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Who needs “normal” peptides?

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Abstract If you ask anyone, “What is a peptide?”, you will probably get a stock answer involving a chain of 2 or more amino acids which link together via a “peptide” linkage (-C(O)-NH). You might learn there are 20 natural amino acids, and they are all in the same L- stereo configuration. You might also learn that they are great at getting the body to do stuff, but they don’t make great drugs because they have short half-lives. So, we need to modify natural peptides so that they behave more like drugs – we’ll find ways to make them more stable – but still have them doing all the nice things we like about them. We’ll cyclise them, stick fat on them, PEGylate them, conjugate them to make them better. This article looks at some of the ways peptides are modified, but also recognizes that unmodified peptides still have a role to play.

INTRODUCTION

The interest in peptides as therapeutics have greatly increased over the last 10 years or so, though they are not everyone’s first choice as drugs. On the plus side peptides tend to have high specificity and affinity for the receptors they are targeting and have good toxicity profiles. On the other hand, they are easily metabolized and have short half-lives. Orally available peptides are extremely rare, and most are administered as depots or injectables.

Despite the practical disadvantages, peptides remain a very active area of interest with over 70 approved peptide therapeutics (1), and a predicted market of \$25Bn in 2018 (2). In addition, there are reported to be over 600 peptides in various stages of preclinical and clinical development (2). Many of these peptide APIs rely on structural modifications to increase stability, but others, for example peptide vaccines, comprise only native peptide sequences.

PEPTIDE DECORATION

A significant amount of research is ongoing to design modifications to peptides that impart favorable properties. In fact, as I write this article shortly after attending the Royal Society of Chemistry’s symposium for young researchers in the UK (3), seven out of the eight talks were about doing just that: increasing half-life, stapling to achieve structural configuration that promotes cell permeability, functionalizing for conjugation, or improving linkers for conjugating peptides with proteins.

Much research is focused on increasing peptide stability and systemic half-life. This is particularly prevalent in the

Type II diabetes field where numerous companies are developing GLP-1 analogues with long half-lives that enable great reduction in the frequency of injections and build towards weekly or even monthly dosage. The Novo Nordisk drug, Liraglutide, has a lipid side chain conjugated to a Lys in the sequence which imparts binding affinity for system human serum albumin, thus protecting it from enzymatic degradation, and increasing half-life. In a second generation product, Semaglutide, further stability is achieved by use of an Aib residue which confers DPPiv stability, and two fatty acid chains linked through specifically designed spacers. In a third option, GSK developed Albiglutide, a GLP-1 linear dimer which is directly fused to the N-terminus of albumin.

In other areas, the concept of peptide “stapling” is an increasingly popular pursuit. In this case, effort is being made to constrain peptides in an α -helical configuration in order to impart cell penetrating properties. Perhaps the most famous examples take advantage of olefin metatheses chemistry to form an olefin “staple” between two amino acids involved in the helical structure. Aileron Therapeutics have taken such stapled peptides into clinical trials.

One by-product of inventing new methodology is that others look for the weak spots, and try to make improvements. As a result, several other stapling chemistries now exist, such as perfluorinated aromatics, although it remains to be seen which will be the best, or indeed if any of the approaches identified so far, ultimately reach the desired therapeutic goals.

Other common modifications to standard peptide structures that involve a non-natural element include

the use of D-amino acids, PEG conjugates, and bicyclic peptides. All of the described modifications result in some degree of variation in the manufacturing methods that need to be applied. Some are fairly straightforward, but others can be more complex and often result in significant cost of goods impact. Manufacturing organizations need to have the ability to keep pace with the inventors to ensure that the products can be manufactured for a reasonable cost.

Not all peptide therapeutics rely on modified versions of a native sequence. Many therapeutic candidates are based on the native sequences that have not been structurally altered.

NATIVE PEPTIDES STILL HAVE A ROLE

One therapeutic class where native peptides are used is in therapeutic peptide vaccines. There are a number of clinical programs that utilize multiple peptide epitopes in vaccine products. The aim with such products is to train the body into recognizing characteristic elements of a harmful entity, such as a cancer cell, or allergen, so that an immune response to such entities is developed. The peptides may be derived from mapping a large protein to identify regions (antigens) that illicit an immune response, or may reflect epitopes for different population subunits. The primary aim is for each peptide to be an exact representation of the antigen of interest, and so sequence modification is not desired.

