

Final report for projects funded by the Leibniz Association's Competition Procedures
Project title: Leibniz ScienceCampus Berlin – Comprehensive Center for Chronic Inflammatory Diseases

Project number: W55/2019

Reporting period: 1.10.2020 – 30.09.2024

Second funding period

Executive Summary

The Leibniz ScienceCampus Berlin – Comprehensive Center for Chronic Inflammatory Diseases (CID) aims to promote the strong integration between the Leibniz Institute DRFZ and Charité Universitätsmedizin on research about CID. In the second funding period we have employed the established structures to sharpen our research mission, focusing on the identification and therapeutic targeting of sensors, cells and mechanisms controlling the initiation and chronicity of inflammation in different tissues, as well as of signatures predicting responses to therapy in order to achieve a patient tailored treatment. These aims have been pursued by reinforcing the strong cooperation between a large group of basic and clinical scientists from the DRFZ and Charité and extending it by the acquisition of new excellent PIs and novel technologies.

Scientifically, we aimed to resolve the inflammatory immune cell units as well as the environmental triggers driving and maintaining pathology of selected CID by directly investigating the tissues as the central matrix of inflammation persistence. Moreover, the Leibniz Campus has continued its mission to train the next generation of leaders in the clinics and scientific field of CID and to establish new research initiatives in the field of tissue immunity and CID.

1. Achievement of objectives and milestones

The second funding period started on 1.10.2020, with a budget cut of 25%. Therefore, the financial plan was adjusted accordingly. Moreover, the COVID-19 pandemic has impaired recruitment of new staff for scientific positions during end of 2020 and 2021, as compared to the original financial plan. Despite these modifications, the scientific program has progressed according to plans. In line with the scientific aim of the Campus, namely resolving the inflammatory immune cell units as well as the environmental triggers driving pathology and its persistence in selected CID, we have investigated the innate and adaptive cells enriched in tissues, with a special focus on innate lymphoid cells (ILCs) and pathogenic memory cells, as the central matrix of inflammation persistence. Here we provide an update and summarize the main scientific achievements obtained during the funded period.

WP1. Determining the atlas and the core inflammatory cellular units of CID

In this WP, the Campus aimed to achieve a global overview on the signatures, the imprinting and topography of immune and non-immune cell units in non-affected and inflamed tissues by using different multi-omic approaches, focusing on four main units:

A) “Joints and Juvenile idiopathic arthritis (JIA)”: Here, in a cooperative effort by the groups of M-F. Mashreghi, T. Kallinich and C. Romagnani, scRNA/CITE-seq analysis of the cellular landscape enriched in the synovial fluid versus peripheral blood of oligoarticular JIA has been performed. The experiments led to the identification of specific signatures of activation in infiltrating T cells (Maschmeyer et al, 2021) and in ILCs, in particular Natural Killer (NK) cells (Knight et al, manuscript in preparation). A project on „Identification and modulation of new immune targets in juvenile idiopathic arthritis (JIA)“ (SAW-TargArt, K259/2019) in the

frame of the Leibniz-Kooperative Exzellenz Programm led by these PIs has been funded to co-finance this part of the project.

B) “Intestine and Inflammatory Bowel Diseases (IBD)”: This unit coordinated by B. Siegmund has established an efficient pipeline for the analysis of intestinal biopsies of patients with Crohn’s disease and Ulcerative Colitis, the main CID of the gastrointestinal tract. In a joint effort with Erlangen, co-partner of the CRC TRR241 initiative on IBD led by B. Siegmund, the group has created the “IBDome” an integrated molecular, histopathological, and clinical atlas of IBD, where an extensive multi-omic and multimodal analysis of 1,002 clinically annotated IBD patients and non-IBD controls, incorporating whole-exome and RNA sequencing of normal and inflamed gut tissues, serum proteomics, and histopathological assessments from images of H&E-stained tissue sections was performed (Plattner et al, bioRxiv 2025). Moreover, the groups of A. Hegazy, B. Siegmund, C. Weidinger, A. Diefenbach, A. Radbruch, HD. Chang and C. Romagnani, all PIs of the CRC TRR241, have conducted scRNAseq and flow cytometry analysis of peripheral blood as well as of intestinal immune and non immune cells derived from IBD patients. These studies have led to the identification of novel predictors for response to selected biologics in IBD (Horn et al, Gastroenterology. 2025). Moreover, by combining studies with patient samples as well as experimental models of colitis, the group of H. Hegazy, together with B. Siegmund, M-F. Mashreghi, A. Diefenbach, and C. Romagnani has shown a role for epithelial cells in producing the pro-inflammatory cytokine oncostatin M, which promotes intestinal inflammation and tumorigenesis (Cineus et al, Nat Immunol, in press). The group of C. Romagnani, in cooperation with HD. Chang and M-F. Mashreghi identified a novel network of transcription factors regulating innate lymphoid cells (ILC) differentiation and intestinal epithelial competence, which could represent attractive targets (Hernandez et al, Immunity 2021; Stehle et al, Nature Immunology 2021). Finally, the group of A. Kruglov has shown that TNF hampers intestinal tissue repair in colitis by restricting IL-22 bioavailability (Ninnemann et al, Mucosal Immunol 2022).

