Clinical Research Unit 257: Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)

Speaker
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Aims and structure
The Clinical Research Unit 257 “Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)” was established in 2012 by the DFG. The grant was concluded after the maximal funding period of six years in July 2018. The research focus was on the development and (pre-)clinical testing of novel diagnostic and therapeutic approaches for inflammatory bowel diseases (IBD). IBD include the two major forms Crohn’s disease (CD) und ulcerative colitis (UC). Both disorders are characterized by episodes of inflammatory flares and periods of remission. IBD patients typically suffer from abdominal pain, diarrhea, anemia, weight loss, and fatigue. Additional to physicians, biologists, and biotechnologists from the Department of Medicine 1, physicians and biologists from the Departments of Medicine 3, of Surgery, of Dermatology and from the Division of Immune Modulation were included into the research program of the clinical research unit. Aim of the unit was to evaluate the crosstalk between immune cells and epithelial cells in the gut in order to develop new, innovative, and effective treatment strategies for the therapy of IBD patients. Moreover, KFO 257 evaluated concepts of IBD pathogenesis in order to develop new diagnostic and therapeutic approaches for the clinical management of these diseases. This translational research approach was conducted in a close interaction between clinically and scientifically active IBD specialists and experienced basic scientists in Erlangen. Together, physicians and scientists worked in three research areas:

A: Regulatory mechanisms of mucosal immune cells
- TP01: Cytokine mediated mechanisms in the immune-pathogenesis of IBD
  PI: Prof. Dr. C. Becker / PD Dr. S. Wirtz (Medicine 1)
- TP03: Functional analysis of the immune modulator scDB3 in the pathogenesis and therapy of IBD
  PI: Prof. Dr. A. Steinkasserer / PD Dr. M. Lachmann (DIM)
- TP11: Neutrophil extracellular traps orchestrate the immune response in IBD
  PI: Prof. Dr. M. Herrmann / Dr. M. Leppkes (Medicine 3/Medicine 1)

B: Regulatory mechanisms of gut resident cells
- TP05: Immune regulation of angiogenesis in IBD
  PI: Prof. Dr. M. Stürzl / Dr. M. Waldner (Surgery/Medicine 1)
- TP10: Neuropeptides and TRP receptors as effectors of immune cell activation in IBD
  PI: PD Dr. M. Engel (Medicine 1)
- TP12: Functional characterization of prenylated Rho proteins in the pathogenesis of IBD
  PI: Dr. I. Atreya (Medicine 1)

C: Therapy and prediction of therapy response
- TP07: Analysis of the molecular mode of action of cyclosporine A in IBD
  PI: PD Dr. B. Weigmann (Medicine 1)
- TP08: Characterization and expansion of regulatory T cells for cell-based therapy of IBD
  PI: Prof. Dr. M.F. Neurath / Dr. C. Bosch-Voskens (Medicine 1/Dermatology)
- TP13: In vivo endoscopic molecular imaging to predict therapeutic response to anti-adhesion molecule therapy in CD patients
  PI: Prof. Dr. R. Atreya (Medicine 1)
- TPZ: Central project to coordinate the scientific program of KFO 257
  PI: Prof. Dr. C. Becker (Medicine 1)

Research
One of the major problems during therapeutic treatment of IBD patients is that subgroups of patients do not respond to a given therapy for unknown reasons. Numerous achievements have been made during the funding with potential for future therapeutic improvements. The project TP13 focused on the improvement of the predictability of therapy response of biological therapies. By using a fluorescently labeled antibody against TNFα, it was demonstrated that patients with high numbers of mTNF expressing cells showed significantly higher response rates to subsequent anti-TNF therapy. Project TP08 successfully established a GMP conform method to greatly expand regulatory T cells isolated from the peripheral blood of UC patients. Based on this method, a study protocol for Treg treatment of UC patients was developed and submitted to the Paul Ehrlich Institute for approval. A clinical phase I trial using such expanded Treg will start once the protocol is approved. The clinical research unit was also successful on identifying novel molecular pathways involved in IBD pathogenesis. Accordingly, TP12 demonstrated for the first time that a post-translational activation of a specific enzyme determines the maintenance of epithelial integrity and immune homeostasis in the gut. TP01 found an unexpected function of IL-33 as a regulator of epithelial barrier functions, which further on promotes the antimicrobial defense. The influence of IFNγ on IBD pathogenesis was analyzed in the TP05. They demonstrated that IFNγ is increased in IBD patients and had a direct influence on epithelial cells in IBD tissues. Project TP07 focused on the underlying signaling axis of Cyclosporine A that is already used for IBD treatment. It could be shown that Cyclosporine A modulated the production of inflammatory cytokines and the survival of T lymphocytes in UC patients. In addition to the scientific achievements, the clinical research unit has been able to recruit and train highly motivated national and international doctoral candidates. It also promoted the careers of clinician scientists by enabling laboratory rotations for clinicians. Five projects were led by young physicians setting up or consolidating their own research groups.

Teaching
Seminars on IBD:
- Immune pathogenesis and treatment of IBD
- Molecular medicine
- Molecular mechanisms of tumor development in the intestine
- Physiology and pathophysiology of the gut
- Seminar internal medicine, pathophysiology of IBD
- Academic research in medicine: Insights into current clinical-immunological research and dissemination of methodologies knowledge

Current scientific literature (topic: Research publications on IBD)
Research progress seminar (topic: Current research findings of KFO 257)