Fighting superbugs with medical nanomachines

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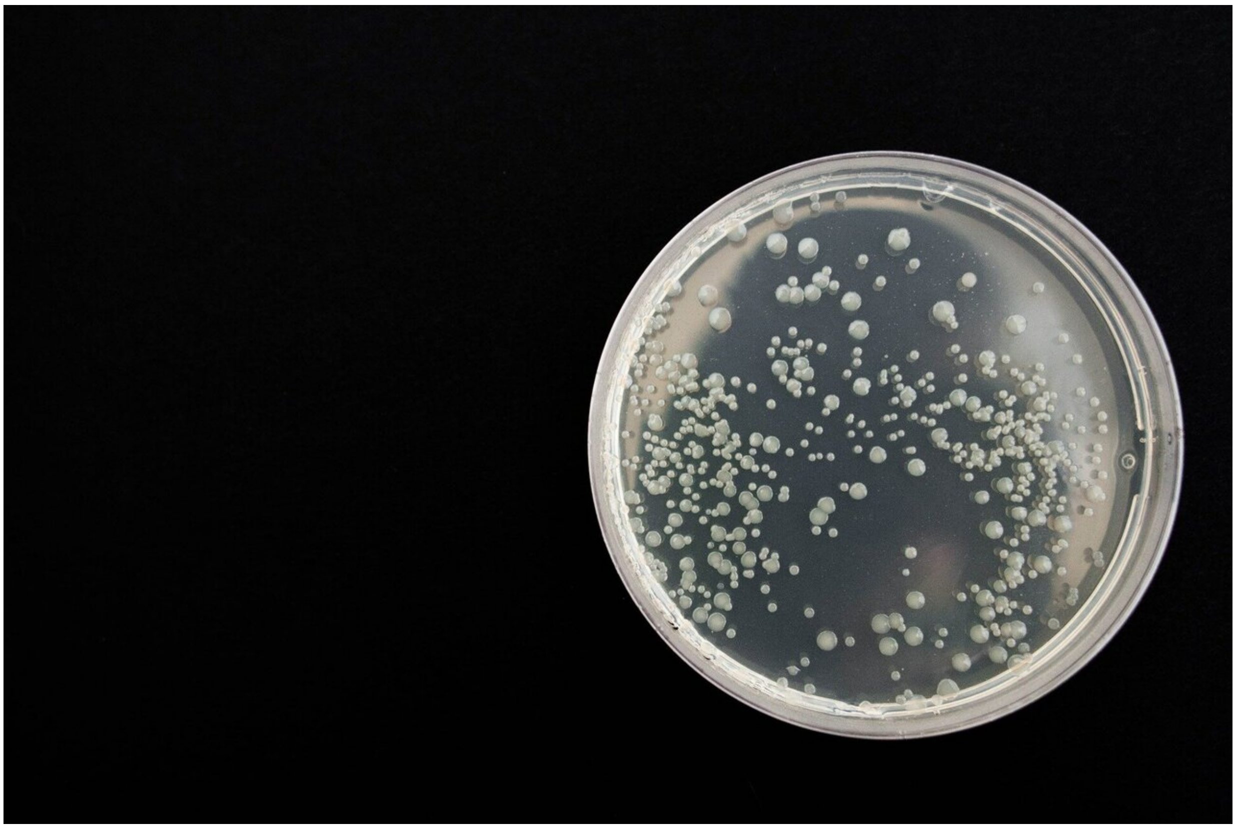

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Instruments smaller than a human hair are being designed to eradicate antibiotic-resistant bacteria and fight cancer.

Dr. Ana Santos becomes emotional when describing what happened several years ago: Her grandfather and an uncle died of urinary tract infections and a good friend succumbed after an accidental cut got infected.

She was shocked. In an age of antibiotics, such misfortunes weren't supposed to happen.

Rise and fall of antibiotics

"My family members were dying of infections," said Santos, a microbiologist at the Health Research Institute of the Balearic Islands, or IdISBa, in Spain. "I started to realize that we are going back in time—our antibiotics are no longer effective."

This is a global challenge. Almost 5 million deaths worldwide were linked to antibiotic-resistant bugs in 2019, according to *The Lancet* medical journal.

Six types of resistant bacteria inflict the most harm. The World Health Organization has warned that drug-resistant diseases could directly cause 10 million deaths by 2050.

Santos has been part of the fight to head off such alarming numbers: she led a research project that received EU funding to develop microscopic machines that can kill resistant bacteria. Called REBELLION, the project ran for 39 months until April 2023.

"I came across this concept of molecular machines that drill into cells," said Santos. "We have to start thinking outside the box."

Alexander Fleming, a Scottish physician, in 1928 famously discovered the first true antibiotic—penicillin—made by a type of mold. Other antibiotics, often made by soil microbes, were then found, saving millions of lives.

But in what was effectively an arms race, microorganisms evolved various defenses to survive antibiotics.

Bacteria borers

When her two relatives and friend lost their lives from infections, Santos was studying how bacteria live and die under conditions of starvation. She then decided to change her research focus.

