In with the Old, in with the New
Anti-infective Agents to Combat the Antibiotic Resistance Crisis
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Antibiotic resistance is an important public health problem around the globe. In the US, it is estimated that at least 2 million people are infected with an antibiotic-resistant microorganism each year, and that at least 23,000 people die as a direct result of these infections. In addition, antibiotic prescriptions are frequently inappropriate or unnecessary. If antimicrobial resistance continues to increase, we risk entering a postantibiotic era (i.e., patients will be infected with microorganisms that are resistant to all antimicrobials that are available for treatment). If this occurs, infection-related mortality will drastically increase.

Preventing and reversing this trend is an area of high public health priority. Several complementary approaches are necessary to combat the growing problem of antibiotic resistance, such as antibiotic development and antimicrobial stewardship. An expanded repertoire of rapid diagnostic methods to diagnose infection and inform targeted antimicrobial therapy (or avoid antimicrobial therapy when it is unnecessary) is a key component for improved utilization of our existing antimicrobial agents. For example, rapid diagnostics are necessary to differentiate between bacterial and viral infections to reduce the erroneous use of antibiotics to treat viral infections.

In addition to rapid diagnostics to inform appropriate antimicrobial use, development of new antimicrobials is an essential component of the arms race against resistant microorganisms. Unfortunately, antimicrobial development has not been a high priority for many pharmaceutical companies, as the return on investment is much less than for other types of drugs; most antimicrobials are prescribed for days rather than for life, which is very different from many other agents in development. As a result, the lower return on investment results in reduced incentive for development.

In recent years we have seen a handful of new anti-infective agents come to market, which is an exciting advancement. The approach to development of new anti-infective agents has involved both modification/modulation of existing compounds and novel approaches.

<table>
<thead>
<tr>
<th>Novel antimicrobial</th>
<th>Mechanism of action</th>
<th>Anticipated use or target microorganisms</th>
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<tbody>
<tr>
<td>ETX1317</td>
<td>Binds to and inhibits beta-lactamase (rescues the function of beta-lactam antibiotics)</td>
<td>Intravenous administration. Anticipated use is in hospitalized patients infected with multi-drug resistant bacterial pathogens</td>
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<tr>
<td>ETX0282</td>
<td>Binds to and inhibits beta-lactamase (rescues the function of beta-lactam antibiotics)</td>
<td>Oral administration. Anticipated use is in the outpatient setting for patients with infections such as urinary tract infections with multi-drug resistant bacterial pathogens</td>
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<tr>
<td>Teixobactin</td>
<td>Binds to peptidoglycan and teichoic acid (components of the bacterial cell wall) thereby inhibiting cell wall synthesis</td>
<td>Methicillin-resistant Staphylococcus aureus, Streptococcus pneumoniae, Clostridium difficile, Mycobacterium tuberculosis</td>
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<tr>
<td>Myxopyronin</td>
<td>Binding to RNA polymerase</td>
<td>Potential for broad-spectrum anti-bacterial activity</td>
</tr>
<tr>
<td>CRISPR-Cas3</td>
<td>Subvert the bacteria’s immune system; Cas3 cuts and degrades DNA</td>
<td>Potential to be broad-spectrum; initial applications are focused on Clostridium difficile and Escherichia coli</td>
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to drug development. Two antibiotics that have been recently developed are great examples of each approach. Delafloxacin is an anionic fluoroquinolone (i.e., a modification of a previously well-established class of antibiotic). Cefiderocol is a novel siderophore cephalosporin. A recent article in Nature (1), describes several truly innovative anti-infective agents that are in development. The investigators working in this area are taking a variety of approaches to addressing this important problem, such as subverting the immune system of the microorganism and rescuing the activity of β-lactam antibiotics (described in Table 1).

The creativity and dedication of the scientific community working in the space of antimicrobial development is encouraging. However, it is challenging to stay one step ahead of the microbes, so continual advances are essential to avoid the return to an era without antibiotics to treat infection.

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Reference

LIMA1:
A Newly Identified Player in the Field of Cholesterol Control
Leslie J. Donato*

Higher concentrations of LDL cholesterol (LDL-C) are causally linked to risk for cardiovascular disease (CVD). Correspondingly, lowering cholesterol leads to a proportional lowering of risk in randomized control trials. Thus, a key objective of CVD risk mitigation is lipid lowering—and the lower, the better. The Odyssey randomized control trial suggests that there is no LDL-C concentration too low for safety, and those achieving the lowest values displayed the greatest risk reduction.

What complicates the matter is the multifaceted nature of lipid homeostasis. Although approximately half of cholesterol variability is controlled by genetic variability (other factors being diet and lifestyle), only a small percentage of risk has been linked to genetic variance. Furthermore, lipid screening is poor at identifying individuals with genetic lipidemias. For example, it is estimated that only 2% to 3% of individuals with extremely high cholesterol concentration have a known genetic variant linked to familial hypercholesterolemia. Clearly there is more to be discovered about the genetics of cholesterol control.

A new genetic player in the orchestra of cholesterol homeostasis has recently been discovered in a remote Chinese family with inherited low LDL-C concentrations and reported in Science (1). The causal single-nucleotide variant is isolated to the LIM domain and actin binding (LIMA1) gene, a locus that previously has never been linked to lipid regulation. LIMA1 protein is highly expressed in the brush border of the small intestine and binds to both NPC1L1 and myosin Vb—2 proteins required for efficient intestinal cholesterol absorption. LIMA1 knockout mice display significantly inhibited cholesterol absorption and low LDL-C plasma concentrations, mimicking the human phenotype. Treatment of LIMA1 knockout mice with ezetimibe, which

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