Infect to Protect

Skip Derra

The idea sounds a bit haphazard, and coming from a man with flowing grey hair and beard you wonder why it also sounds so enticing. Roy Curtiss wants to vaccinate children and animals alike in the far regions of the world, those who have not benefitted from traditional vaccinations, from the most basic scourges of the Earth—typhoid fever, pneumonia, influenza, tuberculosis.

But to do that effectively he must get them to swallow Salmonella-laced liquids.

It sounds a bit scary—infect to protect—but after years of labor, the technology seems to be sitting right there on the very reachable horizon for Curtiss and his colleagues.

“About 30 years ago, I got this idea that we could genetically modify Salmonella,” Curtiss explains. “We could kind of fix it so it would induce an immune response to give life long immunity against Salmonella itself. Then we could use this modified Salmonella to induce immunity to other pathogens.”

Salmonella is an entire genus of organisms. The tiny, rod-shaped bacteria are bad news. They are responsible for diseases ranging from food poisoning to typhoid fever. Because Curtiss is an eminent biologist and one of the leading microbial virulence experts in the U.S., people listen to his ideas, no matter how unconventional they may sound.

Working in their labs at the Biodesign Institute at Arizona State University, the Curtiss team has turned in an array of advances to make this idea viable. The latest advance is the design of a universal platform for delivering highly potent DNA

vaccines via a cleverly re-engineered bacterium to speed delivery to host cells in the vaccine recipient.

For Curtiss, director of the Center for Infectious Diseases and Vaccinology, and Wei Kong, a research assistant professor at ASU's Biodesign Institute, this could be their best work yet.

"Delivery of DNA vaccines by Salmonella and Shigella were first described in 1995, but until our work no one had developed a means for safe, low-cost, efficacious delivery of a DNA vaccine to induce protective immunity," Curtiss says.

"By using DNA vaccine delivery by our regulated delayed-lysis Salmonella, we can deliver DNA sequences encoding protective antigens from any virus, any fungus and any parasite, independent of whether the gene product requires post-translational modification since the protective antigen would be synthesized within cells in the immunized animal host," he adds. "Our technology is a platform with unlimited possible applications."

Designing a vaccine that is both safe and effective is a kind of Catch-22 for researchers. Live pathogenic strains typically generate a robust immune response, mimicking natural infection, but formidable challenges exist in ensuring such strains do not cause illness or escape into the environment. Killed pathogen strains or vaccines produced from pathogen subunits sacrifice some of their immunogenic effectiveness for enhanced safety, and could require subsequent booster doses to ensure continued effectiveness.

The Curtiss team has diligently worked to combine safety and effectiveness in orally administered vaccines that can be produced at a fraction of the cost of traditional methods. To do this, they have pioneered techniques using Salmonella as a “cargo vessel” to deliver a suite of disease antigens to the recipient. The result has been the development and ongoing refinement of recombinant attenuated Salmonella vaccines (RASVs), capable of provoking an intense, system-wide immune response and conferring effective immunity.

One of the key innovations developed earlier by Wei Kong and other members of the Curtiss group, is a specialized Salmonella strain that can be timed to self-destruct in the body once it has carried out its immunization duties. To create this strain, the researchers modified the bacterium so it can only survive on a non-naturally occurring form of sugar. Once the Salmonella cells exhaust their store of specialized sugar, supplied to them as part of the vaccine, they are unable to maintain the integrity of their cell walls and essentially implode.

“This crucial safety feature ensures that Salmonella are unable to persist as living organisms to survive if excreted into the environment,” Kong says.

This self-destruct feature can be fine-tuned so that the bacteria fully colonize host cells, provoking a strong response from both humoral and cell-mediated arms of the immune system. Inside host tissues, recombinant Salmonella are able to synthesize protective antigens, releasing their contents when they become unstable and lyse into the intracellular fluid or cytosol.

The group demonstrated the effectiveness of this delayed-lysis bacteria in vaccine experiments with a variety of pathogens, including influenza and mycobacteria (causative agent of tuberculosis), and an RASV vaccine developed in the Curtiss lab against infant pneumonia is currently in FDA Phase I clinical trials.

Because the DNA vaccines stimulate cellular and humoral immune responses, they allow for the production of antigens that undergo host cell modification through the addition of carbohydrates via glycosylation. Such modified antigens, which occur in a broad range of pathogenic viruses, fungi and parasites require synthesis by host cells, rather than by the attenuated bacteria.

“I’m optimistic we can use our perfected and still improving RASV technologies to make vaccines against not only infectious diseases, but other diseases and non-desired physiological states in animals and humans,” Curtiss adds.

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