A Broadly Neutralizing Molecule Against Clostridium Difficile Toxin B

Tech ID: 32923 / UC Case 2020-668-0

BRIEF DESCRIPTION

Researchers at UCI have developed a family of recombinant protein therapeutics against Clostridium difficile designed to provide broad-spectrum protection and neutralization against all isoforms of its main toxin, TcdB. These antitoxin molecules feature fragments of TcdB's human receptors (CSPG4 and FZD) which compete for TcdB binding, significantly improving upon existing antibody therapeutics for Clostridium difficile infections.

SUGGESTED USES

·Treating Clostridium difficile infections (CDIs)

FEATURES/BENEFITS

·Increased potency: bi-specific molecules that block two toxin binding events are likely more potent than a therapeutic blocking one binding event.

·Broad-spectrum protection: these antitoxin proteins are effective against multiple toxin isoforms, including those from hypervirulent clinical strains.

·Reduced resistance risk: the toxin gene cannot mutate to resist antitoxin binding without compromising its native toxic function.

·Low immunogenicity: these antitoxin molecules are comprised of all human proteins, minimizing the risk of immune clearance.

FULL DESCRIPTION

Clostridium difficile (C. difficile) is a bacterium that causes diarrhea and colitis and is classified as one of the top urgent antibiotic resistance threats by the CDC. In the US, Clostridium difficile infections (CDIs) affect more than 223,900 patients, resulting in approximately 12,800 deaths in 2017. C. difficile harms patients predominantly through the protein toxin TcdB, while many TcdB isoforms have been identified from a growing number of diverse C. difficile strains. To treat CDIs, Merck developed an anti-TcdB antibody therapeutic, bezlotoxumab, approved by the FDA in 2016. While bezlotoxumab is effective against some TcdB isoforms, it has low potency against many TcdB isoforms that have mutated to diminish bezlotoxumab binding and neutralization during evolution, including those from hypervirulent clinical strains.

To address this, researchers at UCI have developed a family of recombinant protein therapeutics to treat CDIs. Importantly, these antitoxin molecules are designed to provide broad-spectrum protection and neutralization against all isoforms of TcdB. Building molecules with fragments of TcdB's human receptors allows these antitoxins to simultaneously compete with two native receptors for TcdB binding, while the toxin gene cannot mutate to resist antitoxin binding without compromising its native toxic function. Using human-derived parts can minimize the risk of immune clearance and increase half-life in serum. Overall, these antitoxins offer significant improvements upon existing antibody therapeutics for C. difficile infections.

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OTHER INFORMATION

CATEGORIZED AS

» **Biotechnology**
» Health
» **Materials & Chemicals**
» Biological
» **Medical**
» Diagnostics
» Disease: Digestive System
» Disease: Infectious Diseases
» Research Tools
» Therapeutics

STATE OF DEVELOPMENT

Researchers have successfully produced the antitoxin molecules, purifying them to high homogeneity. Preliminary assays demonstrated the molecules drastically exceed the FDA-approved bezlotoxumab for potency on TcdB from a hypervirulent C. difficilestrain, while being comparable to bezlotoxumab for neutralization on TcdB from the referencestrain. Cryogenic electron microscopy (cryo-EM) studies confirmed the simultaneous binding of the antitoxin to two distinct sites on the toxin.

RELATED CASES

2020-668-0

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Published Application	20240033354	02/01/2024	2020-668

OTHER INFORMATION

Country	Type	Number	Dated	Case
Patent Cooperation Treaty	Published Application	2022051540A1	03/10/2022	2020-668

RELATED MATERIALS

» Chen, Peng and Jin, Rongsheng. “Receptor binding mechanisms of Clostridioides difficile toxin B and implications for therapeutics development.” The FEBS Journal, 2021, doi: https://doi.org/10.1111/febs.16310. - 12/04/2021

» Chen, Peng et al. “Structural basis for CSPG4 as a receptor for TcdB and a therapeutic target in Clostridioides difficile infection.” Nature Communications, vol. 12, no. 3748, 2021, doi: https://doi.org/10.1038/s41467-021-23878-3. - 06/18/2021