**An approach to drug discovery for amyotrophic lateral sclerosis based on proteomic information.**

○ Eiichi Tokuda[1], Shin-ichi Ono[1,2] , and Takashi Suzuki[1]

[1]Research Unit of Clinical Medicine, College of Pharmacy, Nihon University

[2]Division of Neurology, Akiru Municipal Medical Center

Amyotrophic lateral sclerosis (ALS) is a lethal motor neuron disease. Riluzole, a glutamate antagonist, is the only approved drug for therapeutic use for ALS. However, its therapeutic effects are unsatisfactory. Mutations in copper/zinc superoxide dismutase (SOD1) have been found in some familial cases of ALS. Mice expressing human mutant SOD1 proteins replicate the clinical and pathological hallmarks of ALS. Therefore, mutations in *SOD1* are believed to cause motor neuron death through "toxic gain-of-function" rather than loss of its original enzymatic activity; however its essence remains unclear.

The identification of mutant SOD1 toxicities would provide clues to the disease pathogenesis and the subsequent process for drug discovery. Proteomic analysis is a powerful tool to investigate redox status including mutant SOD1. The analysis has shown that oxidized mutant SOD1 proteins themselves play parts of "toxic gain-of function". Oxidized mutant SOD1 proteins provoke aggregation of motor neurons, which result in motor neuron death. It is also known that copper ions facilitate oxidative modification of mutant SOD1 proteins through Fenton-like reactions.

To remove copper ions and attenuate the oxidative process of mutant SOD1 proteins, we administrated tetrathiomolybdate (TTM), a selective copper-chelating drug, to a mouse model of ALS. TTM effectively removed copper ions from mutant SOD1, and ameliorated ALS-like symptoms such as the onset, progression and mortality of disease. Especially, the effect of TTM on survival period was approximately twofold as long as that of riluzole.

It is shown that proteomic analysis is able to find therapeutic targets of ALS as well as reveals key players in the pathogenesis of disease.