"I was feeling frustrated because I was seeing this urgent problem and I was not doing anything about it," Santos said. "People are increasingly dying of infections that are resistant to antibiotics."

She sought out researchers in this area to lend a hand and partnered with a group in Spain to test how tiny molecular machines skewer bacteria. The machines consist of two parts of a molecule linked by a chemical bond; when light hits, the top part begins to spin rapidly like a drill.

Antibiotics often latch onto a specific bacterial protein, much like a key fits into a lock. The trouble is that bacteria can undergo a physical change so that the key no longer fits the lock. The antibiotics are left outside.

The idea behind the nanomachines is that they would be tougher for bacteria to evade.

Santos pushed forward these bug-killing machines as part of REBELLION.

Superbug killer

Their two parts are smaller than 100 nanometers, so 1,000th the width of a human hair—effectively making them minnows alongside larger bacteria.

Santos released many millions of her nanomachines in clumps of bacteria in her laboratory. The machines bound to the bacteria and, once exposed to light, began spinning and drilling into them.

Santos was jubilant at what she observed through her microscope: bacteria cells riddled with tiny holes.

Further experiments showed that the tiny drills can kill an array of strains that commonly infect people.

Then she tried something else: fewer machines against methicillin-resistant Staphylococcus aureus, or MRSA, a notorious superbug that's especially deadly in hospitals. Having a lower concentration of machines would lessen the risk of damage to human cells.

The instruments punctured the MRSA with enough holes so that it was once again vulnerable to antibiotics.

"It is very hard for bacteria to develop resistance against this action," Santos said. "It's like dropping bombs on them."

Wounds healer

To deploy this new weapon against resistant bacteria, the researchers will need to ensure that the nanomachines are safe to use on patients. That means being sure that bacteria rather than human cells get targeted.

One early reason for optimism is that the nanomachines are positively charged. As a result, they prefer to attach themselves to negatively charged bacteria rather than to human cells, which are more neutral.

In the experiments by Santos, the nanomachines caused no harm to worms when injected into them. Keen to move this strategy closer to patients, she is preparing for the next step: safety tests in mice.

If successful, the first patients treated might be ones with wound infections—especially people with severe burns, which are prone to infection.

The nanomachines could be placed on their skin and switched on by light to drill into bacteria that are infecting the wound.

Top European team

Nanomachines have a history in the limelight.

Professor Ben Feringa at the University of Groningen in the Netherlands won the Nobel Prize in Chemistry in 2016 for nanomachines with molecular motors that could be turned on by ultraviolet light.

The molecules change shape when struck by light and, as a result, can be used as switches or triggers. Feringa even built a nanocar made up of a single molecule that could move along a copper surface.

He helps supervise an EU-funded research project that is training early career scientists in molecular machines. Named BIOMOLMACS, the project runs for four and a half years through June 2024.

While they have yet to reach hospitals, nanomachines have the potential to treat cancer patients in ways that excite scientists and doctors. Today's cancer drugs often inflict side effects such as loss of hair, nausea, fatigue or immune-system weakness. This is because the drugs can maim healthy bystander cells.

A future scenario could involve nanomachines delivering cell-killing drugs precisely to a patient's cancer, perhaps burrowing inside any tumor.

Professor Maria Vicent at the Valencia Biomedical Research Foundation in Spain is a BIOMOLMACS supervisor who designs tiny carriers to deliver drugs to breast-cancer cells.

Another supervisor is Professor Jan van Hest at Eindhoven University of Technology in the Netherlands. He constructs materials that can be used to ferry vaccines or nanomedicines inside cells, including cancers.

Van Hest, Vicent and Feringa have other leading researchers from elsewhere in Europe contributing their own expertise.

Professor Remzi Becer at the University of Warwick in the U.K. is creating polymer nanoparticles to deliver future gene therapies to precise locations inside patients. The particles are often coated sugars because they are able to act as a key to open cells in the body.

"These synthetic sugars can interact with cell membranes and can give the particle a key to open the door and get a gene inside the cell," said Becer, who is mentoring two early career scientists and coordinating the whole project with 15 doctoral candidates.

Also in the U.K., Professor Robin Shattock at Imperial College London works on lipid nanoparticles, which are tiny spheres made of fats that can safely get inside cells. Lipid nanoparticles were the real breakthrough needed for COVID-19 vaccines.

Emerging talent

The students of these top-tier European researchers can be part of a new wave in medicine.

"The next big change for the pharma industry will be to train our genes to prevent cancer or to fight against cancer," said Becer.

He said that BIOMOLMACS can prep scientists for careers at some of the companies developing nanomachines to deliver such biological therapies to specific organs.

Meanwhile, Santos of REBELLION hopes that her work too can make a difference to cancer patients, whose treatments can leave them vulnerable to bacterial infections.

"My good friend had beaten cancer but then she died of an infection," she said. "I remember when the doctor said, "the bacteria is resistant to everything—there's nothing we can do."'

Her goal is to prevent doctors from ever having to utter such lines.

More information:

- REBELLION
- BIOMOLMACS

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