Compounds Inhibiting Cholera Toxin and Other Similar Bacterial Toxins

Background
Bacterial toxins have been known to be primary mediators of a number of diseases both of the intestinal tract and of other organ systems. Some bacterial toxins are known as AB-type toxins, since they are composed of a catalytic A subunit and a cell binding B subunit. Examples of such AB-type toxins include cholera toxin (CT), the E.coli heat-labile toxin (LT) responsible for traveler's diarrhea, the B. pertussis toxin responsible for the symptoms associated with whooping cough, exotoxin-A produced by Pseudomonas aeruginosa strains found in cystic fibrosis patients or on damaged skin of burn victims, Shiga toxin, and similar toxin produced by enterohemorrhagic E.coli which has been associated with contaminated produce and ground beef products. Typically, the diseases caused by these bacterial toxins have been treated symptomatically because drugs effective against the toxins themselves have not been available. Accordingly, there is a great need for drugs that would act directly against these toxins.

Recently UCF researchers demonstrated that isolated cholera toxin A1 polypeptide (CTA1) is a thermally unstable protein and can spontaneously unfold at physiological temperature when separated from the holotoxin in the endoplasmic reticulum (ER). This unfolding event triggers a host mechanism which exports the toxin A chain from the ER to the cytosol where its cellular target resides. Because CTA1 is actually in an unfolded state at physiological temperature, a cytosolic chaperone must provide the driving force for CTA1 export from the ER. Thus, CTA1 passage into the cytosol and CT intoxication could also be prevented by inhibiting the chaperone that provides the driving force for CTA1 export from the ER. Sodium 4-phenylbutyrate (PBA), a non-toxic drug candidate that has already been FDA-approved for use in treating urea cycle deficiencies, was shown to prevent thermal unfolding of CTA1 and prevent CT intoxication of cultured cells. Geldanamycin (GA), an inhibitor of Hsp90 that is in phase I clinical trials as an anti-cancer agent, has been identified as second therapeutic anti-toxin agent.

Invention
The present invention proposes a new mechanism by which extracellular AB-type toxins gain access to the affected cells of the body and identifies several therapeutic agents for inhibition of bacterial toxins.

Application
PBA and GA are potential therapeutics for cholera toxin as well as other AB-type toxins mentioned above.

Advantages
• Therapeutic agents, PBA and GA, that were shown to be effective in suppressing entry of cholera toxin and possibly other types of AB-type toxins are already in clinical use for other indications.

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Selected References

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