SYNTHESIS OF FLUOROGENIC PROBES FOR STABILIZATION OF SUPEROXIDE DISMUTASE (SOD1)

Viktoria Mrđen Debono[a,b], Robert Schirmacher[a,b], Lisa Marie Funk[c], Ulf Diederichsen[a], Kai Tittmann[c], Franziska Thomas[a,b*]

[a]Georg-August-Universität Göttingen, Institute of Organic and Biomolecular Chemistry, Tammannstr. 2, 37077 Göttingen, Germany
[b]Center for Biostructural Imaging of Neurodegeneration, Von-Siebold-Straße 3a, 37075 Göttingen, Germany
[c]Georg-August-Universität Göttingen, Schwann-Schleiden-Forschungszentrum Department of Molecular Enzymology, Julia-Lermontowa-Weg 3, 37077 Göttingen, Germany

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease indicated by the loss of motor neurons following fatal pareses, and can be divided into sporadic ALS (sALS) and famililal ALS (fALS). More than 150 mutations present in 20% of all fALS cases are found in the superoxide dismutase (SOD1) protein that has an important role as cellular antioxidant. The mechanisms leading to the failure of the motor neurons caused by SOD1 are not fully understood, however, some studies suggest that dissociation of the SOD1 dimer causes misfolding and aggregation as two sources of toxicity. [1, 2]

We designed fluorogenic probes using *in silico* docking studies, whose biphenyl core structures may be able to stabilize the SOD1 dimer. Additionally, a small molecule labelling tag would mediate transfer of a fluorescent dye to SOD1. Initial testing of the synthesized lead structure indicated binding affinity to the SOD1 protein. Therefore, we enlarged the library of the small molecules by changing the substituents of the biphenyl core structure to improve the binding affinity. The design of affinity-based fluorogenic probes is envisaged as an extended approach and should help to understand the mechanisms leading to the SOD1-related fALS.

[1] Rachel L. Redler, Nikolay V. Dokholyan, The Complex Molecular Biology of Amyotrophic Lateral Sclerosis (ALS), Editor(s): David B. Teplow, In Progress in Molecular Biology and Translational Science, Academic Press, 107, 2012, 215-262

[2] Banci L, Bertini I, Boca M, Girotto S, Martinelli M, et al. (2008) SOD1 and Amyotrophic Lateral Sclerosis: Mutations and Oligomerization. PLOS ONE 3(2): e1677