ProtALS - Proteomic approaches for subtyping of ALS patients

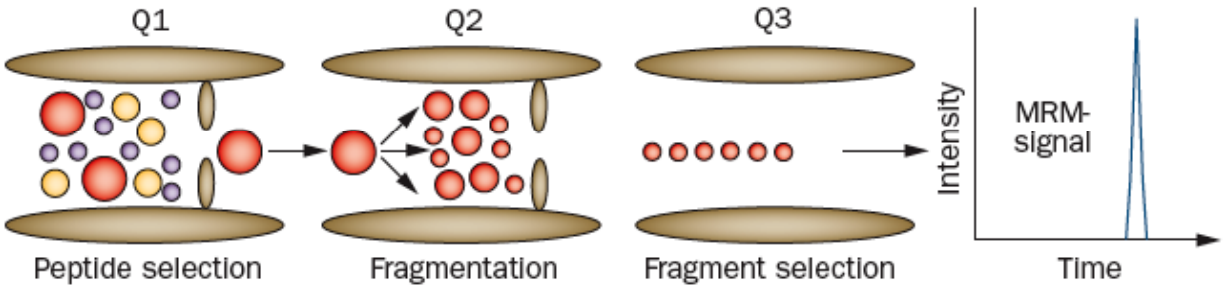
Call for projects 2011
Grant: 180 000 €
Project Duration: 2 years

Investigators: Markus Otto, Johannes Brettschneider, Olaf Jahn, University of Ulm, Germany

Updated results December 2012

So far, it is unknown why some patients with ALS deteriorate much slower and survive much longer than others. Consequently, an important challenge to ALS research is to find out how endogenous factors modify the disease to account for these different courses.

The discovery of marker proteins (biomarkers) associated with different rates of progression could help us to understand the underlying biological mechanisms and could offer new targets for disease-modifying therapies. Furthermore, such markers could help to identify beneficial drugs in clinical trials and support optimum planning of patient care. The cerebrospinal fluid (CSF) is anatomically close to the sites of disease in brain and spinal cord. It could therefore reflect pathological changes associated with the disease. Within the first year of our project we have now set-up a technique to analyse the whole CSF protein content in patients with different rates of disease progression. In a gel-free and antibody free approach (so called multiple reaction monitoring) we were able to quantify proteins which were so far not detectable by other methods. By using this approach we hope to gain a better understanding of the mechanisms which determine survival and disease progression in ALS.



Workflow of an MRM analysis inside a triple quadrupole mass spectrometer.
Abbreviations: MRM, multiple reaction monitoring; Q, quadrupole

Proteomic approaches for subtyping of ALS patients

Markus Otto, Ulm, Germany

Grant: 180 000 €

ALS is characterized by a very heterogeneous clinical presentation and course of disease. Despite a uniformly fatal outcome after a median of 2–4 years, the disease shows a wide range of survival times from a few months to several decades. Furthermore, subtypes of disease with a predominant involvement of the upper or lower motor neurons can be associated with prolonged survival. Similarly, phenotypes that predominantly affect specific body areas can be associated with extremes of disease progression e.g., presentation with a flail arm syndrome tends to follow a slower disease course , whereas bulbar-onset disease is usually associated with a more rapid decline.

So far, it is unknown why some patients with ALS deteriorate much slower and survive much longer than others. Consequently, an important challenge to ALS research is to find out how endogenous factors modify the disease to account for these different courses.

The need for biomarkers of disease progression: A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathological process or a pharmacological response to a therapeutic intervention. The discovery of biomarkers associated with different phenotypes and rates of progression could offer new insights into the pathophysiological determinants of disease progression in ALS. They could further our understanding how disease expression is modified by endogenous factors once the pathological process has been triggered. Such markers could support the identification of patients who are likely to have unusually fast (or slow) progression of disease, and could thus support optimum planning of care (e.g. earlier access to non-invasive ventilation) . Presently, clinical trials in ALS mainly rely on binary outcome measures such as survival time, which takes many months to interpret. They have applied rather insensitive, non-parametric surrogate markers as exemplified by forced vital capacity and the revised ALS functional rating scale (ALSFRS-R) to assess progression of disease. The discovery of sensitive biomarkers of disease progression could support the rapid identification of disease modifying beneficial drugs and could help to decrease the length of clinical trials.

The cerebrospinal fluid (CSF) is anatomically close to the sites of disease in brain and spinal cord. It could therefore reflect pathological changes associated with the disease. To detect changes associated with different rates of disease progression, we plan to analyze the whole CSF protein content (proteome) in patients with different rates of disease progression. To achieve this aim, we plan to implement highly sensitive modern tools which can comparatively analyze the proteome of different subgroups of disease. These complementary methods include a two dimensional gel-based approach (so called 2D-DIGE) and a gel-free approach (so called iTRAQ). Both methods have been established in our laboratory and optimized for the analysis of CSF. By using these methods to analyze the CSF of a large group of patients, we hope to gain a better understanding of the mechanisms which determine survival and disease progression in ALS.