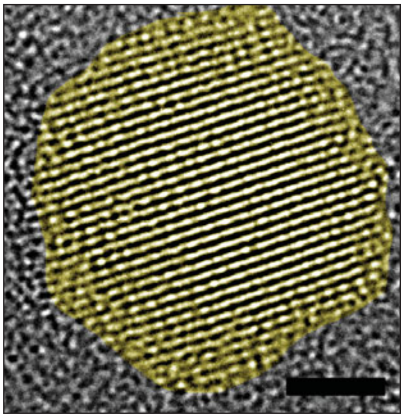
Bio Focus

Light-activated quantum dots kill antibiotic-resistant superbugs

With the growth and spread of "superbugs," bacteria resistant to multiple drugs, the world is quickly approaching a post-antibiotic era defined by incurable bacterial infections. To try to avoid this fate, researchers have devised alternative means to kill these hardy bacteria, such as using different types of nanoparticles, with varying degrees of success.

In a major step toward this goal, scientists at the University of Colorado Boulder (UCB) have developed photoexcitable (light-activated) quantum dots that can effectively and specifically kill superbugs without harming mammalian cells. The semiconductor nanoparticles, described recently in *Nature Materials* (DOI: 10.1038/NMAT4542), were able to kill 92% of multidrug-resistant bacteria in culture tests.

"The problem of superbugs is current, it's real, it's alarming," said study co-lead author Anushree Chatterjee, a chemical engineer at UCB. "We are out of antibiotics and we really, really need therapeutics that can work. This invention is important for this reason, and we have an extreme need to move forward to clinical trials."



Light-activated cadmium telluride nanoparticle quantum dot (shown here in a high-resolution transmission electron micrograph with a scale bar of 2 nm) designed to kill a number of multidrug-resistant bacteria without harming mammalian cells. Credit: Chatterjee and Nagpal labs, University of Colorado Boulder.

The overuse and misuse of antibiotics has recently led to a global epidemic of drug-resistant bacteria. In the United States alone, superbug infections affect nearly two million people and kill at least 23,000 each year, according to the Centers for Disease Control and Prevention. Some strains of bacteria, such as *Neisseria gonorrhoeae* (gonorrhea) and *Klebsiella*, are resistant to nearly all antibiotics, rendering them nearly untreatable.

Various research groups have investigated nano-therapeutics—in particular, light-activated metal nanoparticles that destroy bacteria through heat or other means—as a replacement for antibiotics. While they are sometimes effective in killing superbugs, a common problem with these approaches is their non-specificity, or the propensity for the nano-therapeutics to be toxic to or damage mammalian cells.

A different and promising approach with nano-therapeutics is to use them to attack superbugs with reactive oxidative species. Aerobic bacteria are able to mitigate or use free oxidative species to survive, but introducing specific oxidative species, such as superoxide radicals and peroxide, can disrupt the bacteria's redox homeostasis and cause cell death; various antibiotics, such as ampicillin, gentamicin, and ciprofloxacin, are known to work through a similar process.

While trying to develop intelligent, non-natural therapeutics to target antibiotic-resistant bacteria, Chatterjee teamed up with UCB chemical engineer Prashant Nagpal, co-lead author who was initially working on developing nanoelectronic techniques for single-molecule DNA and RNA sequencing. "During those studies, we realized that these strains have a propensity to be susceptible when there is oxygen present in the aqueous media," Nagpal said. "The superbugs are susceptible to certain potentials and radicals, so let's go back and design nanoparticles that make use of that."

Chatterjee, Nagpal, and their colleagues created CdTe quantum dots with a bandgap of 2.4 eV (517 nm). They used simple solution chemistry in which they synthesized the quantum dots directly in aqueous media from NaHTe and $CdCl_2$ at 98°C. "The cadmium telluride had just the redox potential that we were looking for," Nagpal said.

When illuminated with light above 2.4 eV, the quantum dots donated photoexcited electrons, producing superoxide radicals that, in turn, caused side reactions that possibly generated peroxide, other oxygen radicals, and reactive oxidative species. Illuminated 2.4 eV CdTe quantum dots killed up to 92% of multidrug-resistant *E. coli* after eight hours. In other tests, the treatment killed 29% of multidrug-resistant *Staphylococcus aureus* (specifically methicillin-resistant *Staphylococcus aureus*, or MRSA), 59% of *Klebsiella pneumoniae*, and 56% of *Salmonella typhimurium* in culture.

The researchers conducted a number of different experiments to show that the reduction and oxidation potentials of the nanomaterial drive the photoexcited quantum dots' bacteria-killing effect. They found that changing the size of the nanoparticles changed their bandgap, ultimately reducing their reduction potential and therapeutic effect. Additionally, increasing the light intensity increased the therapeutic effect, and using an anaerobic environment removed the therapeutic effect.

The team also found that they could cause the bacteria to proliferate by using CIS quantum dots, which have different potentials than CdTe. This effect could prove useful in improving cell growth in bioreactors, among other things.

A primary benefit of the quantum dots, Nagpal said, is how easy they are to modify and tailor, which is important considering how quickly pathogens evolve. "We have a moving target for these therapies," he said. "We cannot assume that the strain that is dominant now is the one to conquer because [a different strain] could come in tomorrow that is the new dominant species."

