Scientists design new molecules capable of overcoming resistance to conventional antibiotics

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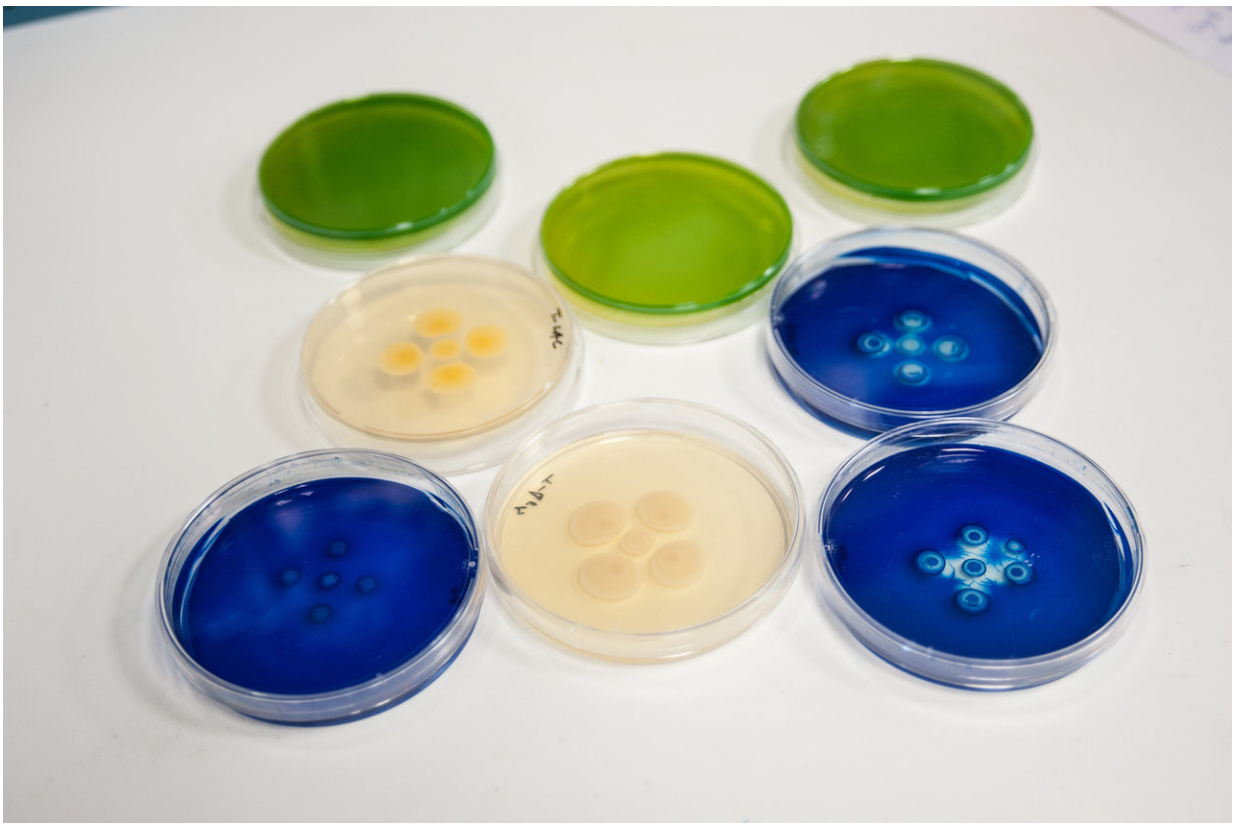


Superbugs in laboratory. Credit: ANDRÉS DÍAZ / CSIC Communication.

A team led by researchers from the Spanish National Research Council (CSIC) has made an important breakthrough in the battle against

superbugs and their resistance to multiple drugs. Scientists have designed molecules that can break the cellular mechanisms of bacterial resistance conventional antibiotics. The results of this discovery are published in the latest issue of the journal *Cell*.

