Overcoming Challenges in *Staphylococcus aureus* Vaccine Development

Meeting Summary

National Institute of Allergy and Infectious Diseases
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Contents

Executive Summary

Staphylococcus aureus is the leading cause of human bloodstream, skin and soft tissue infections. The emergence of antibiotic resistant *S. aureus* strains has resulted in dramatic increases in human mortality, owing to the failure of current antibiotic therapies. An effective vaccine against *S. aureus* infections could significantly improve public health.

The National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, along with the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), sponsored a one-day meeting on June 7, 2013 to address the current challenges in the development of *Staphylococcus aureus* vaccines. This meeting was in follow-up to the first Staphylococcal Vaccine Workshop held on May 10, 2010, and brought together government, academic, non-profit and industry stakeholders to discuss recent developments in staphylococcal vaccine design and to address mechanisms to overcome staphylococcal vaccine research challenges. Major topics of discussion included:

1. The results and lessons learned from previous staphylococcal vaccine clinical trials
2. Major challenges in *S. aureus* basic research, translational research, and clinical trial design
3. Epidemiological insights to facilitate *S. aureus* vaccine development
4. Available government resources to overcome *S. aureus* vaccine research challenges

Detailed Summary

V710 Trial – Results and Lessons Learned

Richard Haupt, M.D., Merck

Dr. Richard Haupt from Merck commenced the workshop with a case study on the Phase II/III clinical trial of Merck's investigational *Staphylococcus aureus* vaccine, V710. The V710 vaccine contains the iron surface determinant B (IsdB), a highly conserved *S. aureus* surface protein. Previous studies have shown that V710 is protective in animal challenge models and immunogenic within 14 days after a single-dose vaccination in healthy volunteers. The Phase IIb/III trial was initiated to evaluate the safety and efficacy of preoperative vaccination with nonadjuvanted lyophilized V710 in preventing serious *S. aureus* infections in patients about to undergo a median sternotomy for cardiothoracic surgery. The independent data monitoring committee recommended termination of the study after the second interim analysis due to safety concerns and low efficacy. Among patients undergoing cardiothoracic surgery with median sternotomy, V710 vaccine use, as compared with placebo, did not reduce the rate of serious postoperative *S. aureus* infections and was associated with increased mortality among patients who developed *S. aureus* infections. These findings do not support the use of the V710 vaccine for patients undergoing surgical interventions.

Dr. Haupt described in detail the pre-clinical drivers for candidate selection and formulation, the thinking behind the design of multiple clinical trials, and the trial data analysis for both safety and efficacy. It was concluded that V710 was not efficacious in preventing *S. aureus* bacteremia and/or deep sternal wound infection, despite eliciting a robust antibody response. Although the overall mortality rates for vaccine and placebo recipients were not significantly different, V710 appeared to be associated with multi-organ failure. Among patients who developed *S. aureus* infection, those in the V710 group were significantly more likely to die than those in the placebo group, although causality is difficult to established due to many confounding factors.

While the V710 trial was not considered a success, it produced an important collection of insights and "lessons learned" that may be leveraged for future efforts. The panel discussion outlined some of the current programs in staphylococcal vaccine development by major developers, and revealed a wide breadth of approaches to address the medically important need for a safe and effective staphylococcal vaccine. Alternative vaccine development strategies were put forward that advocate the use of multiple antigen preparations and the inclusion of adjuvants, and/or focus on targets representing specific virulence mechanisms. Dr. Haupt then concluded the session with some of the following major challenges in *S. aureus* vaccine research and design:

- Simply measuring the humoral response after vaccination is not sufficient to predict clinical outcome: measurement of "functional" antibody is required to assess vaccine potential.
- Better assays that reflect physiological endpoints (e.g., opsonization, T cell-mediated immunity) may be useful in evaluating host potential to recognize and eliminate *S. aureus*.

- Current animal models for staphylococcal disease do not have good predictive value to guide such clinical efforts.
- Identification and validation of clinically-relevant correlates of protection represent a major bottleneck to further vaccine development.
- The selection of appropriate patient populations and the need for specific regulatory guidance on their use were cited as significant concerns that may impact future trials.

Re-assessing Staph Vaccine Development – Next Steps and Basic Research Needs

Moderator: Mark Feinberg, M.D., Ph.D., Merck

Dr. Mark Feinberg from Merck chaired a session on the current status of *S. aureus* vaccine research and development (R&D) at several biotechnology companies.

