Structural and functional characterisation of the Staphylococcal superantigen-like protein 11 (SSL11)

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Abstract

*Staphylococcus aureus* is a human pathogen with significant socioeconomic impact. It is the causative agent of many life-threatening disease states, including sepsis, staphylococcal toxic shock syndrome and necrotizing pneumonia. *S. aureus* is associated with 1% of all hospital stays and estimated costs of US$9.5 billion / year (for 2000 and 2001) in the USA alone (Noskin *et al.*, 2005).

Recently, a novel family of virulence factors produced by *S. aureus* was identified, which share sequence and structural homology to the infamous superantigens (Arcus *et al.*, 2002; Williams *et al.*, 2000) – proteins that cause a range of symptoms, including food poisoning and toxic shock. This family of staphylococcal superantigen-like proteins (SSLs) includes 14 members, of which 11 (SSLs 1-11) are closely linked within a mobile genetic element, called a pathogenicity island (Kuroda *et al.*, 2001). To date, the literature suggests that the SSLs exhibit important host immune-evasion functions that are distinct from the superantigens. SSL5 has been reported to inhibit leukocyte rolling, a key process in their recruitment to sites of infection (Bestebroer *et al.*, 2006). SSL7 inhibits serum-mediated killing of bacteria (Langley *et al.*, 2005). This thesis describes the investigation into the structure and function of the related protein, SSL11.

The binding specificity of SSL11 has been identified as the trisaccharide Neu5Acα2-3Galβ1-4GlcNAc, where Neu5Ac is essential for interaction, whereas the NAc sidechain of GlcNAc is not, but is highly favoured. The interaction between the related carbohydrate, sialyl Lewis X (sLe^x^, or Neu5Acα2-3Galβ1-4[Fucα1-3]GlcNAc), and SSL11 has been characterised at an atomic level by X-ray crystallography. The dissociation constant of SSL11 binding to sLe^x^ was determined by surface plasmon resonance to be in the micromolar to sub-micromolar range. Investigation into the effects of SSL11 on neutrophils reveals that nanomolar concentrations of SSL11 inhibited neutrophil rolling on a P-selectin surface *in vitro*. Additionally, SSL11 was rapidly internalized, exhibited a cytoplasmic distribution and caused changes in actin, visible by 2-D gel analysis.

The characterization of the interaction between SSL11 and the previously-identified ligand, FcαRI (the myeloid immunoglobulin A receptor), is also described. The dissociation constant
of SSL11 binding to FcαRI was determined by surface plasmon resonance to be in the micromolar to sub-micromolar range and was found to be sialic acid-dependent. Binding of SSL11 to FcαRI inhibited the binding of its native ligand, IgA.

The sialic acid-dependent glycan-binding site of SSL11 is the sole site of interaction with the neutrophil surface, shown by neuraminidase treatment of cells and complete abrogation of binding by a site-directed functional knockout mutant. Residues involved in glycan binding were found to be conserved in SSLs 2-6, giving rise to a potential related function between this subset of the SSL family.
Acknowledgements

I owe gratitude to so many people that have contributed to this thesis in many different ways. I wish to start by thanking Professors Ted Baker and John Fraser for giving me the opportunity to work on this project. Thank you for your support, direction and enthusiasm. I have enjoyed this experience and am grateful for your guidance.

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Go team toxin!

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## Table of Contents

Abstract ........................................................................................................................................... I  
Acknowledgements ..................................................................................................................... III  
Table of Figures ............................................................................................................................ IX  
Table of Tables ............................................................................................................................. X  
Abbreviations ................................................................................................................................. XI  

### Chapter 1 - Introduction ........................................................................................................  1  

