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Antibody-based Biologics and Their Promise to Combat *Staphylococcus aureus* Infections

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Abstract

The growing incidence of serious infections mediated by methicillin-resistant *Staphylococcus aureus* (MRSA) strains poses a significant risk to public health. This risk is exacerbated by a prolonged void in the discovery and development of truly novel antibiotics and the absence of a vaccine. These gaps have created renewed interest in the use of biologics in the prevention and treatment of serious staphylococcal infections. This review focuses on efforts towards the discovery and development of antibody-based biologic agents and their potential as clinical agents in the management of serious *S. aureus* infections. Recent promising data for monoclonal antibodies (mAbs) targeting anthrax and Ebola highlight the potential of antibody-based biologics as therapeutic agents for serious infections.

Keywords

MRSA; Biologics; Antibody; Infectious Diseases; Immune Evasion

Staphylococcus aureus disease burden

Staphylococcus aureus (*S. aureus*) is a human pathogen that greatly impacts individuals in both hospital and community settings and is capable of causing a wide spectrum of diseases, ranging from mild, and usually self-limiting conditions like impetigo to severe, and potentially life-threatening diseases like pneumonia, endocarditis, and sepsis. In 2011, the Centers for Disease Control (CDC) identified 80,461 cases of diagnosed, severe infections mediated by MRSA in the U.S resulting in 11,285 deaths and was associated with the highest case fatality rate of all bacterial pathogen threats recognized (http://www.cdc.gov/drugresistance/threat-report-2013). While the overall prevalence of invasive MRSA

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infections in the hospital setting has shown a downward trend since 2005, the incidence rate of community-acquired infections has remained relatively constant and community-onset, hospital-treated infections account for the greatest number of MRSA related deaths [1]. Such infections commonly occur in individuals who are receiving outpatient dialysis treatment or who have been recently discharged from acute hospital care. Given their high risk for severe infection, these patients would be potential candidates that may benefit the most from prophylactic treatment with a biologic agent targeting *S. aureus*.

S. aureus pathogenesis

S. aureus is a commensal bacterium carried by 30–50% of the human population, and while colonization is associated with an increased risk for infection, natural carriers generally exhibit less severe infections than what is typically seen in non-carriers [2]. This observation demonstrates that that pre-exposure to the bacterium provides an advantage in thwarting off invasive infections. While it has not been conclusively shown what mediates this protection, it is known that persistent *S. aureus* carriers typically have higher levels of antistaphylococcal IgG (immunoglobulin G) than non-carriers[3, 4]. The pathogenesis of this bacterium is mediated by a vast array of surface associated proteins, carbohydrate structures, and secreted factors that are capable of suppressing complement activity, inhibiting antibody function, lysing host cells, and exerting toxic effects at sub-lytic concentrations (Figure 1) [5, 6]. Having a multifaceted set of virulence proteins facilitates the inhabitation of multiple anatomical sites within the human body and helps counter both innate and adaptive arms of the host immune system. A number of these *S. aureus* proteins have been the targets of monovalent vaccine and immunization strategies, yet none have yet progressed to approval for clinical use. In this review, we will highlight the pitfalls of previous immunization strategies and move onto discussing how novel anti-staphylococcal antibody-based molecules hold great promise for reversing the trend of failed clinical trials seen with previous *S. aureus* candidate therapies.

Antibody therapies evaluated in patients

The increasing prevalence of antibiotic resistant *S. aureus* strains has bolstered the need for a dependable *S. aureus* immunization strategy. Unfortunately, all active and passive immunization (See glossary) approaches to date have failed in clinical trial. While this review primarily focuses on antibody-based passive immunization approaches, it should be recognized and it has been reviewed elsewhere, that both passive and active immunization strategies have implemented similar *S. aureus* targeting tactics and criteria for preclinical proof-of-efficacy [7–11]. Commonalities that exist within these studies include the use of single, cell surface-associated *S. aureus* antigens as targets, *in vitro* opsonophagocytosis assays that demonstrate bacterial uptake and/or killing as readouts for opsonic potential of antibodies, and animal models of infection that serve as indicators of *in vivo* efficacy.