Dr. Dominique Boutriau from GlaxoSmithKline presented the lessons learned from two failed StaphVax efficacy trials conducted in patients with end-stage renal deficiency (ESRD). The failure of efficacy trials highlights the need to better understand what type of immune response a vaccine should aim for. Deficiencies or dysfunctions in innate immunity (neutrophils defects) or T cell-mediated immunity (e.g., Th17 deficiency, CD4+ T cells) lead to higher risk of *S. aureus* infections while persistent carriage appears to protect against the most severe forms of *S aureus* infection. She refers to a model for immunological tolerance of *S. aureus*, in which defective antigen-presenting cells render host immunity ineffective. For future staphylococcal vaccine trials, she advocated the need for better clinical research design, and the need for adequate pre-clinical and/or clinical proof-of-concept (POC) studies.

Dr. Clare Kahn from Pfizer presented their successful Phase 1 trials for *S. aureus* vaccine candidates, SA3Ag and SA4Ag. These vaccine antigens target several virulence mechanisms, including those related to phagocytosis, host adherence, and divalent cation scavenging. However, because *S. aureus* exhibits diverse clinical presentations, the company, like all other companies, faces the same challenges with respect to selection of appropriate target populations for vaccination.

Dr. Fabio Bagnoli from Novartis presented the company's genomics approach to identify combinations of antigens with diverse protective properties and roles in virulence. Its current vaccine preparation contains 4 antigens: FhuD2, EsxAB, Hla, Sur-2. Although the resulting vaccine preparation has been demonstrated protective using three different mouse challenge models (peritonitis, pneumonia, and abscess), the company faces similar challenges with regard to appropriate target population selection, reliable efficacy readouts, and the use of adjuvants in the design of POC testing in humans.

Dr. Javad Aman from Intergrated BioTherapeutics presented his company's approach for the rationally designed attenuated toxoid vaccine. While anti-cell surface and opsonophagocytic antibodies aim to destroy bacteria and provide sterile immunity, neutralizing antibodies against *S. aureus* toxins can prevent or mitigate clinical disease by protecting immune cells and tissues, and by balancing the inflammatory response. He presented promising data on the company's multivalent toxoid vaccine, which contains attenuated alpha-toxin, leukocidin, phenol-soluble modulin (PSM) peptides, delta-toxin, and superantigens.

Dr. Bachra Rokbi from Sanofi Pasteur shared many concerns about the current animal models for *S. aureus* infection. While animal models work very well for predicting the efficacy of small molecule drugs (especially with respect to pharmacokinetics and pharmacodynamics), they are problematic in predicting the efficacy of experimental vaccines. The panel was in agreement that there is a need to develop a more relevant animal model using hosts other than mice. Dr. Rokbi then mentioned that vaccine antigen selection is critical, and that both humoral and cellular immunity, and in particular, Th17 involvement, should be considered when evaluating a vaccine. Understanding the mechanism of action (MOA) of *S. aureus* vaccines will help to predict and improve safety profiles. Lastly, Dr. Rokbi emphasized that more translational research using human clinical samples and tissues should be conducted to better understand *S. aureus* disease in humans and to aid in the identification of target populations for vaccine studies. With such information at hand, we can develop new models that better mimic particular clinical presentations of *S. aureus* infection.

Basic Research Challenges – Host Immune Responses and Vaccine Development

Moderator: Jean Lee, Ph.D., Brigham and Women's Hospital, Harvard Medical School

Dr. Jean Lee from Brigham and Women's Hospital, an affiliate of Harvard Medical School gave a general overview of this session, which focused on the preclinical aspects of vaccine development. She began with stating that because we do not understand the natural immunity to *S. aureus* infections, we can only hope to induce immunity by a vaccination approach. Dr. Lee then raised the following additional key points with regard to *S. aureus* research:

- *S. aureus* strains are geographically diverse and very versatile in their antigenic repertoire.
- *S. aureus* possess a whole array of virulence factors that aid in the evasion of host immune responses.
- There are certain types and numbers of antigens that could/should be used in order to induce protective immunity.
- It is important to determine whether a vaccine that protects against *S. aureus* soft-tissue infection is also protective against other forms of *S. aureus* infection (bacteremia, pneumonia, and/or osteomyelitis).

Dr. Lee concluded the overview by mentioning some of the novel approaches to staphylococcal vaccine design. Such examples include the design of multicomponent vaccines (with targets to *S. aureus* toxins, polysaccharides, transporters, and adhesins), vaccines that generate functional opsonizing antibodies, vaccines that neutralize toxins or prevent bacterial adhesion, and vaccines that generate robust T cell-mediated immunity.

