The need for new antibiotics is undisputed (1). Recent studies estimate that more people die from the methicillin-resistant *Staphylococcus aureus* (MRSA) bacterium than from HIV in the United States (2), and the Centers for Disease Control and Prevention estimates that more than 90,000 people die from hospital-acquired bacterial infections in the United States each year. Numerous reports have illustrated the “perfect storm” of rising bacterial resistance to antibiotics and an industry pipeline ill-equipped to address the need for new antibacterial drugs (3, 4) (see the figure). Consequently, the reports by Haydon et al. on page 1673 in this issue (5) and by Rasko et al. (6) are important because they validate and illustrate the therapeutic potential of two new antibacterial drug targets. In addition, the paper by Hiratsuka et al. on page 1670 in this issue (7) identifies a biosynthetic pathway that may provide new antibacterial strategies for certain species of bacteria.

Haydon et al. report the discovery of a class of drugs that targets the bacterial protein FtsZ. FtsZ is related to the human cytoskeletal protein β-tubulin and is essential in bacterial cell division in most Gram-positive and Gram-negative pathogens, where it polymerizes to form a ring at the mid cell that enables septum formation. The authors show by crystallographic analysis that their lead molecule (PC190723) binds to the region of FtsZ that is analogous to the site that the anticancer drug Taxol binds to in β-tubulin (Taxol interferes with microtubule dynamics and blocks cell division). Moreover, they show that PC190723 possesses in vitro potency against MRSA, and is effective in a mouse model of *S. aureus* infection. Importantly, through mutational and bacterial physiology experiments, Haydon et al. show that the antibacterial effect of PC190723 is via inhibition of FtsZ. The discovery of these inhibitors of FtsZ illustrates the potential of this protein as a novel and exploitable antibacterial drug target.

Whereas inhibition of FtsZ prevents bacterial growth, Rasko et al. describe an alternative drug approach that cripples the bacteria’s ability to maintain an infection. The authors discovered a compound (LED209) that inhibits the bacterial enzyme QseC. This target is a histidine kinase that autophosphorylates upon sensing either host signaling molecules (the hormones norepinephrine and epinephrine) or bacterial molecules (called autoinducers) associated with quorum-sensing (cell-to-cell communication among bacteria). This phosphorylation event leads to the expression of key virulence genes, and *Escherichia coli* with a mutant form of QseC is unable to trigger expression of these virulence genes and shows decreased growth in an animal infection model. QseC homologs are found in most clinically important Gram-negative pathogens. Rasko et al. elegantly demonstrate that LED209 inhibits QseC-dependent expression of virulence genes triggered by either the autoinducer AI-3 or by epinephrine. In animal models of infection, LED209 was not effective in protecting against *E. coli* infection, but oral dosing of LED209 3 hours before and after infection with *Salmonella typhimurium* protected mice from infection. In addition, fewer bacteria were recovered from the spleens and livers of animals treated with LED209 compared with controls. Therefore, this work demonstrates the potential of an “antivirulence” strategy for tackling bacterial infections. None of the currently available antibiotics employ such a mechanism of action.

Hiratsuka et al. illustrate the power of bacterial genomics to identify potential new targets for anti-infective strategies. Most microorganisms use a biosynthesis pathway encoded by the *men* genes to produce menaquinone, a molecule needed for bacterial anaerobic respiration. However, the authors deduced that some bacteria such as *Streptomyces coelicolor*, *Helicobacter pylori*, and *Campylobacter jejuni* lack these genes, yet still synthesize menaquinone. To identify this new route of synthesis, the authors compared the genomes of microorganisms that use the known *men* pathway with bacteria that lack the *men* genes. This eventually led to four candidate genes, each of which were previously annotated as encoding “hypothetical proteins.” Each of these genes was disrupted, and the resulting mutants all required menaquinone for growth. The authors then used biochemical and analytical approaches to identify the various intermediate molecules at each step in the new menaquinone synthetic pathway. The discovery of a new menaquinone biosynthesis pathway may provide new antibacterial drug targets.

**PERSPECTIVES**

David J. Payne

New approaches for discovering the next generation of antibiotics are needed to combat the rise in bacteria that are resistant to current drugs.

**MAJOR CONCERNS**

- Global pandemic of MRSA infection
- Global spread of drug resistance among common respiratory pathogens, including *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*
- Epidemic increases in multidrug-resistant (and increasingly, truly pan-resistant) Gram-negative bacilli (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*)

**Bad bugs need drugs**. Three major areas of concern that need new antibiotics [as defined by the Infectious Diseases Society of America (4)].

