

Cross-Reactive Shellfish-Specific Monoclonal IgE Antibodies Discovered from Highly Allergic Individuals

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Rationale

The prevalence of shellfish allergy is 1.5-2.5% in the United States and is even higher in Southeast Asia. Shellfish antigens can elicit potent IgE responses in individuals with severe allergies; however, the difficulty of discovering human monoclonal IgE antibodies has slowed progress in understanding the origins of allergen cross-reactivity at the molecular level.

Methods

IgGenix applied its single-cell RNA-sequencing platform to isolate rare human B cells that expressed IgE antibodies from the peripheral blood of individuals with shellfish allergies. Human IgE antibodies were engineered into IgG4 antibodies for recombinant expression and characterization. The purified IgG4 antibodies were subsequently evaluated for their specificity and affinity toward mollusks, crustaceans and dust mites.



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.

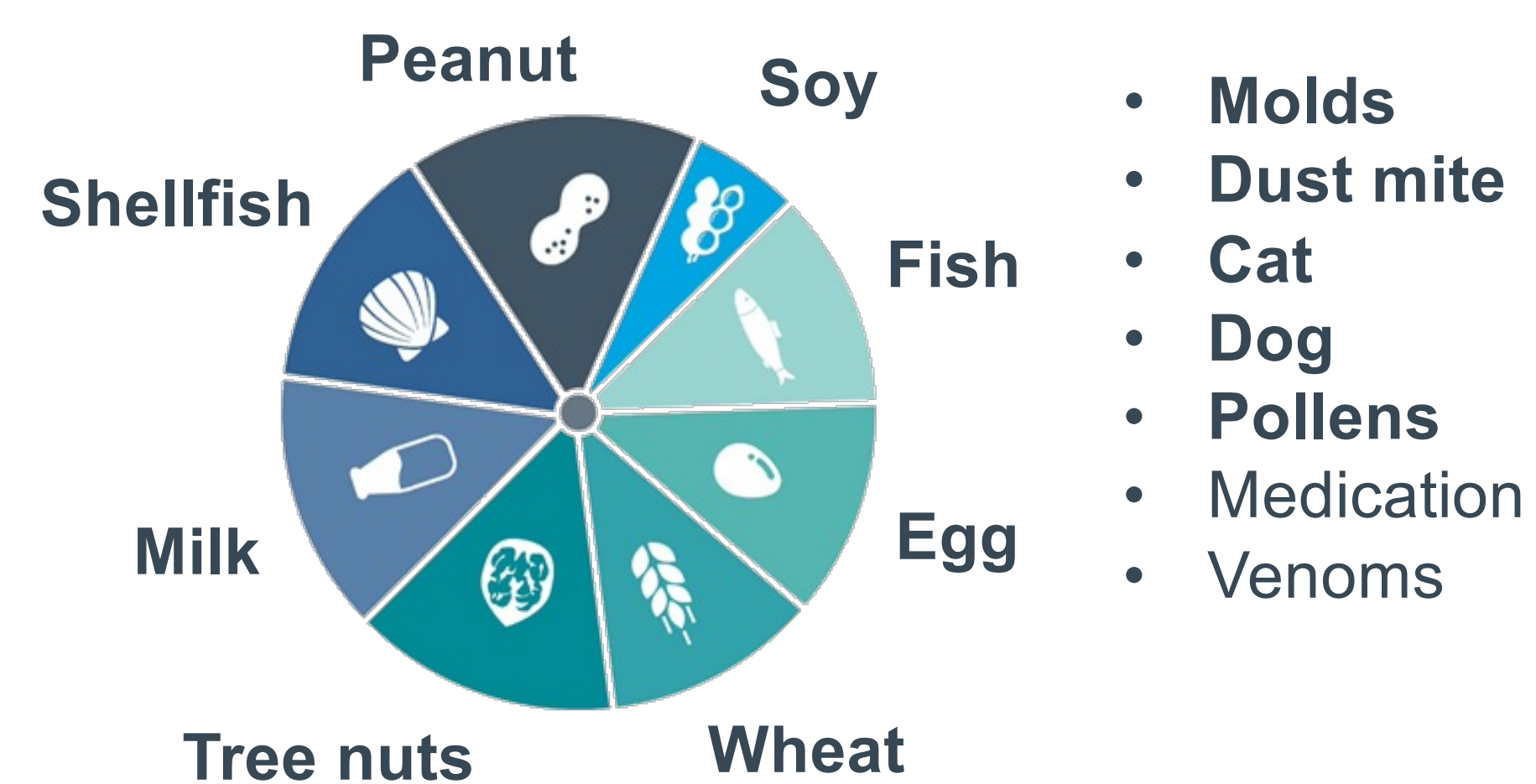


Fig. 2. Our unbiased scRNA-seq discovery approach can isolate monoclonal human IgE antibodies specific to any allergen humans mount an IgE response against. The “big 8” food allergens and major groups of non-food allergens are shown. Allergens for which we have discovered monoclonal antibodies (mAbs)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

Tropomyosin is a Conserved and Immunodominant Shellfish Allergen

Tropomyosin is a commonly recognized allergen in shellfish allergies. It is a protein that is found in many shellfish species, including shrimp, crab, lobster, clam, and has been associated with the development of shellfish allergies. Among other invertebrates, dust mite tropomyosin is also highly conserved relative to crustaceans’ counterparts.

