IgGenix

Title: Deconstructing the Human IgE Response in Peanut Allergy

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The severity of peanut allergy and its increasing prevalence pose challenges to allergic individuals, their caregivers, and the healthcare industry. Despite extensive characterization of allergenic peanut proteins involved in mediating reactivity, a molecular understanding of how patient IgE interacts with specific epitopes on major allergenic proteins has been absent due to technological limitations of isolating human monoclonal IgE antibodies from allergic individuals.

IgGenix applied its SEQ SIFTER single-cell RNA-sequencing platform to discover monoclonal IgEs from a diverse cohort of peanut allergic individuals. Monoclonal IgG4 antibodies, re-engineered from monoclonal IgE antibodies, were screened for their specificity to peanut allergens Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, and Ara h 9. A subset of antibodies were then characterized using affinity measurement and epitope binning. High affinity antibodies from unique epitope bins were then evaluated in functional assaying including plasma IgE blocking ELISAs, mast cell activation tests (MATs), and basophil activation tests (BATs).

The repertoire of IgE antibody specificities discovered in an unbiased way was skewed strongly towards binding Ara h 2 and/or Ara h 6, in line with existing literature on the immunodominance of these allergenic proteins. At the molecular level, epitope binning revealed strong evidence for the immunodominance of particular Ara h 2 and Ara h 6 epitopes. The functional importance of these epitope bins was demonstrated in blocking ELISAs and cell-based assays that led to the design of an approach to significantly inhibit peanut-mediated cellular degranulation.

A molecular understanding of peanut allergy, developed through a methodical approach beginning with unbiased IgE discovery, can serve as the foundation for therapeutic design that addresses the drivers of allergic reactivity. Owing to the absence of adverse events associated with allergen administration, IgG4 antibody-based biologics are poised to become a promising treatment option for allergic individuals, especially those seeking a fast onset of action or don't qualify for other treatment options.