

## Preview

# Toward the development of a protein-based group B *Streptococcus* vaccine

Kristen Dominguez<sup>1</sup> and Tara M. Randis<sup>1,2,\*</sup><sup>1</sup>Department of Molecular Medicine, University of South Florida; Morsani School of Medicine<sup>2</sup>Department of Pediatrics, University of South Florida; Morsani School of Medicine\*Correspondence: [trandis@usf.edu](mailto:trandis@usf.edu)<https://doi.org/10.1016/j.xcrm.2022.100536>

Clinical trials of protein-based vaccines to prevent Group B streptococcal infections are underway. In this issue of *Cell Reports Medicine*, Pawlowski et al.<sup>1</sup> provide an extensive characterization of the immune response generated by the recently tested GBS-NN vaccine.

Group B *streptococcus* (GBS) is a leading cause of neonatal infectious mortality throughout the world. Administration of intrapartum antibiotic prophylaxis (IAP) to at-risk or GBS-colonized women is the only available strategy to prevent invasive disease in neonates. While this resource-intensive approach has substantially reduced the incidence of early-onset infection (occurring in the first 6 days of life), it has failed to impact the incidence of late-onset disease in infants or other well-known GBS-associated obstetrical morbidities including chorioamnionitis, stillbirth, preterm delivery, and maternal sepsis. Furthermore, the unintended consequences of IAP are not trivial. The threat of emerging antimicrobial resistance and the deleterious effects on the developing neonatal microbiome are increasingly recognized and have strengthened the calls for an effective vaccine.<sup>2</sup>

In 1976, Baker et al. provided the first clue that passively acquired immunity may protect vulnerable newborns from GBS infection when they demonstrated that infants with invasive disease were more likely to be born to mothers deficient in GBS-specific antibodies.<sup>3</sup> In the decades that followed, numerous studies confirmed this critical observation and thus, the quest for an effective GBS vaccine began. Today, several phase I and II trials of candidate vaccines are ongoing in both pregnant and nonpregnant cohorts. Capsular polysaccharide (CPS)-based vaccines comprise the majority of these studies. However, the serotype-specific protection they offer poses a substantial limitation. Protein-based vaccines

have the potential to not only confer broad protection across all GBS serotypes but may also alleviate growing concerns regarding the threat of serotype replacement or serotype (capsular) switching: phenomena observed following widespread introduction of CPS-based vaccines for other streptococcal pathogens.<sup>4</sup>

Fisher et al. recently published the first phase I clinical trial of a GBS protein subunit vaccine.<sup>5</sup> They reported that this vaccine, known as GBS-NN, was safe and immunogenic in a cohort of 240 healthy adult women. GBS-NN is derived from a fusion protein comprised of N-terminal domains from two ubiquitous GBS alpha-like surface proteins (Alps): Alpha C and Rib. The functionally active N-terminal domains of Alps (Alp-Ns) extend outward through the GBS polysaccharide capsule and aid in the invasion of host cells and translocation across epithelial barriers.<sup>6</sup> Five different Alp-Ns have been described thus far, though they exhibit extensive sequence homology.<sup>7</sup> The genes encoding Alpha C and Rib are relatively conserved as they are present in more than 70% of GBS invasive isolates in the US.<sup>8</sup> Previous data indicate that the presence of naturally occurring antibodies against Alpha C and Rib is associated with reduced risk of neonatal GBS infection,<sup>9</sup> further strengthening the rationale for the development of vaccines targeting these proteins.

In the current study, Pawlowski et al. extensively characterize the immune response generated by a two-dose vaccine regimen implemented in the phase I trial described above.<sup>1</sup> Using serum specimens from study participants, they reveal

that the GBS-NN vaccine elicits a robust and persistent IgG and IgA response against both homotypic and heterotypic Alp-Ns. Importantly, they demonstrate that IgG1, the antibody subclass most efficiently transferred across the placenta to the fetus during the third trimester of pregnancy, dominates the generated IgG response. Vaccine-induced protection against heterotypic Alps was not as robust and appeared to be dependent on pre-existing GBS immunity. The authors acknowledge that this heterotypic immune response may not be sufficient to ensure broad protection from GBS and note the ongoing development and testing of an alternative vaccine that will contain additional Alp-Ns (Alp1 and Alp2/3).

In addition to examining antibody concentrations and specificity, the authors employ a variety of assays to characterize the functionality of GBS-NN-induced immunity. They use bacterial flow cytometry to demonstrate functional binding of serum antibodies to more than 30 clinically relevant GBS isolates. Although this analysis was limited to strains possessing the gene encoding the Rib protein, they included representative strains from four different GBS serotypes. They used opsonophagocytic killing assays to demonstrate that vaccine-induced IgG exhibits efficient killing of GBS strains with homotypic and heterotypic Alp-Ns. Finally, they show that heat-inactivated immune serum directly inhibits GBS invasion of human cervical epithelial cells *in vitro*. This reconfirms the specific contribution of Alps to GBS pathogenesis, providing



preliminary evidence that this vaccine could offer protection from intrauterine GBS infection (i.e., chorioamnionitis and stillbirth) in addition to its potential to reduce infant sepsis.

