Executive Summary: Novel Drugs for Bacterial Pathogens

A number of bacterial pathogens recognize their human host environment by detecting certain host-specific molecules. Once detected, pathogenesis initiates, toxins are made, and disease begins.

Blocking this sensing mechanism and the resulting pathogenesis is an attractive strategy to counter disease caused by a number of important gram negative pathogens.[1]

Such pathogens sense their human host environment by a receptor called "QseC" that is activated by human hormones epinephrine and norepinephrine.

Qsec inhibitors:

- block pathogenesis of certain Gram-negative bacteria (Table)
- should be active against multiple drug resistant strains
- affect a key pathogen receptor (unlikely to be affected by weaponization or deletion)
- pre-screening for pathogen toxicity minimizes development of resistance

Selected Gram-negative Pathogens with QseC homologs

Pathogens with QseC Homologs	Disease(s)	% Similarity / % Identity to QseC	*In vitro* antagonist Activity	*In vivo* antagonist Activity
EHEC, EPEC	Bloody diarrhea, diarrhea	**100 / 100**	**Yes**	**?**
UPEC	UTIs	**100 / 99**	**Probably**	
Shigella flexneri	Shigellosis, dysentery	93 / 92		
Citrobacter koseri sp.	UTI, infant meningitis, sepsis	89 / 80		
Salmonella typhimurium	Gastroenteritis, food poisoning	**87 / 79**	**Yes**	**Yes**
Salmonella enterica typhi	Typhoid fever	87 / 78		
Klebsiella pneumoniae	Pneumonia, VAP, UTI,	83 / 71		
Enterobacter sp.	UTI, pneumonia, VAP, sepsis	83 / 69		
Haemophilus influenzae	Pneumonia, meningitis	66 / 44		
Pasteurella multocida	BRD, fowl cholera	65 / 46		
Actinobacillus pleuropheum	Swine respiratory pathogen	61 / 38		
Chromobacterium viol.	Sepsis, liver abscesses	58 / 42		
Francisella tularensis	tularemia (rabbit fever)	**57 / 32**	**Yes**	**Yes**
Bordetella parapertussis	Pertussis; pneumonia in sheep	56 / 37		
Legionella pneumophila	Legionnaires' disease	54 / 30		
Pseudomonas aeruginosa	VAP, HAP, CF	51 / 31		
Yersinia pestis	Black plague	50 / 33		
Yersinia enterocolitica	Yersiniosis, enterocolitis	50 / 31		
Coxiella burnetti	Q-fever; animal abortions	49 / 32		
Chlamydia sp.	STD, various animal diseases	Not available		

Opportunity and Development Interests

1. Accelerate preclinical development, currently funded by a UO1 grant from NIAID
2. Test and develop therapeutics for other pathogens
3. Test against existing, drug-resistant pathogens
4. Test and develop therapeutics for animal health and agricultural markets

Vanessa Sperandio, Ph.D.
Associate Professor of Microbiology & Biochemistry
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX 75390-9048
vanessa.sperandio@utsouthwestern.edu
214-648-1603

Don R. Stewart, Ph.D.
President & CEO
Omm Scientific, Inc.
2600 N. Stemmons Frwy, Ste 129
Dallas, TX 75207-2119
dstewart@ommscientific.com
214-350-9156

[1] Rasko et. al Science 321, 1078 (2008).

Gram-negative bacteria with QseC homologs

As of November 2009

Bacteria with QseC Homologs	Disease(s)	% Similarity / % Identity to QseC	*In vitro* antagonist Activity	*In vivo* antagonist Activity
EHEC, EPEC	Bloody diarrhea, diarrhea	**100 / 100**	**Yes**	**?**
UPEC	UTI	**100 / 98**	**Probably**	
Shigella flexneri	Shigellosis, Bacillary dysentery	93 / 92		
Citrobacter koseri sp.	UTI, infant meningitis, sepsis	89 / 80		
Salmonella typhimurium	Gastroenteritis, food poisoning	**87 / 79**	**Yes**	**Yes**
Salmonella enterica typhi	Typhoid fever	87 / 78		
Klebsiella pneumoniae	Pneumonia, VAP, UTI,	83 / 71		
Enterobacter sp.	UTI, pneumonia, VAP, sepsis	83 / 69		
Yersinia mollaretii		75 / 61		
Erwinia caratovora	Potato, vegetable & tree pathogen (soft rot, black leg, slime flux; stem rot)	69 / 56		
Haemophilus influenzae	Pneumonia, meningitis	66 / 44		
Pasteurella multocida	Bovine Resp. Disease, fowl cholera	65 / 46		
Actinobacillus pleuropheumoniae	Swine respiratory pathogen	61 / 38		
Chromobacterium violaceum	Sepsis, liver abscesses	58 / 42		
Ralstonia eutropha	Another species is a crop pathogen (solanacearum)	58 / 37		
Francisella tularensis	tularemia (rabbit fever)	**57 / 32**	**Yes**	**Yes**
Bordetella parapertussis	Pertussis; pneumonia in sheep	56 / 37		
Legionella pneumophila	Legionnaires' disease	54 / 30		
Burkholderia phymatum	Plant symbiont	53 / 36		
Pseudomonas. aeruginosa	VAP, HAP, CF	51 / 31		
Pseudomonas. fluorescens		52 / 31		
Yersinia pestis	Black plague	50 / 33		
Yersinia enterocolitica	Yersiniosis, enterocolitis	50 / 31		
Yersinia pseudotuberculosis	Yersiniosis	50 / 32		
Coxiella burnetti	Q-fever, animal abortion	49 / 32		
Vibrio sp.	Cholera, gastroenteritis, sea-food poisioning	48 / 29		
Chlamydia sp.	STD, pneumonia, & various animal diseases	Not available		
Thiobacillus denitrificans		Not available		