# Normalization of the blood-brain barrier deficiency in ALS with inhibitors of the Platelet-Derived Growth Factor CC (PDGF-CC) pathway

**Investigator: Ulf Eriksson, Stockholm, Sweden**

**Grant: 160 000€**

**Project duration: two years**

Amyotrophic lateral sclerosis (ALS) is a condition where motor neuron cells, controlling muscle function located in the brain and spinal cord, die resulting in paralysis and patient death. Brain and spinal cord need continuous supply of nutrients from the vascular system. Since some of the blood components are harmful to the brain a barrier exists between the two, called the blood-brain barrier (BBB). Malfunction of this barrier has been observed in several neurological conditions including Alzheimer's, Parkinson's disease and ALS.

Our group has been interested in finding ways of preventing the BBB disruption. We have found that a protein called platelet-derived growth factor C (PDGF-CC) is involved in the opening of the barrier in ischemic stroke, where blood circulation to the brain is halted. We have observed In the SOD1 G93A ALS mouse model that the PDGF-CC protein becomes upregulated in the spinal cords on both protein and mRNA levels. Additionally, the blood vessels with increased uptake of IgG are expressing the receptor for PDGF-CC called PDGF receptor alpha (PDGFRα). Imatinib – a small molecule inhibitor of PDGFRα have been able to decrease the vascular uptake of IgG as well as other exogenous tracers.

In the proposed study we plan to observe the effect of BBB restoration on the course of ALS in the SOD1 G93A mouse model. By treatment with Imatinib and by crossing of the G93A ALS mice with another strain displaying

**The neurovascular unit**

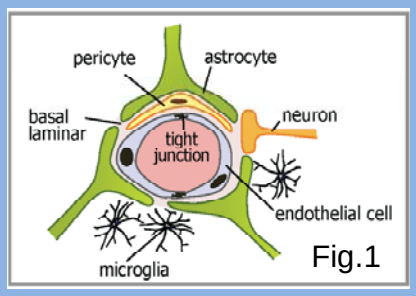


Fig.1

Vascular and nervous systems have evolved an interface known as the **blood brain barrier** (BBB). The functional component of this crossing point is termed the **neurovascular unit** (NVU). The NVU consists of an endothelial cell monolayer, neighbouring pericytes or smooth muscle cells and astrocytic endfeet (Fig.1). Its main function is to maintain the barrier properties and simultaneously orchestrate metabolite exchange between blood and CNS parenchyma.

genetic PDGF-CC deficiency we expect to decrease the vascular permeability before the disease onset and diminish the severity of ALS symptoms. A successful outcome of this study would allow novel means of therapy for human forms of ALS.

The research will be done at the Karolinska Institute in Sweden in the division of Vascular Biology. The Fondation Thierry Latran is the first to sponsor ALS focused research in our group.

**Ulf Eriksson** is a Professor of Vascular Biochemistry, at the Division of Vascular Biology within the Department of Medical Biochemistry and Biophysics at Karolinska Institutet in Stockholm, Sweden.

**His five most relevant primary research articles are :**

1. Su, EJ, et al. Activation of PDGF-CC by plasminogen activator impairs blood brain barrier integrity during ischemic stroke. **Nature Medicine**, 14;731-737, 2008.
2. Poesen, K, et al. Novel role for VEGF-receptor-1 and its ligand VEGF-B in motor neuron degeneration. **Journal of Neuroscience**, 28:10451-10459, 2008.
3. Hagberg, CE, et al. Vascular Endothelial Growth Factor B controls endothelial fatty acid uptake. **Nature** 464:917-921, 2010
4. Fredriksson L, et al. Platelet-derived growth factor C deficiency leads to abnormal cerebral vascularization, loss of neuroependymal integrity, and ventricular abnormalities. **American Journal of Pathology** 180:1136-1144, 2012,
5. Abrams, MB, et al. Imatinib enhances functional outcome after spinal cord injury. **Plos One**, 7:e38760, 2012

The Eriksson lab (from left): Hong Li, Xun Wang, Hanna Gladh, Sebastian Lewandowski, Annika Mehlem, Manuel Zeitelhofer, Christine Mössinger, Daniel Nyqvist, Erika Folestad, Lars Muhl, Ingrid Nilsson, Sofia Wittgren, Annelie Falkevall, Ulf Eriksson