Table S1. Non-M protein vaccine candidates.

Non-M protein-based Vaccine Candidate	Vaccine candidates	Antigens	Adjuvants/ Delivery System	Stage of Development	Comments	Ref.
GAS Carbohydrate (GAC)	GAC-TT	GAC isolated from strain D58X, an M protein–negative mutant	Alum	Animal study: mice, NAS, SC	Immunized mice were protected against systemic or nasal challenge with GAS and no cross-reactivity was observed.	[1]
	Oligosaccharide	Synthetic oligosaccharides	Alum	Animal study: mice, IP; rabbit, SC	The synthetic conjugate vaccine candidates have similar efficiency conjugates of natural GAC.	[2]
Surface-bound C5a Peptidase (SCPA)	SCPA49	Recombinant SCPA49 mutated protein	-	Animal study: mice, NAS	SCPA49 induced antigen-specific salivary secretory IgA and serum IgG.	[3]
	SCPAw alone or SCPAw-CTX	C5a peptidase loss-of-function mutants SCPAw	Cholera toxin (CT)	Animal study: mice, NAS	Intranasal immunization with SCPA induced antibodies which are able to clear GAS from the oral-nasal mucosa and lung.	[4,5]
Fibronectin-binding Protein	1) LCP-J14-FNBR-B 2) LCP-P25-FNBR-BT 3) LCP-P25-J14	J14 and/or FNBR-B or FNBR-BT	LCP & BPPCysMPEG	Animal study: mice, NAS	LCP-1 stimulated strong J14-specific cellular immune responses.	[6,7]
	1) LCP-J8-FNBR 2) LCP-J8 3) LCP-FNBR	J8 and/or FNBR which contain B and T-cell epitope	LCP & MALP-2	Animal study: mice, NAS	Better protective immunity by a dual antigen vaccine candidate against GAS	[8]

	SfbI-CTB	SfbI protein	CTB	Animal study: mice, NAS; & mouse skin infection model, SC	Anti-SfbI immunity: Effective against pharyngeal colonization. Inadequate for protection against systemic infections after skin colonization.	[9]
	FBP54-CT	FBP54	CT	Animal study: mice, SC, NAS or OR	High salivary levels of IgA antibodies were detected after oral and nasal immunizations. Mice subcutaneously or orally immunized with FBP54 survived significantly longer following GAS challenge	[10]
	FbaA-FA	FbaA	Freund's adjuvant (FA)	Animal study: mice, SC	FbaA has similar ability to M protein in inducing protective immunity against GAS challenge in mice	[11]
Serum Opacity Factor (SOF)	1) SOF-SfbI-CTB 2) SOF	SOF, SfbI	CTB	Animal study: mice, NAS	Immunization with SOF-SfbI stimulated strong systemic and mucosal immune responses against both antigens Vaccinated with SOF alone were not protected against a mucosal challenge	[12]
Streptococcal Pyrogenic Exotoxins (Spe)	SpeB (extracellular cysteine protease)	A highly conserved extracellular cysteine protease SpeB	-	Animal study: mice, SC, IP	The SpeB vaccine induced non type-specific immunity to challenge with heterologous GAS.	[13]

	SpeC	Y15A/N38D or Y15A/H35A/N38D SpeC mutant	-	Animal study: Rabbit, SC, IP	These mutants were highly immunogenic but nonmitogenic for rabbit splenocytes and human PBMCs These mutants may be useful as toxoid vaccine candidates	[14]
IL-8 Protease (SpyCEP)	J8-DT plus S2-DT combination vaccine	J8 & SpyCEP epitopes (S1-S6)	Alum	Animal study: mice, SC	The combination induces complete protection against hypervirulent GAS mutant CovR/S	[15]
Streptococcal Secreted Esterase (Sse)	Sse	Recombinant protein Sse	Alum	Animal study: mice, SC; mouse skin infection model, SC	Immunization with Sse induced protection against subcutaneous infection by more than one GAS serotype. Anti-Sse antibodies are not opsonic Anti-Sse antibodies cannot control systemic GAS infection.	[16]
Protein G-related Alpha2-macroglobulin Binding Protein (GRAB) & Metal Transporter of Streptococcus (MtsA)	1) EKL24-KLH 2) EIN19-KLH	EKL24, EIN19	Keyhole lymphocyanin (KLH)	Animal study: mice, SC;	Conjugates did not induce opsonic immune responses.	[17]
Superoxide Dismutase (SOD)	SodA	Recombinant SodA	-	Animal study: mice, SC mouse skin infection model, SC	Immunised mice produce high antibody titers that can opsonize GAS but did not offer protection during challenge.	[18]

Streptococal Inhibitor of Complement (SIC)	-	SIC	-	Identified only	SIC interferes with coagulation and fibrinolysis and thereby enhances bacterial survival	[19]
Extracellular Streptodornase D (SdaD)	-	SdaD and its homologue Sda1	-	Identified only	A natural mutation which led to longer Sda1 and SdaD was proved to confer increased activity on the protein.	[20,21]
Streptolysin O (SLO)	Combination vaccine SLO-SpyCEP-SCPA-ADI-TF	SLO; SpyCEP; SCPA; Arginine deiminase (ADI); Trigger factor (TF)	Alum	Animal Study: mice, IM	This combination vaccine induced high-titer antigen-specific antibody responses with bactericidal activity	[22]

IM: intramuscular; NAS: intranasal; SC: subcutaneous; IP: intraperitoneal; OR: oral

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