Harnessing silicon nanoparticles to fight infections

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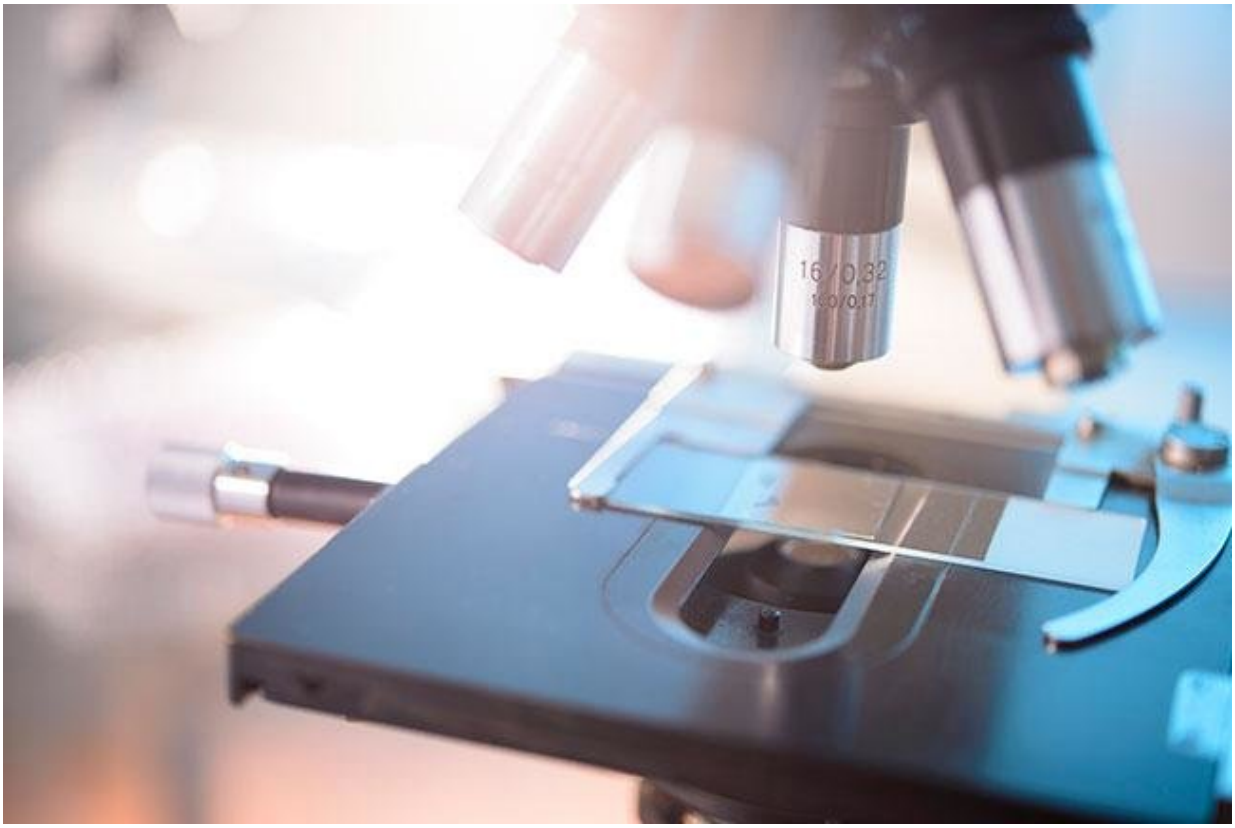

There is an urgent need for better methods to treat bacterial infection in the race between developing new antibiotics and the emergence of drug-resistant bacteria.

Presently, antimicrobial resistance is responsible for 23,000 deaths annually in the United States and 700,000 deaths worldwide. A Wellcome Trust 2016 study predicted the present rate of emergence of new virulent strains will outstrip the U.S. Food and Drug Administration approval rate for new antimicrobial agents by 2050—which means deaths from antimicrobial resistant strains will exceed deaths from cancer.

University of Minnesota researcher Hongbo Pang assisted in discovering the first example of an effective gene therapeutic against lethal bacterial infections using a nanotherapeutic to deliver short interfering RNA (siRNA) that targets immune system cells. This research, published in the journal *Nature Communications*, was conducted by a team from the University of Minnesota; University of California, San Diego (UCSD); Sanford Burnham Medical Discovery Institute (SBMDI); and the Korea Advanced Institute of Science and Technology (KAIST).

"This study perfectly demonstrates the great potential of targeted nanotechnology in treating various human diseases," said Pang, an assistant professor in the University of Minnesota College of Pharmacy.

"This is a really great example of convergent research," said Michael Sailor from the University of California, San Diego. "To get this concept to work, we needed to combine our nanomaterials expertise at UCSD and the membrane and cell biology expertise at KAIST with the peptides and disease models developed by our biomedical collaborators at the SBMDI and UMN."

The research team further explored gene therapeutic, an under-utilized approach to fight bacterial infections and to bolster the body's immune system. siRNA gene therapeutics are able to enhance the ability of some innate immune cells to attack bacteria while shutting down the immune system's inflammatory response that can interfere with recovery.

With this treatment, the hope is a wide range of bacterial infections, including emerging strains, can be attacked. While delivering siRNA in the body is notoriously difficult, the study found siRNA therapy produced a full recovery from a lethal bacterial infection by rescuing 100 percent of mice infected with a lethal dose of Staph. aureus pneumonia.

"A short strand of peptide can recognize macrophages, an important immune cell type, selectively in the infection site," added Pang. "In combination with nanomaterial of unique advantages as drug carriers, we could deliver gene therapeutics efficiently to where they are needed, and achieve a full recovery from a lethal bacterial infection."

The research team incorporated three features into their nanoparticle design:

- generated a porous nanoparticle host that protected its siRNA payload from premature degradation in the bloodstream;
- discovered a peptide that selectively targets macrophage cells, a type of white blood cell which attacks foreign microbes and signals an invader is present
- engineered a chemical coating, called a fusogenic lipid, that allowed the nanoparticle to penetrate into the macrophage and deliver its gene therapeutic to the proper compartments in the cell.

According to Pang, the study is the first example of an effective gene therapy for lethal bacterial infections, using a nanotherapeutic to deliver siRNA to target macrophage cells. The research team, for the first time, have demonstrated that siRNA therapeutic can generate a full recovery from a lethal bacterial infection.

More information: Byungji Kim et al. Immunogene therapy with

fusogenic nanoparticles modulates macrophage response to Staphylococcus aureus, *Nature Communications* (2018). DOI: 10.1038/s41467-018-04390-7

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