Infectious Disease

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Executive Editor

Innovative Therapeutic Technologies to Fight against Drug-Resistant *Pseudomonas aeruginosa* Infections

Pseudomonas aeruginosa (P. aeruginosa) is a ubiquitous Gram-negative bacterium. It belongs to the family Pseudomonadaceae that is known to survive in a wide range of environments. *P. aeruginosa* exhibits a relatively large genome (5.5–7 Mbp) compared to other sequenced bacteria such as *Bacillus subtilis* (4.2 Mbp), *Escherichia coli* (4.6 Mbp) and *Mycobacterium tuberculosis* (4.4 Mbp). Further, it encodes a large proportion of regulatory enzymes important for metabolism, transportation and efflux of organic compounds [1-4]. P. aeruginosa is known to be an opportunistic pathogen, which causes morbidity and mortality in cystic fibrosis (CF) patients and immunocompromised individuals. It is therefore, of paramount clinical importance to eradicate *P. aeruginosa*. However, it is a significant challenge to eliminate this highly harmful pathogen due to its remarkable capacity to resist antibiotics (Figure 1) [1].

Clinical studies have shown that the lung of a CF patient provides a conducive environment for bacterial growth and colonization. Thus, it is believed that *P. aeruginosa* is the predominant pathogen causing CF lung infections [1]. Further, researchers have shown that chronic infection with *P. aeruginosa* is recalcitrant to antibiotic treatment that subsequently results in declined pulmonary functions and ultimately to mortality in CF patients [5]. In addition, it has been shown that over 5% of infectious exacerbations in patients with chronic obstructive pulmonary disease (COPD) are caused by *P. aeruginosa* that has been associated with increased mortality of these patients [6].

New Antipseudomonal Antibiotics and Therapeutic Strategies for Treatment of P. aeruginosa Infections

The rise of multidrug-resistant strains of *P. aeruginosa* poses a major therapeutic challenge for the applications of conventional antibiotic therapies against infections [7]. Hence, there have been growing demands for the discovery and development of alternative therapeutic strategies including new antipseudomonal antibiotics that present

novel avenues against *P. aeruginosa* infections. Most of the studies that have reported several innovative therapeutic technologies with demonstrated effectiveness in fighting against drug - resistant *P. aeruginosa* strains are in the pre-clinical state of studies [1].

