Prospects for Peptide Anti-Infective Agents

With a mode of action that can circumvent drug resistance in target pathogens, a broad spectrum of activity and the possibility of advances/cost reductions in manufacturing, the prospects for peptide anti-infective agents are at their most promising.

The over-use of antibacterial, antifungal and, more recently, antiviral therapies since their phased introduction to medical practice from the 1940s onwards has led rapidly to a global degree of drug resistance in key pathogen groups, leaving the application and success of our current armoury of antimicrobial therapies ever more limited. Traditional, chemistry-led small molecule-based strategies have failed to deliver much – if anything – in the way of recent innovation towards new classes of antimicrobial compounds with distinct or significantly superior clinical performance than their predecessors.

Has traditional small molecule chemistry exhausted its potential on the front line of anti-infective drug discovery? The paucity of and dramatic recent decline in anti-infective drug approvals certainly points to this as being true (see Figure 1). As such, the focus in small molecule anti-infective research and development remains largely on extending the clinical utility and life span of the existing drug classes through modification and reformulation.

A step-change is very obviously and acutely required in global antimicrobial therapeutic strategy. Central to this is the development and introduction to clinical practice of truly novel medicines based on technology that is not only safe and efficacious in eradicating its target pathogen(s), but that centres on a mode of action that minimises or even negates the risk of resistance development and therefore a perpetuation of this leading current issue. Nature has already pointed us towards the answer, having already developed and refined exactly such a technology over more than two billion years of evolution: the endogenous antimicrobial peptides that form the first line of eukaryotic (and to a lesser degree, prokaryotic) defence against the range of pathogens with which we are in constant contact (see Figure 2, page 64) (1-4).

OBVIOUS DRUG CANDIDATES

Through an elegantly simple mode of action, endogenous antimicrobial peptides neutralise target pathogens through deleterious interactions with membrane components resulting in perturbation and/or lysis, or an inability to replicate or enter target mammalian cells; they would thus appear to be obvious candidates as drug targets for application against not only existing, but a growing number of already drug-resistant and emerging bacterial, viral and fungal pathogens (1-4). A further advantage of a membrane-targeted mode of action is that peptide antimicrobials are active against both metabolically active and non-metabolising microorganisms, whereas most current antimicrobial agents are active only against replicating microbes because they target key metabolic pathways required for multiplication (1-4).

It is hardly surprising with all of these properties in mind that, against the backdrop of the innate immunology
Figure 2: Antimicrobial peptides: highly conserved cationic cornerstone of eukaryotic immunity

Source: Nature Reviews - Immunology

<table>
<thead>
<tr>
<th>Synthetic compound</th>
<th>Company</th>
<th>AMP type (species)</th>
<th>Clinical trial outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pexiganan (MSI-78)</td>
<td>Genexa (Plymouth, PA, US) formerly Magainin Pharmaceutical Inc</td>
<td>Magainin 2 (Xenopus frog)</td>
<td>No advantage over conventional antibiotics in a Phase 3 trial for topical Rx of diabetic foot ulcers. Failed to gain FDA approval</td>
</tr>
<tr>
<td>Iseganan (IB-367)</td>
<td>Intrabiotics Pharmaceuticals Inc (Mountainview, CA, US)</td>
<td>Protagain (Pig)</td>
<td>Failed two Phase 3 trials as mouth-rinse for stomatitis in high-risk patients. Failed Phase 3 trial as aerosolised Rx in ventilator-associated pneumonia</td>
</tr>
<tr>
<td>Omiganan (MBI-226)</td>
<td>Microbiologix Biotech (Vancouver, BC, Canada)</td>
<td>Indolicidin (Bovine)</td>
<td>Failed Phase 3 trial as topical Rx to prevent or reduce venous catheter-related bloodstream infections</td>
</tr>
<tr>
<td>MBI 594AN</td>
<td>Microbiologix Biotech (Vancouver, BC, Canada)</td>
<td>Indolicidin (Bovine)</td>
<td>Phase 2b trial showed efficacy as topical Rx for acne</td>
</tr>
<tr>
<td>P113 P113D</td>
<td>Demegen (Pittsburgh, PA, US) Dow Pharmaceutical Sciences (Paloalma, CA, US)</td>
<td>Histatin (Human)</td>
<td>Completed Phase 2 trial as mouth-rinse for oral candidiasis in HIV patients</td>
</tr>
<tr>
<td>XMP629</td>
<td>Koma (Berkeley, CA, US)</td>
<td>BPI (Human)</td>
<td>Failed Phase 3 trial as topical Rx for acne</td>
</tr>
<tr>
<td>Neuprex (8BP21)</td>
<td>Koma (Berkeley, CA, US)</td>
<td>BPI (Human)</td>
<td>Failed Phase 3 trial as adjunctive parental Rx to reduce mortality in paediatric meningococcaemia</td>
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</tbody>
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Summary of antimicrobial peptides in clinical development

