Possibili strategie preventive?

LE INFEZIONI INVASIVE DA STREPTOCOCCUS PYOGENES: UPDATE 2024

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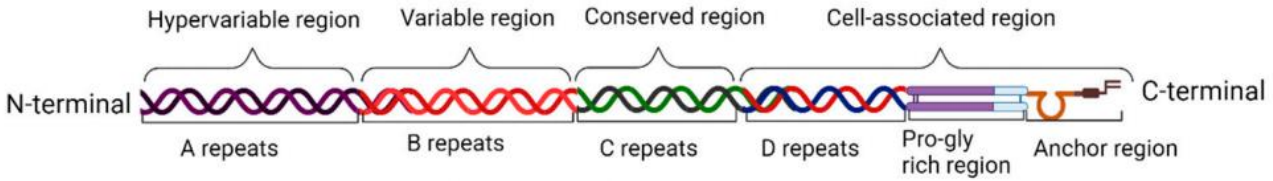
Group A Streptoccus (GAS): M serotypes and associated diseases

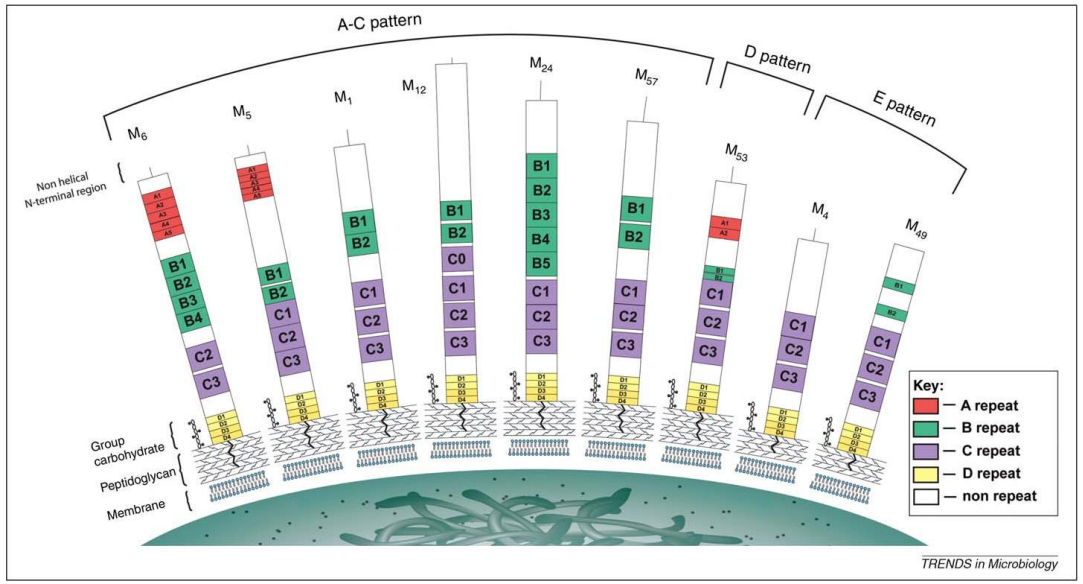
>700 million cases /y of superficial diseases such as pharyngitis and impetigo

>600,000 cases/ y of serious invasive infection

>400,000 cases /y of immune sequelae such as acute rheumatic fever and acute post-streptococcal glomerulonephritis

M protein (*emm* gene)





Clinical Diseases	GAS Serotypes of M Proteins
Pharyngitis	M1, M3, M5, M6, M12, M14, M17, M19, M24
Scarlet fever	M4, M28, M1, M3
Impetigo	M33, M41, M42, M52, M53, M70
Meningitis	M1, M12
Streptococcal toxic shock syndrome	M1, M3
Acute post-streptococcal glomerulonephritis	M1, M2, M12, M55, M49, M60, M73
Acute rheumatic fever	M1, M3, M5, M6, M14, M18, M19, M24, and M29
Rheumatic heart disease	Unknown

Issues in the clinical development of a «universal» GAS vaccine

1) complexity of the epidemiology of GAS infections and concerns about potential efficacy and vaccine coverage
2) perceptions of the risk of autoimmune complications triggered by the vaccines.
3) inadequate animal models of infection
4) absence of defined human immune correlates of protection which could support the down-selection of candidate antigens
5) the uncertainty about a market for a GAS vaccine in high-income countries
6) lack of commercial interest and reluctance to invest

Correlates of protection (CoP) in GAS infection and elicitation of adaptive immunity

- Humoral response and circulating antibodies are the main correlates of protection, with different functional activities
  - promote opsonophagocytosis (often M-type specific)
  - neutralization of toxin or virulence factor neutralization
  - blocking of bacterial adhesion by B cell-derived antibodies and

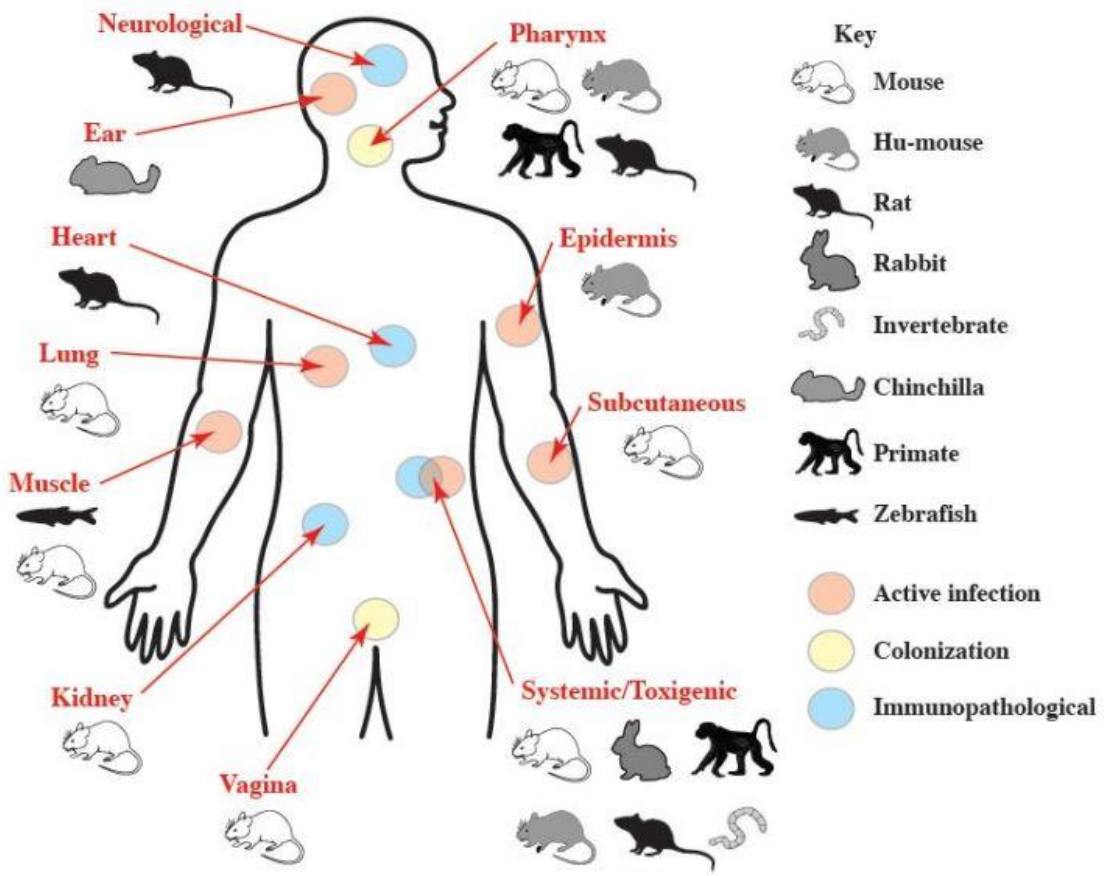
    phagocytes, supported by T cells, cytokines, chemokines, and

