

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*.¹ An increasing body of evidence now also supports a role for *S aureus* in the pathogenesis of AD in genetically susceptible subjects.² 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.³ However, these findings only partially explain the complex role of this organism given that another birth cohort⁴ 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.⁵ 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.⁶

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 Dichotomous views of an “outside-in” versus an “inside-out” disease process have been superseded by the recognition that AD is characterized by the interplay of both a compromised skin barrier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 T_H2-deviated inflammation has been long recognized as central to disease expression, T_H22- and T_H17-mediated inflammation are now also implicated to varying degrees across specific patient age profiles and ethnicities.⁷

S aureus is also now recognized as an additional key pathogenic factor in patients with AD, including its critical role in amplifying T_H2-mediated responses. *S aureus* exploits decreased filaggrin expression resulting from inherited loss-of-function mutations and acquired through T_H2 polarization and reduced antimicrobial peptide levels secondary to cutaneous dysbiosis (Fig 1).² 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.⁸ *S aureus* cell-wall components, including peptidoglycan, amplify the T_H2-driven response,⁸ 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,⁹ topical calcineurin inhibitors,⁹ narrow-band UVB phototherapy,¹⁰ and ciclosporin,¹¹ 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 T_H2 cytokines IL-4 and IL-13 in *S aureus*-colonized versus noncolonized patients with AD.¹² However, active infection causing flares still requires the use of antibiotics, highlighting the role of alternative approaches, including active and passive vaccination strategies (Table I).^{13–23} 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.⁸ 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*.²⁴ 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

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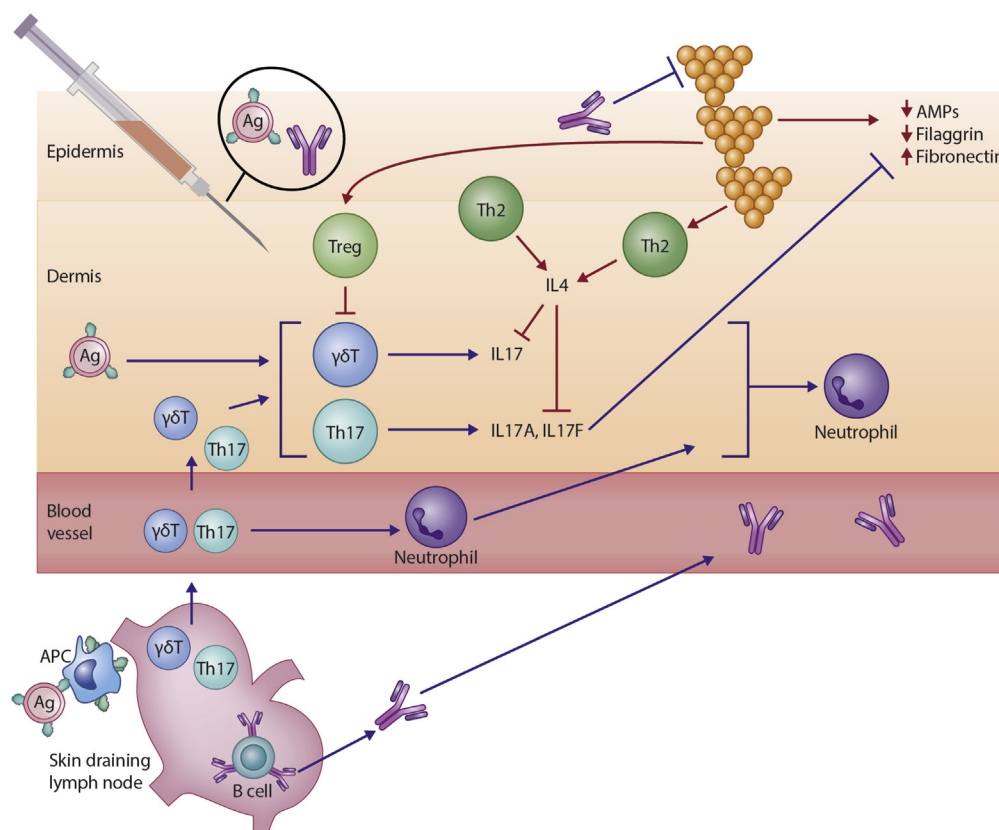


FIG 1. Vaccination with a model anti-*S aureus* vaccine for atopic dermatitis consisting of T cell and antibody-inducing antigens. An effective vaccine will encompass novel antigen and adjuvant combinations that can induce antibody responses required for the direct inhibition of *S aureus* adherence to damaged skin and neutralization of secreted toxins in addition to facilitating opsonophagocytic killing. However, such a vaccine would also stimulate $\gamma\delta$ T cell and T_H17 responses required to orchestrate an efficient neutrophil response required for *S aureus* clearance while simultaneously downregulating the effects of *S aureus*-enhanced T_H2 responses, including downregulation of surface antimicrobial peptides. Regulatory T cells induced on exposure to *S aureus* might suppress vaccine-induced effector T-cell responses, and novel approaches to prevent this suppression might be required to ensure optimal vaccine efficacy. Skin-draining lymph nodes also act as a source of protective clonally expanded $\gamma\delta$ T cells. Note: Vaccine-induced responses are highlighted with blue arrows. *S aureus*-induced responses are shown with red arrows. *S aureus* is represented by yellow circles. Ag, Antigen; AMPs, antimicrobial peptides; APC, antigen-presenting cell; Treg, regulatory T.

