

Conformational modeling of *Streptococcus pneumoniae* serogroup 23 capsular polysaccharides provides insight into antibody binding and cross-reactivity

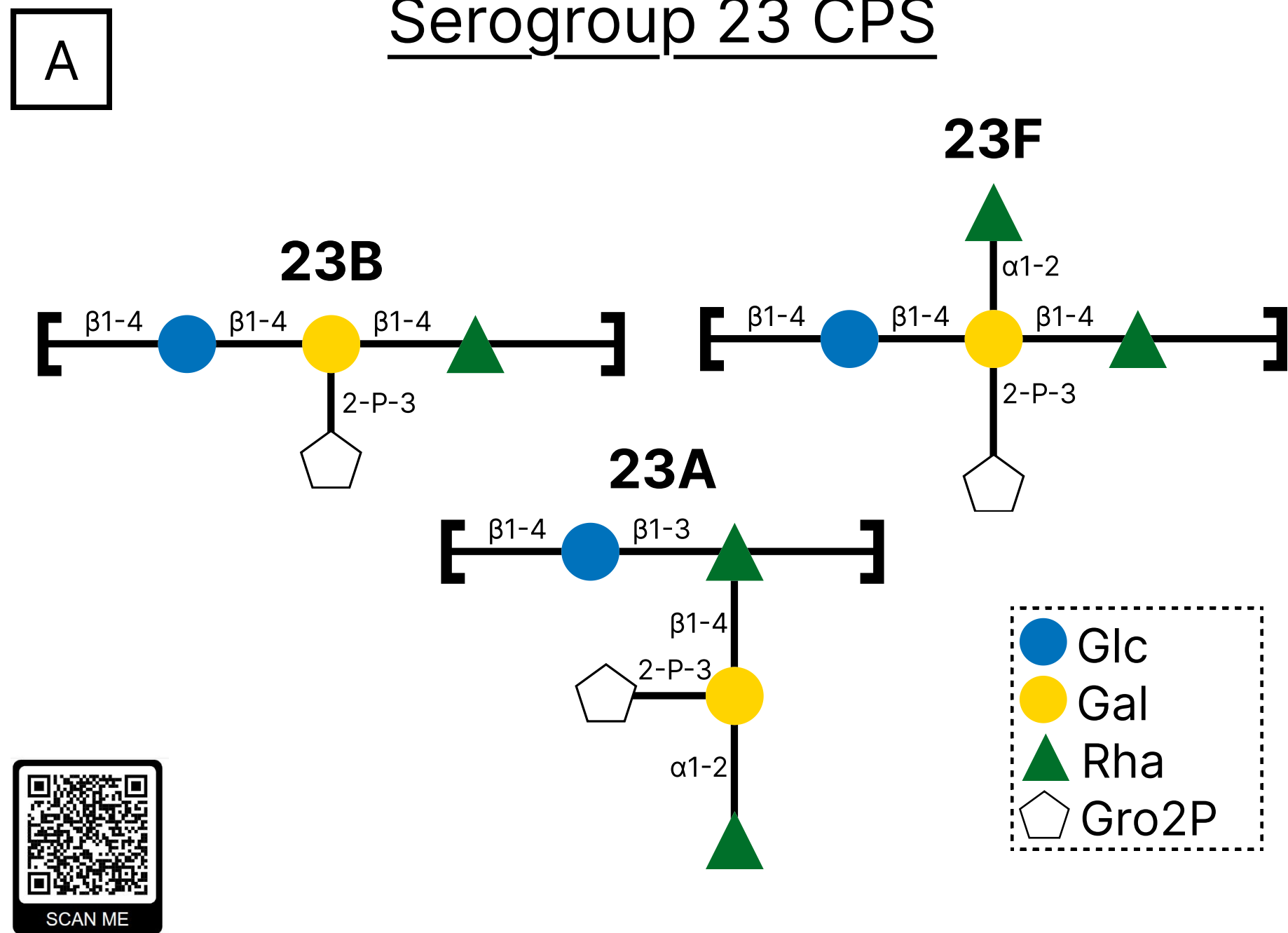
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Introduction

Serogroup 23 CPS



Pneumococcal conjugate vaccines contain and protect against *streptococcus pneumoniae* serotype 23F but show no cross-protection against serotypes 23A and 23B, despite similarly structured capsular polysaccharide (CPS) antigens [1]. We use molecular dynamics simulations to investigate conformational mechanisms responsible for the lack of cross protection.