After the session overview, Dr. Lee presented recent data from her own research, which employs a novel glycoengineering technology to create multicomponent staphylococcal vaccines. Specifically, they utilized a simple recombinant *E. coli* system to enzymatically link polysaccharide antigens with protein antigens. Proteins involved in *S. aureus* capsular polysaccharide (CP) biosynthesis (e.g., PglB, an oligosaccharyl transferase) were co-expressed in *E. coli* with an antigenic protein carrier (non-toxic alpha-hemolysin [Hla_{H35L}] or clumping factor

A [$ClfA_{N221-559}$]). Bioconjugate vaccines, composed of N-glycosylated Hla_{H35L} conjugated with CP5 (CP5-Hla) or N-glycosylated $ClfA_{N221-559}$ conjugated with CP8 (CP8-ClfA), were purified from the periplasmic extracts of *E. coli*. Rabbits and mice immunized with the CP5-Hla vaccine produced opsonic antibodies that also neutralized the lytic activity of native Hla. Antibodies generated by the CP8-ClfA vaccine were also opsonic and inhibited the binding of *S. aureus* to immobilized fibrinogen. Active and passive immunization strategies targeting the CPs protected mice against staphylococcal bacteremia, while vaccines targeting Hla protected against lethal pneumonia. The CP-Hla bioconjugate vaccine provided protection against both bacteremia and pneumonic infection, indicating that multicomponent vaccines containing different *S. aureus* polysaccharide and protein antigens may provide broad-spectrum efficacy against invasive disease. Furthermore, Dr. Lee's research also demonstrates that glycoengineering technology has broad applicability for use in vaccine development against encapsulated microbial pathogens, such as *S. aureus*.

Dr. Sandip Datta from the Division of Intramural Research at NIAID presented his research, conducted in collaboration with Dr. Michael Daly from the Uniformed Services University of the Health Sciences, which aims to elucidate and overcome the lack of protective adapted immunity against *S. aureus* after primary infection. Their work focuses on the production of a lethally irradiated *S. aureus* vaccine, which utilizes radio-protective Mn^{2+}-decapeptides as a means to preserve the integrity and immunogenicity of antigenic epitopes. Vaccination of mice with the irradiated *S. aureus* vaccine was able to protect against staphylococcal skin infection. The immune response generated after vaccination was dependent on B cells, and to an even greater extent CD4 T cells (and in particular, Th17 cells). Dr. Datta then concluded with the observation that cytokines that are induced during other skin conditions, such as the production of IL-20 subfamily cytokines during psoriasis, are similar to the cytokines induced during *S. aureus* skin infections.

Dr. Gerald Pier from Brigham and Women's Hospital, an affiliate of Harvard Medical School, discussed research efforts focused on poly-*N*-acetyl-β-(1-6)- glucosamine (PNAG), a key surface polysaccharide antigen that is expressed and conserved among a broad range of pathogenic Gram-negative and Gram-positive bacteria (with the exception of *P. aeruginosa*), pathogenic fungi, and pathogenic protozoa. For *Staphylococcus aureus*, most clinical isolates have been shown to produce PNAG, regardless of whether or not they display hemolytic activity. Expression of PNAG in *S. aureus* co-localizes with the CP5/CP8 capsular polysaccharide antigens in both liquid culture and biofilms. Furthermore, analysis of human samples isolated from patients infected with *S. aureus* showed that PNAG was present along with other key target extracellular *S. aureus* antigens. Dr. Pier's current research focuses on the use of conjugate vaccines containing synthetic oligoglucosamines and monoclonal antibodies (as passive therapeutic agents) to prevent or treat infections with various microbial pathogens. Thus far, the conjugate oligoglucosamine-containing vaccines have been shown to be effective using different animal models of *S. aureus* infection. Dr. Pier then commented that about 5 percent of healthy humans have natural opsonic/protective antibodies to PNAG.

Dr. Rachel McLoughlin of Trinity College Dublin pointed out that one of the fundamental challenges in developing a staphylococcal vaccine is to understand what constitutes a protective immune response against *S. aureus* infections. She emphasized that the field now recognizes that