"This is very interesting work of potentially high value highlighting a great need we have today to identify materials that can kill antibiotic-resistant bacteria," said Thomas Webster, a chemical engineer who runs the Webster Nanomedicine Laboratory at Northeastern University. "This study

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provides a convincing series of data on the versatility of the quantum dots developed to kill numerous strains of antibiotic-resistant bacteria when activated."

But Webster, who was not involved in the study, is still concerned about the potential toxicity of the quantum dots. "Mammalian cell toxicity of the quantum dots was only tested against one cell line and a transformed cell line that is not an accurate representation of the numerous healthy cells in our body," Webster said, adding that Cd and Te also have toxicity concerns that need to be monitored in future studies (the researchers used a low dose of CdTe to minimize its harmful effects).

"Moving forward, we are refining the design of our nanoparticles," Chatterjee said. "We are trying to push the limit of how far can we go in designing new therapies and making nanoparticles safer." Eventually, the team hopes to conduct clinical trials using these quantum dots.

Joseph Bennington-Castro

Bio Focus

Hybrid semiconductor-bacterium self-photosensitization improves artificial photosynthesis

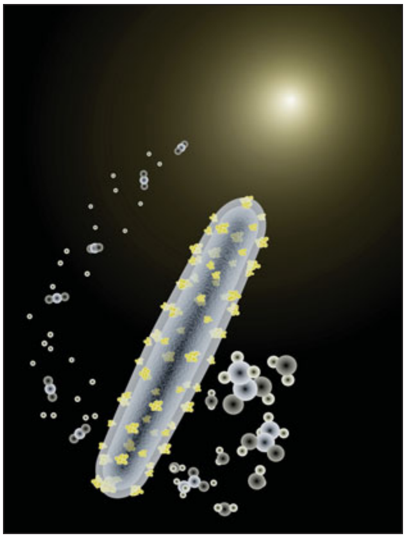
Researchers from the University of California–Berkeley and Lawrence Berkeley National Laboratory have developed a hybrid system for artificial photosynthesis by combining nanoparticles of an inorganic semiconductor with self-photosensitizing bacteria to produce acetic acid using only solar energy. Kelsey K. Sakimoto, Andrew Barnabas Wong, and Peidong Yang combined nanoparticles of the semiconductor cadmium sulfide (CdS), which is an excellent harvester of light, with a self-photosensitizing bacteria *Moorella thermoacetica*. The nanoparticles were precipitated on the surface of the bacteria, ensuring biocompatibility and a strong interface. These results are reported in a recent issue of *Science* (DOI: 10.1126/science.aad3317).

In natural photosynthesis, solar energy is used to oxidize water to oxygen and reduce carbon dioxide to make the chemicals that sustain life. Semiconductors are better at absorbing solar radiation than biological materials, but cannot compete with biocatalysts in terms of specificity, cost, or their ability to self-replicate and repair. By combining both, one can then achieve the best of both worlds.

Nonphotosynthetic bacteria are preferred in synthetic biology because they can produce a variety of products by reducing CO_2. For this study, the researchers chose *Moorella thermoacetica*, which is a nonphotosynthetic bacteria. They added cadmium nitrate and cysteine—a source of sulfur—to the growing culture so that CdS could be precipitated on the surface of the bacteria. Scanning electron microscopy, scanning transmission electron microscopy, and energy-dispersive x-ray spectroscopy confirmed the presence of CdS particles with sizes of under 10 nm. The self-photosensitization of the nonphotosynthetic bacteria was induced with the cadmium sulfide nanoparticles, enabling the photosynthesis of acetic acid. A maximum yield of 90% acetic acid, as a natural waste product of respiration, was obtained.

The cell counts of the *Moorella thermoacetica*-CdS system nearly doubled after a day, demonstrating that this self-reproducing hybrid organism can be sustained purely through solar energy. Under blue light (wavelength 435–485 nm) the quantum yield (defined as rate of production of acetic acid per unit of photon flux) was 52% ± 17%, as compared with the 22% reported previously for analogous systems. A fourfold increase in the loading of the bacteria-CdS hybrid gave a quantum yield of 85% ± 12%. When the system was exposed to simulated day-night cycles, an unexpected result followed—the acetic acid concentration increased during illumination as well as in the dark. The quantum yield was 2.44% ± 0.62%, higher than the yearlong average of 0.2–1.6% for plants and algae.

Yang, who has joint appointments with the Departments of Chemistry and Materials Science at Lawrence Berkeley National Laboratory and is a co-director of the Kavli Energy NanoSciences Institute at Berkeley, said, "This study opens up several new avenues. Exploring more materials capable of biologically induced precipitation will increase photosynthetic efficiency. Genetic engineering tools can be used in further development of the final product selectivity. Synthetic biology can play an important role in the rational design of hybrid organisms."



Inorganic–biological hybrid bacterium, *Moorella thermoacetica*-cadmium sulfide, photosynthetically produces acetic acid from CO_2 through a novel self-photosensitization mechanism. The hybrid system is self-replicating through solar energy and exhibits efficiencies comparable to natural photosynthesis. Photo credit: Kelsey Sakimoto.

The practical applications are significant. Starting with pure acetic acid, rather than biomass (which requires processing), makes it easier to produce biodegradable plastics, pharmaceuticals, and liquid fuels. This results in sustainable chemical production and least climate change. Any effort to convert CO_2 to useful products rather than burying it is welcome. With decreasing natural green cover on earth, natural photosynthesis may need to be augmented by an artificial one. The system developed in this study can also be modified for wastewater purification and biomass conversion.

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