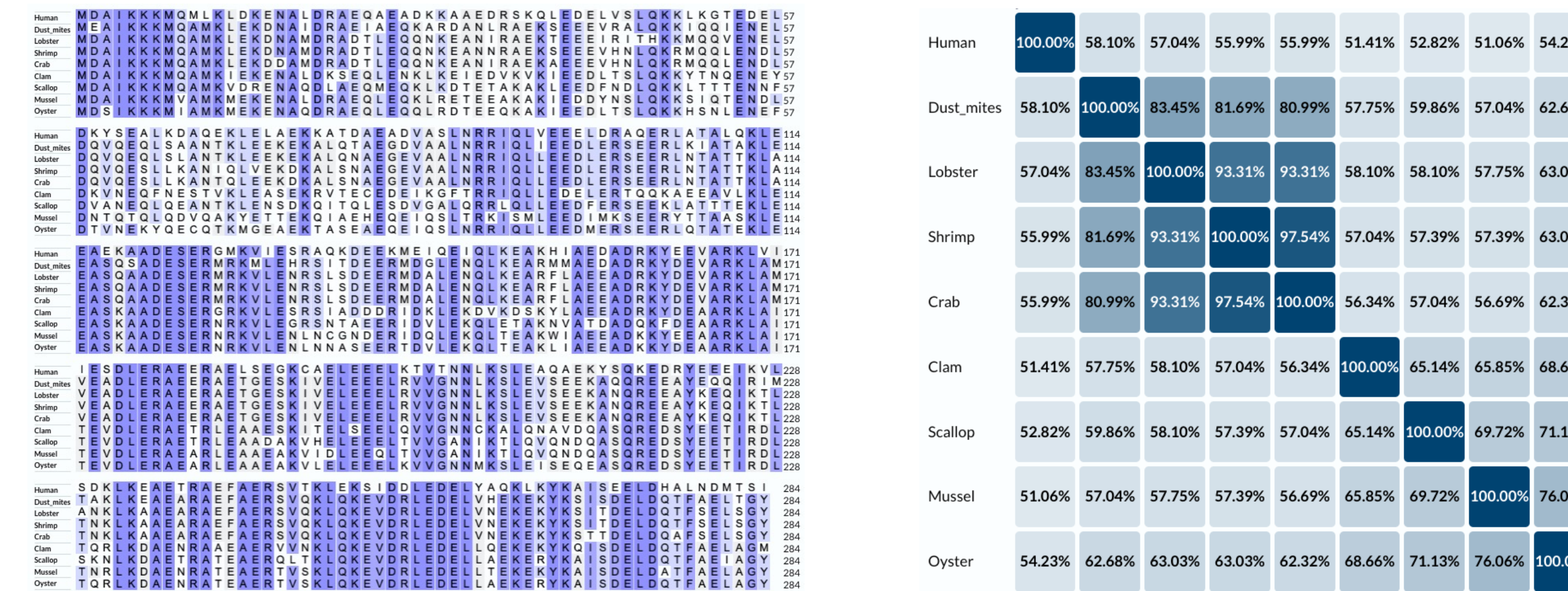


Fig. 3. Left: Multiple sequence alignment (MSA) of common shellfish, dust mite, and human tropomyosin. Right: Similarity matrix of tropomyosin listed in the MSA.

IgE Antibodies with Diverse Sequence Bind to Major Allergen Tropomyosin with High Affinity

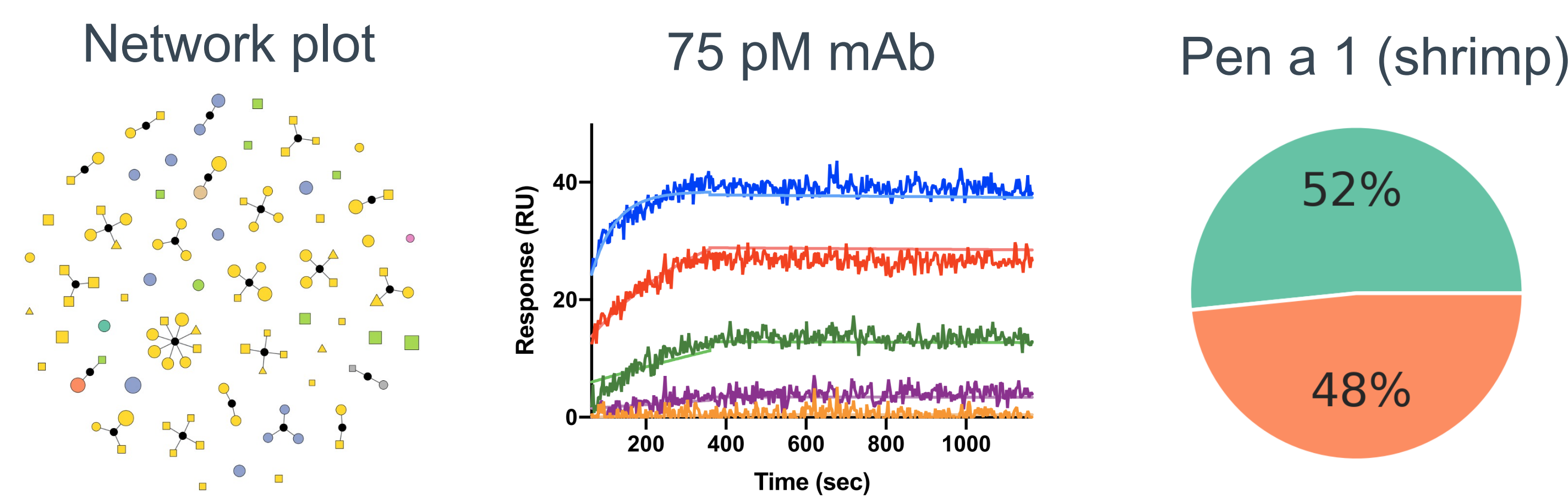


Fig. 4. Left: Network plot of 99 mostly IgE antibodies obtained from patients, differentiated by color (representing the individual of origin), shape (circles for IgE, squares for IgG, triangles for IgA) and size (larger symbols indicating higher levels of heavy chain somatic hypermutation). Middle: High-affinity shellfish mAb with sub-nanomolar affinity assayed by SPR. Right: Over half (52%) of the discovered IgE exhibit sub-nanomolar affinity to shrimp Pen a 1.

