A new class of antibiotic candidates for fighting against superbugs
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The research team of the State Key Laboratory of Chemical Biology and Drug Discovery of PolyU's Department of Applied Biology and Chemical Technology (ABCT) develops “Nusbiarylins”, a new class of antibiotic candidates for fighting against superbugs. The research team is led by Dr MA Cong. Credit: ResearchSEA

The novel small molecules, based on new target, new chemical structure and new antimicrobial mechanism, are different from those of existing antibiotics. The new drug candidates demonstrate much effective abilities of inhibiting bacterial growth than commonly used antibiotics, yet with no toxicity to human cells.

Drug resistance has been declared as one of the biggest threats to global health in 2019 by the World Health Organization, with MRSA becoming one of the most serious concerns. Hong Kong cannot be spared from the worsening scourge of MRSA. In 2018, there were 1,218 reported cases of community-associated MRSA (CA-MRSA), or a seven-fold of the figure in 2007—the year the disease became notifiable in Hong Kong. As of August this year, there were already 839 cases reported. Despite of tremendous pharmaceutical research and development investments worldwide, the search for new antibiotics has showed no progress since mid-1980s.

The development of “Nusbiarylins,” a new class of antimicrobial agents, by the research team of the State Key Laboratory of Chemical Biology and Drug Discovery of PolyU's Department of Applied Biology and Chemical Technology (ABCT), is thus a breakthrough in the battle against multi-drug resistant bacterial infections. The interdisciplinary team, led by Dr. MA Cong, Assistant Professor in ABCT, comprises of experts from both PolyU and Faculty of Medicine of The Chinese University of Hong Kong.

“Our research is now in the stage of animal studies, conducting infectious model studies and pharmacokinetic studies. These are the critical steps preceding clinical trials on human for drug development. At this moment, there are very few antibiotic related studies being able to complete such stage worldwide. Our findings so far are very promising. We believe further studies on these compounds will contribute to a new era of antibiotic discovery, contributing towards the fight against superbugs,” said Dr. Ma.

New target being identified by innovative antimicrobial mechanism

Most antibiotics currently in the market fight against bacteria through disrupting its DNA synthesis or protein functions. The innovative antimicrobial mechanism developed by PolyU team focuses on inhibiting the interaction between two proteins, NusB and NusE, which is crucial for synthesis of bacterial ribosomal RNA (rRNA). By designing small molecules to disrupt NusB-NusE interaction, bacterial cell proliferation can thus be curbed.

The team developed a model basing on the structure of NusB and NusE, and applied computer-aided screening to screen about 5,000 small
molecule compounds with drug-like properties to explore for inhibitors for NusB-NusE interaction. The shortlisted compounds were then put to tests for antimicrobial activity against different MRSA strains. A compound, (E)-2-[(3-ethynylphenyl)imino]methyl]-4-nitrophe nol (hereafter addressed as MC4), was identified as having much effective antibacterial abilities than the commonly used antibiotics. The Minimum Inhibitory Concentration (note: MIC denotes the lowest concentration of a chemical/drug for preventing bacterial growth) of MC4 for some MRSA strains are as low as 8 ?g/mL, compared to the MICs of >64 ?g/mL demonstrated by two antibiotics in the market, oxacillin and gentamicin.

Test of MC4 on human lung and skin cells (infections caused by MRSA often occur in these tissues) indicated no significant toxicity. The fact that NusB and NusE exist only in bacteria and not human cells has also addressed toxicity concern.

"Nusbiarylins"—a new class of antibiotic candidates

The research team has further structurally modified MC4 for optimization, and 167 analogues were synthesized so far. The new class of compounds are named as "Nusbiarylins" (basing on their target protein "NusB" and their "biaryl" structure). Laboratory test of Nusbiarylins against a panel of MRSA strains proved their consistent antibacterial activity, some with MIC as low as 0.125 ?g/mL, much better than commonly used antibiotics, including vancomycin with the MIC of 1 ?g/mL which is labeled as the "last resort" antibiotic drug in the United States.

Further preclinical studies on the in vitro pharmacological properties of Nusbiarylins on human cells indicated that the compounds:

- leading to nearly no hemolysis (i.e. human blood cell breaking), an indication of being safe for injection; and
- with excellent result in intestine absorption, implying being effective for oral administering.

More information: Yangyi Qiu et al, Nusbiarylins,