

## Anti-Infective Drugs: Why Should We Pay Attention?

Hisham R. Ibrahim\*

The Graduate School of Agricultural Sciences, Kagoshima University, Kagoshima, Japan

Infectious disease is not a problem of the past; despite significant breakthroughs achieved during the last century in the development of antibiotic drugs, the control of many infectious diseases has not been accomplished. The concern is the problems of rapidly developing drug resistance, re-emerging disease, and the speed of appearance of virulent strains posing global threats. Thus, antibiotic resistance is now a global healthcare threat and today's armoury of antibiotics is increasingly limited. For some pathogens, the choice from available drugs is now greatly reduced. Increasing mortality from infections caused by resistant strains, and the increasing levels of hospital-acquired infections, together with escalating healthcare costs, have put antibiotic resistance at the top of the healthcare agenda.

According to the US Centers for Disease Control and Prevention and studies on deaths attributable to a differing selection of multi-drug resistance (MDR) infections show that, each year, these infections result in an estimated 25,000 deaths in 29 countries in Europe (5.1 per 100,000 inhabitants) and 12,000 deaths in the US (4.0 per 100,000 inhabitants) [1-3]. If all MDR infections and other infections with problematic resistance profiles were included in these studies, the estimate of deaths would be much higher. These figures show that antibiotic resistance has reached a critical point, as human and economic costs escalate. Many pathogens are now completely resistant to beta-lactam antibiotics and MDR resistant *Gonorrhoeal* strains have emerged [4].

Resistance is a familiar problem in antibiotic therapy, because bacteria have evolved genetic attributes "resistome", which specifically enable them to withstand antibiotics, which they produce naturally. Killing pathogens is the goal of antibiotic therapy, but there is now a need to extend the capabilities of anti-bacterial therapies, to develop novel anti-infective drugs and strategies that both destroy pathogens and also undermine resistance mechanisms in more effective ways.

### Prospects and the Needed Rigorous Research

Endogenous host defense peptides (HDPs) have retained evolution-tested efficacy against pathogens that have become refractory to traditional antibiotics. Evidence indicates that HDPs target membrane integrity and bioenergetics of microbes that may be less mutable than conventional antibiotic targets [5]. HDPs have, thus, received increasing attention as templates for development of potential anti-infective therapeutics. The HDPs are short cationic amphiphilic peptides with antimicrobial and/or immunomodulatory activities are present in virtually every life form, as an important component of (innate) immune defenses [6]. These HDPs provide a template for two separate classes of antimicrobial drugs. Direct-acting antimicrobial peptides can be rapid-acting and possess an unusually broad spectrum of activity; consequently, they have prospects as new antibiotics, although clinical trials to date have shown efficacy only as topical agents. But for these peptides to fulfill their therapeutic promise and overcome clinical drawbacks, further work is needed to understand their mechanisms of action and reduce the potential for unwanted toxicity, to make them more resistant to protease degradation and improve half-life in serum, as well as to devise means of manufacturing them on a large scale in a consistent and cost-effective manner. In contrast, the role of cationic host-defense peptides in modulating the innate immune response and boosting infection-resolving immunity while dampening potentially

harmful pro-inflammatory (septic) responses gives these peptides the potential to become an entirely new therapeutic approach against bacterial infections.

However, advances toward this goal have proven insufficient, owing to limited understanding of structure-activity and selective toxicity relationships *in vivo*, and the difficulty of cost-effective production of such peptides on a large scale. Thus, innovative technology and advanced molecular insights could lead to novel HDP-based and mimetic anti-infective peptide candidates designed to overcome these limitations. Although initial setbacks have presented challenges to therapeutic development, emerging studies continue to highlight the potential of HDP-based anti-infective as a platform for next-generation therapeutics that will help address the growing threat of multidrug-resistant infections [6].

Another scientific rationale for the development of novel anti-infective strategies is the exploration of probiotics, which exert their beneficial effects *in vivo*. Probiotic is defined as a live organisms that, when ingested, exerts a health benefit to the host. The commonly used probiotics are lactic acid bacteria (LAB) and non-pathogenic yeasts. Not only the live LAB, but also dead bacteria, bacterial components, bacterial DNA and substances elaborated by commensal strains have been shown to exert antibacterial, anti-inflammatory, immunomodulatory and other effects similar to those exhibited by live organisms. Potential studies on individual Probiotic organisms or in cocktails have shown that probiotics metabolically interact with pathogens, produce chemical products (such as bacteriocins) that directly inhibit other bacteria or viruses, inhibit bacterial movement (translocation) across the gut wall, enhance mucosal barrier function and signaling with the epithelium and immune system to modulate the inflammatory/ immune response [7-9].

