 Jan;48(1):161-167. Epub 2017 Sep 29.*

Microbiota-induced IgA-secreting plasma cells and TH17 cells, which reside in the mucosal lamina propria, are key host mediators of the crosstalk between microbiota and the intestinal immune system. Intestinal regulatory T cells (Treg) are able to constrain Th17 cell and IgA responses. We identified the transcription factor c-Maf as crucial for intestinal Treg function and thus as a key regulator of intestinal immune homoeostasis.

c-Maf-dependent Treg cell control of intestinal TH17 cells and IgA establishes host–microbiota homeostasis. *Christian Neumann, Jonas Blume, Urmi Roy, Peggy P. Teh, Ajithkumar Vasanthakumar, Alexander Beller, Yang Liao, Frederik Heinrich, Teresita L. Arenzana, Jason A. Hackney, Celine Eidenschenk, Eric J. C. Gálvez, Christina Stehle, Gitta A. Heinz, Patrick Maschmeyer, Tom Sidwell, Yifang Hu, Derk Amsen, Chiara Romagnani, Hyun-Dong Chang, Andrey Kruglov, Mir-Farzin Mashreghi, Wei Shi, Till Strowig, Sascha Rutz, Axel Kallies and Alexander Scheffold; Nature Immunology 2019*

In the last years, the DRFZ identified adaptations of presumptively pathogenic T lymphocytes to chronic inflammation and attempted to exploit them for selective ablative therapies. The transcription factor Twist1 and the microRNA-148a controlled by it, are such adaptations. Recently, we could show in the murine model of transfer colitis, that antagomir-148a selectively depletes miR-148a expressing T lymphocytes and amelio rates chronic inflammation to the same degree as ablation of all T cells does. This proves that Twist1/miR-148a expressing T cells are indeed the relevant pathogenic T cells driving chronic inflammation. At the same time this is the first preclinical test demonstrating that therapeutic oligonucleotides are efficient and selective *in vivo*.

Selective targeting of pro-inflammatory Th1 cells by microRNA-148a-specific antagomirs in vivo. *Maschmeyer P, Petkau G, Siracusa F, Zimmermann J, Zügel F, Kühl AA, Lehmann K, Schimmelpfennig S, Weber M, Haftmann C, Riedel R, Bardua M, Heinz GA, Tran CL, Hoyer BF, Hiepe F, Herzog S, Wittmann J, Rajewsky N, Melchers FG, Chang HD, Radbruch A, Mashreghi MF. J Autoimmun. 2018 May;89:41-52. Epub 2017 Dec 1.*

We have shown recently that the cytokine TNF, expressed by different cell types, can have entirely different effects in rheumatoid arthritis (RA), e.g. promote or block chronic inflammation. RA is primarily driven by macrophage-derived TNF. To target myeloid cells expressing TNF, we now developed a bi-specific antibody (MYSTI - myeloid-specific TNF inhibitors). This is a novel concept to develop cell type-specific anti-cytokine therapies.

Cell-type-restricted anti-cytokine therapy: TNF inhibition from one pathogenic source. *Efimov GA, Kruglov AA, Khlopchatnikova ZV, Rozov FN, Mokhonov VV, Rose-John S, Scheller J, Gordon S, Stacey M, Drutskaya MS, Tillib SV, Nedospasov SA. Proc Natl Acad Sci U S A. 2016 Mar 15;113(11):3006-11.*

What is the role of cells of the innate immune system in immune regulation and chronic inflammation?

Innate lymphoid cells (ILCs) protect the body and play an important role in maintaining the function of tissues. However, they can also promote chronic inflammation. So far, it has been assumed that the Natural Killer (NK) cells, a subclass of the ILC, exclusively recognize molecular patterns, rather than T cell specific antigens.

We could demonstrate for the first time that NK cells recognise and react to distinct peptides of human cytomegalovirus. To this end they use their activating receptor NKG2C, controlling clonal-like expansion and differentiation. This discovery challenges the prevalent paradigm that innate lymphocytes only recognise molecular patterns, and makes them candidates for specific "personalised" regulation of (chronic) immune reactions.

Peptide-specific recognition of human cytomegalovirus strains controls adaptive natural killer cells. *Hammer Q, Rückert T, Borst EM, Dunst J, Haubner A, Durek P, Heinrich F, Gasparoni G, Babic M, Tomic A, Pietra G, Nienen M, Blau IW, Hofmann J, Na IK, Prinz I, Koenecke C,Hemmati P, Babel N, Arnold R, Walter J, Thurley K, Mashreghi MF, Messerle M, Romagnani C. Nat Immunol. 2018 May;19(5):453-463.*

Environmental genotoxic factors challenge the genomic integrity of epithelial cells at barrier surfaces, can induce mutations, and give rise to cancer. We showed that innate lymphocytes of the type ILC3 act like sensors for food components damaging the genetic material. If these cells detect sources of genotoxic stress like the metabolites of glucosinolates, contained e.g. in numerous cabbage species, they express Interleukin-22. IL-22 in turn is required for effective initiation of the DNA damage response (DDR), a cellular response pathway culminating in cell-cycle arrest and DNA repair or apoptosis. These findings not only reveal a previously unknown control loop with which the body protects itself against colon cancer, but they also point to the fact that the immune system monitors the healthy growth and function of different organs.

Interleukin-22 protects intestinal stem cells against genotoxic stress. *Gronke K, Hernández PP, Zimmermann J, Klose CSN, Kofoed-Branzk M, Guendel F, Witkowski M, Tizian C, Amann L, Schumacher F, Glatt H, Triantafyllopoulou A, Diefenbach A. Nature 2019 Feb; 566(7743):249-253. doi: 10.1038/41586019 -0899-7. Epub 2019 Jan 30.*

How can ineffective or even harmful therapies be avoided?

The DRFZ has established original approaches to use hematopoietic cells of peripheral blood as "biosensors" for individualised diagnosis allowing for prediction of disease progression and response to therapies.

Earlier, we identified Siglec-1 as a representative biomarker indicating an impending systemic lupus erythematosus flare driven by type 1 interferons. The reliability of the detection exceeds the existing standards in lupus diagnostics, such as autoantibody titres or the decrease of complement factors, and was included in the portfolio of the „Labor Berlin" as a prognostic biomarker. We could now show that a high expression of siglec-1 on monocytes of pregnant women with certain autoantibodies indicates an increased risk for the development of autoimmune congenital heart disease in the newborn.

High maternal expression of SIGLEC1 on monocytes as a surrogate marker of a type I interferon signature is a risk factor for the development of autoimmune congenital heart block. *Lisney AR, Szelinski F, Reiter K, Burmester GR, Rose T, Dorner T (2017). Ann Rheum Dis 76: 1476-1480.*

Therapeutic targeting of tumour necrosis factor (TNF)-a is highly effective in ankylosing spondylitis (AS) patients, but one-third of patients treated do not show an adequate clinical response. We showed that the frequencies of natural killer (NK) cells, and in particular CD8-positive (CD8+) NK cell subsets in peripheral blood, were most predictive for therapeutic outcome in AS patients. Responders showed significantly increased frequencies of CD8+NK cells compared to non-responders. This is the first study demonstrating that the composition of the NK cell compartment has the power for prediction of therapeutic outcome for anti-TNF-α blockers. Furthermore, it identifies CD8+NK cells as a potential new player in the TNF-α-driven chronic inflammatory immune response of AS.

An explorative study on deep profiling of peripheral leukocytes to identify predictors for responsiveness to anti-tumour necrosis factor alpha therapies in ankylosing spondylitis: natural killer cells in focus. *Schulte-Wrede U, Sörensen T, Grün JR, Häupl T, Hirseland H, Steinbrich-Zöllner M, Wu P, Radbruch A, Poddubnyy D, Sieper J, Syrbe U, Grützkau A. Arthritis Res Ther. 2018;20(1):191. Open access.*

How safe and effective are new therapies for the treatment of rheumatic diseases in children and adults?

In 2001, the DRFZ established the longitudinal register RABBIT to observe treatment of rheumatoid arthritis (RA) with innovative therapies. About 18,500 patients have been enrolled so far. An overall good safety profile of the new treatments was identified and a number of drug specific risks were established. In European collaboration, an increased risk of lymphoma could be ruled out (1) and good evidence for no increased risk of melanoma was found (2). The risk of stroke was associated with uncontrolled high disease activity as well as prior serious adverse events (3). The increased risk of lower intestinal perforations under IL-6 blockade was shown for the first time in real world data (4). Previous treatment failures are negative predictors of treatment success in most treatments. Tocilizumab seems to be an exception with equal effectiveness regardless of the number of previous therapy failures (5)

1 Mercer LK, Regierer AC, Mariette X, Dixon WG, Baecklund E, Hellgren K, Dreyer L, Hetland ML, Cordtz R, Hyrich K, Strangfeld A, Zink A, Canhao H, Hernandez MV, Tubach F, Gottenberg JE, Morel J, Zavada J, Iannone F, Askling J et al. (2017) ***Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project.*** *Ann Rheum Dis 76: 2025-2030*

2 Mercer LK, Askling J, Raaschou P, Dixon WG, Dreyer L, Hetland ML, Strangfeld A, Zink A, Mariette X, Finckh A, Canhao H, Iannone F, Zavada J, Morel J, Gottenberg JE, Hyrich KL, Listing J (2017) ***Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers.*** *Ann Rheum Dis 76: 386-391*

3 Meissner Y, Richter A, Manger B, Tony HP, Wilden E, Listing J, Zink A, Strangfeld A (2017) ***Serious adverse events and the risk of stroke in patients with rheumatoid arthritis: results from the German RABBIT cohort.*** *Ann Rheum Dis 76: 1583-1590*

4 Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, Aringer M, Meissner Y, Zink A, Listing J (2017) ***Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs.*** *Ann Rheum Dis 76: 504-510*

5 Baganz L, Richter A, Kekjow J, Bussmann A, Krause A, Stille C, Listing J, Zink A, Strangfeld A (2018). ***Long-term effectiveness of tocilizumab in patients with rheumatoid arthritis, stratified by number of previous treatment failures with biologic agents: results from the German RABBIT cohort.*** *Rheumatol Int 38(4):579-587*

Archive of questionnaires from the long-term cohorts.

How is the quality of care for people with rheumatic diseases?

For more than 25 years the national database of the German Collaborative Arthritis Centres has provided annually updated information on the health care situation of around 17,000 adult patients with inflammatory rheumatic diseases. Over time, the clinical status has improved significantly, the burden of disease due to pain and loss of function as well as sick leave has been reduced. Nevertheless, it still takes too long for patients to receive specialised care.

Versorgung der rheumatoiden Arthritis 2014. *Albrecht K, Huscher D, Eidner T, Kleinert S, Späthling-Mestekemper S, Bischoff S, Zink A. Z Rheumatol 2017;76:50-57*

The paediatric database substantiates similar improvements for children with arthritis. However, children with juvenile idiopathic arthritis were found to have a higher risk of other autoimmune diseases such as type 1 diabetes which was twice as common as in the general population.

Schenck S, Rosenbauer J, Niewerth M, Klotsche J, Minden K, Schwarz T, Foeldvari I, Horneff G, Weller-Heinemann F, Holl RW, Thon A (2018). ***Comorbidity of type 1 diabetes mellitus in patients with juvenile idiopathic arthritis.*** *J Pediatr 192:196-203*

Using claims data linked to patient questionnaires in the research programme PROCLAIR, large differences were found in treatment strategies between rheumatologists and general practitioners, leading to insufficient treatment of one third of patients in the population (1). Persons with RA had a higher prevalence of co-morbidity compared to those without RA, in particular diabetes and depression (2). Low socioeconomic status was associated with high burden of disease and decreased work participation (3). In ankylosing spondylitis (AS), about one third showed moderate to severe symptoms of depression. Depression was associated with both severity of the disease and social status (4). Diagnostic delay in AS was nearly 6 years and

there was no improvement over the last two decades, highlighting the importance of better referral strategies (5). In osteoarthritis, a high disease burden and substantial treatment deficits were found (6). Problems with transition from paediatric to adult care were identified: One in two young adults with JIA did not reach specialist care after having left paediatric rheumatology (7). The burden of co-morbidity in patients with RA was substantially higher than in the age and sex matched general population. Co-morbid conditions were associated with poorer outcomes of the rheumatic disease and poorer quality of life (8).

1 Albrecht K, Luque Ramos A, Callhoff J, Hoffmann F, Minden K, Zink A (2018)[**Outpatient care and disease burden of rheumatoid arthritis : Results of a linkage of claims data and a survey of insured persons**]. Z Rheumatol 77: 102-112

2 Albrecht K, Luque Ramos A, Hoffmann F, Redeker I, Zink A (2018) **High prevalence of diabetes in patients with rheumatoid arthritis: results from a questionnaire survey linked to claims data.** Rheumatology (Oxford) 57: 329-336

3 Callhoff J, Luque Ramos A, Zink A, Hoffmann F, Albrecht K (2017) **The association of low income with functional status and disease burden in German patients with rheumatoid arthritis: results of a cross-sectional questionnaire survey based on claims data.** J Rheumatol 44: 766-772

4 Redeker I, Hoffmann F, Callhoff J, Haibel H, Sieper J, Zink A, Poddubnyy D (2018). **Determinants of psychological well-being in axial spondyloarthritis: ana analysis based on linked claims and patient-reported data.** Ann Rheum Dis 77:1017-24

5 Redeker I, Callhoff J, Hoffmann F, Haibel H, Sieper J, Zink A, Poddubnyy D (2019). **Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. Rheumatology** Mar 21, pii: kez090. doi: 10.1093/rheumatology/kez090. [Epub ahead of print]

6 Postler A, Luque Ramos A, Goronzy J, Günther KP, Lange T, Schmitt J, Zink A, Hoffmann F (2018). **Prevalence and treatment of hip and knee osteoarthritis in people aged 60 years or older in Germany: an analysis based on health insurance claims data.** Clin Interven in Aging 13:2339-2349

7 Luque Ramos A, Hoffmann F, Albrecht K, Klotsche J, Zink A, Minden K (2017) **Transition to adult rheumatology care is necessary to maintain DMARD therapy in young people with juvenile idiopathic arthritis.** Semin Arthritis Rheum 47: 269-275

8 Luque Ramos A, Redeker I, Hoffmann F, Callhoff J, Zink A, Albrecht K (2019). **Comorbidities in patients with rheumatoid arthritis and their association with patient-reported outcomes: results of claims data linked to questionnaire survey.** J Rheumatol; 10.3899/jrheum.180668: https://www.ncbi.nlm.nih.gov/pubmed/30647170.

During Evalutation, 2018

How can we predict the course of the disease?

Guidelines recommend therapy decisions to be based on prognostic factors. Using data from three cohorts, high disease activity, functional limitation, smoking and obesity were identified as poor prognostic factors for the achievement of remission or low disease activity, while ACPA positivity and presence of erosions were not predictive (1). Elevated CRP and various biomarkers were identified as predictors of structural damage in axial spondyloarthritis (2).

1 Baganz L, Richter A, Albrecht K, Schneider M, Burmester GR, Zink A, Strangfeld A. **Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts.** Semin Arthritis Rheum. 2018; 10.1016/j.semarthrit.2018.09.003: https://www.ncbi.nlm.nih.gov/pubmed/30316460.

2 Poddubnyy D, Listing J, Haibel H, Knüppel S, Rudwaleit M, Sieper J (2018). **Functional relevance of radiographic spinal progression in axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort.** Rheumatology (Oxford). 57(4):703-711.

The early juvenile idiopathic arthritis (JIA) cohort ICON has shown that children and adolescents in specialised care achieve a quality of life comparable to that of the general population (3). Demographic risk factors and specific biomarkers, such as S100 protein and vitamin D serum levels, have been identified as predictors of disease manifestation and outcome (4,5).

3 Listing M, Mönkemöller K, Liedmann I, Niewerth M, Sengler C, Listing J, Foell D, Heiligenhaus A, Klein A, Horneff G, Ganser G, Haas JP, Klotsche J, Minden K. **The majority of patients with newly diagnosed juvenile idiopathic arthritis achieve a health-related quality of life that is similar to that of healthy peers – results of the German multicentre inception cohort (ICON).** Arthritis Res Ther 2018;20:106.

4 Tappeiner C, Klotsche J, Sengler C, Niewerth M, Liedmann I, Walscheid K, Lavric M, Foell D, Minden K, Heiligenhaus A. **Risk factors and biomarkers for the occurrence of uveitis in JIA: data from the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis (ICON-JIA) study.** Arthritis Rheumatol 2018 Oct;70(10):1685-1694.

