Quest for edible malarial vaccine leads to other potential medical uses for algae

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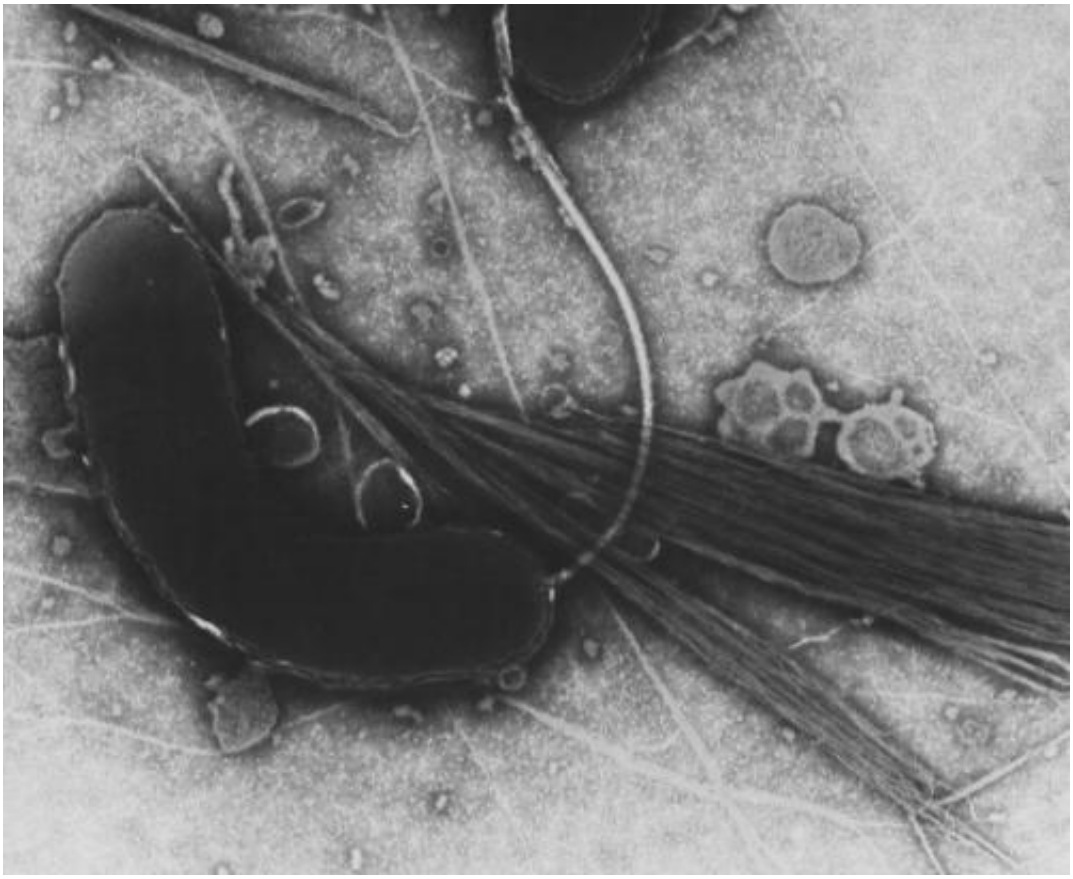


The scientists used a protein produced by the bacterium responsible for cholera, Vibrio cholera, that binds to intestinal epithelial cells. Credit: Wikimedia

(Phys.org) —Can scientists rid malaria from the Third World by simply feeding algae genetically engineered with a vaccine? That's the question

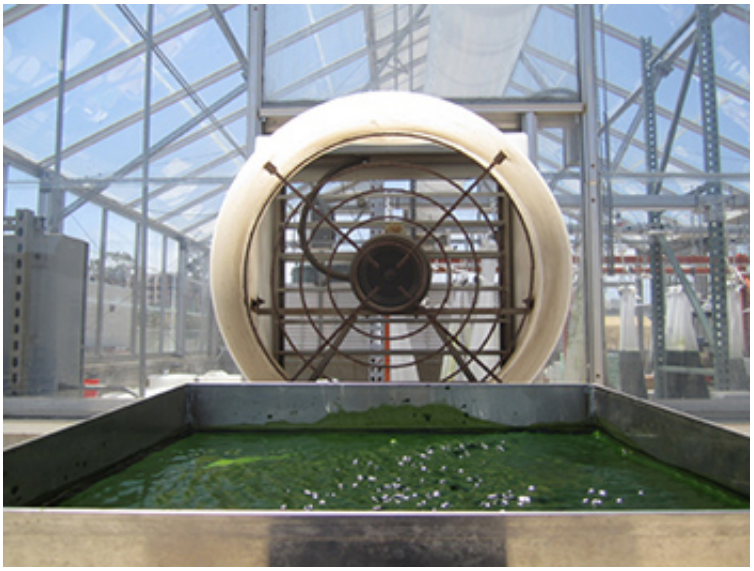
biologists at UC San Diego sought to answer after they demonstrated last May that algae can be engineered to produce a vaccine that blocks malaria transmission. In a follow up study, published online today in the scientific journal *Applied and Environmental Microbiology*, they got their answer: Not yet, although the same method may work as a vaccine against a wide variety of viral and bacterial infections.

