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Editorial of Special Column "Novel Peptides and Peptidomimetics in Drug Discovery"

Since insulin, a natural peptide composed of 51 amino acids, was first isolated and commercialized in the 1920s, peptide drugs have greatly reshaped our modern drug discovery area[1]. To date, the total number of approved peptide drugs for human use worldwide has exceeded 60[2]. Popular peptide drugs such as liraglutide (Victoza)[2] and glucagon-like peptide 1 (GLP-1)[3] are the top-selling drugs for type 2 diabetes. However, significant hurdles associated with natural peptide sequences as therapeutics, such as metabolic instability and, consequently, have low oral bioavailability and shorter half-life[4], are still remaining. To overcome the limitations of natural peptides and further optimize their advantages, peptidomimetics emerged as an alternative strategy.

As the name implies, peptidomimetics are molecular entities that mimic structure and function of peptides, and have evolved into a synthetic tool of drug discovery in the nearby half-century[5]. A diversity of approaches to design peptidomimetics could be: (1) L to D amino acid substitution: compared with natural L-amino acids, incorporating D-amino acids into biologically active peptides can improve metabolic stability because few human enzymes hydrolyze the peptide bonds of D-amino acids[6]. For example, desmopressin (1-desamino-8-D-arginine vasopressin) is a synthetic substitute for vasopressin[7], whereas the first amino acid has been deaminated and L-Arg has been substituted with D-Arg at the eighth position. Hence, the metabolic stability of desmopressin is better compared with vasopressin[7]. (2) Non-natural amino acid-containing peptidomimetics: these peptidomimetics can maintain selectivity and potency of therapeutic peptides as well as improve metabolic stability[6]. Such as α-peptides[8], β-peptides[9], peptoids[10], and others[11−13] have been explored over the past several decades. (3) β-turn mimetic: the β-turn is one of the three main secondary structural motifs that control protein−protein interactions. More than 100 G protein-coupled receptors (the most encouraging drug targets) that identify peptides are activated by β-turn motifs[13]. Whitby and co-workers have demonstrated that the design of the β-turn mimetic library can target protein−protein and peptide−receptor interactions[14]. (4) Cyclization: cyclic peptides'

conformational rigidity results in improved bioactivity compared to the linear analogs. Conformational constraint and/or lack of amino and carboxyl terminus make these cyclic molecules are resistant to hydrolysis by peptidases[15]. Eptifibatide is a synthetic cyclic peptide derived from rattlesnake venom. It displays greater stability than the parent peptide. The drug exhibits a great effect on preventing blood clots or heart attack in people with severe unstable angina or other conditions[16]. The rapid and achievable development of peptidomimetics in drug discovery keep encourage scientists to investigate novel peptidomimetics. This special column proposes to contribute insight into developing novel peptides and peptidomimetics as potential therapeutics to readers.

Combinatorial library screening is a versatile tool for drug discovery and optimization by which can at once generate huge possible peptidomimetics and allow fast screening against specific drug targets[17,18]. Zheng et al.[19] reported a combinatorial library bearing one-bead-two-compound (OBTC) unnatural macrocyclic γ-AApeptides (oligomers of γ-substituted-N-acylated-N-amino-ethyl amino acids) and screened it against human epidermal growth factor receptor 2 (HER2). They further designed and synthesized an artificial antibody based on the strongest binding affinity of library screening positive hit by using a dimerization strategy. Li et al.[20] designed a series of duodecimal synthetic peptide derivatives based on a previously identified efficacious dodecameric peptidomimetic termed PMI (TSFAEYWNLLSP)[21] to find potential molecules for targeted molecular therapy to suppress tumor. They obtained the most potent duodecimal peptide termed in PMI-M3 (LTFLEYWAQLMQ) for the inhibition of the P53-MDM2/MDMX interactions (an applicable therapeutic paradigm for cancer treatment).

The stapled peptides are fast-developed synthetic peptides that are constrained with hydrocarbon stapling. Li et al.[22] designed and synthesized stapled peptides that target KRAS[G12C] mutations (an important driving force of non-small cell lung cancer). The lead stapled peptide exhibited a stable α-helical structure with

enhanced affinity and stability, intensify resistance to proteolysis, and improved biological activity.

Derivatives from natural products offer an efficient approach to discover potential therapeutics, as well. Chen et al.[23] discovered a new ω-conotoxin Bu8 derived from genes of *Conus bullatus*. The biological activity results demonstrated that Bu8 has high potency and reduced side effects to inhibit N-type voltage-gated calcium (CaV2.2) channels. Consequently, Bu8 displayed strong analgesic activity to intense pain and inflammatory pain. Harms et al.[24] designed a novel potential antagonist of chemokine receptor CXCR4 that is derived from a natural fragment of serum albumin called EPI-X4. The optimized EPI-X4 derivative is the first CXCR4 inhibitor that has effective treatment for atopic dermatitis. More excitingly, the derivatives exhibited more efficiently in mouse models of atopic dermatitis and asthma compared with the FDA-approved small molecule AMD3100.

Scientists have been committed to discovering and optimizing efficient synthetic methods to synthesize peptidomimetics. Al-Hamashi et al.[25] used a rational structure-based drug design approach to develop a series of novel bisubstrate inhibitors targeting several protein arginine methyltransferases (PRMTs). The lead compound was proven to be as a potent and selective inhibitor for PRMTs. The study offers an achievable and useful synthetic method to develop bisubstrate inhibitors for PRMTs. Disotuar et al.[26] reported a new enzymatic strategy to synthesize insulin derivatives with high efficiency which can be used for future insulin analogs design and development.

Membrane active peptidomimetics are a bright aspect to explore next generation drugs to combat bacteria and cancer that exhibit great capacity for combating drug resistance[27−29]. Lin et al.[30] reviewed the recent advances of membrane-disruptive peptides/peptidomimetics (MDPs), which are developed as antimicrobials or anticarcinogens and present a general killing mechanism through physical disruption of cell membranes. The review summarizes the structure–activity relationships and acting mechanisms of MDPs, the potential of the combination therapy of MDPs with small-molecule drugs, metal materials, and photoresponsive materials, and the evaluation of various MDP-based drug delivery systems *in vivo* therapeutic operability.

We would like to thank all the authors for their admirable work and compelling contributions to novel peptides and peptidomimetics design, synthesis, and application in drug discovery. We truly hope that this special column will help place research accomplishments and current challenges in the field of peptidomimetics, and will inspire further endeavors to guide the future development of peptide and peptidomimetics in drug discovery.

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