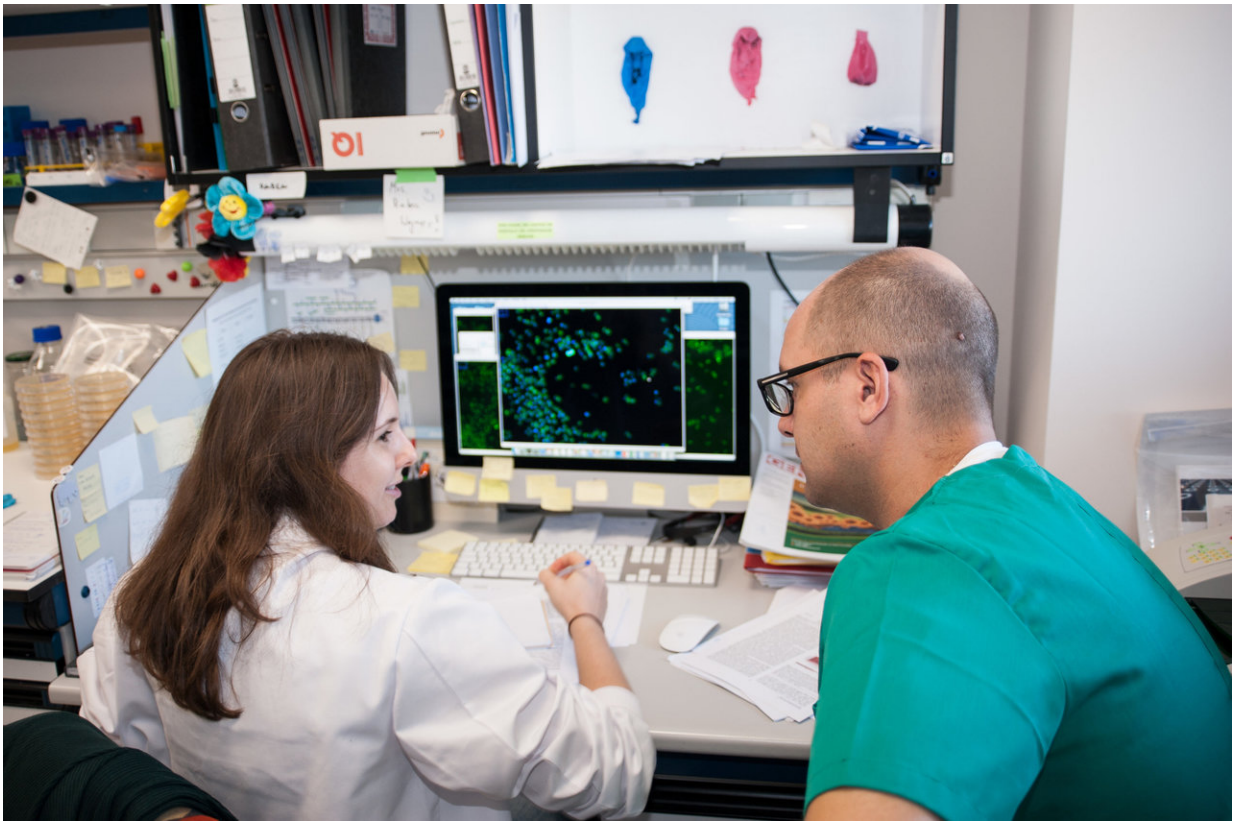
Superbugs are strains of bacteria resistant to several types of antibiotics. Their main characteristic is their ability to mutate their DNA from one generation to the next, making themselves resistant to the most common antibiotics. This is exacerbated by other factors including the imprudent and indiscriminate use of antibiotics, mainly through not completing the full treatment period, and unnecessary self-medication.

The research was carried out in vivo on mice and on the bacterium Staphylococcus aureus, one of the most life-threatening strains, given its resistance to methicillin, especially in hospital environments. According to the World Health Organization, people infected with this resistant strain are 64 percent more likely to die than those infected with non-resistant strains.

The work focused on directly attacking those areas of the bacteria where the proteins assemble to form complexes. "These microdomains in the cell membrane, called lipid rafts, are crucial, because they form many protein complexes related to resistance to antibiotics," says Daniel López, researcher at CSIC's National Centre for Biotechnology.

Sophisticated cellular organisation

To date, bacteria had not been shown to have the complex cellular organization based on the assembly platforms present in eukaryotic cells. In these areas of the cell membrane, the proteins responsible for forming large complexes do so efficiently. López says, "If they are confined to these tiny farms, the formation of molecular complexes important for the physiology of the bacteria is successfully achieved."



Researchers at work in laboratory. Credit: LUCAS MELCÓN / CSIC Communication

After characterization of the bacterium's proteins and lipids using advanced techniques such as cryotomography, the researchers chose a group of molecules capable of disassembling the lipid rafts. Many of these molecules are the same as those sometimes prescribed to treat high cholesterol.

"Since we know that many of the proteins related to antibiotic resistance are assembled in these microdomains, what we have done is to generate a strategy to break them down and attempt to eliminate their resistance. The molecules we have designed make all these proteins stop working

and become disorganised. In short, they succeed in making a resistant bacteria stop being resistant," points out the CSIC researcher.

Combined treatment

The researchers propose using these molecules in combination with methicillin in the treatment of invasive infections by superbugs. Lopez says, "Firstly, resistance would be disassembled before aiming a direct attack on the bacteria with a common antibiotic. It's interesting, because the option now opens to combat superbugs using an entirely new approach."

According to the scientists, the work offers a new possibilities for conventional antibiotics in the fight against superbugs, provided they are always used in combination with the molecules they have created. "With this, mortality caused by invasive infections would be reduced," says the CSIC researcher.

But what if the bacteria were to mutate once again, building resistance to this new treatment? According to López, the chances of that happening are remote, since eliminating the lipid rafts "takes away biological pressure on the bacteria to change. That is, it does not affect their survival and, therefore, they do not undergo the changes that would generate resistance."

More information: Esther García-Fernández et al, Membrane Microdomain Disassembly Inhibits MRSA Antibiotic Resistance, *Cell* (2017). DOI: 10.1016/j.cell.2017.10.012

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