IS02-3 Disease-Modifying Therapy through Enhancement of Neprilysin Activity for Alzheimer's Disease

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Aggregation and deposition of amyloid-β peptide (Aβ) in the brain are triggering events of the long-term pathological cascade of Alzheimer's disease (AD). Neprilysin is a rate-limiting peptidase involved in brain Aβ catabolism. Mounting evidence that expression levels of neprilysin are decreased in the hippocampus and cerebral cortex of AD patients from the early stages of disease development and also with aging in humans, suggests a close association of neprilysin with the etiology and pathogenesis of AD. Thus, a subtle but long-term decline in neprilysin activity appears to be at least partly responsible for the memory-related symptoms of AD, and up-regulation of neprilysin is considered to be a promising strategy for disease-modifying therapy of AD.

We successfully developed an adeno-associated virus vector capable of providing neuronal gene expression throughout the brains after peripheral blood administration, and have started a preclinical study of neprilysin gene transfer using the vector to confirm safety and efficacy in aged non-human primates. Concurrently, we have screened compounds modulating neprilysin activity using a natural product library, and found that catechins were capable of up-regulating neprilysin via gene expression in cultured neuronal cells. Especially, catechins alkylated to increase bioavailability strongly up-regulated not only neprilysin but also α-secretase, which acts to preclude Aβ production. The lipophilic catechins would be also promising drug candidates for AD therapy.