

## CSC-RUB PhD Project Proposal

**Title:** The role of mitochondria at neuro-immune interfaces

**Sector of research:** Molecular and Cellular Neuroscience

**Degree awarded:** PhD in Neuroscience

**Keywords:** mitochondria, innate and adaptive immunity, neurodegeneration, neuroinflammation, microbiome, gut-brain axis, bioenergetics, cellular signaling, super-resolution microscopy

### Supervisor of PhD project:

Prof. Dr. Konstanze F. Winklhofer

Department of Molecular Cell Biology, Institute of Biochemistry and Pathobiochemistry  
Ruhr University Bochum, Universitätsstrasse 150, 44801 Bochum

[konstanze.winklhofer@rub.de](mailto:konstanze.winklhofer@rub.de)

[https://twitter.com/winklhofer\\_lab](https://twitter.com/winklhofer_lab)

### Research focus of supervisor:

The major aim of our research is to uncover molecular mechanisms underlying neurodegenerative diseases, which is a prerequisite to develop causative therapeutic strategies for these disorders. Specifically, we are studying the role of the proteostasis network in preventing protein aggregation and in promoting degradation of misfolded proteins linked to neurodegeneration. Another focus of our work are mitochondria as key organelles in orchestrating cellular signaling, interorganellar communication, and in regulating viability and bioenergetics. There is increasing evidence that mitochondria play an important role not only in neurodegenerative but also in neuroinflammatory diseases, such as Multiple Sclerosis. We therefore are studying which mitochondrial pathways are implicated in neuroprotective and anti-inflammatory signaling.

We have a longstanding expertise in cell biology, molecular biology, protein biochemistry, and advanced cellular imaging, including super-resolution microscopy and live cell imaging.

### Publications:

van Well EM, Bader V, Patra M, Sánchez-Vicente A, Meschede J, Furthmann N, Schnack C, Blusch A, Longworth J, Petrasch-Parwez E, Mori K, Arzberger T, Trümbach D, Angersbach L, Showkat C, Sehr DA, Berlemann LA, Goldmann P, Clement AM, Behl C, Woerner AC, Saft C, Wurst W, Haass C, Ellrichmann G, Gold R, Dittmar G, Hipp MS, Hartl FU, Tatzelt J, **Winklhofer KF** (2019). A protein quality control pathway regulated by linear ubiquitination. **EMBO J** 38(9): e100730.

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, Gattermann 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**, 2020 Mar 19;180(6):1067-1080.e16.

Woerner AC, Frottin F, Hornburg D, Feng LR, Meissner F, Patra M, Tatzelt J, Mann M, **Winklhofer KF**, Hartl FU, Hipp MS (2016). Cytoplasmic protein aggregates interfere with nucleo-cytoplasmic transport of protein and RNA. **Science** 351(6269): 173-6.

Müller-Rischart AK, Pils A, Beaudette P, Hadian K, Deinlein A, Funke M, Patra M, Motori E, Schweimer C, Kuhn PH, Hrelia S, Lichtenthaler SF, Wurst W, Trümbach D, Langer T, Krappmann D, Dittmar G, Tatzelt J, **Winklhofer KF** (2013). The E3 ligase parkin maintains mitochondrial integrity by increasing linear ubiquitination of NEMO. **Mol Cell** 49(5): 908-21.

Henn IH, Bouman L, Schlehe JS, Schlierf A, Schramm JE, Wegener E, Nakaso K, Culmsee C, Berninger B, Krappmann D, Tatzelt J, **Winklhofer KF** (2007). Parkin mediates neuroprotection through activation of IKK/NF- $\kappa$ B signaling. **J Neurosci** 27: 1868-1878.

### Summary of research plan

#### Background:

Mitochondria are essential organelles for the maintenance of neuronal integrity, based on their manifold functions in regulating cellular metabolism and coordinating cell death and viability pathways. Accordingly, mitochondrial damage, dysfunction, or ineffective mitochondrial quality control is associated with neurological disorders and can occur as a cause or consequence of pathological processes. Moreover, mitochondria play a central role in orchestrating both innate and adaptive immune responses, thereby providing a link between neurodegenerative and neuroinflammatory processes. We recently found that specific metabolites from gut microbiota decrease disease progression and neurodegeneration in Multiple Sclerosis by restoring mitochondrial function in regulatory T cells (Duscha et al., Cell, 2020).

#### Study objective:

The aims of the project are

- to study which mitochondrial aspects are affected by gut microbe metabolites in neurons and immune cells and which signal transduction pathways are mediating these effects
- to get insight into mechanisms of how mitochondria influence neuroinflammation and neurodegeneration.

#### Expected Results:

By identifying the molecular targets of protective metabolites from gut microbes and the pathways mediating their effects we expect insights into mechanisms implicated in both neuroinflammatory and neurodegenerative diseases. These targets may be exploited for therapeutic strategies to suppress neuroinflammation and to halt neurodegenerative processes.

At least one research article and one review article should be published based on this project.

**Methods:**

Advanced cellular imaging (super-resolution microscopy, live cell imaging), state-of-the-art techniques in cell biology, biochemistry, molecular biology, such as CRISPR/Cas genome editing, mitochondrial bioenergetics, ELISA, cellular signaling assays, immunoprecipitation, immunoblotting, immunocytochemistry, immunohistochemistry, reporter gene assays, mass spectrometry.

**Candidate Requirements:**

We are seeking a highly motivated, enthusiastic candidate with good communication skills, fluency in English and the ability for teamwork.

**Motivation for CSC application** (max 250 words):

We offer a stimulating international research environment with numerous national and international collaborations, integration in research centers (RESOLV Cluster of Excellence, DFG Research Unit 2848, Parkin Consortium of the Michael J. Fox Foundation, International Max Planck Research School for Living Matter), and admission to the Ruhr University Research School for interdisciplinary skills development and mentoring. Laboratory work is supplemented by seminars, summer schools, elective workshops, career development training and participation in national and international conferences.