CSC-RUB PhD Project Proposal

Title: Modulation of chronic inflammation in progressive Multiple Sclerosis

Sector of research: PhD

Degree awarded: Neuroscience (International Graduate School of Neuroscience)

Keywords: Multiple Sclerosis; progression; neuroprotection; chronic inflammation; microglia; BTK

Supervisor of PhD project:
Ass. Professor Dr. Simon Faissner; Department of Neurology, Ruhr-University Bochum, Germany, e-mail: simon.faissner@rub.de

Research focus of supervisor:

The research of Simon Faissner focuses on immunological and neurodegenerative mechanisms underlying chronic inflammation in Multiple Sclerosis and other inflammatory CNS disorders, especially the progressive phase of Multiple Sclerosis and related disorders such as neuromyelitis optica. The main goal of his research is the development of therapeutic approaches to target chronic inflammation and enhance neuroprotection in a translational approach. For this purpose, Dr. Faissner and his group use cell culture models (primary, cell lines) and animal models such as experimental autoimmune encephalomyelitis (EAE) and transgenic models such as opticospinal encephalomyelitis (OSE). One focus is to target inflammation of microglia and iron mediated neurotoxicity using neuroprotective medications in different MS models (Faissner S, Nature Comm, Nature Reviews). Moreover, the group focusses on markers of inflammation and degeneration in MS patients aiming at reducing the risk of MS progression.

Publications:

Publications last 5 years: 36 (Pubmed listed); 40 (Web of Science); 22 (Reviews and commentaries, not Pubmed listed)

H-Index last 5 years: 11 (Web of Science); 17 (Google Scholar)


Second Supervisor of PhD project: Dr. Jeremias Motte, Department of Neurology, Ruhr-University Bochum

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<th>Summary of research plan:</th>
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<td><strong>Background:</strong> Multiple sclerosis (MS) is a multifactorial disease of the CNS which leads to damage of the myelin sheath with consecutive chronic disability. Most patients (85%) present initially with a relapsing-remitting phenotype of the disease (RRMS) characterized by influx of leukocytes into the CNS, leading to damage of the myelin sheath and axonal damage with consecutive neurological symptoms. 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 important for progressive MS are undertreated so far. Medications which more efficiently target drivers of progression such as damage by deposition of iron and chronic inflammation are strongly desired by the MS population. Regarding this, several approaches have been pursued by me [1,3-5] and others. In this research proposal we seek to investigate how inflammation by microglia contributes to progression in a chronic MS mouse model. Moreover, we will investigate how a new class of medications targeting the Bruton´s tyrosine kinase might promote neuroprotection.</td>
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<td><strong>Study objective:</strong> Modulation of chronic inflammation in EAE.</td>
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<td><strong>Expected Results:</strong> Chronic inflammation in EAE will be targeted using inhibitors of BTK. We hypothesize that this approach will alter activation of innate immune cells and B cells, thereby promoting neuroprotection. Taking advantage of primary cells and cell lines, neuroprotective potential of BTK inhibition of microglia and immune cells will be analysed following BTK treatment in vitro. In a collaboration, effects on iPSCs will be assessed (PI Dr. Motte, Dr. Gisevius). Results will be published in an international high-impact journal.</td>
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<td><strong>Methods:</strong> The team of the Center for Neuroimmunology, Department of Neurology (group leader MS-research group Jun.-Prof. Dr. Faissner, head Prof. Dr. Ralf Gold), is a world leader in translational neuroimmunology. The group uses the whole spectrum of state-of-the art neuroimmunology. The PhD student will learn how to induce and handle EAE mice (immunization, scoring, harvest of organs), deep immunophenotyping (FACS), analysis of transcriptome, western blotting and handling of cell culture (primary, cell lines).</td>
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**Candidate Requirements:** The PhD candidate must have an accomplished MSc 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 PI has long-lasting international experience and received training at excellent neuroimmunological facilities. Following his doctoral thesis (*summa cum laude*, department Prof. Gold, Neuroimmunology, Ruhr-University Bochum) he accomplished a post-doc
at the Hotchkiss Brain´s Institute, University of Calgary, Canada (department Prof. V. W. Yong, former President of the International Society of Neuroimmunology). The candidate will learn the whole spectrum of state-of-the-art neuroimmunology (see method´s section). Moreover, the PI is part of the International Graduate School of Neuroscience, under which umbrella the candidate will receive a structured PhD program. 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.