humoral immunity is not enough and that a cellular immune response is also needed. In her opinion, there are three major challenges in understanding the cellular immune response to *S. aureus* infections that need to be addressed before moving forward. The first challenge is to identify the specific types of T cells that are involved. Dr. McLoughlin's research points to an important role for γ-δ T cells. The second set of challenges is to identify the types of antigen(s) and adjuvant to use for vaccination in addition to the route of vaccination. Different adjuvants in particular are known to modulate the type of T-cell response and Dr. McLoughlin pointed to studies demonstrating that the induction of a particular type of immune response (using the same antigen) can vary depending on the kind of adjuvant used. Lastly, the third challenge is to translate knowledge gained from *in vitro* systems and animal models into humans, who are often not immunologically naïve to *S. aureus* as a consequence of colonization. Dr. McLoughlin presented preliminary results from her own research that attempts to better understand the nature of the immune response against *S. aureus* infection in humans. Her laboratory is analyzing samples obtained from human patients with *S. aureus* bacteremia and examining antigen-specific T-cell populations and their phenotype. In summary, Dr. McLoughlin thinks that in order to develop a successful *S. aureus* vaccine, we should consider expanding specific T-cell subsets, looking beyond conventional peptide antigens, and selecting the proper adjuvants.

The Basic Research Challenges session concluded with a discussion that covered many diverse topics and novel ideas. The following are examples of key points and questions raised that remain to be answered:

- The selection of antigens that are conserved among strains versus the selection of variable antigens as a target to make *S. aureus* incompatible with human colonization.
- The importance of IL-17 in skin versus systemic infections.
- The importance of IL-17 in hyper-IgE patients that suffer recurrent *S. aureus* infections.
- Whether patients with bacteremia are the right cohort for characterizing the immune response to staphylococcal infection.
- Is it possible to screen patients for colonization status before enrolling them into a vaccine trial?
- How many samples are needed to determine that a response to *S. aureus* infection is meaningful and real?
- Is it possible to develop a library of samples to benefit staphylococcal vaccine researchers that avoids geographical bias?
- Is it possible that resistance to *S. aureus* infection is based on a single mechanism, or is the mechanism of resistance something that lacks uniformity?

Translational Research Challenges – Developing *S. aureus* Animal Models

Moderator: Steve Projan, Ph.D., MedImmune

Dr. Steve Projan from MedImmune provided an overview of the Translational Research Challenges session, which focused on the use of animals models in *S. aureus* vaccine development. He emphasized that while animal models have worked very well for translating the efficacy, pharmacokinetics, and pharmacodynamics of small molecule antibiotics into humans, when it comes to vaccines, animal models have proven problematic in terms of predicting efficacy.

Dr. Ali Fattom from NanoBio Corp. presented results from two previous clinical trials of their *S. aureus* vaccine candidates. Both clinical trials were based on two different lots of the same antigen. Interestingly, one of the trials was partially successful, while the other trial was not at all successful. Additionally, vaccination with both lots yielded similar results with regard to opsonic activity and antibody affinity; however, the clinical outcomes of vaccination with both lots were strikingly different. Experiments performed after the trials using the murine hog mucin challenge model demonstrated a clear difference in survival rates between the vaccine that failed and the vaccine that showed partial success (37 percent vs. 84 percent survival, respectively). Further experiments demonstrated that, by changing the adjuvant formulation of the failed vaccine to alum (as opposed to saline, as used in the original clinical trials), post challenge survival in the same hog mucin model could be increased from 6 to 73 percent. The increase in survival was also mirrored by a significant increase in antibody affinity following vaccination with the alum-containing vaccine. The presentation concluded by emphasizing once more that there are no good alternatives to human data, and that when it comes to vaccines, there are no perfect animal models of human disease. Nevertheless, it was also emphasized that poor vaccine performance in a "relevant" animal model should always raise a red flag.

Dr. Lisa Herron-Olson from Syntiron presented studies on *S. aureus* vaccines directed against iron-regulated membrane proteins and the animal models used to characterize them. She began with a brief description of the mouse model for *S. aureus* sepsis, and mentioned that this model is commonly associated with low statistical power, low rates of reproducibility and poor feasibility. In contrast, the mouse model of *S. aureus* cutaneous infection is known to induce a more consistent disease response and generate better statistical power. However, this model also generates a great deal of variability among mouse strains with respect to lesion dynamics, making it very difficult to identify which results can be translated into humans. The difficulty of translating findings in mice to humans was further illustrated by a recent publication by Seok *et al.* (Proc. Natl. Acad. Sci. USA 2013, 110(9):3507-12), which examined 5,000 genes related to inflammatory responses during burn injury, trauma, and endotoxemia in humans and mice. In particular, this study demonstrated that inflammatory responses are fairly consistent in humans, but not in mice. Thus, two important questions remain as to whether mouse responses to *S. aureus* infection are concordant with human responses, and how this impacts vaccine development. Dr. Herron-Olson then suggested that it may be worth focusing research efforts more on natural hosts for *S. aureus* infection, such as rabbits, dogs, poultry, cows and pigs. In these hosts, disease progression often better mimics human disease, and lower challenge inocula are able to establish infection.

