Taking the Guesswork out of Vaccines

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Picking the right strain of a pathogen against which to develop a seasonal vaccine has always been an educated guess, and not always successful. Now UCSB researchers have found the key to creating vaccines effective against multiple strains.

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Vaccines are one of the great successes of modern medicine?they?ve saved millions of lives by preventing infections by a wide variety of pathogens. Unfortunately, the organisms they?re supposed to protect against come in many different varieties, while most vaccines only offer a defense against, at most, a handful of closely-related germs.

That?s why new flu vaccines are produced every year, carefully tailored to fight the specific strains predicted to be the most widespread around the world in the coming flu season. It?s also why vaccines don?t work against pathogens that are constantly mutating, resulting in a broad spectrum of strain variants against which conventional vaccines are ineffective.

?That?s the Achilles? heel of vaccines,? says Michael Mahan, a bacterial geneticist in UCSB?s Department of Molecular, Cellular, and Developmental Biology. Together with Douglas Heithoff ? Mahan?s former student, now a research scientist in the department ? and colleagues at the University of Utah, he?s working to develop a new generation of vaccines, termed cross-protective, that protect against many strains of a given pathogen.

In the past, vaccines have been developed using a somewhat empirical approach. ?They work, but you usually don?t know why,? Heithoff says. ?We?re trying to use a mechanistic approach toward vaccine design.?
To do that, they first took a careful look at how microbes operate during infection. 
"We're working to understand the mechanisms of disease at the molecular level," Mahan says, "in order to make better medicines."

They've been studying Salmonella, a bacterium that is found in the digestive tracts of mammals, reptiles, birds, and insects, and is spread in feces. Salmonella infects up to 1.5 billion people annually worldwide, with more than a million cases in the U.S. alone. There are around 2,500 known strains of the bacterium, and any given strain can cause sickness in some hosts but not in others. In humans, different strains of Salmonella can cause food poisoning, blood poisoning (sepsis), and typhoid fever.

For most people, gastroenteritis caused by Salmonella is unpleasant, but short-lived. In the elderly, the very young, and people whose immune systems are compromised by HIV or cancer treatments, however, an infection can be fatal. In these severe cases, bacteria may spread from the intestines to the blood and then to other organs.

Humans usually pick up Salmonella from contaminated beef or chicken. Vegetarians aren't immune though, since Salmonella carried in animal waste can contaminate fields where vegetables are grown and facilities where food is processed or prepared. A Salmonella outbreak that hit headlines early this year was traced to contaminated peanut butter and other products containing peanuts. It infected hundreds of people in dozens of states and has been linked to at least nine deaths.

One strain of Salmonella causes typhoid fever, a sometimes-fatal illness that is very rare in the U.S., but affects more than 20 million people in the developing world each year, according to the Centers for Disease Control. That strain is only known to infect humans, and spreads as a result of poor water sanitation and hygiene practices.

There is a vaccine against typhoid, developed decades ago, but it's not particularly effective, Mahan says. It offers protection only against a few related strains of typhoid-causing Salmonella, so it's no help in fighting the other strains that can sicken or kill.

In their earlier work on Salmonella, Mahan and Heithoff studied how the bacterium is able to lurk benignly in some hosts, and then rapidly wreak havoc once it finds its way into others. They discovered an enzyme that acts as a master switch. This switch controls "many, many virulence functions," Mahan says, allowing the bacterium to quickly transform from harmless hitchhiker to deadly invader.

While this switch is a great asset for the microbe, it's also its greatest vulnerability — and a terrific target for a new vaccine. Mahan and Heithoff created one by inactivating the
switch, thereby disarming the bacterium. They used this crippled Salmonella ? which can?t cause illness, but still provokes an immune response ? as a vaccine.

They?ve tested their new Salmonella vaccine in mice, chickens, and cows, and found that it gave the animals immunity to more than 20 strains of Salmonella isolated from various infected animals from around the world.

Mahan and Heithoff?s vaccine has another advantage over those that are currently in use: It doesn?t cause an increase in a specific type of inhibitory immune cells?cells that are associated with immune declines in cancer patients. The researchers have also shown that these inhibitory cells become more abundant with the normal aging process, which Mahan says, ?may explain why the aged are more susceptible to disease and why they are difficult to effectively vaccinate.? He continued, ?We?re currently working on interventions that negate these inhibitory cells?those interventions have the potential to reduce disease susceptibility and increase vaccination efficiency in the elderly.?

Although the researchers have focused on developing a new vaccine for Salmonella, the same kind of master switch is found in other dangerous bacteria, including those that cause cholera, dysentery and the plague. Mahan believes that one day cross-protective vaccines will be developed against those and other infectious microbes.

Viruses, like those that cause the flu, are a trickier target, Mahan says, ?because they rapidly mutate and have very little genetic material.? He?s optimistic, however, that a new generation of human vaccines can be developed against both bacteria and viruses, offering a broader, more effective defense against multiple strains of microbes, rather than against just one or two variants.

His biggest reservation is that currently unknown pathogens could turn up in humans, surprising us and leaving us ill-prepared for their attack. ?Cross-protective vaccines may work against a wide range of strains of germs, but what about the ?bugs? we don?t know about?? he asks.

In the meantime, Mahan, Heithoff, and their colleagues are continuing to test their Salmonella vaccine in animals, with good results. Used in humans, a vaccine effective against many strains of the bacterium could save thousands of lives, and could spare millions of other people from very unpleasant illnesses.

Mahan and Heithoff predict that cross-protective Salmonella vaccines will one day be approved for human use, but ?The first of them is at least 10 years away?? Heithoff
Human benefits from their research, however, are closer than that: when their new vaccine is cleared for use in livestock—which isn’t too far in the future, according to Mahan—it will reduce human food-borne illnesses by reducing levels of Salmonella in farm animals. That, in turn, will ensure that less of the pathogen finds its way into kitchens and restaurants, and ultimately into people’s digestive tracts.

“We have to make the food supply safer,” Mahan says. “It’s unacceptable to me that a child could eat a cheeseburger and die, or spend the rest of his or her life on dialysis. We can do better, and we’re making good progress?”

Links:

Michael Mahan’s homepage: lifesci.ucsb.edu/mcdb/faculty/mahan

UCSB’s Department of Molecular, Cellular and Developmental Biology: lifesci.ucsb.edu/mcdb

NIH’s Medline Plus page on Salmonella: nlm.nih.gov/medlineplus/salmonellainfections.html

CDC Salmonella home page: cdc.gov/salmonella

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