5 Sengler C, Zink J, Klotsche J, Niewerth M, Liedmann I, Horneff G, Kessel C, Ganser G, Thon A, Haas JP, Hospach A, Weller-Heinemann F, Heiligenhaus A, Foell D, Zink A, Minden K. **Vitamin D deficiency is associated with higher disease activity and the risk for uveitis in juvenile idiopathic arthritis - data from a German inception cohort.** Arthritis Res Ther 2018 Dec 13;20(1):276.

Honors and awards

2018 The annual Mitchison Prize for Rheumatology, supported by the Schering Foundation, is awarded to Quirin Hammer, former group member of the Romagnani group, now at the Karolinska Institute in Sweden.

2018 Frank Buttgereit and Falk Hiepe are each awarded a Sanofi iAward Europe for their innovative translational projects on arthritic joint diseases and mysthenia gravis.

2017 Fritz Melchers is awarded the Cothenius Medal of the National Academy of Sciences Leopoldina in recognition of his outstanding scientific life achievements.
2018 He is appointed Leibniz Chair for Lifetime by the Leibniz Association.

2017 Ahmed Hegazy is awarded the Postdoctoral Award for Immunology by the Robert Koch Foundation in recognition of his research on the pathogenesis of chronic diseases. In addition, he receives the Clinical Scientist Award of the Berlin Institute of Health (BIH).
2018 He is awarded a Lichtenberg Professorship by the Volkswagen Foundation.

2017 Andreas Radbruch is awarded the Franziskus Blondèl Medal of the City of Aachen for his achievements in rheumatology.
2019 he starts his three-year term as president of the European Federation of Immunological Societies (EFIS).

Photo: Gero Breloer

Traudl Herrhausen truly would deserve a special prize for her work as president of the DRFZ Board of Trustees until the end of 2017. She has been very committed to the interests of the DRFZ and has consistently promoted its development. She will remain a contact person to the Berlin Senate for the Board of Trustees.

Photo: private

2018 The DRFZ recruits the theoretical biophysicist Kevin Thurley from the University of California. His junior group is funded by the Leibniz Association under the umbrella of the Best Minds Programme. The group will apply advanced mathematical modelling and data analysis techniques to investigate immunoregulation in chronic inflammatory diseases.

2018 Julia Polansky-Biskup and Antigoni Triantafyllopoulou have both been awarded a prestigious Starting Grant of the European Research Council (ERC). With this highly competitive funding line, the ERC supports excellent and ground breaking projects by outstanding young scientists.

2018 The German Society for Rheumatology (DGRh) awards the Kussmaul Medal to the team of the National Database of the German Collaborative Arthritis Centres (Kerndokumentation), for its continuous collection and analysis of physician- and patient-reported data since 1993. The award ceremony takes place during the opening of the 46th Congress of the DGRh in Mannheim.

The DRFZ in public

From left: A new start in life - Insanity or therapy? Radical treatment gives new hope to patients with autoimmune diseases (Süddeutsche Zeitung, 10./.11.2.2018, Dr. Tobias Alexander, Charité); New approaches to chronic inflammation, (Berliner Zeitung, 06/2018, Mir-Farzin Mashreghi, DRFZ); „Inflammation - the silent danger" (Focus, 01/2018). The DRFZ regularly edits a section in the journals „Zeitschrift für Rheumatologie" and „Mobil".

Public events throughout the year

The DRFZ regularly organises events for the public, especially for patients and their relatives. Our goal is to communicate the mission of the DRFZ. The large number of visitors each year confirm the great interest in research on rheumatic diseases.

Day of Immunology (April 29)

The Day of Immunology was initiated a few years ago by the European Federation of Immunological Societies (EFIS). Since the beginning, the DRFZ has been inviting school classes and groups of children between the age of 5 and 17 to learn more about the "bad guys" in autoimmune diseases in hands-on experiments.

World Lupus Day (May 10)

Physicians and scientists of the DRFZ are engaged in various societies and associations, e.g. in the German Society for Lupus Research. In 2017, this society invited patients to the DRFZ on „World Lupus Day" to learn about preclinical research and the latest therapeutic approaches.

Long Night of Science (June)

Once a year, the DRFZ opens its laboratories to visitors during the Long Night of Science, together with around 70 other research institutions in Berlin and Potsdam. During guided tours, lectures and hands-on experiments, our guests can explore the objectives and methods of our research. Together with the Leibniz ScienceCampus Chronic Inflammation, an extensive programme is offered.

During this event, we work closely together with the local clinics for rheumatology and the local patient organisations of the "Rheuma Liga" and the "Deutsche Gesellschaft für Morbus Bechterew". The number of visitors varies between 500 and 1500.

Day of Immunology - hands on experiments with school classes in the DRFZ lab.

World Arthritis Day (October 12)

This event for patients is held regularly together with the Rheumatology Department of the Charité and the "Rheuma Liga Berlin". Around 100 guests learn about the latest research and therapy approaches.

The DRFZ at the newsstand

The DRFZ is mentioned on average about 300 times per year in the press.

Scientists at the DRFZ and our partners are recognised as experts in the field of rheumatology, and are invited for interviews and articles in daily press newspapers and journals.

Publishing in journals for physicians and patients

For many years, Andreas Radbruch and Angela Zink have been editors 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 initiated and edits the section "*Neues aus der Forschung*" in the "Mobil", a journal for patients published 6 times a year by the Deutsche Rheuma Liga e.V. with a circulation of 240,000 copies. The section informs about research highlights and novel therapeutic concepts.

Selected events in 2017...

Review of CRC TRR 130 B cells

The CRC TRR 130 "B cells: Immunity and Autoimmunity" was successfully assessed by the German Research Foundation (DFG).
Second funding period: 2017 – 2021.

Day of Immunology

Four school classes visited the DRFZ on the Day of Immunology. With hands-on experiments they got an insight into our research.

World Lupus Day

50 visitors came to the DRFZ on World Lupus Day, jointly organised with the Charité and the German Society for Lupus Research (DGLF).

Long Night of Sciences

at the DRFZ with 1,800 visitors. Doctors of the clinics for rheumatic diseases in Berlin, two patients' organisations and about 45 DRFZ staff members informed the guests about our research.
Photo: Arne Sattler

Meeting of the Rheuma Liga Berlin

Angela Zink reported on the quality and outcomes of care for people with rheumatic diseases at the meeting of the Rheuma Liga Berlin e.V.: "Rheumatism needs a strong voice (Rheuma braucht eine starke Stimme)".

Visit of the president of the Leibniz Association

Matthias Kleiner, President of the Leibniz Association, during his "inaugural visit" to the DRFZ.

Annual Review by the Scientific Advisory Board of the DRFZ

During the poster session, reviewers and research groups discussed the scientific results.

The „Rheumahaus"

The DRFZ desk at the "Rheumahaus" at the annual congress of the German Society for Rheumatology (DGRh) in Stuttgart, an annual meeting spot for participants, institutes, patients' organisations and support groups.

Hasinger Lecture and Mitchison Award

Albrecht Hasinger Lecture by Stefan Rose-John (Kiel, second from right) and award of the Avrion Mitchison Prize for Rheumatology of the Ernst Schering Foundation to Rafael Leite Dantas (Münster, centre). *Photo: Arne Sattler*

...and 2018

Science in the dinosaur hall

Andreas Radbruch gave a lecture on Immunological Memory in an exciting environment at the Naturkundemuseum Berlin (Natural History Museum, MfN). The lecture is organised by the MfN and the Humboldt - University Berlin.

GerMaNet Meeting

First meeting of the GerMaNet Network, funded by the German Research Foundation (DFG).

Meeting of the EFIS-IL study group

..."non-coding RNA and epigenetic regulation in immune cells", coordinated by Jürgen Wittmann, Erlangen, DE and Mir-Farzin Mashreghi, DRFZ.

Long Night of Sciences

900 visitors joined the event and met clinicians, members of patients´ organisations and DRFZ scientists. Especially the lab tours fascinated young and old.

10th German - Japanese Symposium "New Concepts in Immunology for Controlling Immunity and Immunopathology",

... held in Ettal, Bavaria, June 2018. Organised by Andreas Radbruch and Shimon Sakaguchi. *Photo:private*

Advanced Cytometry Course at the ECI in Amsterdam

For the second time, the DRFZ (Hyun-Dong Chang) organised a one-day course on cytometry as a satellite to the annual meeting of the European Congress of Immunology (ECI).

Evaluation by the Leibniz Senate at the DRFZ

In October 2018, the Leibniz Senate evaluated the DRFZ. Each Leibniz Institute is evaluated every seven years at the latest in the interest of a quality control.

30 Years DRFZ - a reason to celebrate

In November 2018, the DRFZ celebrated its 30th anniversary.

Hasinger Lecture and Mitchison Award

The annual Albrecht Hasinger Lecture was given by Richard Burt, Chicago, USA (centre); the Avrion Mitchison Prize of the Ernst Schering Foundation was awarded to Quirin Hammer, DRFZ/ Karolinska Intitute, SE (first from right).


Ria Baumgrass


Frank Buttgereit


Hyun-Dong Chang


Andreas Diefenbach


Thomas Dörner


Anja Hauser


Ahmed N. Hegazy


Falk Hiepe


Andreas Hutloff


Tilmann Kallinich


Andrey Kruglov


Hiromi Kubagawa


Fritz Melchers


Raluca Niesner


Julia Polansky-Biskup


Andreas Radbruch


Chiara Romagnani


Kevin Thurley


Koji Tokoyoda


Antigoni Triantafyllopoulou


Margitta Worm

Programme Area

Pathophysiology of Rheumatic Inflammation

This programme area investigates the causes of chronic rheumatic inflammation at the cellular and molecular level. Central questions are: How do these diseases develop and what drives them? How can they be targeted and finally cured? The research goal is to develop selective and at best curative therapies. The strategy is to erase the pathogenic immunological memory for inflammation without impairing the protective immunological memory. The researchers are also developing reliable prognostic biomarkers to be able to reliably assess the course of disease or the response to a specific form of therapy.

www.drfz.de

Signal Transduction

Regulation of cytokine expression in different T cell subsets

KEYWORDS
T cell activation, T cell differentiation, transcription factors, cytokines, multi-parametric analysis, combinatorial protein expression

GROUP LEADER
apl. Prof. Dr. rer. nat.
Ria Baumgrass

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

A detailed molecular understanding of the mechanisms of T lymphocyte activation and activation-induced cell fate decisions will contribute to understanding their role in the induction and perpetuation of chronic inflammation, and eventually allow a window to address them therapeutically.

To this end, we investigate the molecular regulation of cytokine co-expression, digital decision making and protein-based pattern recognition of immune cells under physiological and pathological conditions in systemic lupus erythematosus (SLE) and multiple sclerosis (MS).

Global unbiased approaches and multi-parametric visualisation tools help us to decipher which cells are hyperactive in chronic inflammatory diseases (e.g. rheumatoid arthritis, SLE, MS, atopic dermatitis) and how they change during the course of the disease. For this purpose, we continuously use high-dimensional single cell protein data (cytometry data) and our newly developed tool for the analysis and visualisation of multi-parametric data “Pattern Recognition of Immune Cells (PRI)”.

Using these techniques, we have collected the first evidence with multi-parametric cytometry data (own flow and public mass cytometry data) that our bioinformatic approach PRI is useful for a comprehensive characterisation of Th cell subsets. We have also identified and characterised a novel Tfh-like subset having super-functional cytokine producing properties and can provide B-cell help in lupus nephritis mice in an IL-21- and CD40L-dependent manner. Using combinatorial cytokine expression studies of healthy controls and MS patients, we discovered certain patterns of cytokine co-production along with activating and inhibitory receptors in memory Th cell subsets. Furthermore, comprehensive interactom analysis at the foxp3-TSDR revealed a sequence-specific recruitment of the histone-methyltransferase Ehmt1 and the transcription factor WIZ in conventional T cells. Their deletion promotes foxp3 expression and thereby Treg cell induction.

Our results will help us to find further decisive switches in T cells not only to attenuate hyperreactive T cells, but also to modify them in such a way that the immune system readjusts itself. In addition, our results could also be useful for diagnostic and prognostic purposes by identifying and characterising immune cell subpopulations multi-parametrically.

GROUP MEMBERS

PhD students
Stefanie Gryzik
Yen Hoang

MD student:
Ariana Mekonnen

Bachelor/Diploma/Master
Matthias Sikora
Martin Schädlich
Alexander Rybak
Tom Janatzek
Josephine Poetsch

Glucocorticoids and Bioenergetics

How do immune cells adapt to oxygen and nutrient deficiencies in inflamed tissue?

Acute and chronic inflammation can lead to a pronounced lack of oxygen and nutrients in the area of inflammation. How does the immune system manage to remain active despite this?

In acute inflammatory processes such as in the initial phase of a fracture haematoma and during tissue regeneration, but also in chronic inflammation, such as rheumatoid arthritis, cells sometimes need more nutrients and oxygen than the body provides. This can lead to hypoxia at the site of inflammation – a pronounced lack of these vital substances. In order to be able to continue functioning, immune cells and other cell types such as endothelial cells that accumulate in the area of inflammation or in a haematoma have a number of adaptation mechanisms, which finally re-establish homoeostasis. Hypoxia driven angiogenesis is a fundamental process of tissue regeneration, inflammation but also tumour growth. It is regulated by the master regulators of adaptation to hypoxia, namely hypoxia-inducible factor (HIF)-1 and -2. Demonstrating the distinct functions HIF-1 and HIF-2 in bioenergetic adaptation and angiogenic tubular formation, we also observed overlapping and in part redundant regulation of pro-angiogenic factors including the macrophage migration inhibitory factor. These kind of sophisticated cellular adaptation mechanisms are essential to re-balance a de-balanced system and therefore to determine fate and function of all cellular systems. These adaptation mechanisms also offer starting points for drug therapies, for example from the active substance classes of glucocorticoids and Disease-modifying anti-rheumatic drugs (DMARDs).

The adaptation mechanisms of immune cells to a changed microenvironment in inflammatory reactions differ from species to species. Therefore, we are establishing *in vitro* models based on human cells in order to mimic acute and chronic inflammation such as found in the initial phase of fracture healing and in the inflamed joint. To this end, we are generating a variety of different *in vitro* 3D disease models that exclusively consist of the involved human cells in shape with a 3D architecture under the influence of an inflammatory microenvironment. These models will provide tools for the analysis of arthritis and fracture healing as well as for preclinical drug screening and testing thereby reducing the amount of animal experiments.

KEYWORDS
Bioenergetics of immune functions, Hypoxia and angiogenesis, Glucocorticoids, Autoimmune diseases, Fracture healing

GROUP LEADER
Prof. Dr. med.
Frank Buttgereit

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

GROUP MEMBERS

Scientists
Dr. rer. nat. Timo Gaber, (Scientific head)
Dr. rer. nat. Cindy Strehl, (Administrative head)
Dr. rer. nat. Dimas Abdirama
Dr. med. Sandra Hermann
Dr. vet. med. Annemarie Lang
Dr. med. Robert Biesen

PhD students
Moritz Pfeiffenberger, M. Sc.
Alexandra Damerau, M.Sc.
Siska Wilantri, M.Sc.

MD students
Lisa Ehlers
Pierre-Louis Krauß
Franziska Heinsohn
Edgar Wiebe
Antonia Brinkman
Marie-Christin Weber
Kim Zeiner

Bachelor/Diplom/Master
Justyna Pienczykowski

Technicians
Manuela Jakstadt
Gabriele May

Students
Aditi Kuppe, Pelle Löwe

Schwiete Laboratory for Microbiota and Inflammation

How does the intestinal microbiota influence chronic inflammation and cancer?

KEYWORDS
Microbiota
IgA
Microbiota Cytometry,
Chronic Inflammation

GROUP LEADER
Habil. Dr. rer. nat.
Hyun-Dong Chang

Dr. Rolf M. Schwiete Stiftung

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

Approximately 10% of the German population suffers from chronic inflammatory diseases such as rheumatoid arthritis or inflammatory bowel disease. In many patients with chronic inflammatory diseases, the composition of the intestinal flora (intestinal microbiota) is altered compared to healthy people (dysbiosis). Several studies have shown that these alterations can correlate with the clinical course of disease, response to therapy, and the risk of developing cancer. However, causal relationships between components of the intestinal microbiota and disease/clinical response are largely unknown. Supported by the Dr. Rolf M. Schwiete Foundation, we try to identify pathogenic and protective components of the microbiota and unravel the dialogue between such bacteria and the immune system to gain insight into the role of the microbiota in the development and chronification of inflammation.

