Development of the Computational Antibiotic Screening Platform (CLASP) to Aid in the Discovery of New Antibiotics

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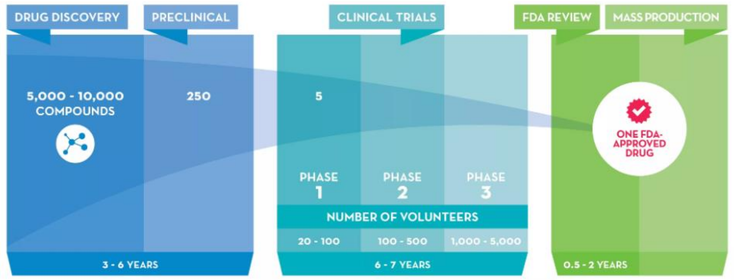
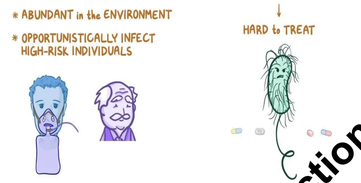
Introduction

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. As antimicrobial resistance to all known antibiotics continues to rise, there is an urgent need to accelerate the drug-discovery pipeline.

Pseudomonas aeruginosa is one of the Gram-negative bacterial species that demonstrates intrinsic resistance to antibiotics due to their highly impermeable outer membrane and size-selective channels or porins.

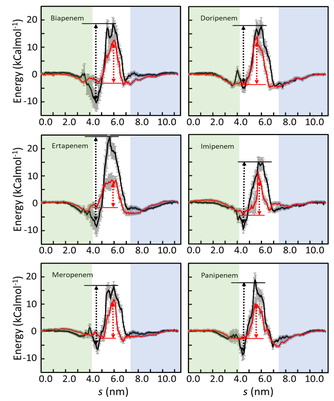
The Stages of Drug Development

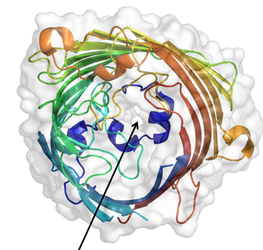




Results

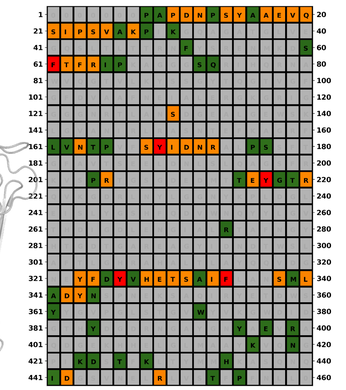
Potential of Mean Force Profile

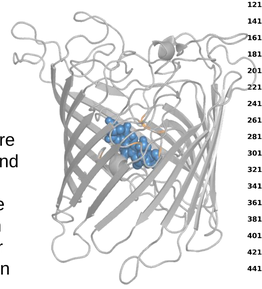




OccD3 channel has 2-3 nm constriction zone lined by key residues that provide selectivity to the porin and make penetration of antibiotics into *P. aeruginosa* cells much harder.