C) “Kidney and lupus nephritis”: Analysis of samples of patients affected from Systemic lupus erythematosus (SLE) has been coordinated by T. Dörner, with particular focus on flow cytometric analysis of B cells, which are major mediators of disease pathogenesis (Rincon-Arevalo et al, 2021; Wiedemann et al 2021). The group of A. Triantafyllopoulou has performed scRNAseq analysis of the kidney of mice in an experimental model of lupus nephritis. They identified a cross-talk between macrophages and group 1 ILCs as a central node regulating diseases severity (Biniaris et al, Nature 2024). Moreover, P. Enghard has identified and characterized autoantigen-specific T cells in the frame of human lupus nephritis (Tesch et al, Sci Rep 2020) and show the predictive value of T cells in different kidney disease disorders (Bertolo et al, Front Immunol 2020; Grothgar et al, Front Med 2022; Sonnemann J. Kidney Int Rep. 2023; Prskalo et al, J Am Soc Nephrol. 2024).

D) “Explorative/prospective CID research”: Key cooperation to extend the analysis of cellular circuits and pathogenic mechanisms to other organs have been established. In particular, a new line of research aiming at investigating pathogenic mechanisms driving hepatic nonalcoholic steatosis and fibrosis has been initiated with F. Tacke, Gastroenterology and Hepatology, Charité Berlin, a new clinical partner enrolled in the Campus during the second funding period. F. Tacke together with Campus PIs C. Romagnani, B. Siegmund and A. Diefenbach have applied for a new DFG CRC initiative on metabolic dysfunction-associated steatotic liver disease (MASLD) (TRR CRC 412, final decision May 2025) identifying novel targets for the treatment of acute and chronic liver diseases (Puengel et al, Int J Mo Sci 2022; Guillot et al, Hepatology 2023; Heymann et al, Hepatol Commun 2023; Peiseler et al, Science 2023; Niemietz et al, Hepatology 2024).

WP2. Targeting the environmental triggers and perpetuators of CID

In this WP, we aimed to identify major environmental signals, such as diet and microbiota, and target the sensing receptors, expressed on innate but also adaptive immune cells, which initiate and maintain chronic inflammation. The groups of HD. Chang and A. Kruglov have employed microbiota cytometry and the generation of microbiota-specific IgA to identify protective and pathogenic populations of microbiota in different experimental models of CID and in CID patients (Budzinski et al, Eur J Immunol 2024; Budzinski et al, Methods Cell Biol

2024; Budzinski et al, Gut Microbes 2025). The impact of diet components, in particular of vitamin D and retinoic acid on the immune system, as well as on tissue responses and CID has been investigated by the group of M. Worm (Treptow S et al, Eur J Immunol. 2021; Heine G et al, Allergy 2021; Scholz J et al, Allergy 2021).

WP3. Targeting memory of inflammation

This WP coordinated by A. Radbruch was devoted to study and target antigen-experienced, and functionally imprinted “memory” cells, such as memory plasma cells, pathogenic T cells and defined ILC subsets. Characterization of memory cells, their life style and survival niches in different tissues has been performed using cutting-edge imaging technologies *in vivo* and *ex vivo* by PI A. Radbruch, A. Hauser and R. Niesner (Ferreira-Gomes et al, Nat Commun 2024; Ulbricht et al, Front Immunol 2023; Cendón et al, EJI 2022; Pascual-Reguant et al, Nat Commun 2021; Ulbricht et al, Meth Mol Biol 2021; Cornelis et al Curr Opin Immunol. 2021; Maschmeyer et al Nat Rev Rheumatol. 2021). Work from the Romagnani group aiming at identifying epigenetic and transcriptional features underlying innate memory has provided evidence that AP-1 footprints represent a universal marker of inflammatory memory shared by innate lymphocytes and propagated in a clonal fashion (Rückert et al, Nat Immunology 2022; Rückert et al, Immunol Reviews 2024).