Peptide vaccines are of particular interest in the oncology field where the peptide cocktails represent tumor associated antigens. Most recently, the field has developed to research the efficacy of personalized cancer vaccines. Patient specific mutations in a tumor, neoantigens, are identified through gene sequencing, mass spectrometry and bioinformatics, and the resultant peptide targets used in a totally individualized vaccine. It is early days for this personalized approach, and it remains to be seen if the concepts can be put into practice.

Peptide antigens are also used in anti-allergy vaccines, where instead of targeting cancer cells, the peptides represent allergens. Unfortunately, this field experienced a setback recently with a late phase trial not demonstrating sufficient benefit relative to placebo, but hopefully this area of research can be continued.

A third application of native peptide sequences is in the imaging agent field. Companion diagnostics are used increasingly in order to stratify patients for effective cancer treatment. In this case, the agents are often applied locally to determine if specific receptors are present before choosing to apply the potential chemotherapy. The local application of such agents means that the usual issue of systemic metabolism of the peptide are not such a concern.

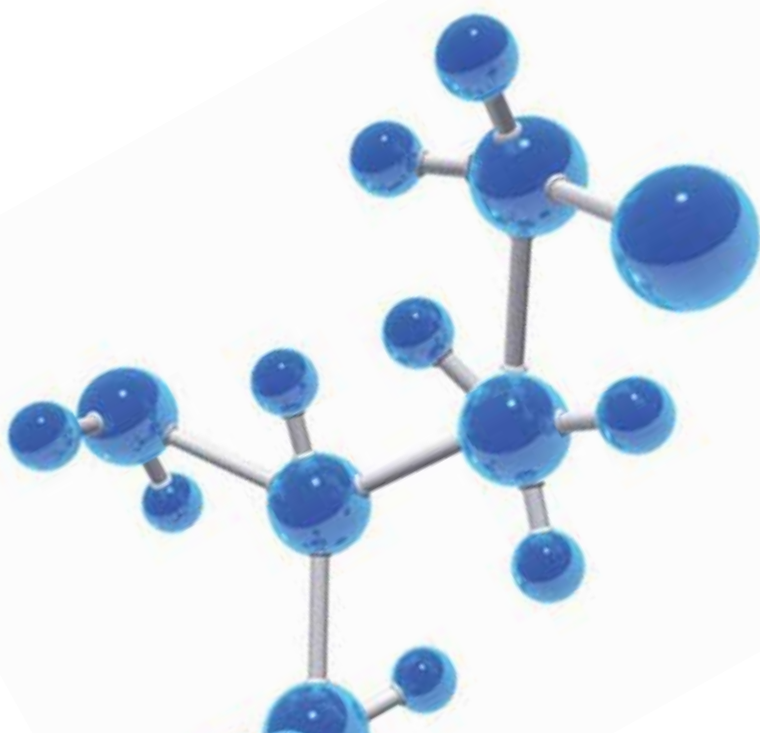
CONCLUSIONS

Pleasingly, the peptide therapeutic field is alive and well in classic medicines and vaccine arenas.

High levels of creativity have been demonstrated in order to decorate native peptide sequences in order to impart more favourable physical properties. However, these may present manufacturing challenges, and cost of manufacture should be taken into account when considering molecular structure. The use of native peptides is not discarded, however, and remains the primary vehicle for therapeutic vaccines.

REFERENCES

1. Rodney Lax, TIDES Oligonucleotides and Peptide Therapeutics, May 9-12 2016, Long Beach, California, USA.
2. Keld Fosgerau and Torsten Hoffmann, *Drug Discovery Today*, 2015, 20(1), 122-128
3. PPSG Early Stage Researcher Meeting, September 14 2017, Durham University, UK. 



About the author

With a PhD in synthetic organic chemistry, **Alastair M. Hay** has been with Almac for over 15 years. During that time, he managed the Custom Synthesis group in Edinburgh, Scotland, and Process Development groups at the Almac Head Quarters in Craigavon, Northern Ireland. In 2015, Alastair moved from an operational role to providing global support for Almac's business development activities in peptides as Account Manager.

