Next-generation anti–*Staphylococcus aureus* vaccines: A potential new therapeutic option for atopic dermatitis?

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Disease severity in patients with atopic dermatitis (AD) is directly correlated with colonization by *Staphylococcus aureus*. An increasing body of evidence now also supports a role for *S. aureus* in the pathogenesis of AD in genetically susceptible subjects. Increased prevalence of *S. aureus* preceding and coinciding with AD onset in an infant cohort suggests that early skin colonization can contribute to the development of clinical AD. However, these findings only partially explain the complex role of this organism given that another birth cohort did not demonstrate *S. aureus* colonization before development of infantile AD but did show a protective effect of commensal staphylococci against later development of AD.

A vaccine against *S. aureus* in patients with AD could potentially reduce the incidence of and prevent or attenuate symptoms in a subpopulation of high-risk atopic subjects. Such a targeted approach could reduce or eliminate the role of broad-spectrum antibiotics to treat *S. aureus*–mediated flares of AD in an era of increasing antimicrobial resistance. This would also avoid the suppression of potentially beneficial commensal strains of coagulase-negative staphylococci, such as *Staphylococcus epidermidis* and *Staphylococcus hominis*, which exert anti-inflammatory and selective antimicrobial activity against *S. aureus* and are also under investigation as potential therapeutic agents in patients with AD.

Our understanding of the cause of AD, a complex heterogeneous condition, has evolved considerably in the past decade. Dichotomous views of an “outside-in” versus an “inside-out” disease process have been superseded by the recognition that AD is characterized by the interplay of both a compromised skin barrier and aberrant local and systemic immune responses. Although Th2–mediated inflammation has been long recognized as central to disease expression, Th2- and Th17-mediated inflammation are now also implicated to varying degrees across specific patient age profiles and ethnicities.

*S. aureus* is also now recognized as an additional key pathogenic factor in patients with AD, including its critical role in amplifying Th2–mediated responses. *S. aureus* exploits decreased filaggrin expression resulting from inherited loss-of-function mutations and acquired through Th2 polarization and reduced antimicrobial peptide levels secondary to cutaneous dysbiosis (Fig 1). These factors contribute to high colonization rates in atopic skin. Once established, *S. aureus* releases multiple virulence factors, including serine proteases, exotoxins, and lysins, such as phenol-soluble modulins. These exacerbate underlying barrier dysfunction and perpetuate endogenous dysregulated proinflammatory pathways. *S. aureus* cell-wall components, including peptidoglycan, amplify the Th2–driven response, leading to increased expression of adhesion molecules (fibronectin and fibrinogen) and reduced expression of antimicrobial peptides (human β-defensin 2 and cathelicidin antimicrobial peptide) and barrier proteins (filaggrin and loricrin).

Studies on established therapies for AD, including topical corticosteroids, topical calcineurin inhibitors, narrow-band UVB phototherapy, and ciclosporin, have shown that symptomatic improvement corresponds to reduced *S. aureus* colonization. To date, these effects have been attributed to recovery of skin barrier function and immunomodulation, particularly suppression of superantigen-activated T cells. Research is currently underway to investigate the effects of dupilumab, an anti–IL-4 receptor α blocker targeting the Th2 cytokines IL-4 and IL-13 in *S. aureus*–colonized versus noncolonized patients with AD. However, active infection causing flares still requires the use of antibiotics, highlighting the role of alternative approaches, including active and passive vaccination strategies (Table 1). Passive immunization strategies using mAbs against specific *S. aureus* toxins are under investigation, although typically as adjuncts to standard antibiotic regimens in high-risk patient groups.

*S. aureus* occupies a niche as both a commensal and pathogenic organism in human hosts. It has evolved over time to manipulate host immunity to its survival advantage, as shown by the prevalence of recurrent and chronic infections and the lack of readily identifiable markers of protective long-term immunity. As a result, antibody-based active vaccination strategies, which are effective against other opportunistic bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, have been unsuccessful in the context of *S. aureus*. These previous failed approaches have been attributed in part to *S. aureus* virulence factors that interfere with antibody function, including immunoglobulin-binding proteins, such as staphylococcal protein...
A and Staphylococcus binder of IgG; vaccine testing in murine models, which do not adequately replicate human clinical phenotypes; and, more significantly, poor recognition of the importance of cellular immunity in human hosts.

There is now a consensus that individual T-cell subsets play a pivotal role in controlling S aureus colonization and infection at specific sites by coordinating downstream phagocytic responses. Targeting specific effector T-cell subsets, in combination with inducing specific neutralizing anti-toxin antibodies, will be required to improve the efficacy of next-generation anti–S aureus vaccines. TH1 cells driving an IFN-γ–mediated macrophage response are critically important in both clearance and immunologic memory against S aureus bloodstream infections, whereas IL-17–producing γδ and Th17 T cells are crucial at cutaneous sites. A recent study has also identified TNF/IFN-γ–producing γδ T cells in skin-draining lymph nodes, which protect against subsequent S aureus skin challenges and which could represent novel targets for next-generation vaccines.

Given the tissue-specific roles of T-cell subtypes, it is unlikely that a single vaccine will address the burden of all S aureus–mediated disease. Additionally, challenges can arise in overcoming S aureus–mediated immune dysregulation. Adaptive tolerance refers to the generalized inhibition of T-cell responses after prolonged antigen exposure and has been reported in patients with S aureus infection. Expansion of regulatory T cells, for example, which can exert considerable immunosuppressive effects, are described in patients with chronic S aureus infection. Other cell types implicated in S aureus–mediated immunosuppression include dendritic cells, which have a reduced ability to activate T cells when exposed to phenol-soluble modulins and can inhibit Th1 differentiation, and also myeloid-derived suppressor cells, which suppress T-cell responses, facilitating S aureus survival. Identifying and overcoming these immunosuppressive strategies of S aureus in a broad spectrum of patients with AD will be critical in the development of a vaccine, aiming to promote effector γδ T and Th17 cell subsets.

Although a direct causal role for S aureus in patients with AD has not been definitively established, a select cohort of patients at risk of severe S aureus–exacerbated atopic disease could derive considerable benefit from new targeted treatments, including
anti-\textit{S\ auresu}s vaccines. Reduction or elimination of \textit{S\ auresu}s skin colonization offers an exciting new avenue to eliminate or reduce this major AD disease amplifier; however, negotiating the amplification challenges, these novel treatment approaches, if successful, could herald a new era in AD management.

### REFERENCES


