ORAL PEPTIDE THERAPEUTICS

a holy grail or quixotic quest?

Technologies have been honed to overcome many of the challenges of administering peptide therapeutics orally, but obstacles remain before drug developers can fully realise the vast potential.

By Dr Paul Shields

Proteins and peptides are the building blocks of life and have evolved to become a very promising basis for targeting a range of diseases. Over the past 30 years, and especially the last 10 years, there has been a rapid growth in the development of therapeutic proteins, with a dramatic increase in the number of protein-based drugs on the market.

The cornerstone of protein therapeutics was laid with the regulatory approval of insulin by the US Food and Drug Administration in 1982. As the first commercially-available recombinant protein, insulin soon became the gold-standard therapy for patients suffering from diabetes. Three decades have passed since insulin's market introduction, and its success has inspired the development of myriad new therapeutic proteins for a wide range of ailments.

The advent of peptide-based therapeutics can be traced to the success of the initial protein biologics, with protein and peptides now being utilised across numerous indications, including cancer, autoimmune, neurological and endocrine disorders. Currently, there are more than 200 approved therapeutic proteins and more than 100 peptides on the market, accounting for approximately 10% of the pharmaceutical market at a value of $40 billion per year. With hundreds of protein and peptide drugs in clinical trials and many more in preclinical development, this market is expected to continue to grow substantially over the next 5-10 years. A significant percentage of this growth is expected to come from peptide-based drugs.

Peptides occupy a therapeutic niche between small molecules and large biologics, and are generally classified as being a chain of amino acids containing 40 amino acids or less. Currently, the disease areas driving the therapeutic use of peptide drugs are oncology, driven by a rising mortality and need for chemotherapy replacement, and metabolic diseases. The treatment of metabolic diseases via peptide therapeutics has largely centred around the epidemic growth in type 2 diabetes. Examples of such peptide drugs on the market today include Byetta, Victoza and Trulicity, which are part of the family of glucagon-like peptide-1 (GLP-1) receptor activators. These peptide drugs work by interacting with a receptor on the surface of pancreatic beta cells to stimulate the release of insulin for diabetes. In addition to metabolic disease and oncology, the movement of the pharmaceutical industry into rare diseases and orphan drugs has also been extended to peptides, and peptides are being further targeted at infectious diseases and inflammation.

Research has demonstrated that peptide therapeutics can offer several advantages that are distinct and desirable. Peptides serve a highly specific set of functions in the body that cannot be mimicked by simple chemical compounds. Thus, compared with small-molecule active pharmaceutical ingredients, peptides are able to exhibit increased potency and selectivity due to specific interactions with their targets. As a result, peptides have the potential for decreased off-target side-effects and

decreased systemic toxicity. Moreover, because the body naturally produces peptides, peptide-based therapeutics are often well-tolerated and are less likely to elicit immune responses.

Given their attractive pharmacological profile and intrinsic properties, peptides represent an excellent starting point for the design of novel therapeutics, and their specificity has been seen to translate into excellent safety, tolerability and efficacy profiles in humans. Furthermore, peptide therapeutics are typically associated with lower production complexity compared with protein-based biopharmaceuticals and small molecules.

Though peptide therapeutics offer numerous advantages, and the growth of such drugs is strong, there remains a significant gulf between 'market actual' and 'market potential'. This is largely attributable to challenges with the route and method of delivery of peptide drugs.

Peptides and proteins are high molecular weight biopolymers and contain both hydrophilic and hydrophobic appendages in their structure. These properties make it difficult for peptides to be absorbed by the intestine. Peptides also degrade in the stomach and duodenum, given the digestive roles of these organs, so they may not even be available of absorption by the intestine. Simply said, our bodies recognise peptides as food when ingested.

Given these barriers, most peptide drugs are administered parenterally, with approximately 75% given via injectable routes such as subcutaneous, intravenous and intramuscular administration. While the market for injectable proteins is strong and growing, alternative administration forms are gaining increasing traction.