Passive immunization candidates that have been evaluated for efficacy are listed in Table 1. The human polyclonal immunoglobulin G (IgG), Altastaph, was the first antibody-based *S. aureus* therapy to go into Phase II clinical trial [12]. Altastaph is IgG obtained from the plasma of human donors immunized with a vaccine composed of *S. aureus* type 5 and type 8

capsular polysaccharide (CPS) [13]. Altastaph was shown to provide protection in mice infected with *S. aureus* and to enhance opsonophagocytosis of *S. aureus* [13]. However, in a study that was primarily designed to study the safety and kinetics of Altastaph, there was no indication that Altastaph protected against the development of bacteremia [12, 13]. While likely not the sole reason for its failure, in targeting *S. aureus* CPS 5 and 8, Altastaph has a limited potential for broad utilization, as 10–15% of the contemporary strains do not produce CP5 or CP8 due to mutations in the capsule coding genes or in capsule regulatory loci [14, 15]. Interestingly, it was recently shown in a large geographical screen of isolates from the *S. aureus* USA300 lineage, which is responsible for the current community-associated (CA) MRSA outbreak in the USA, that the strain has multiple mutations in the *cap5* locus (*cap5* promoter, *cap5D* nucleotide 994, and *cap5E* nucleotide 223) that makes it negative for CPS type 5 [16]. Veronate™ was an additional anti-*Staphylococcus* candidate therapy to make it to clinical trial with the use of pooled human antibodies [17]. Veronate™ is composed of human sera exhibiting high antibody titers to the staphylococcal fibrinogen-binding proteins clumping factor A (ClfA) of *S. aureus* and to the Ser-Asp dipeptide repeat G (SdrG) of *S. epidermidis* [18]. Despite demonstrating an opsonic driven ability to promote bacterial uptake, protection in mouse infections with *S. aureus*, and the ability to disrupt *S. aureus* fibrinogen binding, Veronate™ failed to reduce the incidence of late-onset sepsis in Phase III clinical trial [17, 18].

Attempts to treat infections with mAbs targeting *S. aureus* surface proteins have also been evaluated in clinical trials but have thus far failed to progress to regulatory approval. Like Veronate™, the mAb tefibazumab targets ClfA and was evaluated as an adjunctive therapy to standard antibiotic treatment in *S. aureus* bacteremia patients. Tefibazumab was shown to protect rabbits from *S. aureus* infection and while the authors elected to not publish the data, Tefibazumab also demonstrated opsonophagocytic activity [19, 20]. Tefibazumab was shown to be tolerated well in a Phase II trial focused on safety and pharmacokinetics. However, the makers of Tefibazumab indefinitely suspended trials pending the outcome of licensing negotiations [19, 21, 22]. Pagibaximab, a mAb that targets lipoteichoic acid (LTA), a key component of the bacterial Gram-positive cell wall, was shown to enhance opsonophagocytosis of *Staphylococcus epidermidis* (no data on *S. aureus*). Despite showing promise in Phase II studies for the prevention of *S. aureus* sepsis in low birth weight neonates, Pagibaximab ultimately failed in a more comprehensive Phase III sepsis trial [23–25]. The single-chain mAb fragment, Aurograb, targets the *S. aureus* ATP-binding cassette (ABC) transporter GrfA. This molecule was selected from an innovative screen that identified immunodominant antigens in the sera of septic patients [26]. While Aurograb was demonstrated to work synergistically with vancomycin to reduce *S. aureus* burden in the organs of infected mice, the drug was shown to be ineffective in a Phase II trial [26–28]. Of note, no peer-reviewed preclinical data has been made available for Aurograb. Finally, the exploratory efficacy of SAR279356 (F598), a mAb from the company Sanofi, targets poly-N-acetylated glucosamine (PNAG) and was investigated in the prevention of infections in mechanically ventilated patients in the intensive care unit. However, according to a press release from Sanofi, the clinical trial was prematurely terminated due to a slow enrollment rate [29].

Currently, there are three anti-staphylococcal mAbs being evaluated for clinical efficacy. In contrast to previous failed passive immunization studies, which have targeted surface-attached antigens, two of these mAbs target a secreted virulence factor, specifically alpha-toxin (AT). AT binds to host target cells in a receptor-dependent manner and forms permeable pores in their plasma membranes, which eventually lead to cell death [30]. Isogenic mutants for *hla*, the gene encoding AT, are attenuated in their ability to cause disease in MRSA pneumonia, SSTI, and bloodstream infection models [30–34]. The human mAb MEDI4893 from MedImmune (a division of AstraZeneca) targets a specific domain of the AT protein, which blocks AT-receptor binding [35]. This potential therapy has been shown to be protective prophylactically in the *S. aureus* mouse model for acute pneumonia [36]. Similarly, Aridis Pharmaceuticals states that the human mAb AR-301 prevents AT from generating pores in the host membrane, thus preventing cell death [37]. Both agents are being studied in the prevention of staphylococcal pneumonia. Lastly, Xbiotech is testing a human-derived mAb, for which the target has not been disclosed, as an adjunctive therapy to standard of care antibiotics in patients with diagnosed staphylococcal bacteremia [38].

Why so many clinical failures?

