Progress Toward a Global Group A Streptococcal Vaccine

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RATIONALE FOR GROUP A STREPTOCOCCAL VACCINES

Vaccines against Streptococcus pyogenes (the Lancefield group A streptococcus [GAS]) have been a goal of researchers and public health authorities since the beginning of the last century. The desire for an effective vaccine arises from the large burden of disease caused by the bacterium, particularly rheumatic fever and rheumatic heart disease. Rheumatic fever is an uncommon disease today in most resource-rich countries including the United States,1 but it remains the major cause of acquired heart disease in children, adolescents and young adults in the developing world, responsible for at least 350,000 premature deaths per year.2 In addition, invasive GAS disease is a frequent cause of sepsis in children and adults and has a high-case fatality rate leading to at least 150,000 deaths worldwide, although this figure is almost certainly an underestimate because of sparse data from many developing countries.2 Further adding to the burden of GAS disease is poststreptococcal glomerulonephritis, which likely contributes to the high rates of end-stage renal failure in many GAS endemic regions.3 More superficial conditions—GAS pharyngitis and impetigo—are responsible for the greatest absolute number of GAS infections each year.2 GAS pharyngitis affects approximately 8%–15% of school-aged children per year, whereas GAS impetigo is a very common infection in children in tropical developing countries, with prevalence of >10%, and up to 50%, in some settings.4,5

There is no evidence that the burden of GAS diseases is decreasing other than as a result of economic development. In other words, serious GAS diseases appear to be waning in some middle income countries, probably because of improved living conditions and access to health services. Current approaches directed specifically at reducing the overall burden of GAS diseases appear to have little impact on the lower income countries where, if anything, these diseases are on the rise. For this reason, and because even in wealthy countries GAS diseases exact a toll in terms of mortality, morbidity and economic costs, a GAS vaccine is sorely needed.

CURRENT GAS VACCINES IN DEVELOPMENT

GAS vaccines can be broadly divided into M protein–based and non–M protein–based vaccines (Table 1).6 The GAS is a gram-positive organism with a hyaluronic acid capsule and a broad armamentarium of virulence factors, but it is the M protein that is the major virulence determinant of the organism. The M protein is a coiled-coil protein consisting of 3 domains: an A-repeat/N-terminal domain, which is highly variable and is used for epidemiologic molecular typing (emm typing); a B-repeat domain (antibodies against this region are not opsonic) and a conserved C-repeat domain. The 2 vaccines that have entered or are nearing clinical investigation are the N-terminal M protein–based multivalent vaccines (26-valent and 30-valent vaccines) and conserved M protein vaccines (the J8 vaccine and the StreptiCor vaccine). There are a variety of other vaccine candidates that are at various stages of discovery and development, some of them identified using reverse genetics (Table 1).

26-Valent and 30-Valent Vaccines

These vaccines consist of fused recombinant peptides from the N-terminal region of M proteins from multiple different emm types of GAS.6 The original prototype multivalent vaccine was a hexavalent vaccine that was evaluated in a phase I trial and later expanded to a 26-valent vaccine and most recently a 30-valent vaccine.6–8 The 26-valent vaccine underwent a phase II/II clinical trial in human adult volunteers and was shown to be safe and immunogenic.6 Functional opsonic antibodies were induced against all emm types of GAS in the vaccine. The 26-valent vaccine was reformulated into a 30-valent vaccine to increase “coverage” of circulating emm types in the United States, Canada and Europe as well as developing countries.3 Epidemiologic surveys suggest that the 26-valent vaccine would provide good coverage of circulating strains of GAS in industrialized countries (over 72%) but poor coverage in many developing countries (as low as 24% in the Pacific region).9 In preclinical studies, the 30-valent vaccine has been shown to induce functional opsonic antibodies against all emm types of GAS represented in the vaccine. An intriguing finding of the studies of the 30-valent vaccine is that antibodies produced by the vaccine were shown to cross- opsonize a proportion of nonvaccine emm types of GAS.5 The extent, physiologic basis and applicability to human immunity of this cross-opsonization are currently under investigation. However, the implication of these findings is that this cross-protection may mitigate, to a greater or lesser extent, the limited coverage of the 26-valent vaccine in many tropical developing settings where GAS disease is endemic. A phase I clinical evaluation of the 30-valent vaccine in adult volunteers is anticipated in 2013.

