EDITORIAL

The urgent need to develop new antibiotics has been a major force behind the advancement of antimicrobial peptides as therapeutics and preventatives. Over the last decade, there have been significant improvements in methodology that are essential to drive the evolution of peptides into marketable drugs. The development of sensitive, high-throughput tools to screen libraries of peptide compounds has enabled the discovery of next-generation molecules active against a broad spectrum of microbes. By looking at the effect that peptide compounds have on the protein expression of both the host and the pathogen, the fields of genomics and proteomics have been invaluable resources in the discovery process. More recently, combinatorial chemistry has played an increasing role in the design of next-generation peptides. Much like current combination antibiotic treatments, 'designer peptides' could likely emerge, whereby antimicrobial peptide cocktails would be formulated specific to each pathogen. However, the convergence of the aforementioned technologies is still in its infancy, and thus it may still be too soon to know how antimicrobial peptides come to meeting the specifications of agents for topical or systemic administration.

In this special issue of *Combinatorial Chemistry and High Throughput Screening*, we have included contributions from scientists with diverse perspectives on developing antimicrobial peptide-based drugs. The first article by Ganz provides an introduction and historical overview of the discovery of defensins and other antimicrobial peptides. This perspective offers an elegant interpretation of seminal discoveries from visionaries such as Ehrlich and Metchnikoff, and proceeds to trace other important contributions that shaped modern innate immunology. Other topics that set the stage for this issue are also discussed, including the mechanism of antimicrobial activity, microbial resistance, and structure-function considerations that are essential in the development of therapeutics. Kristensen and colleagues follow with a detailed account of high-throughput screening systems that have been developed to optimize antimicrobial peptides. The advantages and disadvantages of two approaches are discussed in depth: computational *in silico*-based screening systems and cell-based *in vivo* screening systems.

Peptidomimetics called "peptoids" are unique, non-natural *N*-alkylglycine oligomers that can be easily adapted to combinatorial chemistry approaches. The paper by Masip, Pérez-Payá, and Messeguer discusses properties of peptoids that render these molecules suitable antibacterial agents. Importantly, lead compounds ("hits") against diverse pharmaceutical targets have been discovered through iterative screening of peptoid libraries.

The next article describes studies of the mechanism of action of antimicrobial peptides utilizing membrane model systems for the rational design of novel peptide antibiotics. Lohner and Blondelle provide an in-depth review of the use of biophysical studies in the engineering of peptide antibiotics with improved therapeutic indices. In this article, models of membrane perturbation are discussed, with particular focus on the role of membrane lipid composition in membrane disruption by, and translocation of, antimicrobial peptides.

In designing peptide-based antimicrobial agents, it is imperative to investigate the host's response to infection and the effect of antimicrobial peptides on this process. McPhee, Scott and Hancock examine the role of structure in the design of cationic antimicrobial peptides that also confer enhancement of the host's natural immunity. This report pursues the design and characterization of select prototypical cationic peptides, their modulating effects on the host immune system, and how certain bacteria mount strategies to evade peptide action. While the primary target of cationic antimicrobial peptides is thought to be the microbial membrane, this group also discusses an emerging concept: non-membrane targets for antimicrobial peptides. The report is rounded out by an honest delineation of hurdles in peptide development, and how we are attempting to overcome these obstacles.

The last article in the series by Sørensen and Borregaard reminds us that combinatorial chemistry was not just an invention by humankind – indeed, nature has evolved a unique family of antimicrobial peptides called "cathelicidins", an extremely diverse group of peptides released by mammalian epithelia and neutrophils. Several properties of cathelicidins are discussed, which render them ideal templates for advanced combinatorial approaches. The authors conclude by commenting on an important, but frequently overlooked, facet of antibiotic design – screens for efficacy must include biologically relevant systems that reflect the environment(s) in which the antimicrobial peptides are designed to function.

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