In their most recent study, which the authors made freely available on the *Applied and Environmental Microbiology* website, the researchers fused a protein that elicits an antibody response in mice against the organism that causes malaria, *Plasmodium falciparum*, which afflicts 225 million people worldwide, with a protein produced by the bacterium responsible for cholera, Vibrio cholera, that binds to intestinal epithelial cells. They then genetically engineered algae to produce this two-protein combination, or "fusion protein," freeze dried the algae and later fed the resulting green powder to mice. The researchers hypothesized that together these proteins might be an effective oral vaccine candidate when delivered using algae.

The result? The mice developed Immunoglobulin A (IgA) antibodies to both the malarial parasite protein and to a toxin produced by the cholera bacteria. Because IgA antibodies are produced in the gut and mucosal linings, they don't protect against the malarial parasites, which are injected directly into the bloodstream by mosquitoes. But their study suggests that similar fusion proteins might protect against infectious diseases that affect mucosal linings using their edible freeze-dried algae.

"Many bacterial and viral infections are caused by eating tainted food or water," says Stephen Mayfield, a professor of biology at UC San Diego who headed the study. "So what this study shows is that you can get a really good immune response from a recombinant protein in algae that you feed to a mammal. In this case, it happens to be a mouse, but presumably it would also work in a human. That's really encouraging for

the potential for algae-based vaccines in the future."



The edible algae Chlamydomonas, seen here at UC San Diego, can be grown in ponds anywhere in the world. Credit: SD-CAB

The scientists say bacterial infections caused by *Salmonella*, *E. coli* and other food and water-borne pathogens could be prevented in the future with inexpensive vaccines developed from algae that could be eaten rather than injected. "It might even be used to protect against cholera itself," said James Gregory, a postdoctoral researcher in Mayfield's lab and the first author of the paper. In his experiments with mice, he said, Immunoglobulin G (IgG) antibodies—which are found in blood and tissues—were produced against the cholera toxin, "but not the malaria antigen and we don't quite understand why."

Part of the difficulty in creating a vaccine against malaria is that it requires a system that can produce structurally complex proteins that resemble those made by the parasite, thus eliciting antibodies that disrupt

malaria transmission. Most vaccines created by engineered bacteria are relatively simple proteins that stimulate the body's immune system to produce antibodies against bacterial invaders.

Three years ago, a UC San Diego team of biologists headed by Mayfield, who is also the director of the San Diego Center for Algae Biotechnology, a research consortium seeking to develop transportation fuels from algae, published a landmark study demonstrating that many complex human therapeutic proteins, such as monoclonal antibodies and growth hormones, could be produced by the common algae *Chlamydomonas*. That got Gregory wondering if complex malarial transmission blocking vaccine candidates could also be produced by *Chlamydomonas*. Two billion people live in malaria endemic regions, making the delivery of a malarial vaccine a costly and logistically difficult proposition, especially when that vaccine is expensive to produce. So the UC San Diego biologists set out to determine if this alga, an organism that can produce complex proteins very cheaply, could produce malaria proteins that would inhibit infections from malaria.

"It's too costly to vaccinate two billion people using current technologies," explained Mayfield. "Realistically, the only way a malaria vaccine will ever be used in the developing world is if it can be produced at a fraction of the cost of current vaccines. Algae have this potential because you can grow algae any place on the planet in ponds or even in bathtubs."

Collaborating with Joseph Vinetz, a professor of medicine at UC San Diego and a leading expert in tropical diseases who has been working on developing vaccines against malaria, the researchers showed in their earlier study, published in the open access journal *PLoS ONE* last May that the proteins produced by the algae, when injected into laboratory mice, made antibodies that blocked malaria transmission from mosquitoes.

The next step was to see if they could immunize mice against malaria by simply feeding the genetically engineered algae. "We think getting oral vaccines in which you don't have to purify the protein is the only way in which you can make medicines dramatically cheaper and make them available to the developing world," says Mayfield. "The Holy Grail is to develop an orally delivered vaccine, and we predict that we may be able to do it in algae, and for about a penny a dose. Our algae-produced malarial vaccine works against malarial parasites in mice, but it needs to be injected into the bloodstream."

Although an edible malarial vaccine is not yet a reality, he adds, "this study shows that you can make a pretty fancy protein using algae, deliver it to the gut and get IgA antibodies that recognize that protein. Now we know we have a system that can deliver a complex protein to the right place and develop an immune response to provide protection."

Mayfield is also co-director of the Center for Food & Fuel for the 21st Century, a new research unit that has brought together researchers from across the campus to develop renewable ways of improving the nation's food, fuel, pharmaceutical and other bio-based industries and is this week hosting a major symposium on the subject at the Institute of the Americas at UC San Diego.

Provided by University of California - San Diego