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Miniature scaffolding could support fight against superbugs

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Tiny molecular scaffolding that joins molecules together could be the key to our battle against antibiotic resistance. Research published in Bioorganic & Medicinal Chemistry Letters shows that carbon nanodot scaffolding assembled with small molecules called polyamines can kill some dangerous drug-resistant bacteria, including Acinetobacter baumanii and Klebsiella pneumonia.

According to the World Health Organization, antimicrobial resistance is one of the biggest public health threats we face today; there were about 480,000 new cases of multidrug-resistant tuberculosis in 2013. Standard treatments are failing and there is an urgent need to develop more effective antibiotics.

Scientists working in this area have found that some large positively charged compounds, called polycationic dendrimers, are antimicrobial. The researchers behind the new study, from Winston-Salem State University in the US and Universiti Malaysia Sarawak in Malaysia, have found that adding similar, but smaller polycationic molecules onto a new kind of material called carbon nanodots makes them even better at killing drug-resistant bacteria.

"We urgently need new and better antimicrobial materials if we are to tackle drug-resistant bacteria," said Dr Maria Ngu-Schwemlein, lead author of the study from Winston-Salem State University. "Our study shows that carbon nanodots can serve as a molecular scaffold for building antimicrobial materials; it's exciting because carbon nanodots

are relatively easy and cheap to make, they're non-toxic and soluble in water."

Carbon nanodots are tiny particles of carbon that are useful in imaging, sensing, drug delivery and many other applications. They can be made easily from starch and they're non-toxic, making them suitable for use in medicine.

There are chemical groups coating the surface of carbon nanodots that can help control the fluorescence properties of these tiny dots. This coating can also turn the nanodots into a molecular scaffolding for tethering small molecules together to enhance their potential.

The researchers used them to assemble molecules called PAMAM (poly(amidoamines)) together. PAMAM can vary in size, with the larger molecules showing some antimicrobial activity, which is not exhibited by the smaller ones. The team wanted to make the smaller, more flexible molecules better and efficient antimicrobials by attaching them to the carbon nanodot scaffolding, so they built two different molecules: CND-PAM1 and CND-PAM2.

The team tested both versions of CND-PAM and found that they both can kill Escherichia coli and Staphylococcus aureus at very low concentrations. The molecules exhibit greater antimicrobial activity against E. coli, so the researchers tested them against similar bacteria, including drug-resistant strains: Klebsiella pneumonia, Pseudomonas aeruginosa and Acinetobacter baumannii. In the case of K. pneumonia, the molecules were four times more effective at killing the drug-resistant than the normal strain.

The researchers also looked at whether the molecules with scaffolding helped make existing antibiotics work better. Adding CND-PAM1 to the antibiotic tetracycline made it more effective against resistant K.

pneumonia, and adding CND-PAM2 to colistin made it four times stronger against A. baumannii.

"We hope our research will lead to more effective antibiotics, and also that it will inspire other researchers to use carbon nanodots as scaffolding for a variety of applications," said Dr. Ngu-Schwemlein.

More information: Maria Ngu-Schwemlein et al. Carbon nanodots as molecular scaffolds for development of antimicrobial agents, *Bioorganic & Medicinal Chemistry Letters* (2016). DOI: 10.1016/j.bmcl.2016.02.047

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