28. Development of the recombinant lysosomal enzyme replacement therapy targeted to brain

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Enzyme replacement therapy with the recombinant enzymes produced by the genetically engineered mammalian cell lines has been spreading as a fundamental treatment for a group of lysosomal diseases (lysosomal enzyme deficiencies) based on endocytosis via glycoreceptors on the target cell surface, including cation-independent mannose-6-phosphate receptor and mannose receptor. To expand the application to lysosomal diseases with neurological manifestations, we are developing the novel systems and techniques by using recombinant β-hexosaminidase A (HexA, αβ heterodimer) and Sandhoff disease (Hex β-subunit deficiency) model mice. Our approaches are as follows: 1) development of a double gene expression system with the human *HEXA* and *HEXB* genes encoding Hex α- and β-subunit, respectively, and a yeast mutant for mass production of the human HexA with the oligosaccharides containing mannose-6-phosphate residues. 2) molecular design of the super-functional human HexA and its antigenic epitopes based on homology modeling and molecular pathology of Tay-Sachs and Sandhoff diseases. 3) establishment of the central nervous system (CNS) cell lines derived from Sandhoff mice, including glial-restricted precursor, oligodendrocyte precursor and microglial cells, for evaluating enzyme replacement effects via glycoreceptors. 4) brain-targeted delivery of recombinant proteins conjugated or fused with the newly identified tag sequence directed to brain parenchyma across the blood-brain barrier.