PolySSL Vaccine for *S. aureus*

A vaccine using Staphylococcal Superantigen-Like proteins to provide protection against staph infections

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IDEAS TO LIFE RANGAHAUA KIA WHAI HUA

UNIVERSITY OF AUCKLAND
Waipapa Taumata Rau
NEW ZEALAND

Executive Summary

We are developing a fusion protein vaccine which targets Super-Antigen-Like proteins (SSLs), primordial proteins that play a key role in the immune-evasion strategies employed by virtually all strains of *S. aureus*. Our vaccine consists of 3 inactive SSLs and is referred to as **PolySSL**.

The PolySSL protein is readily manufactured as a stable recombinant protein in *E. coli*.

Injected into mice as a prime and two boost regimen, the PolySSL protein stimulates high-titre antibodies against 3 essential staphylococcal virulence factors SSL3, SSL7 and SSL11 and protects mice from challenge with a hypervirulent mouse adapted staphylococcal strain. Immunised mice show a 4-6 log reduction in staphylococcal colony forming units in kidney and liver.

We have filed a patent based on the novel findings that the three SSLs provide superior protection when linked as a fusion protein, and, that the order of linking is important for enhancing protection.

The clinical application is protection of patients at high risk of developing staphylococcal infection (e.g. post-surgical infection, age-care facilities).

A vaccine based on the PolySSL protein would likely consist of 5ug each of 2 allelic variants of PolySSL representing the most common disease-causing strains, with the likely ROA being intramuscular as a prime and two boost strategy.

We are currently working to identify the adjuvant(s) which will provide the strongest level of protection and determining the duration of protection.

Introduction and Overview

Antibiotic resistant *Staphylococcus aureus* is a WHO priority pathogen. Methicillin resistant *S. aureus* (MRSA) is wide-spread and there is emerging resistance to vancomycin, a drug of last resort.

S. aureus infects skin, bone, blood, muscle and soft-tissue causing a wide varitey of illness, including mastitis, bacterima, endocarditis, Toxic Shock, pneumonia, cellulitis, and bone infections.

S. aureus is a leading cause of hospital-acquired infections and increasing antibiotic resistance is driving the need for new strategies for combating this pathogen.

To date all vaccines targeting *S. aureus* have failed in the clinic.

We are developing a novel polyprotein vaccine constructed from 3 secreted virulance factors common to all strains of *S. aureus*.

Mice immunised with the PolySSL protein display a 4 – 6 log reduction in bacterial burden after challenge with *S. aureus*.

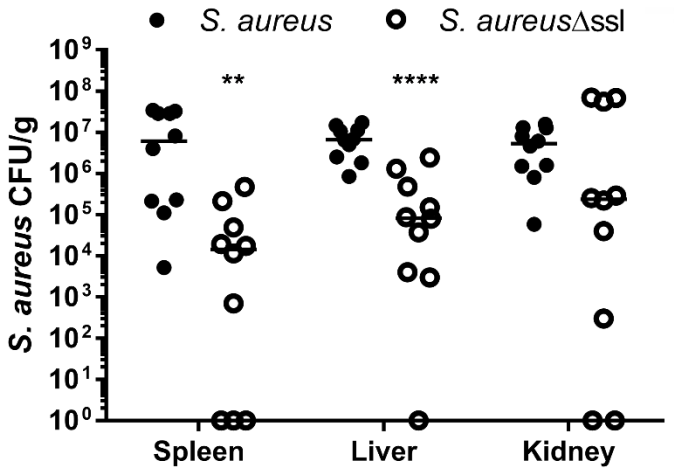
The SSLs are conserved virulence factors expressed by all strains of *S. aureus*. They are important for bacterial survival in mice and humans

SSL isogenic knockout reduces survival of JSNZ, a hypervirulent strain in mice (left fig).

