Screen for Inhibitors Of The Bacterial Type III Secretion System

Tech ID: 33228 / UC Case 2014-239-0

BACKGROUND

As currently available antibiotics become ineffective due to the rise in antibiotic resistance among pathogenic bacteria, development of completely new classes of antibiotics is critical. Classic antibiotics target pathogens and commensal bacteria indiscriminately; therefore, their use puts selective pressure on both populations. Because of the abundance of commensals within a mammalian host, antibiotic resistance is thought to arise more frequently in commensal bacteria and is horizontally transferred to pathogens. In contrast to classic antibiotics, virulence blockers are compounds that selectively inhibit the expression or function of a virulence factor in a pathogen or group of pathogens. Advantages of virulence blockers are twofold. For one, selective pressure on a limited number of microbes, i.e., only pathogens expressing the molecular target of the virulence blocker, should limit the evolution of resistance. Second, the decreased commensal killing by virulence blockers has the potential to preserve a healthy microbiota, which is critical for maintaining gut homeostasis and defending against opportunistic pathogens.

Type III secretion systems (T3SS) are bacterial appendages required by dozens of pathogens to cause disease, including Salmonella, enteropathogenic Escherichia coli (EPEC), Shigella, Pseudomonas, and Yersinia, but they are largely absent in nonpathogenic bacteria. Bacteria use T3SS to inject bacterial effector proteins into target host cells to manipulate host processes for the benefit of the pathogen. Seven T3SS injectisome families have been identified and share a number of homologous membrane-associated components with the flagellar basal body.

Agents that target T3SS would be key virulance blockers for a set of pathogens that are very important to human and animal health as are methods of screening for such agents.

TECHNOLOGY DESCRIPTION

UC Santa Cruz researchers discovered and initially characterized natural products with T3SS (Type III Secretory System) inhibitory activity that were derived from a marine Actinobacterium. Bacterial extracts containing piericidin A1 and the piericidin derivative Mer-A 20268 inhibited Yersinia pseudotuberculosis from triggering T3SS-dependent activation of the host transcription factor NF-kB in HEK293T cells, but were not toxic to mammalian cells.

As the Yersinia T3SS must be functional in order to trigger NF-KB activation, these data indicate that piericidin Al and Mer-A 20268 block T3SS function. Consistent with this, purified piericidin A1 and Mer-A 20268 dose dependently inhibited translocation of the Y pseudotuberculosis T3SS effector protein YopM inside CHO cells. In contrast, neither compound perturbed bacterial growth in vitro, indicating that piericidin A1 and Mer-A 20268 do not function as general antibiotics in Yersinia. In addition, when Yersinia was incubated under T3SS-inducing culture conditions in the absence of host cells, Mer-A 20268 and piericidin A1 inhibited secretion of T3SS cargo as effectively or better than several previously described T3SS inhibitors, such as MBX-1641 and aurodox. This suggests that Mer-A 20268 and piericidin A1 do not block type III secretion by blocking the bacterial-host cell interaction, but rather inhibit an earlier stage such as T3SS needle assembly. In summary, Mer-A 20268 and piericidin A1 possess previously uncharacterized activity against the bacterial T3SS.

Patent claims include methods of inhibiting bacterial type III secretion system mediated effector protein translocation from a Gram negative bacterium into a eukaryotyic cell that involve administering Piericidin A1 or Mer-A 2062B as well as method of screening compounds for activity as inhibitors of the bacterial type III secretion system.

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OTHER INFORMATION

KEYWORDS

Gram Negative, Type III Secretion System, Antibiotics, Virulence Blockers, Yersinia, Salmonella, Shigella, Pseudomonas, Enteropathogenic E. coli, E. coli infection, Natural Products, Piericidin A1, Chemical Screening

CATEGORIZED AS

- Medical
  - Disease: Infectious Diseases
  - Screening
  - Therapeutics

RELATED CASES

2014-239-0

Currently, screen is performed in a *Pseudomonas aueruginosa* rather than *Yersinia* system.

APPLICATIONS

- Antibiotics
- Virulence blockers
- Targeting gram-negative bacteria
- Screening methods

ADVANTAGES

- More difficult for pathogens to develop antibiotic resistance to these agents
- These agents would target only pathogenic bacteria and spare bacteria required for a healthy microbiome
- Robust screening methodology that is already used in high throughput screening

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,588,897	03/17/2020	2014-239
United States Of America	Issued Patent	10,080,745	09/25/2018	2014-239

RELATED MATERIALS

- Synthetic Cyclic Peptomers as Type III Secretion System Inhibitors - 08/24/2017
- Piericidin A1 Blocks Yersinia Ysc Type III Secretion System Needle Assembly - 02/15/2017

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