

EDITORIAL



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Translation of experimental immunotherapy

The continuing exploration of new strategies for allergen immunotherapy in mouse models raises the need to consider the obstacles encountered in clinical translation. In this issue, Korotchenko et al¹ report that ovalbumin conjugated with the glycan laminarin markedly ameliorated allergic responses induced by ovalbumin when delivered by laser facilitated epicutaneous application. The conjugation targeted the allergen to the C-type lectin-like receptor Dectin-1 on dendritic cells and reduced the IgE-binding capacity of the allergen without affecting its ability to induce IgG blocking antibody. Pre-existing respiratory allergy was markedly ameliorated and adverse local reactions produced by unconjugated allergen did not occur. Adding a new dimension, the laser delivery lessened the stimulation of the IgE antibody induced by the therapy, a hallmark of human subcutaneous immunotherapy that was found in parallel experiments with the model.

Laser facilitated epicutaneous delivery, which increases skin permeability and attracts dendritic cells has been explored extensively for anti-microbial vaccination in humans and mice with different types of laser exposure inducing different adjuvant effects.² Laser machines are readily available and have widespread use for scarring and tattoo removal and exposures of a minute can be effective without producing adverse reactions or discomfort. As summarized by Korotchenko et al, it has already been used in mouse experiments to show its potential for desensitization using purified real-life allergens and inhalation models employing house dust mite and pollen extracts. Strategies with mannan glycoconjugates that engage a broader spectrum of C-type lectin-like receptors have similarly been tested and warrant further investigation. While further experiments with allergen specificity would be useful, and there are differences in Dectin-1 receptor expression and signalling between mice and men, experiments in humans would seem overdue. Epicutaneous immunotherapy with allergen applied in skin patches has been trialled for food allergy with a good safety and tolerability profile but with questionable efficacy³ and skin patch treatments with pollen extracts have shown some efficacy albeit with local adverse reactions.⁴

The prospect of translating new strategies into short-course immunotherapy raises the spectre of previous failures. The most analogous venture was the use of ragweed allergen conjugated with a TLR9 CpG oligonucleotide ligand. The conjugated Amb a 1, like the laminarin conjugate here, showed reduced IgE binding and repeated studies in mice showed that short courses of prophylactic and therapeutic immunizations ameliorated aeroallergy-related symptoms including conjunctivitis induced by

the chronic administration of pollen extracts. Human studies showed that a short course of subcutaneous injections reduced Th2 immune responses, increased cells with a regulatory T-cell phenotype and suppressed seasonal increases in IgE antibody.⁵ A paper reported that a double-blind, placebo-controlled phase 2 trial failed to meet its primary endpoint of reducing secretions in nasal provocation tests but did improve symptom scores and quality of life assessments.⁵ Press releases then disclosed that a larger trial somehow failed and there has been no further investigation or analysis in scientific journals. It would seem that immunotherapy with defined and innovative reagents needs to be trialled for efficacy with little scope for optimization and experimentation. This contrasts with the many trials of allergen extracts being conducted that continue to show partial amelioration of symptoms, the need for years of repeated administrations and poor compliance, including for sublingual delivery. Looking back at the Amb a 1- immunostimulatory oligonucleotide it is clear that, in contrast to the preclinical studies, the injection regimen trialled did not induce IgG antibody and this has had an enduring association with successful immunotherapy. A recent clinical trial of a short course of injections of recombinant fusion allergen peptides designed to induce IgG responses to important grass pollen allergen components accomplished this⁶ and produced a therapeutic outcome similar to that historically achieved with the repeated administration of extracts. The recently demonstrated therapeutic effect of monoclonal antibody administration to cat-allergic subjects directly points to IgG antibody being mechanistically important and not just a marker.⁷ Other strategies could also be effective, and it can be noted that the amelioration of allergic inflammation by the Amb a 1-immunostimulatory oligonucleotide in mice was incomplete and goblet cell mucus was unaffected.⁸

Korotchenko et al not only used a single defined allergen for their laminarin-conjugate experiments but meticulously defined the conjugation and purification to the allergen, noting that variations of conjugation in the mannan glycoconjugate model seriously affected efficacy. The knowledge that allergen extracts typically contain deficiencies and imbalances in important allergen components adds to the benefit of introducing defined medicaments. Knowledge-based selections of important allergens have been made for grass pollen⁶ and house dust mite allergy,⁹ and for the grass pollen, their application has shown clinical efficacy. The purification method used for the Amb a 1 experiments⁸ would not have captured the basic Amb a

1 isoallergens and the selection of Amb a 1 alone ignored the known large variation of the contribution of the anti-Amb a 1 specificities to anti-ragweed IgE antibody in different patients. While mouse experiments have shown that immunotherapy with a single component can decrease responses to co-administered allergens the extent to which this can be accomplished is unknown and it would seem important to examine it in humans. As a corollary prevalence measurements do not show the importance of allergen components in the allergic responses so antibody titres or equivalent measurements are needed.

Preclinical experiments with mice are critical for exploring new types of immunotherapy. They have already demonstrated the potential for new strategies to become established treatments with benefits both to patients and healthcare systems. Translation to human treatment, however, remains problematic. The gap might be straddled by further facilitating human experiments to gain knowledge rather than obtain regulatory approval for new therapies. With the increasing attention directed to IgG antibody, a significant advance that is readily achievable would be for mouse experiments to measure absolute titres of antibodies so different studies and human experiments can be compared.

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CONFLICT OF INTEREST

Wayne Thomas is an inventor of house dust mite allergen patents licensed by the Telethon Kids Institute, Western Australia.

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REFERENCES

1. Korotchenko E, Schiesl V, Scheiblhofer S, et al. Laser-facilitated epicutaneous immunotherapy with hypoallergenic beta-glucan neoglycoconjugates suppresses lung inflammation and avoids local side effects in a mouse model of allergic asthma. *Allergy*. 2020. <https://doi.org/10.1111/all.14481>
2. Kashiwagi S, Brauns T, Poznansky MC. Classification of laser vaccine adjuvants. *J Vaccines Vaccin*. 2016;7(1):307.
3. Fleischer DM, Spergel JM, Kim EH, et al. Evaluation of daily patch application duration for epicutaneous immunotherapy for peanut allergy. *Allergy Asthma Proc*. 2020;41(4):278-284.
4. Senti G, von Moos S, Tay F, Graf N, Johansen P, Kündig TM. Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. *Allergy*. 2015;70(6):707-710.
5. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med*. 2006;355(14):1445-1455.
6. Niederberger V, Neubauer A, Gevaert P, et al. Safety and efficacy of immunotherapy with the recombinant B-cell epitope-based grass pollen vaccine BM32. *J Allergy Clin Immunol*. 2018;142(2):497-509.
7. Orengo JM, Radin AR, Kamat V, et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. *Nat Commun*. 2018;9(1):1421.
8. Santeliz JV, Van Nest G, Traquina P, Larsen E, Wills-Karp M. Amb a 1-linked CpG oligodeoxynucleotides reverse established airway hyperresponsiveness in a murine model of asthma. *J Allergy Clin Immunol*. 2002;109(3):455-462.
9. Huang HJ, Curin M, Banerjee S, et al. A hypoallergenic peptide mix containing T cell epitopes of the clinically relevant house dust mite allergens. *Allergy*. 2019;74(12):2461-2478.