Dr. Mark Shirtliff from the University of Maryland, Baltimore, began his presentation by identifying potential causes for the limited successes of *S. aureus* vaccines. Such potential causes include the heavy dependence of BALB/c mouse models in proof-of-concept testing, the disregard of differences in antigen expression related to multiple modes of bacterial growth (planktonic vs. biofilms), and the assumption that a log reduction in bacterial burden equals protection. To illustrate these points, Dr. Shirtliff referred to a study by Stephen Elek (Ann. NY Acad. Sci. 1956, 65(3):85-90) that underscores the importance of biofilms in human staphylococcal skin infections, which is one important area to focus on in animal models for *S. aureus* vaccine development. Dr. Shirtliff then presented results from a study in his laboratory

using a chronic *S. aureus* tibial implant infection model. In particular, this study demonstrated that while BALB/c mice are able to spontaneously clear the biofilm infection, C57BL/6 mice, as with humans, are unable to clear this kind of infection. Furthermore, results from this study indicated that Th2/Treg-skewed responses in BALB/c mice are protective against chronic *S. aureus* implant infection, as opposed to Th1/Th17-skewed responses in C57BL/6, which may play a role in the development of chronic infection (Infect. Immun. 2011, 79(12):5010-8). From additional vaccine studies in his lab, Dr. Shirtliff concluded that multiple antigens expressed in biofilm and planktonic cultures are needed in a vaccine to accomplish protective efficacy against *S. aureus* infections.

Dr. Todd J. Merkel from the FDA echoed concerns of the previous presenters that the current *S. aureus* animal models for sepsis and pneumonia are not appropriate for vaccine development. Dr. Merkel then presented his research, which focuses on the development of a better skin and soft tissue animal model that mimics the progression and characteristics of human skin infections. In the existing models, animals (typically mice) are infected by intradermal injection, abrasion, or subcutaneous injection, which resembles more of a wound/surgical infection, rather than a true *S. aureus* skin infection. Dr. Merkel then stressed that these models are extremely difficult to replicate and are plagued with technical hurdles. To develop a better model for *S. aureus* skin infections in mice, he pointed out two innovations that his laboratory is utilizing: the use of Morrow-Brown skin testing needles for inoculation (which are needles designed to give a very shallow incision with very reproducible incision size and depth); and the use of the ears as the site of infection. This new model produces highly reproducible and consistent data, and better mimics the high bacterial burden early during infection (4-7 days post-infection), the progression of infection, and the immune response to infection as observed in humans.

The Translational Research Challenges session concluded with a follow-up discussion, which focused on the limitation and utility of current animal models. While animal models allow us to better understand the molecular mechanisms of disease and protection, they will never fully recapitulate human disease. Nonetheless, data from animal models serve as an important foundation to ask critical questions in human populations prior to moving forward with clinical trials.

Clinical Trial Design Challenges – Efficacy Correlates and Target Populations

Moderator: Robert Daum, M.D., University of Chicago

Dr. Robert Daum from the University of Chicago began the session by presenting the clinical aspects of *S. aureus* infection. In addition to asymptomatic colonization, *S. aureus* is also an important pathogen, causing a wide spectrum of clinical infections, ranging from boils (furunculosis) to invasive disease, often characterized by clinical sepsis. Moreover, *S. aureus* is a leading cause of nosocomial and community-acquired infection associated with significant morbidity and mortality. Over the last decade, the U.S. has seen an exponential rise and epidemic of *S. aureus* infections, mostly caused by MRSA, or methicillin-resistant *Staphylococcus aureus*, which are resistant to nearly all ß-lactam antibiotics. An ideal *S. aureus* vaccine would protect against the wide array of clinical syndromes caused by *S. aureus*, specifically including invasive

disease, pneumonia, and skin infections, the latter of which causes frequent complications within emergency rooms and hospitals. The development of such a vaccine is extremely challenging, in that different clinical syndromes are thought to produce different microbial-host pathophysiologies and immunologic responses, and may require different mechanisms of protective vaccination. So far, the development of *S. aureus* vaccines has followed the traditional pathway of identifying 'protective' antigens to produce a vaccine that elicits a protective opsonophagocytic antibody response. However, it is difficult to identify the ideal protective antigens, and it is not clear whether this vaccination approach will provide broad protection against some or all *S. aureus* syndromes. Lastly, Dr. Daum concluded his presentation by presenting an argument for universal administration of a successful *S. aureus* vaccine. Dr. Daum cited an example of a previous hepatitis B vaccine strategy, which failed to successfully immunize many high-risk populations. However, with the implementation of a universal vaccine administration strategy, which includes populations with a variable risk of infection, the prevalence of hepatitis B disease in humans has dropped significantly. Along these lines, because *S. aureus* infects patients of all ages and backgrounds, many researchers in the field concur that a universal administration plan seems like a justifiable vaccination strategy to reduce the burden of *S. aureus* disease.