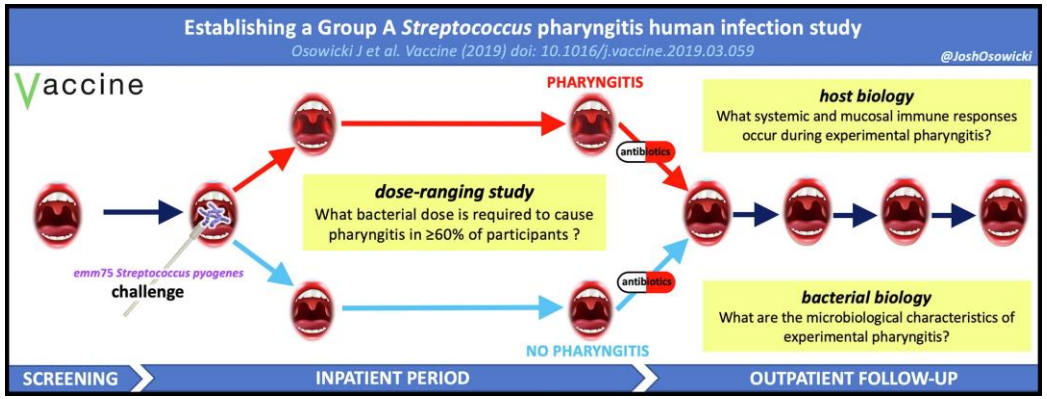
    components of innate immunity

- Cell-mediated immunity contributes to long term

Improved animal models and human experimental infections to accelerate vaccine development

Major established models for studying GAS vaccine candidates able to represent specific aspect of human GAS





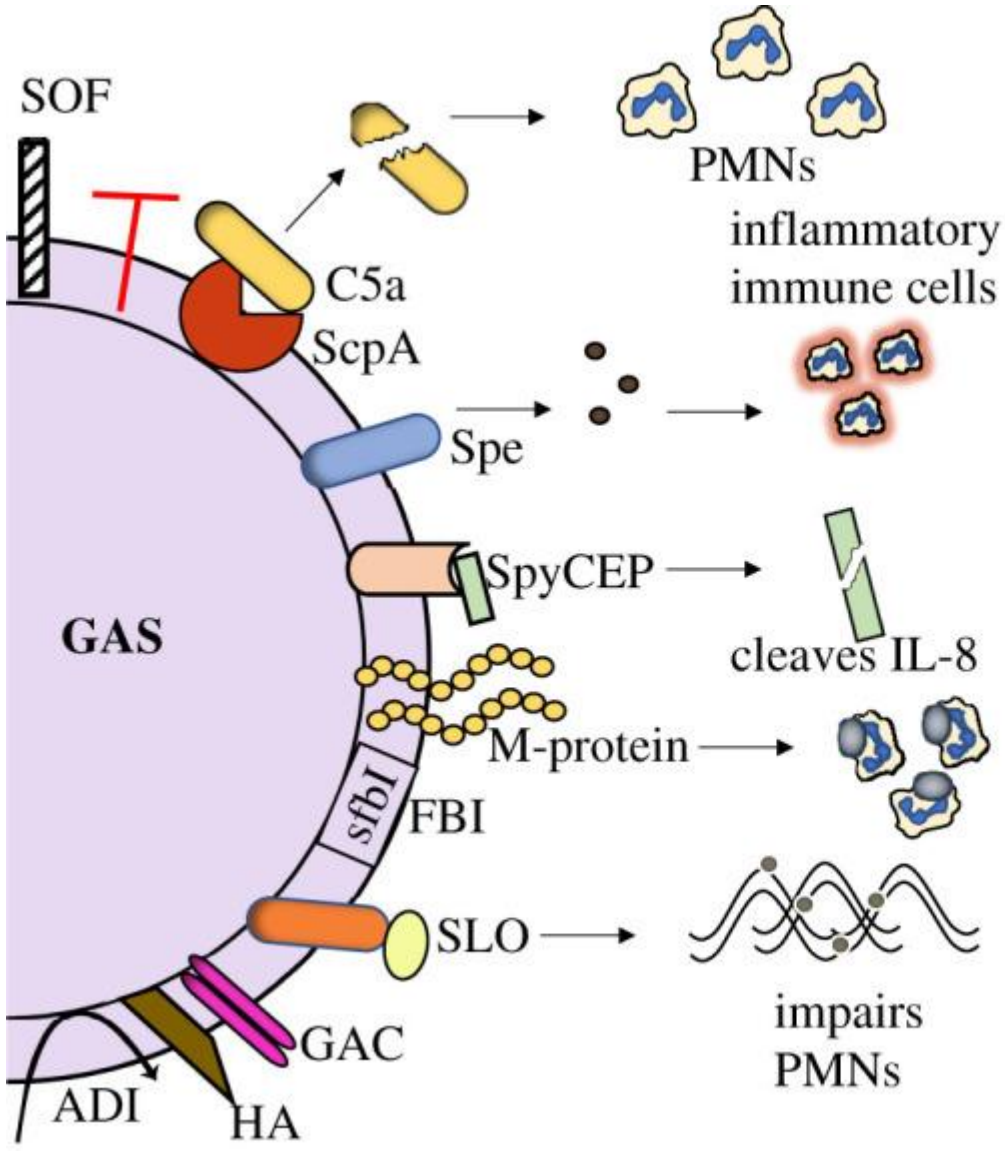
Controlled Human Infection for Vaccination Against *S pyogenes* (CHIVAS-M75) study aimed to identify a dose of *emm*75 *S. pyogenes* that causes acute pharyngitis in at least 60% of volunteers

http://clinicaltrials.gov/show/NCT03361163

Joshua Osowicki, et al. , 2019, Vaccine, 37(26): 3485-3494

Watson ME Jret al. 2016 In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes : Basic Biology to Clinical Manifestations.

