Peptide-based Medicinal Chemistry from Small Peptide-like Molecules to Antibody Drug Conjugates

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For over two decades, our group has been focused on a wide range of peptides or peptide–like natural products to develop therapies for cancer, genetic diseases, infectious diseases and metabolic diseases. This presentation will highlight some of these projects. It will include a discussion of the development of dipeptidic anti-microtubule agents plinabulin (Phase III)[1] and KPU-300[2]. They can be used as vascular disrupting agents (VDA), and complex with human IgG1 (Herceptin) as a non-covalent-type antibody-drug conjugates (ADC) through the conjugation with a peptide that recognizes the Fc region of such antibody.[3] The peptide-plinabulin conjugate, which was synthesized using our developed solid-phase disulfide ligation method,[4] enhanced antigen-dependent cytotoxicity of Herceptin against HER2-positive SKBR-3 breast carcinoma.

Muscular diseases are another important target for the recent drug development. We have focused on myostatin (growth differentiation factor 8, GDF-8), a member of the TGF-β protein family, which inhibits muscle differentiation and growth. Inhibiting peptides with about 20 amino acids in length have been developed.[5] These peptides resulted in improved muscular mass in mice upon direct intramuscular injection.

For an anti-obesity drug development, we focused on human neuromedin U, which is an anorexigenic peptide sharing a common C-terminal amidated heptapeptide sequence among mammals and is responsible for an activation of NMU receptor types 1 (NMUR1) and 2 (NMUR2). An extensive structure-activity relationship study discovered hexapeptide agonists highly selective to each of human receptors.[6] These agonists inhibited the body weight increase in ddY mice, and thus would be a promising lead in the development of an anorexigenic drug and contribute to understanding endocrinological functions of hNMU.

References

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