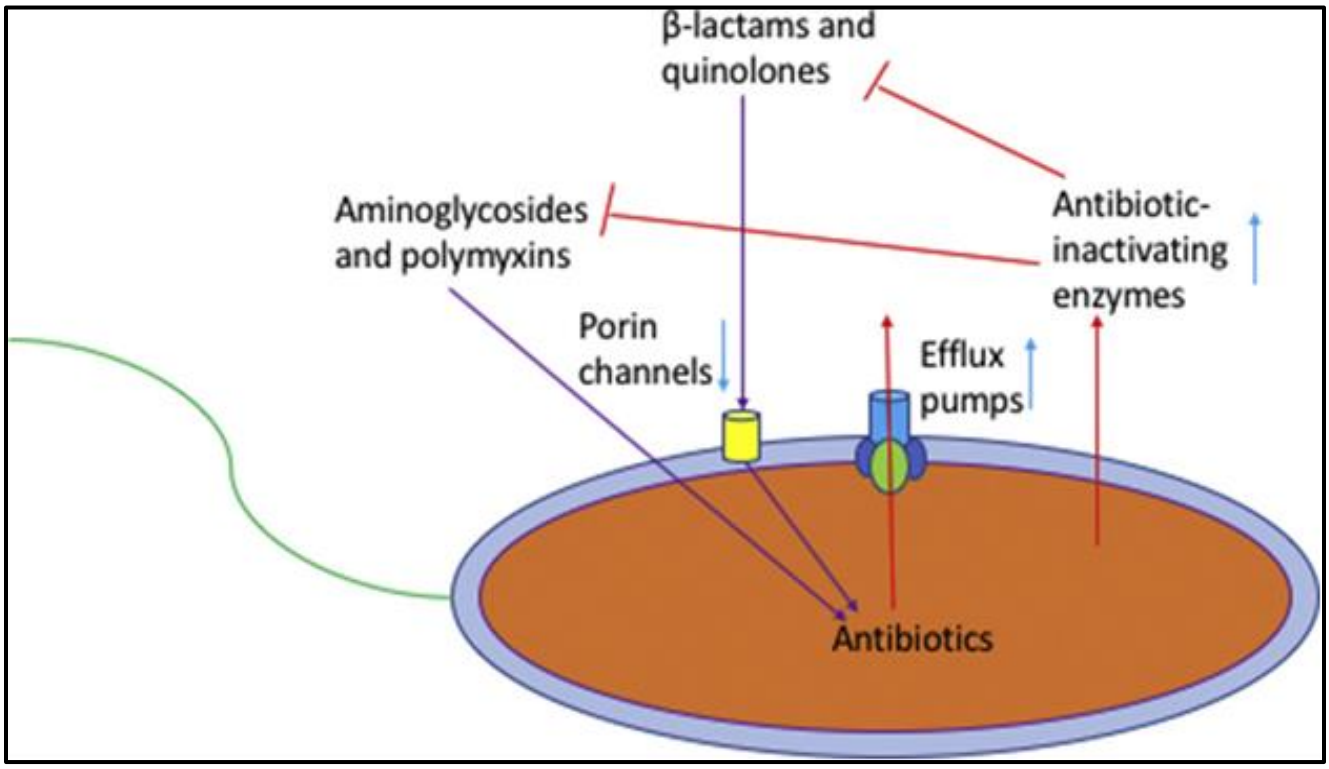

*Figure 1: A schematic representation of the underlying mechanisms showing intrinsic antibiotic resistance in P. aeruginosa that include restricted outer-membrane permeability, efflux systems that pump antibiotics out of the cells and production of antibiotic-inactivating enzymes. Further, β-lactams and quinolones penetrate cell membranes through porin channels. By interacting with P. aeruginosa lipopolysaccharides on the outer membrane, aminoglycosides and polymyxins promote their own uptake [**Source:** Biotechnology Advances, 37 (2019)].*

The use of different antibiotic combinations along with development of new antibiotics constitute a major part of current therapeutic strategic options for *P. aeruginosa* treatment [8]. The new antibiotics that are in the process of getting into clinical trials have shown their effectiveness in killing P. aeruginosa pathogens. These new antibiotics have also demonstrated a lower frequency of resistance development compared to existing antibiotics. This is due to their novel modes of therapeutic action, efficient drug delivery including inhaled antibiotics and also resistance to modification by bacterial enzymes [1, 7]. New alternative therapeutic approaches include quorum sensing inhibitors, phages, probiotics, anti-microbial peptides, vaccine antigens and antimicrobial nanoparticles (Figure 2) [1]. Researchers have shown that these novel therapeutic strategies can act either alone or in combination with conventional therapies to combat *P. aeruginosa* infections [1, 7, 8].