Together with the group of Prof. Susann Müller from the Helmholtz Institute for Environmental Research in Leipzig, we have recently developed a method for assessing the composition of the intestinal microbiota by flow cytometry. This "microbiota cytometry" discriminates single bacteria based on DNA content, light scatter properties, and, in addition, on mucosal antibody coating, to specifically identify bacteria which have come in contact with and are seen by the immune system. Microbiota cytometry allows us to simply and rapidly compare the composition of the microbiota between individuals, healthy versus diseased, at multiple time points and identify and isolate by cell sorting bacterial populations of interest for taxonomic and functional analyses. Together with our clinical partners at the gastroenterology department of the Charité Universitätsmedizin Berlin, we are looking at defined cohorts of patients with inflammatory bowel diseases, i.e. patients with Crohn's disease and ulcerative colitis, as well as patients with spondylarthropathies and rheumatoid arthritis with the aim of identifying bacteria that have a positive or negative influence on the clinical course of the disease, or on concomitant diseases such as cancer, and on the response to therapy.

To increase the resolution of the microbiota flow cytometry analysis for the identification of specific bacterial taxons, we are developing multi-parameter microbiota cytometry using monoclonal bacteria-specific antibodies in close collaboration with the group of Andrey Kruglov (Chronic Inflammation Group).

In our studies we have already identified potentially pro-inflammatory bacteria which determine the capacity of pro-inflammatory T helper lymphocytes to induce intestinal inflammation in a pre-clinical model of colitis. We have also identified a bacterium with potential anti-inflammatory properties, due to its ability to induce the expression of TGF-β. TGF-β is an important anti-inflammatory cytokine and also promotes the production of IgA antibodies in the gut. IgA antibodies are an important component of the intestinal barrier and control the composition of the intestinal microbiota by directly binding to bacteria. Thus, the bacteria could have therapeutic potential in inflammatory bowel diseases as an inducer of TGF-β and IgA antibodies to dampen inflammation and strengthen the intestinal barrier.

It is our overall goal to gain a molecular understanding of how selective bacterial species contribute to the induction and maintenance of chronic inflammatory diseases and develop innovative therapeutic approaches through the specific manipulation of the intestinal microbiot.

GROUP MEMBERS

Scientists
Dr. Alexander Beller
Dr. Pawel Durek
Dr. Ute Hoffmann

PhD students
Lisa Budzinski, M.Sc.
Victoria von Goetze, M.Sc.
Kevin Heiking, M.Sc.
Aayushi Shah, M.Sc.

Bachelor/Diplom/Master
Tanisha Momtaz, B. Sc.
Georgia Lattanzi, B.Sc.

Technicians
René Maier
Sabrina Freytag
Toni Sempert

Developmental and Mucosal Immunology

Development and function of the innate immune system

Our current and future research is focused on a molecular understanding of how components of the innate immune system promotes tissue homoeostasis by contributing to the adaptation of multicellular organisms to pernicious environments, such as those at barrier surfaces (e.g., intestine, skin).

We are addressing three major questions:

1. Transcriptional control of ILC development and function

Our lab has recently contributed to the discovery of innate lymphoid cells (ILCs), a group of tissue-resident innate lymphocytes located at border surfaces that release cytokines specifically acting on epithelial cells thereby contributing to tissue homoeostasis and to the adaptation of the host in response to noxious compounds and tissue damage. A focus has been the analysis of transcriptional programmes controlling lineage specification, commitment and function of ILCs. We recently identified a common, Id2-expressing progenitor to all 'helper-like' ILC lineages, the CHILP (Klose, Cell 2014). Our previous work has revealed that functional perturbations of ILC predispose to intestinal infections and to chronic inflammatory bowel diseases. It is likely, that such studies will identify new targets for the treatment of debilitating chronic inflammatory disorders.

2. The role of the indigenous microbiota in calibrating innate immunity

The role of environmental factors (microbiota, nutrients) for the formation of an effective and well calibrated innate immune response is recognized. Mononuclear phagocytes germ-free mice were unable to produce most pro-inflammatory cytokines (in particular type I IFN), and, consequently, germ-free mice were more susceptible to infections with viruses (Ganal, Immunity 2012). On a mechanistic level, we showed that signals of the microbiota are needed to remove a chromatin barrier required for the transcription of genes after ligation of pattern recognition receptors (PRR). Ongoing studies address the mechanistic underpinnings of this process as well as the microbiota-derived signals that tune mononuclear phagocyte responses. As many autoimmune diseases have a type I IFN signature, it is possible that dyscalibration of the mononuclear phagocytes by the microbiota may contribute to rheumatic diseases.

3. The role of nutrients for development and function of the innate immune system

Much has been learned about how the microbiota contributes to many aspects of host physiology. In contrast, the role of nutrients for development and function of the intestinal immune system has largely been a matter of speculation owing to the fact that molecular sensors of dietary molecules are widely unknown. Given the broad role of nutrients in metabolic diseases and the impact of intestinal cancer on human health, research into the question of how the power of nutrients can be harnessed for improving human health and for the prevention of disease is much warranted. We have recently found that the aryl hydrocarbon receptor (AhR), a transcription factor activated by small molecular ligands, is required for the development of innate immune system components by serving as a sensor for phytochemicals. Based on these preliminary data, we aim now to systematically define the role of diet-induced changes for the function and differentiation of mucosa-associated innate lymphocytes and to uncover how innate lymphocytes regulate epithelial adaptation by controlling niche support for intestinal epithelial stem cells.

KEYWORDS
Microbiome
Innate immune system
Chronic inflammation
Tissue homeostasis
Innate Lymphoid Cells (ILC)

GROUP LEADER
Prof. Dr. med.
Andreas Diefenbach

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

GROUP MEMBERS

Scientists
Dr. Nora Kofoed-Branzk
Dr. Oliver Hoelsken
Dr. Irene Mattiola
Dr. Mario Witkowski

PhD students
Stylianos Gnafakis
Konrad Gronke
Fabian Guendel-Rojas
Michael Kofoed-Branzk
Bruno Rocha
Laura Schaupp
Omer Shomrat
Caroline Tizian

Technician
Karin Oberle

Lab manager
Thordis Hohnstein

B Cell Memory

Immunomodulatory approaches targeting autoreactive B lineage cells while leaving protective B memory intact

KEYWORDS
B cells, plasma cells, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS)

GROUP LEADER
Prof. Dr. med. Thomas Dörner

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Immune memory protects our body against foreign antigens but can also cause damage in autoimmune diseases (AID). B cells and plasma cells play a central role by producing antibodies and cytokines to activate and regulate other immune cells. A better understanding of B cell functions and selective targeting of B cells holds promise for future therapeutic applications. We characterize B and plasma cell functions during the formation of immunological memory in health and autoimmunity to understand the processes leading to the induction and maintenance of protective versus autoreactive B cells with the goal of selective targeting of autoimmune cells.

In autoimmune patients, we found reduced responsiveness of B cells to B cell receptor (BCR) and Toll-like receptor (TLR)9 stimulation. We defined this phenotype as 'post-activation' and found B cells from patients with systemic lupus erythematosus (SLE) to be characterized by a distinct pattern of checkpoint molecules. The latter are candidates of selective expression and hence distinct treatment targets.

Other differences between healthy and autoimmune individuals may be provided by the dynamics of (auto) antigen reactive cells. Here, vaccination studies in healthy donors showed that antigen-specific B cells are recruited from naïve, as well as from cross-reactive memory B cells, upon primary vaccination, whereas they are recruited from the memory pool upon secondary challenge. In lupus nephritis, PTX3 specific B cells that are candidate antigen-specific regulatory B cells, were found to be reduced in comparison to both SLE patients without nephritis and healthy donors, indicating substantial differences in differentiation.

A better understanding of the maintenance of plasma cell subsets in the bone marrow could help targeting auto-antibody producing cells in AID. We demonstrated that the composition and functionality of B cells are stable at the individual donor level.

As an overall goal, we aim to identify selective therapeutic strategies which include 1) modulating post-activated B cells, 2) using check-point molecules for immunomodulatory approaches and 3) using antigen-specific B lineage cells to improve regulatory and suppress autoreactive cells including selectively targeting harmful autoreactive plasma cells in autoimmune diseases while providing sufficient protective functions.

GROUP MEMBERS

Scientists
Andreia C. Lino, PhD
Dr. Eva V. Schrezenmeier
Dr. Ana-Luisa Stefanski
Dr. Marie Lettau
Dr. Thomas Rose

PhD students
Annika Wiedemann, Dipl.-Ing.
Sarah Y. Weißenberg, M. Sc.
Franziska Szelinski, M. Sc.
Hector Rincon, M. Sc.
Dr. Mariele Gatto

MD students
Arman Aue
Nadja Nomovi
Anna Lisney
Finn Moritz Wilkens

Technician
Karin Reiter

Immune Dynamics

We aim to understand the dynamic interactions of immune cells in the tissue context

If the immune system reacts to a stimulus, a dynamic interplay of different cells is triggered. Circulating and tissue-resident immune cells, as well as tissue-specific non-hematopoietic cells initiate, maintain, coordinate and terminate an immune reaction. In order to develop novel therapeutic strategies, it is necessary to understand these dynamic cellular interactions on a molecular level.

Long-lived plasma cells produce antibodies and are important players of immunological memory. They protect the body from recurrent infections. In the course of certain autoimmune diseases, however, long-lived plasma cells can produce autoantibodies which are detrimental.

The survival of long-lived plasma cells depends on extrinsic signals. It is therefore necessary to analyse their composition in the spatial context of the surrounding tissue. We have developed a novel microscopy technology, which allows us to follow the dynamic processes in these niches deep in the bone marrow over extended time periods. We could show that the blood vessels surrounding the plasma cell niches are highly dynamic and change their localisation relative to plasma cells. We are now investigating to what extent these changes affect plasma cells and the composition of the niches. We are also using multiplexed histological analyses, which allows us to stain up to 80 markers on one single tissue section, in order to decipher the code of the plasma cell niches.

Plasma cells can also be found in high numbers in the gut mucosa, where they produce massive amounts of IgA. We could show that a fraction of those plasma cells can become long-lived. Niches for long-lived IgA+ plasma cells derived from mucosal immune responses are present within the intestinal lamina propria, but also within the bone marrow. We are investigating whether gut-derived plasma cells include autoreactive cells.

In addition to the physiological sites described above, plasma cells can survive in a number of other tissues under conditions of chronic inflammation. We could show that long-lived plasma cells can persist even in the central nervous system, a tissue void of immune cells in healthy individuals. Consequently, we are now investigating whether antibodies produced by those intracerebral plasma cells contribute to neuronal damage, for example in multiple sclerosis.

KEYWORDS
Intravital microscopy
plasma cells
stromal niches
histology

GROUP LEADER
Prof. Dr. med. vet.
Anja Hauser

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

GROUP MEMBERS

Scientists
Randall Lindquist MD, PhD
Dr. rer. nat. Anna Pascual-Reguant
Dr. rer. nat. Karolin Pollok
Dr. rer. nat. Carolin Ulbricht

PhD students
Dipl. Biochem. Karolin Holzwarth
MSc Jonathan Stefanowski

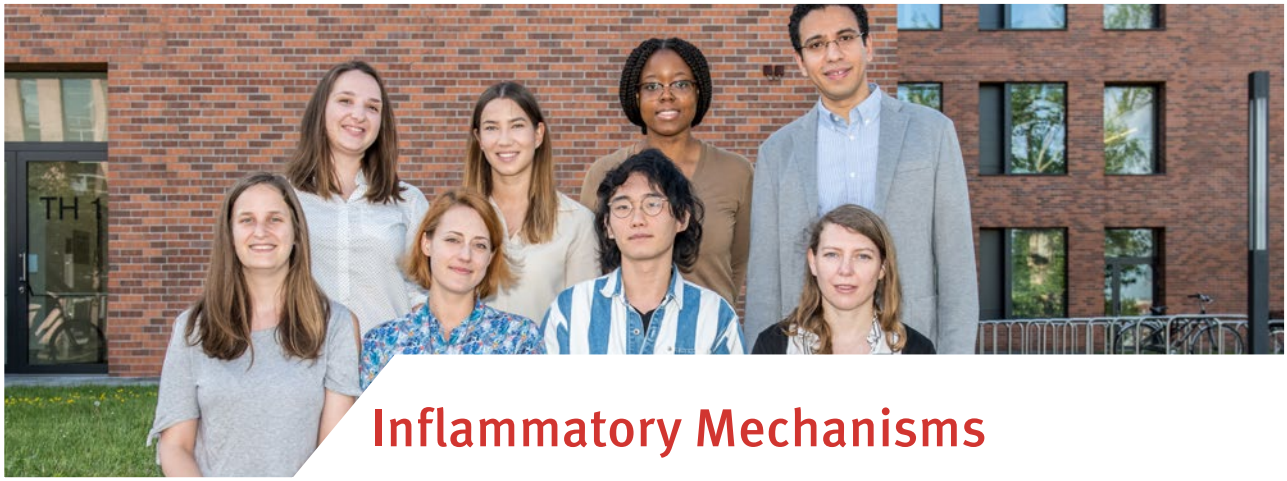
MD -students
Ronja Mothes,
Raphael Raspe

Bachelor/Diplom/Master
Linus Aulich, Sandy Bauherr, Yu Cao, Sven Flatow, Sina-Zoe Hanke, Ariana Rauch, Sylvia Uhlmann

Technicians
Robert Günther,
Ralf Uecker

Student
Alina Liebheit

Microscope Operator
Ralf Köhler
Carina Miggitsch, guest student from Innsbruck University



Inflammatory Mechanisms

Host-Microbiota interactions shape intestinal inflammation

KEYWORDS
T cell differentiation
Microbiota-specific T cells
Intestinal inflammation
Inflammatory Bowel Disease
Host-Microbiota interactions

GROUP LEADER
Prof. Dr. med. Dr. rer. nat
Ahmed Hegazy

The gastrointestinal tract contains a huge number of immune cells and harbours a large population of bacteria that exist in a symbiotic relationship with the host. In inflammatory bowel disease (IBD) this balance is perturbed, triggering pro-inflammatory responses that drive disease symptoms. Our work focuses on untangling the interplay between the host and microbiota during inflammation.

We have several diverse projects running with the common aim of identifying novel inflammatory signatures that may be amenable to therapeutic blockade, or be predictive markers of treatment failure. We wish to examine the link between bacterial opsonisation by the immune system and the CD4+ T cell responses to these bacteria, with the aim of identifying pathogenic and protective T cell signatures. Previous work has identified a novel role for oncostatin M (OSM) in mice and humans. Upregulation of OSM was found to be a predictive marker for anti-TNF treatment failure in IBD and blockade of OSM *in vivo* ameliorated disease symptoms in a mouse model of colitis. Therefore, we wish to exploit dysbiosis- and genetic-driven IBD mouse models and primary human tissue samples to explore the impact of OSM on intestinal epithelial cells and barrier functions in health and disease.

A comprehensive understanding of how the microbiota-immune system crosstalk is perturbed in chronic inflammation is essential, particularly in light of the high rate of treatment failure. Using a combination of mouse and human T cell immunology, mucosal immunology and animal models of disease as well as clinical specimens and sequence based approaches, we aim to identify environmental, microbial and inflammatory drivers that promote maladaptation and gut tissue inflammation. Our focus on clinical samples ensure that the work we carry out is of high relevance to patients and increases the likelihood of us delivering findings of future clinical relevance.

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

VolkswagenStiftung

GROUP MEMBERS

Scientists
Caitlin Jukes, PhD

Physicians
Veronika Horn, MD

PhD students
Zuzanna Borek, Msc
Roodline Cineus, Msc
Yu-hsin hsieh, Msc

Master student
Johanna Tenner

Technician
Diana Boesel, RA

Autoimmunology

New ways of approaching treatment of autoimmune diseases

Our research group is fundamentally involved in analysing 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 to prevent the generation of new plasma cells. Since all these therapies unselectively deplete plasma cells, regardless whether they secrete protective of pathogenic antibodies, we developed an affinity matrix technology for antigen-specific plasma cell depletion. 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. One current study is aimed to demonstrate an improvement of muscle weakness in a murine model of myasthenia gravis after the specific depletion of plasma cells secreting autoantibodies against the acetylcholine receptor.

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 immunoablation 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 basis 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 characterisation 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 personalised therapies.

Along similar lines, we have developed several novel biomarkers, reflecting specific aspects of the pathogenesis of SLE. We have identified serologic (autoantibodies) and cellular biomarkers (Siglec1 expression on monocytes, B and T cell subpopulations in the peripheral blood and urinary immune cells). We believe these biomarkers will enable us to tailor make our treatment in the future for patients and broaden our understanding of the disease pathogenesis.