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. T_H1 cells driving an IFN- γ -mediated macrophage response are critically important in both clearance and immunologic memory against *S aureus* bloodstream infections,²⁵ whereas IL-17-producing $\gamma\delta$ and T_H17 T cells are crucial at cutaneous sites.^{26,27} A recent study has also identified TNF/IFN- γ -producing $\gamma\delta$ T cells in skin-draining lymph nodes, which protect against subsequent *S aureus* skin challenges²⁸ 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.²⁹ 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 T_H1 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 $\gamma\delta$ T and T_H17 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

TABLE I. Clinical trial status of *S aureus* vaccine candidates

	Vaccine components and pharmaceutical companies	Phase	NCT study no.	Reference
Active prophylactic vaccines				
1	NDV-3: recombinant <i>Candida albicans</i> Als3p adhesion protein (homologous to <i>S aureus</i> surface proteins) with alum adjuvant NovaDigm Therapeutics, Brookline, Mass	1	NCT01273922	Schmidt et al, 2012 ¹³
		2	NCT02996448	Not published
		2	NCT03455309	Not published
2	<i>S aureus</i> capsular polysaccharides CP5 and CP8 conjugated to TT, mutated detoxified AT and ClfA ± AS03B adjuvant GlaxoSmithKline, Research Triangle Park, NC	1	NCT01160172	Levy et al, 2015 ¹⁴
3	STEBVax: recombinant SEB with alum adjuvant Integrated BioTherapeutics, Gaithersburg, Md	1	NCT00974935	Chen et al, 2016 ¹⁵
4	HI, SpA5, mSEB, MntC recombinant proteins and aluminum phosphate adjuvants Olymvax, Chengdu, China	1	NCT02820883	Not published
		1	NCT02804711	Not published
5	SA3Ag/SA4Ag Pfizer, New York, NY SA3Ag: CP5, CP8, conjugated to CRM197 and recombinant ClfA SA4g: CP5, CP8, conjugated to CRM197, recombinant ClfA and MntC	1	NCT01018641	Nissen et al, 2015 ¹⁶ Marshall et al, 2016 ¹⁷
		1/2	NCT01364571	Freneck RW Jr, et al, 2017 ¹⁸
		1/2	NCT01643941	Creech et al, 2017 ¹⁹
		1	NCT02364596	Begier et al, 2017 ²⁰
		1/2a	NCT02492958	Not published
		2b	NCT02388165	Not published
6	Recombinant α-toxoid (rAT) and subunit of Pantone-Valentine leukocidin (rLukS-PV). Nabi Biopharmaceuticals, Boca Raton, Fla	1/2	NCT01011335	Landrum et al, 2017 ²¹
Passive prophylaxis (mAbs)				
1	MEDI4893: extended half-life human mAb against <i>S aureus</i> AT MedImmune, Gaithersburg, Md	1	NCT01769417	Ruzin et al, 2018 ²²
		2	NCT02296320	Not published
2	KBSA301/AR 301: mAb to <i>S aureus</i> AT Ardis Pharmaceuticals, San Jose, Calif	1/2a	NCT01589185	Not published
3	514G: mAb to <i>S aureus</i> /MRSA to SpA XBiotech, Austin, Tex	1/2	NCT02357966	Varshney et al, 2018 ²³

Als3p, Agglutinin-like sequence 3 protein; *AT*, α-toxin; *ClfA*, staphylococcal clumping factor A; *CP*, capsular polysaccharide; *CRM197*, cross-reactive material 197, nontoxic mutant form of diphtheria toxin; *HI*, fusion protein consisting of hemolysin A and IsdB (iron-regulated surface determinant protein B); *MntC*, manganese transport protein C; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *mSEB*, mutagenized staphylococcal enterotoxin B; *PVL*, Pantone-Valentine leukocidin; *SAE*, serious adverse events; *SEB*, staphylococcal enterotoxin B; *SpA*, staphylococcal protein A; *TT*, tetanus toxoid.

anti-*S aureus* vaccines. Reduction or elimination of *S aureus* skin colonization offers an exciting new avenue to eliminate or reduce this major AD disease amplifier; however, negotiating the amplified TH2 activation will be key to vaccine efficacy (Fig 1). Enhanced understanding of the complexities of the host-pathogen relationship, including recognition of the importance of both cutaneous and systemic T-cell effector responses to *S aureus*, is essential to inform ongoing efforts to develop a new generation of anti-*S aureus* vaccines tailored to AD. Despite significant outstanding challenges, these novel treatment approaches, if successful, could herald a new era in AD management.

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