High-Throughput Screening of Small-Molecule Transport Through *Pseudonomas aeruginosa*'s OccD3 Protein

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Introduction

Antimicrobial resistance has become a global concern, which threatens at least millions of people each year in the U.S. and costs billions of dollars to treat antibiotic resistant infections. Development of a new class of therapeutics to treat bacterial infections has therefore gained momentum.

The Threat of Antibiotic Resistance

2 Million — the number of people in the US that acquire serious antibiotic-resistant infections each year

23,000 — the number of people in the US that die as a direct result of antibiotic resistant infections each year

250,000 — the number of people in the US that require hospital care for Clostridium difficil (C. difficile: a unique bacterial infection directly related to antibiotic use and resistance) infections each year

14,000 — The number of people in the US that die from C. difficil infections each year

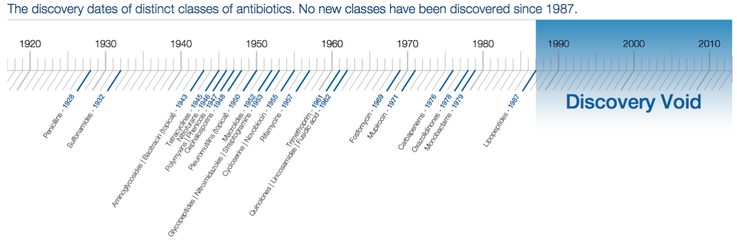
Increase in antibiotic resistance means that the effectiveness of antibiotics used to treat infections is diminished or non-existent.

"The use of antibiotics is the single most important factor leading to antibiotic resistance around the world."

Ways to Prevent Antibiotic Resistant Infections

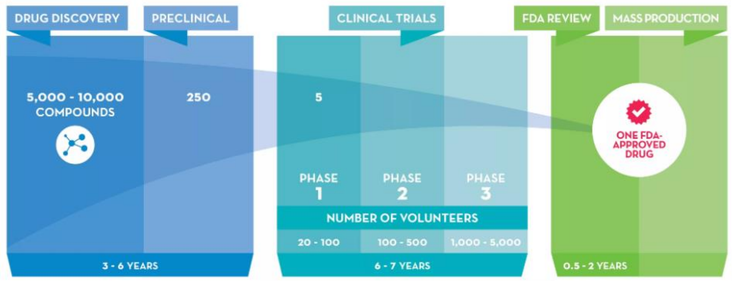
- Prevent infections and prevent the spread of resistance
- Tracking resistant bacteria
- Improving the use of today's antibiotics
- Promoting the development of new antibiotics and developing new diagnostic test for resistant bacteria

The discovery dates of distinct classes of antibiotics. No new classes have been discovered since 1987.

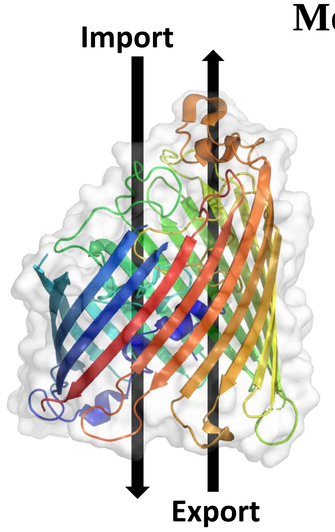


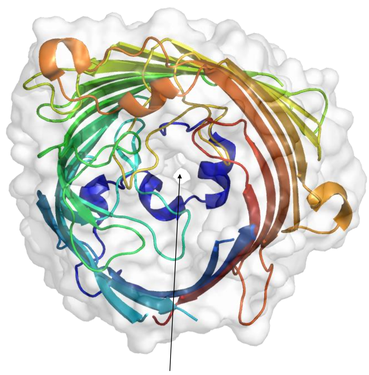
Source: World Economic Forum, adapted from Silver, L.L. Challenges of Antibacterial Discovery. In *Clinical Microbiology Reviews*, 2011, 24:71-109.