The work Pawlowski et al. present here begins to address a sizable challenge in the field of GBS vaccine development: that is, establishing serocorrelates of protection. Clinical trials using invasive neonatal disease as an endpoint to determine vaccine efficacy are unlikely to be feasible as they require prohibitively large sample sizes. Serocorrelates of protection offer indirect evidence of risk reduction and are therefore an alternative strategy to expedite vaccine development and licensure. Consistent and reproducible methodologies to define both threshold concentrations and *in vitro* functionality of vaccine-induced antibodies are necessary. Since the early 2000s, several investigators have examined the correlation between GBS disease risk reduction and CPS-specific antibody concentrations in maternal and infant serum.<sup>10</sup> Notably, fewer studies have included functional assessments of protection or examined the relationship between anti-protein antibodies and GBS disease risk reduction.<sup>10</sup> This study represents an important step forward and we look ahead with anticipation to forthcoming data from trials using

the next generation of Alp-N-based GBS vaccines.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

#### REFERENCES

- Pawlowski, A., Lannergard, J., Gonzalez-Miro, M., Cao, D., Larsson, S., Persson, J.J., Kitson, G., Darsley, M., Rom, A.L., Hedegaard, M., et al. (2022). A Group B Streptococcus Alpha-like protein subunit vaccine induces functionally active antibodies in humans targeting homotypic and heterotypic strains. *Cell Rep. Med.* 3, 100511-1–100511-13.
- Kobayashi, M., Schrag, S.J., Alderson, M.R., Madhi, S.A., Baker, C.J., Sobanjo-Ter Meulen, A., Kaslow, D.C., Smith, P.G., Moorthy, V.S., and Vekemans, J. (2019). WHO consultation on group B Streptococcus vaccine development: Report from a meeting held on 27-28 April 2016. *Vaccine* 37, 7307–7314.
- Baker, C.J., and Kasper, D.L. (1976). Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. *N. Engl. J. Med.* 294, 753–756.
- Croucher, N.J., Kagedan, L., Thompson, C.M., Parkhill, J., Bentley, S.D., Finkelstein, J.A., Lipsitch, M., and Hanage, W.P. (2015). Selective and genetic constraints on pneumococcal serotype switching. *PLoS Genet.* 11, e1005095.
- Fischer, P., Pawlowski, A., Cao, D., Bell, D., Kitson, G., Darsley, M., and Johansson-Lindbom, B. (2021). Safety and immunogenicity of a prototype recombinant alpha-like protein subunit vaccine (GBS-NN) against Group B Streptococcus in a randomised placebo-controlled double-blind phase 1 trial in healthy adult women. *Vaccine* 39, 4489–4499.
- Bolduc, G.R., Baron, M.J., Gravekamp, C., Lachenauer, C.S., and Madoff, L.C. (2002). The alpha C protein mediates internalization of group B Streptococcus within human cervical epithelial cells. *Cell. Microbiol.* 4, 751–758.
- Lachenauer, C.S., Creti, R., Michel, J.L., and Madoff, L.C. (2000). Mosaicism in the alpha-like protein genes of group B streptococci. *Proc. Natl. Acad. Sci. USA* 97, 9630–9635.
- McGee, L., Chochua, S., Li, Z., Mathis, S., Rivers, J., Metcalf, B., Ryan, A., Alden, N., Farley, M.M., Harrison, L.H., et al. (2021). Multi-state, Population-Based Distributions of Candidate Vaccine Targets, Clonal Complexes, and Resistance Features of Invasive Group B Streptococci Within the United States, 2015-2017. *Clin. Infect. Dis.* 72, 1004–1013.
- Larsson, C., Lindroth, M., Nordin, P., Ståhlhammar-Carlemalm, M., Lindahl, G., and Krantz, I. (2006). Association between low concentrations of antibodies to protein alpha and Rib and invasive neonatal group B streptococcal infection. *Arch. Dis. Child. Fetal Neonatal Ed.* 91, F403–F408.
- Le Doare, K., Kampmann, B., Vekemans, J., Heath, P.T., Goldblatt, D., Nahm, M.H., Baker, C., Edwards, M.S., Kwatra, G., Andrews, N., et al. (2019). Serocorrelates of protection against infant group B streptococcus disease. *Lancet Infect. Dis.* 19, e162–e171.