Major GAS virulence antigens are also vaccine candidates



inhibition of chemotactic recruitment

induce inflammation

chemokine degradation

phagocytosis inhibition

modulates PMN function

M protein,
ScpA, streptococcal C5a peptidase
Spe, Streptococcal pyrogenic exotoxin
SpyCEP, Streptococcal pyogenes cell envelope protease
FBI, fibronectin-binding protein
SfbI, , Streptococcal pyogenes fibronectin binding protein
SLO; Streptolysin O,
GroupA Carbohydrate
ADI, Arginine deaminase

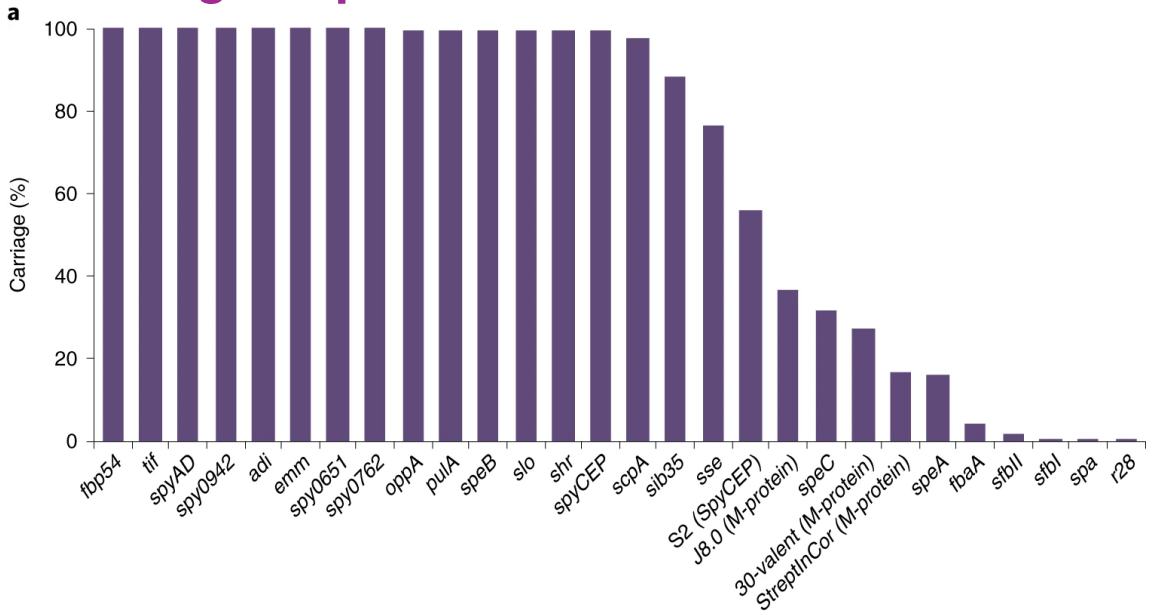
HA, hyaluronic acid
SOF, Serum opacity factor
NET, Neutrophils Extracellular Traps

Atlas of group A streptococcal vaccine candidates

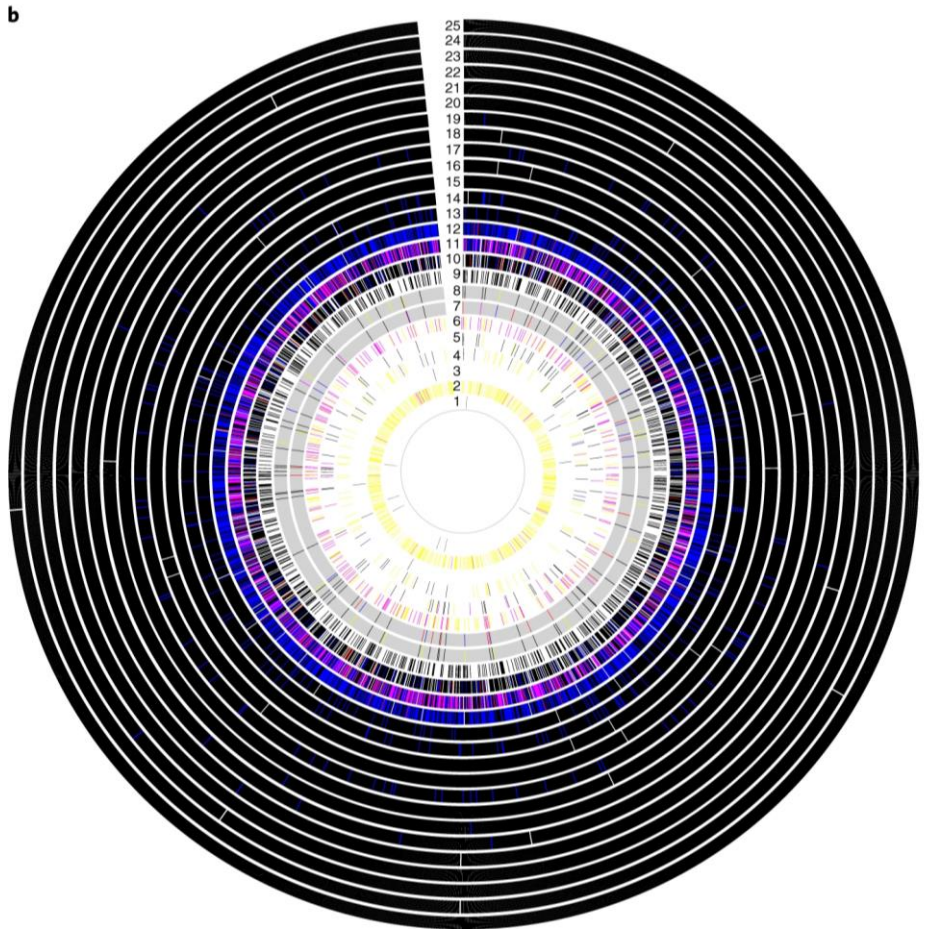
Gene carriage and amino acid variation within 25 protein antigens for each of the 2,083 GAS genomes

2,083 genome assemblies,
150 *emm* types (347 *emm* subtypes),
39 known M protein clusters and
484 multilocus sequence types **(**MLSTs)