Antibody-based passive immunization agents that have thus far failed in clinical trial share a number of commonalities that might explain their lack of apparent efficacy. Firstly, they have all targeted a single cell-surface associated antigen [7–11]. Given the vast array of extracellular factors that *S. aureus* possesses, it is unlikely that focusing on a single antigen will cripple the bacterium. Another potential issue with targeting antibodies to surface proteins arose with the vaccine V710, which targets the cell wall-anchored iron-responsive surface determinant B (IsdB) [39]. In the Phase III clinical trial, patients who were administered this vaccine and developed a *S. aureus* infection were five times more likely to die than unvaccinated patients who developed a *S. aureus* infection [40]. This result reflects the general inadequacy of *S. aureus* therapeutic clinical trials to date and reiterates the complexities of *S. aureus* pathogenesis.

The second issue with previous antibody-based strategies is the emphasis placed on the demonstration of phagocytic uptake and/or opsonophagocytic killing [13, 18, 20, 23, 41, 42]. The use of opsonophagocytosis as an indicator for the efficacy of an antimicrobial immunotherapy became mainstream with the success of pneumococcal vaccines targeting capsular polysaccharides. These vaccines induce the production of opsonizing antibodies that lead to pneumococcal killing [43] and for which opsonophagocytotic antibody titers represent an accepted correlate of clinical protection. However, while a number of preclinical anti-*S. aureus* antibodies have demonstrated both opsonophagocytic activity and antibody efficacy in protecting mice from *S. aureus* infection, there has been no protection reported in human studies. Given the high levels of naturally occurring antibodies directed at *S. aureus* found in humans, it is possible that human serum may provide adequate opsonization and that increasing the amount makes no appreciable difference for *S. aureus* killing [3]. This opens up the concept of *S. aureus*'s often-underappreciated ability to survive within phagocytic cells. It has been demonstrated that *S. aureus*, classically regarded as an extracellular pathogen, is capable of surviving within phagocytic cells [44–48]. *S. aureus* is able to alter its transcriptional profile once inside human neutrophils and

upregulate a number of secreted factors such as hemolysins and leukotoxins in response to neutrophil-derived anti-microbial components, which promote bacterial survival [45, 48]. It was also recently demonstrated that CA-MRSA strains utilize the bi-component pore-forming leukocidin AB (LukAB) and the alpha-phenol soluble modulin (PSM-α) to survive and escape from neutrophils and human monocytes [47, 49, 50]. Thus, when designing immunization strategies, it may be more prudent to place less of an emphasis on *S. aureus* uptake within phagocytic cells, but rather shift the focus to neutralizing *S. aureus* secreted factors that promote bacterial survival within phagocytes.

The lack of translation from *S. aureus* animal models to clinical studies has been the third major issue with failed immunization strategies. The mouse model for *S. aureus* has been especially nefarious, as vaccine and therapeutic antibodies that have shown protection in mice have not proved similarly efficacious in humans. One potential explanation for this paradox is the surplus of human-specific virulence factors produced by *S. aureus*. The deficiency exhibited by mouse models is also echoed in other models including rabbits, rats and non-human primates (*e.g.*, Java monkey and cynomolgus macaques) [39, 51–54]. Thus, the reality is that faithful representative non-clinical models of staphylococcal infections in humans are lacking.

Next generation biologics target immune evasion mechanisms

The failure of first-generation antibody-based biologic agents and the inadequacy of antibiotics in severe, invasive *S. aureus* diseases may in part be accounted for by the array of different mechanisms used by the bacterium to circumvent components of the host immune system [5, 55, 56]. A number of such mechanisms being currently targeted by experimental antibody-based biologic agents are shown in Figure 1. These include: (i) surface-bound proteins that typically mediate adhesion to host tissues, cells and soluble factors, but can also impact the normal complement activation pathway [57], (ii) surface-anchored and secreted forms of immunoglobulin binding proteins, Protein-A and the second immunoglobulin-binding protein (Sbi), that sequester host IgG's and impair their ability to engage elements of the host immune system via their Fc domain [58], (iii) surface-anchored and secreted forms of the GluV8 protease, that cleaves IgGs in the antibody hinge region and inactivates effector function [59], (iv) superantigens (SAgs), a family of potent immuno-stimulatory exotoxins that impair normal host immune functions via a number of distinct mechanisms [60], (v) leukocidal toxins that selectively target and kill immune cells including neutrophils and macrophages [61] and (vi) highly immunogenic cell wall autolysins that promote bacterial uptake into non-professional phagocytes, which facilitates the avoidance of the immune response and antibiotic treatment [62, 63]. Table 2 lists a number of preclinical programs described in recent meetings and publications wherein one or more of these immune evasion mechanisms are targeted via antibody-based biologic agents. This is table is meant to broadly depict the state of preclinical anti-staphylococcal therapeutics and does not comprehensively encompass all patents and publications.

