Title: Treating Peanut Allergy with an IgG4 Monoclonal Antibody-based Approach

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Peanut allergy is an increasingly prevalent unmet medical need that affects children and adults worldwide. The standard of care, allergen avoidance and rescue epinephrine administration, is unsatisfactory to patients and caregivers, and while advancements have been made in desensitization approaches such as oral immunotherapy, patients often suffer from frequent adverse events and face extended time horizons to treatment outcomes. Consequently, there remains a need for a safe and efficacious therapeutic with a rapid onset of action that protects against accidental allergen exposure and improves quality of life.

IgGenix isolated rare IgE antibodies from peanut allergic individuals using its proprietary single-cell RNA-sequencing discovery platform technology. IgE antibodies were then re-engineered as monoclonal IgG4 antibodies and assayed for their allergen specificity, affinity, and binding epitopes. Promising candidates were advanced through lead evaluation involving *in vitro* plasma IgE blocking ELISAs, mast cell activation tests, *ex vivo* basophil activation tests, *in vivo* animal models, and developability assessments.

Antibodies discovered in an unbiased manner from numerous peanut allergic individuals preferentially bound Ara h 2 and/or Ara h 6, with a minority of antibodies binding other allergens. Antibodies specific to Ara h 2 and Ara h 6 distributed nonuniformly into a small number of epitope bins, revealing immunodominance of specific epitopes on each allergen. Nearly all antibodies were of high affinity, with many exhibiting double-digit picomolar affinity. Select antibodies, when engineered and combined, were able to inhibit allergic plasma IgE from binding recombinant Ara h 2, inhibit peanut-mediated mast cell and basophil activation, and prevent anaphylaxis mediated by oral peanut challenge in a mouse model of peanut allergy.

An unbiased human IgE discovery platform based on single-cell RNA-sequencing is a powerful foundation from which to generate high affinity IgG4 antibodies that bind to immunodominant allergens and immunodominant epitopes on those allergens. These IgG4 monoclonal antibodies can form the basis of a therapeutic candidate exhibiting strong potency and efficacy *in vitro*, *ex vivo*, and *in vivo*. This enables a new paradigm for food allergy treatment characterized by protection within days of subcutaneous administration and the absence of adverse events associated with allergen administration.