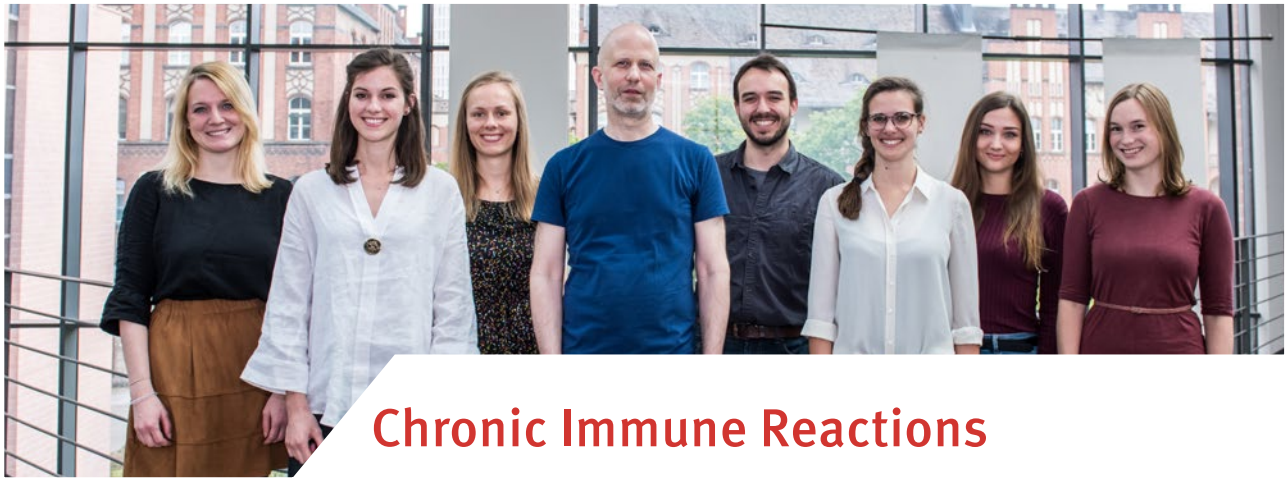
KEYWORDS
Memory plasma cells,
Autoantibodies,
Systemic autoimmune diseases,
Cellular therapies,
Autologous hematopoietic stem cell transplantation

GROUP LEADER
Prof. Dr. med.
Falk Hiepe

GROUP MEMBERS

Scientists
Dr. med. Tobias Alexander
Dr. Qingyu Cheng
Dr. rer. nat. Velia Gerl
Prof. Dr. med. Bimba F. Hoyer (guest scientist),
Laleh Khodadadi, PhD
Dr. Thomas Rose

PhD students
Anne von Bülow
Hannah Brandt
Paul Freund
Nina Görlich
Jacob Kujat
Dominik Lammerding
Spyridon Lipka
Jonas Martin
Sarnai Naran
Lennard Ostendorf
Andreas Pelz
Veronika Scholz
Christopher Skopnik
Lydia Zorn



Chronic Immune Reactions

How dysregulated T cell / B cell interaction drives autoimmunity

KEYWORDS
T cell/B cell cooperation
T follicular helper cells
Chronic inflammation
Tissue-resident memory
T cell costimulation

GROUP LEADER
Dr. rer. nat.
Andreas Hutloff

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

ROBERT KOCH INSTITUT

Successful interaction of antigen-specific T and B cells is 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 centre 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 centre responses resulting in autoimmunity. In particular we are elucidating the role of costimulatory receptors, which are important for fine-tuning 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. Consequently, costimulatory receptors are an attractive target for therapeutic intervention. A special focus of our research is the Inducible T cell Co-Stimulator ICOS, which has originally been identified by our group. ICOS is specifically important for Tfh cell maintenance in late phases of the germinal centre response. Antibodies interfering with the ICOS signaling pathway are currently tested in clinical trials for the treatment of autoimmune diseases.

A second major focus of our research is the transcriptional control of Tfh cells. We identified the transcription factors Klf2 and Bach2 as two central regulators of Tfh cells, which control Tfh cell differentiation and maintenance by different mechanisms.

Another field of interest is T cell/B cell interaction outside lymphoid tissues. Lymphocytic infiltrates are frequently found in inflamed tissues where they substantially contribute to tissue destruction. Using a murine lung inflammation model, we could show 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. In a project within the CRC 130 *(page 26)* we aim to unravel how T/B interaction can take place outside the ordered structure of secondary lymphoid organs. In addition, we are currently investigating the impact of Tfh-like cells for the pathogenesis of different human autoimmune diseases using tissue samples from chronic inflammatory conditions.

GROUP MEMBERS

Scientist
Dr. rer. nat.
Annette Lahmann

PhD students
Laura Bauer (M.Sc.)
Josefine Graffunder (M.Sc.)
Julia Kuhrau (M.Sc.)
Marcel Finke (M.Sc.)
Josephine Scholz (M.Sc. cooperation with AG Worm)

MD student
Lisa-Jasmin Müller

Chronic Inflammatory Diseases of Childhood and Adolescence

Understanding chronic inflammation in the developing children

Juvenile idiopathic arthritis (JIA) is the most frequent chronic inflammatory disease in childhood with a prevalence of approximately 1 : 1000. Since the clinical presentation, the prevalence of co-morbidities, and the prognosis of children with JIA differ significantly from adults with different rheumatic diseases, knowledge about the pathogenesis obtained in adults cannot simply be transferred to children. JIA-specific markers for classifying disease subtypes, defining endotypes and predicting therapeutic response are missing.

In cooperation with the research group of Mir-Farzin Mashreghi, we aim to define molecular immune cell signatures in the inflamed synovia and in the peripheral blood of children suffering from different forms of JIA. With these results we will define markers specific for the different forms of JIA which can be traced in peripheral blood. Using data from newly established cohorts, we aim to analyse the suitability of these tools to classify the disease, monitor the disease activity and finally to predict the response to different therapeutic regimens. This translational approach will help to establish JIA-specific endotypes, which are fundamental for the development of personalised treatment strategies.

Monogenic alterations causing systemic inflammatory diseases usually manifest in early childhood. They are characterized by excessive production of pro-inflammatory cytokines and are referred to as autoinflammatory diseases (AID). In the last decade, analysis of these underlying molecular genetic alterations has uncovered new immunological pathomechanisms, e.g. the dysregulation of the inflammasome reaction. Analyzing our cohort of patients with defined, (e.g. interferonopathies, inflammasomopathies) as well as unassigned AID, we aim to comprehensively immunophenotype different immune cell populations in order to develop diagnostic markers and unravel the pathological processes leading to excessive cytokine production.

KEYWORDS
Juvenile idiopathic arthritis
Autoinflammation
Monogenic diseases
Immunophenotyping

GROUP LEADER
PD Dr. med.
Tilmann Kallinich

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

BIH Clinical Fellow, supported by the Charité foundation

GROUP MEMBERS

Clinical Scientist
Dr. Carl Christoph Goetzke

Clinicians
Dr. Sae-Lim von Stuckrad
Dr. Banu Orak

Chronic Inflammation

Significance of immune system, cytokines and microbiota interplay for the development of chronic inflammation

KEYWORDS
Microbiota
Chronic inflammation
Cytokines

GROUP LEADER
Andrey Kruglov, PhD

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

There is a clear indication that rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis and Crohn's disease, can be influenced by commensal microorganisms, but mechanistic aspects of microbiota contribution to the disease development, pathogenesis, and chronicity remain to be determined. We postulate that microbiota changes might modulate cytokines production and activation of the immune system in the development of chronic rheumatic diseases.

Proinflammatory cytokine production can be influenced by microbiota composition in rheumatic patients. We observed significant changes in microbiota composition in patients with rheumatic diseases, and enhanced capacity of such microbiota to induce Tumor Necrosis Factor (TNF) production from peripheral blood mononuclear cells. TNF blockade in patients leads to significant disease amelioration and tissue repair via poorly understood mechanisms. We have revealed that TNF blocks tissue repair via the downregulation of IL-22 biological activity both in mice and humans. In chronic autoimmune arthritis, we found that TNF is crucial for the regulation of blood monocyte homeostasis via control of T cell responses.

Since one of the mechanisms of immune-mediated control of microbiota composition is the production of microbiota-specific IgA antibodies by intestinal plasma B cells, we are currently dissecting the mechanisms of microbiota control by IgA and utilisation of these mechanisms for microbiota analysis and modulation. To this end, we have generated a set of microbiota-specific IgA antibodies specific to distinct microbiota species, and have identified several antibodies that bind immunologically relevant bacteria in the microbiota.

Altogether, our data reveal interplay between microbiota composition, cytokine production and rheumatic diseases manifestation, and provide potential novel strategies for treating rheumatic diseases by modulating intestinal microbiota.

GROUP MEMBERS

PhD students
Justus Ninnemann
Katharina Kurz

Master student
Julia Röchert

Bachelor
Sarah Khedhayir

Humoral Immune Regulation

Better understanding of structure/function relationship of newly identified IgM Fc receptor

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., FcγRs, FcεRs, FcαR) are expressed by many different immune cells including myeloid cells and are extensively characterized as central mediators coupling innate and adaptive immune responses. Much of the knowledge gained has now been translated to clinical practice. By contrast, the effector function of FcR for IgM, the first antibody appearing in phylogeny, ontogeny and immune responses, has begun to be explored, since it was identified by us in 2009.

Unlike other FcRs, FcμR is selectively expressed by lymphocytes (B, T and NK cells in humans and only B cells in mice), suggesting distinct functions compared to other FcRs. FcμR may have a dual signalling ability: one through a potential as yet unidentified adaptor protein non-covalently associating with the FcμR ligand-binding chain and the other through its own Tyr/Ser residues in the cytoplasmic tail. FcμR binds pentameric IgM with a high avidity (~10 nM) in solution, but more efficiently binds IgM when it is attached to a membrane component via the Fab region on the same cell surface (*cis* engagement).

The findings from four different FcμR-deficient mice clearly indicate an important regulatory role of FcμR in development of autoreactive B cells and in production of autoantibodies. We propose a model how FcμR on B cells regulates autoreactive B cells developing in the bone marrow by *cis* engagement of FcμR and IgM B cell receptor via IgM-opsonized self-antigens. Understanding the mode of action of the FcμR may thus provide an insight in therapeutic options to ameliorate autoantibody-mediated rheumatic diseases.

KEYWORDS
Natural IgM
B cell
Tolerance
Autoantibody

GROUP LEADER
Prof. Hiromi Kubagawa, MD
Guest Senior Scientist

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

GROUP MEMBERS
Master students
Vithurithra Tharmapalan
Eduardo Vieyra Olguin

Lymphocyte Development

We intend to define molecular, cellular and functional properties of quiescent and of activated hematopoietic stem cells

KEYWORDS
Hematopoietic stem cell, stem cell quiescence, miRNA regulation, hematopoiesis, B cell differentiation

GROUP LEADER
Prof. Dr. rer. nat. MD h.c. PhD h.c. Fritz Melchers, Leibniz Chair

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

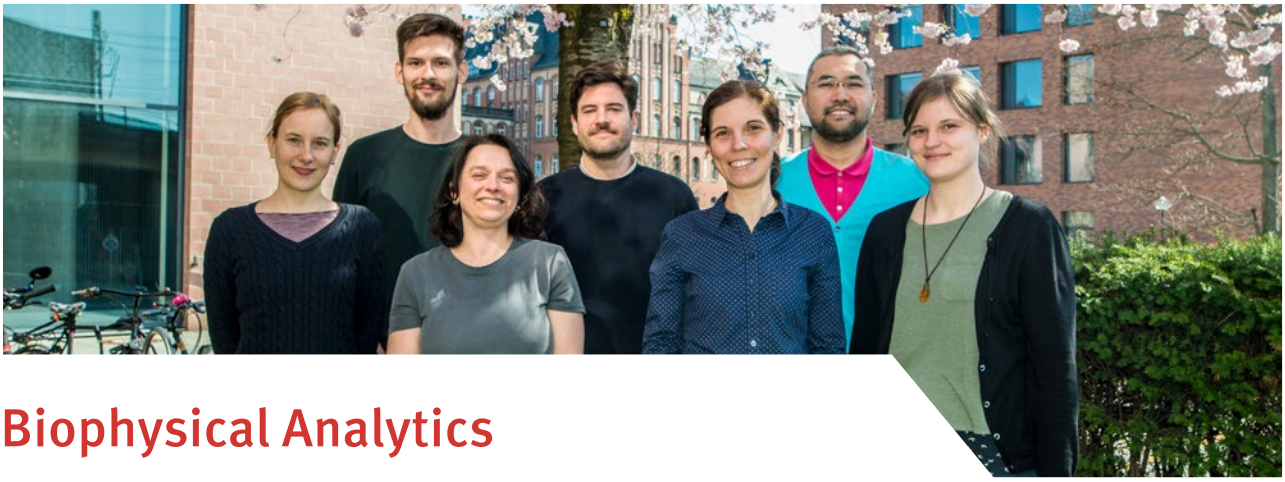
Hematopoietic stem cells (HSC) and memory lymphocytes are maintained as quiescent, long-lived cells, in dedicated, yet poorly characterised niches of the bone marrow. We have shown that quiescent hematopoietic stem cells provide a reservoir for Mycobacteria, the aetiologic agent of tuberculosis. Quiescent memory lymphocytes of the bone marrow are roadblocks to tolerance induction in chronic inflammatory diseases. Our goal is to understand the molecular mechanisms controlling quiescence. Apart from the fundamental progress in understanding life-long hematopoiesis and immunity, this knowledge will generate entirely new options to treat chronic, latent infections, like tuberculosis, and chronic inflammatory (rheumatic) diseases.

In 2019, we started to coordinate an international and interdisciplinary network of experts in stromal cell biology, haematology, , molecular cell biology (in particular RNA biology), immunology, infectiology and inflammation, funded by the Leibniz Association *(page 25)*. The consortium combines experimental *in vivo* and *ex vivo* approaches to define the signals inducing, maintaining or terminating quiescence, the integration of signalling pathways in the hematopoietic and immune cells, and the targets of signalling, which confer long-lasting quiescence.

With the results of this project, we will provide new insights into the molecular mechanisms of quiescence and longevity of HSC, memory B- and plasma cells, as well as of the molecular basis of latency of Mtb infection. In the late phases of the project, this will allow comparisons with the quiescence and longevity of memory lymphocytes of autoimmune responses in autoimmune diseases (NZBxNZW mouse model of systemic lupus erythematosus). This will be informative for deciphering which molecular mechanisms are shared in these long-lived bone marrow-born cells. The analyses of latent tuberculosis infection (LTBI)-derived, Mtb-infected HSC will also provide in-formation on the similarity of gene expression programmes of murine and human HSC.

GROUP MEMBERS

Scientists
Dr. Yohei Kawano
Dr. Georg Petkau
Dr. Peter K. Jani (post-doctoral scholar of the Alexander von Humboldt Foundation)



Biophysical Analytics

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

Recently, we developed and refined an endogenous fluorescence method for *in vivo* microscopy to monitor the NAD(P)H-dependent enzymatic activity in cells. This method allows us to distinguish between various classes of enzymes based on the spatially-resolved fluorescence lifetime of the coenzymes NADH and NADPH. Using this technique, we were able to define the concept of "oxidative stress memory" in the context of chronic neuroinflammation and neurodegeneration, both in mouse models and in patients. We found that astrocytes and microglia within the central nervous system (CNS) of diseased mice show a partially irreversible phenotypic shift towards oxidative stress generation, which is also present in monocytes of MS patients. Due to the persistence of plasma cells in the CNS in the late disease phases, we assumed and found that antibodies maintain this phenotypic shift of astrocytes in human brain slices treated with a NMDA-R antibody.

This project is a collaboration with Dr. H. Radbruch and Prof. Dr. F. Heppner (Neuropathology, Charité), Prof. Dr. F. Paul (Neuroimmunology, Charité) and Prof. Dr. A.E. Hauser (DRFZ). Since we expect a similar phenotypic shift in renal tissue of mice affected by lupus, we are currently performing longitudinal NAD(P)H fluorescence lifetime imaging of the kidney in collaboration with Prof. Dr. R. Voll, Erlangen, CRC TRR 130 *(page 26)*.

Long-lived plasma cells are central players in forming both physiologic and pathologic immunological memory. Due to a lack of technological tools, these cells could not be investigated over their whole lifetime in their natural environment – the bone marrow of long bones. We therefore developed LIMB: Longitudinal Intravital Microscopy of the femoral Bone marrow. In this way, we were able to monitor plasma cells over 157 days in the deep cavity of murine femurs. This technology has also allowed us to repeatedly monitor monocytes and macrophages, as well as vasculature remodelling in models of tissue regeneration after bone injury.