WP4. Biomarkers, experimental therapies and patient health

This WP coordinated by T. Alexander was devoted to the development of new diagnostic/prognostic biomarkers and novel therapeutic approaches. The role of e.g. Siglec1 (or CD169), originally identified by Campus PIs as a potential SLE biomarker has been further explored by Campus PIs T. Kallinich, H. Radbruch and T. Alexander. It was validated as biomarker with potential prognostic and diagnostic functions not only in SLE, but also multiple sclerosis and idiopathic inflammatory myopathies (von Stuckrad et al, Lupus 2020; Ostendorf et al, Sci Rep. 2021; Zorn-Pauly et al, Rheumatology 2021). Moreover, studies by T. Alexander utilizing plasma cells-depletion approaches such as Daratumumab (anti-CD38) for the treatment of SLE (Ostendorf et al, N Engl J Med. 2020) have been extended (Scheibe et al, Eur J Neurol. 2022) to other diseases. Novel therapeutic approaches by repurposing cancer biologics, such as Teclistamab for the treatment of autoimmune disease have been also successfully pioneered by the Alexander group to induce remission in refractory SLE (Alexander T et al, N Engl J Med. 2024) or in relapsed systemic sclerosis (Siegert et al, Ann Rheum Dis. 2025).

COVID-19-related research

In the emerging corona pandemic, the Campus PI team used their expertise in human immunology and single cell analysis to understand immune responses and memory in response to SARS-CoV2, as well as disrupted circuits leading to systemic inflammation, resulting in numerous key publications in the field (see Table 3.1).

2. Activities and obstacles

The COVID-19 pandemic has led to several disruptions of the scientific and educational activities of the ScienceCampus from the end of 2020 to 2021. In particular, it has affected patients sample collection, laboratory experiments, recruitment for scientific positions and general activities. In the second half of 2021, scientific positions have been filled and planned to increase in 2022, to catch up with the scientific program again. Due to the pandemic, all planned on site events had to be canceled. We transformed all scientific discussion of the Chronic Inflammation Forum, a platform of weekly or monthly Scientific Discussion Clubs on different topics relevant for the Campus activities, including basic and clinical science, and technologies (DRFZ Institute seminar, T cell/ILC club, B cell club, Bone and Joint club, Organoid club, Microbiota Club, IBD webinar) first into a virtual and then hybrid platforms. The Leibniz-College on Chronic Inflammation for PostDocs and the Leibniz Graduate School on

Chronic Inflammation (LeGCI, Speakers: A. Hauser and H. Radbruch) has continued its training program in immunology and inflammation of PostDoc and PhD students respectively, in association to the ZIBI (Speaker C. Romagnani), an overarching PhD program which links LeGCI to other Berlin Research Training Group (RTG) initiatives in the field of Immunology, Infection and Inflammation, such as the IMPRS from the MPII-IB (Speaker: A. Zychlinsky). Despite the initial difficulties, the Campus kept working as a platform to promote exchange, networking and support for the scientists and the clinicians affiliated.

3. Results and successes

Despite the corona pandemic, numbers of publications, positively evaluated third-party funding applications, completed theses and dissertations remained high, as mobile working was installed (remote VPN access to electronic data for all members of the DRFZ) with highest priority.

The Else Kröner-Promotionskollegs Berlin - Re-Thinking Health" led by A. Diefenbach, C. Romagnani and F. Knauf has received two rounds of funding to provide additional educational platforms for scientific training of MD students. The new CRC TRR 362 Berlin-Dresden on pathogenic mechanisms driving hepatic nonalcoholic steatosis and fibrosis has been initiated and evaluation has taken place at the beginning of 2025 (decision pending). This initiative led by F. Tacke, Charité Berlin, a new clinical partner enrolled in the Campus during the second funding period, is based on a central contribution of Campus PIs C. Romagnani, B. Siegmund, C. Weidinger, and A. Diefenbach. The application for the second funding period of the CRC TRR241 between Berlin and Erlangen, focused on IBD pathogenesis and led by B. Siegmund, with the participation of several other Campus PI, including C. Romagnani, HD. Chang, A. Diefenbach, A. Triantafyllopoulou, C. Weidinger and A. Hegazy has been approved in 2022. An advanced ERC grant ("MEM-CLONK") has been awarded to the Campus Speaker C. Romagnani to investigate innate immune memory, one of the central scientific themes of the Campus. ImmunoPreCept, a Cluster of Excellence initiative led by Campus PIs B. Siegmund and A. Diefenbach, which seeks to improve the early detection and prevention of diseases such as chronic inflammation and cancer, submitted a full proposal in February 2025 (decision pending).

