Staphylococcus aureus Vaccines: Clinical Trials & Basic Science Challenges

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Full Disclosure

1. Previous Employment: Merck (2008-2010). No consulting or payment since retiring.
2. Scientific Advisory Boards (past 3 years):

a. AmebaGon, Madison, WI: MRSA biofilm; no payments

b. Destiny Pharma, Brighton, UK: Nasal decolonization; receiving consulting payments

c. DePuy Synthes: Antibiotic coated implants (inactive for past 2 years); received one consulting fee

d. Telephus Medical, LLC (Rochester, NY): Active; no payments, no meetings to date; MAb to prevent osteomyelitis

e. Integrated Biotherapeutics: Multivalent Staph Antitoxin vaccine; received consulting fee

f. Green Cross, Corp. Korea: Staph vaccine; Asked to serve, but no meetings, payments, or contract to date

Overview of Lecture

1. *S. aureus* vaccine:
   a) Needs
   b) Predictors of success for bacterial vaccines
2. Challenges for a *S. aureus* vaccine: Many Ag's; Protective immunity unclear; Lack of a biomaker; Resistance to host defenses; Major limitations of animal models; Immune dysregulation in some people
3. Goals of Staph Vaccine: Reduce severity of infection vs. prevention

Epidemiology Establishes the Need for a *S. aureus* Vaccine

Do We Need a Staph Vaccine?

Need for *S. aureus* vaccine:

a. #1 cause for children being hospitalized and needing surgery in the USA; #1 cause of bacteremia > 65 y.o.
b. Invasive disease comparable to *H. influenzae* type b
c. 347 community & 4,000 soldiers SSTI/100,000/yr [Liu *et al*. CID 2008; Morrison-Rodriguez. Epidemiology Intel 2010]
d. 18,650 MRSA deaths/yr in USA [Klevens. JAMA 2007]
e. Bacteremia Rates/100,000/yr: Overall = 20 - 38 (Blacks = 66.5, Whites = 27.7); >70 yo = 100; HIV positive = 1,960 [Tong et al. Clin Micro Rev 28: 603, 2015]
f. Cardiac device = 25% 12 wk mortality; 7-21% mortality with IV Catheter infections

Therefore, when there is a need, there is a way!

Do We Need a Staph Vaccine?

Need for *S. aureus* vaccine: More recent papers show the same story:

a. Mortality of invasive *S. aureus* infections in hospitalized infants = 10.5% [Ericson JE *et al.* JAMA Pediat 169: 1105, 2015]

b. Bacteremia mortality in Taiwan = 33% [Wang JT *et al.* PLoS One 10: e0144710, 2015]

Therefore, there is still a need as deaths occur despite antibiotic therapy, so we must find a way!

All Successful Bacterial Vaccines Have a **Biomarker**

S. pneumoniae, *N. meningitidis*, and *H. influenzae* vaccines

a. Genetic defects in antibody production are strongly associated with increased natural disease
b. Clearly defined Ag's involved in pathogenesis
c. Ab to surface Ag is the major protective immune determinant: Ab level is the **biomarker** that strongly correlates with success

Where toxins are known to the be cause of mortality and anti-toxin antibodies are protective, then tetanus, diphtheria, and pertussis toxoids are highly successful

Bottom line:D**evelopment of successful bacterial vaccines is easier when immune protection is understood**

Challenges for Developing a *S. aureus* Vaccine

Challenges for a *S. aureus* Vaccine

1. **Part of normal flora**: A different relationship with the host than *S. pneumoniae*, *N. meningiditis*, *B. pertussis*, or *H. influenzas*
2. *S. aureus* produces **multiple diseases**: Which disease should be targeted? Multiple *E. coli* vaccines: FimH for UTI; Shiga Toxoid for HUS
3. **Multiple virulence factors**: Which Ag's?
4. **While anti-toxin animal models are consistent with human clinical disease, anti-surface structure antibodies have not replicated human responses**

[Proctor RA. Vaccine 30: 2921, 2012; Merriman JA & Schlievert Future Microb 9: 717, 2014]

Implications from Normal Flora: Co-evolution

1. **Carriers have immunity**
   a. Carriers have **more infections**
   b. Carriers have **lower mortality** from invasive disease

[van Belkum A *et al*. Infect Genet Evolution 9: 32-47, 2009]

2. ***S. aureus* has evolved multiple mechanisms to counteract our immune system**

[Bestebroer, J *et al*. FEMS Micro Rev 2009; Laarman A *et al*. J Mol Med 88: 115, 2010]

What Have We Learned from Clinical Vaccine Trials Aimed at **Preventing** Infections?

