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Opinion

The Emerging Role of Peptides in Drug Discovery

Jesus Seco[1,2]*

[1]*Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona, Spain; Department of Organic Chemistry, University of Barcelona, Barcelona, Spain*

[2]*Iproteos SL, Barcelona, Spain*

***Corresponding Author:** Jesus Seco, Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona, Spain; Department of Organic Chemistry, University of Barcelona and Iproteos SL, Barcelona, Spain.

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Peptides are involved in a variety of pathological processes and play important roles in modulating cellular function. No other class of biological molecules offers a comparable diversity exhibited by peptides and small proteins. In terms of chemical complexity, peptides fill a niche between small molecules and larger biological entities, such as antibodies. Due to this smaller size, peptides can be readily synthesized, optimized, evaluated and do not cause serious immune responses. Simultaneously, peptides do not accumulate in specific organs, minimizing their toxic side effects. In terms of molecular recognition, peptides are the perfect example of nature's language, understood as the process of encoding into a constitutive sequence, the structural elements to communicate and regulate any biomolecular entity.

However, naturally occurring peptides are often not suitable for use as therapeutical modulators because their inherent weaknesses, mainly peptide stability and *in vivo* circulating plasma half-life, ranging from few minutes to a few hours, attributed to the enzymatic degradation and rapid renal clearance [1]. These negative aspects rapidly the usage of small molecule at the very beginning of therapeutic discoveries [2], primarily because of the simplicity in administration (high oral bioavailability), better pharmacodynamic properties and ease of production. Unfortunately, the accumulated experience in multiple drug discovery programs has evidenced several limitations to the small molecule-based approach. First their small size makes them unsuitable to target non-conventional protein targets, especially in those cases where the protein surface at the binding site widely exceeds the potential size of the small molecule. Secondly, the chemical space explored and patented by small molecules is largely crowded, making difficult to find new privileged chemical scaffolds or small molecules without IP conflicts.

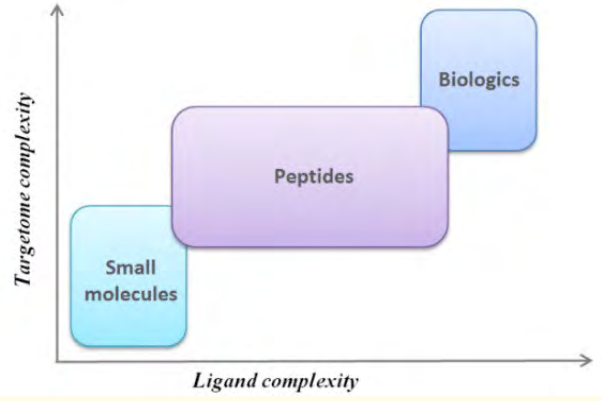

Figure 1: *Projection of target biological space (targetome) vs ligand space Peptides.*

To overcome some of the aforementioned limitations, orthogonal approaches can be conducted. To extend half-life, the former requirement is to determine possible molecular cleavage sites. When identified, selective introduction of N-methyl group into the backbone is usually selected. However, other possibilities have proven to be efficient, such as use of stapling peptide sequences, or by cyclization between N- and C-terminus segments [3]. Additionally, natural amino acid replacement by either substitution of D-amino acids or non-natural building blocks has successfully enhanced peptide stability. Compatible protection against enzymatic cleavage can be induced by incorporating into the sequences short-peptide fragments able to promote better secondary structure packing (i.e folding) [4]. Other strategies include insertion of albumin-binding peptide elements in the peptide backbone, peptide acylation or peptide conjugation to albumin-binding antibody fragments [5]. Polyethylene glycol (PEG)-ylation has been used to limit globular filtration, limiting the elimination of peptides [6], but this approach is becoming less popular because of safety and tolerability concerns.

There have been multiple successful cases over the past decade supporting the use of peptides in drug discovery. For instance, peptide-based medicine Lupron™ (Abbot Laboratories), applied for the treatment of prostate. Glatiramer acetate (Teva Pharmaceuticals), also known as Copaxone, is used for multiple sclerosis. Another example is Lantus™ (Sanofi-Aventis), a long-acting basal insulin analogue to control the blood sugar in patients with diabetes when administered once a day. The annual sales of all the approved peptide drugs is only about $20 billion [7,8], representing a minor fraction (less than 2%) of the global drug market.

These cases clearly exemplify the potential of peptide-drugs as new chemical modulators, in a favored landscape promoted by the number of small drug molecules annually approved that is in continuous decline [7]. Currently, the peptide drug market is expected to be twice as high as that for small molecule [7,8], with around 500 peptides in pre-clinical studies, between 100 - 200 more in clinical trials and more than 60 FDA-approved peptide medicines on the market.

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