Independent of the organ of interest, intravital microscopic investigation faces the challenge of capturing the high complexity of cellular subpopulations and extracellular tissue structures in a dynamic manner. This requires simultaneous multiplexed imaging of the living tissue, as designed and demonstrated by us imaging germinal centre reactions in murine popliteal lymph nodes.

KEYWORDS
Intravital multi-photon microscopy,
NAD(P)H metabolism,
functional in vivo imaging

GROUP LEADER
Prof. Dr. rer. nat.
Raluca Niesner

Freie Universität Berlin

GROUP MEMBERS

Scientists
Dr. Asylkhan Rakhymzhan

PhD students
Ruth Leben
Markus Köhler
Alexander Fiedler
David Reismann

Bachelor/Diplom/Master
Lucie Reuter
Keven Mauersberger

Technicians
Peggy Mex
Robert Günther

Students
Martin Tschaikner
Wjatscheslaw Liublin
Linus Aulich

Immuno-Epigenetics

How the structure of the genome shapes the immune system in health and disease

KEYWORDS
Epigenetics, Epigenetic editing, Immune-regulation, T lymphocytes cellular senescence

GROUP LEADER
Dr. rer. nat.
Julia K. Polansky-Biskup

The 3D structure of our genome – the 'epigenome' – is essential in determining the type and function of a cell. That is why the analysis of the epigenome facilitates deep insights into the developmental history of a cell, its current gene expression profile, and also its future destiny.

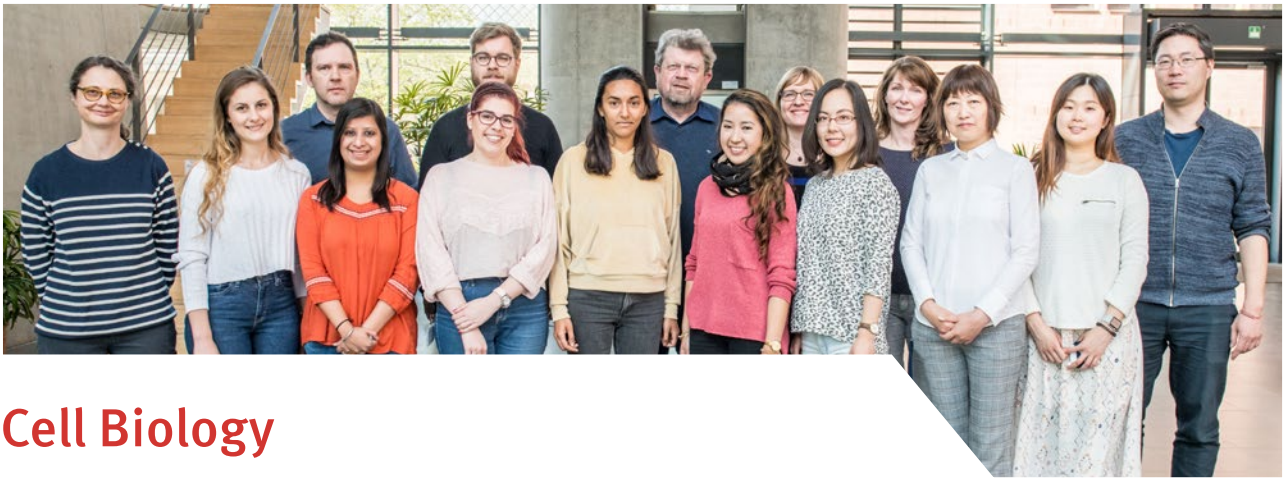
CD4+ T lymphocytes provide immunological protection by differentiation into various functional subtypes. However, they are also one of the main contributors to chronic inflammation and auto-immunity during disease. Therefore, our group focuses on the analysis and interpretation of epigenomic structures of CD4+ T lymphocytes in health and during chronic inflammatory diseases such as rheumatoid arthritis. These insights will not only highlight candidate genes involved in the disease-associated mis-differentiation of T cells, but will also pinpoint promising target elements for therapeutic intervention, as epigenetic modifications are in general reversible and hence, 'druggable'.

In the last two years, one research focus of our group was the establishment of precise methods for the targeted manipulation of epigenetic switch regions in the genome of a living cell. For this, we established a state-of-the-art 'epigenetic editing' technique based on the CRISPR/Cas9-system in our lab and tested it successfully in primary human T cells. With this, we now aim at switching the functional programme of a T cell at will, e.g. for the targeted re-programming of a pathogenic T cell to its normal counterpart. An additional application could be to equip T cell populations with a favourable function for their application in adoptive T cell therapy against auto-immune diseases.

A newly founded project ('Leibniz Competition grant 2018') in our group focuses on the epigenetic changes which occur in T cells during the aging process in humans *(page 25)*. This knowledge could impact on the development of clinical biomarkers for aging and pre-mature aging which is often associated with chronic inflammation.

GROUP MEMBERS

PhD students
M. Sc. Christopher Kressler
M. Sc. Dania Hamo
M. Sc. Marcos Cases



Cell Biology

Immunological memory is a driver of rheumatic inflammation

We usually only get "childhood diseases" once and thereafter, we are protected from them by an "immunological memory" for the rest of our lives. In the case of inflammatory rheumatic diseases, this immunological memory is directed against the patient's own body. Our group is investigating how memory lymphocytes control chronic inflammation, how they contribute to therapy refractoriness, and how we can selectively target pathogenic memory lymphocytes.

In recent years, we have identified memory plasma cells secreting autoantibodies as a major determinant of rheumatic disease refractoriness towards conventional immunosuppressive therapies. Memory plasma cells secrete copious amounts of (auto-)antibodies and persist in dedicated niches in the bone marrow and inflamed tissues organised by stromal cells. Their lifestyle as terminally-differentiated, non-migratory, and quiescent cells makes them refractory to therapies. However, memory plasma cell survival is conditional on signals provided to them in their niches. Understanding the signals required for memory plasma cells to survive will allow us to selectively address these cells therapeutically and to develop successful strategies for the treatment of refractory rheumatic disease.

We have developed a synthetic niche which mimics the survival niche of memory plasma cells in the bone marrow. We have discovered that the memory plasma cells need direct contact with stroma cells and a second signal, the cytokines APRIL or BAFF, to survive. Contact with stroma cells activates the PI3 kinase signalling pathway, while APRIL activates the NF-κB signalling pathway in the plasma cells. If either of the two signalling pathways is blocked pharmacologically, the plasma cells die, both *in vitro* and *in vivo*.

A second type of memory lymphocyte that controls chronic inflammation is the memory T-helper (Th) lymphocyte. Th cells secrete cytokines and chemokines, which stimulate inflammatory reactions and attract and activate granulocytes and phagocytes, inducing and maintaining inflammation. As with memory plasma cells, we have originally found that memory T lymphocytes also persist in bone marrow in dedicated niches, resting in terms of mobility and proliferation, and maintaining functional long-term systemic memory. We can show that memory Th lymphocytes specific for childhood diseases are present in the bone marrow of elderly humans, but are no longer detectable among circulating memory Th lymphocytes. Following booster vaccination, antigen-reactive memory CD4+ T lymphocytes are rapidly mobilised into the blood to mount fast and effective secondary immune responses.

For pathogenic memory T lymphocytes found primarily in inflamed tissues of patients with rheumatic diseases, we have identified the transcription factor Twist1 as critical regulator of molecular adaptations allowing the pathogenic memory Th cells to persist and function in the inflamed tissue. We could show that Twist1 promotes the survival by inducing the microRNA miR-148a which downregulates the pro-apoptotic factor Bim. Twist1 also regulates the energy metabolism of pathogenic Th cells by switching them from glycolysis to complete dependence on fatty acid oxidation. By targeting miR-148a using antagomirs or pharmacological inhibition of fatty acid oxidation, we can selectively eliminate such pathogenic Th lymphocytes.

It is our overall aim to identify and target the immunological memory for rheumatic inflammation while preserving the protective memory to ultimately achieve long-term therapy-free remission in these diseases.

KEYWORDS
Immunological memory
Chronic inflammation
T lymphocytes
B lymphocytes
Plasma cells

GROUP LEADER
Prof. Dr. rer. nat
Andreas Radbruch

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

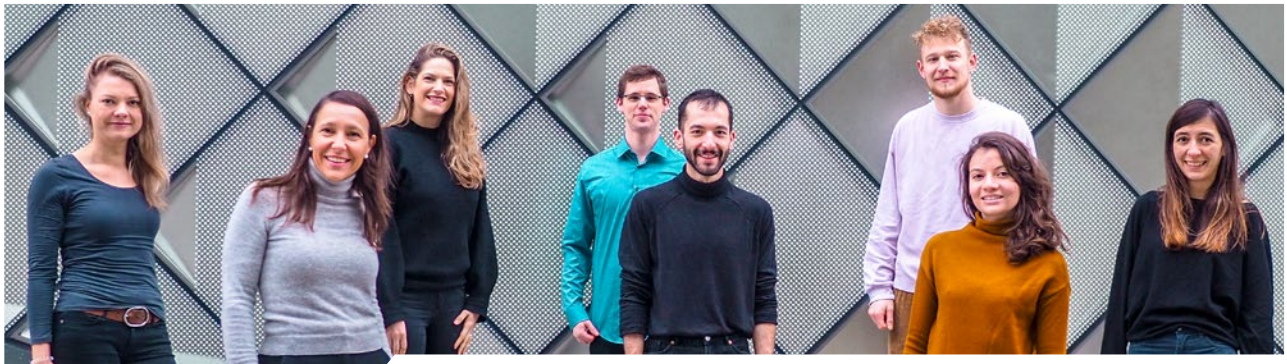
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

GROUP MEMBERS

Scientists
Jun Dong, PhD
Dr. rer. nat. Marta Ferreira Gomes
Elodie Mohr, PhD

PhD students
Richard Addo
Rebecca Cornelis
Stefanie Hahne
Lukas Heiberger
Sandra Naundorf
Francesco Siracusa
Weijie Du

Bachelor/Diplom/Master
Mona Massoud
Ravisha Rawal
Lena Peter
Sofia Uhlig



Innate Immunity

Identifying innate signals initiating and perpetuating chronic inflammation

KEYWORDS
Chronic inflammation
Innate lymphoid cells
Innate receptors
Epigenetic imprinting

GROUP LEADER
Prof. Chiara Romagnani, MD, PhD

Chronic inflammatory disorders, especially rheumatic diseases, are triggered and maintained by effector mediators produced by the adaptive immune system, such as T cell and B cells. In T cells, inflammatory programs are induced by the T cell receptor (TCR) in conjunction with distinct cytokines and/or environmental signals. 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 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. 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.

Recently, we have described a specific recognition strategy by Natural Killer (NK) cells which, in the absence of rearranged receptors, can detect mutated peptides derived from virus and host. Specific peptide recognition drives activation and expansion of a specialized subset of adaptive NK cells and contributes to determine their imprinting of pro-inflammatory cytokines, such as IFN-expression (Hammer et al, Nature Immunology 2018). This data have important implications for our understanding of non-self and self-recognition by lymphocytes and how its dysregulation can lead to loss of tolerance and autoimmunity.

Such innate activating receptors may regulate not only ILC- but also T cell-mediated responses, as in the case of NKG2D. We have recently shown that this innate danger sensor is up-regulated in effector Th1 and pathogenic Th1+Th17 *in vivo* during arthritis model and its deletion in T cells can significantly ameliorate disease severity (Babic et al, under revision in JEM). This data identifies NKG2D as a potential check point and therapeutic target of T cell-mediated inflammatory diseases.

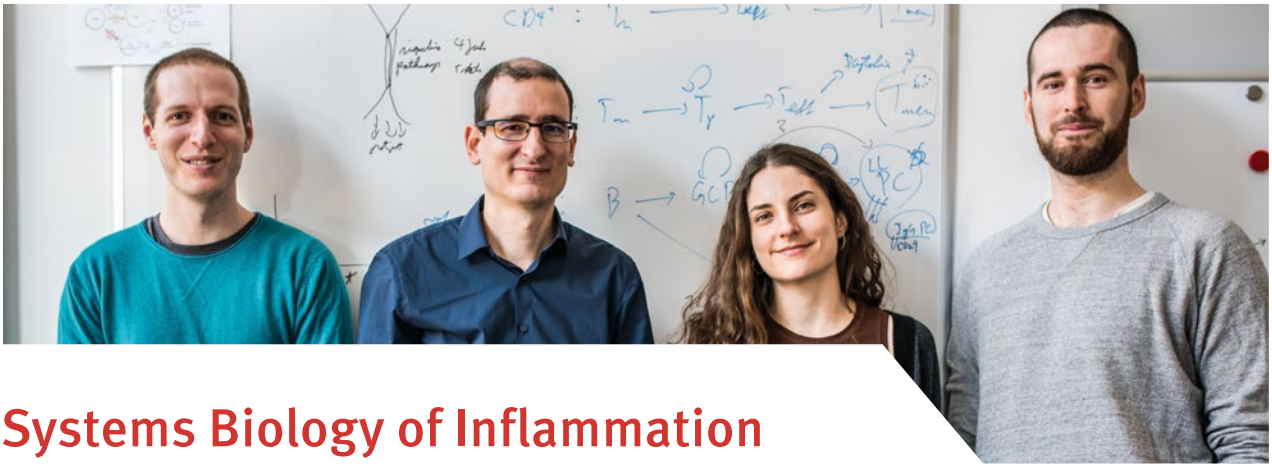
Altogether, the identification of the innate triggers and the specific signals driving the acquisition and the stable imprinting of distinct inflammatory programs in ILCs and T cells will be important to develop potentially new targets for the amelioration of chronic inflammation in rheumatic diseases.

GROUP MEMBERS

Scientists
Kerstin Juelke
Marina Babic

PhD students
Christina Stehle
Quirin Hammer
Timo Rückert
Daniela Hernandez
Nils Müller

MTA
Ulrike Uhlig



Systems Biology of Inflammation

Understanding the complex relationships among immune cells with mathematical tools

TThe mammalian immune response depends on the interaction and collaboration of many highly individual cells. In particular, a network of interacting T cells is critical for the course of an inflammatory response.

However, in certain circumstances the immune system can turn on itself and thus evoke chronic inflammatory diseases such as rheumatoid arthritis. While research has provided an enormous body of knowledge about the regulatory mechanisms behind chronic inflammation, it is difficult to assess the contribution of each individual process with current biological methods. In particular, what are the critical components and conditions triggering a change towards chronic inflammation, despite the multi-faceted mechanisms that promote immune tolerance? Furthermore, can we develop a rationale for improved strategies of therapeutic intervention? Currently available drugs targeting immune cell communication (so-called targeted or “biological” therapies), such as TNF-alpha blockers, often show limited effectiveness and considerable adverse effects.

Analysis of complex networks requires mathematical methods. Our research group will develop and apply advanced mathematical modelling and data analysis techniques to investigate the regulation of immune responses. In particular, we will employ high-throughput image analysis methods to illuminate the spatial distribution of interacting immune cells. Moreover, we will apply and extend the scope of our response-time modelling framework (Thurley, Wu, Altschuler, Cell Systems 2018), an approach to study generic cell-cell communication networks and integrate kinetic data.

Overall, the goal of the group is to develop an interdisciplinary framework for dissecting and rationalizing intercellular communication networks, to investigate the effects of perturbations and thus pave the road for optimization of targeted therapies in the future.

KEYWORDS

Data-driven modeling,
High-dimensional data analysis
T cell communication
biological networks

GROUP LEADER

Dr. rer. nat.
Kevin Thurley

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

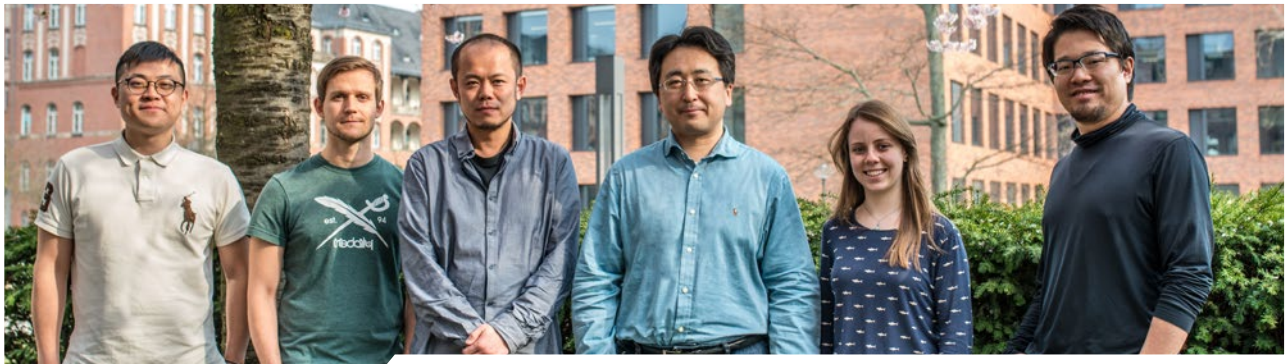
Leibniz Gemeinschaft

GROUP MEMBERS

PhD student
Philipp Burt, Bsc. Biophysics

MD student
Sebastian Serve, Bsc. Mathematics

Master students
Gustav Geißler, Bsc. Physics
Paraskevi Voula Tassopoulou, PharmD



Osteoimmunology

Maintenance of memory lymphocytes in protective and auto-reactive immunological memory

KEYWORDS
Immunological memory
Memory T helper cells
Long-lived plasma cells,
Bone marrow
Stromal niches

GROUP LEADER
Koji Tokoyoda, PhD

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

The focus of our research is detailing out the new concept of the organization of immunological memory in the bone marrow with the aim to identify novel molecular targets for the ablation of pathogenic immunological memory cells.

