Microbial approaches for targeting antibiotic-resistant bacteria

Wing Fei Wong1 and Marina Santiago2,*

1OpenBiome, 2Finch Therapeutics, 200 Inner Belt Rd, Somerville, MA 02143, USA.

Summary
Antibiotic resistant bacterial infections are a global public health challenge that has been increasing in severity and scope for the last few decades. Without creative solutions to this problem, treatment of injuries and infections will become progressively more challenging. A better understanding of the human microbiome has led to a new appreciation for the role commensal microbes play in protecting us from pathogens, especially in the gut. Antibiotics lead to disruption of the gut microbial ecosystem, enabling colonization by antibiotic resistant bacterial pathogens. Many different lines of research have identified specific bacterial taxa and mechanisms that play a role in colonization resistance, and these lines of research may one day lead to microbial therapeutics targeting antibiotic resistant bacteria. Here, we discuss a few of these strategies and the challenges they will need to overcome in order to become an effective therapeutic.

Antibiotic-resistant bacteria pose a threat to public health
A major threat to Sustainable Development Goal 3 (ensuring healthy lives and promoting well-being for all at all ages) is the rise of antibiotic-resistant bacteria (ARB). Without new therapeutic strategies, the World Health Organization has stated that we could be headed for a ‘post-antibiotic era’, in which previously treatable infections are once again deadly (WHO Media Cent, 2014). In the USA alone, the CDC estimates that more than 2 million people contract antibiotic-resistant infections every year, resulting in more than 23,000 deaths (US Department of Health and Human Services, Centers for Disease Control and Prevention, 2013). This results in more than $20 billion in healthcare costs per year, with an additional $35 billion in lost economic output (Roberts et al., 2009; US Department of Health and Human Services, Centers for Disease Control and Prevention, 2013). On an individual patient level, this translates to increased costs, longer hospital stays and a higher likelihood of adverse events and death (Roberts et al., 2009; US Department of Health and Human Services, Centers for Disease Control and Prevention, 2013; Gandra et al., 2014).

Microbial strategies for decreasing antibiotic resistance are promising and sustainable
The human microbiome, which consists of all the bacterial, fungal and viral microorganisms that colonize epithelial surfaces of the human body, may hold the key to fighting ARB. Members of the human microbiome play roles in many aspects of human development (Vaishnava et al., 2008; Dinan and Cryan, 2012; Sommer and Backhed, 2013; Peterson and Artis, 2014; De Santis et al., 2015; Chung et al., 2016). Generally, these organisms are commensal, but under certain conditions, some of these bacteria have been associated with chronic and acute disorders (Becattini et al., 2016; Nagao-Kitamoto et al., 2016; Fung et al., 2017; Sommer et al., 2017; Wen and Duffy, 2017).

Antibiotic-resistant bacterial infections are often a direct result of a disruption of the gut microbiome (Carlet, 2012; Sassone-Corsi and Raffatellu, 2015; Pamer, 2016). A healthy intestinal microbiome consists of a highly diverse population. When this diversity is decreased by antibiotic treatment, niches become available for pathogen colonization. Domination of the gut microbiome by a pathogen places patients at high risk for developing infection by that pathogen as the gut barrier integrity weakens, enabling pathogen translocation across the epithelial barrier (Taur et al., 2012). Furthermore, ARB-colonized patients can serve as vectors of ARB transmission.

There are two major microbial strategies that are being pursued for combating ARB. These include the following: (i) bacteriophage-based strategies can target...
specific strains that colonize patients and cause chronic infections, and (ii) microbial remediation of the gastrointestinal tract relies on commensal bacteria for inhibition of ARB growth and transmission. In this review, we will discuss some exciting examples for each of these promising lines of research (Fig. 1).

**Bacteriophage precisely target ARB pathogens**

Bacteriophage-based therapies focus on using phage or its component proteins to target highly specific strains of bacteria. The approach of using bacteriophage (phage) isolates to treat bacterial infections has traditionally been pursued in the former Soviet Union and Eastern Europe (Sulakvelidze et al., 2001). These reports speak to the safety profile of this therapy (Weber-Dabrowska et al., 2000; Bruttin and Brüssow, 2005). In addition, phage are readily modifiable to combat emergence of newly arising bacterial threats (Samson et al., 2013). However, current research into whole phage therapies lacks rigorous proof of efficacy, namely properly conducted randomized placebo-controlled studies. There are concerns over immunogenicity of phage therapy, as well as development of bacterial resistance to bacteriophages (Lu and Koeris, 2011; Pires et al., 2016). Furthermore, requirement of regulatory approval in the United States, among other obstacles, prevents widespread use of phage therapy.

