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Perspective

Can the Rise of Foldamers Herald the Fall of Antibiotic Resistance?

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The rise of antibiotic resistance is quickly becoming an issue of worldwide concern. Whilst to some people it may appear to be tomorrow's problem, to many others, tomorrow has now arrived and it is time to address it. In essence, we are losing the battle against infectious diseases because—to coin a phrase from England'sChief Medical Officer, Professor Dame Sally Davies—"the drugs don't work"; bacteria are becoming resistant [1]. Through the continued overuse and misuse of antibiotics, the current antibacterial agents we have no longer work like they used to. Moreover, the fact that we are also not developing new drugs fast enough simply compounds the problem.

Research clearly has a huge part to play in combating the resistance to our current arsenal of antibacterial drugs, and none more so than that aimed at the design and preparation of new chemical agents. However, there has been a declining number of pharmaceutical companies working in this area over recent decades, and that can be blamed, at least in part, on the perceived risk of resistance occurring too quickly against any newly developed drugs.Even if pharmaceutical companies were to be successful in developing a new blockbuster antibacterial agent, this most potent of compounds would likely be underused, only to be brought out for the most serious of cases – not a very strong incentive to developing better compounds. Nevertheless, new drugs which work through new mechanisms of action and against newly discovered bacteria-specific targets, are highly sought after, and perhaps the greatest barrier to this goal is the financial incentive or funding to pursue it.

In response to this, the UK government announced the launch of a Commission on Antimicrobial Resistance, designed to arrest the global over-use of existing antibiotics [2]. This has been a timely proposal which will hopefully re-dress the egress of Big Pharma from this research area in which few new classes of antibiotics have been marketed for a quarter of a century. In addition, the winning challenge in the £10 million Longitude Prize (2014) [3], was 'Antibiotics', a research theme chosen by members of the public, which provides an insight into the fact that antibiotic resistance is now considered by many to be one of the greatest issues of our time – the very definition of the Longitude Prize. Furthermore, the Biotechnology and Biological Sciences Research Council (BBSRC, UK) has also announced that one of its key strategic priorities would be to combat antimicrobial resistance, and the Academy of Pharmaceutical Sciences (APS, UK) has recently launched its Microbiology and Anti-Infectives Focus Group, which aims to provide a forum for the promotion of pharmaceutical microbiology and anti-infectives research.

The crisis associated with antimicrobial resistance has generated major world-wide opportunities for science and technology to lead the way in combating the problem, not least in the development of new antibacterial agents and treatments. With this in mind, one area of research that could deliver some of the answers is the field of foldamer research [4-6]. A foldamer can be defined as "a discrete oligomer that folds into a conformationally ordered state in solution", and contemporary research has shown that a number of naturally occurring foldamer constructs (peptides) can interact with,and disrupt,bacterial cell membranesthus making these agents valid candidates for future therapeutics, particularly if selectivity over host cells can be achieved [7].

The fact that the total number of new antibiotic templates increased from 11 in 2011 to 17 in 2013, and that these are predominantly associated with natural foldamers of the antimicrobial peptide class, is promising [8], especially if foldamers are to help combat antibacterial resistance and provide new therapeutics in the future.For example, pexiganan, marketed by Dipexium Pharmaceuticals, Inc. under the trade name Locilex®, is a 22-amino acid peptide isolated from the skin of the African Clawed Frog and is used for the treatment of diabetic foot infections. It has a bactericidal mechanism of action which works by disrupting the cell membrane, and is able to lyse the membranes of both Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains. Biophysical studies have shown that whilst this peptide is unstructured in solution, it forms precise folded amphiphilic helices upon binding to the membrane, and goes on to disrupt the membrane via toroidal-type pore formation [9]. Furthermore, this antimicrobial peptide foldamer has not generated resistant bacteria systemically, has not generated cross resistance with other antibiotics, and has not caused any significant safety issues in over 500 patients treated in clinical trialsto date [9].

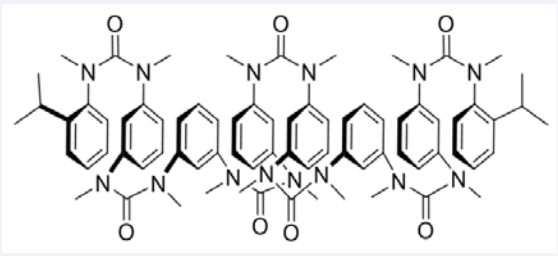

Figure 1 An aromatic foldamer which mimics a membrane-active antimicrobial α-helical peptide [12].

Another foldamer which exert its effects through a membrane-disruptive mode of action is daptomycin, a lipopeptide capable of depolarising the membrane of Gram-positive bacteria, which is currently marketed in the United States for the treatment of *C. difficile*-associated diarrhoea by Cubist Pharmaceuticals. Similarly, the peptide-derived foldamersbrilacidin, LTX-109 and LL-37 are all membrane disruptive or membrane lytic compounds which are active against both Gram-positive and Gram-negative strains of bacteria and which are currently in phase II clinical trials for the treatment of bacterial skin infections or wound healing [8].