Memory T helper (Th) cells and long-lived 'memory' plasma cells are critical for long-lasting immunological memory to pathogens and autoantigens. Despite their central role, the generation and maintenance of memory Th cells and memory plasma cells in the body has remained unclear. In our group, we have characterized the microenvironment 'niches' for survival of memory Th cells and memory plasma cells in the bone marrow (BM). CD69, integrin α2 (CD49b), integrin β1 (CD29) and CXCR4 are required as receptors for the generation and maintenance of memory Th cells and memory plasma cells in the BM. These molecules can be used as therapeutic target molecules to block the generation and maintenance of pathogenic memory Th cells and memory plasma cells in autoimmune diseases. The major research interest in our group is to understand how memory Th cells and memory plasma cells are generated and maintained in infectious and autoimmune diseases.

Recently, we have shown that *Salmonella (S.) Typhimurium* specifically reduces the numbers of IgG-secreting plasma cells in the BM thereby preventing the generation of an efficient humoral memory response against it. The Salmonella-secreted protein SiiE plays a major role in this process as attenuated SiiE-deficient S. *Typhimurium* induces high and lasting titers of specific and protective *S. Typhimurium*-specific IgG and qualifies as an efficient vaccine against *S. Typhimurium*. A SiiE-derived peptide with homology to laminin β1 is sufficient to ablate IgG-secreting plasma cells from the BM, interacting with a laminin receptor, integrin β1, in competition with laminin β1. Laminin β1 is also defined as a component of niches specific for IgG-secreting plasma cells in the BM. It therefore might qualify as a unique therapeutic option to selectively ablate IgG-secreting plasma cells in autoimmune diseases and multiple myeloma. In addition, this is a potentially vital clinical finding as it points to the fact that *S. Typhimurium* may cancel humoral immune memory which has been already generated by vaccination.

GROUP MEMBERS

Scientists
Shintaro Hojyo, PhD

PhD students
Jana Sarkander
Mathias Mursell
Tsung-Yen Wu
Yuzuru Yamasaki

Bachelor student
Gabriela Hernández

Macrophage Biology and Innate Networks in Chronic Inflammatory Diseases

Innate Immunity in Rheumatic Diseases

Our group aims to understand innate immune biology in chronic diseases with the ultimate goal to unravel the spectrum of mechanisms leading to organ damage, and thus lay the ground for personalised medicine. Our work is driven by the concept that innate immune cells, such as macrophages, are programmed by their microenvironment. The latter is specific for each tissue, each disease and each patient. In the last years, we have focused on the mechanisms of macrophage differentiation and function in chronic granulomatous and autoimmune pathologies.

Prominent examples of granulomatous diseases are infectious diseases such as tuberculosis, but also several inflammatory diseases, with unknown infectious triggers, including sarcoidosis, inflammatory bowel disease, rheumatoid arthritis and giant cell arteritis. The common hallmark of granulomatous diseases is the presence of granulomas, structures of organised inflammation that form in response to a persistent stimulus and replace healthy tissue. In granulomas, macrophage precursors acquire epithelial and polyploid programmes. We showed that the DNA Damage Response, a fundamental cellular process activated in response to genotoxic stress, is not only significant for cancer development, but also instructs macrophage programmes in chronic granulomatous diseases (Herrtwich et al. Cell 2016; reviewed in Horn et al, Curr Opin Immunol 2018). Current work aims to dissect the mechanisms of granuloma macrophage programming and the role of granulomas in disease progression. This project area is supported by an ERC Starting Grant, DDRMac, *(page 29)*, as well as by the German Research Foundation (DFG), CRC TRR241, *(page 26)*.

A large number of autoimmune pathologies arise in the context of loss of tolerance against self-nucleic acids. This induces a chronic type I interferon response. We have shown that macrophages activated by type I interferons are programmemed to promote epithelial cell proliferation and glomerulonephritis (Triantafyllopoulou et al. PNAS 2010). Current work, supported by the DFG Programmes CRC 1160, CRC TTR84 and SPP1937 *(page 27)*, aims to dissect the innate immune cell network that determines target organ susceptibility to autoimmune organ damage.

KEYWORDS
Macrophages
Innate immunity
Chronic inflammation
Granulomatous diseases
Autoimmune organ damage
Rheumatic diseases

GROUP LEADER
Dr. med.
Antigoni Triantafyllopoulou

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

erc
European Research Council
Established by the European Commission

GROUP MEMBERS

Scientists
Stylianos-Iasonas Biniaris-Georgallis
Dr. med. Tom Aschman

MD students
Zhen Zeng
Manuel Knoll

Technician
Frauke Schreiber

Allergology

Novel therapeutic approaches of type I-allergy by immunomodulation

KEYWORDS
Allergy
B-cells
Immune modulation
Anaphylaxis

GROUP LEADER
Prof. Dr. med.
Margitta Worm

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

The "Allergology" group is focused on immunomodulation of Immunoglobulin E (IgE)-dependent type I allergies. Currently, approx. 20% of the German population are affected by hay fever, allergic asthma or atopic dermatitis. Our research aims to understand the key molecular and cellular events for the development and maintenance of IgE production. Special interests among our group include the immunomodulatory functions of nuclear receptor ligands that are involved in specific immunotherapy anaphylaxis and regulation of skin homoeostasis.

Nuclear receptor ligands include molecules like vitamin D and retinoids. We have shown that vitamin D profoundly modulates B cell activation and hampers the IgE response. We are currently studying the molecular and cellular signalling events involved in this in more detail and we have also initiated a clinical translation programme. 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 studies on specific immunotherapy anaphylaxis and regulation of skin homoeostasis include the investigation of patient cohorts upon treatment or bedside reaction. However, the application of targeted mouse models enables us to set up models with targeted deletion of specific mediators and their receptors to unravel mechanistic functions upon defined pathophysiological conditions.

The overall perspective of our research is to develop novel strategies for innovative treatment protocols in allergy by transferring our experimental data into clinical trials and clinical practice.

GROUP MEMBERS

Scientists
PD Dr. med. Guido Heine
Dr. rer. nat. Magda Babina
Dr. rer. nat. Kristin Franke
Dr. rer. med. Sabine Dölle-Bierke
Dr. med. Wojciech Francuzik
Dr. rer. nat. Diana Willmes

PhD students
Josephine Scholz, Dipl. biol.
Sandra Treptow, M.Biotech.
Ramanarayanan, Padma, M.Sc.
Davender Davender, M.Sc.

MD students
Valerie Glatzel
Samira Sarah Saleh

Technician
Dennis Ernst

Student
Firdevs Murad

Others
Study Unit: (n=6)

Photo: Campus Charité – Universitätsmedizin Berlin
in the centre of Berlin,
Bavaria Luftbild Verlgas GmbH

Max Löhning

Mir-Farzin Mashreghi

Programme Area

Regenerative Rheumatology

Since 2015, this programme area extends the experimental biomedical research at the DRFZ to degenerative rheumatic diseases. Its goal is the development of therapeutic options for the regeneration of destroyed tissue. The strategy is to gain a better understanding of the biology of cartilage-forming cells and to influence cartilage formation in such a way that stable cartilage can be rebuilt in affected joints.

www.drfz.de

Pitzer Laboratory of Osteoarthritis Research

We aim to biologically regenerate cartilage by selection and reprogramming of chondrocytes.

KEYWORDS
Osteoarthritis
pathogenesis
Chondrocyte differentiation
Bone growth regulation
Lymphocyte differentiation
Immunological memory

GROUP LEADER
Prof. Dr. rer. nat.
Max Löhning

The Pitzer Laboratory of Osteoarthritis Research investigates the cellular and molecular mechanisms leading to the development of osteoarthritis (OA). OA is the most frequently occurring joint disease among adults worldwide, it leads to progressive cartilage loss and is often accompanied by inflammatory processes. Recent studies indicate dysfunctional molecular signalling within the cartilage-producing cells of the joints, the chondrocytes. So far, the chondrocytes' in situ biology is not well understood.

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 homogeneous population or to differentiated subtypes. Using a 3D-culture system of human chondrocytes that simulates a hypoxic environment, we could show that the activation of specific immune-related receptors leads to impaired cartilage production and altered metabolic activity. Now we investigate a possible connection to the development or progression of OA. Here, our group's accumulated knowledge on the (re-) programming of T cell subtypes will be transferred to chondrocytes and the field of OA research.

Since we consider the joint as a functional unit, we also analyse the cells building up the bone mass and vascular system. In addition, we examine the infrapatellar fat pad, synovial tissue, and synovial fluid of the material from primary human donors we receive from our colleagues at the Center for Musculoskeletal Surgery of the Charité. After assessing the active genes in specific cell subtypes, we identified a candidate gene that could prove to be important for the therapy of painful ossification processes and osteophyte formation in OA.

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) and used this understanding of molecular processes to reprogramme 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 programmes, and possibilities of reprogramming. Ultimately, we want to reprogramme 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.

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Willy Robert
Pitzer Stiftung

GROUP MEMBERS

Scientists
Dr. rer. nat. Caroline Helmstetter
Dr. phil. Roman Marek
Dr. biol. hum. Anna Rapp
Ph.D. Philippe Saikali
Daniel Schulz
Dr. rer. nat. Ping Shen

PhD students
Tobias Brunner
Nayar Duran
Maria Dzamukova
Adrian Madrigal-Avilés
Dominik Niesen
Mai Dan Nguyen
Valerie Plajer
Sebastian Serve
Domonkos Vince Varga

Technicians
Vivien Holecska
Isabel Panse
Carola Rüster
Peihua Wu

Therapeutic Gene Regulation

With oligonucleotides against „diseased“ cells

We aim to identify and characterize cells that trigger and drive the pathogenesis of rheumatic diseases. We apply state-of-the-art methods (particularly Single-Cell-Sequencing approaches) to determine which genes and regulatory ribonucleic acids (RNAs) are selectively switched on in “disease causing” pathogenic cells versus healthy cells. The identified genes and regulatory RNAs are further functionally characterized in order to elucidate whether they influence the disease directly or indirectly. Genes and regulatory RNAs which keep the pathogenic cells alive would be ideal targets for new therapies. Their suitability as novel therapeutic targets is tested in preclinical models for rheumatic diseases.

All the identified regulatory RNAs and many of the identified genes that are selectively expressed by cells which are involved in the pathogenesis of rheumatic diseases, encode for proteins that act inside these cells, making them inaccessible to modern biologics. We are therefore developing short nucleic acids (oligonucleotides) that inhibit the RNAs that translate information from these genes into proteins. Such oligonucleotides are small inhibitory RNAs (siRNAs) that directly inhibit gene expression, and antagomirs that inhibit regulatory microRNAs and thus indirectly influence gene expression. When these oligonucleotides are coupled to cholesterol, they easily enter all cells, but only affect gene expression in the cells in which a particular gene or regulatory RNA is switched on in, making them therefore, very selective. We want to utilize them for therapeutic manipulation of chondrocytes in patients with osteoarthritis (OA). In OA, chondrocytes fail to build cartilage tissue or even destroy the existing extracellular matrix by secreting matrix-degrading enzymes. In cooperation with the Löhning group, we are determining target genes in order to reactivate the cartilage production of degenerated chondrocytes or to turn precursor cells into active chondrocytes.

Therapeutic oligonucleotides also have great potential for the treatment of chronic inflammatory rheumatic diseases. In an animal model, we were able to show that antagomirs against the microRNA-148a specifically deplete the disease-causing T-helper (Th) lymphocytes and significantly attenuate chronic inflammation due to the dependence on miR-148a for their survival. Protective memory Th lymphocytes generated by a vaccine-like immunization were not affected because they do not express miR-148a. We have thus provided the fundamental proof that therapeutic oligonucleotides can act selectively and efficiently in the organism without significant undesirable side effects.

KEYWORDS
Regulatory RNA
Oligonucleotide therapy
Gene regulation
Single-Cell-Sequencing
Chronic diseases

GROUP LEADER
Dr. rer. nat.
Mir-Farzin Mashreghi

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

EUROPEAN UNION
European Regional
Development Fund

GROUP MEMBERS

Scientists
Dr. rer. nat. Gitta Anne Heinz
Dr. rer nat. Patrick Maschmeyer
Dr. rer. nat. Frederik Heinrich

PhD students
Markus Bardua
Cam Loan Tran

Bachelor/Diploma/Master students
Lorenz Wirth
Jannis Kummer
Sarah Schimmelpfennig
Melanie Klingauf
Vanessa Treffner
Marlen Schulze
Franziska Zügel

Kirsten Minden

Anja Strangfeld

Denis Poddubnyy

Angela Zink

Programme Area

Epidemiology and Health Services Research

This programme area investigates clinical, social and biological factors influencing the course of rheumatic and musculoskeletal diseases (RMD), the long-term safety and effectiveness of therapies and the adequacy of health care for persons with RMD. Research aims to improve the quality of life of children and adults suffering from rheumatic diseases, make treatment safer and address gaps in health care. Research is based on large longitudinal cohort studies carried out in close cooperation with more than 500 paediatric and adult rheumatologists.

www.drfz.de

Paediatric Rheumatology and Health Services Research

Optimization of health care for young people with rheumatic diseases

KEYWORDS
Juvenile rheumatic diseases, juvenile idiopathic arthritis, health care, prognosis, transition

GROUP LEADER
Prof. Dr. med. Kirsten Minden

Supported by the Rheumatism foundation

The group evaluates, with substantial support by the Deutsche Rheumastiftung, the health care situation and outcomes of children, adolescents and young adults with inflammatory rheumatic diseases. Particular attention is paid to juvenile idiopathic arthritis (JIA).

In the National Paediatric Rheumatological Database (NPRD), around 15,000 patients with juvenile rheumatic diseases are recorded annually from 60 paediatric rheumatological centres. We showed that adolescents with JIA have a higher disease burden and a higher risk for an inactive lifestyle, being overweight and having other comorbidities. The frequency of mental health problems is currently being investigated by a short screener on the web-based platform KRhOKo as part of the interdisciplinary research network COACH.

In the JIA inception cohort ICON, 950 JIA patients and almost 500 healthy peers have been observed for approximately 6 years now. The group could show that sociodemographic and clinical parameters such as age at disease onset, JIA category, time between symptom onset and first visit to a rheumatologist, and higher family burden predict the outcome of JIA. In addition, we found an inverse correlation of the 25(OH)-vitamin D serum level with the risk of uveitis and a polyarticular-course of JIA.

The Juvenile arthritis Methotrexate/Biologics long-term Observation (JuMBO) is the follow-up register of the national JIA biologic register BiKeR, in which about 1,500 JIA patients are currently being observed from DMARD start in childhood into adulthood. To date, no serious safety problems have been identified. Rather, we found that the earlier an effective DMARD therapy is started, the higher the chance of drug-free remission and full functional capability and the lower the damage to the joints in adulthood.

In close cooperation with the Deutsche Rheuma-Liga e.V., we evaluate transition resources for young people with rheumatic diseases moving to adult care. According to NPRD data, transition readiness and disease-specific knowledge among young people with JIA are still suboptimal.

Close cooperation with many pediatric and adult rheumatological departments and ophthalmological units is the basis for the successful conduction of the observational studies.