Dr. Sheldon Kaplan from Texas Children's Hospital, an affiliate of Baylor College of Medicine, described the various clinical presentations of invasive *S. aureus* infections in children with no underlying conditions. *S. aureus* is the most common cause of skin and soft tissue infections (SSTIs) as well as some invasive infections such as osteomyelitis or septic arthritis in children. Thus, children represent an important population to include in studies of *S. aureus* vaccines. Furthermore, if an *S. aureus* vaccine is not protective in otherwise normal children, it is not likely to be efficacious in patient populations with underlying conditions. Although *S. aureus* infections in children are very common, a pediatric clinical trial of a *S. aureus* vaccine candidate would need a large number of children to enroll, which would be challenging. However, 20 percent of skin and soft tissue infections are recurrent in otherwise normal children. Thus, a vaccine trial designed to demonstrate a reduction in recurrent infections within a defined period of time, such as 12 months from initial infection, would be more feasible and could be accomplished with a realistic number of children.

Dr. Ruth Lynfield from the Minnesota Department of Health presented statewide surveillance data from 2005 for the state of Minnesota, which illustrated the number of cases of critical or fatal illness due to community-associated *S. aureus* infection (with no traditional healthcare-associated risk factors). Preliminary data include the following: 131 cases [64 methicillin-resistant *S. aureus* (MRSA), 67 methicillin-sensitive *S. aureus* (MSSA)], with the median age for MRSA cases being 34 years, and MSSA cases being 16 years. Fifty-six percent of patients with MRSA, and 34 percent of patients with MSSA had medical co-morbidities. Twenty-seven percent of all MRSA and MSSA infections were fatal, and were more frequently associated with older patients or patients with underlying conditions. Forty-three percent of all community-associated *S. aureus* infections, and 64 percent of fatal cases, were due to *S. aureus*-associated pneumonia and other respiratory infections. Lastly, 78 percent of MRSA infections were caused by the *S. aureus* strain USA300, whereas much more strain diversity was observed among MSSA isolates.

Dr. Mary-Claire Roghmann from the University of Maryland, Baltimore, discussed potential target populations for *S. aureus* vaccine testing based on epidemiological data on *S. aureus* infections. Due to improved and more rapid diagnostic testing for *S. aureus* bacteremia, patients with invasive *S. aureus* infection have become a potential target population for *S. aureus* vaccine testing. Additionally, this target population would require a therapeutic vaccination approach with passive immunization as an adjunct to antibiotics, which would be advantageous because more than half of patients with invasive *S. aureus* infection are immune compromised and unlikely to respond to active immunization. Lastly, potential outcomes using this target population may include complications of infection, such as sepsis and hematogenous sequelae, which are relatively common with invasive *S. aureus* disease.

Epidemiological Insights to Facilitate Vaccine Development

Scott Fridkin, M.D., CDC

Dr. Scott Fridkin from the CDC chaired the next workshop session on epidemiological insights to facilitate *S. aureus* vaccine development. In particular, he noted that measuring the absolute burden of *S. aureus* disease is extremely challenging because of the infection's diverse clinical manifestations, the different levels of care required for treatment, and the resulting variability in morbidity. Starting around 2001-2005, several studies documented an increase in hospitalizations with *S. aureus* infections; most of the increase observed since 1999 was attributable to the increasing frequency of MRSA-associated SSTIs among non-hospitalized patients requiring inpatient therapy. More recent data using similar methodology have demonstrated a plateau in such hospitalizations and even decreases in the subset of hospitalizations related to *S. aureus* sepsis. More definitive assessments using CDC's population-based surveillance system confirm dramatic reductions in the U.S. in the estimated burden of hospital-onset invasive MRSA infections since 2005, while the incidence of community-associated invasive infections has not changed and, in fact, is now similar to that of hospital-onset infections (estimated at 13,000-16,000 infections per year). However, the largest burden of *S. aureus* disease continues to remain with patients who develop invasive MRSA infections in the months following discharge from acute care hospitals, which the CDC estimates at approximately 50,000 infections post-discharge per year in the U.S.

