COMMENTARY

Remodeling vancomycin yields a victory in the battle against bacteria

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The continued emergence of bacteria that are resistant to commonly used antibiotics is a serious danger to public health (1, 2). Policies such as incentivizing the development of new antibiotics (3) and restricting the use of currently effective antibiotics (4) can slow the march of resistant bacteria. Nonetheless, scientific breakthroughs must accompany such actions of governments and international organizations. Recently, a significant advance in the battle against bacteria has been achieved. In PNAS, Okano et al. (5) report the discovery of a new antibiotic that functions via three synergistic modes of action. Importantly, the ability of this agent to attack bacteria using multiple mechanisms dramatically slows the development of resistance.

Vancomycin (Fig. 1) is the prototypical member of the glycopeptide family of antibiotics. Its mode of action involves binding to bacterial cell wall precursor peptides that terminate in a D-Ala-D-Ala sequence. This binding prevents transpeptidase enzymes from cross-linking these strands, thereby impeding the formation of the peptidoglycan protective layer that is critical to the integrity of the bacterial cell wall (6). Despite almost 60 y of clinical use, vancomycin-resistant bacteria have been relatively slow to emerge. However, such organisms are currently viewed as serious threats to human health by both the CDC (7) and the WHO (8). They are able to evade vancomycin by using an ester (i.e., D-Ala-D-Lac) instead of an amide (i.e., D-Ala-D-Ala) as the peptidoglycan precursor. This simple substitution of an oxygen atom for an NH moiety replaces one of the hydrogen bonds that stabilizes the complex between vancomycin and its target with a destabilizing electrostatic repulsion (9, 10).

Previous work from the authors' group involved removing the carbonyl in vancomycin that clashes with the ester oxygen in D-Ala-D-Lac, resulting in an analog that is potent against both vancomycin-sensitive and vancomycin-resistant bacteria. It should be noted that the deletion of this functional group was not a trivial process, requiring the design and execution of a multistep total synthesis (11). Subsequently, the authors demonstrated that attachment of a (4-chlorobiphenyl)methyl (CBP) group onto the amino sugar nitrogen of this binding-pocket–modified vancomycin analog delivered a second-generation analog with increased potency (12). The CBP group is known to enhance the antimicrobial activity of glycopeptide antibiotics, presumably by enabling a second mode of action based on inhibition of the bacterial transglycosylase enzyme (13).

In their current work, Okano et al. (5) developed a third-generation vancomycin analog with an additional peripheral modification that unlocks a third mechanism of action. This compound contains a quaternary ammonium ion that is attached to the C terminus of vancomycin via an amide linkage (Fig. 1). This functional group causes the bacterial cell membrane to become permeable, rendering the analog highly potent against vancomycin-resistant Enterococci (minimum inhibitory concentration = 0.01–0.005 μg/mL). Moreover, the analog exhibits a negligible tendency to induce resistance, as demonstrated by serial exposure at a sublethal level to vancomycin-resistant Enterococci over a period of 50 d. Clearly, it is extremely difficult for bacteria to resist the three distinct yet synergistic mechanisms (i.e., dual D-Ala-D-Ala/D-Ala-D-Lac binding, transglycosylase inhibition, and cell membrane permeabililty) of the third-generation vancomycin analog.

Much remains to be accomplished before this breakthrough can have an impact in the clinic. Okano et al.'s (5) total synthesis route to the vancomycin analog is efficient and suitable for production of the relatively small quantities of material needed to probe its antimicrobial activity. However, it is not amenable to the scale-up that would be required to produce large amounts for clinical trials. Thus, major advances in synthetic methodology are necessary for this work to proceed toward clinical applications. Alternatively, genetic engineering of vancomycin-producing bacteria or biosynthetic enzymes could yield an advanced precursor capable of being transformed into the analog in only a few synthetic steps. This approach will also depend on transformative advances in the ability to manipulate biosynthetic processes.