Issues of using whole phage therapy may be mitigated by using bacteriophage lysins: phage-encoded peptidoglycan hydrolases that induce rapid lytic death (Young, 1992; Young and Blasi, 1995; Wang et al., 2000; Borysowski et al., 2006). Exogenous recombinant lysins effectively target Gram-positive bacteria, as there is no outer membrane to prevent access to the cell wall (Loeffler et al., 2001; Fenton et al., 2010). Lysins are also reported to have narrow host range, which theoretically spares the surrounding commensal microflora (Fenton et al., 2010). However, lysins face similar therapeutic challenges as phage therapy: like all other foreign agents, the host will develop neutralizing antibodies, which will reduce the levels of enzyme during treatment. Furthermore, this therapeutic is largely ineffective in Gram-negative bacteria. While this may be circumvented using outer membrane permeabilizers, there may be cytotoxic effects associated with this approach that limit its safety (Amaral et al., 2007; Walmagh et al., 2013).

Advances in genetic engineering technology have allowed researchers to manipulate phage to enhance antibacterial activity, targeting and delivery. Engineered phages can deliver genes conferring increased sensitivity to antibiotics (Lu and Collins, 2009; Edgar et al., 2012), disrupt biofilm matrices through delivery of biofilm-degrading enzymes (Lu and Collins, 2007) and deliver lethal-agent phagemid particles (Westwater et al., 2003). Using the CRISPR-Cas system, RNA-guided nucleases are delivered via phagemids into bacterial cells, where they target specific genetic sequences and induce a double-strand break, leading to plasmid loss or cell death (Citorik et al., 2014). While engineered phage therapy is promising, more research is required for optimizing vector delivery and minimizing immunogenicity.

**Microbiome restoration inhibits ARB growth and transmission**

Commensal bacteria can provide resistance to ARB by interacting with the host. For example, some Gram-negative obligate anaerobes are known to induce the production of host antimicrobial peptides (Sonnenburg et al., 2006; Brandl et al., 2008; Kinnebrew et al., 2010; Ubeda et al., 2013). In addition, short-chain fatty acid (SCFA) production is intimately involved in pathogen defence. SCFAs are the main source of energy for colonocytes, induce IgA production, reduce inflammation and may be involved in increasing the thickness of the mucus layer (Zimmerman et al., 2012; Earle et al., 2015; Desai et al., 2016; Jones, 2016; Wu et al., 2016; Goverse et al., 2017; Olsan et al., 2017; Rowland et al., 2017). These
strains are vital for preventing bacterial translocation by reinforcing the gut barrier.

Other commensal bacteria can directly attack or inhibit pathogen growth. In fact, co-culture of some commensal and pathogenic strains results in the direct killing of the pathogen through the production of secreted molecules like bacteriocins (Gilmore et al., 2015; Gaca and Gilmore, 2016; Sassone-Corsi et al., 2016). Strains producing these molecules could be used therapeutically to eliminate populations of ARB from the gut.

Predatory bacteria have the potential to play a role in the management of antibiotic-resistant infections. *Bdellovibrio* spp. and *Micavibrio* spp. are proteobacteria whose life cycle contains an attack phase where they attach to, or invade and kill other bacteria. These predators can kill many Gram-negative pathogens, including those resistant to antibiotics of last resort (Markelova, 2010; Kadouri et al., 2013). In vivo experiments with predatory bacteria have established their safety and efficacy at decreasing pathogen burden in mammalian models (Westergaard and Kramer, 1977; Shatzkes et al., 2015, 2016; Boileau et al., 2016; Zurawski et al., 2017). However, one concern is that the observed efficacy is not a result of direct pathogen inhibition, but rather indirect activation of the immune system in surrounding tissues. Future studies assessing safety to the human host and microbiome will shed light on the utility of this approach.

Commensal organisms may be able to combat antibiotic resistance through inhibition of horizontal gene transfer (HGT). Antibiotic resistance genes are often found on mobile genetic elements like plasmids and transposons, which travel to other bacteria through HGT. Commensal microbes may be able to prevent this process; a consortium of four anaerobic bacterial strains can suppress mobilization of KPC, a common beta-lactamase gene, from *E. cloacae* to *K. pneumoniae* in a germ-free mouse model (Nudel et al., 2017).

