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Current Fields of clinical and basic Research

A major focus of clinical and basic research is the autoreactive immunological memory that drives chronic inflammation and maintains autoimmunity. A critical component of this memory, originally identified at this research center, are memory plasma cells secreting pathogenic (auto)antibodies. These memory plasma cells are refractory to conventional therapies, and a novel and major challenge in the treatment of antibody-driven, chronic inflammatory diseases, including rheumatic diseases. Currently we develop therapies targeting pathogenic memory plasma cells, from a molecular understanding of their lifestyle, with the longterm aim to achieve therapy-free remission of chronic inflammatory diseases.

Another important focus is the patient centered approach to tailor state-of-the-art therapies for each patient, according to prognosis of disease development and response to therapy. To this end, cutting-edge cytometric multiparametric technologies are developed, to identify biomarkers expressed by cells of the patient’s blood, using these cells as “biosensors” for the detection of subtle differences in the inflammatory processes, allowing to predict disease development and individual therapeutic targets.

Current Fields of Epidemiological Research

The major focus of research is on the long-term outcomes of inflammatory rheumatic diseases in adults and children. Our data give strong evidence for the critical role of inflammation for major adverse outcomes such as infection, myocardial infarction, congestive heart failure, stroke, growth retardation and uveitis in children, adverse pregnancy outcomes and premature mortality. A second focus is on health services research. Our national databases for adults and children verify significant and clinically important improvements both in the clinical status and quality of life of patients as well as significant savings of indirect costs over the last 25 years. With combined analyses of claims data and patient-reported outcomes we identify gaps in health care. Our data are used for health care planning and policy. We also take statistical responsibility for investigator-driven randomized clinical trials of new therapies.
Examples for Fields of Research:

1. Clinical studies:
   The clinical trial unit participates in several sponsored phase I-IV clinical trials in different indications including rheumatoid arthritis, spondylarthritides, systemic lupus erythematosus, vasculitis, osteoporosis and systemic sclerosis. Furthermore, investigator initiated trials were successfully performed in rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, Sjögren’s syndrome and adult onset Still’s disease.

   Proof-of-principle that immunological memory can drive chronic inflammation:
   The clinical study “IMMUNE-RESET” was developed in close cooperation between clinicians of the Charité and basic researchers of the DRFZ. Resetting the immune system with immunoablation followed by autologous haematopoietic stem cell transplantation leads to long-term treatment-free remissions in refractory autoimmune diseases in 70% of 23 patients with various refractory rheumatic diseases treated in Berlin since 1998.

   Ablation of memory plasma cells ameliorates Systemic Lupus Erythematosus:
   Blocking proteasomes with Bortezomib is an efficient treatment in multiple myeloma, which are transformed plasma cells. Together with colleagues from Erlangen, Cologne, Heidelberg and Freiburg, the center showed in an off-label treatment study that Bortezomib significantly downregulates autoantibody titers and ameliorates disease activity of patients with Systemic Lupus Erythematosus (TAVAB-Study).

   Low-dose IL-2 therapy decreases disease activity in Systemic Lupus Erythematosus:
   A first study in one patient with systemic lupus erythematosus (SLE) showed that subcutaneous low-dose treatment with therapeutic IL-2 decreased disease activity. Currently, 10 SLE-patients refractory to conventional treatment are included in the phase I/IIa study “PRO-IMMUN”. A remarkable expansion and activation of the Treg population was observed and disease activity decreased. These data provide the first evidence for the clinical efficacy of a subcutaneous low-dose IL-2 therapy in SLE, and suggest that this therapeutic concept may be translated to many other chronic inflammatory diseases driven by T cells. Gabriela Riemekasten, who had initiated this project has been appointed full professor and director of the Clinic for Rheumatology at the University Medicine Lübeck.

