A deadly toxin with a romantic name: Panton-Valentine Leukocidin complex

Bacterial toxins targetting host cell membranes

It may have been Valentine's day in February, but if your beloved passes on the **Panton-Valentine Leukocidin complex** you might be in trouble! **Leukocidins** are intriguing proteins, being both soluble and, after undergoing a substantial conformational change, integral membrane proteins.

The leukocidin family consists of staphylococcal toxins, used by pathogens to form pores in host cell membranes to release nutrients which the infecting bacterium can metabolise. Several family members have been isolated from pathogenic bacteria, mostly from staphylococci, but also from *Clostridium* and *Bacillus* species. The first to be characterized was the **Panton-Valentine Leukocidin complex** (**PVL**, ref. 1) which is responsible for the necrotic lesions in the skin of patients infected with *Staphylococcus aureus*. **PVL** is found in the majority of the most dangerous antibiotic-resistant *S. aureus* isolates (MRSA strains - originally from Methicillin-resistant *S. aureus*, common in hospital-acquired infections).

It takes two...

Like other leukocidins, the **PVL complex** is made up of two components, called **F** (**LukF-PV**) and **S** (**LukS-PV**) that interact to make pores and induce cell lysis. Genes for both components appear to have been originally acquired by the pathogens from a bacteriophage. The components, secreted by the pathogens in soluble form, assemble to form the pore complexes at the host cell surface.

The structure of the pore in this system is as yet unknown, but the structures of **LukF-PV** and **LukS-PV**, in the soluble form, have been solved individually (PDB entries 1pvl and 1t5r, respectively). To form the pore, the soluble **S** and **F** components must associate and undergo a conformational change. The mechanism of action seems to be that the **S** component view-1 binds to specific receptors on the host cell, after which the **F** component view-2 binds, leading to complex formation. Multiple **FS** complexes insert into the host-cell membrane to form a pore and start cell lysis.

Functional subdomains

In spite of their relatively low sequence similarity (30% identical matched residues), the **F** and **S** proteins share a common tertiary structure and can be superimposed with a Cα atom RMSD of less than 1.5 Å. To learn about structure superimposition using the **PDBe** service **PDBeFold** have a look at the following tutorial: PDBeFold mini-tutorial.

The single structural domain can be divided into three functional subdomains: a central '**β-sandwich**' which is the heart of the soluble forms (view-3, shown in blue), a protruding '**rim**' (view-3, shown in yellow) and a '**stem**' (view-3, shown in red). The **stem** subdomain is a small motif of two β-strands and it is thought to be key to the pore-forming function of the toxin.

Forming a pore

Analogous to the mechanism suggested for the related toxin **α-hemolysin** (PDB entry 7ahl, view-4), it is likely that the **F** and **S** components cooperate to penetrate the cell membrane by reorganizing their **stem** subdomains and forming a multimeric assembly that creates a barrel-like pore. In this pore, the **α-hemolysin stem** has undergone a major conformational change view-4 to form a long **β-hairpin**. A hairpin is a pair of hydrogen-bonded antiparallel β-strands that are connected by a tight turn. In the case of **α-hemolysin**, seven of these extended hairpins combine to form a complete ring of strands creating a barrel-like pore view-5. The **α-hemolysin** structure shows how the **rim** subdomains of this toxin are positioned as a ring below the **β-sandwich** subdomains where they are likely to interact with the outer surface of the host cell membrane. It is the pore formed by the **stem** subdomains that causes the cell to lyse.

The oligomeric state of the integral membrane form of **PVL** complex is still unknown, but experiments suggest a 1:1 ratio of **LukF-PV** to **LukS-PV**. This makes a heptameric pore similar to that of **α-hemolysin** unlikely but a pore made up of an even number of components could achieve the same goal.

Further exploration

If you want to explore the structures discussed here in more detail then here are some suggestions.

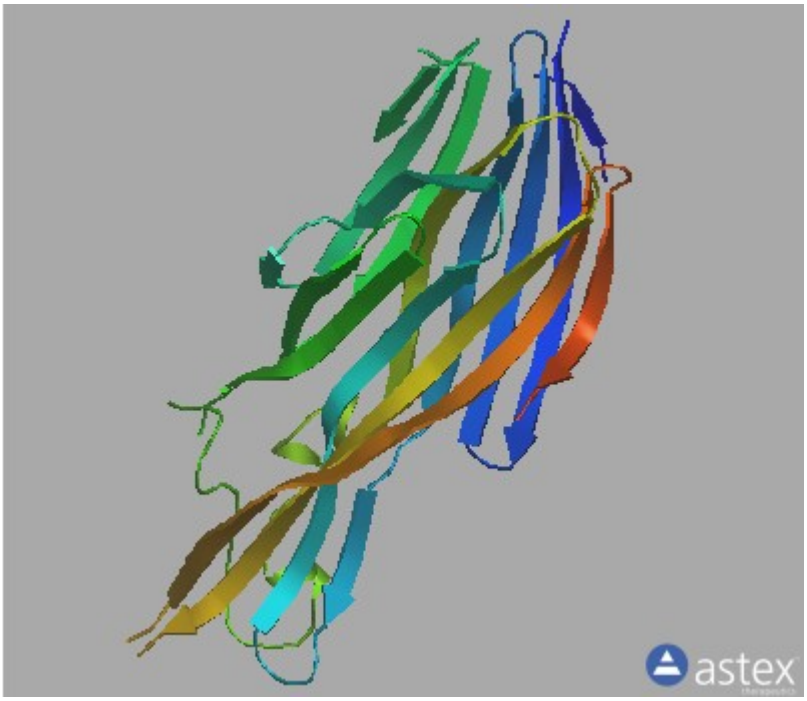
A good starting point is to visit the **PDBe Summary** pages for each component: PDB entries 1pvl and 1t5r. These pages collect together information and visualizations for each part of the **PVL** toxin. Key facts for each entry are summarized with **PDBprints**. This should help you quickly spot that these two entries appear to be from different organisms! The **S** component has in fact been assigned to the bacteriophage from which it is presumed to be derived.

