2020 Call for projects

Therapeutic inhibition of perivascular fibroblast activity in ALS models

Acronym: FIB- ALS

Principal Investigator: Sebastian Lewandowski

Grant: 187 000€

Duration: three years

Summary of the research project

ALS patients have highly inconsistent life expectancy outcomes, which complicates interpretations and design of clinical trials. This clinical variability likely represents an underlying complexity of cell type functions within the central nervous system, which modifies net survival outcomes. In contrast to the often-analyzed mechanisms within neurons, we study cells in blood vessels, which deliver oxygen and nutrients to the brain tissue, allow immune cell infiltration and can likely affect the timing of disease onset and survival in ALS patients. We have recently discovered that perivascular fibroblasts become active before the onset of neuroinflammation and death of neuronal cells in ALS mouse models. These fibroblasts disrupt cerebral blood vessel structures with specific proteins. We have recently shown that in sporadic ALS patients the SPP1 chemokine accumulates in enlarged perivascular spaces, facilitating infiltration, and that levels indicate short survival at disease diagnosis in ALS patients.

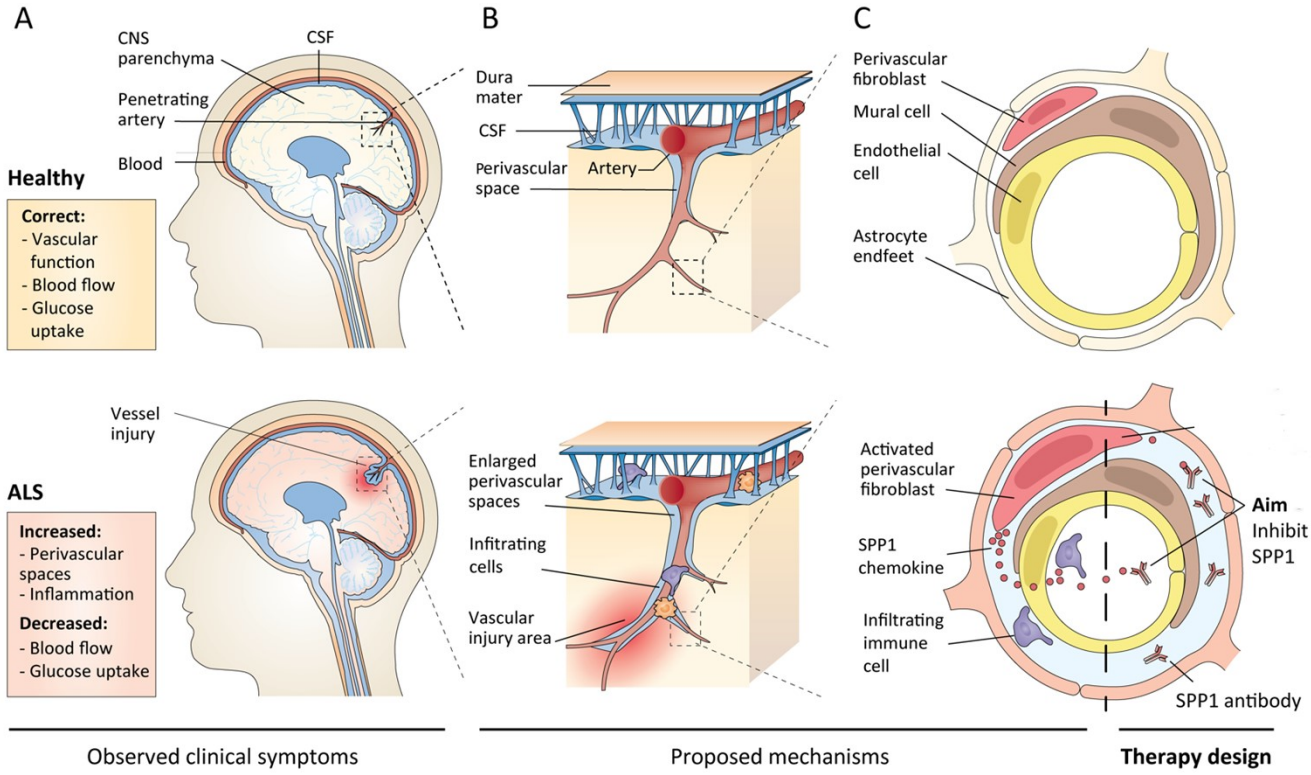
Our project aims to (1) inhibit fibroblast-derived SPP1 protein chemokine activity in order to reduce neuroinflammation. Since our preliminary work showed that SPP1 levels in plasma of ALS patients can reliably indicate short survival we also aim to (2) standardize the tools to detect SPP1 protein in plasma and cerebrospinal fluid of ALS patients and refine the survival prediction value for clinical prognosis. Completion of our project could help to develop preclinical therapeutic tools to inhibit the proinflammatory SPP1 chemokine and improve prognostic accuracy of ALS patients at disease diagnosis.

Potential clinical relevance of the research:

Aggravated neuroinflammation and immune cell infiltration in ALS patients provide a strong rationale for therapeutic intervention, but only few attempts have been reported.

Since SPP1 pro-inflammatory function is successfully inhibited by antibodies in a clinical trial, they

could become a repurposed therapeutic tool for ALS. Completion of our project could help to develop preclinical therapeutic tools to inhibit the proinflammatory SPP1 chemokine and improve prognostic accuracy of ALS patients at disease diagnosis.

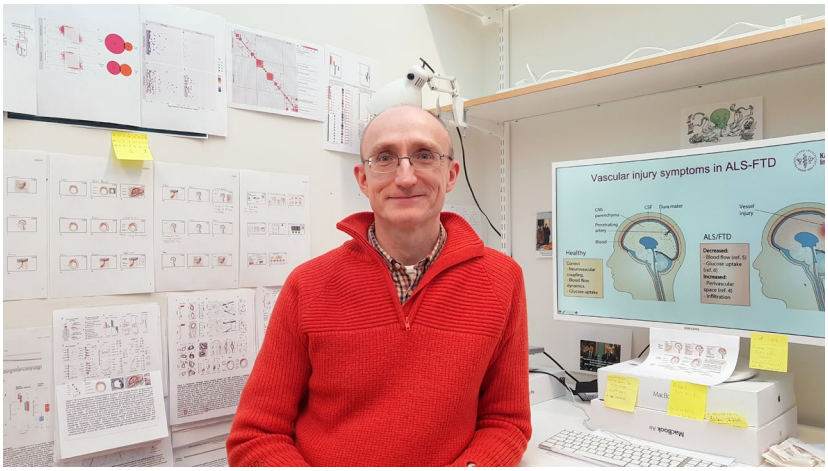


Vascular dysfunction symptoms and proposed treatment strategy in ALS.

(A) Reported vascular injury symptoms in ALS patients.

(B) Enlarged perivascular spaces are continuous with CSF circulation and allow immune cell infiltration in the injured area.

(C) Perivascular fibroblasts (PVF) secrete the SPP1 chemokine within the enlarged perivascular spaces which attracts immune cell infiltration. Therapy design: we propose to inhibit the SPP1 chemokine with neutralizing antibodies as treatment to reduce neuroinflammation.



The study will be conducted by Dr. Sebastian Lewandowski, Researcher, Clinical Neuroscience Department, Karolinska Institute, Stockholm, Sweden.