Conserved M Protein Vaccines

These vaccines contain antigens from the conserved C-repeat portion of the M protein. The StreptiCor vaccine incorporates selected T and B-cell epitopes from the C-repeat region,10 whereas the J8 and J14 vaccines contain single minimal B cell epitopes from this same region.11 Extensive studies in mice, particularly of the J8 vaccine candidate, have shown that these antigens produce opsonic antibodies that protect against challenge.12 Unlike multivalent vaccines, these vaccines have yet to enter clinical trials. These vaccines have the clear advantage of being comprised of single antigens. Limited data available for the J8 peptide indicate that its structure is highly conserved among multiple emm types of GAS and across regions.4

Other Vaccines

Extracellular virulence factor antigen, such as streptococcal C5a peptide, GAS carbohydrate and streptococcal fibronectin-binding proteins, among others, have been the subject of vaccine research for up to 20 years with some encouraging results, particularly for C5a peptide, but none of these candidates has entered clinical trials.11–13 More recently, a number of promising, apparently conserved, vaccine candidates have been identified using reverse genomics.14 In a large study, a number of vaccine
candidate antigens delivered by both subcutaneous and intranasal routes were tested in murine intravenuous and intranasal challenge models with evidence of protection demonstrated in at least 1 of the models for 9 of the antigens. However, their role in protection in human disease remains unknown, and none of these candidates has entered clinical trials.

**OBSTACLES TO GAS VACCINE DEVELOPMENT**

Despite considerable progress having been made with a number of vaccine candidates, as outlined above, there remain a number of significant barriers to vaccine development. These include, but are not limited to: safety concerns, an incomplete understanding of immune protection in humans, inadequate epidemiological data and minimal development of combination antigen vaccines. Concerns regarding vaccine safety are based upon a theoretical risk of autoimmune reactions in vaccinees leading to the development of rheumatic fever. One small study of a crude M protein vaccine suggested that there may be an increased risk of rheumatic fever in vaccine recipients; however, there are a number of concerns about the design of this trial that make it difficult to interpret, and autoimmune reactions have not been observed in the 18 other human GAS vaccine trials involving thousands of study subjects. Since the period of detailed and elegant investigation into protective immunity against GAS in humans by Rebecca Lancefield in the 1950, there have been very few further human studies and, therefore, we are left with an incomplete understanding of human GAS immunity. Human studies are particularly important because GAS is largely a human-specific pathogen and yet small animal studies have formed the basis for preclinical assessments of vaccine candidates. More information is needed regarding immune protection against GAS skin infection, the role of T-cell immunity and the relative contributions of non-M type-specific antigens (common antigens) in inducing protective immunity. Better epidemiologic data are also required, both in terms of assessing burden of disease to further advocate for GAS vaccine development and also for assessing vaccine coverage more systematically with high quality, standardized molecular typing studies in more countries, particularly in Africa and Asia. Combination vaccines may be a viable approach to overcoming “gaps” in emm type coverage achieved with multivalent vaccines alone and to potentially broaden the immune response. However, to date there has been minimal progress in combining antigens in a single vaccine, and such a move would need to overcome proprietary interests and intellectual property rights. Finally, it is unclear exactly why there has been an apparent reluctance of large pharmaceutical companies to invest in clinical development of GAS vaccines. The obstacles listed above, together with the perception of a questionable market for a vaccine in affluent countries, likely combine to create the impression of adverse commercial risk.

**A WAY FORWARD?**

Underpinning all of the obstacles to successful development of GAS vaccines has been the lack of a cohesive plan at an international level. To fill this gap, a roadmap that outlines the key activities and steps necessary to accelerate GAS vaccine development is critical. This roadmap is currently under development in conjunction with the World Health Organization. The strategic goal of this roadmap is to develop and license an effective and affordable vaccine designed to prevent GAS disease globally, with an emphasis on preventing the high mortality due to rheumatic heart disease and invasive disease. Key activities in preclinical and clinical development have been identified that, if achieved, would hasten the progression of vaccine candidates to licensure. These activities include, but are not limited to: defining immune correlates of protection; development of high throughput serologic and bacterioidal assays; standardization of epidemiologic protocols with concurrent establishment of clinical trial sites in GAS endemic countries and harmonization of clinical trial design and safety protocols for these trials. GAS pharyngitis will be the likely endpoint for initial phase III clinical trials, and evaluation of immune correlates of protection will be a critical component of these trials. A key part of the process will be the establishment of collaboration and consultation between academia, industry and public health institutions for sharing of resources and knowledge.

**REFERENCES**

4. Steer AC, Magor G, Jenney AW, et al. emm and C-repeat region molecular typing of