1.1 Overview ................................................................................................................................ 1  
1.2 *Staphylococcus aureus* ............................................................................................................. 2  
1.2.1 Staphylococci ....................................................................................................................... 2  
1.2.2 Pathogenesis of *S. aureus* ................................................................................................ 2  
1.2.3 The *S. aureus* genome and antibiotic resistance ............................................................ 2  
1.3 Host defenses .......................................................................................................................... 3  
1.3.1 The complement system ....................................................................................................... 3  
  i) The three activation pathways ................................................................................................. 4  
  ii) Formation of the membrane attack complex (MAC) ........................................................... 5  
  iii) The anaphylotoxins, C3a, C4a and C5a .............................................................................. 5  
1.3.2 Pro-inflammatory responses ............................................................................................... 6  
1.3.3 Leukocyte recruitment to sites of inflammation ............................................................... 6  
  i) Leukocyte tethering and rolling ............................................................................................... 7  
  ii) Leukocyte adhesion ................................................................................................................ 8  
  iii) Extravasation / diapedesis ....................................................................................................... 9  
  iv) Paracellular migration ............................................................................................................ 9  
  v) Transcellular migration .......................................................................................................... 10  
1.3.4 Neutrophil killing of bacteria ............................................................................................. 11  
1.3.5 Phagocytosis ....................................................................................................................... 11  
1.3.6 Oxidative burst ................................................................................................................... 12  
1.3.7 Lactoferrin ........................................................................................................................ 12  
1.3.8 Neutrophil extracellular traps (NETs) ............................................................................... 13  
1.4 Host evasion by *S. aureus* ....................................................................................................... 13  
1.4.1 Complement evasion by *S. aureus* ................................................................................... 14  
  i) Inhibition of the initiation of the complement system ............................................................ 14  
  ii) Inhibition of C3 convertase ..................................................................................................... 15  
  iii) Inhibition of the complement cascade through C3b .......................................................... 15  
  iv) Inhibition of chemotaxis by C5a .......................................................................................... 15  
1.4.2 Evasion of neutrophil killing by *S. aureus* ....................................................................... 16  
  i) Factors that inhibit opsonophagocytosis of *S. aureus* ...................................................... 16  
  ii) Factors that inhibit lysis of *S. aureus* in the phagolysosome .......................................... 16  
  iii) Toxins that lyse neutrophils .............................................................................................. 17  
1.4.3 Other evasion mechanisms ............................................................................................... 17  
1.5 Virulence factors produced by *S. aureus* ........................................................................... 18  
1.5.1 Exfoliative toxins ............................................................................................................... 18  
1.5.2 Panton-valentine leukocidin ............................................................................................. 18  
1.5.3 Superantigens .................................................................................................................... 19  
  i) Three-dimensional structure of classical bacterial SAgs .................................................... 21
Chapter 2 - Methods and Materials .................................................................31

2.1 Materials .................................................................................................31
2.1.1 DNA analysis .......................................................................................31
   i) Common buffers ....................................................................................31
   ii) Oligonucleotides ..................................................................................31
   iii) Plasmids ..............................................................................................31
   iv) Bacterial strains ...................................................................................32
2.1.2 Protein analysis ...................................................................................32
   i) Antibodies .............................................................................................32
   ii) Buffers and solutions ..........................................................................32
   iii) Media ....................................................................................................33
2.1.3 Cell analysis .........................................................................................33
   i) Cell lines ...............................................................................................33
   ii) Cell culture media ................................................................................34
2.2 Methods ..................................................................................................34
2.2.1 DNA analysis .......................................................................................34
   i) Purification of genomic DNA from S. aureus ........................................34
   ii) Purification of genomic DNA from E. coli ...........................................34
   iii) Plasmid preparation by alkaline lysis ....................................................35
   iv) Plasmid preparation for sequencing ......................................................35
   v) Agarose gel electrophoresis .................................................................36
   vi) Restriction endonuclease digestion of DNA ........................................36
   vii) Preparation of T-tailed plasmid .........................................................36
   viii) Polymerase Chain Reaction (PCR) ......................................................36
   ix) Purification of DNA from agarose gel ...............................................37
   x) Ligation of DNA ..................................................................................37
   xi) Site-directed mutagenesis by overlap PCR .......................................37
   xii) Production of chemically competent E. coli ....................................38
   xiii) Transformation of chemically competent E. coli .............................38
2.2.2 Protein analysis ...................................................................................38
   i) Production of IDA and GSH sepharose ..............................................38
   ii) Protein expression and purification from E. coli .............................39
   iii) Using the pGEX3C expression system ..............................................39
   iv) Using the pET32a3C expression system ..........................................40
   v) Large scale preparation of recombinant protein expressed by E. coli 40
   vi) Size exclusion chromatography .......................................................41
   vii) Anion exchange chromatography ....................................................41
   viii) Protein separation by SDS polyacrylamide gel electrophoresis (PAGE) 41
   ix) Coomassie Blue staining of proteins ................................................41
Chapter 3 – Investigating the interaction between SSL11 and FcαRI ......53

