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# A soluble auto-assembling heptameric *Staphylococcus aureus* alpha-hemolysin as a vaccine candidate

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Alpha-hemolysin (Hla) is a major cytotoxic agent released by *Staphylococcus aureus* and the first identified member of the pore forming beta-barrel toxin family. The *S. aureus* Hla protein monomer assembles into heptameric pores on eukaryotic cellular membrane during bacterial infection causing lysis, apoptosis and junction disruption. The proposed pore forming mechanism consists in a three steps model according to which the Hla promoter binds the membrane, forms a heptameric pre-pore structure and finally rearranges itself into the complete pore structure. Herein we present the design and the three dimensional structure obtained by single-particle reconstruction of a newly engineered *S. aureus* alpha-toxin Hla PSGS, a recombinant protein devoid of the portion responsible for toxic activity. The structure, determined to medium resolution, maintains the homo-oligomeric heptameric assembly while missing the solvent-filled channel present in the Hlawt. This protein demonstrates conclusively the three step mechanism as it retains the wild type overall conformation and polymerization capabilities, forming complete heptameric pre-pore structures but lacks the hemolytic competency of the complete pore structure. Furthermore we demonstrate that the portion responsible for toxic activity is not essential for membrane binding or for the formation of an oligomeric pre-pore intermediate. The Hla PSGS heptameric structure provides insight into the principles of membrane interaction and transport activity of beta-barrel pore-forming toxins. Finally, the absence of cytotoxicity makes this molecule a safe vaccine candidate.

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