Synthetic saponins

By Lauren Martz, Staff Writer

Memorial Sloan-Kettering Cancer Center researchers have designed vaccine adjuvants that are synthetic derivatives of **Antigenics Inc.**'s QS-21,[1] a purified fraction of a plant extract containing a mixture of two natural saponin isomers. The team thinks its molecules could be safer and more stable than the parent compound, although the efficacy of the synthetic adjuvants still needs to be proven.

Adjuvants are inherently risky, as their job is to elicit and increase the body's reaction to a given vaccine. Indeed, the only approved vaccine adjuvants in the U.S. are aluminum salts, which are generically called alum, and AS04, which is a combination of aluminum hydroxide and monophosphoryl lipid A (MPL). Alum and AS04 are safe, but have low immunogenicity and thus low efficacy.

Antigenics gained rights to QS-21 through its acquisition of Aquila Biopharmaceuticals Inc. in 2000 and hopes the compound will improve immunostimulation compared with alum. QS-21 is in Phase III testing as an adjuvant to vaccines from **GlaxoSmithKline plc** for malaria, non–small cell lung cancer (NSCLC) and metastatic melanoma.

Compared with alum, "antibodies appear earlier with treatment using QS-21 and can reduce the required antigen dose," said Charlotte Kensil, formerly VP of research at Antigenics who now is an independent consultant working with the company. "This can save material if the antigen is in short supply, for a production benefit. Another feature of QS-21 is that it is able to generate cell-mediated immune responses to subunit antigens. Aluminum hydroxide does not."

However, the company has encountered variable molecular composition and chemical instability with QS-21,[2,3] which could raise concerns about safety and consistency.

David Gin and colleagues at Sloan-Kettering have been seeking to capture QS-21's efficacy profile while improving its safety by designing hydrolytically stable and homogeneous synthetic saponins.

As the team reported in the *Journal of the American Chemical Society*, mice receiving subcutaneous injections of a synthetic saponin adjuvant plus a melanoma vaccine had higher antibody titers against melanoma-associated antigens than mice receiving either the vaccine plus QS-21 or the vaccine alone.

Also in mice, injection of one of the derivatives with the melanoma vaccine resulted in significantly less weight loss than injection of QS-21 plus the vaccine ($p \leq 0.025$). The melanoma vaccine alone caused no weight loss. The researchers used weight loss as a good "standard initial overall assessment of toxicity," they wrote in the paper.

Giampietro Corradin, associate professor in the Department of Biochemistry at the **University of Lausanne**, wanted to see "more extensive studies on the potential adverse reactions" instead of just weight loss measurements.

Don Diamond, director of the Division of Translational Vaccine Research and a professor in the Department of Virology at the **Beckman Research Institute at City of Hope**, has a similar view.

"Body weight is just a collective measure of toxicity" and the effects from other adverse events, he noted. "More elaborate toxicity studies covering broader parameters, including metabolic profiles and physiologic indicators of latent toxicity, will be required."

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> ***—Don Diamond, Beckman Research Institute at City of Hope***

One step beyond

In addition to wanting more detailed safety studies, researchers contacted by *SciBX* also said the Sloan-Kettering group should show that the QS-21 derivatives improve the efficacy of vaccines.

"Simply eliciting antibodies doesn't prove the adjuvant has done its job," said Diamond. "They will need to show that the adjuvants and antigens protected against or cleared up a disease better than the antigens alone."

"These researchers have partially solved the issue of toxicity and heterogenicity of saponins, but it is not clear to me that they have reliable efficacy," said 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**. "The things that have to be done are to prove *in vivo* efficacy in raising antibodies that will protect against something and do a much more detailed toxicity workup."

Chuanhai Cao, assistant professor in the Department of Molecular Pharmacology and Physiology at the **University of South Florida College of Medicine**, said the QS-21 derivatives should be tested in a larger number of animals. He said there are always hyper- and hypo-responses in some animals, so larger numbers of animals per group will give a better result.

In addition, Cao noted that the *JACS* studies did not look at the effects of the adjuvants in the absence of a vaccine. "The next study should consider doing so," he said.

Manufacturing

The Sloan-Kettering researchers declined to discuss their next steps, but City of Hope's Diamond thinks the derivatives could be combined with therapeutic vaccines for cancer and other serious diseases.

"The seriousness of the condition will be weighed against the toxicity of an adjuvant. Higher toxicities may be tolerated for more efficacy when used with therapeutic vaccines," he said. "This is in strong contrast to the use of adjuvants in prophylactic vaccines, which must have a pristine safety record for use in the general public."

Regardless of indication, Corradin thinks the synthetic derivatives described in *JACS* have value because they are "more homogenous, better characterized and more stable" than the parent compound.

Cao suggested it will be easier to produce and modify the derivatives than the natural saponins. He said it is truly difficult to extract saponins from the plant for large-scale preparation.

Kensil, however, said that producing the derivatives was not straightforward. "A concern is that the derivatives are a product of a complex, multistep process. Overall yield might be low and costs might be high," she said.

Kensil added: "The yield of QS-21 using the current extraction process is more than sufficient to meet clinical and expected commercial supply needs at a cost acceptable to all stakeholders. Current screening techniques ensure a reproducible starting material meeting strict criteria. There is no issue getting materials that meet the requirements."

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COMPANIES AND INSTITUTIONS MENTIONED

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