The repeated inadequacies and lack of solid epidemiology displayed by antibody-based biologics that have targeted single *S. aureus* surface antigens are indicative of the likely futility of such a strategy. Hence, numerous novel pre-clinical programs are focused on the

combination of antibodies targeting different antigens or in the design of multivalent biologic agents. One such approach from Dutta *et al*. (2015) utilizes a mAb cocktail consisting of two distinct antibodies to the SAg protein staphylococcal enterotoxin B (SEB) that yield synergistic efficacy in mice. This cocktail was shown to neutralize toxin and provide protection from intoxication with purified SEB in mice. One potential limitation in targeting SEB is the geographical driven variation that exists in the frequency of this toxin [65]. Precedents for the use of mAb cocktails in passive immunization therapy include the investigational anti-Ebola treatment ZMapp [66] and the combination of actoxumab and bezlotoxumab that neutralize the cytotoxic/cytopathic effects of *Clostridium difficile* toxins TcdA and TcdB, which are currently being evaluated by Merck in Phase III studies [67]. Given the complexity of *S. aureus*, it is unreasonable to think that the successful tactics used to combat other pathogens will directly translate to *S. aureus*, but the efficacy shown in targeting toxins with biologics is encouraging. In addition to passive immunization approaches that exploit multivalent biologic agents, a number of anti-staphylococcal vaccines are in development that are composed of multiple antigens. For example, 4C-Staph is an experimental multivalent vaccine developed by Novartis (now GSK) that leads to the production of antibodies that target three secreted virulence factors and two surface-attached proteins [68]. This vaccine shows protection in multiple mouse models for infection and all antigens were needed to generate an optimal immune response.

Aside from the afore-mentioned agents that singly target AT, several of groups have reported the identification and characterization of antibodies that neutralize the cytolytic activity of additional *S. aureus* toxins and therein may protect further classes of immune cells (Figure 2). For instance, Rouha *et al*. recently described a single mAb that targets AT and 3 bi-component leukocidins; gamma hemolysin (HlgABC), leukocidin ED (LukED), and Panton-Valentine Leukocidin (PVL) [69]. This multivalent mAb was shown to inhibit the cytotoxicity of these molecules *in vitro* and to provide protection in mouse sepsis and pneumonia models, reflecting the activity of this mAb against AT [69]. Additional current examples of targeting immune evasion/altering factors, include the staphylococcal super-antigen SEB (Dutta et al., 2015) [70], Protein-A [71, 72], the glucosaminidase subunit of autolysin (Atl) [73], and the immunodominant staphylococcal antigen A (IsaA) [74].

Finally, there is a growing appreciation of the ability of *S. aureus* to persist intracellularly within different classes of host cells and therein is protected from the host immune system [5, 56]. With this understanding, a number of approaches are being explored towards the tailoring of therapeutics that attack *S. aureus* in both extracellular and intracellular environments. In one such effort, Genentech has described an antibody-drug conjugate that combines an anti-staphylococcal antibiotic with an opsonic antibody that facilitates phagocyte uptake and antibiotic-mediated killing within the phagosome [75, 76]. This novel antibody-antibiotic conjugate specifically targets both replicating and non-replicating intracellular bacteria, as the conjugated rifamycin-class antibiotic is not activated through proteolytic release until reaching the phagolysosome. In contrast, Janssen Research and Development has recently described a series of multi-valent biologics that combine as fusion proteins anti-staphylococcal mAbs with novel protein binding domains referred to as ‘centyrins’ [77, 78]. Specifically, these IgG-centyrin fusion proteins (referred to as

'mAbtyrins') target a family of Serine-Aspartate Repeat (SDR) surface-anchored adhesin proteins via the mAb portion of the molecule, and bind and neutralize the leukocidins via appended centyrin domains. In addition, the Fc portion of the mAb has been further engineered to resist hinge-directed proteolysis via GluV8 protease and eliminate Protein A and Sbi binding while retaining normal Fc-mediated interactions with the host immune system (Brezski et al., Pat. App. US 2014/069347)). These novel multi-valent biologics exhibit activity against MRSA *in vitro*, *ex vivo* and *in vivo* and are thought to be active intracellularly via combination of effective opsonization via the mAb portion of the molecule and neutralization of LukAB-mediated phagosome lysis (Sause *et al*., unpublished data).

