2020 Call for projects

Preclinical study for inhibiting neuroinflammation in C9orf72 ALS

Acronym: C9-Inflam

Principal Investigator: Dieter Edbauer

Grant: 200 000€

Duration: three years

Summary of the research project

Massive inflammation particularly in the corticospinal tract is a key feature of ALS. Biomarkers for neurodegeneration and inflammation strongly increase at the clinical onset in genetic ALS but it is unclear whether inflammation contributes to disease progression or reflects a protective response. We developed a fast-progressing mouse model for C9orf72 ALS expressing poly-GA that shows motoneuron loss, paralysis and weight loss requiring termination at ~6 weeks. Transcriptomic analysis of these mice revealed an inflammatory response distinct from the "disease-associated microglia" signature reported in Alzheimer mouse models, but similar to interferon-enriched microglia populations found in acute injury models. We found this interferon (IFN) signature also in sporadic ALS with further enrichment in C9orf72 cases. In addition, our mouse model shows pronounced activation of the complement system that is also altered sporadic ALS possibly by promoting synaptic pruning. With this proposal, I will test the causal role of interferon signaling and complement activation in ALS in various C9orf72 mouse models. Pharmacological depletion of microglia and inhibition of IFN-signaling enables therapeutic studies symptomatic mice. Viral expression of antibodies and decoys blocking complement and IFN allows fast screening of several molecular targets in the IFN and complement system, which will be confirmed using knockout mice and targeted pharmacological intervention in symptomatic mice. The key objective is to identify compounds targeting inflammation for repurposing in ALS patients.

Potential clinical relevance of the research:

All initial studies are done in a fast C9orf72 mouse model, but the IFN and complement pathway are also activated in sporadic ALS and we will replicate positive data in TDP-43 mice. Several small molecules and (human-specific) therapeutic antibodies targeting the IFN and complement pathway are approved for other diseases. For example, an antibody (eculizubmab) blocking complement effector

function is the standard of care for patients with paroxysmal nocturnal hemoglobinuria. We will test the analogous mouse-specific antibody in our ALS models. Several antibodies neutralizing IFN-α/β (anifrolumab) and IFN-γ (fontolizumab) are approved or in development for systemic lupus erythematosus. We will block IFN signaling using approved drugs in mice. Based on promising preclinical data in mice, studies for repurposing these drugs for ALS could be initiated quickly.

Our new mouse model that will be used heavily for the project has just been published:

LaClair, K.D., Zhou, Q., Michaelsen, M. et al. Congenic expression of poly-GA but not poly-PR in mice triggers selective neuron loss and interferon responses found in C9orf72 ALS.

Acta Neuropathol ***140,*** *121–142 (2020).* *https://doi.org/10.1007/s00401-020-02176-0*

The study will be conducted by Prof. Dr. med. Dieter Edbauer, Research Group Leader, Cell Biology of Neurodegeneration, at the Munich site of the German Center for Neurodegenerative Diseases.