Antibody-making bacteria promise drug development

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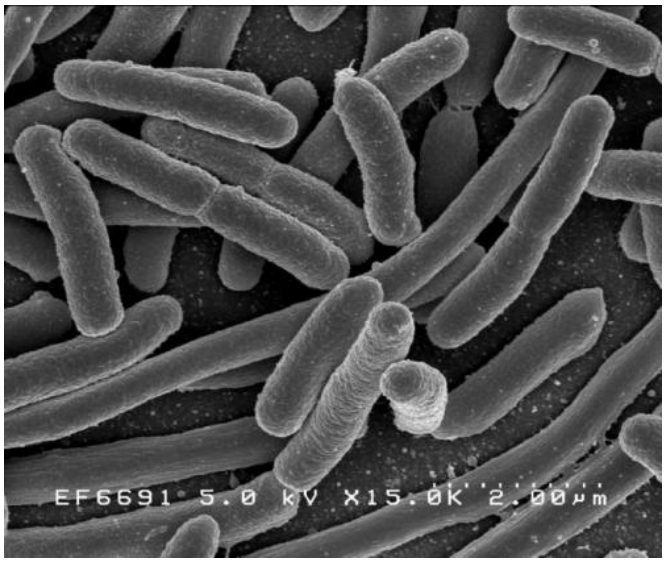

Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

Monoclonal antibodies, proteins that bind to and destroy foreign invaders in our bodies, routinely are used as therapeutic agents to fight a wide range of maladies including breast cancer, leukemia, asthma, arthritis, psoriasis, Crohn's disease and transplant rejection. Humira, a treatment for arthritis and Crohn's disease, was among the first lab-engineered antibody drugs.

Typically, monoclonal antibodies are manufactured in animal cell lines, such as Chinese hamster ovary (CHO) cells, with long development times that can drive up cost. A team of Cornell chemical engineers and New England Biolabs scientists have devised a shortcut. They've done it using an engineered E. coli bacterium that carries machinery for human antibody production and can churn out complex proteins, including many of today's blockbuster, life-saving antibody drugs, in as little as a week.

A *Nature Communications* paper published Aug. 27 details the feat, led by co-senior author Matthew DeLisa, the William L. Lewis Professor of Engineering, and first author Michael-Paul Robinson, a graduate student in the field of chemical engineering. They worked with a team led by co-senior author Mehmet Berkmen, a staff scientist at New England Biolabs.

The work built on a previously commercialized E. coli strain invented by Berkmen, called "SHuffle," which could make shorter, simpler proteins such as antibody fragments that had less therapeutic value than their full-sized, monoclonal antibody counterparts. Now, the researchers report producing full-length antibodies using the specially engineered SHuffle bacterium, including ones that fight the avian flu virus, the anthrax pathogen Bacillus anthracis, and a replica of the therapeutic antibody Herceptin that is used to treat breast cancer.

"We can engineer new antibodies in SHuffle almost as quickly as our bodies can. Customizing an antibody requires only simple edits to the bacterium's DNA, which opens up a low-effort way to prototype new ideas for future therapeutics," Berkmen said.

The SHuffle bacterium harbors genetic modifications that allow it, unlike other bacteria, to assemble antibodies and other human proteins into their natural, functional shape. A unique aspect of the method is the "all-in-one-pot" manner in which the large, complicated antibody molecules are assembled, taking place exclusively in the cytoplasmic compartment of the bacterium.

This method effectively bypasses some of the key bottlenecks in the multi-compartment biosynthesis inherent to such production hosts as CHO cells. Preliminary experiments indicate the SHuffle-made antibodies could be recognized by the human immune system as robustly as the originals.

"We think this is going to be a very powerful way of biomanufacturing existing antibodies, or even developing entirely new ones from scratch, that is much faster than current methods," DeLisa said.

While immunotherapeutics invented in bacteria may one day become useful medicines, other uses may abound.

"Many diagnostic tests, such as those performed on tumor biopsies, depend on finely-tuned antibodies," DeLisa said. "Scientists also depend upon antibodies to make the molecular mechanics of living organisms visible, but sometimes they lack antibodies that work well enough for their experiments."

The paper is titled "Efficient expression of full-length antibodies in the cytoplasm of engineered bacteria," and the work was supported by the National Institutes of Health, the Ford Foundation and the National Science Foundation.

More information: "Efficient expression of full-length antibodies in the cytoplasm of engineered bacteria." *Nature Communications* 6, Article number: 8072 DOI: 10.1038/ncomms9072