COMBINING NOVEL AND TRADITIONAL APPROACHES OF VACCINE DEVELOPMENT TO OVERCOME THE CHALLENGES OF FIRST-IN-HUMAN TRIAL FOR GROUP A STREPTOCOCCUS

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For nearly 30 years, from 1979 to 2006, clinical trials for a Group A Streptococcus (GAS) vaccines were banned in the U.S after a study suggested there may be an increased risk of acute rheumatic fever (ARF) in vaccine recipients. That study, conducted in 1968, used a crude M protein vaccine to immunize children – following administration, two children developed ARF (Massell BF, 1969). More than a decade since the FDA lifted the ban, safety concerns are still high and new vaccine candidates for Group A Strep face additional scrutiny entering first-in-human trials. This presentation focuses on a case-study for the development of a new vaccine for GAS diseases, specifically the various strategies used to overcome the safety concerns and maximize the chances for successful testing in clinical trials. VaxForm’s proprietary vaccine “VaxiStrep,” is the result of a combination of novel and traditional approaches in vaccine development. The novel approach entails using a novel recombinant fusion protein as the antigen. While most researchers have focused on combinations of M protein serotypes as the antigen(s) (up to a 26-valent vaccine), VaxForm chose to avoid the inevitable design complexity and stability issues that arise when formulating a multivalent vaccine. VaxiStrep’s antigen is a recombinant fusion protein of two streptococcal pyrogenic exotoxins (Spe), SpeA and SpeB, that are widely expressed in GAS strains. In addition to the selection of a safe antigen, VaxForm performed toxicity studies in vivo and in vitro (human PBMCs) to further demonstrate its safety. An ELISA was developed to show the lack of molecular mimicry between SpeAB and the protein responsible for ARF. SpeAB detoxification was shown by comparing polyclonal T-cell activation of SpeAB vs wild type toxins in human mononuclear cells (PBMCs).

Another important part of vaccine design and development is the adjuvant selection. VaxForm decided to explore aluminum-based adjuvants options. Aluminum adjuvants are the most commonly used adjuvants – there is extensive evidence that show their safety, they are approved by the FDA and used in licensed products. Adjuvant dose-response and adsorption studies for VaxiStrep were performed to narrow down the optimal dose and adsorption rate of the antigen. These types of studies followed the more traditional approach of vaccine development, giving the vaccine candidate a better chance for first-in-human approval and clinical trial success. Finally, another aspect that VaxForm selected as a priority was vaccine stabilization. Long term stability studies were performed that demonstrated a shelf-life of over two years when stored refrigerated. Animal studies comparing the potency of a two-year old vaccine lot to a fresh lot showed similar immune response. In addition, titers to the vaccine are long lasting as antibody titers remained at high levels 14 weeks after the booster injection. Conclusions: Bringing a new concept to clinical trials is always a long and challenging task. Learning and understanding the historical perspective when developing a new vaccine can be key in selecting the best approach. In this case, designing a GAS vaccine that would cause the least safety concern was prioritized due to the history of vaccine-induced ARF. Additionally, to avoid delays in clinical trials, robust efficacy and long-term stability of the vaccine was demonstrated in pre-clinical studies. We believe these choices will maximize the chances for VaxiStrep to reach first-in-human trial.