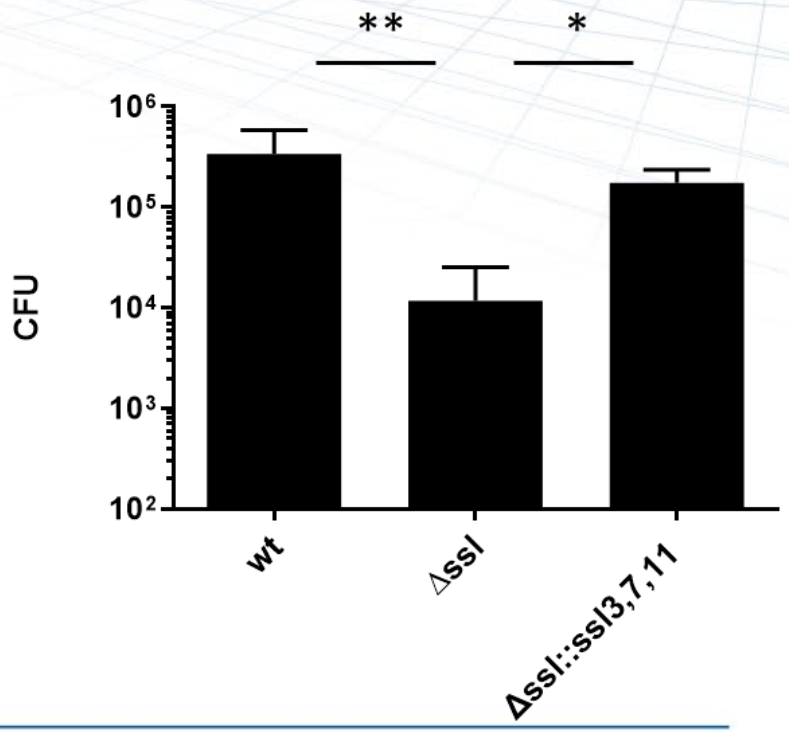
Complementation with SSL3, 7 and 11 genes increases survival in mice (not shown).

These findings are replicated in human blood assays (right fig).

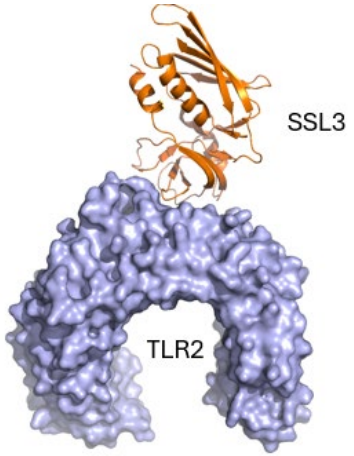
Mouse bacteraemia



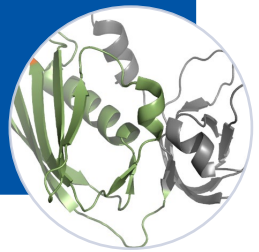
Human blood survival

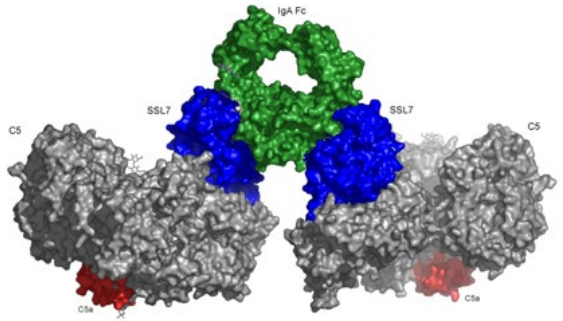


PolySSL consists of 3 inactive virulence factors - SSL3, SSL7 and SSL11 - joined end-to-end as a soluble fusion protein. They have non-redundant activities that target innate immunity

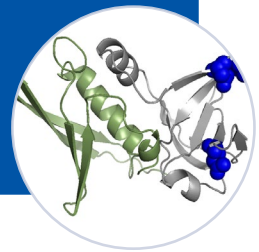


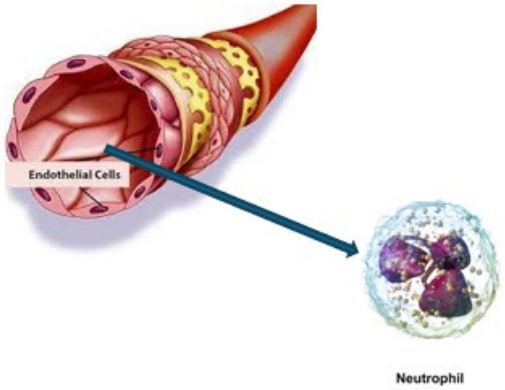
SSL3 binds TLR2 and inhibits innate response





