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The emergence of peptides in the pharmaceutical business: From exploration to exploitation

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ABSTRACT

This minireview touches upon the challenges and opportunities peptides experience on the track to become an approved pharmaceutical.

Peptide attributes originally considered troublesome with respect to drug development may now turn out to be more convenient rather than unfavourable.

Besides characteristic high target affinity, biological peptides often exhibit higher than expected stability. Clearly natural selective pressure has optimised these biomolecules beyond what can be anticipated solely on the basis of their chemical nature. This concept is gradually finding its way into the pharma and biotech industry, as illustrated by a rise in medicinal peptide patent applications and developmental work.

1. Introduction

Drug development pipelines, which in the first century of the industry have been dominated by small molecules, are characterised by high attrition rates. The road to market authorisation has many obstacles and next to efficacy and tolerability, new drug candidates have to meet several other requirements. Besides essential pharmacodynamics, pharmacokinetics, toxicity, and safety issues, also economic factors are vital, including producibility, market competition, intellectual property, and others. This is why in a typical drug development process of today, >90% novel drug candidates fail between their identification and being put on the market.

As peptides are readily degraded inside the human body, which is equipped with roughly 600 molecularly different proteases [37], this class of (bio)chemicals has long been held ineligible for drug development, and deemed widely inferior to small molecules. Despite such neglect, a number of recent technological breakthroughs and advances have sparked major interest in their usage both as diagnostics as well as therapeutics. In particular, modern-day analytical methods, which greatly excel in sensitivity, resolution and throughput over those available to the traditional pharmaceutical

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industry, facilitate the discovery and identification of a wealth of novel peptides with pharmaceutical potential. Furthermore, present combinatorial chemistry provides the means to modify them and to create completely artificial variants and alternatives. Some pharmacodynamic 'weaknesses' of peptides cannot be fully abolished this way, but clever formulations may mask or amend them. In combination with an in-depth study of the complete biology of peptides in their original natural sources, current (bio)technologies have the potential to generate an ample spectrum of efficacious and safe peptide drugs.

Here, we review the steady rise of therapeutic peptides which is apparent in the pharmaceutical and biotech industry of today. We will focus on how a peptide drug candidate passes the various phases in the traditional pharmaceutical development pipeline and the differences herein to both small molecules and the larger biopharmaceuticals. With this, we aim to reveal that peptides are by far not 'undrugable', but, instead, offer immense medicinal potential.

2. Concept/history

In terms of chemical complexity, peptides fill a niche between typical small molecule chemicals and the larger proteins. Just as the latter, they feature a modular structure with amino acids linked by peptide bonds as base units. Their size is limited, with arbitrary boundaries set at up to 100 residues [20]. Nonetheless, within these limits, peptides exhibit multifarious structures with regard to amino acid sequence, post-translational modifications and resultant spatial shape.

Starting about a century ago (World War I), the advent of the modern drug era came with pioneering therapeutic compounds like the opiate morphine and the cyclic peptide penicillin, followed in the early 1920s by the (poly)peptide insulin. These drugs introduced a new standard in disease treatment. Although peptides thus held their place among the initial therapeutic discoveries [50], small molecules rapidly took preference in the drug development industry, primarily due to their ease of production, simplicity of administration (as oral 'pill') and superior pharmacodynamic properties. Meanwhile, the rapid enzymatic breakdown of peptides in biological systems and the consequently more challenging administration routes (e.g. injection such as for insulin) led to more and more neglect of this biochemical class in the traditional drug development process.

In the 21st century, the pharmaceutical business is experiencing dramatic changes. Stringent safety regulations, lengthy compound development processes and massive financial efforts (Vlieghe, Lisowski et al., 2010) all incur concern that, despite the increasing investment into research and development, medicinal innovation is declining. Especially the last decade has seen a major paradigm shift in the scope of the pharmaceutical sector, focusing more on orphan or repurposed drugs and reducing production costs, as to endure the high expenses associated with drug development. Fewer new drugs make it to the market and the patent protection of current blockbuster drugs is deteriorating, with a resulting drainage of the drug pipelines. All this may ultimately push the pharmaceutical industry towards a new frontier in modern drug development. Fresh strategies are needed to revive pharma's lost momentum and we agree with Vlieghe and coauthors (Vlieghe, Lisowski et al., 2010) that the sector's hope (partly) lies in peptides.

3. Peptide discovery

3.1. *Natural sources*

Nature harbours an impressive variety of biologically active peptides expressed in virtually all living species and, therefore, represents one of the most promising sources for peptide drug discovery (see also www.NP2D.com).

Within the multicellular body, peptides exert diverse biological roles, most prominently as signalling/regulatory molecules in a broad variety of physiological processes, including defence, immunity, stress, growth, homeostasis, and reproduction [24].

Through evolution, numerous peptides have evolved to exhibit their 'natural' bioactivity outside of the producing organism. Many of these have been isolated and characterised from the skin of frogs and toads [49,55]. These genetically encoded compounds have been shown to protect and defend their manufacturers against many foes, both predators and pathogens [13]. Hitherto, over 300 antimicrobial peptides have been identified from amphibians that hold promise for future antibiotic research and development [33].

Intriguingly, many externally active peptides have evolved as means of active predation, especially in venomous animals such as spiders, snails and snakes (see [64]). While the toxicity arises from interfering with neuronal transmission (blocking synaptic signalling, ion channel; e.g. conotoxins) or, in general, disrupting critical biochemical signalling networks within the prey's body [61], low doses of these peptides can actually counteract disturbances from diverse disorders. Accordingly, toxic peptides may aid in treating pain [41], neurological and cardiovascular diseases, diabetes and cancer [32]. A prominent example is the type 2 diabetes drug *Exenatide*, a synthetic version of a glucagon-like peptide-1 analogue found in the venom of the Gila monster *Heloderma suspectum* [7].

As bioactive peptides obtained from natural sources have been subject to aeons of selective pressure, they show considerable plusses over artificially/chemically conceived peptide-like compounds. Namely, they excel in stability and target affinity, both of which are extremely challenging to achieve or reproduce through rational peptide design, screening of libraries of randomly composed peptides or peptidomimetics. Although we appreciate the intelligence of peptide medicinal chemists, and other traditional (bio)chemistry based pharmacologists, we believe that much is still to be discovered from the natural bioactive peptides used all over the biological taxonomy (from microorganisms over plants to animals). With so many of these being used as drugs by so many different species for so many different purposes, it is clear that mankind can still learn a lot from the implied biology. We would, therefore, wholeheartedly support an adjustment of the name of the 'Natural Peptides to Drugs' NP2D discussion forum to 'NP4D' (Natural Peptides for Drugs).