Blood from Highly Allergic Donors Yields High-Affinity IgE Antibodies to Food and Non-food Allergens

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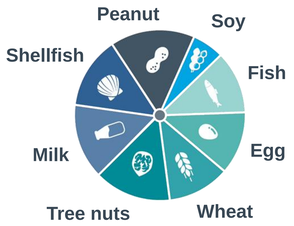
Rationale

Individuals with severe forms of allergic disease have evolved potent IgE responses to otherwise innocuous antigens. The B cells that produce these IgE antibodies are rare, however, and the technical challenge of isolating them has impeded progress toward a molecular understanding of allergen recognition and slowed the pace of therapeutic development.

Methods

IgGenix applied its state-of-the-art single-cell RNA-sequencing platform to capture extremely rare human B cells expressing IgE antibodies from peripheral blood of individuals with food and nonfood allergies [1]. IgG antibodies, designed to block the interaction of endogenous IgE with allergen and therefore prevent type I hypersensitivity reactions, were engineered from these human IgE antibodies and assessed for their specificity and affinity to major allergens.

Fig. 1. High level overview of the IgGenix platform. Extremely rare IgE-producing B cells are isolated from the blood of individuals with allergies (left) and scRNA-seq is used to recover the full-length, paired heavy and light chain sequences comprising monoclonal IgE antibodies (center). These IgE antibodies are then re-engineered such that they retain their allergen-specific IgE variable regions (Fv) but have the IgE Fc replaced with an IgG Fc.



- **Molds**
- **Dust mite**
- **Cat**
- **Dog**
- **Pollens**
- Medication
- Vaccines
- Venoms

Fig. 2. Our unbiased scRNA-seq discovery approach can isolate monoclonal human IgE antibodies specific to any allergen humans mount an IgE response against. The "big 8" food allergens and major groups of non-food allergens are shown. Allergens for which we have discovered monoclonal antibodies (mAbs) are bolded.

Convergent evolution of peanut-specific mAbs

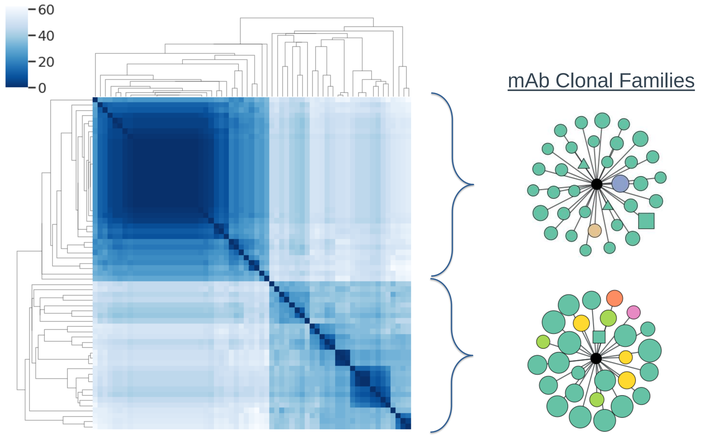


Fig. 3. Left: Pairwise Levenshtein edit distance clusters 63 mAb heavy chain amino acid sequences into two large clonal families (CFs) of peanut-specific mAbs. Right: network plot of each CF showing mAbs (nodes) according to the following legend: color = individual of origin; shape = mAb isotype (circle = IgE, square = IgG, triangle = IgA); size = heavy chain somatic hypermutation (larger = more SHM). Both CFs have mAbs of multiple colors, thereby depicting convergent evolution between unrelated individuals.

High affinity, allergen-specific mAbs derived from human allergic individuals

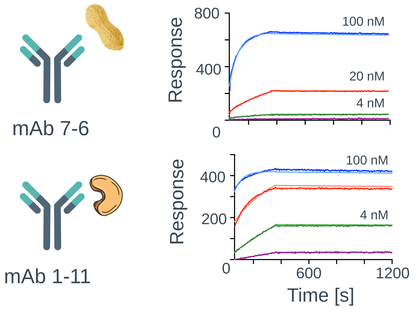


Fig. 4. mAb 7-6 binds the major peanut allergen Ara h 2 with an affinity of 72 pM. This IgG mAb was re-engineered from an IgE mAb isolated from a peanut-allergic individual.

Fig. 5. mAb 1-11 binds the major cashew allergen Ana o 3 with an affinity of 120 pM. This IgG mAb was re-engineered from an IgE mAb isolated from a tree nut-allergic individual.

Unbiased discovery from multi-allergic individuals yields mAbs to numerous allergens

	Plasma IgE titer
Total [kU/L]	745
Peanut [kUA/L]	330
Hazelnut [kUA/L]	16

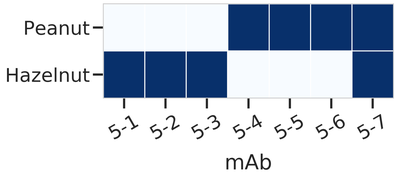
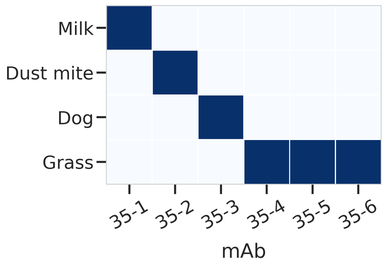


Fig. 6. Examples of peanut- and hazelnut-specific mAbs isolated from a peanut- and tree nut-allergic individual. Dark blue heatmap cells represent mAb (columns) binding to allergen (rows). mAb 5-7 is cross-reactive as it binds to both peanut and hazelnut extracts.



	Plasma IgE titer
Total [kU/L]	10742
Milk [kUA/L]	73

Fig. 7. Examples of mAbs specific to milk, dust mite, dog, and grass discovered from a highly atopic individual with milk and non-food allergies. Heatmap legend as in Fig. 6.

Conclusions

An unbiased discovery approach using IgGenix's optimized scRNA-seq platform yields antibodies to a wide range of allergens. Because these antibodies are high-affinity and of human origin, they serve as promising leads for developing therapeutics with superior efficacy, safety, and faster onset of action compared with allergen immunotherapy approaches.

References & Declaration

1. Croote, D., et al. *Science* 362.6420 (2018).

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