Clinical Trials:

[Proctor RA: Vaccine 30: 2921, 2012; Proctor RA. Clin Infect Dis 54: 1179, 2012; Fowler & Proctor, Clin Microb Infect 20 (Suppl 5):66-75, 2014; Sause WE *et al*. Trend Pharm Sci 37: 231, 2016]

1. Passive immunization aimed at SdrG, ClfA, LTA, types 5 and 8 capsules, and GrfA have failed.
2. Active immunization with IsdB (V710; Merck), SEB, types 5 and 8 capsules (Nabi), and LTA have failed.
3. On-going trials with rAls3p-N; rLukS-PV/rAT; Eap/GST-Can/His-Clf; CP5/CP8/rmClfA/rMntC; and SdrD/SdrE/IsdA/IsdB; SpA (Xbiotech); mAb against 6 toxins for VAP (Arsanis); mAb to Hla in pnuemonia (MedImmune; Aridis); Awaiting outcome results.

Do We Know Why Vaccines Failed?

1. What was measured in failed trials?
   a. Antibody levels in **opsonophagocytosis** (OSP) assays (sometimes bactericidal assays)
   b. StaphVAX (Nabi), Aurexis (Inhibitex), & V710 had high levels of OSP activity, yet failed
2. Lessons:
   a. **Ab levels and even bactericidal tests have not predicted protection from *S. aureus* infections**, but they do for pneumococcal and HiB vaccines.
   b. Additional opsonophagocytic antibodies may not be needed in most humans.
   c. The K_D for mAb too low to block Fg - ClfA interaction [Ganesh VK et al. EBio Medicine 13: 328-338, 2016]

If Antibody Does Not Protect, Then What Do We Know about Human *Protective* Immunity to *S. aureus*?

Which Immune Deficiencies Have More *S. aureus* infections?

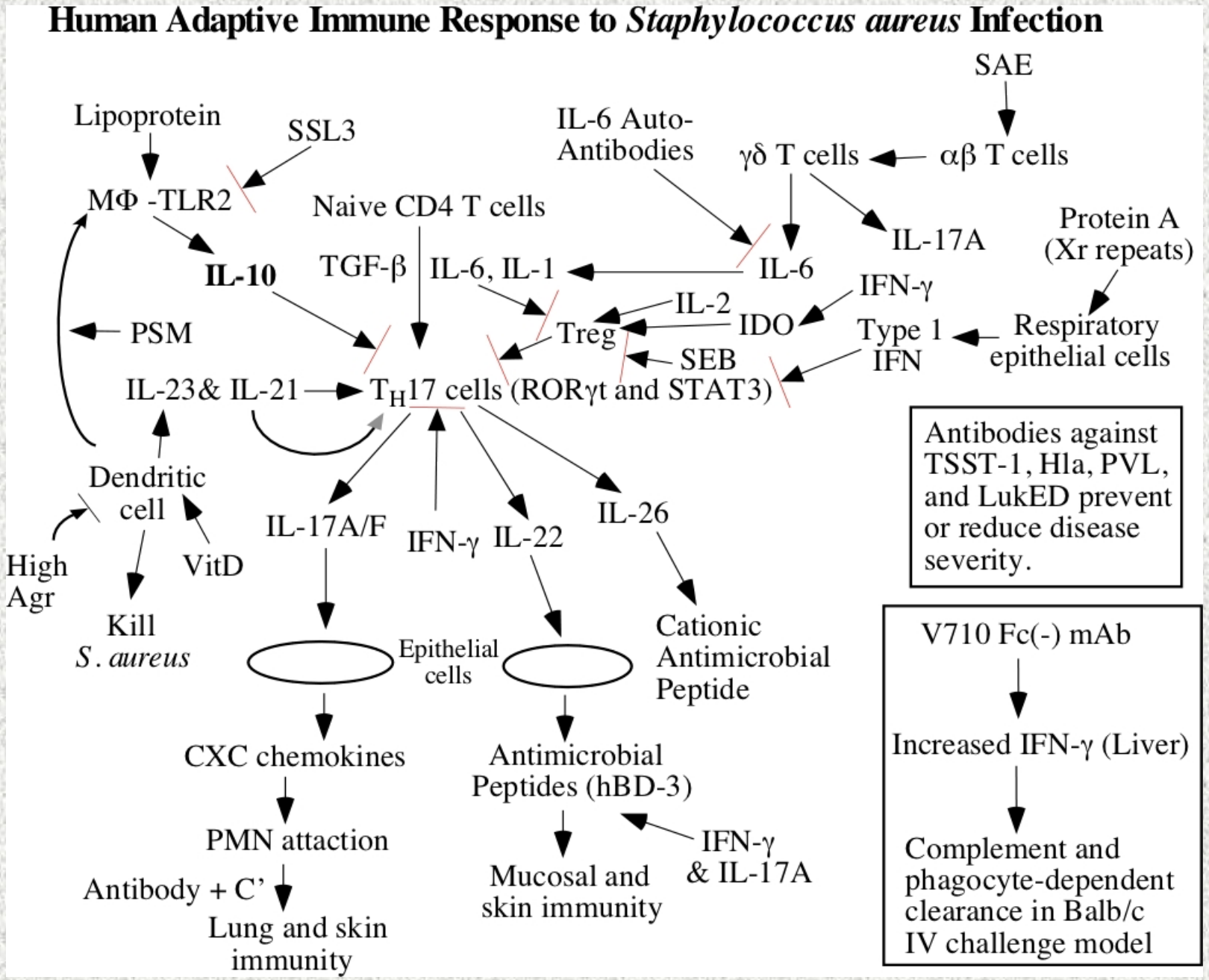
1. **Neutrophil disorders: Yes, more *S. aureus* infections**
   i. Chronic Granulomatous Disease
   ii. Job's Syndrome (STAT3 mutations; decreased IL-17)
2. **Defects in humoral immunity: No increase infections**
   i. Antibody defects were <u>not</u> involved in increased *S. aureus* infections despite the conclusion in a recent review [Holtfreter S *et al. Inter* J Microb 300: 176,, 2010] Ab was needed for group B Strep in one paper; two citations concerned PMN and T cell disorders
   ii. B-cell defective mice [Spellberg B *et al.* Infect Immun 76: 4574,2008]
3. **Cell-mediated immunity: Yes** (HIV, Prednisone); IFN-γ defective mice [Lin L *et al.* PLoS Pathog 5: e1000703, 2009; Crum-Cianfione N *et al.* AIDS Pt Care STDS 23: 499, 2009]