Shellfish Antibody Specificity Recapitulates Phylogenetic Similarity of Tropomyosin

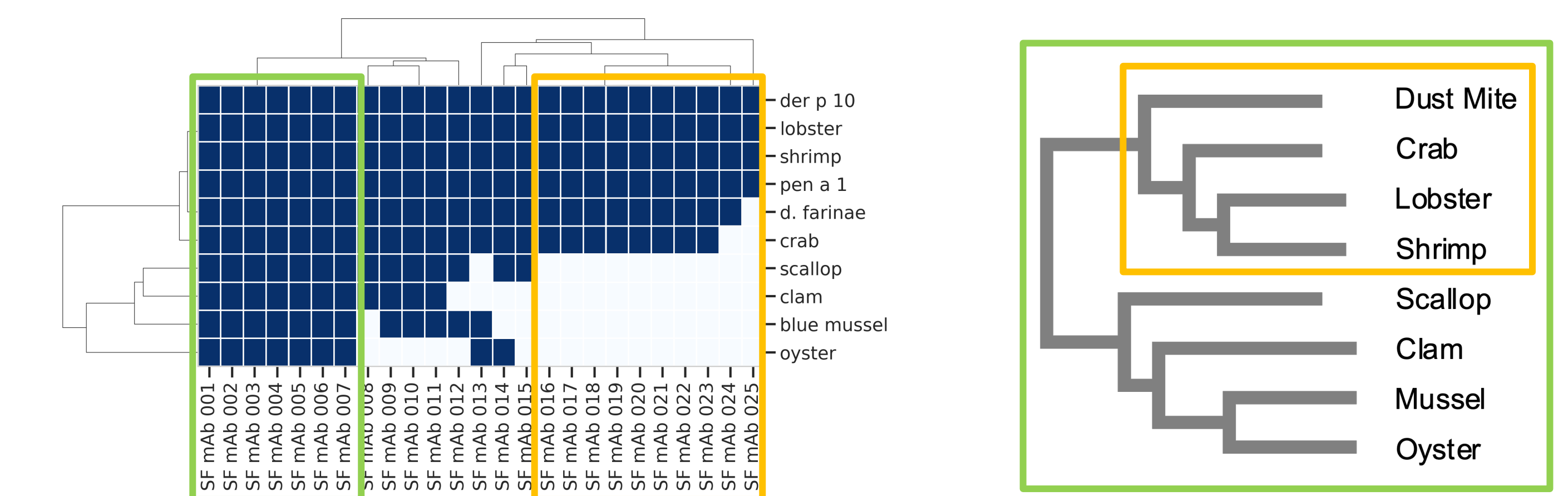


Fig. 5. Left: Shellfish antibody specificity to crustacea (shrimp, Pen a 1, lobster and crab), dust mite Der p 10, and mollusks (scallop, clam, mussel, and oyster). Right: Phylogenetic tree of crustacea, dust mites, and mollusks. The yellow box indicates the mAb that are specific only to crustacea and dust mites. The green box shows the mAb that are cross-reactive to all shellfish and dust mites.

The discovery that nearly all IgE antibodies from shellfish allergy patients are cross-reactive with dust mite tropomyosin is captivating. The interplay between dust mites and shellfish allergies has been researched extensively, but IgGenix’s IgE discovery platform offers a new perspective on exploring the complexities of allergen recognition in shellfish allergies through monoclonal antibodies.

Conclusions

IgGenix’s optimized scRNA-seq platform enabled the unbiased discovery of high-affinity antibodies against shellfish like crustaceans and mollusks. In addition to enabling insight into IgE specificity and cross-reactivity, these monoclonal antibodies with high affinity and human origin show potential as promising candidates for developing allergen-specific therapies with improved efficacy, safety, and rapid onset of action.

References & Declaration

1. Croote, D., et al. *Science* 362.6420 (2018).
Conflict of interest & funding: all authors are employees of IgGenix. Work was funded by IgGenix.