Medicinal Science Studies on the Basis of Peptide Chemistry

○Yoshiaki Kiso
（Kyoto Pharm. Univ.）

Creation of new biologically active compounds for life science research leading to therapeutic drugs is extremely important and interesting research topic. We engaged in such themes to make bridges between organic chemistry of amino acids, peptides and proteins as basic biological compounds and medicinal chemistry.

Based on the substrate transition state, we designed and synthesized novel classes of inhibitors of aspartic proteases such as HIV protease, malarial plasmepsin II, containing the hydroxymethylcarbonyl (HMC) isostere. Among them, tripeptide KNI-272 was a highly selective and superpotent HIV protease inhibitor. Physicochemical studies suggested that the HMC isostere is an ideal transition-state mimic [1, 2]. We applied the substrate transition state concept to develop inhibitors against ß-secretase (BACE1) targeting Alzheimer's disease (AD) [3, 4, 5].

We successfully designed a novel BACE1 inhibitor, KMI-429 that reduced amyloid ß peptide production in transgenic and wild-type mice [6]. The native Aß1-42 tends to aggregate due to uncontrolled polymerization complicating AD research. On the basis of our study with the "O-acyl isopeptide method" [7, 8, 9], we developed novel photo- and pH-triggered "click" peptides that readily convert to the native Aß1-42 upon activation. Click peptide Aß1-42 analogs migrated to generate Aß1-42 with a 'click' reaction via an O-N intramolecular acyl migration [7-10]. The BACE1 inhibitors and amyloid ß 'click' peptide that we developed will pave the way to defy Alzheimer's disease.

[1] Biopolymers, **51**, 59 (1999). [2] Biochemistry, **42**, 8459 (2003), highlighted in Science, **301**, 143 (2003). [3] Bioorg. Med. Chem. Lett., **15**, 211 (2005). [4] Drugs of the Future, **31**, 53 (2006). [5] Current Pharmaceutic. Design, **12**, 4295 (2006). [6] J. Neurochem., **96**, 533 (2006). [7] Biopolymers, **76**, 344 (2004). [8] ChemBioChem, **7**, 1549 (2006). [9] J. Peptide Sci., **12**, 823 (2006). [10] J. Am. Chem. Soc., **128**, 696 (2006).