Researchers identify starting point for designing drugs that cure clostridium difficile

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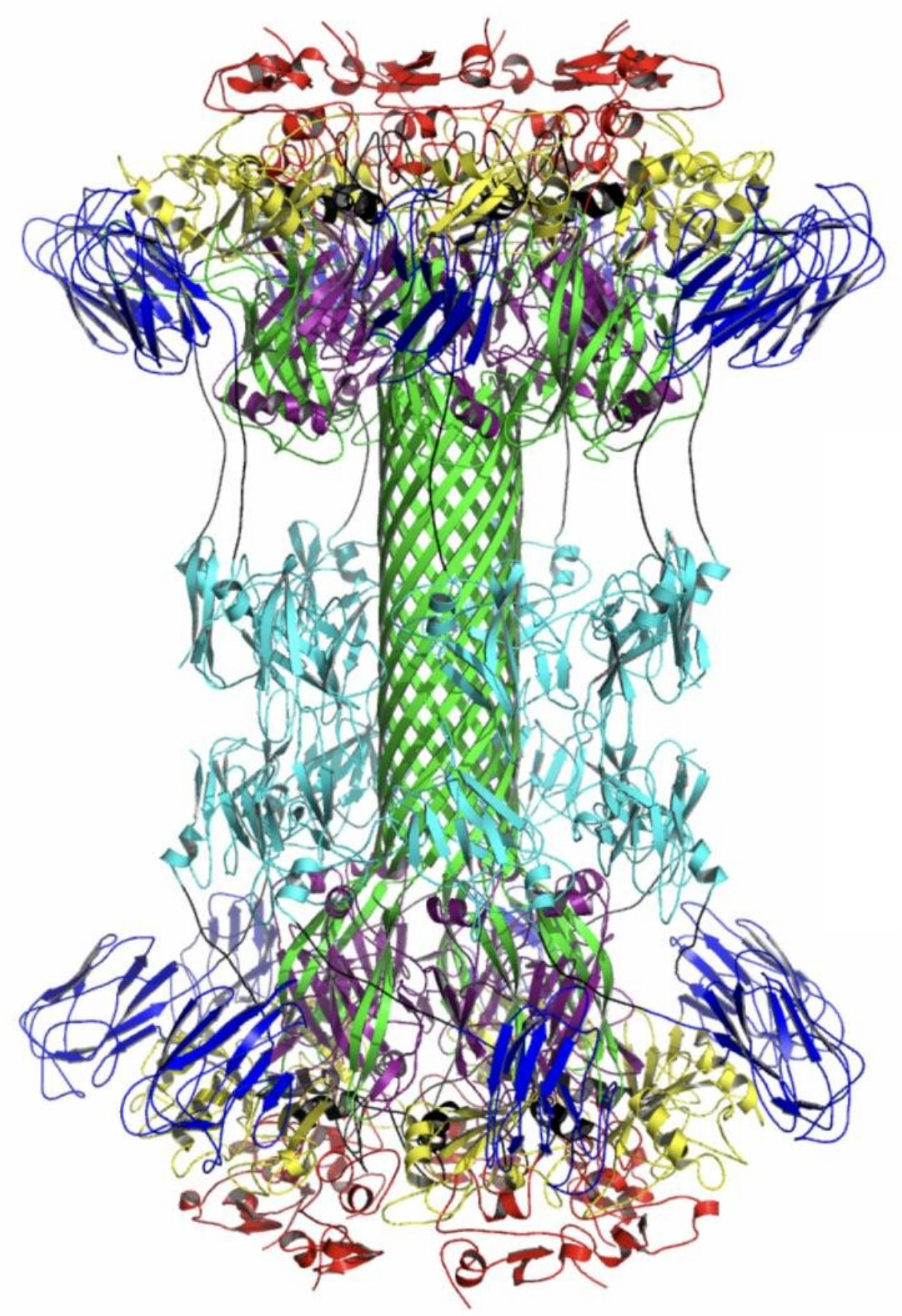

This atomic illustration shows the newly identified CDTB component of the binary C. diff toxin, which researchers now know attaches to the surface of human cells and injects the CDTA portion of the toxin inside the cell. Credit: Xingjian Xu and Edwin Pozharski

A newly published paper in *PNAS* details a research breakthrough that provides a promising starting point for scientists to create drugs that can cure *C. diff*—a virulent health care-associated infection that causes severe diarrhea, nausea, internal bleeding, and potentially death. The bacteria affects roughly half-a-million Americans and causes nearly 15,000 deaths in the U.S. annually.

Overuse of antibiotics has increasingly put patients in heath care facilities at risk for acquiring *C. diff* and made some strains of the bacteria particularly hard to treat. But newly discovered information about a type of toxin released by the most dangerous strains of *C. diff* is providing researchers with a map for developing drugs that can block the toxin and prevent the bacteria from entering human cells.

"The most dangerous strains of *C. diff* release a binary toxin that first binds to cells and then creates a pore-forming channel that allows the toxin to get inside and do harm," said Amedee de Georges, the study's principal investigator and a professor with the Advanced Science Research Center at The Graduate Center, CUNY's Structural Biology Iniative. "We were able to combine several increasingly popular biophysical imaging techniques to visualize and characterize every atom of this binary toxin and show us where they are positioned. These details provide a critical and extremely useful starting point for designing drugs

that can prevent *C. diff* infection."

Researchers used a combination of tools—cryogenic electron microscopy, X-ray crystallography, nuclear magnetic resonance, and small angle X-ray scattering—to observe and identify the *C. diff* toxin's structure and mode of action. Researchers believed that it is a binary toxin (meaning it needs two components to function) that might employ a similar method to anthrax toxin to enter cells. Using that as their starting point, they sought to characterize how *C. diff* toxin is different than anthrax.

"We observed two similar but distinct forms of the *C. diff* toxin—one where we see the pore-forming channel and one where it is invisible," said the first author, Xingjian Xu, a Graduate Center, CUNY Ph.D. student and a researcher in de Georges' lab. "This gives us clues as to how to prevent the formation of the channel and stop the bacteria from entering the cell."

Researchers also identified a novel calcium binding site on one of the *C. diff* toxin's domains. This type of binding structure hasn't been identified on any other similar toxins, suggesting that calcium plays a critical role in regulating the formation and transition *C. diff* into cells.

The study's findings will guide the design of drugs targeting *C. diff* infections, and specifically, the more severe *C. diff* bacteria strains.

More information: Xingjian Xu et al, Structure of the cell-binding component of the Clostridium difficile binary toxin reveals a di-heptamer macromolecular assembly, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.1919490117