

Use of Toxin-Specific Single Domain Antibodies to Treat C. difficile Infections

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Technology description

Clostridium difficile is a gastrointestinal pathogen that is a leading cause of hospital-related infections in developed nations. It is responsible for *C. difficile*-associated disease (CDAD) in humans, with symptoms ranging in severity from mild cases of antibiotic associated diarrhea to fatal colitis. The recent emergence of hypervirulent, antibiotic-resistant, *C. difficile* strains with increased morbidity, mortality and recurrence rates have warranted the development of novel, non-antibiotic, treatment regimes. The development of antibodies targeting virulence factors - such as bacterial toxins - would help reduce the selection pressure that antibiotics place upon pathogens and also be useful to control the infection's recurrence. *Clostridium difficile* is a Gram-positive pathogen that produces two primary virulence factors, enterotoxins A and B, which are responsible for CDAD. Monoclonal antibodies specific for toxin A and toxin B have been shown to effectively treat CDAD and prevent disease relapse in animal models and in humans. A superior alternative to monoclonal antibodies for antitoxin immunotherapy is to use variable heavy-chain single-domain antibodies (VHHs) isolated from Camelid species. These VHHs maintain many characteristics of conventional mAbs, including high target affinity and specificity, with the added advantages of small size (~15 kDa), easy genetic manipulation, amenable to library screening and selection, inherent thermal and proteolytic stability, and high-yield, low-cost recombinant production in bacteria, yeasts, plants, and mammalian cells. In particular, toxin-specific VHHs engineered to resist the acidic pH and proteases of the gastrointestinal tract would make these VHHs efficacious oral therapeutics.

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