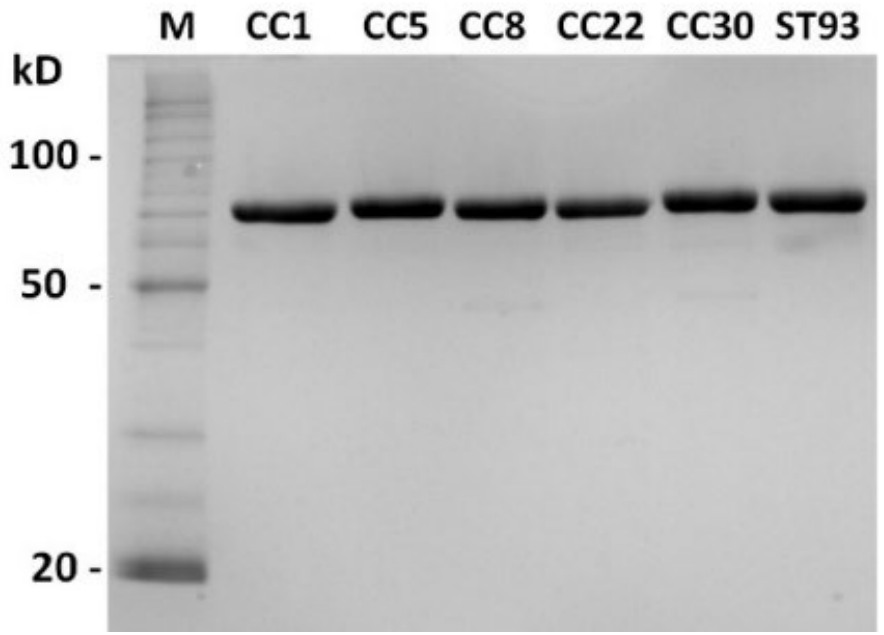
SSL7 blocks activation of complement C5

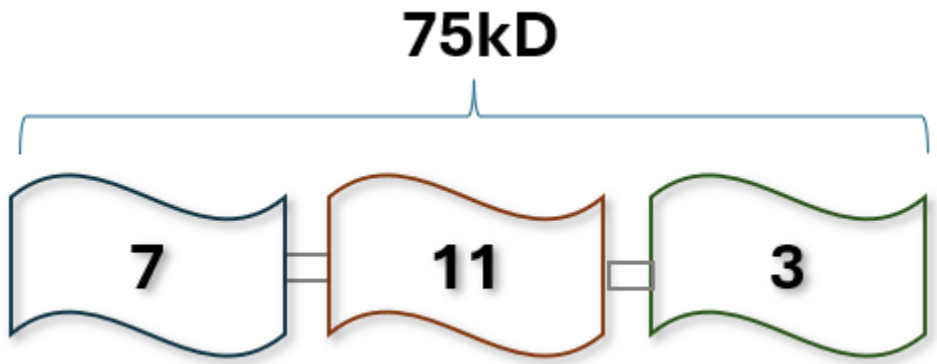




SSL11 inhibits phagocyte extravasation

PolySSL is a fusion protein that is readily produced as a stable, soluble protein at high yield as a recombinant protein from *E. coli*





Competitive Landscape

As far as we are aware, Chengdu Olymvax Biopharmaceuticals has the only vaccine in the clinic for treating *S. aureus*, it's currently in Phase III trials for MRSA infections.

To date all other vaccine candidates for *S. aureus* have failed in the clinic, despite successful preclinical studies in mice.

