Do-it-yourself adjuvants

By Lauren Martz, Staff Writer

An unexpected finding by researchers at **The University of Chicago** could open up a new application—vaccine adjuvants—for a class of self-assembling peptides the team is primarily studying for use in regenerative medicine.¹ Although these immunogenic biomaterials produce a strong antibody response, the group has not yet established that the compounds will contribute to the immune memory of the kind provided by a T cell response.

In 2009, Joel Collier and his team developed self-assembling peptide matrices from a fibrilizing peptide called Q11.² The peptide self-assembled to form β -sheet-rich nanofibers and could be tweaked to display a desired amino acid sequence or chemical group on its surface. The team has been pursuing the material as a scaffold for regenerative medicine products because it does not induce an immune response.

However, Collier and colleagues noted that the amino acid sequences they had expressed on the surface of the self-assembling peptides in their study were all only weakly immunogenic. To determine whether the weak immunogenicity was a characteristic of the biomaterial itself or a result of the chosen peptides, the team set out to display stronger epitopes on the self-assembling peptides.

Collier is assistant professor in the Department of Surgery at the University of Chicago.

Collier's team designed a peptide containing both a self-assembling domain from Q11 and a 17-amino-acid sequence from ovalbumin, a highly immunogenic peptide from chicken eggs. The peptide, dubbed O-Q11, self-assembled in solution and expressed the ovalbumin sequence on its surface.

Surprisingly, in mice, O-Q11 induced IgG1, IgG2 and IgG3 antibody titers that were comparable to those induced by the ovalbumin antigen in combination with complete Freund's adjuvant. O-Q11 also induced higher levels of IgM than ovalbumin plus Freund's adjuvant.

At the same time, the self-assembling peptide with antigen did not increase levels of the T cell-mediated cytokines interferon- γ (IFN γ), IL-2 or IL-4, suggesting that the immune response is independent of T cells.

In splenocytes from immunized mice, O-Q11 did not induce apopto-

sis, suggesting that the self-assembling adjuvants are not toxic.

Results were published in the *Proceedings of the National Academy of Sciences*.

Chuanhai Cao, assistant professor in the Department of Molecular Pharmacology and Physiology at the **University of South Florida College of Medicine**, said the result could be “purer and cheaper” adjuvants.

Don Diamond, director of the Division of Translational Vaccine Research and professor in the Department of Virology at the **Beckman Research Institute at City of Hope**, told *SciBX* that the researchers now “need to show that the self-assembling peptides are able to be used in conjunction with antigens that could generate antibodies that have a real function in life, such as neutralizing pathogens. They need to assess if antibodies elicited as a result of immunization with the peptide-antigen complex could be protective.”

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—Joel Collier,
The University of Chicago

Collier agreed the next step is to “evaluate the applicability of this approach to specific disease-related epitopes” rather than just to ovalbumin. He also wants to “assess the short-term and long-term safety of the molecule. This is a self-assembling molecule and it will be necessary to determine whether it is completely and safely cleared.”

Cao noted that it also will be important to make sure the self-assembling peptides themselves or epitopes on their surface have no homology to human proteins. “Overall, it is a

novel idea to use these peptides as adjuvants, but a homology analysis will be required. Homology to human proteins will cause serious safety problems,” he said.

Memorizing multiple epitopes

To minimize adverse effects that are sometimes triggered by whole-organism or whole-protein vaccines, researchers use synthetic peptides representing discreet epitopes found on a virulent microorganism, also called subunit vaccines. But there are trade-offs.

First, synthetic peptides usually are poorly immunogenic, requiring extra help to establish an immune response.

Second, an effective immune response to infectious agents requires targeting multiple epitopes rather than only one.

“The peptides carry a single epitope—infectious agents have many epitopes, including mutated epitopes and epitopes masked on the surface,” noted Robert Hancock, director of the Centre for Microbial Diseases and Immunity Research, and Canada research chair and professor in the Department of Microbiology and Immunology at **The University of British Columbia**.

Third, the approach does not induce an immune memory response.

Immune boosters such as particulates, oil emulsions, toll-like receptor (TLR) ligands and immunostimulatory complexes are used to address the first issue, but these products are composed of heterogeneous material and can thus have complex and undesired effects.³

Addressing the second issue could reduce the potential cost advantage of the peptide approach, according to Hancock. Although the self-assembling peptides described in the *PNAS* paper “can probably display multiple epitopes because of the nature of the strategy, this could significantly increase cost of production,” he noted. “The benefit of this system is probably the reduced cost. The cost of generating self-assembling peptides with multiple epitopes might eliminate that advantage.”

Finally, Hancock said that “an important limitation to the adjuvants is that they don’t really elicit T cell help. It is true that you can get strong T cell-independent immune responses, but generally speaking—and especially in young children—you need to have T cell help.”

Diamond agreed. “The self-assembling peptide scaffold doesn’t elicit a T cell-dependent response. I would therefore worry about its potential. No T cell response generally will mean that there won’t be any memory when the primary antibody-producing cells decay,” he said.

“It is not yet known how well these materials provide for long-term memory or protection against a given pathogen,” Collier told *SciBX*. “But we are working rapidly to clarify this question.”

However, he added, “even if these materials do not generate long-lasting memory, they may still find clinical use for immunotherapeutics not aimed at vaccination but at more acute conditions,” such as cancer.

Collier said a provisional U.S. patent application has been filed for the self-assembling sequence as an immune adjuvant and the IP is available for licensing.

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