13 antigens present in 99% of isolates



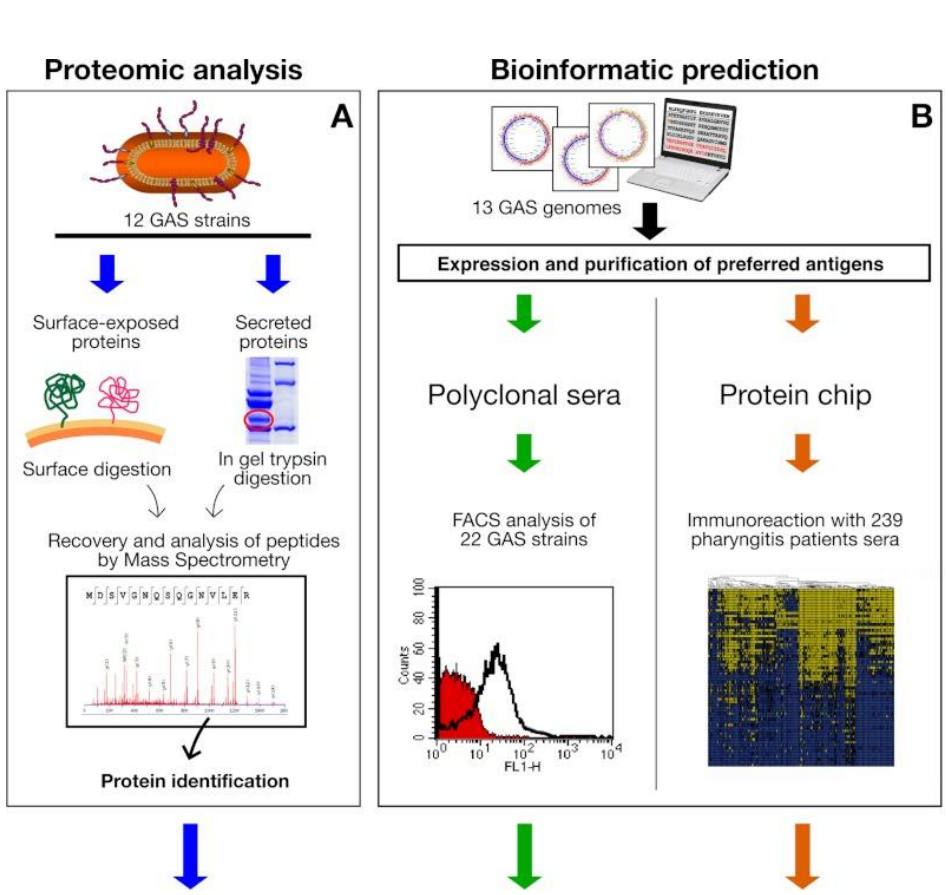
18 antigens with high sequence conservation (>98%)

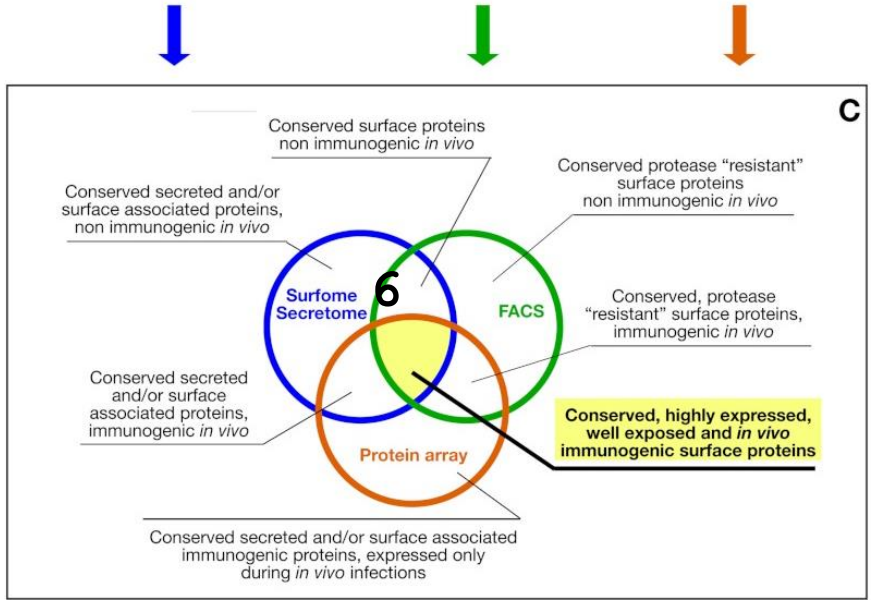


1) R28
2) Sfb1
3) Spa;
4) SfbII
5) FbaA
6) SpeA
7) M1 (whole protein)
(8) M1 (180bp N-terminal)
9) SpeC
10) Sse
11) Sib35
12) ScpA
13) SpyCEP
14) PulA
15) SLO
16) Shr
17) OppA
18) SpeB
19) Fbp54
20) SpyAD
21) Spy0651
22) Spy0762
23) Spy0942
24) ADI
25) TF

Davies, M.R., *et al.* 2019, *Nat Genet* **51**, 1035–1043

Multi-Omics strategies to identify a broadly protective GAS vaccine





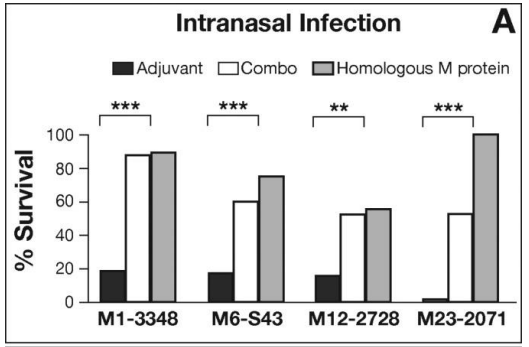
Expression and immunogenicity of the identified protective GAS antigens

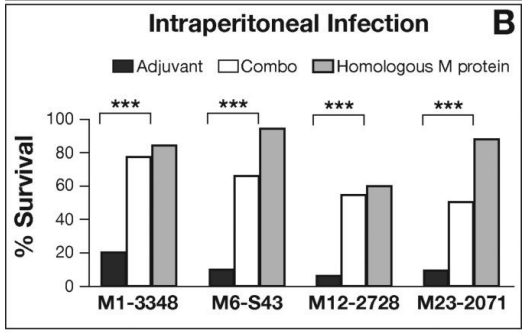
SPy	PSORTb	Product	Proteome[a]	Protein array[b]	FACS[c]
SPy0167	extracellular	streptolysin O precursor	3/6	63	47
SPy0269	cell wall	putative surface exclusion protein	4/6	89	84
SPy0416	cell wall	putative cell envelope proteinase	4/6	62	61
SPy0019	extracellular	putative secreted protein	2/6	49	59
SPy1361	lipoprotein	putative internalin A precursor	1/6	80	0
SPy2010	cell wall	C5a peptidase precursor	6/6	67	90

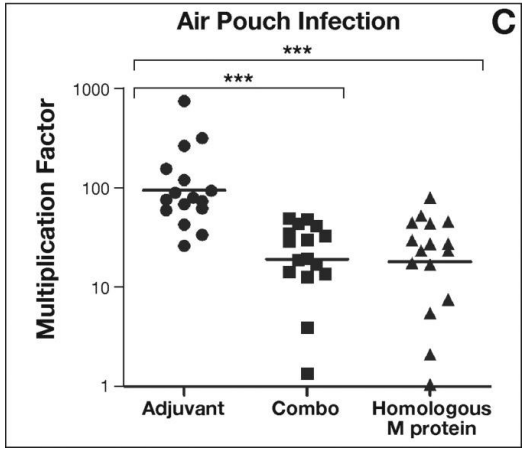
[a] Number of positive strains on the total number of strains analyzed.

