VACCINES teach the immune system to fight disease by mimicking what the body would encounter during a natural infection. The immune system’s response to a live bacteria or virus is similar to its reaction to the attenuated (weakened) or inactivated (dead) version of a pathogen used in a vaccine. After vaccination, reexposure to the live microbe causes the body’s immune system to “recall” the prior reaction, stopping the infection more quickly than it would have without the initial encounter. This immunological memory is the basis for vaccine-mediated protection.

Many licensed vaccines use attenuated viruses or bacteria, which stimulate a strong response and confer robust immunity, but these types of vaccines have some drawbacks. Individuals with immune deficiencies may be unable to receive them safely. Furthermore, the attenuated microbe, once inside the human body, could mutate into a more virulent form—although this scenario is unlikely. In addition, live vaccines must be stored at low temperatures and therefore may be impractical for areas with limited refrigeration, such as war zones and developing regions.

Inactivated vaccines, on the other hand, cannot mutate, are safe for nearly everyone, and can often be transported without refrigeration. Unfortunately, most inactivated vaccines, which provoke a weaker immune response than do live vaccines, may require booster shots to maintain immunity and so may provide only partial protection against exposure.

A different type of vaccine—one that uses components of a pathogen rather than the whole organism—could offer the best...
Vaccines
Numerous universities and companies to develop this approach. In a collaborative effort, Livermore scientists have worked with S&TR and thus are unlikely to be flagged by the immune system as a dangerous disease tularemia.

Delivery Makes the Difference

As part of efforts to defend soldiers and first responders against bioterrorism and biowarfare, Lawrence Livermore researchers have made exciting breakthroughs in subunit vaccine research. In vivo rodent studies, for instance, have shown that Livermore's nanoparticle delivery platform increases the efficacy of subunit vaccines, making the approach viable for a range of bacterial and viral threats. More recently, with support from the Laboratory Directed Research and Development Program and the Defense Threat Reduction Agency, a team of Laboratory scientists and their academic collaborators became the first to demonstrate a subunit vaccine capable of providing 100 percent protection in test animals against Francisella tularensis, the pathogen that causes the dangerous disease tularemia.

Pathogen Generates Complex Response

Vaccine development is rarely quick or easy, but the path to success for a F. tularensis vaccine has been strewn with a greater-than-usual number of obstacles. Research on such bioterrorism agents requires advanced containment facilities, of which a limited number exist. Furthermore, past studies have lacked standardization in such areas as the species and genetic strain of the test animal and the bacterial strain used, making it difficult for researchers to compare with and build on previous findings. For example, mice have been used extensively to study immune response to F. tularensis but are not an optimal choice because of their high susceptibility to all strains, even those that do not cause illness in humans. Researchers now use a type of rat for such studies that better mimics human vulnerability to the pathogen.

According to Amy Rasley, Livermore biomedical scientist and F. tularensis vaccine development project lead, the biggest challenge is that biologists often do not fully understand the specific immune responses that a successful vaccine should provoke to this complex organism. She explains, "Most routine childhood vaccines focus on generating antibody responses. Past research suggests that antibody production is essential but not sufficient for protection against tularemia. Success rates for any vaccine drop when multiple immune responses are needed to combat the pathogen. Given the relative rarity of the illness in humans and the incomplete understanding of what constitutes a protective immune response, vaccine researchers must rely on rigorous experimentation and iteration, as well as patience.

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From What to Why

After identifying an effective vaccine, the team set out to understand why the formula works—a challenging investigation made somewhat easier by the subunit vaccine's relative simplicity and strict standardization. Fischer explains, "Determining what protects the host in a vaccine based on a whole, attenuated bacterium can be difficult because of the hundreds of synergistic components involved. In contrast, our formulation has only three components, so we can sort out the protection mechanism systematically. Once we understand the mechanism, we can see why it's working and identify correlates." Correlates are additional standards by which the researchers can determine whether the vaccinated animals are protected, beyond simply testing whether the animal survives exposure. Identifying these correlates will be crucial for subsequent evaluations of how effective these vaccines are in other animal species, as well as in humans. Determining the protection mechanisms and correlates will occupy the next three to five years, according to Rasley. "We have a lot of important science to do," she states. The team is also reaching out to companies that specialize in producing vaccines at scale in accordance with reliable manufacturing processes. Although the Laboratory will not be commercially releasing the vaccine, demonstrating viable manufacturing at scale is another key step on the long path to vaccine approval and distribution—and the ultimate goal of robust protection against a dangerous pathogen.

—Rose Hansen

Key Words: antibody, antigens, attenuated bacterium, bioterrorism, Francisella tularensis, immune response, nanoparticle (NLP), subunit vaccine, tularemia.

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