Over the past decade, numerous evaluations have identified certain populations to be at extreme risk for serious or invasive infection with *S. aureus*, including patients on dialysis, neonates with very low birth weights, and patients undergoing certain surgical procedures (e.g., cardiac surgery). Recent evaluations by CDC that combine national surveillance data on MRSA bloodstream infections with national data on a variety of underlying illnesses and age groups allows for an estimation of incidence by specific population groups. In particular, the CDC estimates that the annual incidence of invasive MRSA infection is about 1,000 per 100,000 persons for long-term care residents, about 100 per 100,000 for non-institutionalized persons over 65 years old, about 75 per 100,000 for adults with diabetes, and about 15 per 100,000 for adult private household residents. Furthermore, CDC surveillance for post-operative infections, combined with national data on post-operative *S. aureus* bacteremia and pneumonia, provide further insight into high-risk surgical populations. Surgical procedures such as ventricular shunt placement (1.31 percent), refusion (1.13 percent) or fusion (0.68 percent) of the spine, and

total/partial hip (0.61 percent) or knee (0.41 percent) athroplasty represented populations with the highest likelihood of a serious *S. aureus* infection within 30 days after surgery.

Overall, although trends in invasive MRSA are downward, a large burden of illness still exists, especially among patients who have recently been discharged from hospitals, who are elderly, and who are long-term care residents. Although some surgical procedures put patients at high risk for serious *S. aureus* infections, these procedures result in a small fraction of all *S. aureus* disease that may be affected by a vaccine. Considering this, the potential impact for prevention though vaccination strategies in the post-discharge setting is very attractive. Although dialysis and surgical patients may be attractive primary targets for candidate vaccine trials for a variety of reasons, broader vaccine strategies will have a larger public health impact. Even if vaccine research and development efforts lead to candidate vaccines that are effective at providing protection for at least a few months, this would potentially lead to an enormous public health impact by providing protection around the time of healthcare delivery across a variety of age groups and patient settings.

Government Resources to Overcome Vaccine Research Challenges

Drusilla Burns, Ph.D., FDA; Michael Ellis, M.D., Uniformed Services University and Department of Defense (DoD); Alexandra Freeman, M.D., NIAID; Kimberly Taylor, Ph.D., NIAID; Jonathan Seals, Ph.D., HHS/BARDA

The workshop concluded with a panel discussion with experts from various U.S. Government agencies, including the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH); the U.S. Food and Drug Administration (FDA); the Department of Defense (DoD); and the Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services. Each panelist discussed the resources available through their respective organizations for researchers in the field of staphylococcal vaccine development.

Dr. Drusilla Burns from the FDA discussed the key steps in the vaccine development pipeline from the pre-IND and IND phases to the licensing and post-marketing stages. Dr. Burns stressed that researchers in vaccine development should ideally contact the FDA in the pre-IND phase, so that FDA feedback can be incorporated as early as possible in the non-clinical development of the vaccine. Also, the more scientific information that can be provided to the FDA by the researchers, the easier it is for the FDA to respond and provide feedback on the development of the vaccine candidate.

Dr. Michael Ellis from the Uniformed Services University of the Health Sciences/DoD, began his presentation by highlighting that SSTIs are the leading cause of hospital admissions in the first two years of military service. He proceeded by noting that the military station in Fort Benning, GA, is an ideal place to conduct *S. aureus* research due to the large number of reported *S. aureus* cases. Dr. Ellis then mentioned the Staph Vaccine Working Group, which partners with various research organizations such as the Uniform Services University in Bethesda, MD; the Naval Medical Research Center in Silver Spring, MD; and the Martin Army Community

Hospital in Fort Benning, GA. In all, these organizations as well as the DoD serum repository provide researchers with much-needed resources for staphylococcal vaccine development.

Dr. Alexandra Freeman from the NIH/NIAID Laboratory of Clinical Infectious Diseases provided some examples of clinical studies on *S. aureus* that are currently being conducted by the NIAID Division of Intramural Research (DIR). In particular, she highlighted three main clinical programs at the NIAID DIR: (1) the STAT3 mutated hyper IgE syndrome clinical program, which has enrolled 70 patients who have recurring *S. aureus* skin and soft tissue abscesses and pneumonias; (2) the chronic granulomatous disease clinical program, which focuses on invasive infections such as liver abscess, lymphadenitis and osteomyelitis; and (3) clinical studies on *S. aureus* infections in healthy individuals.