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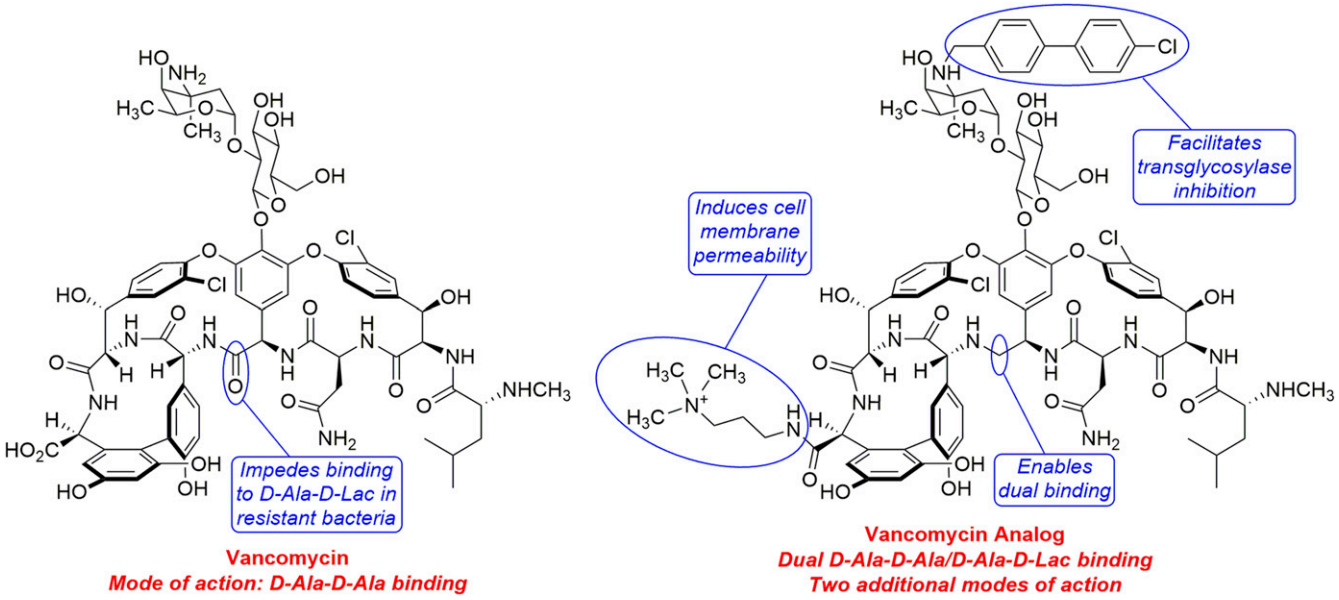

Fig. 1. Vancomycin and the vancomycin analog created by Okano et al. (5). Vancomycin is susceptible to resistance in bacteria that can use the ester D-Ala-D-Lac instead of the amide D-Ala-D-Ala in construction of their cell walls. The analog combines a binding-pocket modification that enables binding to the cell wall precursors of both vancomycin-sensitive and vancomycin-resistant bacteria with peripheral modifications that permit the agent to attack bacteria by two additional mechanisms. As a result of having three independent yet synergistic modes of action, the analog exhibits negligible susceptibility to acquired resistance.

The third-generation vancomycin analog designed and constructed by Okano et al. (5) incorporates two peripheral structural alterations into a compound possessing a key binding-pocket modification that renders the compound potent against both vancomycin-sensitive and vancomycin-resistant bacteria. Each of these changes introduces an additional mechanism or means of attacking bacteria. These three modes of action operate synergistically, resulting in a highly potent antimicrobial agent. Furthermore, it is extremely difficult for bacteria to simultaneously develop resistance to all three mechanisms. Future work will undoubtedly be focused on the synthetic and biosynthetic breakthroughs that will enable advancement of this exciting compound toward the clinic.

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