

# Novel molecules can boost vaccine potency

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Two novel proteins studied by a University at Buffalo professor of microbiology and immunology appear to have the potential to enhance the production of antibodies against a multitude of infectious agents.

Terry D. Connell, Ph.D., professor of microbiology and immunology in the Witebsky Center for Microbial Pathogenesis in the UB School of Medicine and Biomedical Sciences, developed and patented the LT-IIa and LT-IIb enterotoxins and their respective mutant proteins as new mucosal adjuvants, or “boosters,” that can enhance the potency of existing and future vaccines.

Connell and colleagues published five papers in 2007 describing their advances. They are the only research group in the scientific community investigating the immunology of these adjuvants.

The researchers currently are working to develop a safe and effective method to deliver the immune-enhancing molecules to the body’s mucous membranes -- the first line of defense against most pathogens -- to elicit protective immune responses on those membranes.

“Almost every bacterium and virus that attacks us doesn’t bore through the skin,” said Connell. “These infectious agents enter by colonizing the mucosal surfaces on the eye, sinuses, mouth, gut lining, lungs and genital tract.”

To date Connell and colleagues have determined, using a mouse model, that the nasal passage is the best mucosal surface on which to apply LT-

IIa and LT-IIb as mucosal adjuvants. Mixing a very small amount of LT-IIa or LT-IIb with an existing antigen and dripping the mixture into a mouse's nose subsequently produces a strong antigen-specific immune response in the nasal passages, as well as in saliva, the urogenital tract and the bloodstream, their research showed.

In contrast, immunizing the mouse with only the antigen generates a much lower level antigen-specific immune response at those sites.

This method of application is particularly suitable for immunizing populations in underserved areas, said Connell.

“If I want to immunize somebody in Uganda with a vaccine that must be injected, for instance, I have to bring needles, everything must be sterile and everything must be kept cold, which means we need refrigeration.

“But if I can vaccinate through the nose, all I have to do is dry the antigen and my adjuvant. When I get to the middle of Uganda, I boil some water, pour in the antigen and adjuvant, stir it up, put it in an atomizer and ‘sniff.’ The mixture doesn’t even have to be sterile, because the nose isn’t sterile.”

Connell began studying the two adjuvants as a postdoctoral researcher at the Uniformed Services University of the Health Sciences (USUHS) in Washington, D.C., in 1989. The molecules had been isolated five years earlier by Randall Holmes, M.D., Ph.D., his post-doctoral advisor. Connell began his investigations into the activities of LT-IIa and LT-IIb at the USUHS by mapping the regions of the two enterotoxins that were important for receptor binding, toxicity and for assembly of the multisubunit proteins.

LT-IIa and LT -IIb are similar to cholera toxin in 3-dimentional structure and toxic activity. Yet, the amino-acid sequences of the binding subunits

of LT-IIa and LT-IIb are significantly different from the amino-acid sequence of the binding subunit of cholera toxin. These amino acid differences underlie the specificity of LT-IIa and LT-IIb for ganglioside receptors, which are different from the ganglioside bound by cholera toxin. [A ganglioside is a complex molecule that contains both lipids and carbohydrates and is found in the outer membrane of many kinds of cells.]

Connell hypothesizes that it is these different ganglioside-binding activities that contribute to the unique immunological activities of LT-IIa and LT-IIb.

“Basically, LT-IIa and LT-IIb are molecules you can add to any vaccine candidate to augment the immune response to that protein, whatever it may be,” Connell stated.

The one problem researchers may encounter and on which they are working currently is to ensure that their vaccine booster doesn’t travel to the brain via the olfactory nerve, or if the booster does traffic to the brain, that it doesn’t have harmful properties. Connell said some of the mutant LT-IIa and LT-IIb adjuvants they have developed appear to exhibit no toxicity in cells, and thus have the potential to exert no harmful effects on neuronal cells. His molecules may be ready for human trials in a year, he said.

Source: University at Buffalo

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