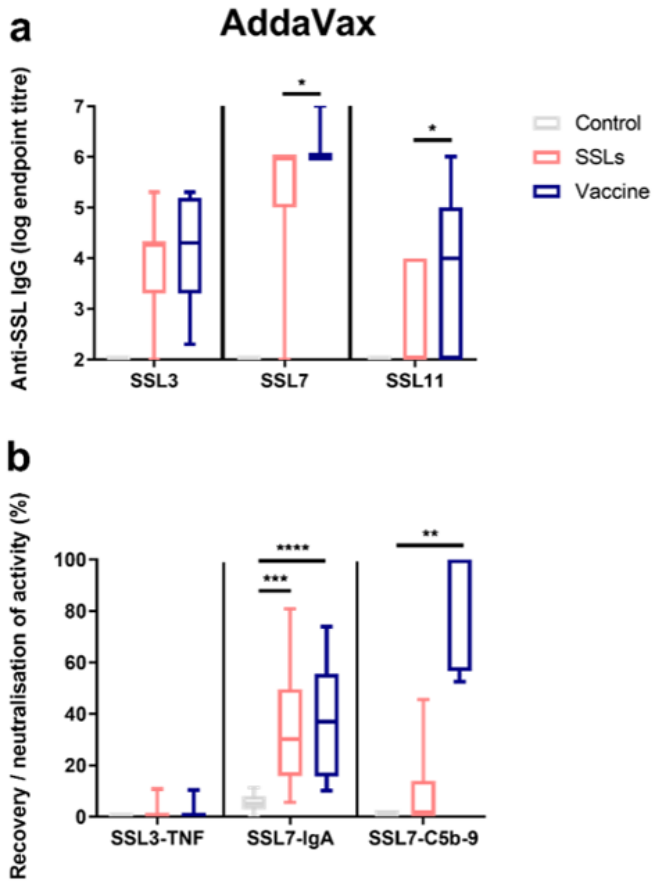
The competitive advantage of our vaccine is that it promotes both innate cell-based and antibody mediated immunity.

PolySSL generates high-titre anti-SSL antibodies in mice which allow recovery of immune activity

Mice were vaccinated at days 0, 14 and 28, with IP challenge given on day 39.

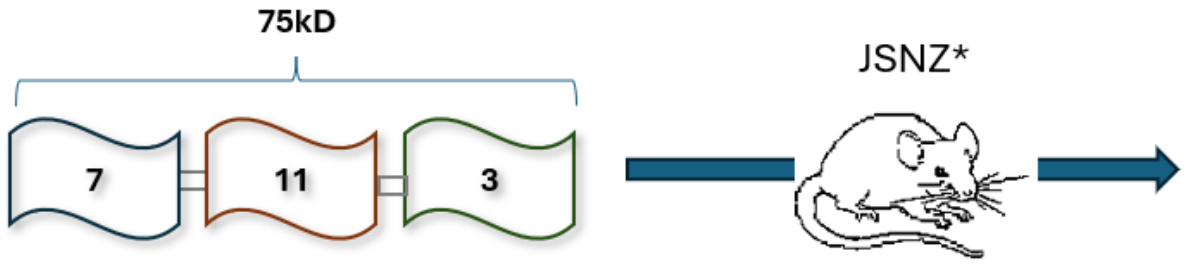
Top figure shows antibody titres against each SSL, delivered either as single SSLs (shown in red) or as part of the PolySSL vaccine (shown in blue).

Bottom figure shows neutralising activity in assays using sera from vaccinated mice.