Table 1: Summary of antimicrobial peptides in clinical development (at 2005) (modified from 5)

The renaissance of the 1990s, a number of groups looked to develop synthetic fragments and analogues of natural antimicrobial peptides as therapeutic molecules for a range of infectious conditions (see Table 1) (5). All were unsuccessful however – at least in terms of meeting their primary therapeutic and commercial aims – largely because, in trailblazing a field of research that has since strongly re-emerged, they did so before the highly complex and pleiotropic nature of endogenous peptide antimicrobials was fully understood. The field has still not fully arrived at a point where we can say that the biology of peptide antimicrobial is fully elucidated, but what is now clear is that third- and fourth-generation variants of endogenous forms of peptide anti-infectives are much more viable therapeutic targets – namely simpler, smaller synthetic peptides that retain the requisite degree of functional commonality to their natural counterparts, but are truly druggable targets in their physicochemical and functional characteristics. A number of companies, including NovaBiotics, are successfully developing therapeutic candidates through this rational drug design approach, and the first in a next generation of peptide anti-infective agents will hopefully be approved for market in the near future.

A BROAD RANGE OF APPLICATIONS

Small, synthetic, cationic antimicrobial peptides have the potential for application across a range of topical and systemic infections, as well as in coating a number of medically relevant devices (such as catheters and stents). A number of antifungal, antibacterial and antiviral peptides are being developed with appropriate physicochemical properties that provide flexibility for formulation for a broad range of delivery routes and target indications. Furthermore, advances in delivery and half-life extension enabling technologies expands the clinical horizons for peptide anti-infective agents even further.

Another major advantage of peptide anti-infectives over conventional small molecule therapies in clinical practice is their broader spectrum of activity and potential, therefore, to treat complex polymicrobial infections – a single antimicrobial agent eradicating multiple microbes – as well as infections caused by a single or dominant microorganism. Because resistance development is much less of an issue for peptide anti-infectives, empirical treatment of certain infections prior to identification of the causative pathogen(s) is less of a clinical risk. This is of particular relevance for systemic infections caused by slow-growing fungal pathogens for which no reliable molecular identification techniques are available. In the same context, peptide anti-infectives are better candidates than current therapeutic options for prophylactic application. This might be a particularly attractive strategy for antiviral peptides in controlling potential influenza epidemics, for example, and for antifungal peptides in immunocompromised individuals at risk of developing potentially life-threatening conditions such as candidaemia, aspergillosis and cryptococcosis.

From a regulatory perspective, synthetic novel peptide structures fall somewhere between a traditional small molecule novel chemical entity and a biologic, and so to a great extent their development path is somewhat
CONCLUSION

In summary, global healthcare is facing an unprecedented crisis in terms of the current and predicted future unmet clinical need for effective, safe and resistance-free anti-infective therapies to combat bacterial, fungal and viral disease. The potential of peptide anti-infectives as a solution to this major clinical and economic problem has long-since been recognised, but only now is this beginning to be realised in clinical development and commercialisation. The refinement of antimicrobial peptide development with rational drug design of third- and fourth-generation variants of endogenous forms – combined with improvements in manufacturing, reduced costs of goods, formulation advancements and enabling technologies to increase half-life and stability in vivo – is a very significant factor for the future. The current regulatory and commercial climate for peptide drugs is a key element in this progress and, as such, we can look forward to the introduction to clinical practice of a new class of peptide anti-infective agents which benefit from the desirable antimicrobial properties of their natural counterparts but in a highly druggable form.

References


Deborah A O’Neil is Chief Executive and Scientific Officer at NovaBiotics Ltd (Aberdeen, UK), a company that she founded in August 2004. An immunologist by training with over a decade’s experience in the field of natural antimicrobials, she studied at University College London, UK and then worked in internationally acclaimed laboratories in San Diego (CA, US) and Ghent (Belgium) before moving to Aberdeen. It was here where, in order to fully develop the commercial potential of novel antimicrobial peptide therapies, NovaBiotics was formed. Deborah has since grown the business to a leading global biotechnology company with clinical-stage compounds, and a robust and exciting pipeline of anti-infective peptide drug candidates. Email: deborah@nabbiotics.co.uk

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