These mechanisms, among others, may contribute to the success seen using faecal microbiota transplants (FMTs) for decolonization of ARB. FMT has been used extensively for treatment of recurrent *Clostridium difficile* infections with a remarkably high efficacy rate (85%; Drekonja et al., 2015). FMT is thought to act by delivering commensals that (i) directly compete for niches with *C. difficile*, (ii) convert primary bile acids, which are required for *C. difficile* spore germination, into secondary bile acids, and (iii) activate the immune system and help

Table 1. FMT decolonizes antibiotic-resistant bacteria from the human gut.

| Report                        | # Patients | VRE | CRE | ESBL-E | Others | Results                                           |
|-------------------------------|------------|-----|-----|--------|--------|--------------------------------------------------|
| Freedman, 2014                | 1          | X   |     |        |        | 1/1 decolonized for at least 8 months             |
| Singh, 2014                   | 1          |     |     |        | X      | 1/1 decolonized at 2 weeks                        |
| Stripling, 2015               | 1          |     | X   |        |        | 1/1 reduced relative abundance and no further VRE infections for 1 year |
| Crum-Cianflone, 2015          | 1          | X   |     |        | X      | 1/1 reduced MDRO colonization and no episodes of sepsis for 2 years |
| Jang, 2014                    | 1          |     |     |        | X      | 0/1 decolonized at 3 months                       |
| Lombardo, 2015 (SER-109)      | 8          |     | X   |        |        | 8/8 titers decreased > 2 fold at 4 weeks          |
| Bilinski, 2016                | 1          |     | X   |        |        | 1/1 decolonized at 10 days                        |
| Lagier, 2015                  | 1          | X   |     |        |        | 1/1 decolonized at 7 days                         |
| Wei, 2015                     | 5          |     |     |        | X      | 5/5 decolonized of MRSA for 3 months              |
| Eysenbach, 2016               | 9          | X   |     |        |        | 9/9 decolonized at first time point measured post-FMT  |
| Dubberke, 2016                | 11         |     | X   |        |        | 8/11 decolonized at last available follow-up      |
| Jouhten, 2016                 | 8          |     |     | X      | X      | 8/8 reduction in number and diversity of antibiotic resistance genes |
| Millan, 2016                  | 20         | X   |     | X      | X      | 20/20 reduction in number and diversity of antibiotic resistance genes |
| Garcia-Fernandez, 2016        | 1          | X   |     |        | X      | 1/1 decolonized at 6 weeks                        |
| Sohn, 2016                    | 3          |     |     |        | X      | 0/3 decolonized for 3 months                      |
| Davido, 2017                  | 8          | X   |     |        |        | 2/6 CRE decolonized at 1 month, 1/2 VRE decolonized at 3 months |
| Ponte, 2017                   | 1          |     |     |        | X      | 1/1 CRE decolonized at 15, 45, and 100 days      |
| Bilinski, 2017                | 20         | X   |     | X      | X      | 15/20 decolonized at 1 month                      |
| Total:                        | 101        | 38/46 (83%) | 45/57 (79%) | 50/54 (93%) | 39/39 (100%) | 83/101 (82%) decolonized or decreased in antibiotic resistance genes at primary endpoint |

VRE, Vancomycin Resistant Enterococcus; CRE, Carbapenem Resistant Enterobacteriaceae; ESBL-E, Extended Spectrum Beta Lactamase Producing Enterobacteriaceae; FMT, fecal microbiota transplant.

Unless otherwise noted, patients were treated with fecal microbiota transplant. Some patients were co-colonized with multiple pathogens.

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maintain the gut barrier, reducing bacterial translocation across the epithelial layer and preventing pseudomembranous colitis (Khoruts and Sadowsky, 2016).

Faecal microbiota transplant success in the context of C. difficile has led to the reporting of many small case studies assessing the efficacy of FMT for decolonization of other ARB. To date, 18 studies with a total of 101 patients have been published that use FMT to decolonize some of the most concerning ARB (Freedman, 2014; Jang et al., 2014; Singh et al., 2014; Lagier et al., 2015; Lombardo, 2015; Nancy et al., 2015; Striping et al., 2015; Wei et al., 2015; Bilinski et al., 2016; Dubberke et al., 2016; Garcia-Fernández et al., 2016; Jouhten et al., 2016; Millan et al., 2016; Smith, 2016; Sohn et al., 2016; Bilinski et al., 2017; Davido et al., 2017; Ponte et al., 2017). A pooled analysis of these data shows that 82% of patients were found to be decolonized or have a significantly reduced ARB load after FMT (Table 1). Unfortunately, while patients with C. difficile infection are willing to accept FMT treatment, patients who are simply colonized with ARB are asymptomatic and therefore may be less willing to be treated with FMT. Furthermore, scaling up of FMT manufacture to treat the millions of people around the world colonized with ARB would be incredibly challenging. In the future, we expect that microbial therapeutics for ARB will more closely resemble over-the-counter probiotics, but to bring these to the clinic, we will need more detailed mechanistic information on how FMT exerts its effect against ARB. Fortunately, recent work has shed some light on how FMT can treat infections and/or eradicate ARB pathogens from the gut are likely to be valuable additions to our anti-infective arsenal. While there are still many questions that need to be answered before microbial products targeting antibiotic resistance reach the clinic, we are excited for the future of this very promising field of technology.

Conflict of Interest

None declared.

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