[b] Percent of sera which positively recognize the antigen.

[c] Percent of positive strains.

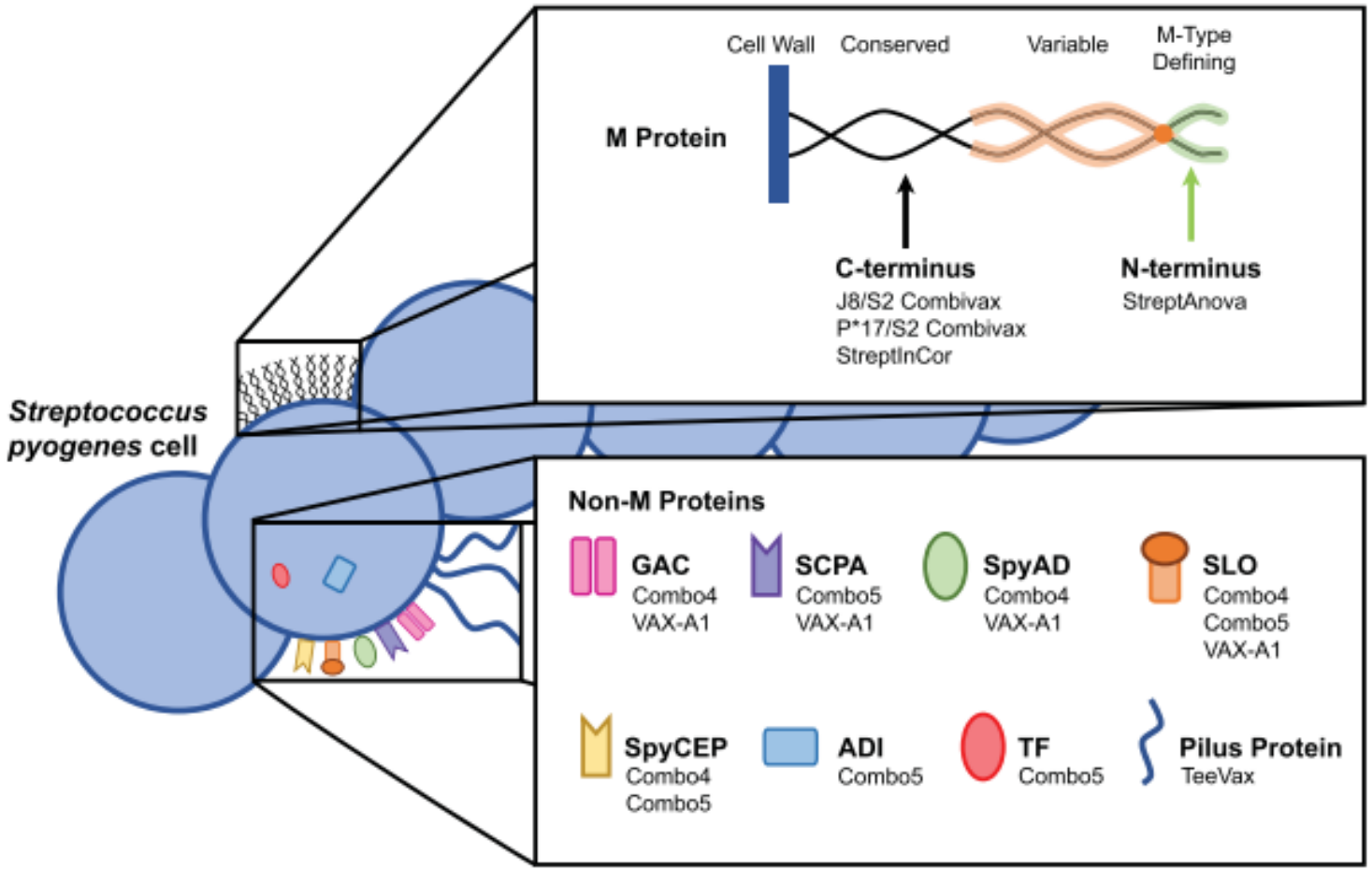






Bensi G, *et al.* Mol Cell Proteomics. 2012 11:M111.015693.

GAS antigens and corresponding vaccine candidates



Walkinshaw DR, *et al.* NPJ Vaccines. 2023 8:16.

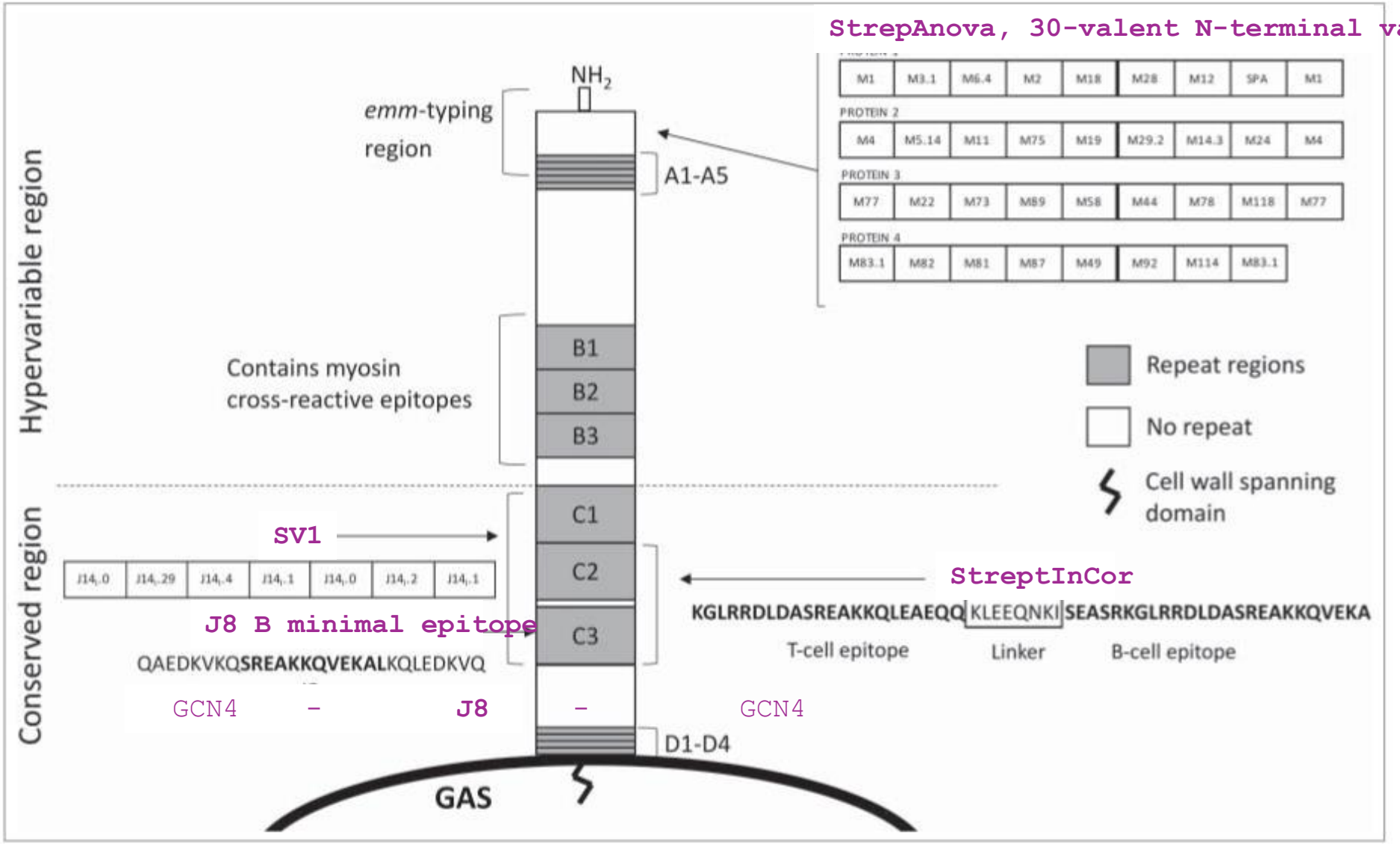
Most advanced M-based vaccines development programs