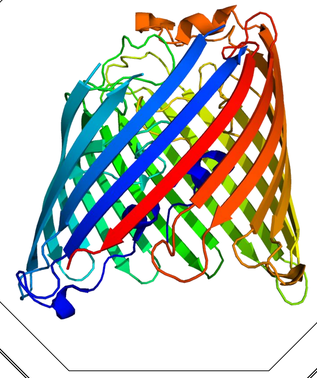
Amino Acid Contact Map

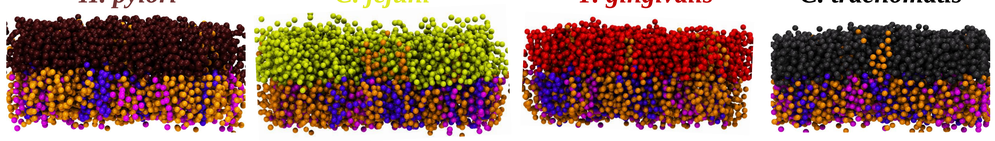


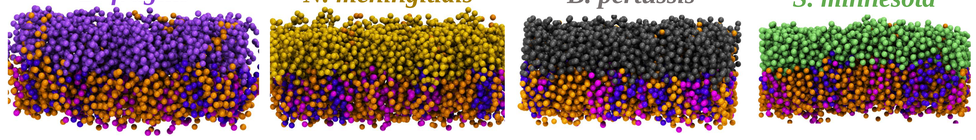


The translocation profiles show a barrier in the pore center. There is an energy minima appeared around D=4.2 nm, which revealed a binding site in the entrance of OccD3 channel. The energy has since increased to its maxima at D=6 nm, which is often defined as the constriction zone that has narrower cavity compared to the other part inside the protein tunnel.

OccD3 Protein

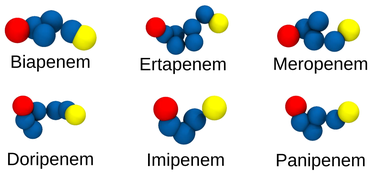


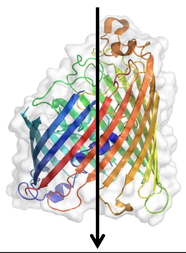




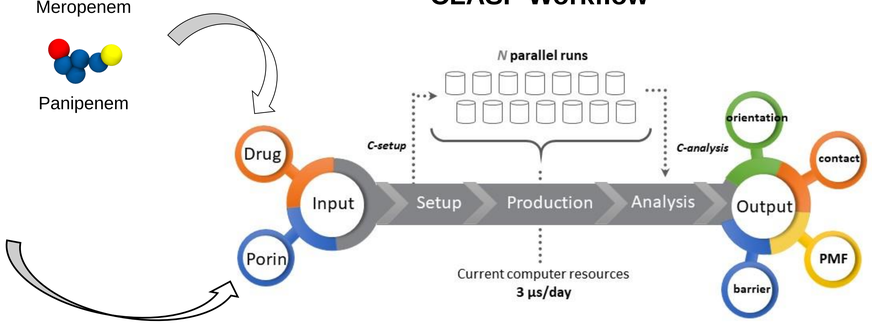
Method

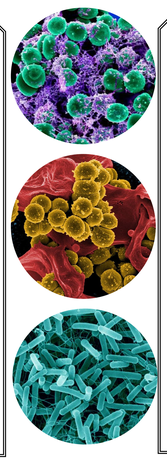
To contribute to the antibiotic discovery, we have developed the **C**omputationa**L** **A**ntibiotic **S**creening **P**latform (CLASP) for high-throughput screening of potential drug molecules through the porins embedded in the bacterial outer membrane. As a proof-of-concept, we used CLASP to study six antibiotics from the carbapenem family through *P. aeruginosa's* OccD3 porin to obtain comprehensive thermodynamic and kinetic data of antibiotic transport.





CLASP Workflow





Conclusions

CLASP is designed to generate comprehensive thermodynamic and kinetic data of antibiotic transport, which makes it a promising powerful technique for antibiotics screening. CLASP is advanced in other aspects as below:

- Highly automated
- Supports all types of protein channels if their crystal structures are identified
- Applicable to multiple bacterial species
- Simple input files, high performance, real time monitoring
- No scripting is needed, user friendly

In our recent work, CLASP was applied to investigate six types of carbapenem antibiotics translocating through *P. aeruginosa's* OccD3 protein channel, and the following is what we have learnt:

- Carbapenems penetrate bacterial cells through OccD3 channel within microseconds
- With the generated potential of mean force data, energy barriers, rate constants and half-lives of each carbapenem molecule through OccD3 can be easily calculated
- Key amino acid residues were analyzed in the carbapenem translocation pathway
- Molecular orientation of antibiotics were restrained by porin channel

Acknowledgments

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