Where Are New Antibiotics Coming From? A Molecule-Centered Prospective

Written by Phil Vinall

Microbial resistance to antibiotics currently spans all known classes of natural and synthetic compounds. There is a need for new compounds and targets to treat the resistant antibiotics. Christopher T. Walsh, PhD, Harvard Medical School, Boston, Massachusetts, USA, spoke about the need for "promising chemical matter for prosecution of new and existing antibiotic targets" from a molecule-centered perspective.

Over the past 100 years antibiotics have been either a result of natural product discovery (6-lactams, macrolides, and aminoglycosides) or synthetic chemicals turned into antibiotics (eg, sulfa drugs, fluoroquinolones, and linezolid). Between 1940 and 1960 most classes of antibiotics were derived from nature. Between 1960 and 2000, the age of medicinal chemistry, modifications of antibacterial natural products accounted for most new antibiotics. Semisynthetic antibiotics result from the convergence of natural product biosynthesis and medicinal chemistry modifications. A classic example is penicillin N (natural product) → amoxicillin (second generation) → pipericillin (third generation). Other examples are shown in Table 1.

Table 1. Examples of Semisynthetic Modifications of Antibacterial Natural Products.

• 4 generations of cephalosporins → ceftazidime
• 3 generations of erythromycins → telithromycin
• 2 generations of carbapenems → ertapenem
• 3 generations of tetracyclines → tigecycline

There is a constant need for new products to replace the existing drugs. "Whenever we discover and employ a new antibiotic, resistance is sure to follow," said Dr. Walsh.

In a study of multidrug resistance of soil-dwelling bacteria, 480 actinomycete strains were isolated from a soil sample and tested for resistance to 21 antibiotics. Most strains were resistant to 7 or 8 antibiotics, and 2 strains were resistant to 15 antibiotics [D'Costa VM et al. *Science* 2006]. In clinical situations, resistance can emerge rapidly, sometimes within 1 to 3 years after introduction of a new antibiotic.

The best means to develop new antibiotic products is to "keep the molecular warhead intact and tinker with the periphery of the molecule." For example, multiple generations of tinkering with all but the central nucleus have made the quinolones successful in dealing with new waves of resistant organisms. Novel approaches to medicinal chemistry have revitalized polyketide antibiotics.

However, the pace has been slow and infectious disease specialists worry that the useful lifetimes of subsequent generations of antibiotics may decrease. There is a 4-decade gap between the introduction of the fluoroquinolones in the 1960s and next new class of antibiotics, the oxazolidinones in 2000 and daptomycin in 2003. New antibiotics launched since 2000 include 12 natural product drugs, half of which were in the class of β-lactam; new synthetically derived antibiotics include 8 fluoroquinolones and 1 oxazolidinone. Dr. Walsh and others worry that such minimal diversity of products will be a major problem for the whole industry. Currently there are 39 products in active

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clinical development; 5 are undergoing phase 3 clinical trials (4 natural product derived and 1 synthetically derived oxazolidinone; Table 2).

Table 2. Examples Antibiotics in the Clinical Pipeline.

Natural Product Derived	
Name	**Class**
Amadacycline (PTK-0796; MK-2764)	Tetracycline
Oritavancin	Glycopeptide
Dalbavancin	Glycopeptide
Cethromycin	Macrolide (ketolide)
Torezolid phosphate (TR-701; DA-7218)	Oxazolidinone

Butler MS and Copper MA. Antibiotics in the clinical pipeline in 2011. *J Antibiot* (Tokyo). 2011 Jun;64(6):413-25.

There is a need to re-examine underexploited targets such as peptidoglycan transglycosylase, lipid II and processing enzymes, RNA polymerase, the LPS biosynthetic pathway, and ATP-dependent enzymes, including chambered proteases. Peptidoglycan transglycosylase blocks cell wall crosslinking, targeting the transpeptidation of transglycosylases (TPase) to glycosylatransferase (TGase). Moenomycin A (MmA), the only known natural antibiotic that inhibits bacterial cell wall synthesis, binds to a TPase that catalyzes formation of the carbohydrate chains of peptidoglycan and inhibits the peptidoglycan TGase. Although used in veterinary medicine to treat infection, MmA has poor PK and PD profiles, making it unsuitable for use in humans; however, its structural and biological uniqueness make it an attractive starting point for the development of new antibacterial drugs.

Lipid II is a membrane-anchored cell-wall precursor that is essential for bacterial cell wall biosynthesis and is the target for at least 4 different classes of antibiotics, including vancomycin. Since resistance to vancomycin has increased, there is new interest in the therapeutic potential of other classes of compounds that target lipid II, including lantibiotics, mannopeptimycins, and ramoplanin.

Nisin, a member of the lanthionine family, binds to lipid II, increasing membrane permeabilization. The novel lipid binding structure of nisin offers a template for structure-based design of other antibiotics [Hsu ST et al. *Nat Struct Mol Biol* 2004]. Another class of molecules that will target lipid II is the fungal defensing proteins. Plectasin is a 40 amino acid defesin-like peptide that binds lipid II and inhibits cell wall biosynthesis.

Multiresistant Gram-negative pathogens are currently the greatest threat. Present treatment options include β-lactams, fluoroquinolones, sulfamethoxazole/trimethoprim, aminoglycosides, and glycylcyclines, but there remains a pressing need for new antibiotics to treat Gram-negative pathogens. LpxC (UDP-3-O-[R-3-hydroxymyristoyl]-GlcNAc deacetylase) is an essential enzyme in the lipid A biosynthetic pathway in Gram-negative bacteria, which can be blocked with LpxC inhibitors. Inhibitors with a diacetylene scaffold design effectively overcome point mutation resistance mechanisms and can ameliorate variation in potency against different Gram-negative pathogens [Lee CJ et al. *Chem Biol* 2011].

Chemical genetic network approaches using antisense interference to broadly identify new drug targets that potentiate the effects of existing antibiotics have recently been developed. Developing drug-like leads to these targets may help cultivate effective combination agents when paired with existing β-lactam antibiotics to restore their efficacy against methicillin-resistant Staphylococcus aureus. *S. aureus* fitness test using 245 antisense RNA strains led to the discovery of kibdelomycin (natural product), the first structurally novel type II topoisomerase inhibitor discovered in more than 60 years [Donald RG et al. *Chem Biol* 2009]. This may open a new chapter for ATP-dependent drug targets such as ATP-producing/consuming enzymes like chambered proteases and topoisomerases. The grandfather of ATP-utilizing enzymes is DNA gyrase, the target of fluoroquinolones and aminocoumarins.

The last issue Dr. Walsh discussed was the eventual use of combination therapy, currently standard practice to treat HIV infections and in cancer chemotherapy, to treat the next generation of bacterial infections, a therapy approach he feels is inevitable.

Drug resistance among all antibiotic classes has dramatically eroded the efficacy of current therapeutics. Novel structural drug classes either existing in nature or derived from smart screens of chemical libraries, combinatorial chemical libraries, and/or combinatorial biosynthesis are needed. There is also a need for new therapeutic strategies, including more combination therapy, the optimization of therapeutic choices, and real-time detection of disease-causing organisms.