# Team builds viruses to combat harmful 'biofilms'

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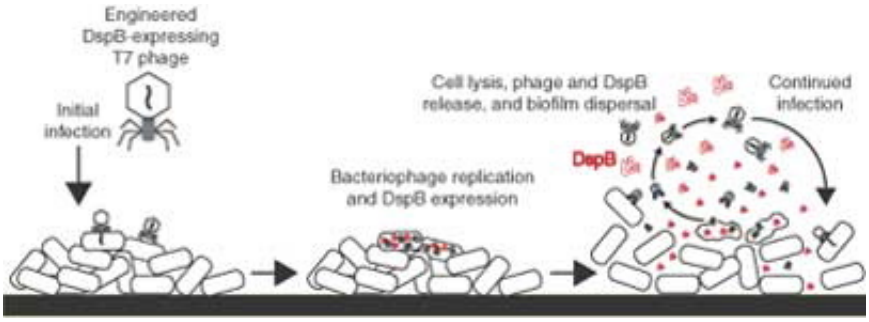


This diagram shows how an engineered virus,T7, destroys a biofilm composed of E. coli bacteria. Graphic courtesy / Timothy Lu and James Collins

In one of the first potential applications of synthetic biology, an emerging field that aims to design and build useful biomolecular systems, researchers from MIT and Boston University are engineering viruses to attack and destroy the surface "biofilms" that harbor harmful bacteria in the body and on industrial and medical devices.

They have already successfully demonstrated one such virus, and thanks to a "plug and play" library of "parts" believe that many more could be custom-designed to target different species or strains of bacteria.

The work, reported in the July 3 *Proceedings of the National Academy of Sciences*, helps vault synthetic biology from an abstract science to one that has proven practical applications. "Our results show we can do

simple things with synthetic biology that have potentially useful results," says first author Timothy Lu, a doctoral student in the Harvard-MIT Division of Health Sciences and Technology.

Bacterial biofilms can form almost anywhere, even on your teeth if you don't brush for a day or two. When they accumulate in hard to reach places such as the insides of food processing machines or medical catheters, however, they become persistent sources of infection.

These bacteria excrete a variety of proteins, polysaccharides, and nucleic acids that together with other accumulating materials form an extracellular matrix, or in Lu's words, a "slimy layer," that encases the bacteria. Traditional remedies such as antibiotics are not as effective on these bacterial biofilms as they are on free-floating bacteria. In some cases, antibiotics even encourage bacterial biofilms to form.

Lu and senior author James Collins, professor of biomedical engineering at BU, aim to eradicate these biofilms using bacteriophage, tiny viruses that attack bacteria. Phage have long been used in Eastern Europe and Russia to treat infection.

For a phage to be effective against a biofilm, it must both attack the strain of bacteria in the film and degrade the film itself. Recently, a different group of researchers discovered several phages in sewage that meet both criteria because, among other things, they carry enzymes capable of degrading a biofilm's extracellular matrix.

This discovery led Lu and Collins to consider engineering phages to carry enzymes with similar capabilities. Why? Finding a good naturally occurring combination for a given industrial or medical problem is difficult. Plus, "people don't want to dig through sewage to find these phages," says Lu.

So Collins and Lu defined a modular system that allows engineers to design phages to target specific biofilms. As a proof of concept, they used their strategy to engineer T7, an Escherichia coli-specific phage, to express dispersin B (DspB), an enzyme known to disperse a variety of biofilms.

To test the engineered T7 phage, the team cultivated E. coli biofilms on plastic pegs. They found that their engineered phage eliminated 99.997% of the bacterial biofilm cells, an improvement by two orders of magnitude over the phage's nonengineered cousin.

The team's modular strategy can be thought of as a "plug and play" library, says Collins. "The library could contain different phages that target different species or strains of bacteria, each constructed using related design principles to express different enzymes."

Creating such a library may soon be feasible with new technologies for synthesizing genes quickly and cheaply. "We hope in a few years, it will be easy to create libraries of phage that we know have a good chance of working a priori because we know so much about their inner-workings," says Lu.

Synthetic biology also makes it possible to control the timing of when a gene is expressed in an organism. For instance, Lu inserted the DspB genes into a precise location in the T7 genome so that the phage would strongly express it during infection rather than before or after. Such control was possible because T7 was extremely well characterized by other researchers such as MIT synthetic biologist Drew Endy, an assistant professor of biological engineering.

Though phages are not approved for use in humans in the United States, recently the FDA approved a phage cocktail to treat Listeria monocytogenes on lunchmeat. This makes certain applications, such as

cleaning products that include phages to clear slime in food processing plants, more immediately promising. Another potential application: phage-containing drugs for use in livestock in exchange for or in combination with antibiotics.

Source: MIT