Overcoming Challenges to Provide Affordable Treatments

Peptides and proteins have a wide range of therapeutic uses. These options come, however, with their own advantages and limitations, which must be identified before selecting the right treatment

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Since the first application of insulin for diabetes patients almost a century ago, peptide and protein therapies have been developed to treat a wide range of diseases, including cancer, autoimmune diseases, neurological disorders, and cardiovascular and metabolic diseases. The advancement of recombinant DNA technologies in the 1980s has allowed the large-scale and consistent manufacturing of a wide range of peptides and proteins from genetically engineered cells. As a result, many hard-to-treat diseases now have better therapeutic options thanks to innovations such as recombinant enzymes or antibody derivatives.

Biologics, which include a wide variety of products derived from humans, animals, or microorganisms using biotechnology, are attractive drug candidates for several reasons. One key benefit is their specificity – unlike small chemicals that often have off-target effects, protein drugs can target defective biological processes selectively to avoid unwanted side effects. Once they have had their desired effect, protein drugs can often be broken down into amino acids by the body's natural protein degradation processes without the risk of causing metabolic stress or toxicity to patients.

However, affordability and accessibility of biologics remains a major challenge. The cost per day of biologics is roughly 22 times that of small molecules, and their high unit price is reflected in the fact that 12 of the top 20 drug sales in 2020 were biologics (1). Despite the establishment of patient outreach programmes by Big Pharma companies, many patients in developing countries still do not have access to these treatments. For those who do have access, these therapies represent a heavy financial burden to the healthcare system.

Peptides: A Promising Alternative

Peptides can overcome some of these challenges by combining the benefits of both small molecules and biologics. This gives them several advantages over proteins.

First, peptides that are shorter than 40 amino acids in length fall into the small molecule category and can be filed under new drug applications (NDAs) with simpler manufacturing regulations. According to FDA guidelines, small molecules are approved under rules for NDAs, while protein-based drug candidates are regulated under biologics licence applications (BLAs). While both market approval pathways need to demonstrate safety and efficacy of drug candidates, BLAs have stricter regulations regarding manufacturing facilities and product purity.

Second, the new development of validated synthesis and purification technologies, such as solid-phase peptide synthesis and high-performance liquid chromatography, means the cost and time of peptide drug development can be greatly reduced. Third, peptides are often functionally similar to proteins and exhibit specific, targeted interactions with their binding partners. Therefore, peptides can have remarkably high potency and selectivity with low toxicity.

Last, while the targets of protein drugs are usually limited to molecules in the extracellular environment, some specialised peptides can penetrate the cell membrane and

access the intracellular space more effectively, expanding their therapeutic potential.

Given these advantages, it is no surprise that many drug developers have turned their heads to peptides in the past two decades. The number of peptide drugs approved from 2000 to 2019 almost doubled compared to the previous 20 years. Currently, 80 peptide drugs are on the global market, more than ten of which are blockbusters generating over $1 billion per year. On the research side, about 150 peptides are in clinical stages and over 400 peptide candidates are in preclinical stages (3).

Peptide Challenges Remain

However, despite their great market potential, peptide drugs have some limitations. The main challenge is their stability both *in vitro* and *in vivo*. Usually, unmodified peptides are cleared from blood plasma *in vivo* within minutes, either by proteolytic degradation and/or renal clearance. Different chemical modifications can help to stabilise and alter peptide structure to prevent degradation, or to increase the molecular weight to avoid renal clearance. For example, lipidation, PEGylation, acetylation, disulfide bond mimetics, stapling, cyclisation, and unnatural amino acid substitution can increase the half-life and bioavailability of drugs, reducing their dosing frequency (3). On the other hand, by improving the formulation, it is possible to develop peptides that can maintain their *in vitro* stability to achieve a longer shelf-life and more convenient storage for patients. Alongside these advances, new technologies are being developed to provide alternative routes of administration besides injection, such as oral pills, skin patches, or nasal sprays. Solving the stability issues of peptides will allow drug developers to expand the applications of peptide therapeutics and create affordable medicines with high patient adherence.

PDSP: Demonstrating the Potential of Novel Peptides

One promising source of novel peptides is pigment epithelium-derived factor (PEDF), a multi-functional protein with neurotrophic and anti-inflammatory properties. The functional domains of PEDF can be made into fragments called PEDF-derived short peptides (PDSPs) to excert many different functions. One of these fragments, consisting of 44 amino acids (44mer), has stem cell regenerative properties with a unique mechanism of action that can promote the 'stemness' of certain types of stem cells, including mesenchymal stem cells. Because of its unique properties, 44mer can be applied to treat a broad range of diseases that require faster tissue repair. In the eyes, 44mer stimulates proliferation and differentiation of corneal limbal stem cells, which, as a result, speeds up the corneal repair process and heals the ocular wounds of dry eye patients. PDSPs can also be used to develop regenerative medicine treatments for osteoarthritis, by promoting cartilage regeneration to repair damage and relieve joint pain.

> *Solving the stability issues of peptides will allow drug developers to expand the applications of peptide therapeutics*

References

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Maria Chen, PhD, VP of Business Development at **BRIM Biotechnology**, has more than 14 years' research and seven years' commercial experience. Maria has extensive knowledge of biotechnology and pharmaceutical business development. She received her PhD in Biochemistry at the State University of New York at Stony Brook in 2007 and did post-doctoral research in the Department of Pathology, UCSF. She later joined Immunwork, Inc., a Taiwan-based start-up, where she helped to establish the company's business and fund-raising strategies. At BRIM, Maria leads the company's international PR and business development efforts and manages the current alliance in China.

With more than 30 years' experience in the pharmaceutical industry, CEO of **BRIM Biotechnology**, **Haishan Jang**, PhD, was previously a member of senior management at Centocor, DuPont, and Sanofi, and was the former President at TWI Biotechnology, Taiwan. Haishan has contributed to the development of many leading drugs, including Uroxatral®, Tirazon®, Remicade®, Simponi®, and Stelara®. Her breadth of experience and translational science expertise has led BRIM to advance discoveries into the clinic, and successfully spin-out Ascendo Biotechnology, Inc. In 2013, Haishan co-founded BRIM Biotechnology with Dr Frank Lee.