Clinical utility of antibody-based biologics targeting *S. aureus*: potential indications and concerns

In the treatment of *S. aureus* infections, mAb-based biologics offer the promise to decrease unacceptably high levels of morbidity and mortality in severe, invasive disease states like pneumonia and bacteremia as agents adjunctive to available antibiotics. Clinical benefit of such adjunctive therapy could arise directly through synergy at the mechanistic level and/or indirectly through effective boosting of antibiotic efficacy through enhanced assistance from host innate and adaptive immune defense pathways. Should such success be realized, additional benefits would include providing physicians with alternate options to limit the unnecessary use of antibiotic agents "of last resort" and potentially preserve such agents with regard to the development and spread of antibiotic resistance. Indeed, for antibody-based biologic agents used in acute critical care treatment settings, the development of resistance by *S. aureus* is not anticipated through traditional mechanisms and therein one can anticipate a long shelf-life of clinical utility. Furthermore, developments in the field of molecular diagnostics that enable the rapid identification and characterization of infectious pathogens should facilitate targeted therapy in patients with predicted susceptibility to antibody-based biologic agents (see Outstanding Questions). Finally, should trends in the increasing emergence and spread of *S. aureus* isolates that exhibit reduced susceptibility to vancomycin, daptomycin or linezolid continue, the use of antibody-based biologic agents could conceivably play a role in the first-line management of serious infections in the absence of the development of truly novel classes of antibiotic agents that circumvent existing resistance mechanisms.

Antibody-based biologic agents also have potential clinical utility in the prevention of disease in subjects at high-risk for *S. aureus* infections. In this setting, acute (single dose prophylaxis) use in patients undergoing elective or emergency invasive surgical procedures at highest-risk for hospital-acquired infections, represent a key target population with initial clinical development likely as therapy adjunctive to prophylactic antibiotics. Additional clinical utility may also be realized in patients that undergo periodic procedures that place them at risk of *S. aureus* infections; for instance, hemodialysis in patients with chronic kidney disease. In such settings, chronic (repeat dose) use of antibody-based biologic agents may require monitoring of patients to determine that anti-drug antibodies are not generated in patients that trigger adverse immune reactions to, or diminish the effectiveness of, such

agents. Such a phenomenon would likely be more problematic for antibody-based biologics that are elaborated over and above simple human-derived or humanized mAbs. Relatedly, the chronic use of antibody-based biologics in individual patients could conceivably result in the emergence of genetic “escape” variants with reduced susceptibility to the agent through antigenic drift (see Outstanding Questions). Such a concern also applies to anti-staphylococcal vaccines along with the potential that broad community use of vaccines may facilitate the selection and emergence of new epidemic clades that evade such vaccines. In considering the future overall potential roles of anti-staphylococcal vaccines and antibody-based biologic agents, the use of the latter would presumably be favored in both prophylactic and treatment setting in acute care patients that do not have time to develop an effective immunological response to a vaccine. Similarly, antibody-based biologics would presumably also be favored in immune-suppressed patients or in elderly patients with immune senescence.

The practicalities of drug discovery and development in the modern era dictate that new antibody-based therapies for bacterial infections will necessitate relatively high initial pricing equivalent to, or increased over, current “premium” priced antibiotics currently reserved for use in second or third line therapy. However, over and above the benefits afforded to individual patients receiving mAb-based anti-staphylococcal therapy, the anticipated high costs of a truly effective agent would presumably be offset through projected reductions in the overall healthcare costs associated with shorter hospitalization stays and a lower incidence of infections or secondary complications. In the longer term, it is hoped that technological developments in the manufacturing of mAb-based biologics will facilitate reductions in the costs of production and enable their broader adoption and utilization.

Concluding remarks

The first successful therapeutic serum treatment of a child suffering from a bacterial infection, diphtheria caused by *Corynebacterium diphtheriae*, occurred in 1891 and for this success and later accomplishments Emil von Behring was recognized by the award of the first Nobel Prize in medicine in 1901. However, despite more than a century of research in understanding the pathophysiology of key human pathogens and developments in the synthesis and production of antibodies, approval of the first monoclonal antibody produced by recombinant DNA technology did not occur until 1998 with the approval of Synagis® (MedImmune). Indeed, Synagis® remains the only mAb approved today for routine infectious disease clinical practice and is limited to use in the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.

With regard to staphylococcal disease, this review has highlighted potential reasons underlying the failures of past efforts to develop effective vaccines and antibody-based biologics and reasons to believe that a new generation of mAb therapies may offer hope in the prevention and/or treatment of severe, invasive disease for which antibiotic therapy is too often inadequate. These include agents that seek to neutralize virulence factors that target elements of the host immune system and therein should boost or restore host

immunity and potentiate antibiotic effectiveness and multi-valent agents designed to target the bacterium's elaborate extracellular and intracellular lifestyles (see Outstanding Questions). While additional clinical failures are likely, lessons learned from the preclinical and clinical evaluation of these new agents, combined with further advances in our understanding of the pathophysiology of *S. aureus*, hold real promise for the future utility of mAb-based biologic agents in the prevention and treatment of serious disease mediated by this remarkable human-centric pathogen.