3.1 Introduction .................................................................53
3.2 Analysis of ssl11 from clinical isolates of S. aureus ..........................53
3.3 Cloning, expression and purification of SSL11 ........................................57
3.4 Comparison between SSL11 from GL10 and US6610 .........................59
3.5 Seroconversion to SSL11 ......................................................59
3.6 Binding studies of SSL11 ..........................................................60
3.7 Cloning, expression and purification of biotin ligase (BirA) .....................61
3.8 Biosensor analysis of human IgA binding to an FcαRI surface ................61
3.9 Steady state affinity of SSL11 binding FcαRI ........................................62
3.10 Carbohydrate inhibition of SSL11 binding to FcαRI ..........................64
3.11 SSL11 binding to FcαRI is Sia dependent ........................................67
3.12 SSL11-US6610 binds to leukocyte populations .....................................68
3.13 SSL11-GL10 inhibits IgA binding to neutrophils ..................................69
3.14 SSL11-US6610 but not SSL11-GL10 causes neutrophil aggregation ....70
3.15 Discussion .................................................................72
Chapter 4 – The three-dimensional structure of SSL11 and its interaction with sLe\textsuperscript{x} .................................................................74

4.1 Introduction .................................................................................................74
4.2 Crystallization of SSL11-US6610.................................................................74
4.3 X-ray diffraction data from SSL11-US6610 crystals .......................................75
4.4 Determination and refinement of the SSL11-US6610 crystal structure ..........76
4.5 The monomer structure of SSL11-US6610.....................................................78
4.6 Dimerisation of SSL11-US6610 .................................................................81
4.7 Allelic variation in SSL11 .............................................................................83
4.8 Attempted co-crystallization of SSL11-US6610 with Sia or Fc\textalpha RI ............84
4.9 Sialyl Lewis X (sLe\textsuperscript{x}) .........................................................................84
4.10 Crystallization of SSL11-US6610 in complex with sLe\textsuperscript{x} .......................85
4.11 Determination and refinement of the SSL11-US6610:sLe\textsuperscript{x} crystal complex ................................................................................85
4.12 The crystal structure of SSL11-US6610:sLe\textsuperscript{x} .......................................86
4.13 The sLe\textsuperscript{x} binding site .........................................................................89
4.14 The SSL11:sLe\textsuperscript{x} dimer .........................................................................93
4.15 Comparison of SLe\textsuperscript{x} binding site with other SSLs ...........................96
4.16 Flow cytometric analysis of SSL11 competition with an anti-sLe\textsuperscript{x} mAb ....98
4.17 Genetic analysis of SSL11 binding to sLe\textsuperscript{x} ........................................99
4.18 Competition binding studies with Fc\textalpha RI and sLe\textsuperscript{x} .........................100

Chapter 5 – Investigating the binding specificity of SSL11 and its effect on neutrophils .................................................................................. 104

5.1 Introduction ..................................................................................................104
5.2 Identification of SSL11 ligands .....................................................................104
5.3 Determination of the carbohydrate specificity of SSL11 ...............................106
5.4 Confirmation of the sLe\textsuperscript{x}-binding site of SSL11-US6610 by site-directed mutagenesis .................................................................111
5.5 Binding studies of SSL11-T168P ....................................................................112
5.6 In vitro neutrophil rolling assay .....................................................................113
5.7 Cellular internalisation of SSL11-US6610 ....................................................114
5.8 Neutrophil two-dimensional gel electrophoresis ...........................................116
5.9 Discussion .....................................................................................................119

Chapter 6 - Discussion .................................................................................... 124

