Adventures in Drugging Undruggable Targets

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Pharmaceutical chemistry research has traditionally focused upon a limited set of biological targets. Many other human disease-related targets have been termed ‘undruggable’ as they have proved largely impervious to modulation by small molecules. However, it is becoming increasingly evident that such targets can indeed be modulated; they are simply being challenged with the wrong types of molecules. Research using conformationally constrained peptides should provide hits against a broad range of targets with high frequency, including ‘undruggable’ targets.

Protein−protein interactions (PPIs) have emerged as attractive drug discovery targets in recent years due to their key roles in mediating various cellular functions. PPIs are however notoriously challenging to target; therefore, they have been termed ‘undruggable’. The interfaces that characterize PPIs are often large, shallow, and highly flexible, making rational drug design difficult. Nevertheless, there is growing interest in exploring these, particularly through harnessing peptides as PPI-targeting drugs due to their potency, high specificity, and low toxicity. Peptides are also viewed as a bridging class of drugs that could potentially combine the desirable properties of small molecules with those of biologics. Despite numerous successful examples of peptide-based drugs that have already reached the market, peptides are often considered poor drug candidates because of their low bioavailability, rapid elimination, poor in vivo stability, and administration. These limitations are now gradually being mitigated by advances in peptide delivery and synthetic methodologies. An important advance in the development of peptide-based drugs is the introduction of the “stapling” strategy.

Incorporation of staples (conformational constraints) within the peptide has been extensively used to improve the bioavailability of these molecules; consequently, it is not surprising that a plethora of stapling techniques has been developed and has had a significant impact on the development of peptide therapeutics. Among the numerous stapling techniques known, two-component methodologies allow facile and divergent functionalization of peptides. The author’s laboratory has pioneered a stapling technique that makes use of the double Cu-catalyzed azide–alkyne cycloaddition between di-azido peptides and functionalized di-alkynyl staples. In recent years, the author’s laboratory has created biologically active, conformationally constrained peptides functionalized with cell-penetrating peptides, fluorescent tags, and photo cross-linking moieties, demonstrating the wide applicability of this methodology. The impact, advantages, limitations, and future applications of this technology and other two-component peptide stapling techniques on the development of clinically relevant peptides will be highlighted.

References: Adv. Therap. 2018, 1, 1800052; Molecules 2018, 23, 959.