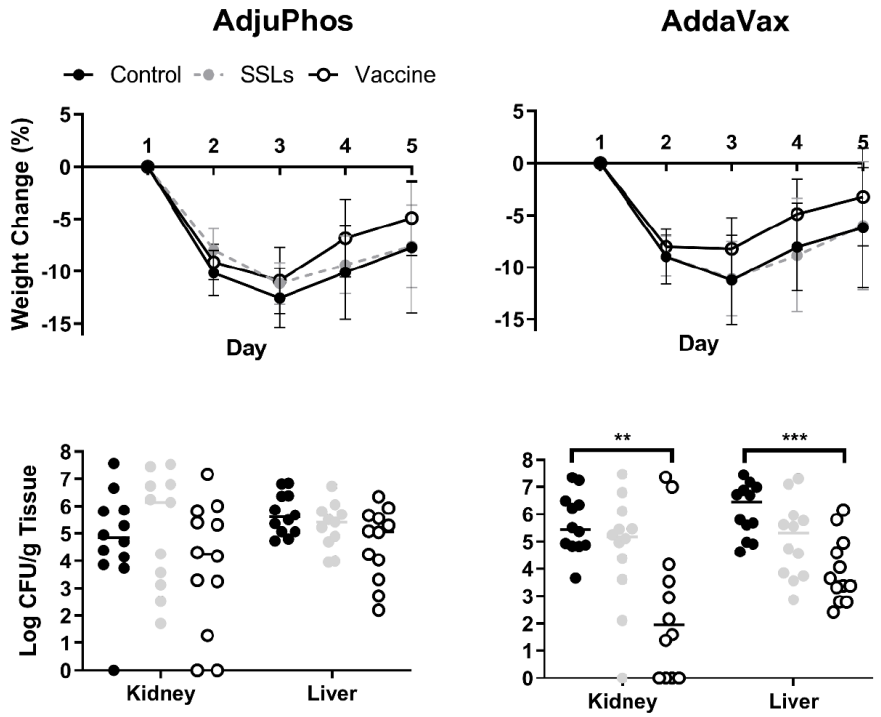


A unique feature is that SSL3, 7 and 11 must be linked together for protection against infection

75kD end-to-end soluble SSL polyprotein construct



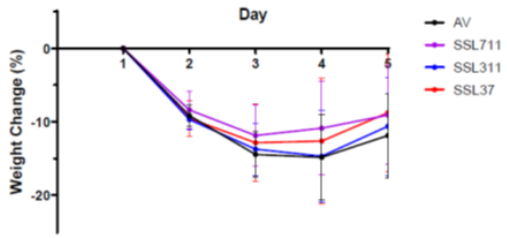
* JSNZ is a mouse adapted strain of *S. aureus* used in murine challenge model

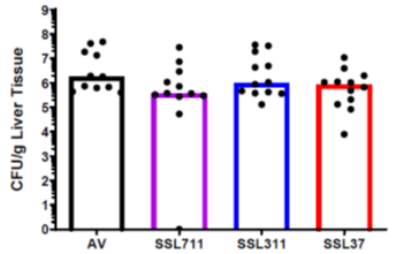


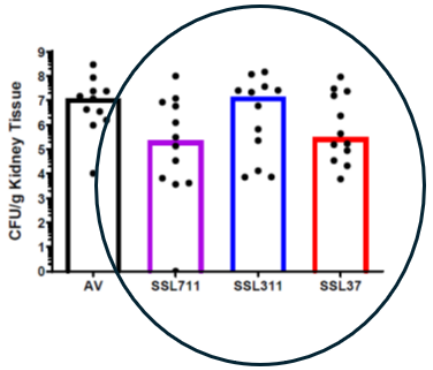
Combined data from two independent experiments, S. aureus challenge ~0.5 x 10^8 CFU i.p.

All three proteins are required for significant attenuation of infection and SSL order is important

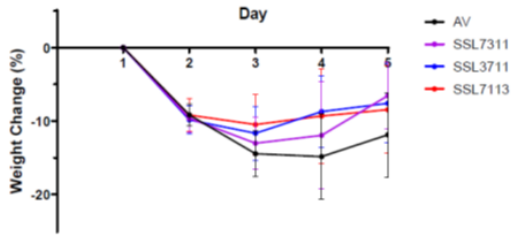
DualSSL Proteins

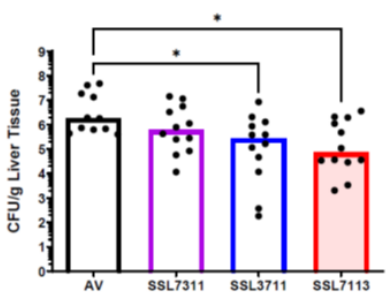


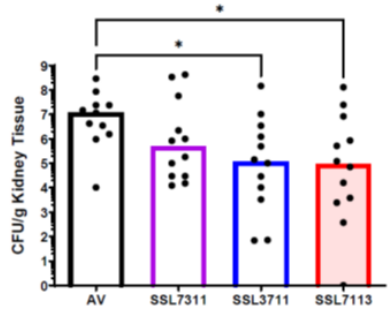




PolySSL Proteins







Combined data from two independent experiments, S. aureus challenge 0.5 – 1 x 10^8 CFU i.p.

