



Staphylococcal Vaccines

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S*taphylococcus aureus* is an important bacterial pathogen that is responsible for a diverse spectrum of human infections. Interest in the development of new approaches for the prevention of staphylococcal infections is a result of the worldwide dissemination of multiresistant strains of *S. aureus* and the increasing role of this microorganism in both nosocomial and community-acquired staphylococcal infections. The ideal vaccine against *S. aureus* would induce antibodies to prevent bacterial adherence, promote opsonophagocytic killing by leukocytes, and neutralize toxic exoproteins produced by the bacterium. Many impediments to the design of an effective staphylococcal vaccine exist, including the multitude of staphylococcal virulence determinants (adhesins, exoenzymes and exotoxins), and the complex pathways by which *S. aureus* regulates these factors. Although it would be difficult to justify an active vaccination program aimed at the general population, a likely target group for active vaccination would be individuals needing medical care that increases their risk for staphylococcal infections.

Ongoing efforts to design an *S. aureus* vaccine have targeted known virulence factors of this organism and include staphylococcal surface proteins, polysaccharides, exoproteins, and toxins elaborated by this pathogen. Whether some combination of purified *S. aureus* components can be included in a vaccine that will provide broad range protection against staphylococcal infections is the challenge faced by researchers in this field. Studies to date have focused on the use of single or, in the case of capsular polysaccharides, dual-component *S. aureus* vaccines.

Capsular polysaccharides (CPs) elaborated by many pathogenic bacteria are important virulence factors, and antibodies directed toward capsular antigens are often protective against infections induced by encapsulated microbes. Several published reports have indicated that antibodies elicited to the CPs of *S. aureus* are protective in animal models of experimental staphylococcal infection. Because polysaccharides are poorly immunogenic and generally elicit a T cell-independent antibody response, the most prevalent *S. aureus* CP types (serotypes 5 and 8) have been conjugated to recombinant *Pseudomonas aeruginosa* exotoxin A. The conjugate vaccines were highly immunogenic in mice and humans and induced antibodies that opsonized encapsulated *S. aureus* for phagocytosis. Antibodies elicited by immunization with the CP5 and CP8 conjugate vaccines were protective in a mouse model of *S. aureus* lethality and disseminated infection and in a rat model of catheter-induced staphylococcal endocarditis.

The CP5- and CP8-conjugate vaccines have been combined into a bivalent vaccine called StaphVAX™ that is intended for immunization of humans at high risk for *S. aureus* infection. Between 1998 and 2000, a phase III clinical trial to evaluate the efficacy of StaphVAX was conducted at the Kaiser Permanente Vaccine Study Center

in California. This randomized, double-blinded, placebo-controlled study was designed to assess safety, immunogenicity, and ability to prevent bacteremia in patients with end-stage renal disease receiving hemodialysis. Half of the patients were administered a placebo, and the other half were immunized with the bivalent StaphVAX. In this clinical trial, the patients were monitored for culture-proven *S. aureus* bacteremia. At the end of the study period (54 weeks), the vaccine reduced the incidence of bacteremia in the study population by only 26% (not significant). It was notable that the vaccine efficacy at 40 weeks was 57% ($p = 0.02$). However, after that time period, the antibody levels in the vaccinated patients declined, mirroring the decline in efficacy of the vaccine. StaphVAX was the first staphylococcal vaccine to reach clinical trials, and additional studies of this vaccine and its protective efficacy are planned.

S. aureus produces a variety of cell wall-associated proteins that interact with extracellular matrix proteins of the host. These staphylococcal adhesins have been dubbed “microbial cell surface components recognizing adhesive matrix molecules” (MSCRAMMS). Staphylococcal proteins that bind to fibronectin, fibrinogen, and collagen have been investigated as components of vaccines to protect against experimental *S. aureus* infections in laboratory animals.

Most *S. aureus* strains carry two fibronectin-binding proteins (FnBps) arranged in tandem on the bacterial chromosome. The binding motifs within these proteins occur in repeat regions and are designated D1-3. Several investigators have prepared recombinant fusion proteins of *S. aureus* FnBp and used these proteins to immunize experimental animals. The resulting antibodies blocked the binding of *S. aureus* to immobilized fibronectin in vitro, and immunization with the fusion protein provided some protection against experimental endocarditis and mastitis compared with control animals.

The staphylococcal collagen-binding protein (Cna) is present on 30% to 60% of *S. aureus* strains and represents an important virulence factor in the pathogenesis of staphylococcal septic arthritis, endocarditis, and keratitis. Immunization with purified Cna did not protect rats against staphylococcal endocarditis or arthritis. However, vaccination with the domain A fragment of the *S. aureus* collagen adhesin protected mice against sepsis-induced lethality. Mice passively immunized with Cna-A antibodies were also protected against sepsis-induced death.

S. aureus produces a number of cell-associated proteins that bind to fibrinogen. One of the best-characterized proteins is clumping factor A (ClfA). Mice immunized with the purified binding region A of ClfA and challenged with the homologous *S. aureus* strain had less severe arthritis and weight reduction than did the mice immunized with BSA. However, the numbers of *S. aureus* recovered from the infected kidneys and joints was not significantly different between the two groups of animals. A reduction in *S. aureus*-induced arthritis was also observed in mice passively administered with anti-rClfA immunoglobulin. Additional animals were vaccinated and challenged with heterologous *S. aureus* strains. Mortality was reduced by rClfA immunization but there was no protection against arthritis or weight loss. Additional studies are warranted to determine whether immunization with recombinant ClfA fragments will elicit broad range protection against staphylococcal infections.

Alpha toxin, a pore-forming and hemolytic exoprotein produced by most strains of *S. aureus*, is a major staphylococcal virulence determinant. Antibodies raised to detoxified alpha toxin have been shown to protect monkeys against the toxic and lethal actions of purified alpha toxin. However, animals immunized with alpha toxoid and challenged with live bacteria are not generally protected from infection with alpha toxin-producing strains of *S. aureus*, although the clinical severity of their disease may be less than that in nonimmunized controls. Passive immunization of mice with rabbit antiserum to a nontoxic alpha-toxin mutant protected the animals against lethality induced by injection of purified alpha toxin.

Summary

Major factors that have sparked renewed interest in the development of a vaccine for individuals at high risk for staphylococcal infections include multidrug resistance among clinical isolates and the increased incidence of community-acquired, methicillin-resistant staphylococcal infections. As part of the effort to develop a multicomponent vaccine against *S. aureus*, several vaccine candidates are currently being evaluated in human clinical trials or in animal models of staphylococcal infection. The most promising candidates to date include the capsular polysaccharides type 5 and 8, the adhesins (fibronectin-binding protein, collagen-binding protein, and fibrinogen-binding protein [clumping factor]) and a nontoxic alpha-toxin mutant.

References

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