This trend is guided by three dynamics – patient compliance, prescriber preference and market expansion. As one can appreciate, frequent injections, inconsistent blood drug concentrations and low patient acceptability make parenteral administration of peptide-based drugs less desirable. As a result, pharmaceutical developers continue to explore alternate routes of delivery for peptide therapeutics that have the potential to maintain the drug's potency, while enhancing the ease of administration, patient compliance and market penetration.

Against this backdrop, the oral delivery of peptides has caught the imagination of drug developers far and wide. The majority of drugs on the market today are given as a pill or capsule and, thus, represent the form most patients are accustomed to taking. Long hailed as the Holy Grail of drug delivery, orally-administered peptides offer vast potential but also present considerable development challenges.

Challenges and opportunities in oral peptide therapeutic development

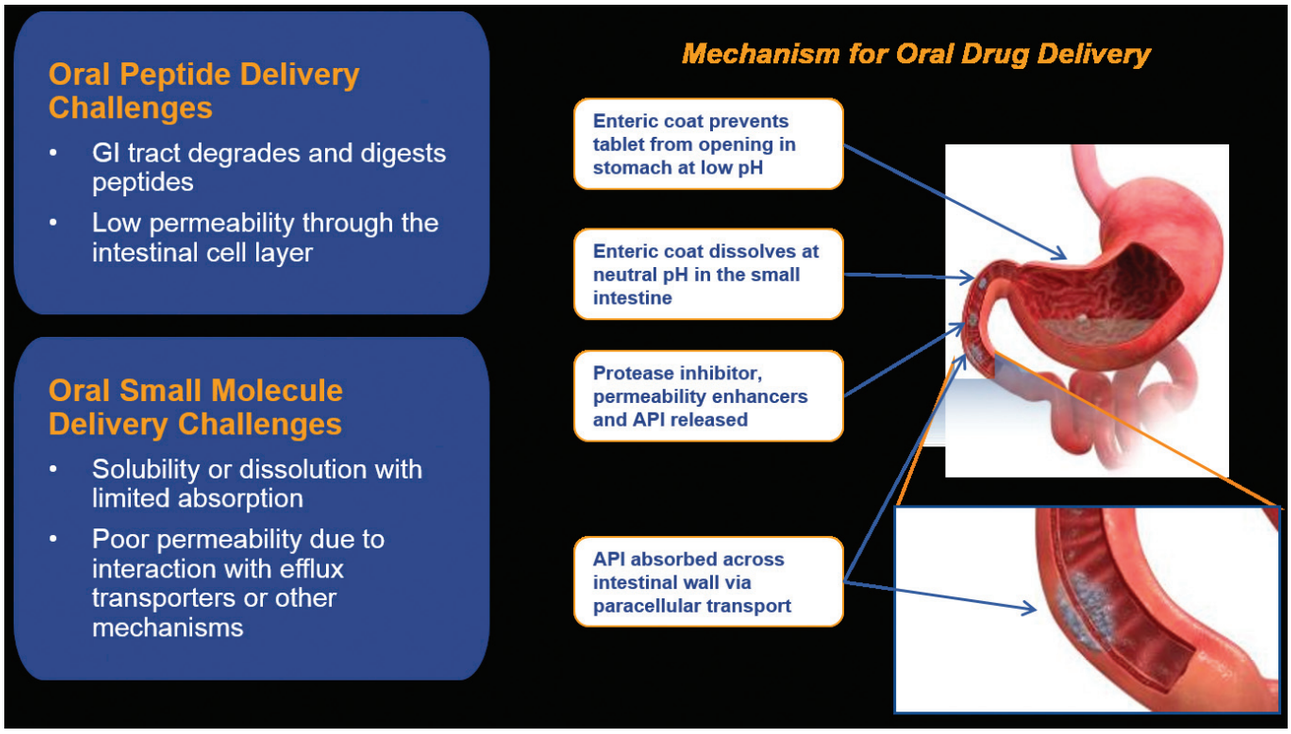
Numerous technologies are currently in development that are designed to enable the oral delivery of peptides. Though each has its unique set of properties and capabilities, all must overcome key obstacles to successfully deliver peptides via the oral route. First, the oral formulation has to remain intact in the highly acidic environment of the stomach. Once through the stomach, the tablet design must then promote dissolution in the higher pH environment of the small intestine, while simultaneously protecting the peptide payload from degradation by protease enzymes. Finally, mechanisms must be present which facilitate the absorption of the peptide into the relatively impermeable intestinal epithelium.