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biosynthesis pathway (which they named the futalosine pathway, after the first intermediate molecule). The lack of this pathway in humans and its presence in bacteria such as *Chlamydia* (which causes urethritis and respiratory tract infections), *H. pylori* (which can cause stomach ulcers), *C. jejuni* (which causes gastroenteritis often associated with food poisoning), and *Spirochaeetes* (which cause syphilis and Lyme disease) could make it an attractive antibacterial drug target for these specific pathogens.

The development pipeline for systemic antibiotics consists almost entirely of new versions of decades-old classes of antibiotics, such as β-lactams, quinolones, macrolides, and glycopeptides. New classes of antibacterial drugs directed against new bacterial targets are urgently needed. Unfortunately, there are insufficient novel antibiotics in development to address this challenge, partly because of increased development and research in this sector and also because of the substantial difficulty of finding small-molecule drug leads. Despite a wealth of new bacterial targets, high-throughput screening for inhibitory compounds in this therapeutic area has been less successful than in any other, a likely cause being the unique chemical diversity needed to inhibit bacterial enzymes. Consequently, the work by Haydon *et al.* and Rasko *et al.* is important because they have identified inhibitors of their targets with the potential for pharmaceutical development. However, turning these “leads” into drugs remains a challenge. For example, antibacterials typically need to be administered at higher doses than most other drugs, emphasizing the need for compounds that can achieve high exposures in humans but that are also extremely safe at these high doses.

For the last 10 to 15 years, antibacterial research and development has focused on the validated approach of designing small molecules that inhibit bacterial growth. However, perhaps now is the time to consider alternative strategies. For example, targeting virulence factors as described by Rasko *et al.* may create more effective drugs with a lower propensity to select for resistance. However, the amount of attenuation achieved by such antivirulence drugs and the consequences of potentially not eradicating the bacteria from the infection need careful consideration. Such drugs may need to be combined with antibacterial agents to achieve their full potential. Other promising approaches include developing inhibitors of bacterial drug resistance mechanisms or bacterial drug efflux pumps for combination with specific antibacterials that could rejetentive entire classes of antibiotics against multidrug-resistant pathogens. In addition, rather than the traditional approach of seeking antibotics that cover a broad set of pathogens, exploiting targets that are specific for only certain pathogens, such as those described by Hiratsuka *et al.*, may be a more productive strategy. This would also have the advantage of creating antibiotics that will enable highly targeted therapy and remove the considerable drug discovery challenge of having to identify a single molecule that penetrates, and is equopotent against, a range of potentially diverse species of bacteria. However, this approach will succeed only be with the availability of diagnostics that can very rapidly and accurately identify the specific infecting pathogen, and it may be some time before such tools are available for a range of common pathogens. Consequently, the need for new antibiotics merits investment across a spectrum of traditional and higher-risk approaches to optimize the chances of creating promising new antibiotics.

References

10.1126/science.1164586

**CHEMISTRY**

**Fluorous Tags Unstick Messy Chemical Biology Problems**

Dennis P. Curran

Everyone knows that nothing sticks to Teflon-coated products, such as cookware, raincoats, and ski waxes (and, figuratively, even to some politicians). The prevalence of “nonstick” products coated with Teflon [poly(tetrafluoroethylene)] shows that with some engineering effort, Teflon can adhere to metals, textiles, and plastics. At the molecular level, the perfluoroalkyl groups [–(CF<sub>2</sub>)<sub>n</sub>–] that comprise Teflon tend to repel organic and inorganic molecules but have attractive interactions with other perfluoroalkyl (R<sub>f</sub>) groups and along with fluorinated solvents can form separate fluororous phases. Organic chemists exploit perfluoroalkyl groups in small-molecule synthesis and separation by applying them as tags for separations with fluorous silica gel and solvents. Recent innovations suggest that a wide range of potential applications of fluorous tags could be realized in chemical biology as well, not only in separations and derivatization but also in identification because of the distinctive signatures of these tags in mass spectrometry.

Separation tags can enable rapid partitioning of a relatively complex mixture (such as cell isolates or products of cell-based protein synthesis) into tagged and untagged fractions. For example, a streptavidin affinity column will fasten molecules with a biotin tag and let the untagged molecules pass. Separation tags that are commonly used with biomolecules include polymer beads or surfaces, as well as other molecular tags such as polyhistidine.

Given the success of these commonly used separation tags, why are fluorous tags of interest? First, separation tags typically also have to accommodate—better yet, facilitate—biomolecule synthesis and analysis methods. Fluorous tags provide separation handles that are relatively inert and do not compromise synthetic reactions or analysis operations.

Second, tag systems such as streptavidin–biotin rely on very strong fastening interactions (covalent bonds or powerful ionic or molecular recognition forces) that may be difficult to unfasten during product recovery. Fluorous tags behave more like molecular “Post-it notes.” For example, when synthetic chemists use fluorous solid-phase extraction

Separation and identification of biological molecules from complex mixtures can be made easier with fluorinated labeling groups and separation media.