Glossary

S. aureus	Staphylococcus aureus
MRSA	Methicillin-resistant *Staphylococcus aureus*
mAbs	monoclonal antibodies
Active immunity	immunity provided by antibodies that are generated in response to an antigen, such as a vaccine.
Bacteremia	bacteria in the bloodstream
Opsonophagocytosis	phagocytosis of an opsonized pathogen.
Passive immunity	short-term immunity provided by exogenous antibodies.
SSTI	skin and soft tissue infection

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Outstanding Questions Box

- Will targeting of *S. aureus* host immune evasion factors by antibody-based biologic agents enhance antibiotic efficacy in serious invasive disease states through effective boosting of host immune functions?
- How will new advances in molecular diagnostics facilitate the clinical development and use of new *S. aureus* vaccines and biologic agents?
- If approved, will *S. aureus* vaccines and repeated use of antibody-based biologic agents select for insensitive phenotypic variants through antigenic drift?

Trends Box

- Community-onset, invasive infections mediated by *Staphylococcus aureus* infections represent a growing concern in global healthcare
- The paucity of novel antibiotics for the treatment of serious invasive diseases caused by *S. aureus* has spurred renewed interest in the discovery and development of alternate therapies including antibody-based biologic agents
- Past failures in the clinical development of anti-staphylococcal antibodies for the treatment and prevention of *S. aureus* infections have focused on single antigens displayed at the bacterial cell surface
- Two antibody-based biologic agents currently under clinical evaluation target the secreted virulence factor alpha-hemolysin
- A series of novel approaches are being explored towards the discovery and development of antibody-based biologic agents that target multiple *S. aureus* antigens including host immune evasion factors and intracellular reservoirs of the bacterium

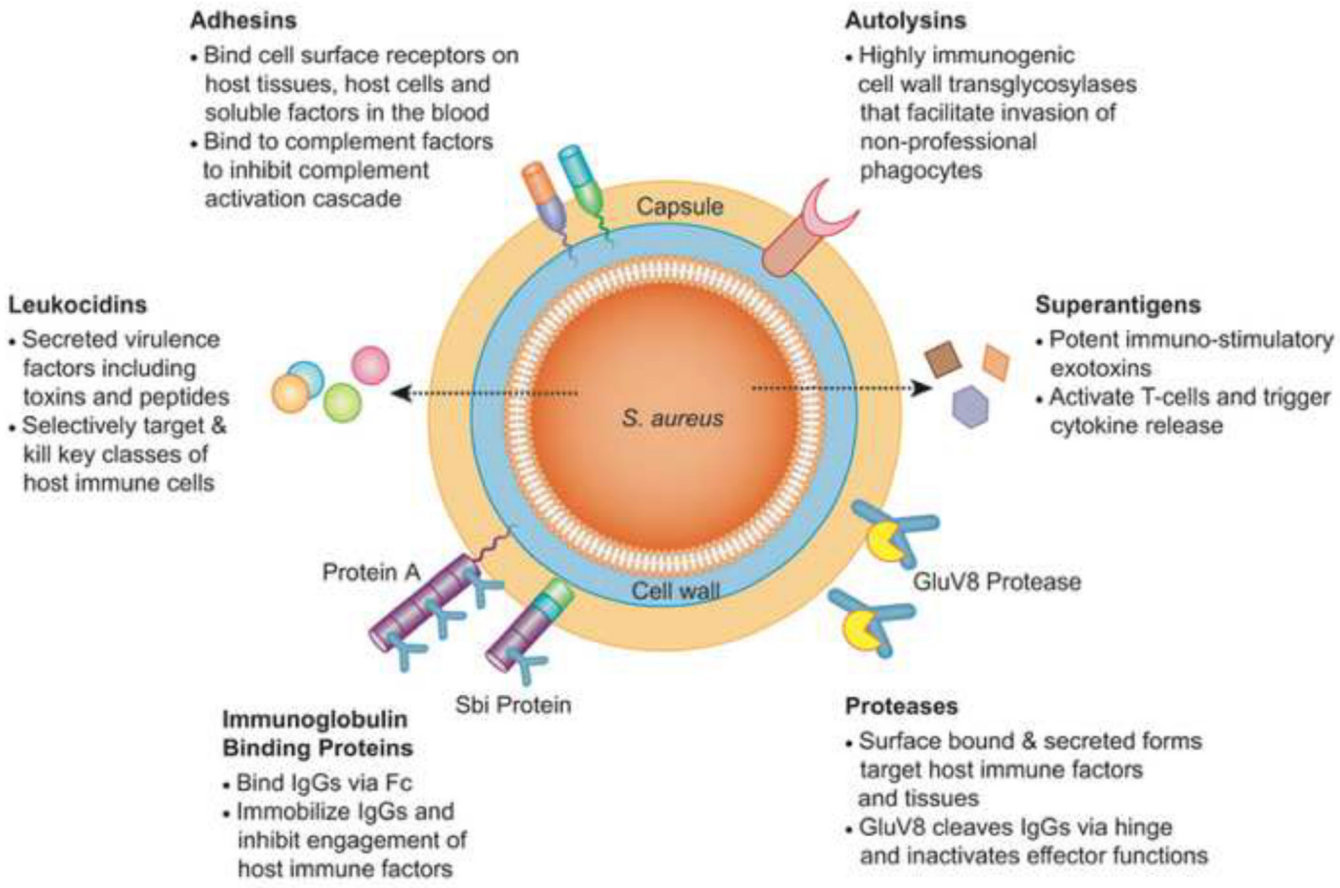

Figure 1. *S. aureus* Immune Evasion Factors Targeted by Experimental Biologic Agents