6.1 SSL11 exhibits a high variation in primary sequence ....................................124
6.2 SSL11 is immunogenic ................................................................................125
6.3 Structural comparison of SSL11 with CHIPS ............................................125
6.4 Potential effects of glycan binding by SSL11 ..............................................126
   i) Sia-recognising Ig-superfamily lectins (Siglecs) ..................................126
   ii) Selectins .................................................................................................129
   iii) Gangliosides .........................................................................................130
   iv) Sia-dependent adhesion of S. aureus ...................................................132
6.5 Internalisation of SSL11 ...............................................................................132
6.6 Future directions ..........................................................................................133
   i) Identifying a receptor for SSL11 on S. aureus ......................................133

- VII -
ii) Determining the interaction of SSL11 with other SSLs ...................... 133
iii) Designing inhibitory drugs against the SSLs .............................. 134
iv) Defining the role of SSL11 in phagocytosis ............................. 135
v) Determining the effect of SSL11 on actin .................................. 136

6.7 Conclusions ............................................................................. 136

Chapter 7 - Appendix ........................................................................ 137

7.1 Oligonucleotides ..................................................................... 137
7.2 Plasmids .................................................................................. 138
7.3 S. aureus strains ...................................................................... 142
7.4 Serum samples from S. aureus-infected patients ....................... 142
7.5 Seroconversion ....................................................................... 143
7.6 MALDI-MS Results ................................................................. 144
7.7 Glycan array v2.1 ................................................................... 149
7.8 QStar Results ......................................................................... 156

Chapter 8 - Bibliography ................................................................ 160
Table of Figures

Figure 1.1 - The Complement system ..........................................................4
Figure 1.2 - Leukocyte recruitment ..................................................................7
Figure 1.3 - Diapedesis ..................................................................................9
Figure 1.4 - Inhibition of the Complement system ......................................13
Figure 1.5 - Neighbour-Joining tree of SAgs and SSLs .................................19
Figure 1.6 - The SAg fold ...........................................................................22
Figure 1.7 - The OB fold ............................................................................23
Figure 1.8 - The β-Grasp / Ubiquitin fold ....................................................23
Figure 1.9 - The ssl genes in pathogenicity island 2 ..................................25
Figure 1.10 - Evolution of the ssl genes in pathogenicity island 2 ..............26
Figure 1.11 - Crystal structures of SSL5 and SSL7 .................................29
Figure 3.1 - Amplification of ssl11 by PCR ..................................................54
Figure 3.2 - N-J tree of SSL11 from S. aureus isolates ...............................55
Figure 3.3 - Variation between SSL11 alleles ............................................56
Figure 3.4 - The purification of SSL11-US6610 ........................................57
Figure 3.5 - SDS-PAGE of two alleles of SSL11 expressed using the pET32a3C system ..............................................58
Figure 3.6 - Statistical analysis of seroconversion results .........................60
Figure 3.7 - Expression and purification of BirA .........................................61
Figure 3.8 - Biosensor analysis of IgA binding to an FcαRI surface ..............62
Figure 3.9 - Steady state curves of SSL11 binding FcαRI ............................63
Figure 3.10 - The effect of carbohydrate on the interaction between SSL11 and FcαRI ..........................................................65
Figure 3.11 - Sialic acids ............................................................................66
Figure 3.12 - Western analysis of SSL11 binding to FcαRI ..........................67
Figure 3.13 - Flow cytometry of leukocytes ..............................................68
Figure 3.14 - Inhibition of IgA and anti-FcαRI mAb binding to neutrophils by SSL11-GL10 ..................................................69
Figure 3.15 - Neutrophil aggregation by SSL11-US6610 ............................71
Figure 3.16 - Recombination in ssl11 ............................................................72
Figure 4.1 - SSL11-US6610 crystals .............................................................75
Figure 4.2 - The crystal structure of SSL11-US6610 ....................................79
Figure 4.3 - Structural variation between the four molecules of SSL11-US6610 ..................................................80
Figure 4.4 - Dimerisation of SSL11 .............................................................82
Figure 4.5 - Structural conservation of SSL11 ............................................83
Figure 4.6 - Chemical structure of sLex ..........................................................84
Figure 4.7 - Crystals of the SSL11-US6610:sLex complex ........................85
Figure 4.8 - The citrate and sLex binding sites of SSL11-US6610 .................87
Figure 4.9 - Superposition of the SSL11 molecules ...................................88
Figure 4.10 - The sLex binding site of SSL11-US6610 ...............................89
Figure 4.11 - Interaction of ligands with the surface of SSL11 ......................90
Figure 4.12 - Hydrogen bonding of the sLex sugars ...................................92
Figure 4.13 - The SSL11 dimer in the crystal structure of SSL11:sLex .............94
Figure 4.14 - Amino acid sequence alignment of the SSLs ..........................96
Figure 4.15 - SSL5 can potentially bind sLex ................................................97
Figure 4.16 - Inhibition of anti-sLex mAb binding to neutrophils by SSL11-GL10 ..........................................................98
Figure 4.17 - Steady state curves of SSL11 binding to sLe ..........................99
Figure 4.18 - sLe regeneration of an FcαRI surface ......................................100
Figure 5.1 - Leukocyte pulldown by SSL11-US6610 ...................................105
Figure 5.2 - Glycan array v2.1 ..................................................................106
Figure 5.3 - Steady state curves of SSL11 binding FcoRI .....................................................112
Figure 5.4 - SSL11 inhibits neutrophil tethering .................................................................113
Figure 5.5 - Neutrophils stained with SSL11-US6610-FITC ................................................114
Figure 5.6 - Confocal microscopy .......................................................................................115
Figure 5.7 - 2-D gel analysis of neutrophils .................................................................117
Figure 6.1 - Comparison of CHIPS to SSL11-US6610 .........................................................126
Figure 6.2 - Binding specificities of siglecs .......................................................................128
Figure 6.3 - The binding site of sialoadhesin .......................................................................128
Figure 6.4 - Binding of E- and P-selectin to sLe\(^\alpha\) .........................................................129
Figure 6.5 - Theoretical drug design against SSLs ..............................................................135

