Scientists hope bacterial blueprints will soon give doctors and nurses fewer sleepless nights

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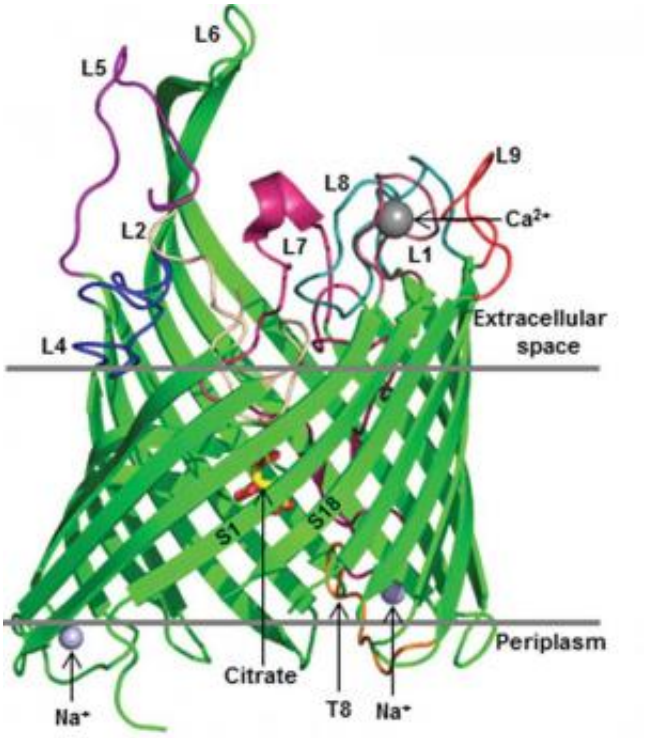

Crystal structure (ribbon model) of the alginate transporter from the outer membrane of a Pseudomonas aeruginosa bacteria viewed from the membrane plane, determined by x-ray crystallography. Credit: From J. Tan et al., Acta Cryst. D70, 2054 (2014).

One of the most common types of bacterial infection might soon give doctors and nurses fewer sleepless nights, thanks to a discovery made by scientists at Trinity College Dublin. The scientists used X-ray

crystallography techniques to provide a blueprint of the cellular machinery used by Pseudomonas aeruginosa. They now hope these structural plans can be used to design specific drugs that will throw spanners in the bacterial works and prevent a potentially deadly component from being shipped out.

Pseudomonas aeruginosa is a resilient and adaptable species of bacteria that causes disease by infecting damaged tissue and overpowering people whose immune response is compromised in some way. It is particularly associated with cystic fibrosis, thrives on moist surfaces, and is often implicated in cross-infection cases in hospitals.

Pseudomonal infections are challenging from a therapeutic point of view, in part because the bacteria produce a moist, viscous 'biofilm' that is hard to attack and in which they and other potentially harmful microbes tend to thrive. Alginate, a major component of this biofilm, is made in the bacterial cells and passed out via a pore in the outer membrane. This outer membrane helps to 'ring-fence' each bacterium from its external environment, while the pores in it provide controlled 'gateways' through which the alginate can exit.

Professor of Membrane Structural and Functional Biology at Trinity, Martin Caffrey, is corresponding author of the paper that was recently published in the international journal *Acta Crystallographica Section D*. He said: "If we can knock out the functioning of this pore, we might be able to stop alginate being added to the troublesome biofilm. Blocking the release of this virulence factor is likely to weaken the bacterium, which should make it more susceptible to host defences."

In addition to using X-ray crystallography techniques to provide the blueprints, Professor Caffrey's colleagues at the University of Oxford used computer simulations of the molecular docking procedures that open and close the pores to build a more complete picture of the process.

Loops that extend from opposite ends of the specific pores make these gateways flexible, while the team also believes that a protein found in between the inner and outer cell membrane acts as a molecular 'chaperone' in escorting alginate to the correct gateways.

Although developing a new drug to interfere with this newly characterised Pseudomonal machinery will take some time, the finding has major implications for associated research. Almost 50% of drugs on the market target cell membrane proteins, because interfering with their function can have major effects on their virulence. It is therefore vital that scientists are able to draw up the all-important structural blueprints to look for weaknesses and/or areas to attack.

Professor Caffrey, who recently helped to develop a high-throughput method that is much more efficient at producing protein crystals for use in drawing up protein blueprints (see here), added: "The method is proving to be hugely useful and is being implemented in academic and industrial labs worldwide. Of particular note is the contribution it made to the 2012 Nobel Prize in Chemistry awarded to my collaborator, Professor Brian Kobilka, at Stanford University School of Medicine."

More information: A conformational landscape for alginate secretion across the outer membrane of Pseudomonas aeruginosa, *Acta Cryst.* (2014). D70, 2054-2068. DOI: 10.1107/S1399004714001850

Provided by Trinity College Dublin