Since not all probiotics have been isolated from human gastrointestinal tract and thus cannot be regarded as human commensals and not all commensals exert probiotic effects, an understanding of the normal human microbiome and of its interactions with the host lies at the heart of the scientific basis of Probiotic therapy. While some real progress has been made, we certainly need more high quality trials of probiotics in digestive disorders as well as laboratory investigations of mechanism of action. The benefits of probiotics are often demonstrated under defined laboratory experimental conditions, but these beneficial effects may fail to be compatible in clinical trials. Clinical trials are essential for establishing the practical and scientific logic of the probiotic therapy.

\*Corresponding author: Hisham R. Ibrahim, PhD, Professor, The Graduate School of Agricultural Sciences, Kagoshima University, Kagoshima, Japan, Tel: 099-285-8658; Fax: 099-285-8525; E-mail: [hishamri@chem.agri.kagoshima-u.ac.jp](mailto:hishamri@chem.agri.kagoshima-u.ac.jp)

Received March 09, 2012; Accepted March 13, 2012; Published March 19, 2012

Citation: Ibrahim HR (2012) Anti-Infective Drugs: Why Should We Pay Attention? J Develop Drugs 1:e112. doi:10.4172/2329-6631.1000e112

Copyright: © 2012 Ibrahim HR. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Quorum sensing is a mechanism by which bacteria regulate gene expression, in response to changes in the population, and is integral to the virulence process [10]. This mechanism is based on the release of chemical messengers (auto-inducers), the levels of which fluctuate within bacterial cell populations. Processes that are regulated through quorum sensing include virulence, competence, conjugation, antibiotic production, motility, and biofilm formation. The importance of quorum sensing in the regulation of bacterial populations makes this mechanism a potential target for antimicrobial agents. Research pipeline should include biopeptides and Probiotic strains developed to target quorum sensing of pathogens. Eventually, despite the critical need for new antimicrobial agents, the development of these agents is declining. Solutions encouraging and facilitating the development of new antimicrobial drugs should also be given a great importance.

### References

1. The bacterial challenge: time to react. ECDC/EMA Joint Technical Report: Eur Cntr Dis Prevent Ctrl (2009).
2. Zell BL, Goldmann DA (2007) Healthcare-associated infection and antimicrobial resistance: moving beyond description to prevention. *Infect Control Hosp Epidemiol* 28: 261-264.
3. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, et al. (2009) Bad bugs, no Drugs: no ESCAPE! An Update from the Infectious Diseases Society of America. *Clin Infect Dis* 48: 1-12.
4. Lewis DA (2011) Antimicrobial-resistant gonorrhoea in Africa: An important public health threat in need of a regional gonococcal antimicrobial surveillance programme. *South Afr J Epidemiol Infect* 26: 215-220.
5. Yount NY, Yeaman MR (2012) Emerging themes and therapeutic prospects for anti-infective peptides. *Annu Rev Pharmacol Toxicol* 52: 337-360.
6. Hancock RE, Sahl HG (2006) Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. *Nat Biotechnol* 24: 1551-1557.
7. Thomas CM, Versalovic J (2010) Probiotics-host communication: modulation of signaling pathways in the intestine. *Gut Microbes* 1: 148-163.
8. Qin H, Zhang Z, Hang X, Jiang Y (2009) *L. plantarum* prevents enteroinvasive *Escherichia coli*-induced tight junction protein changes in intestinal epithelial cells. *BMC Microbiol* 9: 63.
9. Resta-Lenert S, Barrett KE (2003) Live probiotics protect intestinal epithelial cells from the effects of infection with enteroinvasive *Escherichia coli* (EIEC). *Gut* 52: 988-997.
10. Fontaine L, Boutry C, Guedon E, Guillot A, Ibrahim M, et al. (2007) Quorum-Sensing Regulation of the Production of Blp Bacteriocins in *Streptococcus thermophilus*. *J Bacteriol* 189: 7195-7205.