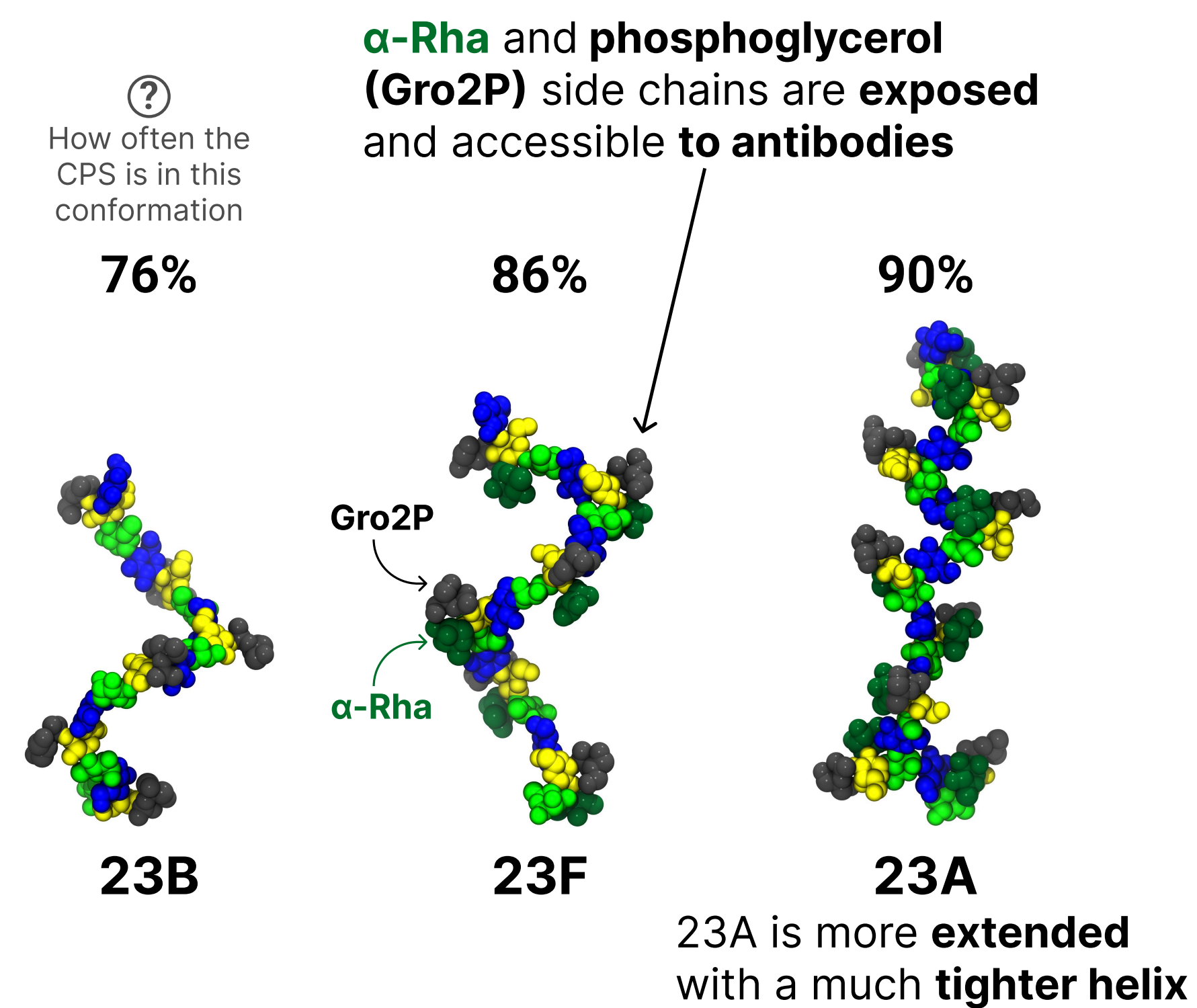
Aims and Methods

Molecular Dynamics simulations (1000ns) - using CHARMM force field and NAMD software to compare the conformation and dynamics of serotype **23F**, **23A** and **23B** CPSs (Fig. A). We aim to provide an explanation for the lack of cross-protection conveyed from serotype 23F antibodies to serotypes 23A and 23B.

Results

Backbone Conformation

All three CPS chains adopt rigid **helices**



This **does not explain** the **lack of cross-protection**. The **α -Rha** and **Gro2P** epitopes require closer examination

Epitope Analysis

① A **23F** antibody (Ab) tightly binds the **immunodominant α-Rha** epitope with **Gro2P** in the **orange** conformation



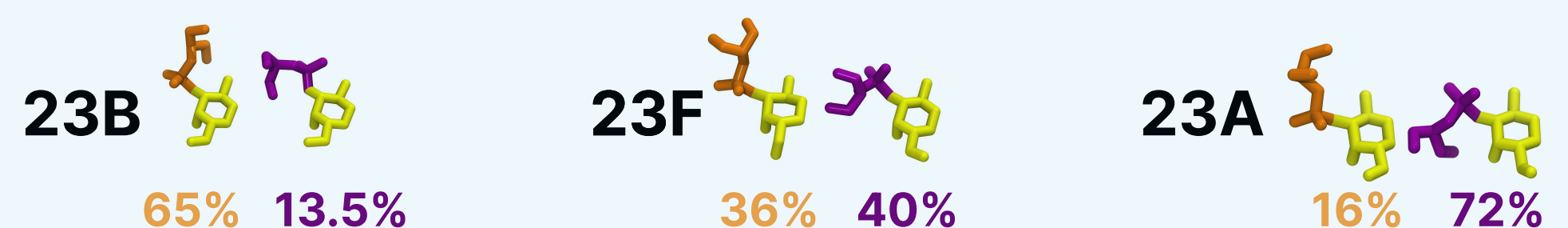
② But the α -Rha epitope is ...

23B absent in **23B** ... resulting in NO cross-protection

23A shielded from Ab's in **23A**

The diagram illustrates the structural differences between two bacterial strains, 23B and 23A, specifically regarding the accessibility of the α -Rha epitope. On the left, strain 23B is shown with a yellow α -Rha epitope that is labeled 'absent in 23B'. Below it, text states '... resulting in NO cross-protection'. On the right, strain 23A is shown with a yellow α -Rha epitope that is labeled 'shielded from Ab's in 23A'. Above it, text says 'But the α -Rha epitope is ...'. The structures are represented by 3D models with various colored components (yellow, orange, purple, green, blue) and labels indicating the specific epitopes and their accessibility to antibodies.

③ All three serotypes share common **phosphoglycerol** epitopes resulting in low levels of cross-reactivity



Conclusions

The lack of cross-protection conveyed from serotype 23F to serotypes 23A and 23B may be due to **differing presentations of the α -Rha epitope** (Fig. C). An **immunodominant epitope in 23F**, (Fig. C1) it is **absent in 23B** and **shielded by neighboring residues in 23A** (Fig. C2). Observed low levels of **cross-reactivity** are likely **due to common phosphoglycerol epitopes**, present in all three serotypes (Fig. C3). This work supports the inclusion of both 23A and 23B in higher valency PCVs in order to provide protection against serogroup 23 disease.

References and Acknowledgments

[1] Ganaie, et al., 2025. Update on the evolving landscape of pneumococcal capsule types: new discoveries and way forward. Clinical Microbiology Reviews.

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