CSC-RUB PhD Project Proposal

Title: Improved biomarker identification pipeline in neurodegenerative diseases

Sector of research: Proteomics and Bioinformatics in Neuroscience

Degree awarded: PhD in Neuroscience

Keywords: neurodegenerative disorders, (functional) proteomics, protein chemistry, mass spectrometry, method development, bioinformatics, biostatistics, machine learning

Supervisor of PhD project: Prof. Dr. Katrin Marcus & PD Dr. Martin Eisenacher, Medizinisches Proteom-Center & Center for Protein Diagnostics, Medical faculty, Ruhr-University Bochum

Research focus of supervisor: One of our research focuses lies on the elucidation of pathomechanisms underlying neurodegenerative processes as well as the identification of e.g. diagnostic and prognostic biomarkers for neurodegenerative diseases. With state-of-the-art proteomics methods such as mass spectrometry, laser microdissection, immune-based methods and protein chips complemented by sophisticated bioinformatics strategies and high performance computing infrastructure we detect altered proteins associated to Parkinson's (PD) and Alzheimer's disease (AD). Prof. Marcus as Biochemist and Dr. Eisenacher as Bioinformatician form an optimal team for the supervision of the proposed PhD-project.

Publications:

1. MaCPepDB: a database to quickly access all tryptic peptides of the UniProtKB (2021) Uszkoreit J, Winkelhardt, D, Barkovits K, Wulf M, Roocke S, **Marcus K, Eisenacher M**, J Proteome Res, 20(4), 2145-2150
2. Proteomic Characterization of Synaptosomes from Human Substantia Nigra Indicates Altered Mitochondrial Translation in Parkinson's Disease (2020) Plum S, Eggers B, Helling S, Stepath M, Theiss C, Leite REP, Molina M, Grinberg LT, Riederer P, Gerlach M, May C, **Marcus K**, Cells, 9(12), 2580
3. A patient-based model of RNA mis-splicing uncovers treatment targets in Parkinson's disease, Boussaad I, Obermaier CD, Hanss Z, Bobbili DR, Bolognin S, Glaab E, Wołyńska K, Weisschuh N, De Conti L, May C, Giesert F, Grossmann D, Lambert A, Kirchen S, Biryukov M, Burbulla LF, Massart F, Bohler J, Cruciani G, Schmid B, Kurz-Drexler A, Parkinson Disease Genetic Sequencing Consortium (PDGSC), May P, Duga S, Klein C, Schwamborn JC, **Marcus K**, Woitalla D, Vogt DM, Weisenhorn J, Wurst W, Baralle M, Krainc D, Gasser T, Wissinger B, Krüger R (2020), Science Transl Med, 12(560), eaau3960
4. Quantification of artificial blood contamination in CSF and its impact on the quantitative analysis of alpha-synuclein, Barkovits K, Kruse N, Uszkoreit J, Linden A, Tönges L, Pfeiffer K, Mollenhauer B, **Marcus K**, (2020) Cells, 9(2), pii: E370
5. Reproducibility, specificity and accuracy of relative quantification using spectral library-based data-independent acquisition, Barkovits K, Pacharra S, Pfeiffer K, Steinbach S, **Eisenacher M**, **Marcus K*** & Uszkoreit J* (2020) Mol Cell Proteomics, 19(1),181-197

H-Index and No of publications (2016-2021)

Prof. K. Marcus: H-Index: 13, No of Publications: 88

PD Dr. M. Eisenacher: H-Index: 15, No of Publications: 56

Summary of research plan

Background: Protein and lipid biomarkers are the focus of many studies investigating central nervous system disorders because the main issue for the clinical diagnosis of such disorders is still nonspecific clinical symptomatology. Thus, new biomarkers reliably and easily detectable in liquid biopsies (CSF and/or plasma) are urgently needed. Indeed, the classification of patients is complicated by the heterogeneity of the clinical picture of the disease. E.g. Parkinson's disease in particular cannot be generalised as there are many different subtypes. Moreover, proteomic and lipidomic analysis of body fluids is still a challenge due to their complexity.

Study objective: Our aim is to

- optimise a strategy for subgroup identification of PD and AD patients and respective control samples on the basis of medical measurement/clinical data (routine medical measurements such as laboratory values, sleep measurements, MRI and ECG, as well as psychological and motor questionnaires and tests). These may be “more specific / homogeneous” subgroups within an experimental group or even yet unknown disease subgroups.
- develop new mass spectrometric strategies and bioinformatics workflows for an improved detection and quantification of difficult-to-access proteins, peptides and lipids in CSF and plasma.

Expected Results: Our preliminary results indicate that the classification of patients based on clinical data improves a selection of samples for our subsequent proteomics and lipidomics studies. Those results should be transferred to other patient cohorts and verified. Moreover, we expect our new mass spectrometric methods to improve protein analysis in general which is of high interest for the whole proteomics community. The ultimate goal is to identify new biomarkers for PD and AD, or for specific subgroups of those patients, in order to improve clinical diagnosis.

Methods used in this project: Protein extraction and separation methods, HPLC, mass spectrometry (DDA, DIA, PRM), bioinformatics and biostatistics methods (multivariate methods like clustering such as K-means, density-based, hierarchical methods and univariate measures such as t-test to characterize significant differences between subgroups). All infrastructure needed for successful implementation of the studies is available at MPC.

Candidate Requirements: We welcome applications from students of biology, biochemistry, chemistry, biotechnology, bioinformatics or a related field of study with a keen interest in medical research and cutting-edge bioanalytical methods. Preferable are experiences in one or more of the following fields: instrumental analytics, mass spectrometry, proteomics,

lipidomics, nanoHPLC, UHPLC. Besides creativity, a strong ability for problem solving combined with an enthusiasm for scientific research is highly desirable. Teamwork and good communication skills, fluent English as well as the ability to work in an interdisciplinary field of research are necessary.

Motivation for CSC application: We are one of the leading institutes in Europe for proteomic analysis and are equipped with high end and state-of-the-art equipment, e.g. including five mass spectrometers, 100s of terabyte data storage and high-performance servers with virtualization and cloud functionality. We offer a qualified introduction to the methods and topic, individual supervision (each PhD candidate is practically closely accompanied by a PostDoc or highly experienced PhD student), work in a young and committed interdisciplinary research team. The candidate will be integrated into the interfaculty RUB research school which allows the members to participate in specialized courses to train their personal in parallel to their scientific skills.