Combating Multidrug-Resistant Bacteria Using Chemokine-Derived Antimicrobial Peptides

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Multi-drug resistant (MDR) bacteria

- Anti-microbial resistance occurs when bacteria adapt to antibiotics they are exposed to, making antibiotics ineffective and allowing for persistent infections
- New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death.

- <u>Clinical Problem</u>:
  - Worldwide, MDR causes >700,000 deaths/year
  - If left unchecked, it is estimated that by 2050, MDR will be responsible for ~10 million deaths/year with reduction in world's GDP by trillions of dollars annually

Some of most challenging MDR Gram-positive and Gram-negative bacterial pathogens:

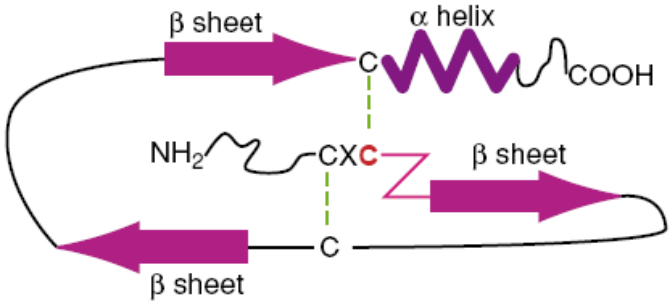
***E**nterococcus faecium*
***S**taphylococcus aureus*
***K**lebsiella pneumoniae*
***A**cinetobacter baumannii*
***P**seudomonas aeruginosa*
***E**nterobacter spp.*

CXCL10 as Novel Antimicrobial Agent

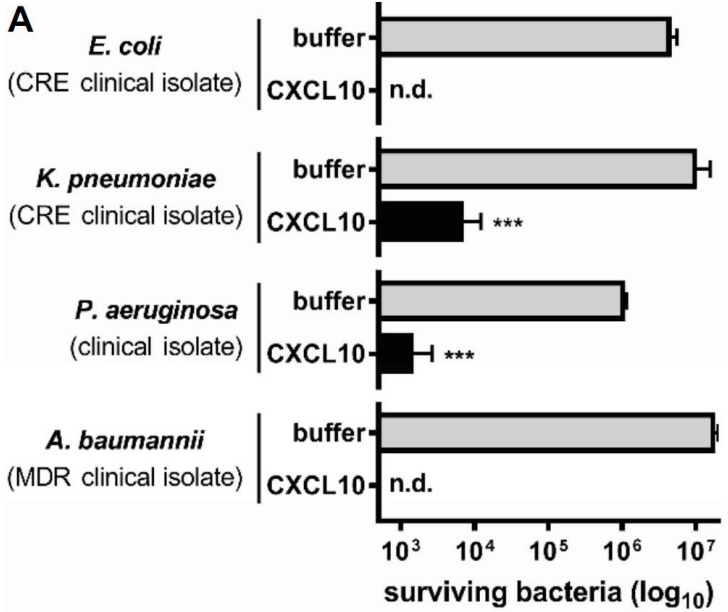
Solution: Researchers at the University of Virginia have determined that CXCL10-derived peptides have direct antimicrobial activity against a variety of pathogens

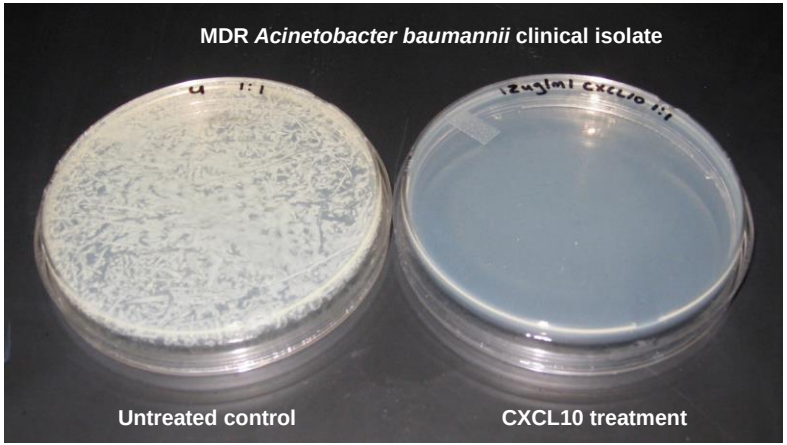
- Very potent at recruiting immune cells to sites of inflammation via interaction with its mammalian receptor CXCR3
- Provides a new treatment strategy for combating infections caused by MDR pathogens and potentially assists in promoting host defense

Schematic of CXCL10 - a small, 10 kD protein produced by wide variety of host cells



CXCL10 kills MDR Gram-negative clinical isolates





Survival of MDR bacteria following exposure to recombinant CXCL10 or buffer alone. Viability was measured by CFU determination, as demonstrated.

Antimicrobial activity of CXCL10-derived peptides

Peptide #	*B. anthracis* bacilli	*B. anthracis* spores	CRE *E. coli*	*mcr-1*$^{+}$ *E. coli*	CRE *K. pneumoniae*	*mcr-1*$^{+}$ *K. pneumoniae*	*A. baumannii*	*P. aeruginosa*
1	Y[2]	Y	Y	Y	Y	Y	Y	Y
9	N	N	Y	Y	Y	Y	Y	Y

CXCL10-derived peptides were tested for bactericidal activity against Gram-negative and Gram-positive organisms (Y=antimicrobial activity (85-95% killing), N=no antimicrobial activity). Peptide 1 exerted broad-spectrum bactericidal activity against all organisms and Peptide 9 was effective at killing Gram-negative bacteria.

Ongoing Development

- Optimization of combinations and formulations of CXCL10-derived peptides 1 and 9

Relevant Publications

- PNAS. 2011 Oct 11;108(41)17159-17164. **Hughes MA**, et. al.
- PLoS Pathogens. 2010 Nov;6(11)e1001199. **Hughes MA**, et. al.
- Infect Immun. 2009 Apr;77(4)1664-1678. **Hughes MA**, et. al.

Intellectual Property

- US Patent 9,937,234 issued April, 10, 2018
  - Compositions And Methods For Using And Identifying Antimicrobial Agents
- Subsequent provisional application under development