Note: Carriers: Higher rates of infection, but lower mortality with bacteremia [Verkaik NJ *et al.* J Infect Dis 199: 625, 2009]

Where Do PMN's & CMI Coincide?

1. Why measure Ab levels? An indicator that an immune response has occurred, including a CMI response [Lin L *et al*. FEMS Microb 55: 293, 2009]

2. **CMI and PMN come together with Th17 cells and IL-17**, which are critical for recruiting and activating PMN's. Also, **IL-17 activates keratinocytes and respiratory epithelial cells for killing of *S. aureus***.



Modified from Proctor RA. Eur Cell & Materials 30: 315-326, 2015

Do We Know Why There Was Increased Mortality in the V710 Trial?

V710 Recipients: 15/29 died Placebo recipients: 4/ 22 died

			Mortality (%)	Relative Risk with Undectable IL/ dectable IL	Mortality (%)	Relative Risk with Undectable IL/ dectable IL
IL2 level	Day of vaccination	Undetectable	**12/12 (100%)**	5.6	1/13 (8%)	0.2
		Detectable	3/17 (18%)		3/9 (33%)	
	Day of admission	Undetectable	**11/11 (100%)**	5.6	1/10 (10%)	0.4
		Detectable	3/17 (18%)		3/12 (25%)	
IL17a level	Day of vaccination	Undetectable	**9/10 (90%)**	2.8	0/10 (0%)	0
		Detectable	6/19 (32%)		4/12 (33%)	
	Day of admission	Undetectable	**10/10 (100%)**	4.5	0/10 (0%)	0
		Detectable	4/18 (22%)		4/12 (33%)	

Low IL-2 levels would result in low Treg activity, hence enhanced Th17 and IL17a; perhaps leading to a systemic immune response and multi-organ failure.

McNeely, TB *et al*. Human Vaccines Immununother. 10: 3513 - 3516, 2014

Analysis of Fatalities in V710 Trial

1. Excess mortality occurred in vaccine because of multiple organ failure, suggestive of a hyper-immune response to invasive *S. aureus* infection. Was this due to high Th17? [Gupta Dl *et al*. Cytokine 88: 214-221, 2016]
2. Undetectable levels of IL-2 and IL-17a on the day of vaccination and day of admission strongly correlated with mortality (3-5 fold increase).
3. Low pre-vaccination levels of IL-2 raise concern that patients should be screened for immune predisposition (dysregulation) to lethal hyper-immune response due to reduced Treg activity in future clinical trials.

Bottom Lines:

1. All clinical trials aimed at prevention have been based upon opsonophagocytic Ab's and all trials have failed.
2. No animal model, including the monkey model, predicts human responses.
3. Will novel targets or antibodies with higher affinity provide better results?

Thank you!

Questions?