Another quite interesting feature of 1t5r is that it has an apparently **octameric** assembly. Does this have any bearing of the structure of the pore? Try comparing the assembly in 1t5r with that in the functional pore assembly 7ahl described above. It seems likely that in fact the **1t5r** octamer is an artifact deriving from non-physiological contacts during crystallization. You can use the **PDBe** Quaternary structure analysis service **PDBePISA** to check this.

Finally, to find out how to use the **PDBeFold** service to compare the structures of the two **PVL** components and superimpose them on **α-hemolysin**, you can follow the following **PDBeQuips** tutorial: PDBeFold mini-tutorial.

References

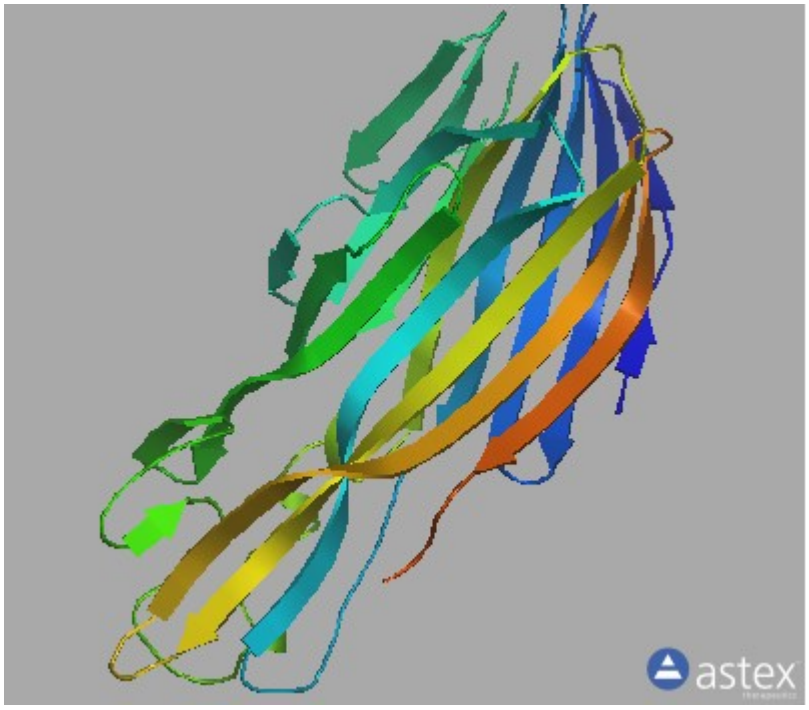
Ref.1 : Lancet 1932 219 506.



View-1

Cartoon of 1t5r - the S component of PVL

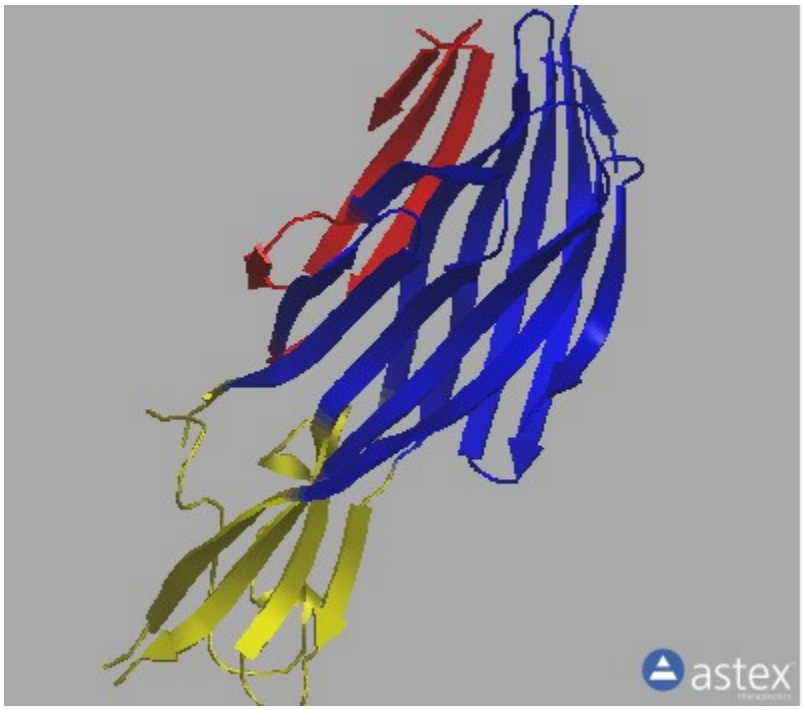
To understand the topology (fold) of a protein, a cartoon that gradually changes colour from blue (amino terminus) to red (carboxy terminus) can help you follow the path of the polypeptide chain through the structure.