The Stages of Drug Development

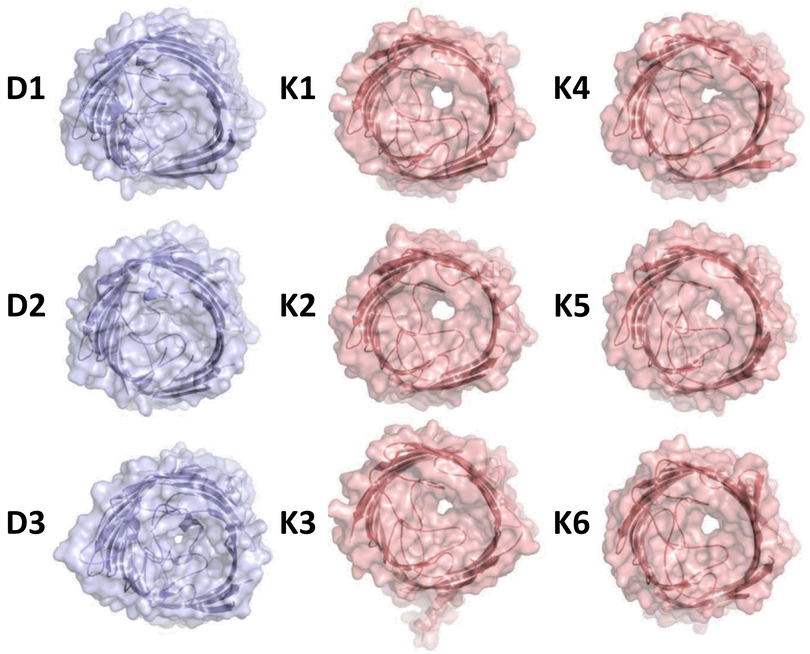


Motivation



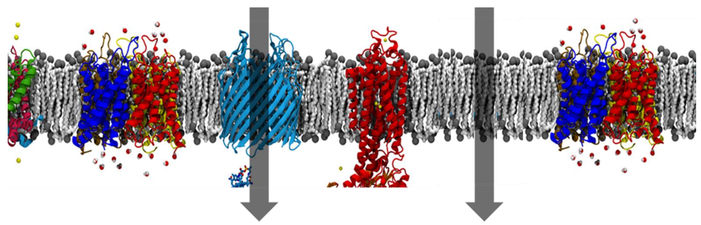


***P. aeruginosa* outer membrane carboxylate channel family**

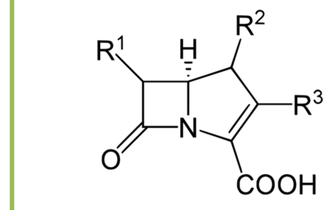


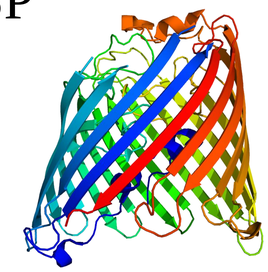
Approach

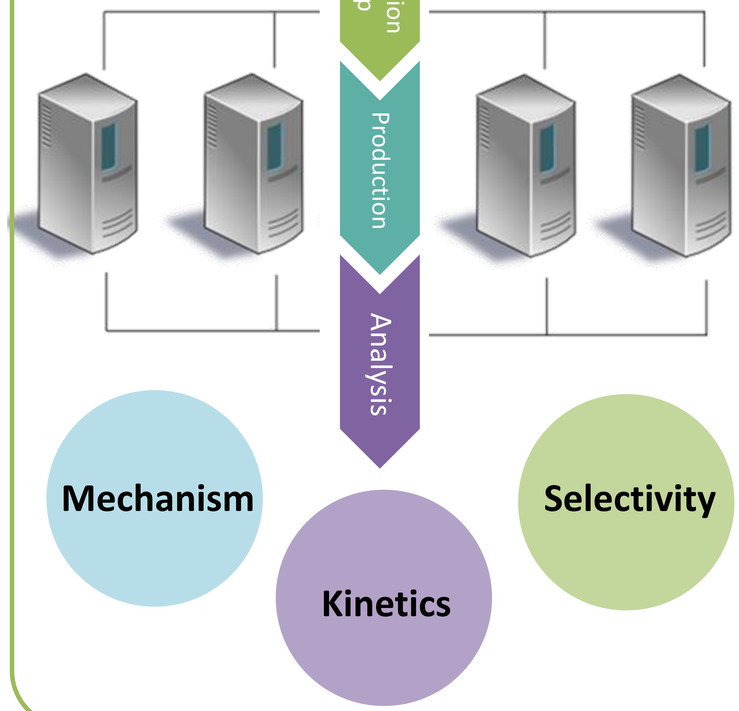
We developed a computational antibiotics screening platform (CLASP) for the quantitative assessment of transport of a library of small molecules through the porin channels of *P. aeruginosa*.



CLASP







Conclusions & Future Work

- We have developed a platform (CLASP) to study the transport behavior of small molecule penetration through bacterial cell wall
- The platform can be used to perform any small molecule, as well as other Gram-negative and Gram-positive bacterial membrane
- The simulation results and analysis could provide insights into the design of drugs with higher uptake and permeability
- We envision expanding the CLASP platform to new small-molecule libraries in an effort to accelerate the drug-discovery pipeline

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