2. Immune Monitoring: Predicting disease development and response to therapy
   By immune monitoring we aim to identify immunophenotypic signatures of blood leukocytes as biomarkers for monitoring disease activity and predicting treatment responses. With new cell-based assays we use the circulating leukocytes as “biosensors” for subtle differences and changes of systemic and local inflammations, combining global gene expression analyses and multiparametric single cell fluorescence and mass cytometric technologies to identify cell-type specific “biosignatures” that reveal detailed information about cytokines, chemokines and signals involved in the inflammation of a given patient, and may even serve to predict the patients response to a therapy targeting specifically such signals. Along those lines, we have identified Siglec-1 as a new biomarker for the diagnostics of SLE. This adhesion molecule, when expressed on monocytes, outperforms conventional gold standards of lupus diagnosis. It has been successfully translated into clinical diagnostics.
3. **Tissue engineering:**

Another focus of our current research is to develop tissue engineering technologies based on multidisciplinary knowledge for cell biology, cell culture and biocompatible delivery materials. This group is primarily working with cells from mesenchymal tissues and has extensive experience in 3D cell cultures and in the translation of research into therapies. Major focus is the development of regenerative therapies for cartilage, intervertebral disc, tendon, bone and heart muscle and for in vitro models of inflammatory pathomechanisms and targeted therapies.

4. **Glucocorticoid-induced osteoporosis:**

Glucocorticoids remain to be among the most important and most frequently used anti-inflammatory and immunosuppressive or immune-modulatory acting drugs to treat rheumatic diseases. However, the available data describing frequency and severity of their adverse effects are fragmentary which is especially true for the Glucocorticoid-induced osteoporosis (GIOP) in the context of chronic inflammatory rheumatic disease. Therefore, we currently collect and analyze disease- and bone-related data from patients with chronic inflammatory rheumatic diseases and therapy with glucocorticoids in order to build a large respective GIOP-Databank.

5. **Epidemiological Studies**

With our biologics register RABBIT we were able to verify for the first time results from animal experiments: We found a significantly lower risk for sepsis after infection in patients who were exposed to biologic agents at the time of the infection. This puts current treatment strategies into question. We also showed a significantly decreased overall mortality in patients exposed to biologic agents. With the RABBIT risk score for serious infection which allows for treatment, comorbidity and patient risk factors, we developed a tool for clinical practice that helps to balance out benefits and risks of treatments. We also established evidence for a significantly increased risk of gastrointestinal perforation under IL-6 blockade.

In juvenile idiopathic arthritis we found strong evidence for the need of a treat-to-target strategy: Time to first remission was the most important predictor of long-term outcome. These results influence new treatment recommendations.

We provide robust evidence for improvements in health care: In patients with rheumatoid arthritis treated in routine rheumatological care in Germany the mean DAS28 score decreased from a high activity of nearly 5 to a state of low disease activity (<3.2) over the last 20 years. This is accompanied by tremendous reductions in sick leave and work disability. Days of sick leave decreased from an average of 35 to 8 days per patient and year. Children with JIA today have the same quality of life as children without the disease, a development not imagineable 20 years ago. Using claims data, we found significant differences in health care of patients with rheumatic and musculoskeletal diseases according to the specialty of the physician, the region of residence and the social status.
6. Experimental rheumatology:

6.1 Targeting the pathogenic memory driving chronic inflammation:

Experimental research is focussed on imprinting and memory of the immune system, as the driving force of chronic inflammation, refractory to conventional therapies, and thus roadblocks for the regeneration of immune tolerance, i.e. termination of inflammation. We aim at the selective ablation or manipulation of pathogenic memory cells, as compared to protective ones, from a molecular understanding of their lifestyle. So far, we have identified memory plasma cells as an independent and refractory compartment of immunological memory, have allocated protective longterm memory to systemic pathogens to resident memory cells of the bone marrow, have introduced the concept of memory cell niches, organized by mesenchymal stromal cells, and defined molecular adaptations of pathogenic memory T cells to chronic inflammation.