S. aureus possesses an elaborate arsenal of extracellular virulence factors that serve as targets for the current class of anti-staphylococcal biologics being developed. These targets include: (1) surface bound adhesins that promote host colonization and disruption of complement pathways, (2) immunoglobulin binding proteins (Protein A, Sbi) that bind to IgGs and prevent engagement of host immune factors, (3) surface-associated and secreted proteases (GluV8) that digest IgG antibody components and diminish effector function, (4) a family of immune-stimulatory exotoxins called superantigens (SAgs), (5) potent leukocidal toxins that kill critical classes of immune cells, and (6) immunogenic cell wall autolysins that are important for bacterial uptake into non-professional phagocytes.

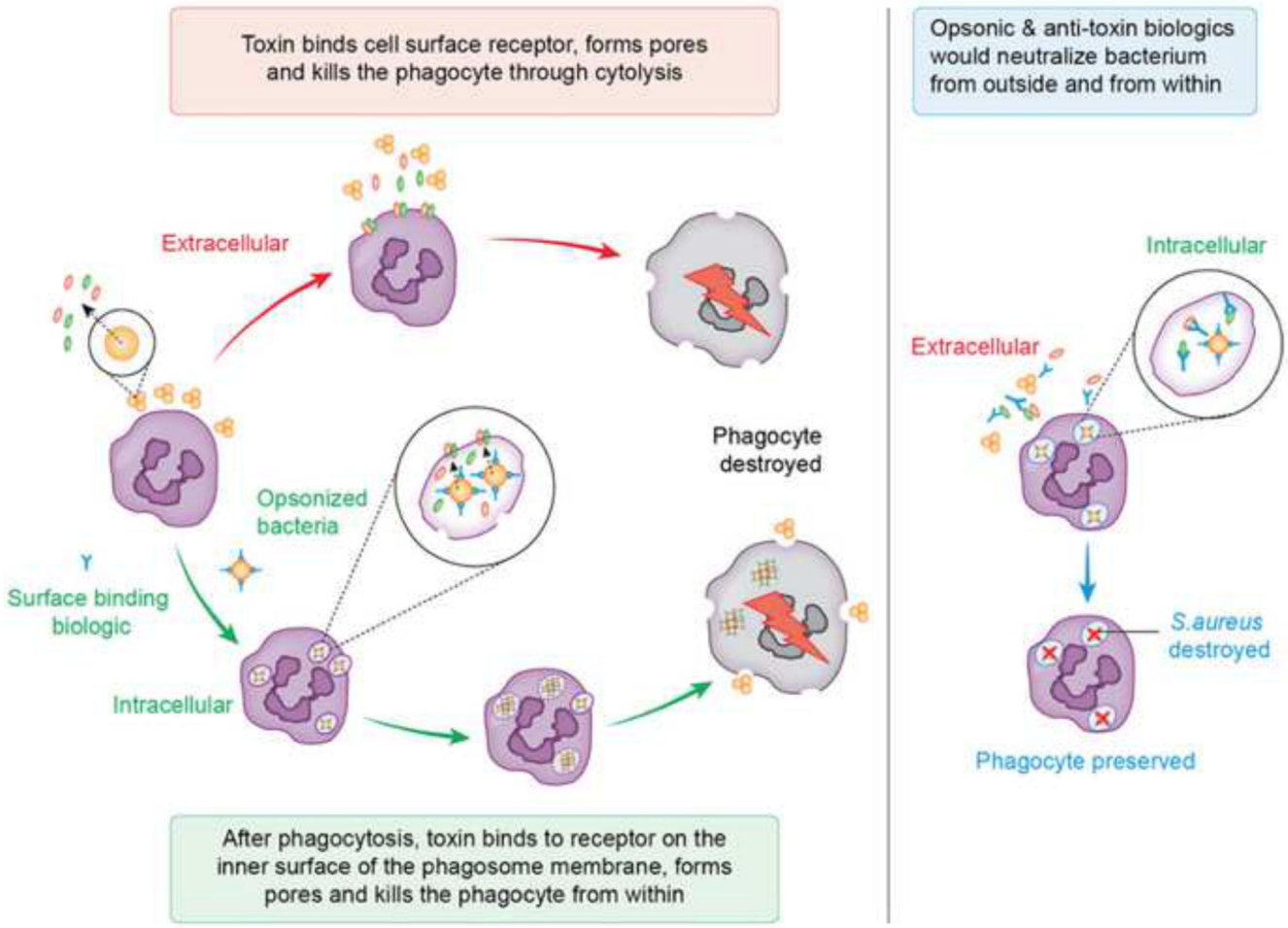

Figure 2. Extracellular and Intracellular killing mediated by *S. aureus* toxins

S. aureus implements a multi-pronged strategy to kill host immune cells from both outside of the cell and from within. Extracellular cytolysis: On the surface of the host cell, *S. aureus* delivers pore-forming toxins that target specific host receptors and destroy the phagocyte through cell lysis. Intracellular cytolysis: *S. aureus* is opsonized with immunglobulins and complement, which leads to phagocytosis of a subset of this population. Intracellular bacteria then promote their survival by releasing toxins that disrupt the integrity of the phagolysosome, promote bacterial escape into the cytoplasm, and destroy the phagocyte from within. Approaches to block extracellular and intracellular cytolysis: Current biologics under development attempt to account for all facets of this strategy using molecules that opsonize the bacterium and neutralize the toxins that are responsible for causing cell death, thus disarming the bacterium from the outside and from within. With this approach, the phagocyte is preserved and *S. aureus* is destroyed in the phagolysosome.

Table 1

Antibody-based Biologics Agents Evaluated for Clinical Efficacy

Agent	Sponsor(s)	Product Class	Target or Mechanism	Primary Clinical Indication	Status*
Altastaph	Nabi Biotherapeutics	Pooled human immunoglobulin	Cap5 & Cap8	Treatment of bacteremia	Not in active development
