Challenges and Opportunities of Nontraditional Approaches to Treating Bacterial Infections

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Abstract

Due to increasing rates of antimicrobial-resistant infections and the current inadequacy of the antibiotic pipeline, there is increasing interest in nontraditional approaches to antibacterial therapies. We define "traditional" agents as small-molecule agents that directly target bacterial components to exert a bacteriostatic or bactericidal effect, and "nontraditional approaches" as antimicrobial therapeutics that work through other means (ie, not a small molecule and/or utilizes a nontraditional target). Due to their atypical features, such therapies may be less susceptible to the emergence of resistance than traditional antibiotics. They include approaches such as monoclonal antibodies, virulence disruptors, immunomodulators, phage therapies, microbiome-based therapies, antibiotic potentiators, and antisense approaches. This article discusses both the developmental and regulatory advantages and challenges associated with each of these technologies. By identifying existing regulatory and developmental gaps, we hope to provide a sense of where focusing resources may provide the greatest impact on successful product development.

Keywords

antibiotic resistance; nontraditional approaches; microbiome; phage; antibodies

Rising rates of antimicrobial resistance represent one of the most significant public health threats of our time and create an urgent need to develop new antibiotics [1]. Unfortunately, the antibiotic development pipeline is limited in terms of its depth and diversity. A 2016 survey found that there were only 37 antibiotic candidates in clinical development, compared to >500 candidates for oncology [2]. Furthermore, innovation in antibacterial drug development has declined; no novel class of antibiotics attacking a new bacterial target has entered the market in >45 years for the treatment of gram-negative infections [2]. The number of patents filed for new candidate antibacterial drugs dropped 34.8% from 2007 to 2012 [3]. Given the low rates of antibacterial discovery and development over the last few decades, many observers believe that alternative approaches to treating or preventing infection will be needed. For the purposes of this article, we define "traditional" agents as small-molecule agents that directly target bacterial components to exert a bacteriostatic or bactericidal effect, and "nontraditional approaches" as antimicrobial therapeutics that work through other means (ie, not a small molecule and/or utilizes a nontraditional target).

Importantly, many nontraditional approaches demonstrate a narrow spectrum of activity. In contrast to broad-spectrum antibiotics, narrow-spectrum therapies possess a primary advantage of preserving the microbiome, which plays an important role in maintaining human health [4, 5]. However, the development, regulatory approval, and successful commercialization of narrow-spectrum nontraditional therapies will be challenging. First, empiric use of such therapies will likely not be possible given their narrow spectrum of activity. Clinicians will need rapid, highly sensitive, and specific point-of-care companion diagnostics to identify the patients who would benefit from the treatment (ie, those bearing the targeted pathogens). Currently, there are significant clinical and commercial barriers to operationalizing such diagnostics. Second, and perhaps more important, at present there are significant challenges to conducting randomized controlled clinical trials in a timely and cost-effective manner for narrow-spectrum therapies against many pathogens of interest. For more common pathogens such as *Staphylococcus aureus*, a sponsor can readily conduct a clinical trial that will fully enroll within a reasonable cost and time-frame. In contrast, for pathogenic species with lower prevalence such as *Acinetobacter* species, the slow enrollment of patients may prove too inefficient and costly. In July 2016, the US Food and Drug Administration (FDA) convened a public meeting to explore the feasibility and regulatory pathway for developing narrow-spectrum antibacterial therapies for unmet medical needs [6]. While no definitive path forward emerged from that meeting, we are hopeful that FDA will utilize all flexibilities at its disposal to establish viable pathways for the development and regulatory approval of these emerging technologies.

Furthermore, many of these technologies will be developed as adjunctive therapies to be used in combination with traditional antibiotics. For adjunctive use, the necessary clinical trials could prove too costly and complex. If the investigational product is to be used as an adjunctive therapy, the trial would need to establish the conventional antibiotic as the standard of care, with the investigational arm evaluating treatment with the standard of care antibiotic *plus* the adjunctive therapy. To demonstrate a statistically significant improvement of clinical outcomes between the 2 arms, a large number of patients would need to be enrolled, as the number needed to treat may be relatively high. For therapies targeting less prevalent pathogens, such requirements may make these trials prohibitively costly and thus

commercially unfeasible. Last, there are significant barriers related to payment or reimbursement. Monoclonal therapies approved for use in other therapeutic areas such as oncology and autoimmunity are typically priced much higher than even the most expensive antibacterial treatments. Questions remain as to whether healthcare providers and payers will reimburse the use of nontraditional antibacterial approaches, particularly when used as adjunctive therapies. Table 1 summarizes some of the advantages and disadvantages associated with the various approaches.

