Washington University in St. Louis
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ANTIBIOTIC-SPARING SMALL MOLECULE THERAPY FOR URINARY TRACT INFECTION AND OTHER GRAM-NEGATIVE PATHOGENS

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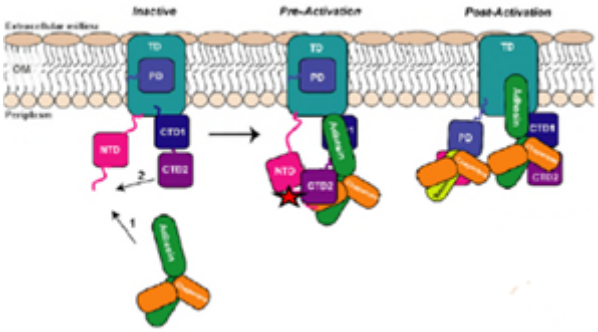
Technology Description

Researchers in Prof. Scott Hultgren's laboratory have discovered an antibiotic-sparing method for treating infections from *E. coli* and other Gram-negative bacteria. This approach is designed to block pathogens from colonizing their host by using small molecule inhibitors of the chaperone-usher pathway for pilus assembly.

Gram-negative pathogens, such as those that cause urinary tract infections, have hair-like adhesive fibers (pili) that assemble on their surface. These pili mediate microbial attachment and are critical for host-pathogen interactions. Therefore, bacterial pathogenicity can be diminished by preventing the pilus assembly. This technology provides a molecular snapshot that elucidates the specific interface where pilus assembly can be blocked by small molecule called pilicides. Revealing this mode of action lays the ground for the future structure-activity-relationship studies that are necessary to develop even more potent inhibitors for novel antibacterial therapies.



Schematic of pilus assembly: red star indicates structural target for small molecule inhibitors

Stage of Research

The inventors solved the first full-length crystal structure of an usher molecule in the process of being activated to assemble pili. This structure revealed a specific interface where pilicides (small molecular weight inhibitors of pilus assembly) bind.

Applications

- **Drug development for antibacterial agents** – identify small molecule compounds to prevent infection from and attenuate virulence in Gram-negative bacteria (for example, agents to treat urinary tract infections (UTIs) caused by *E. coli*)

Key Advantages

- **Antibiotic-sparing –** pilicides offer an alternative to traditional antibiotics:
  - could be effective against antibiotic resistant strains
  - expected to be minimally disruptive to good bacteria

Publications - Omattage, N. S., Deng, Z., Pinkner, J. S., Dodson, K. W., Almqvist, F., Yuan, P., & Hultgren, S. J. (2018). Structural basis for usher activation and intramolecular subunit transfer in P pilus biogenesis in Escherichia coli. *Nature microbiology*, 3(12), 1362-1368.

Patents – Patent application pending

Websites – Hultgren Profile and Hultgren Lab