GROUP MEMBERS

Scientists
Dr. rer. nat. Jens Klotsche
Dr. rer. medic. Florian Milatz
Dr. med. Claudia Sengler
Martina Niewerth, MPH

PhD students
Paula Drechsel
Sabine Kirchner

MD students
Julian Zink
Nina Brüggemann
Michaela Heinrich
Svea Horn
Nadine Betenstehl
Laura Montag

Data manager
Ina Liedmann
Karin Weber
Cornelia Stamme-Schäfer
Dr. rer. nat. Susann Schweitzer
Nils Geisemeyer
Jana Hörstermann
Nadine Grösch

Students
Josefine Karle
Juliane Lenz
Marey Messingschlager
Nina Biernacka
Anneli Rieck

Spondyloarthritides

Early diagnosis and effective therapy of chronic inflammatory spine disease

We investigate disease mechanisms and disease progression of spondyloarthritis (SpA) and try to improve diagnostics and therapy, with a focus on early diagnosis of axSpA.

We established a referral network with primary care physicians and orthopaedic surgeons for the early recognition of patients at high risk of axSpA. A self-referral programme (bechterew-check.de) has been developed and evaluated as a part of the OptiRef project. A nation-wide study to identify the optimal referred strategy (the MASTER study) was conducted. We also initiated the development of the international recommendation for early recognition of axSpA under the auspices of the Assessment of Spondyloarthritis International Society (ASAS).

In order to study the natural course of SpA, we initiated a prospective cohort of patients with axial spondyloarthritis, the German Early Spondyloarthritis Inception Cohort – GESPIC – in which more than 700 patients with early axial spondyloarthritis (axSpA) have provided information on the natural course of axSpA at the early stage. In this cohort, 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) are studied. Most recently, GESPIC was extended to patients with early Crohn's disease and acute anterior uveitis in order to study factors (including microbiome) associated with the development of arthritis phenotype.

We participate in the BMBF supported PROCLAIR consortium with a subproject that investigates disease burden, standards of care and disease related costs based on claims data linked to a survey in axSpA. We could show that patients with axSpA have a high prevalence of depressive symptoms related to both disease and socioeconomic factors. Analyses of the costs of illness in axSpA patients treated with and without biologics as well as the analysis of factors associated with a still large diagnostic delay are ongoing.

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. In 2016 we initiated the 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.

KEYWORDS
Spondyloarthritis
Ankylosing spondylitis
Diagnosis
Treatment

GROUP LEADER
Prof. Dr. med.
Denis Poddubnyy

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

GROUP MEMBERS

Scientists
Prof. Dr. Joachim Sieper
PD Dr. Hildrun Haibel
PD Dr. Uta Syrbe
Dr. Susanne Lüders
Dr. Burkhard Muche
Dr. Fabian Proft
Dr. Mikhail Protopopov
Dr. Judith Rademacher
Valeria Rios Rodriguez
Dr. Laura Spiller
Inge Spiller
Dr. Anne-Katrin Weber

MD students
Agnes Hartl
Lorraine Tietz
Henning Weineck

Technical assistance
Beate Buss
Annegret Langdon
Claudia Lorenz
Bianca Mandt
Anna-Lisa Meinke
Martina Seipel
Petra Tietz

Pharmacoepidemiology

Assessing benefits and risks of new treatments in rheumatology

KEYWORDS
Disease Register, observational cohort, long-term safety and effectiveness

GROUP LEADER
Dr. med.
Anja Strangfeld

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

The mission of our group is to provide robust data on the real-world safety and effectiveness of new therapies in rheumatology. This objective is addressed through three long-term cohort studies, so-called disease registers. RABBIT has enrolled more than 18,000 patients with rheumatoid arthritis since 2001. RABBIT-SpA has extended the focus to axial spondyloarthritis and psoriatic arthritis with around 1,200 patients since 2017. With nearly 1,400 women, Rhekiss is one of the largest pregnancy registers in rheumatology worldwide, with an extensive observation period reaching from preconception to the second birthday of the child *(page 30)*. In order to enable joint analyses with even larger data sets, we coordinate the European Network of Pregnancy Registers EuNeP, funded by the FOREUM foundation *(page 30)*.

Data from these registers provide clinicians with reliable information on the outcomes of treatments in different groups of patients. An example is the RABBIT risk score for serious infection which takes into account patient characteristics, medical history, co-morbidity, treatment of interest, as well as concomitant treatment. A web-based risk calculator (www.biologika-register.de) allows immediate calculation of risk. It has been accessed approximately 25,000 times in 2018.

From our European collaboration with other biologics registers, no increased risk of lymphomas and no shift in lymphoma subtypes associated with the treatment with TNF inhibitors or other biologics compared to conventional synthetic treatments was found. Following safety concerns, the risk of malignant melanomas was as well analysed in this collaboration, leading to the reassuring result of no increased risk with TNF inhibitor treatment.

Overall, the results from RABBIT underline the importance of tight control of disease activity. Uncontrolled high disease activity was shown to be a major driver of preterm mortality, myocardial infarction and stroke.

Due to the high numbers of patients and patient-years, the registers also allow for the investigation of very rare events, such as lower intestinal perforations. For the first time outside of randomised clinical trials, interleukin-6 blockade has been shown to increase (at least fivefold) the risk of this severe and life-threatening complication compared to other treatments.

Future analyses will address spondyloarthritides and pregnancies, as well as new treatment options such as biosimilars and JAK inhibitors, taking the interplay of risks arising from the disease itself, conditions of the patient including comorbidity, and the novel treatments into account. This will allow tailoring treatment to the risk profiles of individual patients.

GROUP MEMBERS

Scientists
Lisa Baganz MSc
Dörthe Kühl-Habich MSc
Dr. Doreen Huschek
Dr. rer. med. Yvette Meißner
Dr. rer. nat. Martin Schäfer
Anja Weiß MSc

Medical documentalists/ Data manager
Tanja Ellmann, Mandy Grope, Juliana Hoffmann, Ulrike Kamenz, Lisa Lindner, Steffen Meixner, Andreas Reich, Juliane Reinke, Franca Stein, Carina Wittkopp, Corina Walter, Birgit Wuthe, Susanna Zernicke, Steffi Zühlke

Master student
Tatjana Rudi

Project coordinator
Christina Bungartz

Database development/ Interfaces
Claudia Fritz
Siegfried Kindler
Dina Schreckeis

Doctoral students
Madlen Spilka
Ronja Ramien

Student assistants
Martin Schütz, Lea Karnstedt, Paula Morgenroth, Ronald Müller, Steve Mvogo Ondoua, Jasmin Sandor, Michelle Pieper, Julia Leskow

Health Services Research

Health services research helps to improve outcomes of rheumatic diseases

Research in our group focuses on the systematic and long-term evaluation of the quality and outcomes of health care of people with rheumatic and musculoskeletal diseases in Germany. Using large primary and secondary data bases, developments and deficits in specialized as well as non-specialized health care are investigated. Findings are fed back to the treating physicians and inform clinical and political decision making.

An important instrument of research is the National Database of the German Collaborative Arthritis Centres. Since 1993 it has enabled our group to monitor trends in treatments and outcomes of inflammatory rheumatic diseases in more than 15,000 patients per year. Over the years, these data have substantiated how new therapeutic options and earlier access to rheumatologic care are reflected in continuously improving clinical outcomes of patients. The ability to work has increased significantly, the disease activity and the burden of illness due to pain or functional limitations have decreased.

Our group has been involved in two national research networks funded by the Federal Ministry of Education and Research (BMBF). Taking advantage of routine data from BARMER health insurance, claims data were analysed in the PROCLAIR project in combination with patient-reported outcomes from questionnaire surveys including a total of 20,000 of BARMER health insurance members. Diverging treatment concepts between rheumatologists and non-specialised physicians, as well as regional differences in health care, were detected. In addition, there were substantial differences in the provision of care depending on age and social status. Depression turned out to be an important predictor of poor clinical and socioeconomic outcomes. A collaborative work from the PROCLAIR and METARTHROS projects revealed a high burden of diabetes and other chronic comorbidities in patients with rheumatoid arthritis as well as deficits in specialized care.

All treatment guidelines in RA include recommendations for therapeutic strategies in case of unfavourable prognostic factors. Data from the early arthritis cohort CAPEA showed that autoantibodies and early erosions did not predict achievement of low disease activity or remission whereas baseline disease activity, functional limitation and obesity were predictive.

KEYWORDS
Health care research, claims data, inflammatory rheumatic diseases

GROUP LEADER
Prof. Dr. rer. pol. Angela Zink

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft

GROUP MEMBERS

Scientists
Dr. Johanna Callhoff
Dr. Dörte Huscher

Medical documentalists
Katja Thiele
Sascha Bischoff
Gregor Förster

Research Assistant
Sabine Achtelstetter


Hyun-Dong Chang


Andreas Grützkau


Anja E. Hauser


Thomas Häupl


Andreas Hutloff


Toralf Kaiser


Katrin Lehmann


Mir-Farzin Mashreghi


Henrik Mei


Raluca Niesner

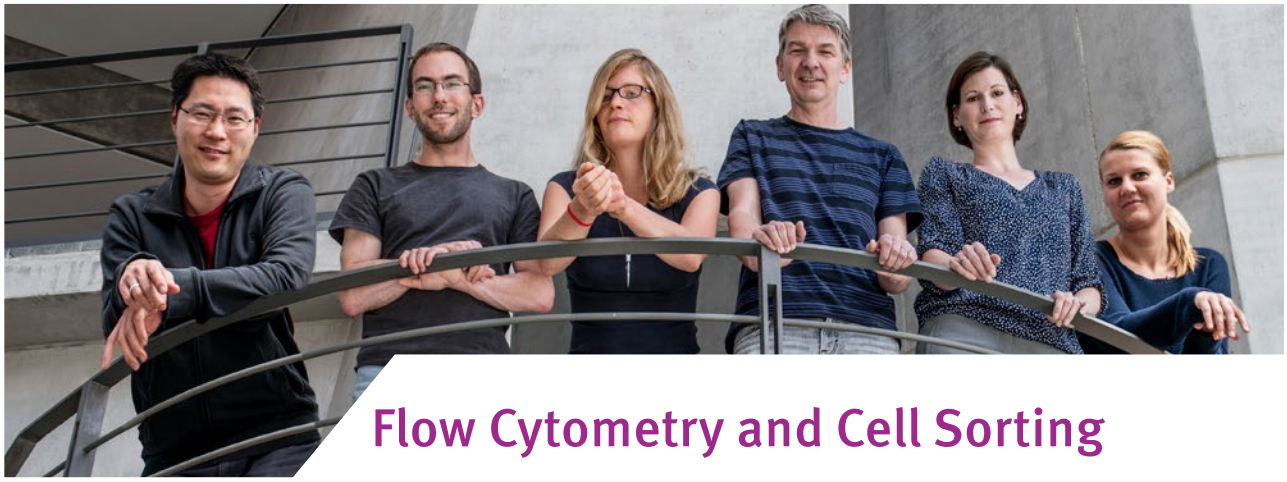

Anja Schulz

Technology Platforms, Shared Resource Laboratories and Support Services

The DRFZ, in collaboration with its partners from Charité and MPI-IB, runs cutting edge technology platforms for the analyses of single immune cells, the cells of their environment and their interactions. These Shared Resource Laboratories (SRL) offer unique opportunities to identify and isolate cells-of-interest, analyse them further in molecular and functional studies and observe them in their natural environment.

The service units offer essential central technological and logistical support to ensure standardised and quality controlled research.

www.drfz.de



Flow Cytometry and Cell Sorting

State-of-the-art cell analysis and cell sorting through technical innovation

The **F**low **C**ytometry **C**ore **F**acility **(FCCF)** was established in 2000 as a Shared Resource Lab of the DRFZ, the Charité - Universitätsmedizin Berlin, and the Max Planck Institute for Infection Biology. With a comprehensive range of services and proprietary technological innovations, the FCCF offers state-of-the-art analyses and sorting of cells.

Methods and applications

Flow cytometry is an analytical method for the quantitative recording of physical, biochemical/cell biological and immunogenetic parameters of individual cells. On this basis, various cell features can be determined. The flow cytometers of the FCCF allow the simultaneous measurement of up to 28 characteristics of a cell at a throughput of up to 20,000 cells per second. In such a "multicolour" approach, it is possible to e.g. analyse cells of patients before and during therapy in order to monitor the success of therapy, but also to investigate the cellular processes underlying rheumatic inflammation.

In addition to the cytometric analysis of cell types of interest, cells can also be isolated for further molecular, genetic and biochemical analyses. For this purpose, cells are first analysed (as in the cell analyser) and then packed into individual droplets. These are given a specific electrical charge and are then directed into collection tubes within an electrical field. With specially adapted sorting protocols, even very sensitive cell types, such as stroma or plasma cells, or very rare cell types, such as autoreactive lymphocytes (in combination with pre-enrichment methods, such as magnetic cell sorting), can be analysed or sorted.

Technological developments

In order to improve the sensitivity of flow cytometry, we are developing a multispectral cytometer together with the Berlin-based company APE. This device detects the entire light spectrum of an individual fluorescence-labelled cell, in contrast to the relatively narrow bandwidth of conventional flow cytometry. Due to the additional light that is captured, the detection sensitivity is increased.

Together with APE, we have also developed an LED-based calibration tool (quantiFlashTM). It enables us to absolutely quantify the measured light intensities of the fluorescence of a cell, and thus to determine the exact number of molecules on or in the cell.

Basic flow cytometry course

Once a month, we offer a two hour basic flow cytometry course on the proper use of the techniques used in flow cytometry. The course is open to all who are interested. However, due to the high demand, we recommend advance online registration: **http://fccf.drfz.de**.

GROUP LEADERS

Dr. rer. nat. habil.
Hyun-Dong Chang

Technical Manager
Dipl. Ing.
Toralf Kaiser

GROUP MEMBERS

Operators
Dipl. Biochem. Jenny Kirsch
Ana Catalina Teichmüller (M. Sc.)

PATENTS

1) T. Kaiser, J. Kirsch, A. Grützkau, WO/2012/048906; US Patent 9,958,393 ***Principle component analysis (PCA) - based analysis of discontinuous emission spectra in multichromatic flow cytometry***

2) T. Kaiser, T. Kolbe, M. Kneissl, European Patent EP2683415B1; US Patent 9,498,550, ***Flow cytometer desinfection module***

3) K. Feher, T. Kaiser, K., von Volkmann, S. Wolf US20170322137A1 ***Method and system for characterizing particles using a flow cytometer***

Mass Cytometry

No cell is left behind – Capturing diversity of cellular systems in rheumatic diseases

Using mass cytometry, we analyze the nature of single cells and the complexity of cellular systems such as the immune cells driving rheumatic inflammation. With more than 50 specific measurement parameters, each single cell can be extensively characterized. Today, this exciting technology serves in immune profiling and biomarkers discovery studies in rheumatoid arthritis, Systemic Lupus Erythematosus (SLE), inflammatory skin and bowel diseases, and in studies exploring the diversity of beneficial vs. pathogenic T and B lymphocytes.

We follow the idea that blood cells contain important yet still hidden information about the patient's condition and response to future therapy. We assume that embedding data-driven approaches such as mass cytometry studies into the existing - and further evolving - conceptual framework of immunology and inflammation facilitate insight in the complexity of normal and pathogenic immune responses, precision medicine in the treatment of chronic inflammation and help developing a diagnostic that can be used to select only effective treatments - individually for each patient.

The DRFZ mass cytometry unit integrates several internal and external collaborations and is at the head of the German mass cytometry network, which was founded in 2017 *(page 27)*.

Further information about mass cytometry can be found in Cossarizza et al. 2017 (Eur. J. Immunol. 2017. 47:1604-08).

KEYWORDS

High dimensional single-cell profiling,
Deep immune phenotyping/Cytomics,
Biosensors, biomarkers and biosignatures,
Cellular diversity

GROUP LEADERS

Dr. rer. nat.
Henrik Mei

Dr. rer. nat.
Andreas Grützkau

GROUP MEMBERS

Scientists
Dr. Sabine Baumgart
Dr. Axel Ronald Schulz
Tyler Burns, PhD

PhD students
Antonia Niedobitek
Marie Urbicht

Bachelor/Diploma/Master students
Lisa Budzinski
Sarah Grässle
Eva Holzhäuser
Edward Rullmann
Julia Schulze

Technicians
Heike Hirseland
Silke Stanislawiak

Students
Vera Bockhorn

Central Laboratory for Microscopy (CINIMA)

From cell to organism

KEYWORDS
Epifluorescence Microscopy
Confocal microscopy
Intravital microscopy
Fluorescence Life Imaging
Chronic neuroinflammation

GROUP LEADERS

Prof. Dr. med. vet. Anja Hauser

Prof. Dr. rer. nat. Raluca Niesner

GROUP MEMBERS
Bioinformatics
Ralf Köhler

By using established and novel technologies of optical imaging, we are able to monitor the orchestration of cells and molecules in tissue which are relevant for a better understanding of chronic inflammatory mechanisms.

The expertise of the **C**ore facility for **IN**novative **IM**aging und **A**nalysis (**CINIMA**) at the DRFZ encompasses standard fluorescence microscopy methods, such as wide-field and confocal microscopy. In addition, our unique customised and self-developed microscopy technologies allow the functional analysis of single cells in organ models and whole living organisms, with a special focus on non-linear optical multi-photon microscopy.

Confocal laser scanning microscopy, multiplexed wide-field microscopy and light-sheet microscopy: imaging living cells and fixed samples

Histological samples which are relevant for many research groups at the DRFZ are typically investigated in an automatized manner using the wide-field microscope (Keyence). For research questions which imply the visualisation of cellular and tissue structures of only few 100 nm, a confocal system (Zeiss LSM 880) is employed. It allows sequential investigation of five spectrally resolved parameters on the same sample.

In order to achieve multiplexing in immunofluorescent histology, a Toponome Imaging Cycler based on a wide-field fluorescence microscope is used. In this way, more than hundred markers can be sequentially visualised on the same sample.

Our major task is to develop adequate evaluation algorithms, which extract the full information contained in the multiplexed data. This technology is used frequently in the frame of the DFG SPP1937 *(page 27)*, to analyse the heterogeneity of innate lymphoid cells in situ and to compare homoeostasis and chronic inflammation.

Since 2018, we offer researchers access and support to a state-of-the-art light-sheet microscope, which enables the visualisation of single cells in the context of whole cleared organs, in a three-dimensional manner.

Optical coherence tomography and multi-photon microscopy for dynamic and functional imaging in living organisms

In order to visualise and quantify cellular dynamics and function deep in the organs of living mice, we develop and provide expertise in intravital multi-photon microscopy methods. Time-resolved multi-photon microscopy methods based on time-correlated single-photon counting (TCSPC) allow the quantification of metabolic enzymatic activity in living cells and tissues based on the endogenous fluorescence of the coenzymes NADH and NADP.

Moreover, we set a main focus of development on longitudinal intravital imaging in different organs of mice such as femoral bone marrow (LIMB), retina, and kidney – thereby providing unique insight into the evolution of chronic inflammatory mechanisms *in vivo*.

Last but not least, we combine these cutting-edge technologies with imaging technologies of living organisms used in clinical setups such as optical coherence tomography (OCT), allowing direct correlation between mechanistic knowledge and clinically accessible information.

The development is performed in the frame of a close collaboration between the groups “Biophysical analytics” on the physics and biophysics side (Niesner) and “Immune dynamics” on the immunology and animal welfare side (Hauser) and is provided to various DRFZ groups Charité groups and groups at the Freie Universität Berlin. Since 2013, CINIMA has been actively providing multi-photon microscopy expertise to the transregional consortium SFB TRR130 *(page 26)* in the frame of a central project.

Central Laboratory

Service facility for experimental research

The Service Unit Central Laboratory 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 of 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

The team of lab managers working in the central laboratory focuses on the production and supply of more than 1000 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.

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 the name of the 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. All preparations go hand in hand with specific quality controls. Additionally, quality control of samples regarding mycoplasma and endotoxin contamination or DNA or RNA quality is offered by the lab managers.

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.

TEAM LEADER
Dipl. Ing. Biotechnology
Katrin Lehmann

GROUP MEMBERS

Lab manager
Dr. rer. nat. Heidi Hecker-Kia (until 12/2018)
Dipl. biol. Tuula Geske (until 04/2018)

Dipl. Ing. Biotechnology
Katrin Lehmann (since 04/2017)
Imme Sakwa, Dr. rer. nat. (since 05/2018)

Christin Kabus (since 11/2018)

Technical assistance
Anette Peddinghaus

Regine von Ramin Lab for Molecular Rheumatology

In search of disease-relevant gene regulation patterns

KEYWORDS
Transcriptome analysis,
Gene signatures,
Micorarray analysis,
Next Generation Sequencing

GROUP LEADERS

Dr. rer. nat.
Andreas Grützkau

PD Dr. med.
Thomas Häupl

Dr. rer. nat.
Mir-Farzin Mashreghi

The Regine-von-Ramin laboratory aims to use high-throughput technologies to detect disease-related changes at the gene regulation level in precisely defined cell populations isolated from tissues such as blood or lymphatic organs. We analyse the activity of all genes, approx. 20,000 in humans, as well as so-called non-coding gene regions and so-called miRNAs. The data sets obtained allow for the analysis of the interaction of different molecules and thus, for deriving new hypotheses on possible disease mechanisms.

In December 2004, the Regine-von-Ramin Laboratory for Molecular Rheumatology (RvR Laboratory) was founded, funded by the generous bequest of Mrs. von Ramin and co-financing from the Berlin Senate Administration WiFoKu.

This service laboratory, which is used jointly by the research groups of the DRFZ and the liaison groups of the Charité, mainly carries out genome-wide transcriptome analyses. Both the chip-based Affymetrix® technology and the Next-Generation Sequencing Technology (NGS) from Illumina® are used. For more than 20 years, a large number of cell-, disease- and tissue-specific transcriptomes have been created, which are a valuable source for future analyses in order to be able to look for corresponding genes or gene signatures in case of new questions or newly developed hypotheses.

For this purpose, employees of the Charité and the DRFZ jointly founded the Charité spin-off "BioRetis" in 2006. Bioretis developed a database or web application that makes most of the approximately 2,000 data sets generated in the Ramin laboratory as well as additional freely available data sets available for analysis purposes (www.bioretis.com).

For even more in-depth analyses, the NGS technology was established which allows not only for analysing known gene sequences, but also the entire transcriptome including non-coding regions and so-called microRNAs, which consist of only very short gene sequences (usually 21 to 23 nucleotides) and above all have gene regulatory tasks. Furthermore, the NGS technology enables the generation of immune receptor repertoires of T- and B-lymphocytes by targeted sequencing, and the determination of the microbiome by 16S sequencing.

GROUP MEMBERS

Scientists
Dr. Gitta Heinz
Dipl. Biotech. Katrin Lehmann

Technician
Heike Hirseland

Immune Monitoring

In search of cell patterns in blood for individualised medicine

Immune monitoring is generally understood to be the combination of various diagnostic procedures intended to provide information on the immune status of a patient. Depending on the clinical application, humoral factors such as 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. A prerequisite for disease and/or therapy specific immune monitoring is the identification of suitable biomarkers, which can be qualitatively and quantitatively measured at the individual cell level, for example by flow cytometry. The development of such biomarkers is as time-consuming as the development of new drugs. New biomarkers are urgently needed, especially in connection with the much praised concept of precision medicine, which promises to be able to offer patients tailored therapy options.

Successful examples of cell-based monitoring are the measurement of plasmablasts or monocytes expressing the adhesion molecule Siglec-1 in systemic lupus erythematosus (SLE). Both parameters correlate well with the disease activity of SLE patients. In particular, Siglec-1, which serves as a surrogate marker for an activated type I interferon system, has undergone extensive validation studies and is now part of the portfolio of the diagnostic laboratory of the Charité, the "Labor Berlin". Due to the technical possibilities offered by state-of-the-art analytical flow cytometers, up to 30 different fluorochromes can be determined simultaneously. Thus, the expression of many antigens can be determined qualitatively and quantitatively in one measurement.

Furthermore, mass cytometry (CyTOF technology) offers a new dimension in multiparametric single cell analysis. CyTOF technology combines single-cell cytometry and mass spectroscopic analysis of heavy metal ions, which are used instead of fluorescence molecules to label antibodies (see "Mass cytometry", *(page 79)*). Theoretically, up to 120 parameters per cell can be measured. In practice, up to 45 measurement parameters are currently combined. In addition to several technological developments that were necessary to standardise mass cytometry to such an extent that it can also be used for immune monitoring in clinical studies, various interdisciplinary studies on different clinical issues have already been initiated. In particular, the Leibniz ScienceCampus Chronic Inflammation *(page 20)*, which was established in 2016, has the goal of conducting interdisciplinary research on chronic inflammatory mechanisms. In addition to the purely phenotypic analysis of leukocyte subpopulations, comparative mass cytometric analyses will also be used to investigate the activation status of leukocyte subpopulations by monitoring phosphorylated signalling molecules.

KEYWORDS
Biomarker
Personalized medicine
Type I interferon signatures
Mass cytometry
Immunophenotyping

GROUP LEADER
Dr. rer.nat.
Andreas Grützkau

GROUP MEMBERS

Scientists
Dr. rer. nat.
Sabine Baumgart
Dr. rer. nat.
Yury Shebzhukov

PhD student
Marie Urbicht

Technician
Heike Hirseland

Animal Facility

Animal welfare and good research go hand in hand

KEYWORDS
Animal welfare, animal protection, 3R principle

ANIMAL FACILITY MANAGEMENT

Dr. med. vet. Anja Schulz

Animal welfare officer
Anna Pfeffer (since 10/2018)

Although the development of methods replacing animal experiments is constantly advancing, some scientific questions still require the use of animal models. The complexity of a living organism is indispensable, especially in understanding multifactorial diseases such as autoimmune disorders, in which a multitude of organs and cell types are involved.

Therefore, the DRFZ runs a state of the art animal facility and houses numerous different mouse strains. Genetically modified mice are an invaluable component of biomedical research. The facility is divided into an experimental facility in Berlin Mitte and a separate breeding area in Berlin Marienfelde. Specially trained animal care takers and veterinarians ensure optimal husbandry conditions and a seamless monitoring of the animals in favour of animal welfare.

All mice are kept under so-called SPF (specified pathogen free) conditions to ensure that they are free from pathogens which could interfere with their well-being and also with experimental studies. For this purpose, the facility is equipped with personnel locks and all supply material is thoroughly autoclaved before being introduced to the facility. Moreover, mice undergo a regular health-monitoring in order to detect potentially pathogenic microorganisms.

As a part of the Leibniz-Gemeinschaft, the DRFZ is obliged to be transparent and openly communicate with the public regarding animal experimentation. It is a member of the German research institutions´ information initiative „Tierversuche verstehen“ (www.tierversuche-verstehen.de), which informs about animal experiments conducted at publicly funded research institutions and promotes the dialogue between science and public. Scientists involved in animal experiments at the DRFZ follow the 3R principle - replace, reduce, refine - in order to minimize any animal distress in the experiment and to improve animal welfare. They are consulted by independent animal welfare officers who furthermore ensure and supervise their adherence to respective rules and regulations.

The animal welfare committee* meets on a regular basis and supports the animal welfare officers in their duties and their animal welfare surveillance.

The DRFZ provides a training programme conducted by veterinarians which educates scientists in terms of European Union and German animal welfare legislation and under close consideration of animal welfare. This training programme is comprised of a theoretical and practical part after which successful participation is officially certified. For all employees working with animals, regular training and further education concerning laboratory animal protection and the 3R principle is offered.

** The animal welfare committee consists of animal welfare officers, animal care staff and scientists working experimentally.*

GROUP MEMBERS

Animal welfare officers
Anna Pfeffer (since 10/2018)
Dr. med. vet. Elena Noe (till 04/2017)
Nancy Ann Erickson (till 08/2018)

Animal care staff
J. Frey (till 12/2018)
S. Gruczek, M. Hoffmann, M. P. Hong , C. Kasprzak, M. Ohde, P. Streckert, V. Theißig, P. Thiemann

Trainee
T. Acosta-Ruediger (from 09/2017)

Embryo Technology Laboratory

Modern technology for animal welfare and efficient breeding management

To maintain the defined health status of the animal facility, all strains imported from other institutes are introduced to the breeding facility via embryo transfer (Fig. 1) by the DRFZ Embryo Technology Laboratory. Moreover, the service of the Embryo Technology Laboratory includes the cryoconservation of strains currently not required for experiments. This helps to reduce the total number of mice bred for scientific purposes.

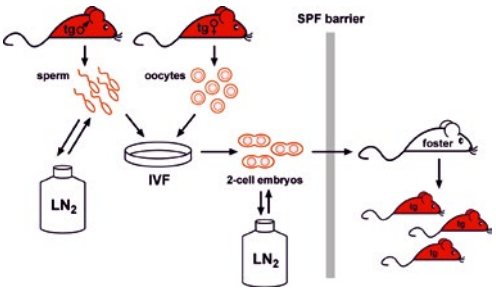


Fig. 1: Workflow of services offered by the Embryo Technology Laboratory. In vitro fertilization (IVF) is used to generate large numbers of embryos. These embryos as well as sperm from transgenic mice can be cryoconserved in liquid nitrogen. To remove any pathogens, embryos are washed extensively before transfer into pseudo-pregnant foster mice inside the SPF facility.

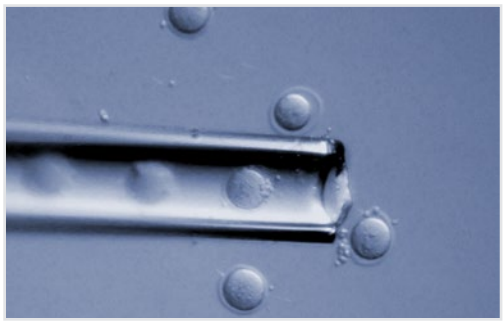


Fig. 2: Washing of embryos. The fertilized oocyte is protected by the zona pellucida which is impermeable for pathogens. Residual sperm is still sticking to the zona.

Fig. 3: Removal of samples for embryo transfer from the cryo conservation tank
Photo: Anja Schulz

■ GROUP MEMBERS

Technical staff
Paolo Rosellini Tognetti

Additional assistant
David Schreiber

■ SCIENTIFIC MANAGEMENT EMBRYO TECHNOLOGY LABORATORY

Dr. rer. nat.
Andreas Hutloff

■ COOPERATION PARTNERS

Dr. Uwe Klemm,
Experimental Animals,
Max Planck Institute for Infection Biology, Berlin, DE

Dr. Geert Michel,
Transgene Facility, FEM,
Charité University Medicine Berlin, DE

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

Frank Zimmermann,
Biotechnology Laboratory,
University Heidelberg, DE

Imprint

The annual report can be requested free of charge from the DRFZ: info@drfz.de

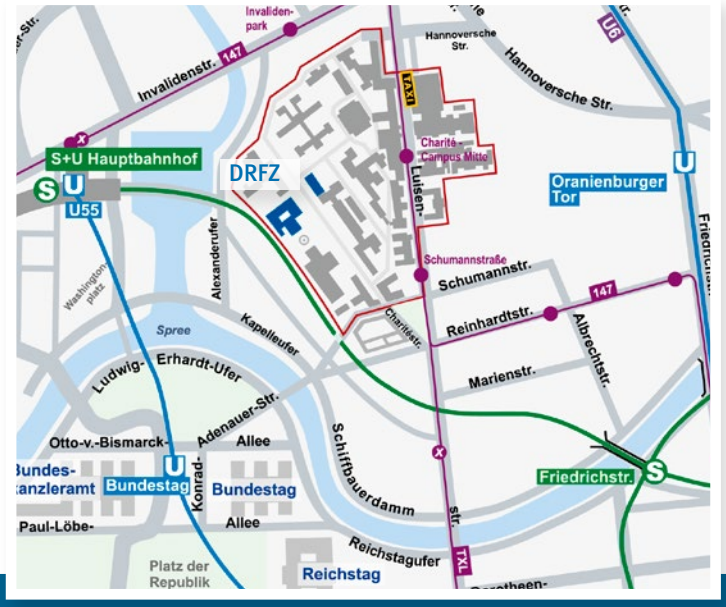
or online in the media centre

www.drfz.de

Picture of the cover:
A bird's eye view of the DRFZ.

Photo: Bavaria Luftbild GmbH

Imprint



The DRFZ (blue) on the campus of the Charité Campus Mitte

Deutsches Rheuma-Forschungszentrum Berlin (DRFZ)
A Leibniz Institute
Charitéplatz 1, 10117 Berlin

Andreas Radbruch, Scientific Director
Petra Starke, Adminstrative Director

Editorial office	Jacqueline Hirscher, Ute Hoffmann, Eva Kreiss, Katrin Moser
Layout	Jacqueline Hirscher
Photos	Jacqueline Hirscher, unless otherwise stated
Translations	Eva Kreiss, Mairi McGrath, Christine Raulfs
Print Shop	Laserline, Berlin, printed on "Recycling Offset weiß Papier (Blauer Engel)"

ISSN 1436-7106

www.drfz.de

Photo: Werner E. Krätzig
Left: Joint building of the DRFZ and the Max Planck Institute for Infection Biology
Right: Charité Centrum 12, housing the DRFZ Programme Area Epidemiology

Deutsches Rheuma-Forschungszentrum Berlin
A Leibniz Institut
Charitéplatz 1 | 10117 Berlin, Germany

www.drfz.de