PremodiALS

A premotor disease signature for ALS

Amyotrophic lateral sclerosis (ALS) is the most frequent motoneuron disease with a devastating prognosis. Even today, it takes on average 12 months from the onset of motor symptoms to establish the diagnosis of ALS and approximately half of the patients are initially misdiagnosed. Although several molecules have been proposed as biomarker candidates, such as neurofilaments in serum and cerebrospinal fluid (CSF), or soluble $p75^{ECD}$ in urine, a clinically established signature for an early or even premotor diagnosis of ALS is not available. Due to the already advanced disease stage at the time of diagnosis as well as rapid disease progression, an early diagnosis is mandatory for efficacious disease-modifying therapies. About 10% of all ALS patients have a genetic cause and genetic testing can identify premotor gene mutation carriers (PGMC) among family members of these familial ALS patients. PGMC are at risk to develop the disease due to the causative gene mutation, but have not yet developed motor symptoms.

In this project, we will develop a clinicomolecular fingerprint of PGMC that will shed light on the molecular pathogenesis of ALS and allow for a timelier diagnosis. We will recruit PGMC (n=80) and control subjects (n=40), through expert centres and their networks in Germany, France, Switzerland, Israel. Longitudinal data and CSF samples from 20 gene carriers who have already developed motor symptoms of ALS will also be included through cooperation with M. Benatar/USA. All subjects will be asked to (1) complete a questionnaire about current and past clinical symptoms and environmental factors spanning the last 10 years of their life, to (2) donate biological samples (blood, urine, tear fluid, and CSF), and perform a smell test. Tear fluid, blood plasma and CSF samples will be used to analyse the proteomic profile of the PGMC cohort using a combination of discovery mass spectrometry and targeted immunoassays. In addition, we will test for established biomarker candidates, such as Nf-L (blood), $sp75^{ECD}$ (urine), tau/p-tau and GFAP (CSF). Clinical data obtained in the questionnaire and molecular data will be integrated to create a clinico-molecular fingerprint of PGMC. Two evaluations will be performed at an interval of one year to characterize the evolution of the fingerprint in ALS and control subjects.

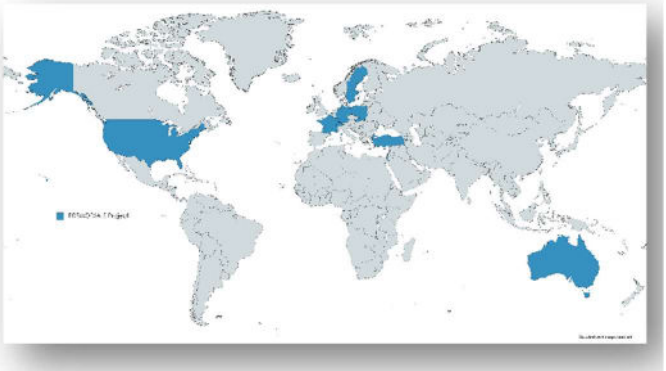
Previously obtained data from multiple studies in ALS patients and control subjects will guide our analysis to identify features in the PGMC fingerprint that have the best discriminatory power for ALS: The questionnaire will leverage the ongoing EARLY-ALS trial which assesses early symptoms and environmental influences based on a patient survey in several hundreds of ALS patients in Germany. Data from the EARLY-ALS trial will be used to adapt the questions for the present project selecting those that most accurately differentiate between ALS and control subjects.

Furthermore, we have characterized the multi-omic landscape of CSF in ALS patients (within the scope of the currently funded E-Rare MAXOMOD consortium) and we recently extended this analysis by the differential proteome derived from tear fluid of ALS patients. Finally, the PGMC fingerprint will be subjected to biological validation on a cohort with pure motor symptoms, which comprises patients at very early stages of ALS, or one of its clinical mimics (n=100). This cohort will be collected in parallel at all clinical sites. We expect that the clinicomolecular fingerprint will not only improve diagnostic accuracy, but also yield information about molecular and pathophysiological causes driving ALS, ultimately empowering efficacious treatment strategies.

Total Funding : 1.91 M€

Duration : 3 years

Coordinator : Prof. Dr. Paul Lingor
☎ : +49 89 4140 8257
✉ : paul.lingor@tum.de



Consortium Members

Paul Lingor, MD	Department of Neurology, Klinikum rechts der Isar der TU München, München, Germany
Christof Lenz	Universitätsmedizin Göttingen, Germany
Michael Menden	Helmholz-Zentrum München, Germany
Nicholas Ashton	Gothenburg University, Sweden
Wojchiech Kuban	Maj Institute of Pharmacology, PAS, Kraków, Poland
Philippe Corcia	CHU Tours, France
Hilmi Uysal	Akdeniz University, Neurology Department, Turkey
Norbert Zilka	Institute of Neuroimmunology Slovak Academy of Sciences, Slovakia
Markus Weber	ALS-Clinic St. Gallen, Switzerland
Michael Benatar	University of Miami, USA
Yossef Lerner	Hebrew University - Hadassah Medical Center Jerusalem, Israel
Mary-Louise Rogers	Flinders University, Australia