Veronate	Inhibitex / Bristol Myers-Squibb	Pooled human immunoglobulin	Surface adhesins ClfA & SdrG	Prevention of infection s in neonates	Not in active development
Aurexis Tefibazumab)	Inhibitex / Bristol Myers-Squibb	Humanized mAb	Surface adhesin ClfA	Treatment of bacteremia	Not in active development
Pagibaximab (BSYX-A110)	Biosynexus Inc. / GlaxoSmithKline / MedImmune	Humanized mouse chimeric mAb	Lipoteichoic acid	Prevention of sepsis in very low birth weight infants	Not in active development
Aurograb	NeuTec Pharma / Novartis	Single chain variable antibody fragment	ABC transporter GrfA	Treatment of severe, deep seated infections	Not in active development
SAR279356 (F598)	Alopexx Pharm / Sanofi - aventis	Human mAb	PNAG	Prevention of pneumonia	Not in active development
Salvecin AR-301, KBSA301)	Aridis Pharm. / Kenta Biotech.	Human mAb	Alpha-toxin	Prevention of pneumonia	Phase 1/2a ongoing
MEDI4893	MedImmune	Human mAb	Alpha-toxin	Prevention of pneumonia	Phase 1/2a ongoing
514G3	Xbiotech	Human mAb	Not disclosed	Treatment of bacteremia	Phase 1/2a ongoing

*Status based on publications and/or review of Sponsor website information and materials accessible via www.clinicaltrials.gov on 06-30-2015.

Table 2

Preclinical Antibody-based Biologics

Target(s) or Mechanism(s)	Class	Sponsor(s)	Key Reference
Wall Techoic Acid (mAb) RNA synthesis or other targets (antibiotic)	mAb-drug conjugate	Genentech	Lehar *et al*., (2015)
Bi-component leukotoxins plus alpha hemolysin	mAb	Arsanis Biosciences	Rouha *et al.*, (2015)
Surface adhesins, Bi-component leukotoxins, protein A, Sbi & GluV8	Multi-valent biologic: mAb-centyrin fusion (‘mAbtyrin’)	Janssen Research & Development / NYU	U.S Patent Application US 2014/069347
Protein A	mAb	NA	Thammavongsa *et al.*, (2015)
Staphylococcal enterotoxin B (SEB)	mAb cocktail	NA	Dutta *et al.*, (2015)
Immunodominant staphylococcal antigen A (IsaA)	mAb	Top Institute Pharma	van den Berg *et al*., (2015)
Glucosaminidase (Gmd) subunit of autolysin (Atl)	mAb	Telephus Medical	Varrone *et al*., (2014)
Staphylococcal enterotoxin B (SEB)	mAb	Integrated BioTherapeutics	Karauzum *et al*., (2012)
Panton-Valentine leukocidin (PVL) and γ-hemolysin C (HlgC)	Multi-valent heavy chain only antibody (HCAb)	NA	Laventie *et al*., (2011)