Antibiotics started to be used almost 90 years ago to eradicate life-threatening infections. The urgency of the problem required rapid, broad-spectrum elimination of infectious agents. Since their initial discovery, these antimicrobials have saved millions of lives. However, they are not exempt from side effects, which include the indiscriminate disruption of the beneficial microbiota. Recent technological advances have enabled the development of antimicrobials that can selectively target a gene, a cellular process, or a microbe of choice. These strategies bring us a step closer to developing personalized therapies that exclusively remove disease-causing infectious agents. Here, we advocate the preservation of our beneficial microbes and provide an overview of promising alternatives to broad-spectrum antimicrobials. Specifically, we emphasize nucleic acid and peptide-based systems as a foundation for next-generation alternatives to antibiotics that do not challenge our microbiota and may help to mitigate the spread of resistance.

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Introduction
Currently, there is a serious global health problem as increasing numbers of multidrug-resistant bacteria are continuously being isolated from hospitals. According to a recent report published by the United Kingdom government, antibiotic-resistant infections are predicted to result in the death of 10 million people worldwide per year by 2050 if new antimicrobial strategies are not discovered [1]. In fact, the rise in antibiotic resistance has led to a post-antibiotic era in which many standard-of-care antimicrobials are no longer effective. This is partly a result of the decline in antibiotic innovation: no new class of antibiotics has been approved for Gram-negative infections in >45 years, and only 37 antibiotic drugs are in either Phase II or III clinical trials as of 2016 [2]. Therefore, there is an urgent need to develop alternative approaches to treat drug-resistant bacterial infections.

Besides leading to emergence of resistant bacteria, antimicrobials may have unintended consequences, such as triggering hyper-inflammatory responses or, most notably, displaying numerous off-target effects (i.e., killing) that disturb beneficial microbiota [3,4]. This is a very significant side effect, as these microbes are associated with our health, and their perturbation can lead to disease. Preserving our microbiota is thus an additional critical aspect to be considered when developing next-generation antimicrobials (Figure 1). Several technologies have been developed for the selective targeting of microbes. In this review, we discuss nontraditional strategies, exemplified in Figure 2, to treat bacterial infections, emphasizing precision approaches that serve as a framework for the design of next-generation antimicrobials.

A call to action: the need to preserve the microbiota
The microbiome plays a key role in human health and disease. Indeed, the composition of the indigenous microbial communities living in the skin, mouth, urinary tract, and especially the gastrointestinal tract profoundly affects many aspects of human health, including immunity and metabolism [5–7]. For instance, a disrupted or unbalanced gut microbiota (i.e., dysbiosis) has been linked to autoimmune disorders (e.g., irritable bowel syndrome and inflammatory bowel disease), obesity, higher propensity to infection, cardiovascular disease, colon cancer, rheumatoid arthritis, depression, Parkinson’s disease, multiple sclerosis, and autism spectrum disorder [8]. Furthermore, dysbiosis can lead to infection
with opportunistic pathogens such as *Enterococcus faecium*, carbapenem-resistant *Enterobacteriaceae*, and *Clostridium difficile* [9,10], the latter being responsible for 14,000 deaths per year only in the US. Consistent with the relationship between microbiota disruption and *C. difficile* infection (CDI), fecal transplantations, which give rise to a healthy human gut microbiota and colonization resistance, are known to prevent the onset of CDI [11].

Microbiome perturbations are of particular concern in children because antibiotics are widely used to treat childhood infections. To put this into perspective, the average child in the US receives three courses of antibiotics by age two, and ten courses by age ten [12].

Therefore, next-generation precision antimicrobials should exhibit high specificity towards target species. We briefly outline nucleic-acid- and peptide-based strategies which may constitute the basis for new types of precision antimicrobials. Additional emerging approaches for the precision killing of bacteria, not covered in this review due to space are the use of bacteriocins, antibodies or anti-virulence compounds [13–21].
Phosphorodiamidate morpholino-oligomers (PMOs)
Like DNA, phosphorodiamidate morpholino-oligomers (PMOs) are synthetic oligomers composed of the base pairs A, G, C, and T; however, they contain a synthetic morpholino and phosphorodiamidate backbone within their sequence [29]. These molecules can be used as antisense strategies as their oligomer sequences are complementary to their target mRNAs. PMOs can be delivered into living cells through different means, for example via conjugation with cell-penetrating peptides. PMOs have shown efficacy both in vitro and in vivo against clinically relevant pathogens such as Acinetobacter baumannii, Burkholderia cepacia complex, and E. coli [31–33] and represent a promising new class of precision antimicrobials. Indeed, a study was recently published in which PMOs targeting essential genes such as acpP, lpxC, and rpsJ were conjugated with the cationic anti-biotic polymyxin B leading to 2-8-fold increased anti-P. aeruginosa activity [34]. The compound targeting acpP also inhibited P. aeruginosa biofilm formation. Biofilms are surface-associated communities of microorganisms that are associated with numerous infections in humans and that exhibit increased resistance to antibiotic therapy. The compound targeting rpsJ synergized with the aminoglycoside antibiotic tobramycin. Importantly, these therapies led to 3-log reductions in bacterial loads in the lungs of mice. PMOs are currently limited mostly by delivery efficiency and in vivo stability.