ANTIBODIES

The use of FDA-approved antibody-based therapies has become commonplace in the treatment of cancer and autoimmune disorders. While antibody-based therapy of bacterial diseases, typically in the form of serum therapy, has a long track record dating back to the development of diphtheria antitoxin in the 1890s, there have been few monoclonal antibody–based products approved for use in infectious disease. The manufacturing methods and safety profile of monoclonal antibodies are well established, significantly reducing these developmental barriers. To date, most antibacterial monoclonal antibodies have been targeted against pathogens that are prevalent enough to allow for clinical trials to be conducted at reasonable cost, such as *Clostridium difficile*, *S. aureus*, and *Pseudomonas aeruginosa*. For less prevalent pathogens, clinical trial execution is often too costly and impractical. In many instances, antibody-based therapies will be used as adjunctive therapies, complicating clinical trial design as previously noted. There is also the potential to use such products for prophylaxis, such as for at-risk patients undergoing procedures that risk opportunistic infection or being admitted to healthcare settings. In both instances, questions about market price and reimbursement would greatly affect the commercialization strategy.

The FDA approved raxibacumab for the treatment and prophylaxis of anthrax in December 2012 and, more recently, bezlotoxumab as a therapy to reduce the recurrence of *C. difficile*–associated diarrhea in October 2016. Raxibacumab and bezlotoxumab, both of which both target secreted toxins, represent the first monoclonal antibody–based therapies approved to address their respective bacterial infections. The market penetrance of bezlotoxumab will likely be greater than for other monoclonal antibacterial therapies, as it is a first-in-class product targeted at the comparatively large market. It will be instructive to monitor the adoption of bezlotoxumab into the commercial market, as it will indicate the potential for return on investment for antibacterial monoclonal antibodies, which may influence other drug companies' decision to enter this market.

PHAGE

The potential for bacteriophage and phage-derived lysin products to serve as narrow-spectrum therapies has been recognized for several decades. The unique selectivity of this approach, as dictated by the tropism of the phage, has both its advantages and disadvantages. A phage's specificity in targeting a single bacterial pathogen (if not a specific strain or serotype) minimizes disruption of the microbiome. An exquisitely narrow spectrum, however, also means that *cocktails* of phage may be needed to cover the strain diversity

exhibited by both the infecting pathogens and its related serovars. The regulatory approval of such phage mixtures may prove prohibitively challenging, suggesting a need for a more modular approach; for example, instead of obtaining regulatory approval for defined cocktails of phage, it may be more effective to create a global repository of phage and develop a regulatory approval process that allows for rapid phage selection, testing, and formulation of a specific cocktail based on the infecting pathogen's susceptibility and the patient's specific needs. Such a capability could be accessed after a patient has failed conventional antibiotic therapies and the specific pathogen has been diagnosed. Of note, this would also allow for clinical data to be collected (albeit in an open-label fashion) to adjudicate potential efficacy and inform future use.

A potential limitation to phage therapy is the fact that bacteria readily evolve resistance to phage infection, but Chan and colleagues used this susceptibility to put selective pressure on multidrug-resistant *P. aeruginosa* to restore their susceptibility to conventional antibiotic therapies [7, 8]. The method used a phage targeting the outer membrane porin M (OprM), leading to a reduction in efflux pump expression.

As the phage-based therapies targeted for the US market advance into the clinic, many challenges will need to be addressed. First, uncertainty remains about the phamacokinetics/ pharmacodynamics, distribution, and elimination of phage in humans, information critical to establishing reproducible exposures and doses. Second, additional work will be needed to develop preclinical models for the evaluation of phage therapies. Third, given that phages are immunogenic, the treatment may trigger complications or diminish in utility over time. Significant work will be needed to fully characterize these risks.

