Cystic fibrosis is an autosomal recessive genetic disease, which causes a variety of symptoms; the defining symptoms being a build up of mucus in the lungs and pancreas. This mucus can create serious digestive problems, and also forms the ideal environment for bacteria such as Pseudomonas aeruginosa to infiltrate the lungs. ExoU, the protein of interest for this study, is one of the proteins found in the virulence mechanism of P. aeruginosa which leads to massive cell death and multiple system failure.

ExoU’s Significance: Cystic fibrosis is an autosomal recessive genetic disease, which causes a variety of symptoms; the defining symptoms being a build up of mucus in the lungs and pancreas. This mucus can create serious digestive problems, and also forms the ideal environment for bacteria such as Pseudomonas aeruginosa to infiltrate the lungs. ExoU, the protein of interest for this study, is one of the proteins found in the virulence mechanism of P. aeruginosa which leads to massive cell death and multiple system failure.

Targeting Virulence Factors vs. Current Antibiotics: The current generation of antibiotics used to treat bacterial infections such as P. aeruginosa target the bacteria themselves, meaning that those bacteria resistant to the antibiotics can proliferate even after treatment. These resistant strains cause numerous issues such as increased mortality and economic costs associated with developing new antibiotics. As shown in the graph below, there are significantly higher levels of antibiotic resistant strains. In conjunction, current antibiotic are non-discriminatory, meaning beneficent fauna are also killed upon treatment. This is especially harmful to P. aeruginosa sufferers, whose digestive systems are already compromised.

Biological Significance: Due to continuing bacterial resistance to antibiotics, it will be necessary for researchers to find different ways to stopping a bacterial infection from harming patients. Virulence factors are secreted by bacteria in order to keep the bacteria alive. They can help the bacteria enter the host cell, suppress the immune system, or obtain nutrition from the host cell. An alternative to current antibiotics is to target different virulence factors. In P. aeruginosa with the phospholipase ExoU, it may be possible to permanently bind a peptide to the binding site of ExoU. This would stop ExoU from binding to lipids and destroying cell membranes. As this does not kill the bacterium, any bacteria that are resistant to the attempts to target ExoU would still have to compete against the normal bacterial flora, preventing the selection of resistant strains.

Imaging Issues with ExoU: Although this is the protein of interest, ExoU is extremely difficult to study. The upper limit for structure determination by Nuclear Magnetic Resonance (NMR) is currently approximately 50 kilodaltons, and ExoU is 74 kilodaltons. There are no size limits on X-Ray crystallography, but despite numerous attempts no one had been able to get ExoU to crystalize. There is evidence that ExoU in its resting state is partially unfolded which explains its failure to crystalize. ExoU requires a eukaryotic cofactor for activation which prevents it from being activated inside a bacterium. So its function in vivo is less understood because of the possible roles of cofactors such as, ubiquitin and superoxide dismutase.

Patatin and ExoU Similarities: In order to study ExoU, researchers depend on the study of a homologous protein—in this case, Patatin. Both Patatin and ExoU are phospholipases. A phospholipase is an enzyme that catalyzes phospholipid hydrolysis for the purpose of membrane remodeling, production of important signaling molecules, and digestion of dietary fat. However, ExoU, a virulence factor found in P. aeruginosa, destroys the host’s cell membrane. The tables to the right show the conserved regions between ExoU and Patatin in red and orange.

References: