CSC-RUB PhD Project Proposal

Title: Investigation of BTK induced neuroprotection in a reverse-translational model of myelinated neurons.

Sector of research: PhD

Degree awarded: Neuroscience (International Graduate School of Neuroscience)

Keywords: Multiple Sclerosis; progression; neuroprotection; chronic inflammation; translational medicine, Bruton´s tyrosine kinase; B cells,

Supervisor of PhD project:

Dr. Jeremias Motte and Dr. Barbara Gisevius

Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital, Bochum, Germany

Research focus of supervisor:

The research of Jeremias Motte and Barbara Gisevius focuses on immunological and neurodegenerative mechanisms underlying chronic inflammation in multiple sclerosis and other inflammatory CNS and PNS disorders, especially the interaction between environmental and metabolomic factors, and disease modifying drugs. The main goal of their research is the deeper understanding of neuroinflammation and neurodegeneration associated with environmental factors and their targeted modification in a translational approach. For this purpose, Dr. Motte and Dr. Gisevius founded an interdisciplinary group consisting of physicians and biologists. They use cell culture models (primary, cell lines), a human biobank and different patient registers. One focus is to target neuroinflammation and -degeneration in different neurological diseases using short chain fatty acids and to translate this into human studies. Moreover, the group focusses on human cell lines as model of inflammation and degeneration in MS patients.

Publications Motte:

Publications last 5 years: 37 (Pubmed listed); 46 (web of Science)

H-Index last 5 years: 9 (Web of Science); 11 (Google Scholar)

1. Motte J, Fisse AL, Köse N, et al (2021) Treatment response to cyclophosphamide, rituximab, and bortezomib in chronic immune-mediated sensorimotor neuropathies: a retrospective cohort study. Ther Adv Neurol Diso 14:17562864219996 3. https://doi.org/10.1177/1756286421999631

2. Klimas R, Skozai M., Motte J., et al (2021) Dose-dependent immunomodulatory effects of bortezomib in experimental autoimmune neuritis. Brain Commun. https://doi.org/10.1093/braincomms/fcab238

3. Grüter T, Blusch A, Motte J, et al (2020) Immunomodulatory and anti-oxidative effect of the direct TRPV1 receptor agonist capsaicin on Schwann cells. J Neuroinflamm 17:145. https://doi.org/10.1186/s12974-020-01821-5

4. Fisse AL*, Motte J*, Grüter T, et al (2020) Comprehensive approaches for diagnosis, monitoring and treatment of chronic inflammatory demyelinating polyneuropathy. Neurological Res Pract 2:42. https://doi.org/10.1186/s42466-020-00088-8 *contributed equally

5. Motte J, Ambrosius B, Grüter T, et al (2018) Capsaicin-enriched diet ameliorates autoimmune neuritis in rats. J Neuroinflamm 15:122. https://doi.org/10.1186/s12974-018-1165-x

Publications Gisevius:

Publications last 5 years: 8 (Pubmed listed); 18 (web of Science)

H-Index last 5 years: 6 (Web of Science); 6 (Google Scholar)

1. Ofengeim D, Hagan N, Woodworth L, Proto J, Zelic M, Mahan A, Saleh J, Kane Jr J., Liu J, Kothe M, Scholte A, Fitzgerald M, Grover D, Madore C, Butovsky O, Haghikia A, Gisevius B, Sancho J, and Li Y (2020) CSF1R signaling is a regulator of pathogenesis in progressive MS, Cell Death & Disease, 2020 Oct 23;11(10):904. doi: 10.1038/s41419-020-03084-7.

2. Duscha A*, Gisevius B*, Hirschberg S*, Yissachar N*, Stangl GI, Eilers E, Bader V, Haase S, Kaisler J, David C, Schneider R, Troisi R, Zent D, Hegelmaier T, Dokalis N, Gerstein S, Del Mare-Roumani S, Amidror S, Staszewski O, Poschmann G, Stühler K, Hirche F, Balogh A, Kempa S, Träger P, Zaiss MM, Holm JB, Massa MG, Nielsen HB, Faissner A, Lukas C, Gatermann SG, Scholz M, Przuntek H, Prinz M, Forslund SK, Winklhofer KF, Müller DN, Linker RA, Gold R, Haghikia A (2020), Propionic Acid Shapes the Multiple Sclerosis Disease Course by an Immunomodulatory Mechanism, Cell, Mar 19;180(6):1067-1080.e16. doi: 10.1016/j.cell.2020.02.035. Epub 2020 Mar 10. PMID: 32160527

3. Schneider R, Bellenberg B, Gisevius B, Hirschberg S, Sankowski R, Prinz M, Gold R, Lukas C, and Haghikia A. (2020), Chitinase 3-like 1 and Neurofilament Light Chain in CSF and CNS Atrophy

in Multiple Sclerosis, Neurol Neuroimmunol Neuroinflamm, 2020 Nov 10;8(1):e906. doi: 10.1212/NXI.0000000000000906. Print 2021 Jan

4. Massa MG, David C, Jörg S, Berg J, Gisevius B, Hirschberg S, Linker RA, Gold R, Haghikia A (2017), Testosterone Differentially Affects T Cells and Neurons in Murine and Human Models of Neuroinflammation and Neurodegeneration, Am J Pathol. 2017 Jul;187(7):1613-1622. doi: 10.1016/j.ajpath.2017.03.006. PMID: 28634006

5. Hirschberg S*, Gisevius B*, Duscha A, Haghikia A. (2019). Implications of Diet and The Gut Microbiome in Neuroinflammatory and Neurodegenerative Diseases. (Review) Int J Mol Sci. 2019 Jun 25;20(12):3109. doi: 10.3390/ijms20123109. PMID: 31242699. Review.

Second Supervisor of PhD project

Ass. Professor Dr. Simon Faissner

Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital, Bochum, Germany

Summary of research plan (ca. 300 words):

Background: Multiple sclerosis (MS) is a multifactorial autoimmune disease characterized by influx of leukocytes in the CNS which leads to damage of the myelin sheath and axonal damage with consecutive chronic disability. While most therapeutic approaches available so far focus on the prevention of leukocytes to enter the CNS with the goal of reducing the formation of new lesions, mechanisms driving chronic inflammation and degeneration important for progression in MS are undertreated so far. Diet and the associated gut microbiome, as environmental risk factors of neuroinflammation, may determine disease onset and subsequent progression in neuroimmunological diseases such as MS. In this field our group focuses on gut microbiome and their metabolites, and its potential to promote immunoregulation and neuroregeneration in interaction with disease modifying drugs. We use a reverse-translational model of MS patient-specific induced primary neurons (iPNs) and myelinating oligodendrocytes (iPO) and co-cultures with different immune cell subtypes to investigate the impact of metabolomic environment in myelinated neurons [2,3,5].

In this research proposal, we aim to investigate how communication between the gut and brain contributes to disease progression in an MS patient-specific primary neuronal cell culture model. Moreover, we will investigate how a new class of drugs targeting the Bruton´s tyrosine kinase (BTK) might promote neuroprotection and brain-gut axis interaction.

Study objective: Investigation of BTK induced neuroprotection in a reverse-translational model of myelinated neurons.

Expected Results: Chronic inflammation in human MS will be targeted using inhibitors of the BTK. We hypothesize that this approach will alter activation of innate immune cells and B cells, thereby promoting neuroprotection in humans. In addition, we hypothesize that the microbiome- gut- brain axis via regulatory B cells and long-lived plasma cells in the gut, have an impact on the mechanism of drug action. In a reverse-translational approach, neurotoxic potential of immune cells from MS patients (PBMC) and the metabolomic environment will be analysed following BTK treatment in a reverse-translational model of myelinated neurons of iPSCs of MS patients with different disease courses. In a collaboration, effects on EAE and primary cell lines will be assessed (PI Dr. Faissner). Results will be published in an international high-impact journal.

Methods:
The team of the Center for Neuroimmunology, Department of Neurology, is a world leader in translational neuroimmunology. The group uses the whole spectrum of state-of-the art neuroimmunology. The PhD student will learn handling of cell culture (primary, cell lines), deep immunophenotyping (FACS), analysis of transcriptome, proteome and metabolome, western blotting, in cooperation to induce and handle EAE mice.

Candidate Requirements: The PhD candidate must have an accomplished M. Sc degree. The candidate must have excellent knowledge about neuroimmunological principles and should have methodological experience with cell culture and animal handling. The candidate should be dedicated to science, diligent and reliable, flexible and a team-player. Very good English language skills are crucial.

Motivation for CSC application: The PIs have long-lasting international experience and received training at excellent neuroimmunological facilities. Following their doctoral thesis in Münster, Germany (Motte, department Prof. Wiendl, Neuroimmunology, University of Münster) and Bochum, Germany (Gisevius, department Prof. Gold, Neuroimmunology, Ruhr-University Bochum) they accomplished a post-doc at Center for Neuroimmunology, Department of Neurology Bochum in collaboration with Prof. Lars Fugger, Oxford Centre for Neuroinflammation and Prof. Luis Querol, Barcelona Neuromuscular center. The candidate will learn the whole spectrum of

state-of-the-art neuroimmunology (see method´s section). The candidate will receive a structured PhD program under the umbrella of the International Graduate School of Neuroscience. The candidate will be part of the Ruhr-University Research School for interdisciplinary skills development including methods courses, medical writing, presentation skill and others. The department of Neurology performs a weekly neuroimmunology seminar series with international speakers and weekly journal clubs. The candidate will work closely with clinician-scientists to get an insight into translational neuroimmunology and current debates about clinical and translational neuroimmunology.