MICROBIOME-BASED THERAPIES

There are increasing data indicating that the human microbiome is critical to the maintenance of health and prevention of disease [4, 5]. Based upon the observed clinical efficacy of fecal microbiota transplantation, several microbiome-based approaches to prevent or treat *C. difficile*–based bacterial infections are now under development. The goal is to develop a cocktail of probiotic bacteria that can reconstitute the intestinal microbiome following antibiotic therapy, thereby preventing pathogenic bacteria, such as *C. difficile*, from spreading opportunistically and causing disease. The early clinical data for many of these approaches appear strong, with patients significantly reducing their rates of recrudescent *C. difficile* infections [9]. However, a recent failure of a microbiome-based product in clinical development has cast some doubts on previous assumptions of clinical efficacy [10].

Manufacturing and producing microbiome-based therapies present significant challenges. Many of the organisms that comprise the cocktail of bacteria are anaerobic and/or spore-forming bacteria. These organisms require dedicated manufacturing facilities for the production of drug substance or drug product, requiring companies to make significant capital expenditures. This situation is akin to the manufacture of β-lactam drugs, which also require dedicated facilities to minimize the cross-contamination of these sensitizing drugs with other products.

An advantage of this technology is that it does not rely on diagnostic capabilities. These products may also benefit from a more flexible regulatory path to approval that, in some cases, may not require a full preclinical assessment of safety prior to entering clinical trials. Assuming a robust safety profile, one could envision administering microbiome-based therapies to anyone placed on long-term broad-spectrum antibiotic therapy. This technology could also prevent or mitigate the spread of other serious infections in healthcare settings, like those of carbapenem-resistant Enterobacteriaceae, by reducing the probability of colonization and carriage of these organisms.

IMMUNOMODULATORS

Modulation of the host's immune system to limit immune-mediated pathology or to ramp up a deficient immune response has long been of interest, and progress has been made recently in the immunotherapy of cancer using immune checkpoint inhibitors. The simplest immunomodulators are corticosteroids, which are used adjunctively for various infections. Macrolide antibiotics also exert immunomodulatory effects, in addition to their direct antibacterial effect. Host-directed strategies make available a wide variety of new biomolecular targets to exploit, and the plasticity of the host's immune system in fighting infections means that immunomodulatory approaches have the potential to exert broad-spectrum activity, potentially eliminating the need for species-specific diagnostics. As immunomodulators are adopted for use in other areas (eg, cancer), it may be possible to repurpose these drugs as antibacterial therapies.

Given that their antimicrobial effect is indirect, immunomodulators can either serve as standalone or adjunctive therapies. Several drugs and nutraceuticals with immunomodulatory properties have shown clinical benefit when used as adjunctive treatments for infection, by either stimulating host-based bactericidal activity and/or suppressing pathogen-induced inflammation. For example, the combination of phenylbutyrate and vitamin D3 has been shown to induce the innate immune system's production of antimicrobial peptides (AMPs), thereby supporting a shorter treatment regimen for tuberculosis [11, 12]. In a more direct approach, it is also possible to develop synthetic peptides based on AMPs that have both immunomodulatory and antibacterial potential, as demonstrated by an engineered version of the AMP clavanin A [13].

Despite these advantages, few immunomodulators for use against infections have advanced to clinical-stage development. Additional work on target validation will be needed, as well as further evaluation of potential side effects and variable responses due to host genetic diversity [14].

The Biomedical Advanced Research and Development Authority (BARDA) is currently investing in a standalone immunomodulatory approach to bacterial infection. In 2014, BARDA initiated a partnership with Atox Bio for the development of AB103, an immunomodulatory approach to treating necrotizing soft tissue infections. AB103 is a peptide that binds the CD28 co-stimulatory receptor that modulates the host's immune response. This significantly dampens the acute inflammatory response that leads to tissue and organ damage. The program is currently in phase 3 clinical development.