CANDIDATE	DEVELOPER	CURRENT DEVELOPMENT PHASE	ANTIGENS	ADJUVANT	THEORETICAL GLOBAL COVERAGE[a]
StreptAnova (30-valent)	University of Tennessee/ Vaxent	Phase 1a Completed 2020	Four protein subunits comprising the N-terminal regions of M proteins from 30 *S. pyogenes* serotypes	Aluminium hydroxide	48%[19] Actual coverage may be higher (e.g. 80% in Africa) due to cross-opsonization[21]
J8/S2 combivax	Griffith University/ University of Alberta	Phase 1a *Ongoing*	J8 peptide from the M protein C-terminus combined with a 20-mer B-cell epitope (K4S2) from SpyCEP	Aluminium hydroxide	37%[19] Actual coverage may be ~98% due to cross-reactivity of J8 alleles[25]
P*17/S2 combivax	Griffith University/ University of Alberta	Phase 1a *Ongoing*	P*17 peptide from the M protein C-terminus combined with a 20-mer B-cell epitope (K4S2) from SpyCEP	Aluminium hydroxide	37%[19] Actual coverage may be ~98% due to cross-reactivity of J8 alleles[25]
StreptInCor	University of São Paulo	Preclinical	55-amino acid sequence peptide from the M5 protein conserved regions (C2 and C3)	Aluminium hydroxide	23%[19] An earlier study showed 71% identity between StreptInCor and several emm types[30]

SpyCEP streptococcal interleukin-8 proteas.
[a]Based on antigen presence across sample of 2,083 *S. pyogenes* genomes[19].

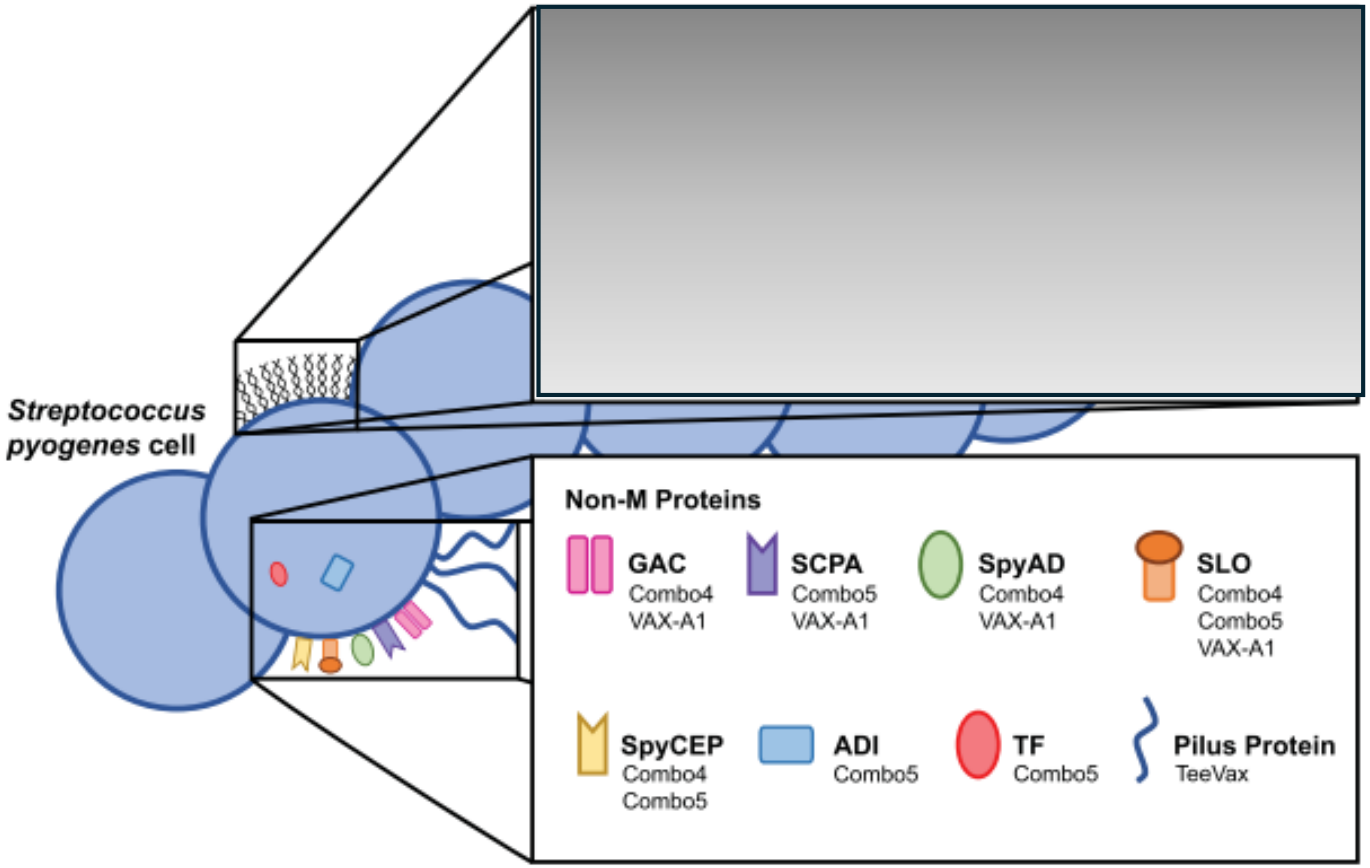
Walkinshaw DR, *et al.* NPJ Vaccines. 2023 8:16.

Molecular components of M-protein based vaccines



Adapted from Ozberk V, Pandey M, Good MF. Hum Vaccin Immunother. 2018;14:2034-2052.

