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***C. difficile* family of products**

Background: *C. difficile* infections are a major problem for the healthcare industry. Hospitalized patients under heavy antibiotic treatment are most vulnerable and are frequently infected with *C. difficile* (CDI). Treatment and support of infected patients is a burden on the medical system and is very debilitating to these patients. *C. difficile* causes diarrhea but this condition can also be the result of many different types of infection. It is important to recognize when *C. difficile* is the cause of an infection in order to treat it appropriately. Since CDI is an important and costly disease, research is active, vaccine development is underway and diagnostic testing is under active development.

Target customers have interest in:

- Vaccine development: either a vaccine company or a testing support company
- Diagnostics: test laboratories running diagnostics or the suppliers of diagnostic tests
- Basic research in the area of infectious diseases

List Biological Laboratories provides:

- Purified *C. difficile* toxins A and B, produced by the native strain (Product Nos. 152 & 153).
- Antibodies directed to *C. difficile* toxins A and B are also available. List provides both Chicken IgY and goat antibody directed to toxin A (Product Nos. 753 & 752) and for toxin B, Chicken IgY, Product No. 754.
- Another major antigen, also produced by a native strain of *C. difficile*, glutamate dehydrogenase (cdGDH) has been purified recently (Product No 159). Antibodies to this antigen will soon be available as Product No. 760.
- *C. difficile* binary toxin recombinant subunits A and B (Product Nos. 157 & 158) and an antibody directed to the B subunit of binary toxin (Product No. 758)
- Toxoids to toxins A and B are also available (Product Nos. 153 & 154).
- The toxins can be custom produced per GMP guidelines as APIs for use in vaccines.

Some interesting facts:

- *C. difficile* toxin A and toxin B both contribute to the disease and must be controlled by therapies. Toxin B is highly cytotoxic and the most sensitive detection of this toxin is an epithelial cell toxicity assay. Cell based assays are becoming very important in determining the cause of the diarrheal disease in hospitalized patients. These assays are made quite accurate with specific antibodies and are called Toxin Neutralization Assays (TNA). If mixing the stool sample with anti-Toxin B antibodies protects the cell culture from the toxic effects, this is considered proof that *C. difficile* toxin B is present in the patient. The List Labs' Chicken anti-*C. difficile* toxin B chicken antibody has been demonstrated to be useful in these TNA cell-based assays.
- *C. difficile* toxin B is a difficult protein to work with. Solutions of the toxin can have a short shelf life. Currently we are working on a new formulation and a new way of handling the toxin to

increase its shelf life. Stability studies demonstrate that we know how to improve the toxin and we will soon release a more stable formulation.

- For diagnosis, the enzyme protein produced by *C. difficile*, early in an infection, cdGDH, is more readily detected by ELISA than the toxins. List Labs has purified this cdGDH protein from *C. difficile* cultures and expects that it will be used to develop test kits. To this end, we have produced the chicken anti-GDH antibody, which is available (Product No. 756).
- Binary toxin is another virulence factor secreted by the epidemic causing strains of *C. difficile*. List Labs has recombinantly produced both A and B subunits of this binary toxin. We also have antibodies to the B subunit that can be used to capture and detect the binary toxin. These products may be interesting for diagnostics and are of considerable interest in infectious disease research.

References:

Use of Toxin Neutralization and GDH testing in clinical assays:

Alfa MJ, Sepehri S (2013) Combination of culture, antigen and toxin detection, and cytotoxin neutralization assay for optimal *Clostridium difficile* diagnostic testing. *Can J Infect Dis Med Microbiol* 24(2) 89-92.

Use of Toxin Neutralization in vaccine testing:

Xie J, Zorman J, Indrawati L, Horton M, Soring K, Antonello JM, Zhang Y, Secore S, Mizejewski M, Wang S, Kanavage AD, Skinner JM, Rogers I, Bodmer JL, Heinrichs JH (2013) Development and Optimization of a Novel Assay to Measure Neutralizing Antibodies Against *Clostridium difficile* Toxins. *Clinical and Vaccine Immunology* 20(4) 517-525.