Atoxic Recombinant Holotoxins of Clostridium Difficile as Immunogens

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Background and Summary: Clostridium difficile is a gram positive, spore forming anaerobic bacillus that produces two exotoxins: toxin A and toxin B. Many strains of this species have acquired resistance to a majority of commonly used antibiotics. The reduction of commensal microflora as an effect of use of antibiotics allows C. difficile to grow and to produce harmful toxins in the intestine, without nutritional competition from normal bacterial flora. Transmitted primarily through contact with contaminated surfaces, C. difficile is a common cause of nosocomial antibiotics-associated diarrhea (CDAD) and pseudomembranous colitis. Infection caused by C. difficile accounts for millions of patient cases and billions of dollars yearly in treatment in hospitals, nursing homes and other care centers. C. difficile –associated disease is mediated mainly by exotoxins A (TcdA) and B (TcdB), which disrupts the epithelial barrier and cause intestinal inflammation. TcdA and TcdB are similar in sizes and structures and share putative receptor binding, transmembrane, and enzymatic domains.

The diagnosis of C. difficile infection remains a challenge. The current diagnostic modalities mainly consist of the detection of the C. difficile organisms and of their toxins in fecal samples which are labor-intensive and time-consuming. Standard therapy depends on antibiotic treatment, which in recent years has become less effective. Many patients who initially appear to have been cured suffer multiple relapses. In recent years, C. difficile –associated disease has emerged as the leading cause of one of the most widespread and potentially serious health care-associated infections acquired during a stay in a hospital or long-term care facility mostly due to the widespread use of broad-spectrum antibiotics and emergence of hypervirulent strains.

Our scientists have developed a rapid cell-based test to detect the function of C. difficile Toxins A and B. This test is highly sensitive and can detect a trace amount of C. difficile toxins, as low as 1pg/ml within 3 hours. Recent development has been focused on generation of inactive forms of TcdA and TcdB and chimera proteins for therapeutic purposes. Multiple mutations in the conserved domains were created to ensure a complete loss of toxicity while the native confirmation remains intact. As a result, our scientists have successfully created a vaccine composition for the treatment of C. difficile –associated disease. Preliminary animal studies have demonstrated that this immunogenic vaccine composition can be used in effective immunization against C. difficile infection.

Market and Applications: The growing incidence and severity of C. difficile –associated disease indicate a need for development of new diagnostic assay and treatment tools. The present inventions provide improved methods of the diagnosis and therapeutics of C. difficile –associated disease. Further efforts are under way to study the efficacy of the vaccine composition in patients infected with C. difficile.

Product Advantages:

- We have developed the cell-based rapid test which is highly sensitive and more efficient than the currently available diagnostic tools.
- The proposed vaccine composition is consisted of atoxic mutant forms of C. difficile Toxins A and B and their chimera proteins with intact native protein confirmation, thus providing a more powerful and practical approach to successful immunization against the infection.
- The mutations were created in the key amino acids known to be responsible for the toxicity and not in the receptor binding domains. Therefore these atoxic Toxins A and B can be internalized without toxicity.
- We have strong IP position including composition of matter and method of use claims.

Licensing Opportunity: An IP portfolio supporting the discoveries is available for licensing.

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