The publications in the context of the relative working programs have been described more in detail in paragraph 1. The publications, completed theses and dissertations as well as acquired third party funds are listed in Tables 3.1, 3.3 and 3.4.

4. Equal opportunities, career development and internationalisation

In the second funding period, the ScienceCampus continued its promotion of equal opportunities to scientists and other staff members. As many members suffered from the corona-pandemic restrictions accompanied by home schooling of kids, mobile working helped to keep in touch with colleagues. The family-friendly timing of meetings and events is an issue of high priority of the ScienceCampus. Events in the Chronic Inflammation Forum do not start after noon. Additionally, the online Media Center enables the online viewing of recorded talks and lectures at any time. Beyond the regular daycare opportunities at the Charité, flexible childcare options have been available within the Campus funding.

5. Structures and collaboration

In the second funding period, besides Prof. Axel R. Pries, Dean of the Charité and Prof. Andreas Radbruch, Scientific Director of the DRFZ, Professor Chiara Romagnani, who accepted the W3S professorship funded by the Campus in 2020, has fully joined as third spokesperson of the ScienceCampus. During this period, the Campus has strengthened the already existing links between the Charité and the DRFZ and initiated new partnerships, especially with PIs from the Gastroenterology and Hepatology as well as Microbiology

Departments of the Charité. Besides the Charité Medical Faculty, which is associated to the Humboldt University and the Free University Berlin, the Campus has closely collaborated and brought together many PIs from different institutions in Berlin, working on relevant Campus topics such as, immunology, CID and key technologies. These include the Max Planck Institute for Infection Biology, (A. Zychlinsky, M. Taylor); the BCRT (A. Thiel), the Max Delbrück Center (MDC), in particular the Berlin Institute for Medical Systems Biology (MDC-BIMSB) (L. Ludwig). Finally, the main Campus PIs have played a crucial role in the development of new cooperative grant applications, as described in Paragraph 3. At the end of 2023, the Campus Speaker C. Romagnani has been appointed Director of the Institute of Medical Immunology at the Charité.

6. Quality assurance

In the last years we have made several efforts to publish open access. Costs for open access publications have been partially supported by the Campus. Every scientist at the DRFZ has complied with good scientific practice, according to DFG guidelines. PhDs enrolled in the graduate program of the Leibniz ScienceCampus “Leibniz Graduate School on Chronic Inflammation” (LeGCI) attended a course instructing them on the topic.

Working with laboratory animals followed strict regulations. In order to comply with legal requirements for animal welfare, the scientists were advised on their projects, but also on breeding and husbandry, by the animal welfare officers. The Animal Welfare Officers were supported in their work by the Animal Welfare Committee. In addition, monthly project presentations take place to discuss and improve the knowledge gained and the actual burdens of animal experimentation. The animal caretakers also took part to these meetings to ensure a *Culture of Care*. Training and further education on animal welfare were initiated and carried out by the veterinarians. In addition to the basic expertise course, the veterinarians offered a teaching program where scientists could regularly refresh and expand their knowledge of animal welfare and related legislation.

All scientists performing animal experiments attended a basic expertise course with examination before they can do animal experiments and they have to undergo regular training on the topics of animal welfare and the 3R principle (Replace, Reduce, Refine), which was systematically applied for all experimental models used.

7. Additional resources

Part of the working time of DRFZ/Charité scientists involved in the Campus activities has been allocated to the Campus. In 2021 the DRFZ has upgraded and supported the existing MELC microscopy and flow cytometry facilities, which has been instrumental for the acquisition and analysis of patient samples. Finally, the DRFZ has supported the Leibniz-College with stipends for postdoctoral fellows and the LeGCI graduate program with stipends for doctoral students. This enabled participation in workshops and virtual scientific meetings.

8. Outlook

The scientific network will continue through the established structures and collaborations. Further translation into clinical application will be pursued through planned clinical studies and collaborations with industry partners.