Dr. Kimberley Taylor from the NIH/NIAID Division of Microbiology and Infectious Diseases (DMID) presented the resources for researchers in vaccine development that are available through the extramural program at NIAID. These resources are provided as individual services on a case-by-case basis to bridge an important gap in the development pathway of a vaccine candidate. Furthermore, they provide researchers with critical data that can be used to acquire additional funding and partnerships. Examples of NIAID resources include a variety of products such as biologics, challenge materials, as well as vaccine components. In particular, NIAID has two main contracts that provide services focused on either vaccine manufacturing or vaccine testing. Dr. Taylor also pointed out certain *S. aureus* animal models, such as the murine *S. aureus* bacteremia model, are currently available for testing of vaccines against *S. aureus*, and are managed by the DMID Bacteriology and Mycology Branch at NIAID.

Dr. Jonathan Seals from BARDA presented BARDA's mission in providing an integrated, systematic approach for the development and purchase of necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies. For example, recurrent *S. aureus* infection falls under their mandate. Specific examples of resources for researchers in *S. aureus* vaccine development include contract support, the availability of animal models and manufacturing facilities, and funding for clinical trials.

Appendix 1: Agenda and Participants List

Overcoming Challenges in *S. aureus* Vaccine Development

June 7th, 2013
5635 Fishers Lane, Room 508/509
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Purpose: To bring together government, academic, non-profit and industry stakeholders to address challenges in the development of staphylococcal vaccines, as well as recent developments and possible solutions.

Time	Activity
8:30-8:40am	**Opening Remarks** Dennis Dixon, Ph.D., *NIAID*
8:40-9:30am	**V710 Trial – Results and Lessons Learned** Richard Haupt, M.D., *Merck & Co., Inc.*
9:30-10:30am	**Re-assessing Staph Vaccine Development – Next Steps and Basic Research Needs** • Framing the issue: Mark Feinberg, M.D. Ph.D., *Merck & Co., Inc.* • Panel discussion: Dominique Boutriau, M.D., *GlaxoSmithKline*; Clare Kahn, Ph.D., *Pfizer, Inc.*; Bachra Rokbi, Ph.D. *Sanofi*; M. Javad Aman, Ph.D., *Integrated BioTherapeutics, Inc.*; Fabio Bagnoli, Ph.D., *Novartis* • Summary of key questions: Mark Feinberg, moderator
10:30-10:45am	Morning Break
10:45-12:00pm	**Basic Research Challenges – Host Immune Responses and Vaccine Development** • Framing the issue: Jean Lee, Ph.D., *Brigham and Women's Hospital* • Presentations: Olaf Schneewind, M.D. Ph.D., *University of Chicago*; Brad Spellberg, M.D., *LA BioMed*; Gerald Pier, Ph.D., *Brigham and Women's Hospital*; Sandip Datta, M.D., *NIH/NIAID*; Rachel McLoughlin, Ph.D., *Trinity College* • Open discussion • Summary of key questions: Jean Lee, moderator
12:00-1:00pm	Lunch

1:00-2:10pm **Clinical Trial Design Challenges – Efficacy Correlates and Target Populations**

- Framing the issue: Robert Daum, M.D., *University of Chicago*
- Presentations: Sheldon Kaplan, M.D., *Baylor College of Medicine/Texas Children's Hospital*; Mary-Claire Roghman, M.D., *University of Maryland*; Greg Moran, M.D., *UCLA-Olive View*; Ruth Lynfield, M.D., *Minnesota Department of Health*
- Opening discussion
- Summary of key questions: Robert Daum, moderator

2:10-2:30pm **Epidemiological Insights to Facilitate Vaccine Development**

Scott Fridkin, M.D., *CDC*

2:30-2:45pm Afternoon Break

2:45-3:55pm **Translational Research Challenges – Developing *S. aureus* Animal Models**

- Framing the issue: Steve Projan, Ph.D., *MedImmune, Inc.*
- Presentations: Todd Merkel, Ph.D., *FDA*; Mark Shirtliff, Ph.D., *University of Maryland*; Lisa Herron-Olson, M.D., *Syntiron*; Ali Fattom, Ph.D., *NanoBio Corp.*
- Open discussion
- Summary of key questions: Steve Projan, moderator

3:55-4:15pm **Government Resources to Overcome Vaccine Research Challenges**

Drusilla Burns, Ph.D., *FDA*; Michael Ellis, M.D., *DoD*; Alexandra Freeman, M.D., *NIH/NIAID*; Kimberly Taylor, Ph.D., *NIH/NIAID*, Jonathan Seals, Ph.D., *BARDA*

4:15-4:30pm **Concluding Remarks and Adjournment**

Dennis Dixon, Ph.D., *NIAID*

Participant List

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