VIRULENCE DISRUPTORS

Strategies that seek to disrupt bacterial virulence factors are also being pursued. These typically involve small molecules that prevent the secretion of protein effectors via gram-negative secretion systems (eg, type III), disrupt quorum sensing, inhibit biofilm formation, or block signaling systems involved with virulence gene expression [15, 16]. By inhibiting these essential approaches to attachment, invasion, or persistence, the bacteria are rendered more susceptible to immunologic killing. Given that these products do not directly target processes essential to normal physiological processes of the bacteria, resistance may be slower to emerge. Virulence disruptors are designed to disarm specific organisms and so should have little impact on the host microbiome. However, as with any narrow-spectrum therapy, there will be a heavy reliance on appropriate diagnoses. Another challenge is in the measure of efficacy; because these products do not kill the pathogenic microorganism directly, there will be a need to develop new in vitro and in vivo models to support regulatory approval. For example, one immediate challenge is the development of an in vitro measure of efficacy. In the absence of a minimum inhibitory concentration, it is difficult to define a breakpoint between susceptible and resistant pathogens. While other measures like bacterial protein secretion, gene expression profiling, and biofilm formation could be measured, those assays would need to be robust, reproducible, and directly tied to clinically observable correlates of efficacy. Similarly, those correlates would need to relate back to the pharmacokinetic/pharmacodynamic measures for the drug so that appropriate dosing and exposures can be established. And because these therapies do not kill the pathogenic microorganism, they may need to be combined with traditional antibiotics as adjunctive therapies.

ANTIBIOTIC POTENTIATORS

One of the newest classes of nontraditional antibacterial approaches is antibiotic potentiators. As the name portends, the general purpose of antibiotic potentiators is to restore or enhance the clinical utility of older antibiotics, and to extend the spectrum and safety (and perhaps shelf life) of newer antibiotics. In principle, such potentiators are being designed to improve the targeting and penetration of antibiotics against bacteria that are otherwise refractory to them. One approach is to develop novel molecules that specifically target the highly polar, negatively charged lipopolysaccharides of the outer membrane of gram-negative bacteria, making them more permeable to otherwise ineffective antibiotics. With this technology, antibiotics previously used exclusively for treating gram-positive infections could be repurposed to treat gram-negative infections. Small bioactive natural products that stimulate and enhance macrophage-mediated bacterial cell killing also show promise as potentiators when used in combination with approved antibiotics [17]. One example of this approach is streptazolin, which shows enhanced bacterial cell killing and macrophage production of immunostimulatory cytokines in vitro, thereby demonstrating a potential new treatment for infections refractory to current antibiotics.

Another example of a host-based potentiation is the combination of a well-known antibiotic, imipenem, with the potentiator cilastatin. Imipenem is rapidly degraded by the kidney enzyme dehydropeptidase, with the resulting metabolites exhibiting nephrotoxic activity. To

counter this effect, the antibiotic is co-formulated with cilastatin, a dehydropeptidase inhibitor that prevents the renal metabolism of imipenem while increasing its half-life and tissue penetration.

Another promising approach is disruption of bacterial biofilms. Biofilms often form during infections and protect the resident bacteria from both attack by the immune system and penetration of antibiotics across the biofilm matrix. Biofilm-disrupting potentiators currently under development include pentadecenyl tetrazole, a compound shown to be effective in vitro when used in combination with gentamicin against biofilm-embedded *S. aureus* [18]. Hamamelitannin is another promising bacterial biofilm disruptor with potential for use against *S. aureus* biofilms [19].

Similarly, synthetic peptides based on naturally occurring host-defense peptides have been found to exert antibiofilm activity. When these peptides are combined with conventional antibiotics, the synergistic effect lowers the concentration of the antibiotic needed to eradicate certain bacterial strains of interest [20–22].

However, challenges remain to antibiotic potentiation. Unclear regulatory pathways, potential for adverse events due to modulation of host immune systems, and a lack of preclinical animal and clinical data to validate their utility have hampered their clinical development. Modest investments in these technologies may clarify and/or resolve many of these risks and issues.

ANTISENSE APPROACHES

With the rapid development and widespread adoption of antisense technologies, it is now possible to explore antibacterial systems based on RNA-guided nucleases. In these systems, a double-stranded DNA nuclease (such as Cas9) uses an anti-sense guide strand of RNA to identify and cleave specific sites in genomic DNA. By engineering the RNA guide to target specific bacterial genes, a nuclease-based system can be engineered to kill bacteria. Notably, this approach has the promise to kill bacterial species selectively, thereby reducing collateral damage to the microbiome.

