Repurposing Drugs: Ritanserin as a Potential Antibiotic

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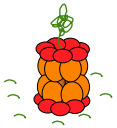
Background

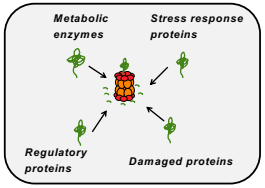
With the surge of multidrug resistant bacteria and increasing antibiotic resistance, there is a critical need for the development of new drug therapies. A new antimicrobial technique revolves around targeting virulence factors. Inhibitors that target pathogenicity hinder the capacity of the bacterium to cause an infection, thus allowing the host immune system to better clear the infection. In this study, we aim to inhibit the ClpXP protease, a highly conserved intracellular protease involved in virulence in different bacterial pathogens. Computational modeling was performed and ten commercially available inhibitors with predicted activity against ClpX were identified, with ritanserin showing the most promise. In this study we explore the antimicrobial effects of ritanserin, a previously identified serotonin 2A receptor antagonist that underwent clinical trials as a potential treatment for schizophrenia and substance dependence. We found that ritanserin increased WT *Bacillus anthracis* susceptibility to the cell envelope targeting antibiotics penicillin and daptomycin, as well as antimicrobial peptides LL-37. This demonstrates that ritanserin could be potentially repurposed as an antibacterial drug with the potential to be used by itself or in combination with antibiotics.

ClpXP Protease



ClpX: regulatory ATPase
Recognizes and unfolds proteins

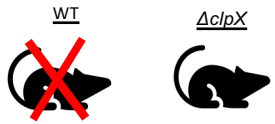
ClpP: proteolytic core
Degrades proteins



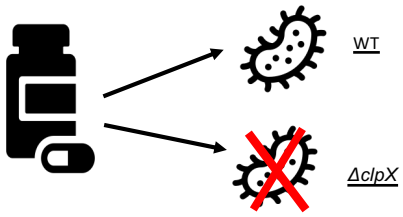
Loss of ClpXP has multiple consequences on the bacterial cell

Loss of ClpX

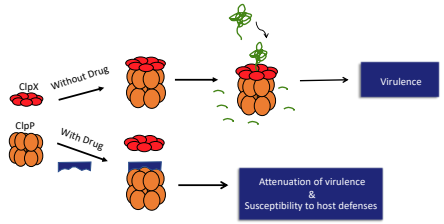
ClpX is necessary for virulence of *B. anthracis*



ClpX is important for resistance to cell-envelope targeting antimicrobials and host defenses

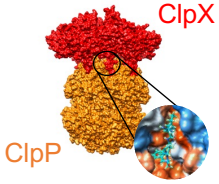


Goal



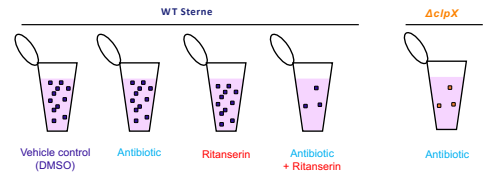
Find a drug that can inactivate the ClpXP protease, making the bacterium more susceptible to host innate defenses and/or antibiotics

Ritanserin



- Found using computational modeling
- Originally developed as a serotonin 2A receptor antagonist
- Targets the ClpX IGF-loop binding site on ClpP
  - Critical site for stabilization of the ClpXP protease

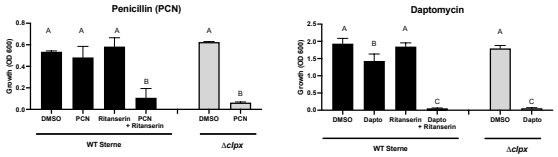
Hypothesis



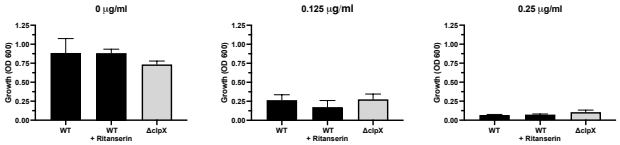
If ritanserin is inhibiting the ClpXP protease in *B. anthracis* Sterne, then the wildtype bacterium should mimic the phenotypes to *ΔclpX*.

Results

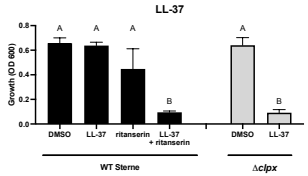
Cell Envelope Targeting Antibiotics



Non-Cell Envelope Targeting Antibiotics: Ciprofloxacin



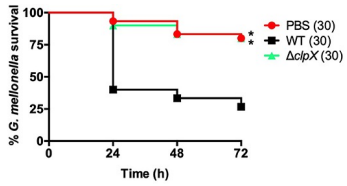
Host Defenses: Antimicrobial Peptides (LL-37)



Future Directions

***In vivo* assay**

- We have previously used *a Galleria mellonella* assay
- Hypothesize that WT pretreated with ritanserin will have similar survival as *ΔclpX*



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Conclusions & Significance

- We believe that ritanserin is inhibiting ClpXP formation as predicted by computational modeling.
- Ritanserin has already cleared some of the hurdles associated with drug development, making it an attractive target for drug repurposing.
- While it is important to develop new drugs, our results also show the potential of reexamining existing drugs, particularly those that have undergone extensive clinical safety testing.

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References