However, before any technology is applied to confront these challenges, developers must first target therapeutic peptides that are appropriate for oral delivery. Practical considerations, such as whether the orally-delivered peptide will enhance patient compliance, increase treatment options and boost marketability, should have priority since, without clear medical and business advantages, there is little motivation to transition from an injectable.

Yet, even if these boxes are checked, oral delivery may not be an option unless one can achieve therapeutically-relevant bioavailability. Numerous factors impact bioavailability, some of which technology can mitigate. However, the molecular weight of the peptide is key to ultimately determining the feasibility of oral delivery, with an inverse relationship between molecular weight and bioavailability.

Illustrative of the challenges and potential of orally-delivered peptide therapeutics is the ongoing development of an oral leuprolide tablet for the treatment of endometriosis. Affecting approximately six million women in the US, endometriosis is one of the most common gynecological disorders and occurs when the endometrial lining begins to grow outside the uterus, leading to lesions. These lesions may grow on the ovaries, fallopian tubes and other areas of the uterus, causing severe pain.

Leuprolide, marketed under the brand name LUPRON DEPOT® (leuprolide acetate for depot suspension), has demonstrated in the clinic and practice to be an efficacious treatment for endometriosis. However, the current parenteral route of administration limits the drug's utilisation due to the irreversibility of the depot injection, which stays in the body for 30-90 days, and the pain and inconvenience of the injections. A daily



oral leuprolide tablet could offer a more patient-friendly alternative to monthly depot injections, potentially encouraging physicians and patients to utilise the medication earlier and more often. Market estimates suggest such a drug could produce revenues in excess of $600 million annually in the US.

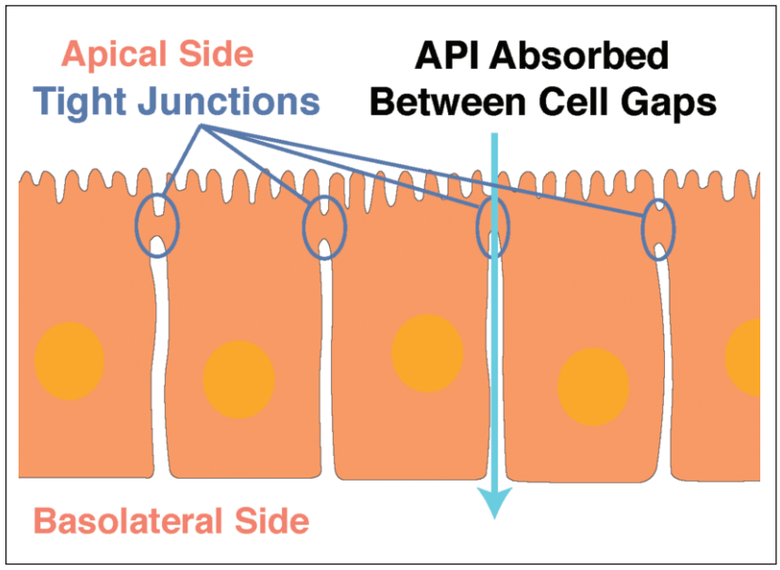
In developing its oral leuprolide tablet, biotechnology company Enteris BioPharma utilised a technology platform designed to provide protection against the harshness of the digestive system and then promote absorption of the leuprolide into the bloodstream. First, to overcome the stomach's highly acidic environment, the oral tablet was encapsulated in an enteric coating. Simple in concept, an enteric coating is a polymer barrier applied to an oral medication that prevents its dissolution in the gastric environment.

Enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, yet dissolves at the higher pH of the small intestine and at locations within the intestinal tract to enable optimal drug absorption. A variety of materials can be utilised as an enteric coating, provided the material shields the peptide drug in the stomach and enables its release in the intestine where absorption into the bloodstream can occur.