GAS antigens and corresponding vaccine candidates



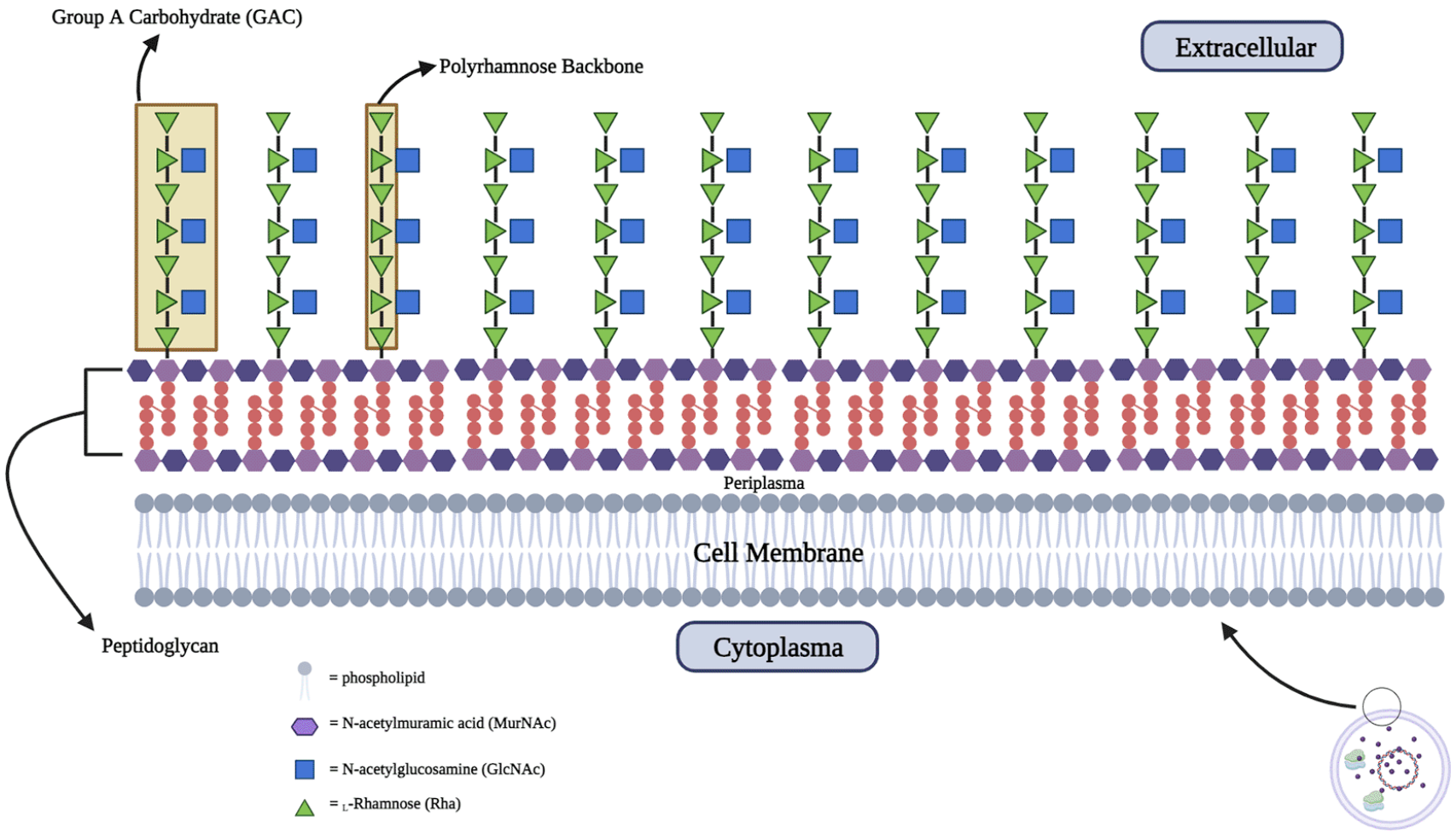
Most advanced NON-M-protein based vaccine development programs

CANDIDATE	DEVELOPER	CURRENT DEVELOPMENT PHASE	ANTIGENS	ADJUVANT	THEORETICAL GLOBAL COVERAGE[a]	KEY REFERENCES
Combo4	GlaxoSmithKline/ GVGH	Preclinical	SpyCEP, SLO and SpyAD recombinant proteins and native GAC conjugated to CRM_{197} carrier protein	Aluminium hydroxide	>99%[19]	41,43,44
VAX-A1	Vaxcyte	Preclinical	SLO and SCPA recombinant proteins and modified GAC (Polyrhamnose) conjugated to SpyAD disease-specific carrier protein	Aluminium hydroxide	>99%[19]	46
Combo5	University of Queensland	Preclinical	Trigger factor (TF), inactivated versions of arginine deiminase (ADI), SLO, SpyCEP and SCPA	Squalene-in-water emulsion containing cholesterol (SMQ)	>99%[19]	49,50,56
TeeVax	University of Auckland	Preclinical	Multiple T-antigen domains from the pilus of the majority of S. pyogenes strains	Aluminium hydroxide	>95%[36]	36,51

SpyCEP streptococcal interleukin-8 protease, *SLO* streptolysin O, *SpyAD* putative surface exclusion protein, Spy0269, *GAC* Group A Carbohydrate, *SCPA* streptococcal C5a peptidase.
[a]Based on antigen presence across sample of 2,083 *S. pyogenes* genomes[19].