Intellectual Property

We have filed a patent (PCT) protecting the novel findings that the SSLs must be combined in order to provide protection and that the order of the SSLs is important.

Next Steps

Confirm mechanism of protection

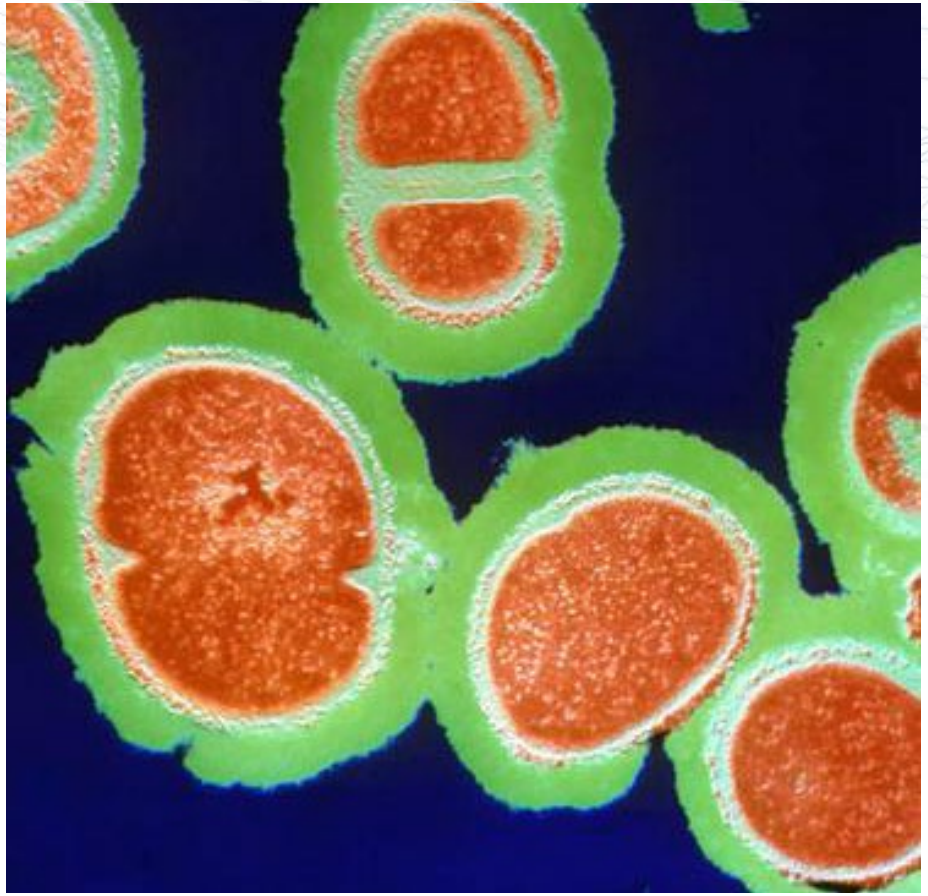
Characterise human assays to quantify immunogenicity, functional antibody and cellular response

Assay to define correlates of protection in humans

Adjuvant optimisation

Determine delivery schedule, regimen and ROA, end points for clinical plan

Optimise protein production, confirm purity, stability, yield



The University of Auckland Staph Team

[Prof John Fraser]

[Dr Fiona Radcliff]

[Dr Ries Langley]

[Fiona Clow]

Contact Us

Dr. Kimberlee Jordan – Senior Investment Manager, Biotechnologies
UniServices
kimberlee.jordan@auckland.ac.nz
(+64) 21 0209 8687

Dr. Pau Medrano – Director of Investment, Biotechnologies
UniServices
p.medrano@auckland.ac.nz