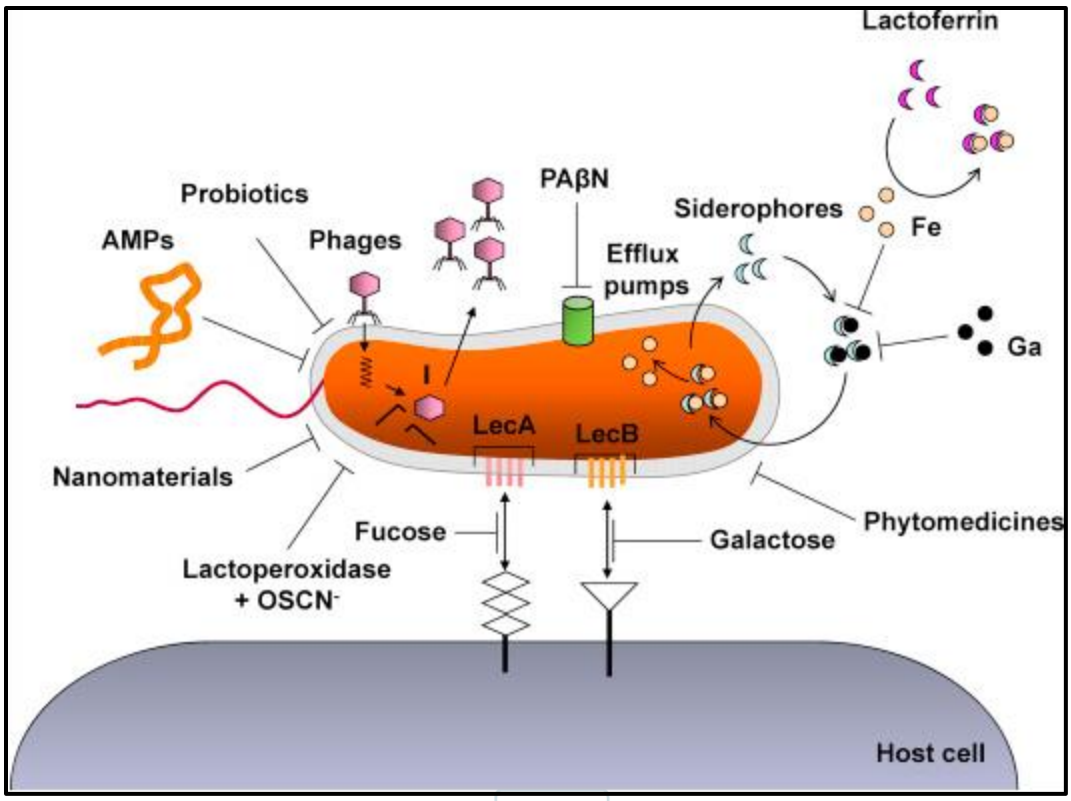

Figure 2: Various novel therapeutic strategies to combat P. aeruginosa *infections [**Source:** Int J Med Microbiol, 306 (2016)].*

Concluding Remarks

It is a significant challenge to treat P. aeruginosa infections that continues to be a serious tough task in the field of bacteria and infectious disease. The current efforts have focused on developing new antibiotics and novel therapeutic strategies that are based on alternative methodologies to tackle the antibiotic resistance problem of *P. aeruginosa*. There has been significant progress made in this direction especially developing novel modes of action, and resistance to modification by bacterial enzymes along with improvements to drug delivery efficiency. However, most of these newer approaches are in the pre-clinical stage and we anticipate that it might take some time before these innovative therapeutic technologies enter into clinical studies for practical applications in humans. We further anticipate that development of new antimicrobial agents and alternative strategies for prevention and treatment of *P. aeruginosa* infections will continue to evolve and shape for potential major breakthroughs and discoveries in therapeutics for the effective elimination of this bacteria.

References for Further Reading

1. Zheng Pang, Renee Raudonis, Bernard R.Glick, Tong-Jun Lin, Zhenyu Cheng, Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies, Biotechnology Advances, 37, 177 (2019).

2. Shyamasri Biswas, Mohammad M. Mohammad, Dimki R. Patel, Liviu Movileanu and Bert van den Berg, Structural insight into OprD substrate specificity, Nature Structural and Molecular Biology, 14, 1108 (2007).

3. Shyamasri Biswas, Mohammad M. Mohammad, Liviu Movileanu, Bert van den Berg, Crystal structure of the outer membrane protein Opdk from Pseudomonas aeruginosa, Structure, 16, 1027 (2008).

4. M.W. Silby, C. Winstanley, S.A. Godfrey, S.B. Levy, R.W. Jackson, Pseudomonas genomes: diverse and adaptable, FEMS Microbiol Rev, 35, 652 (2011).

5. J.B. Lyczak, C.L. Cannon, G.B. Pier, Lung infections associated with cystic fibrosis, Clin Microbiol Rev, 15, 194 (2002).

6. T.F. Murphy, Pseudomonas aeruginosa in adults with chronic obstructive pulmonary disease, Curr Opin Pulm Med, 15, 138 (2009).

7. M. Chatterjee, C.P. Anju, L. Biswas, V. Anil Kumar, C. Gopi Mohan, R. Biswas, Antibiotic resistance in Pseudomonas aeruginosa and alternative therapeutic options, Int J Med Microbiol, 306, 48 (2016).

8. M.N. Hurley, M. Camara, A.R. Smyth, Novel approaches to the treatment of Pseudomonas aeruginosa infections in cystic fibrosis, Eur Respir J, 40, 1014 (2012).