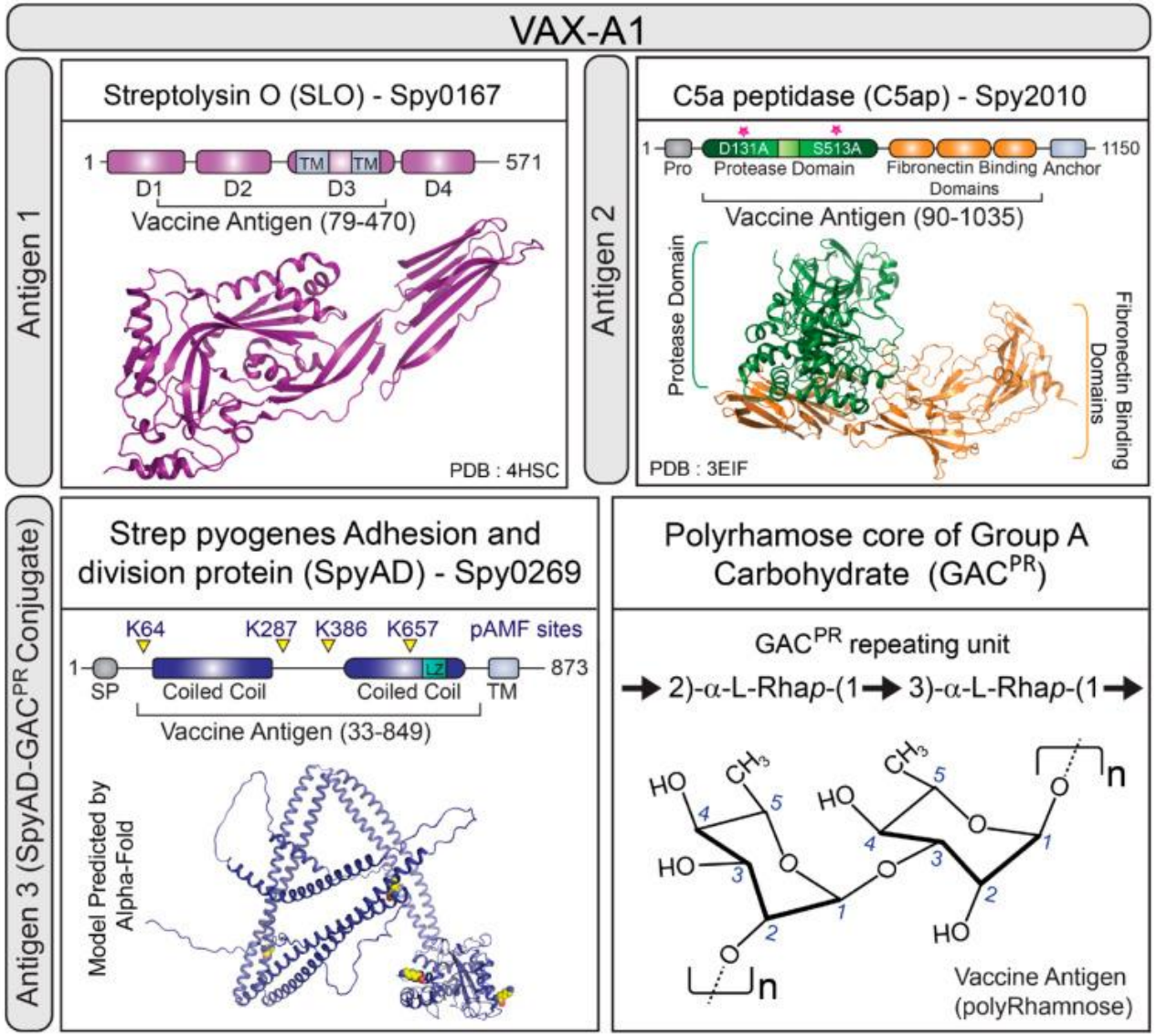
Walkinshaw DR, *et al.* NPJ Vaccines. 2023 8:16.

Molecular components of NON-M protein vaccines: the Group A Carbohydrate



Ambari AM, Desandri DR, Dwiputra B et al. F1000Research 2024, 13:132

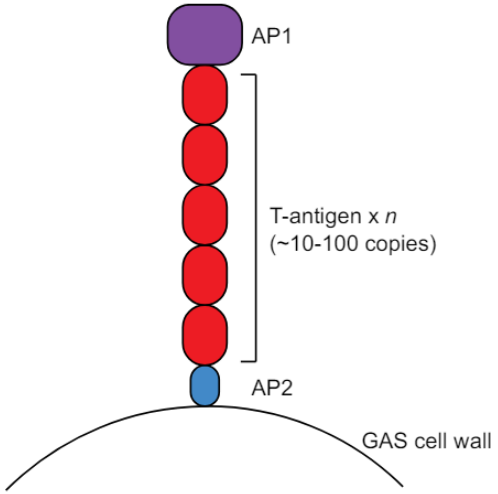
Molecular multi-components of NON-M protein vaccines: VAX-A1

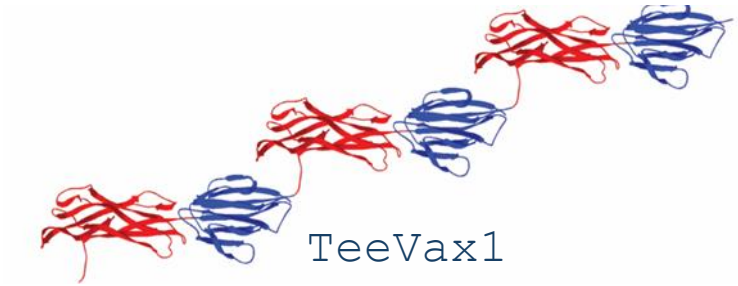


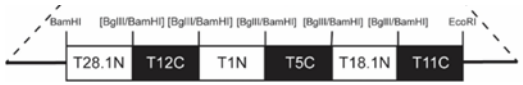
Molecular multivalent components of NON-M protein vaccines:

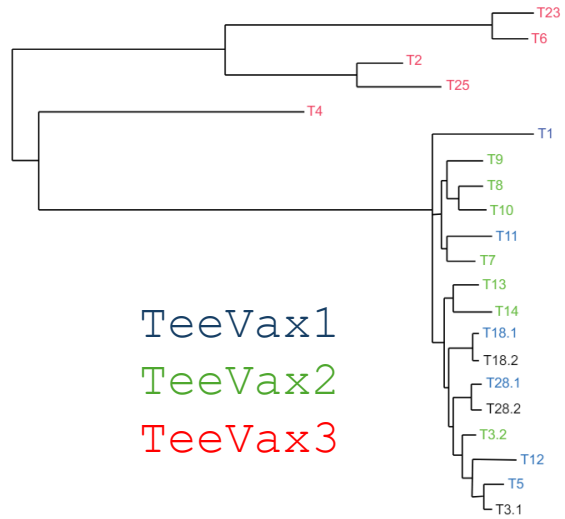
TeeVax:

multiple T antigens domains from the pilus of different GAS strains









N-terminal (red) and C-terminal (blue) domain fusions of six T-antigens.

Loh, J.M.S., et al. Sci Rep 11, 4353 (2021)

Moving forwards to the development of GAS vaccine:

Two key initiatives established in 2019 to ensure the development of safe, effective, and affordable GAS vaccines, and to facilitate connectivity

- The Strep A Vaccine Global Consortium (SAVAC, https://savac.ivi.int/)
- The Australian Strep A Vaccine Initiative (ASAVI, https:// www.asavi.org.au/)

Funding bodies and charities support researchers in developing and validating vaccine candidates in animal models and phase I trial

- CARB-X, Open Philanthropy , Leducq Foundation and Wellcome

  (CARB-X funding support has enabled Vaxcyte and GSK Vaccines Institute for Global Health, to pursue combination vaccine approaches that target GAS specific proteins in conjunction with the GAC)

Conclusions

- M protein- based GAS vaccines are currently in clinical development, but vaccines so far available provide limited cross-protection against different serotypes
- Non M protein-based vaccines are in preclinical development, but are the most promising ones, being more conserved across serotypes and likely to provide broad immunity
- The most promising GAS vaccines are antigen combinations, including multiple virulence protein factors and core group A carbohydrate
- The synergic effort of no-profit funding bodies and charities and pharma companies is accelerating the development of GAS vaccines

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