Title: Cross-Reactive, High-Affinity Monoclonal IgE Antibodies Underlie Tree Nut Co-Allergy

Authors: Croote D., Creeks P., Romero J., Sohail S., Lowman H.B., Wong J. J.W.

Background: Tree nut allergies are growing in prevalence and accidental exposure can result in severe and even fatal anaphylaxis. Consequently, there is a need to understand the molecular bases of clinical phenotypes, including co-allergy to multiple tree nuts. One approach that has been technically limiting until now has been the successful isolation of single B cells in a manner that allows for the sensitive recovery of full length, paired heavy and light chain sequences comprising monoclonal IgE antibodies. Overcoming this challenge provides a path for foundational advancements in our understanding of human IgE biology and allergen immunogenicity.

Methods: IgGenix applied its targeted discovery platform to isolate rare IgE antibodies responsible for allergic reactivity from numerous human subjects allergic to various tree nuts as part of an IRB-approved clinical study. These IgE antibodies were then re-engineered as IgG antibodies and characterized for their allergen specificity and their binding affinity to major tree nut allergens.

Results: Monoclonal antibodies (mAbs) isolated from allergic individuals exhibited a range of affinities, with some demonstrating high affinity in the sub-nanomolar range. Additionally, some mAbs exhibited cross-reactivity to well-characterized tree nut allergens in ways that recapitulate clinical tree nut co-allergy. For example, individual mAbs were discovered that cross-react with major cashew and pistachio allergens. Similarly, individual mAbs were discovered that cross-react with major pecan and walnut allergens.

Conclusions: An unbiased discovery platform based on single-cell RNA-sequencing of rare IgE-producing B cells is a powerful approach to understand the molecular underpinnings of allergen recognition and even clinical phenotypes such as tree nut co-allergy. More broadly, these insights serve as an encouraging beginning for developing therapeutics that target the key allergens driving allergic responses, thereby avoiding adverse events and slow response times consistent with prolonged allergen administration.

Topic:

14. Food allergy → Subtopic: Mechanisms