of toxin-mediated syndromes that are also capable of causing significant morbidity and mortality. The most well known among these is staphylococcal toxic shock syndrome, a systemic inflammatory disease mediated by toxic shock syndrome toxin (TSST)-induced polyclonal T-cell activation (29,31,32). A large collection of staphylococcal enterotoxins contributes to disease of the gastrointestinal system (33), while a family of epidermolytic toxins can cause life-threatening desquamation (34). This wide array of disease processes is typical of *S. aureus*; the advent of CA-MRSA strains has led to the observation of several newer manifestations of disease including severe sepsis, necrotizing pneumonia, and necrotizing fasciitis (15,35–39). Together, these infections impact on millions within the human population, and place a substantial burden on the health care system.

Epidemiology of *Staphylococcus aureus* Infection

Historically, significant *S. aureus* infections were most often associated with the hospital environment. Staphylococci, as a part of the skin flora, capitalize on the disruption of the epithelium that is commonplace in the hospital environment. In-dwelling catheters, medical devices, and surgical wounds are commonly infected by *S. aureus.* Debilitated patients, those with chronic underlying disease and those receiving intensive care therapies are most at risk for the development of nosocomial infection with *S. aureus*. Drug resistance amongst *S. aureus* was first appreciated in the hospital environment. Within six years following the introduction of penicillin in 1941, a 25% resistance rate was reported for *S. aureus* isolates; this was followed by the introduction of the semi-synthetic methicillin in 1961, with MRSA phenotypes emerging shortly thereafter (10). An assessment of methicillin resistance among *S. aureus* isolates in intensive care units in 2003 determined that over 60% of hospital-acquired strains are no longer susceptible to this class of drugs (40). A study conducted in late 2006 by the Association for Professionals in Infection and Epidemiology demonstrated the prevalence of MRSA strains in hospitalized individuals to be 46 per 1000, approximately 10-fold greater than previously estimated (41).

The initial observation of CA-MRSA in healthy adults and children heralded the widespread public health threat that now exists. Strains responsible for community-associated disease are most often resistant to β-lactams but maintain susceptibility to other antimicrobials. A recent study by Klevens et al., assessing the incidence of MSRA disease within nine communities in the United States documented that nearly 14% of all invasive MRSA disease originates in the community (42). In total, the authors estimated that greater than 94,000 cases of invasive MRSA occurred in the United States alone in 2005, resulting in over 18,000 deaths (42).

Host Defense Against *Staphylococcus aureus* Infection

The principal defense against *S. aureus* infection resides in the neutrophil. The most compelling genetic demonstration of the role of the neutrophil in protection against *S. aureus* infection is seen in patients suffering from chronic granulomatous disease (CGD), a genetic disorder that renders the patient's neutrophils incapable of generating a cellular oxidative response. The molecular basis for this disease is a mutation in the multisubunit NADPH oxidase complex responsible for the generation of the superoxide radical in the phagocytic vacuole (43). Reactive oxygen species, along with the acidic vacuolar environment, prove toxic to *S. aureus*, and serve as a primary early means by which to curtail bacterial spread. Patients afflicted with CGD suffer from recurrent *S. aureus* infection.

Several additional components of the innate immune system enhance the early host response to *S. aureus* infection. Antimicrobial peptides (AMPs) such as defensins and cathelicidins are present on mucosal and epithelial surfaces, and facilitate direct lysis of the invading pathogen (44,45). Mutation of *S. aureus* genes encoding the components of the AMP sensor system compromises the ability of the pathogen to survive during murine infection (46). Proteins of the complement cascade are also important in innate host defense against *S. aureus* (47–49). These proteins serve a twofold role—first, several components are capable of binding to the staphylococcal surface, thereby facilitating phagocytic uptake of the pathogen. Second, proteolytic fragments of C3 and C5 are potent chemoattractant peptides for phagocytes, serving to amplify the host response. Underscoring the importance of complement in staphylococcal clearance, complement depletion in experimental animals renders them more susceptible to septicemia (50).

The role of the adaptive immune system in protection against *S. aureus* has not been well elucidated. B cell function clearly facilitates the generation of antibodies specific for *S. aureus*, as these are both present in humans and are known to rise following infection (51,52). Anti-staphylococcal antibodies likely serve the dual role of neutralizing staphylococcal exotoxins and enhancing the phagocytic uptake of staphylococci. It is well appreciated that the generation of specific antibody responses against protein antigens requires a cognate T-cell response to the pathogen. However, the precise role of T cells in anti-staphylococcal immunity is not yet well defined. In fact, studies using surgical wound site infection in an animal model of disease suggest that T-cell recruitment may enhance abscess formation, leading to a localized accumulation of bacteria (53). Mechanistically, the recruited T cells appear to secrete chemokines of the CXC family, thereby augmenting the recruitment of phagocytes to the site of infection (53). It is clear from these data that the host immune system exerts a multifaceted attack on *S. aureus*, requiring a complex response on the part of the pathogen to evade these defenses.

Staphylococcal Virulence Programs

The staphylococcal virulence factors that stand out as prospective targets for immune-based therapeutics can be broadly classified into three main groups: surface molecules that lie at the interface of the organism with the host tissues, secreted toxins and exoenzymes, and factors capable of manipulating the host immune system. Candidate immunogens have been previously identified among these staphylococcal factors and tested for their ability to induce protection in either animal model systems, or, in some cases, human clinical trials.

The complex bacterial surface of *S. aureus* forms the organism's first line of defense against the host immune system. The cell wall of *S. aureus* is comprised of peptidoglycan, providing a rigid structure to the pathogen while serving as a scaffold for the attachment of a collection of bacterial proteins, lipids, and carbohydrates. Together, these surface structures play an essential role in allowing the pathogen to gain access to the host tissues. One vital class of staphylococcal surface proteins is anchored to the cell wall through the activity of the transpeptidase sortase A (SrtA) (54). The substrates of SrtA