Early studies suggest that these systems can be effective when combined with an efficient delivery mechanism. For example, phage can be engineered to carry both the *cas9* gene and a programmable RNA guide, enabling the selective killing of specific bacterial strains [23, 24].

Beyond RNGs, other antisense technologies have antibacterial potential through the silencing of bacterial gene expression. For example, certain synthetic oligonucleotides have demonstrated the ability to silence vital bacterial gene expression, thereby exerting an antibacterial effect [25]. Given that these oligomers do not readily penetrate bacterial walls, these technologies often must be tethered to cell-penetrating peptides for effective delivery.

Despite their promise, these technologies are in the early stages of development. Technical challenges remain; in addition to bioengineering the antisense technology itself, the systems

will need to be paired with effective delivery systems capable of targeting the bacterial strains of interest (eg, phage), each of which brings its own challenges.

CONCLUSIONS

Nontraditional antimicrobial therapeutics represent a reservoir of novel approaches for the treatment and prevention of bacterial infections and for slowing the development of antimicrobial resistance. These approaches include monoclonal antibodies, virulence disruptors, immunomodulators, phage therapies, microbiome-based therapies, antibiotic potentiators, and antisense approaches. They offer several key advantages, but face a number of significant challenges. Their development will require significant alterations in thinking about how clinical trials are conducted for narrow-spectrum agents, how diagnostics are deployed, operationalized, and reimbursed, and how in vitro and in vivo assays for activity/ efficacy are designed and qualified. Coordination among industry, government funders, and regulatory agencies will be required to effectively navigate nontraditional approaches through these obstacles.

Acknowledgments

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Table 1

Selected Advantages and Disadvantages of Nontraditional Approaches

	Advantages		Disadvantages	
Bacteriophage	•	Specific to infecting bacteria	•	Delivery: rapid clearance by immune system
	•	No collateral damage to microbiome	•	Intracellular delivery limitations
	•	Natural predators of the microbe	•	Adjunctive use paradigm
	•	Evolve along with target microbe	•	Regulatory pathway unclear
	•	Historical use	•	Pharmacodynamics/pharmacokinetics
	•	Can be used topically	•	Combination product regulations
	•	Generally regarded as safe for food	•	Will require diagnostic specificity for use
			•	May be overcome by resistance
Lysins	•	Specifically targeted	•	Only gram-positive
	•	Can be administered systemically	•	Crowded gram-positive space with less perceived need
	•	Lower probability of resistance	•	Regulatory pathway unclear
			•	Adjunctive use paradigm
			•	Will require diagnostic specificity for use
Immunomodulators	•	Not pathogen specific	•	Distinct response cascades for infections (eg, gram-negative vs gram-positive)
	•	Collateral damage not expected	•	Adjunctive use paradigm
	•	Large pipeline with sepsis therapies	•	High rate of failure in clinical trials
	•	Repurposing of existing compounds possible		
Virulence factor disruptors	•	Addresses the root of damage causation	•	Treatment paradigm shift
	•	No collateral damage	•	Will require diagnostic specificity for use
	•	Amenable to a variety of approaches		
Microbiome therapies	•	Root cause addressed	•	Lack of complete knowledge of optimal microbiome
	•	Cost is not high	•	Discretionary US Food and Drug Administration enforcement environment for recurrent *Clostridium difficile*
	•	Thrust of major research effort	•	Regulatory pathway unclear
Monoclonal antibodies	•	Specifically targeted	•	Expensive
	•	Already available	•	Adjunctive treatment paradigm
	•	Clear regulatory pathway	•	Infusion reactions
	•	Clinician use comfort	•	Combination product regulations if have >1 component
	•	Lower investment risk		
Antibiotic potentiators	•	Linked to existing antibiotic with well-known characteristics	•	May be overcome by increased resistance
	•	Clear regulatory pathway	•	Rely on a traditional antibiotic for value
	•	Clinician use comfort		

	Advantages	Disadvantages
	• Lower investment risk	
Antisense approaches	• Specifically targeted • Dependent on effective delivery mechanisms (eg, phage) which carry their	• No collateral damage to microbiome own technical challenges • Will require diagnostic specificity for use