Protecting against the acidic gastric environment and enabling dissolution in the small intestine is but the first hurdle that must be addressed. The next, limiting proteolytic degradation in the jejunum, is a considerably more difficult (and critical) proposition as many peptides are highly vulnerable in the soluble form to peptidases in the lumen prior to reaching the systemic circulation. Though it is difficult to completely inhibit the actions of luminal proteases, scientists utilised protease inhibitors to create a protective microenvironment for its oral leuprolide tablet. Without such protective measures, the protease enzymes would immediately act upon the leuprolide, breaking it down for ingestion into the bloodstream; no different than protein consumed as food.

Despite the clear need for protease inhibitors in the oral delivery of a peptide, caution must be heeded when selecting a protease inhibitor, as many are not considered safe for use as excipients and inhibition of such a ubiquitous biological function can be risky. Developers, therefore, are encouraged to utilise technologies that limit the effects of such inhibitors to the GI lumen locally, and transiently, to avoid systemic toxicity.

Though shielding against the digestive system is paramount to administering a peptide orally, success in developing an efficacious oral peptide (one that elicits the desired therapeutic response comparable



to or exceeding the standard of care) ultimately hinges on whether the peptide is absorbed through the intestine and enters the bloodstream as an intact chemical species. As referenced previously, peptides have relatively large molecular weights and hydrophilicity, resulting in poor penetration across the intestinal epithelium. This may be the most challenging barrier to oral peptide delivery.

As peptides reach the intestinal epithelium, they first encounter an exogenous mucus gel layer containing proteases and antibodies, which together reduce the rate of diffusion to the epithelial surface. Attempts to overcome mucoadhesion have focused on incorporation of mucolytics or use of hydrophilic PEGylated nanoparticles, which avoid entrapment in mucus glycoprotein meshes. An alternative approach is to exploit mucoadhesion to increase the residence time of the dosage form in the small intestine.

However, greater success has been achieved via the use of permeability enhancers, such as lauroyl carnitine chloride (LCC), palmitoyl carnitine chloride (PCC) and sodium taurodeoxycholate, which facilitate peptide entry into the bloodstream. Such permeability enhancers function by enabling the transport of peptide molecules through the epithelium via passive movement across the epithelial tight junctions.

Finally, after overcoming these obstacles, the successful development of an oral peptide must accept that the bioavailability of an orally-delivered peptide will be less than that of a comparable dose of a parenterally-delivered peptide. Even the best oral peptide formats are known to have relatively low bioavailabilities of ≤10%. As such, higher doses are required to obtain the same therapeutic effect in an oral formulation. For example, we are currently conducting a Phase IIa trial of its oral tablet leuprolide comparing once- and twice-per-day doses of a 4mg oral tablet with a single, monthly depot injection of LUPRON DEPOT 3.75mg.

Given such differentials, developers must carefully consider the practicality of transitioning a peptide to an oral form based on the cost per goods. Simply put, the cost of the additional API (and production) must be less than the expected market expansion for an oral formulation. If not, then the Holy Grail is but an empty chalice.

While this may seem discouraging on the surface, there has been significant investment in the development of oral peptide dosage forms by specialised drug delivery companies. This is based on the clear advantages that such medications offer patients, prescribers and pharmaceutical developers, alike. Oral leuprolide demonstrates this potential. Not only could an oral leuprolide tablet help to potentially convert current injectable leuprolide to oral, but the oral formulation could drive the use of leuprolide earlier and more often, including use prior to hormonal contraceptives, use pre- and post-surgical procedures and use in women currently untreated. As well, it could enable the expansion of GnRH agonist therapy to indications where an injectable is undesirable, such as the treatment of uterine fibroids.

Ultimately, not all peptide therapeutics are appropriate for oral administration due to various constraints, from physiochemical to economic. However, for those that meet the necessary criteria, advances in formulation technologies coupled with favourable market dynamics will continue to drive interest across the entire prescription drug spectrum for safe and effective orally-administered peptide therapeutics. DDW

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