2020 Call for projects

Investigation of neurofilament turnover in ALS patients using stable isotope labeling kinetics

Acronym: SILK- ALS

Principal Investigator: Markus Otto

Grant: 166 000€

Duration: two years

Summary of the research project

The measurement of neurofilaments (Nf) in CSF and blood is now an established biomarker used in differential diagnosis of ALS. We and others showed that increased levels of Nf appear at the time of disease onset and stay constant during disease progression. However, the origin and role of Nf increase in ALS pathophysiology is still unclear. It is hypothesized that increased Nf levels are due to Nf release from degenerating axons but this cannot explain constant Nf levels during disease progression. The latter could indicate an active secretion of Nf from axons which would also imply an active role of Nf in ALS pathophysiology, in agreement with the link of Nf mutations to ALS. To elucidate the role of Nf in ALS, the study of Nf turnover in ALS patients would give important information about alterations of Nf metabolism and could also show whether Nf might be a possible drug target. This is also true for the proteins UCHL1, MAP2, CAPG and GPNMB which we recently discovered to be changed in ALS and the study of their turnover would give additional information about the origin of these changes.

Stable isotope labeling kinetics (SILK) is an established tool to study protein turnover in human individuals. By administration (oral or i.v.) of a stable isotope-labeled amino acid (13C6-Leu), mass spectrometry can be used to monitor the incorporation of 13C6-Leu into proteins over time and gives information about their synthesis and turnover rate.

We recently established a proteomic workflow enabling the measurement of even low abundant proteins such as neurofilaments in CSF on a proteomic scale using a reasonable amount of CSF (200µL). Thereby, we could confirm increased Nf levels in CSF of ALS patients by mass spectrometry and thus with an independent technique to the normally used immunoassays. In addition, we discovered new protein changes in ALS such as UCHL1, MAP2, CAPG and GPNMB which might be used as biomarkers and involved in ALS pathophysiology.

Investigation of neurofilament turnover in ALS patients using stable isotope labeling kinetics

The aim of the present project is to study protein turnover of neurofilaments, UCHL1, MAP2, CAPG, GPNMB and other proteins in CSF of ALS and control patients using SILK, proteomics and targeted mass spectrometry.

Potential clinical relevance of the research:

The turnover data will contribute to elucidate the origin of increased neurofilament levels in CSF/blood in ALS. This is important for interpretation of changes in CSF/blood and will improve our understanding of the role of neurofilaments in ALS pathophysiology. This will provide important information whether neurofilaments and other proteins are markers of neurodegeneration or can be used as pharmacodynamic markers in clinical trials. Furthermore, we can identify new proteins with changed turnover in ALS and contribute to the understanding of ALS pathophysiology.

The study will be conducted by Prof. Dr. Markus Otto, Professor for Neurology, head of the outpatient unit, Vice-chair Department of Neurology, head of the research laboratory for Neurodegenerative Diseases Diagnostics, Department of Neurology, at Ulm University, Germany.
Other investigator: Dr. Patrick Oeckl, Research Scientist in neuroproteomics and biomarker research, Department of Neurology, Ulm University Hospital.

Markus Otto, the Thierry Latran foundation annual meeting.