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Rapid immunotherapy for hayfever

Jo Whelan, Freelance writer

A new immunotherapy product could provide effective relief from allergic rhinitis (hayfever) after just six weeks of treatment. Researchers at Dynavax Technologies (Berkeley, CA, USA) have conjugated a ragweed allergen with an immunostimulatory DNA sequence to produce a therapy that appeared to be safe and effective in a recent Phase II trial.

Seasonal allergic rhinitis brings misery to over 35 million sufferers in the USA alone [according to the American Academy of Allergy, Asthma and Immunology (AAAAI): http://www.aaaai.org]. Airborne pollens cause runny nose, sneezing, nasal congestion and itchy, watering eyes in susceptible individuals. Symptomatic treatment with antihistamines, decongestants and nasal steroids brings partial relief but is not a satisfactory long-term option for many severely affected patients.

Immunotherapy, in the form of injections of a specific allergen, can be used to modify the immune response mounted to that allergen. It is well documented as effective [1] but its use is limited by the lengthy treatment regimen required: typically 16–24 injections over 3–4 months, followed by maintenance injections every 2–3 weeks for several years. In addition, 1–5% of patients will experience either a serious local reaction or a systemic anaphylactic reaction (according to the AAAAI).

Reprogramming the immune system

Immunotherapy works by changing the immune response to an allergen from a T_H2 to a T_H1-type response; these are mediated by type 2 and type 1 T-helper cells, respectively [2]. The T_H2 pathway is associated with the inappropriate immune reaction seen in allergies, whereas the T_H1 pathway is activated by viral and bacterial infections and does not produce allergic reactions. Short sequences of bacterially derived DNA, called immunostimulatory sequences (ISSs), are known to promote the development of type 1 T-helper cells [3].

Researchers at Dynavax have linked a proprietary ISS to Amb a 1 (Fig. 1), the dominant allergen in ragweed pollen, which is a major trigger of allergic rhinitis. In preclinical studies, the combination was shown to enhance the immunogenicity of Amb a 1 in mice, rabbits and monkeys. It is also less allergenic to humans than unconjugated Amb a 1. Basophils from people with ragweed allergy showed a 30-times reduction in histamine release when challenged with the conjugate compared with Amb a 1 alone or a free mixture of Amb a 1 and the ISS [4].

In a second study, the linked product promoted T_H1 cytokine expression and downgraded T_H2 cytokine expression in PBMC cultures from humans with ragweed allergy [5]. The conjugated product was again more effective than a mixture of free ISS and Amb a 1.

'By putting pieces of DNA on the surface of the allergen we create a physical impediment to IgE recognition of the allergen,' explains Dino Dina, President and Chief Executive of Dynavax. 'We decrease the visibility of the allergen to the IgE system – which is largely responsible for histamine release and the associated symptoms – by between 100- and 500-times. ISSs work by activating antigen-presenting cells via a natural pathway and in doing so they completely block the activation of the T_H2 and IgE system. They instead activate the dendritic cells to present to the T_H1 cells and block the T_H2 presentation pathway through the generation of specific lymphokines and chemokines.'

He continues: 'By linking the ISS and the allergen we force them to go into the same dendritic cell. Based on animal

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studies, this increases the potency of the intervention about 100-fold. If you co-administer them unlinked, the chances of individual cells receiving both elements are low.'

Safety

A randomized, placebo-controlled Phase II clinical trial has recently been completed, and preliminary results were reported by Peter Creticos, Associate Professor of Medicine at Johns Hopkins University [6]. Now known as AIC, the product was given to 25 adults with a history of seasonal allergic rhinitis and positive skin test reactions to ragweed pollen. The volunteers were injected with AIC once a week for six weeks, reaching a maximum dose of 12 μg. Nineteen volunteers completed the course: there were no withdrawals caused by adverse events. AIC was well tolerated, producing minor local reactions only and no systemic reactions. The participants were followed up through the ragweed season.

'AIC has now been tried in over 800 injections in about 200 patients and there have been no adverse events that needed therapeutic intervention,' says Dina. 'In the Johns Hopkins trial we have seen a statistically significant reduction in the level of rhinitis symptoms experienced and a drastic reduction in medication use.' A full analysis of the data is not yet available but Dina says the impact is 'greater than that typically seen with standard anti-IgE therapies'.

'Our studies represent a major advance in the development of new treatment for allergic diseases,' said Creticos. 'This study demonstrates that we can induce a clear clinical response with this brief regimen.' There has not yet been sufficient follow-up time to determine whether maintenance therapy will be necessary. But Dina says that some evidence is emerging that subsequent exposure to the allergen actually enhances the therapeutic effect. More studies will be needed to confirm this.

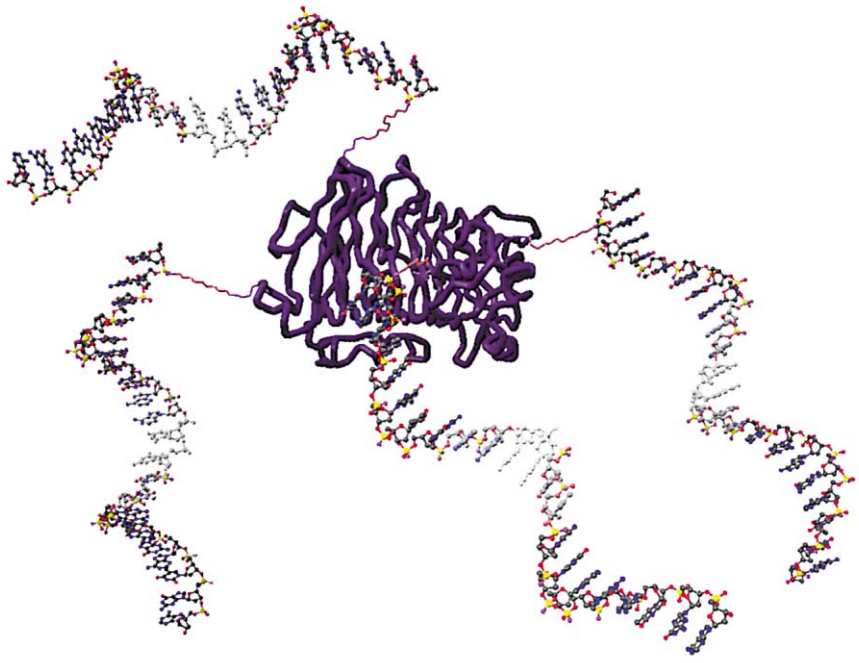

Figure 1. Structure of the ISS-Amb a 1 congugate, AIC. The central domain is the allergen Amb a 1, extracted from ragweed. Linked to it are four molecules of the proprietary immunostimulatory oligonucleotide ISS1018, which is 22 nucleotides long. Attachment is via covalent bonds using a short linker. Figure kindly provided by Dynavax Technologies (Berkeley, CA, USA).

Dynavax is also applying ISS technology to grass pollen and peanut allergens. 'We have already managed to suppress anaphylaxis from peanut allergy in mice,' adds Dina.

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