Development of the coming generation enzyme replacement therapy for lysosomal diseases

○Kohji Itoh and Daisuke Tsuji
(Dept. of Medicin. Biotechnol., Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokushima)

Recent recombinant enzyme replacement therapy (ERT) has made progress in successful treatment of a group of lysosomal storage diseases (LSDs) via intravenous administration, which are primarily due to the germ-line mutations of lysosomal enzyme genes and associated with excessive accumulation of natural substrates and somatic symptoms, including Gaucher, Fabry and Hunter diseases. However, the following improvement should be required for general application to other LSDs: 1) Establishment of a new gene expression system to produce a large amount of safe and inexpensive human enzyme drugs. 2) Genetic alteration of the wild-type enzyme to eliminate the minimal effective dose. 3) Development of a novel delivery system of recombinant enzyme across the blood-brain barrier into the brains of LSD patients with neurological manifestations. Tay-Sachs and Sandhoff diseases are lysosomal β-hexosaminidase A (αβ heterodimer) deficiencies associated with excessive accumulation of GM2 ganglioside in the brain and neurological symptoms. We have been examining therapeutic effects of the genetically engineered human HexA by means of Sandhoff disease model mice. We observed the restoration of enzyme activity in the brain via intravenous and intraventricular administration of the Hex isozymes produced by a methylotrophic yeast *Ogataea minuta* containing the oligosaccharides with terminal mannose-6-phosphate (M6P) residues and cell-permeable peptide tags. We also produced a novel recombinant HexA, on the basis of *in silico* molecular design, that was superior to the wild-type in thermostablity and uptake via M6P receptor by skin fibroblasts derived from the patients. These recombinant HexAs should have therapeutic potential and be applicable to the future ERT for Tay-Sachs and Sandhoff diseases.