An innovative clinically applicable CD95L blocking fusion protein to target peripheral inflammatory monocytes in ALS

Acronym: innateTARGET

Principal Investigator: Pr Jochen Weishaupt

Grant: 98,500€

Project duration: two years

Summary of the research project

Most recent research indicates that an inflammatory type of white blood cells, called monocytes, may be centrally involved in the disease process of ALS. There are principally two different types of monocytes: Aggressive, pro-inflammatory monocytes and more “regenerative” monocytes without detrimental effects in neurodegeneration. Therefore, monocytes represent a promising novel therapeutic target. Drugs acting on monocytes would probably not even be required to pass the so-called blood-brain barrier that hinders many drugs from reaching their site of action. We have found evidence that the protein CD95L shifts the balance towards the inflammatory type of monocytes in neurodegenerative diseases.

Consequently, our project evaluates a **highly innovative, first-in-class type of molecule (APG101)** that is able to efficiently block CD95L and thereby prevents the shift from regenerative monocytes to the aggressive, damaging type. Importantly, the novel drug APG101 has not only been studied in mice and monkeys but has even been successfully tested in recent clinical trials for different diseases other than ALS (e.g. glioblastoma multiforme, myelodysplastic syndromes; www.apogenix.de). The results were most encouraging and without any toxicity or safety concerns. Therefore, even though our study will also be of high basic science interest regarding one of the most recent scientific questions in ALS, the project will clearly focus on providing the final data basis for **direct translation of the CD95L blocking protein APG101 into a clinical ALS trial**, which could realistically be the next step taken after the work proposed in this application

The main goal of the study is to prepare the final preclinical data basis for an **immediate translation of our innovative therapeutic approach** for clinical evaluation in ALS patients. In cooperation with the German Cancer Research Center (DKFZ) and Apogenix GmbH (Heidelberg, Germany), we will test species specific CD95L blocking fusion proteins. The humanized CD95ECD-Fc fusion protein APG101 (Apocept) has very recently been successfully tested for a different neurological application in a clinical study (see www.apogenix.de).

Jochen Weishaupt is Professor of neurodegeneration, group leader in molecular neurology and senior neurologist in the neurology department of the University of Ulm. He is also the coordinator of the ALS outpatient clinic.

Pr Weishaupts' five recent publications relevant to this research:

1. C. Ingre, J.E. Landers, N. Rizik, A.E. Volk, C. Akimoto, A. Birve, A. Hübers, P.J. Keagle, K. Piotrowska, R. Press, P.M. Andersen, A.C. Ludolph, J.H. **Weishaupt**. A novel phosphorylation site mutation in profilin 1 revealed in a large screen of US, Nordic, and German amyotrophic lateral sclerosis/frontotemporal dementia cohorts. ***Neurobiol Aging***, 2012 Nov 8. [Epub ahead of print]
2. T. Frank, F. Klinker, B.H. Falkenburger, R. Laage, F. Lühder, B. Göricke, A. Schneider, H. Neurath, H. Desel, D. Liebetanz, M. Bähr, J.H. **Weishaupt**. PEGylated Granulocyte-Colony Stimulating Factor conveys long-term neuroprotection and improves functional outcome in a model of Parkinson´s disease. ***Brain***, 2012, 135: 1914-25.
3. P. Krumova, E. Meulmeester, M. Garrido, M. Tirard, H.-H. Hsiao, P. Karpinar, Zweckstetter, H. Urlaub, N. Brose, S. Kügler, F. Melchior, M. Bähr, J.H. **Weishaupt**. Sumoylation regulates α-synuclein toxicity and aggregation**. *J Cell Biol***, 2011, 194: 49-60.
4. S. Ganesan, G. Rohde, K. Eckermann, K. Sroka, M.K. Schaefer, C.P. Dohm, P. Kermer, G. Haase, F. Wouters, M. Bähr, J.H. **Weishaupt**. Mutant SOD1 detoxification mechanisms in intact single cells. ***Cell Death Differ*** , 2008, 15: 312-21.
5. K. Meuer, I.E. Suppanz, P. Lingor, V. Planchamp, B. Göricke, L. Fichtner, G.H. Braus, Dietz G.P., S. Jakobs, M. Bähr, J.H. **Weishaupt**. Cyclin-dependent kinase 5 is an upstream regulator of mitochondrial fission during neuronal apoptosis. ***Cell Death Differ***, 2007, 14: 651-61.