Crisis of antibiotic resistant has become a global threat to public health in recent decades [1–4]. Carbapenem antibiotics are a class of atypical β-lactam antibiotics with the broadest antibacterial spectrum and the strongest antibacterial activity. However, carbapenem-resistant *Acinetobacter baumannii* (CRAB) is still emerging, which is a gram-negative bacterium with lipopolysaccharide (LPS), which makes it resistant to several antibiotics and thus difficult to eliminate [5, 6]. As the number one pathogen of nosocomial infection, CRAB can cause severe pneumonia and bloodstream infection, etc. The mortality rate of patients infected with invasive CRAB can be as high as 40% to 60%, and it has been listed as the key pathogen of Class 1 by the World Health Organization. Due to the lack of feasible antibiotic strategies, phage combination therapy has been used in some patients, while the efficacy is limited [7]. Therefore, new discovery and development of antibiotic that targeting CRAB is urgently demand.

Fortunately, Kenneth A. Bradley’s team from the Roche Innovation Center in Basel, Switzerland, recently reported a breakthrough discovery in Nanze, entitled “A novel antibiotic class targeting the lipopolysaccharide transporter” [8]. This work showed that a macrocyclic peptide (MCP) with significant antibacterial activity by combat Carbapenem-resistant *Acinetobacter baumannii* (CRAB), this antibiotic named zosurabalpin carry out the antibacterial activity by blocking the transport of lipopolysaccharides from the plasma membrane to the outer membrane. Current non-clinical data demonstrate the therapeutic potential of zosurabalpin in patients with aggressive CRAB infection, supporting its application as a candidate for clinical development.

The clinical development candidate zosurabalpin was identified by optimizing the physicochemical properties of the compounds. Zosurabalpin showed well efficacy in mice infection in vivo, including against sepsis, thigh, and lung infections caused by CRAB. Gram-negative bacteria, in particular, are challenging to treat because of their dense protective layer of outer and inner membranes, which makes it difficult for most antibiotics to penetrate and be effective [5, 6]. The antibiotic zosurabalpin prevents the movement of lipopolysaccharide (LPS) macromolecules towards the bacterial outer membrane, preventing this protective outer membrane from remaining intact. This causes these molecules to accumulate inside the bacterial cell, leading to toxicity and ultimately the death of the bacterial cell.

The chemical structure of a drug determines its physicochemical properties and directly affects the absorption, distribution, metabolism and excretion of drug molecules in the body. Wu KJY et al. have developed a bridging large bicyclic antibiotic methromycin (CRM) by modifying the sugar segment of the Lincomamide antibiotic to reverse the problem of drug resistance. According to the first generation of R07075573, the researchers in this paper have good antibacterial activity against Acinetobacter, but it can cause the formation of lipoprotein vesicles, which causes tolerance in mice. The lipophilicity of the drug has been reasonably modified, which greatly improves the effect of the drug. Therefore, the structural modification of drugs is an important strategy for the development of new antibiotics, and the research in this paper is very influential, which fills the gap in the research and development of LPS drugs and provides a new research direction. However, the changed lipophilicity may increase the toxicity and side effects of the drug, which is the key to whether the drug can be used, so it is recommended that the toxicology, pharmacology, and metabolic kinetics of the drug can be comprehensively evaluated in the future.

In addition, zosurabalpin have also reduced bacterial levels with CRAB pneumonia and reduced mortality in mice, showing good efficacy in vivo and low plasma precipitation, providing hope for further clinical development in zosurabalpin. The drawback of this finding may be that can only target on the specific bacteria. For a long time, many researchers have focused on searching broad-spectrum antibiotics [9–11]. However, this new approach may be better than some broad-spectrum antibiotics. Traditional drug development for resistant strains of bacteria has focused on several approaches such as the discovery of new antibiotics like Teixobactin and Malacidins, fighting drug-resistant strains through structure optimization and drug design, combination drug strategy, antibiotic adjuvants such as pH and gene engineering [12–19]. Some researchers provide a new supplementary or alternative therapy option for combating bacterial infections. Host-acting antibacterial compounds (HACs) offer additional options to combat bacterial infections in light of this therapeutic dilemma. HACs are less likely to induce drug resistance because they do not target the pathogen directly, thereby reducing the direct selective pressure of the drug on the pathogen [20, 21].

In the same issue of nature journal, Daniel Kahne's team from Harvard University and others published a paper entitled "A new antibiotic traps lipopolysaccharide in its intermembrane transporter"11. This work further illustrated the structural, biochemical and genetic mechanisms of the pharmacology activity of zosurabalpin, which can recognize and capture the substrate binding conformation of LPS transporters to make this transport machine malfunctioning . In addition, they found that the amino acid sequence of the Lpt protein that forms the complex is less evolutionarily-conserved across different bacterial groups (genera), which could explain why zosurabalpin only selectively acts on *Acinetobacter Baumannii* either other Gram-negative bacteria.

Altogether, zosurabalpin has shown strong therapeutic potential against the highly resistant pathogen CRAB and is currently undergoing clinical trials. Whether it can perform this in patients infected with CRAB remains to be seen. Overall, the identification of this new antibiotic provides an important idea for the treatment of other refractory, drug-resistant gram-negative bacteria (such as Pseudomonas aeruginosa, Klebsiella pneumoniae). In addition, zosurabalpin has a unique advantage because it only acts specifically on *Acinetobacter baumannii*, compared with traditional broad-spectrum antibiotics. It is more beneficial to maintain normal intestinal flora homeostasis of patients.

References


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Author contributions
Liu XY conceived the projects. Lv RY wrote and edited the manuscript. Both authors read and approved the manuscript.

Competing interests
The authors declare no conflicts of interest.

Abbreviations
LPS, Lipopolysaccharide; CRAB, carbapenem-resistant Acinetobacter baumannii; MOP, macrocyclic peptide; ORM, bicyclic antibiotic methymycin; HACs, Host-acting antibacterial compounds.

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