View-2

Rainbow colouring of a cartoon of 1pvl - the F component of PVL

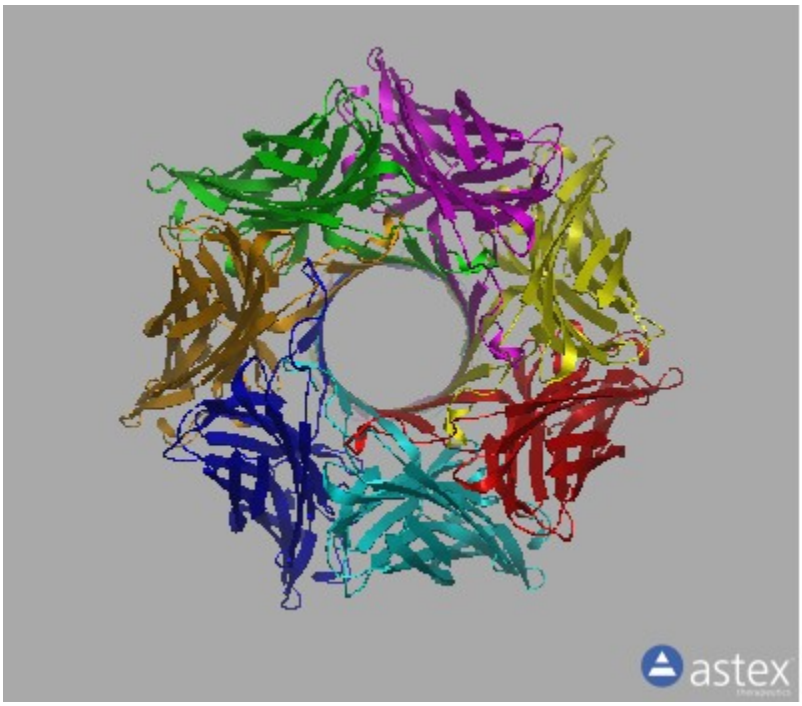
To understand the topology (fold) of a protein, a cartoon that gradually changes colour from blue (amino terminus) to red (carboxy terminus) can help you follow the path of the polypeptide chain through the structure.



View-3

Functional subdomains in the S component of PVL, 1tsr

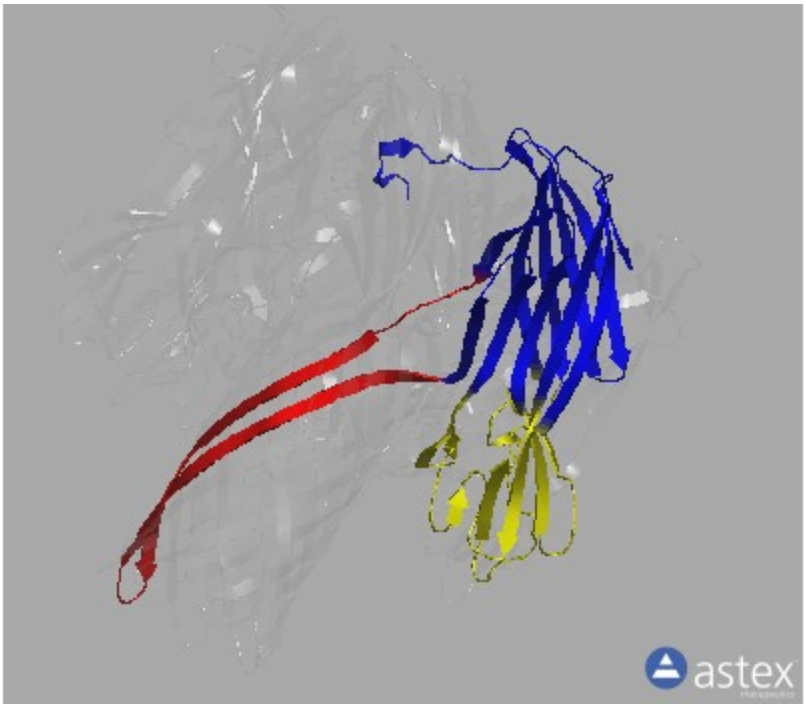
The β-sandwich (blue), stem (red) and rim (yellow) subdomains.



View-4

The heptameric pore in 7ahl – α-hemolysin

Seven protein subunits form a β-barrel pore



View-5

A single subunit in the heptameric pore of α-hemolysin (7ahl)

Isolating a single protein subunit shows the functional subdomains that are shared with the PVL proteins. The stem domain (red) has extended down to form a pair of antiparallel β-strands in the barrel-like pore.