Related to this, our research focuses on taking the known antimicrobial activity of such peptide foldamers and translating it to unnatural, fully synthetic, novel foldamer systems (Figure 1) [10-12]. The folding of macromolecules into well-defined architectures is fundamental to Nature's ability to control reactivity, relying on non-covalent interactions to do so. However, millions of years of evolution are required for biomacromolecules to achieve their high levels of specificity. Nevertheless, by exploiting the virtually infinite number of building blocks available to the organic/medicinal chemist, it is possible to speed up the evolutionary process. In this way, synthetic, unnatural foldamers hold promise in being able to mimic Nature's biomacromolecules, but be highly tunable constructs with which to rationally design better, more selective and potent treatments through disruption of the cell membrane.

By working closely with biophysicists and microbiologists, foldamer chemists are able to design and make new compounds which are able to interact and lyse phospholipid membranes of bacterial relevance[10-12], but there is a long way to go before we can match the finesse of Nature's evolutionary process. Nevertheless, by continuing to work closely within multidisciplinary teams the research is moving forward to begin to find answers to the problem of antimicrobial resistance. The area is currently a hot topic and numerous research groups are interested in using this approach too, not least, the pioneering work in this area of Huc [13] and De Grado [14-16]; recent approaches in the design of peptidomimetics for antimicrobial drug discovery has recently been reviewed [17].

With the additional funding that is now becoming available for research to combat antibacterial resistance and develop new medicines, and by working together, only time will tell if future generations will benefit from the next generation of antibacterial agents, and whether any of the new agents will be based on a foldamer scaffold.

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REFERENCES

1. Davies SC. The drugs don't work: a global threat. Penguin Specials.2013; London.
2. https://www.gov.uk/government/groups/advisory-committee-on-antimicrobial-resistance-and-healthcare-associated-infection
3. http://www.longitudeprize.org/
4. Saraogi I, Hamilton AD. Recent advances in the development of aryl-based foldamers. Chem Soc Rev. 2009; 38: 1726-1743.
5. Huc . Aromatic oligoamide foldamers. Eur. J. Org. Chem. 2004; 1: 17-29.
6. Hill DJ, Mio MJ, Prince RB, Hughes TS, Moore JS. A field guide to foldamers. Chem Rev. 2001; 101: 3893-4012.
7. Dennison SR, Harris F, Mura M, Morton LH, Zvelindovsky A, Phoenix DA. A novel form of bacterial resistance to the action of eukaryotic host defense peptides, the use of a lipid receptor. Biochemistry. 2013; 52: 6021-6029.
8. Butler MS, Blaskovich MA, Cooper MA. Antibiotics in the clinical pipeline in 2013. J Antibiot (Tokyo). 2013; 66: 571-591.
9. Gottler LM, Ramamoorthy A. Structure, membrane orientation, mechanism, and function of pexiganan--a highly potent antimicrobial peptide designed from magainin. Biochim Biophys Acta. 2009; 1788: 1680-1686.
10. Dennison SR, Akbar Z, Phoenix DA, Snape TJ. Interactions between suitably functionalised conformationally distinct benzanilides and phospholipid monolayers.Soft Matter. 2012; 8: 3258-3264.
11. Dennison SR, Snape TJ, Phoenix DA. Thermodynamic interactions of a cis and trans benzanilide with Escherichia coli bacterial membranes. Eur Biophys J. 2012; 41: 687-693.
12. Dennison SR, Phoenix DA, Snape TJ. Synthetic oligoureas of metaphenylenediamine mimic host defence peptides in their antimicrobial behaviour. Bioorg Med Chem Lett. 2013; 23: 2518-2521.
13. Gillies ER, Deiss F, Staedel C, Schmitter JM, Huc I. Development and biological assessment of fully water-soluble helical aromatic amide foldamers. Angew Chem Int Ed Engl. 2007; 46: 4081-4084.
14. Mensa B, Kim YH, Choi S, Scott R, Caputo GA, DeGrado WF. Antibacterial mechanism of action of arylamide foldamers. Antimicrob Agents Chemother. 2011; 55: 5043-5053.
15. Tew GN, Scott RW, Klein ML, Degrado WF. De novo design of antimicrobial polymers, foldamers, and small molecules: from discovery to practical applications. Acc Chem Res. 2010; 43: 30-39.
16. Goodman CM, Choi S, Shandler S, DeGrado WF. Foldamers as versatile frameworks for the design and evolution of function. Nat Chem Biol. 2007; 3: 252-262.
17. Lohan , Bisht GS. Recent approaches in design of peptidomimetics for antimicrobial drug discovery research. Mini Rev Med Chem. 2013; 13: 1073-1088.

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