Table of Tables

Table 3.1 - Detection of reactive sera against SSL5 and SSL11 by ELISA .........................60
Table 4.1 - Refinement statistics .........................................................................................77
Table 4.2 - Similarity between the three-dimensional structures of SSL11-US6610, SSL5 and SSL7 ..................................................................................................................80
Table 4.3 - Similarity between the structure of SSL11-US6610 from the sLe\(^\alpha\) complex, with SSL11-US6610 from the native structure, SSL5 and SSL7 ..................................................................................88
Table 4.4 - Summary of hydrogen bonds formed by sLe\(^\alpha\) ................................................93
Table 4.5 - Summary of kinetic data of SSL11 .....................................................................103
Table 5.1 - Summary of hits from protein identification by MALDI-MS ...............................106
Table 5.2 - Summary of concentration-dependent analysis by glycan array v2.1 ..........110
Table 5.3 - Summary of proteins identified by QStar .........................................................116
Abbreviations

SI prefixes
n  nano- \( (10^{-9}) \)
μ  micro- \( (10^{-6}) \)
m  milli- \( (10^{-3}) \)
k  kilo- \( (10^3) \)

SI units
Å  Ångström \( (10^{-10} \text{ m}) \)
s  second
min  minute
h  hour
L  litre
g  gram