Several pre-clinical approaches, aiming at the selective depletion of pathogenic memory cells are currently studied in our department:

- Antigen-specific targeting of autoreactive plasma cells by an affinity matrix technology, developed at the DRFZ.
- Selective targeting of pathogenic memory Th lymphocytes by inhibiting genes and regulatory RNAs which are molecular adaptations of these cells to chronic inflammation, and required for their activity and survival.
- Studying the epigenetic impact on CD4+ T cell differentiation in health and under chronic inflammatory conditions, to identify potential target genes according to their molecular imprinting.
- A role of innate lymphocytes in organizing immune reactions and in chronic inflammation is emerging. We have identified and analysed NK memory cells and innate lymphocytes qualifying for this.

6.2. Regulation of immune responses

To regenerate immunological tolerance in immune-driven chronic inflammation, we aim at regenerating and strengthening of physiological regulatory mechanisms:

- We have identified regulatory plasma cells that secrete the regulatory cytokines IL-10 and IL-35. These cells regulate immunity to infection and can prevent autoimmune inflammation. Simon Fillatreau, leading this project, has been appointed professor at the Institute Necker-Enfants Malades in Paris, France.
- We have developed a method to identify the physiologic target antigens of regulatory and effector T lymphocytes, and isolate these cells according to their specificity. This enables approaches to selectively suppress defined (inflammatory) immune reactions.
- T follicular helper (Tfh) lymphocytes are critically involved in the generation of high affinity memory B cells and long-lived plasma cells. We analyse this process in molecular detail to identify new ways to interfere with the generation of pathogenic memory plasma cells.
- We found that in experimental arthritis only a limited set of cellular sources (i.e. myeloid cells) are producing ‘pathogenic’ TNF, while other sources (such as T cells) provide TNF with protective functions. Selective targeting of cellular sources producing “pathogenic” TNF as macrophages could become a novel therapeutic strategy.
6.3 Protective and pathogenic microbiota

There is a clear indication that chronic inflammation as rheumatic diseases are associated with dysbiosis – dramatic changes in microbiota composition. We therefore aim to reveal the mechanisms of control of microbiota by the immune system, and vice versa, to find new ways of treating rheumatic diseases by targeting the intestinal microbiota. In that context we have developed a new method for simple and inexpensive analysis of gut microflora composition - the high-resolution "Microbiota-Cytometry".

Tissue regeneration by reprogramming chondrocytes

Osteoarthritis is a chronic degenerative disease that leads to progressive cartilage loss and is mostly accompanied by inflammatory processes. Recent studies indicate a dysfunctional molecular signalling within the cartilage-producing cells of the joints, the chondrocytes. By reprogramming of chondrocyte phenotypes we aim at biological regeneration of cartilage in affected joints.

Selected Publications


44. Poddubnyy D, Listing J, Sieper J. Course of Active Inflammatory and Fatty Lesions in Patients With Early Axial Spondyloarthritis Treated With Infliximab Plus Naproxen as Compared to Naproxen Alone: Results From the Infliximab As First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial. Arthritis Rheumatol 2016;68(8):1899-1903.


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Training of Fellows in Research
Clinical fellows who are doing research work in Charité-DRFZ-Liaison-groups are involved in frequent research seminars at the Charité as well as in all seminars and lecture series at the DRFZ where they present their experimental data, i.e. the “Chronic Inflammation Forum” T cell club or B cell club. Doctoral students in the Epidemiology Unit are involved in the DRFZ-Epi-Club as well as programs from the Berlin School of Public Health. Furthermore medical students could become involved in the Leibniz Graduate School for Rheumatology (LGRh) that is a structured doctoral program open for students from natural science as well as medical students with the aim to educate motivated and talented students to carry out translational research in rheumatology. The LGRh is a joint program of the Humboldt-Universität Berlin, Faculty of Life Sciences, the Charité – Universitätsmedizin Berlin, Division of Rheumatology and Clinical Immunology and the German Rheumatism Research Centre (DRFZ) Berlin, an Institute of the Leibniz Association.

WebPages
http://rheumatologie.charite.de
http://www.drfz.de