A structure-based approach to rationally design chimeric proteins for a broad-spectrum vaccine against Group B Streptococcus infections.

A. Nuccitelli[1], R. Cozzi[1], F. Necchi[2], M. Martinelli[1], J. Telford[1], D. Maione[1], G. Grandi[1] and D. Rinaudo[1].

[1]*Novartis Vaccines, via Fiorentina 1, Siena, Italy;* [2]*Novartis Vaccines Institute for Global Health, 53100 Siena, Via Fiorentina 1, Italy*

Abstract

Despite evident progresses in generating efficacious treatments against many infectious disease agents, bacterial pathogens remain the most important threat to health worldwide. For this reason, new vaccines and methods to improve their development are still needed. Structural vaccinology is a new approach that is increasingly being applied to vaccine design and it focuses on understanding the structural characteristics of immunodominant antigens to improve the rational presentation of the targets to protective immunity.
Streptococcus agalactiae (Group B Streptococcus [GBS]) is the most common cause of sepsis and meningitis in neonates. In the recent years, pilus-like structures have been discovered in GBS as important virulence factors as well as promising vaccine candidates. Bioinformatics analysis revealed three independent loci (named PI-1, PI-2a and PI-2b) that encode structurally distinct pilus types, each of which contains two surface-exposed antigens capable of eliciting protective immunity in mice. The main structural subunit, known as backbone protein of pilus type 2a (BP-2a), showed the highest degree of gene variability among the pilin antigens and was able to significantly mediate opsonophagocitic activity and confer protection in mice only against strains expressing the homologous allele. In order to define the immunodominant and protective epitopes of the allelic variants of BP-2a we first performed a structural characterization of the protein by comparative homology modeling taking advantages of the availability of the 3D structure of a homologous pilin protein. On the basis of structural information we generated protein fragments corresponding to the four IgG-like fold domains identified in the structure. In vitro and in vivo studies showed that the D3 domain appeared to be the most important for the protective immunity of the main four allelic variants analyzed. Finally, we showed that chimeric proteins composed by the single immunodominant domains harboring to the different variant of BP-2a can be generated for a broadly protective vaccine against GBS infection.