Other units / abbreviations
°C  degrees Celsius
2-D  two-dimensional
Abs  absorbance
ADP  adenosine diphosphate
APES  3-aminopropyl triethoxyilane
ATP  adenosine triphosphate
bp  base pair
BSA  bovine serum albumin
CD  cluster of differentiation
CFG  Consortium for Functional Glycomics
CHAPS  3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate
CHIPS  chemotaxis inhibitory protein of \( S. \) aureus
CHO  Chinese hamster ovary
cv  column volume
Da  Dalton
DAPI  4’,6-Diamidino-2-phenylindole dihydrochloride
DNA  deoxyribonucleic acid
dNTP  deoxynucleotide triphosphates
dTTP  deoxythymidine triphosphate
DTT  dithiothreitol
EDTA  ethylenediaminetetraacetic acid
ELISA  enzyme-linked immunosorbent assay
ET  exfoliative toxin
Fc  immunoglobulin crystallizable fragment
FcαRI  myeloid immunoglobulin A Fc receptor
FCS  fetal calf serum
FITC  fluoroscein isothiocyanate
FPLC  fast performance liquid chromatography
Fuc  fucose
g  gravity
Gal  galactose
Glc  glucosamine
Gp  glycoprotein
GSH  reduced glutathione
GST  glutathione-S-transferase
HEPES  4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
HRP  horseradish peroxidase
IAM  iodoacetamide
ICAM  intercellular adhesion molecule
IDA  iminodiacetic acid
IEF  isoelectric focusing
Ig  immunoglobulin
IL  interleukin
IMAC  immobilized metal affinity chromatography
INF  interferon
IPTG  isopropylthio-β-galactosidase
JAM  junction adhesion molecule
K  kelvin
kb  kilobase
K_D  dissociation constant
LAD  leukocyte adhesion deficiency
LB  Luria-Burtani
LFA  lymphocyte function-associated antigen
LPS  lipopolysaccharide
M  Molar
mAb  monoclonal antibody
Mac-1  macrophage-1 antigen
MAC  membrane attack complex
MALDI-MS matrix assisted laser desorption/ionization-mass spectrometry
MHC II major Histocompatibility complex class II
MOPS  3-(N-morpholino)propanesulfonic acid
MPO  myeloperoxidase
MRSA  meticillin-resistant S. aureus
MSSA  meticillin-sensitive S. aureus
NAc  N-acetyl
NET  neutrophil extracellular trap
nH  Hill coefficient
N-J  Neighbour-Joining
NTA  nitrilotriacetic acid
OB  oligosaccharide- / oligonucleotide- binding
PBS  phosphate buffered saline
PCR  polymerase chain reaction
pdb  protein data bank
PE  phycoerythrin
PECAM platelet / endothelial cell adhesion molecule
PEG  polyethyleneglycol
pI  isoelectric point
PMSF phenylmethylsulfonyl fluoride
PSGL-1 P-selectin glycoprotein ligand-1
PVL  panton-valentine leukocidin
RBC  red blood cell
Req response at equilibrium
RFU  relative fluorescence units
rmsd  root mean square difference
rpm  revolutions per minute
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<tr>
<th>Abbr.</th>
<th>Definition</th>
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<tr>
<td>RPMI</td>
<td>Roswell Park Memorial Institute medium-1640</td>
</tr>
<tr>
<td>rsFcαRI</td>
<td>recombinant soluble myeloid immunoglobulin A Fc receptor</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>RU</td>
<td>response units</td>
</tr>
<tr>
<td>SAg</td>
<td>superantigen</td>
</tr>
<tr>
<td>Sak</td>
<td>staphylokinase</td>
</tr>
<tr>
<td>SCIN</td>
<td>staphylococcal complement inhibitor</td>
</tr>
<tr>
<td>SDS</td>
<td>sodium dodecyl sulphate</td>
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<tr>
<td>SDS-PAGE</td>
<td>sodium dodecyl sulphate-polyacrylamide gel electrophoresis</td>
</tr>
<tr>
<td>SE</td>
<td>staphylococcal enterotoxin</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
</tr>
<tr>
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<td>staphylococcal exotoxin-like toxin</td>
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<tr>
<td>Sia</td>
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</tr>
<tr>
<td>sIgA</td>
<td>secretory immunoglobulin A</td>
</tr>
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<td>sialyl Lewis X / Neu5Aα2-3Galβ1-4(Fucα1-3)GlcNAc</td>
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</tr>
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<td>Spe</td>
<td>Streptococcus pyrogenic enterotoxin</td>
</tr>
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<td>SSL</td>
<td>staphylococcal superantigen-like</td>
</tr>
<tr>
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<td>staphylococcal scalded skin syndrome</td>
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<tr>
<td>TBS</td>
<td>tris buffered saline</td>
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<tr>
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<td>T cell receptor</td>
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