

Cross reactivity in OIT

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Goals

1

Review cross reactivity among tree nut, legume, fish and shellfish

2

Distinguish molecular (in vitro) co-sensitization from clinical cross reactivity (co-allergy)

3

Discuss data for inclusion of specific allergens for co-desensitization (specifically tree nuts)

Basis of Cross reactivity

- There is significant correlation at the protein sequence level between immunodominant components of related tree nuts.
- This correlation translates both to sp IgE levels as well as to clinical allergy between these nuts
- Tree nut dyads:
 - Cashew/pistachio Ana o3 levels have high correlation to pistachio sp IgE
 - Walnut/Pecan Jug r1 levels strongly correlate to pecan sp IgE

Clinical⁺ cross reactivity

Tree nuts

FAST 2021

Image from Nadeua article using Jaccard similarity coefficient



Clinical Cross reactivity: tree nuts

- 94% of cashew treated OIT patients passed pistachio “cross-nut” challenge (83/88)
- 97% of walnut treated OIT patients passed a pecan “cross-nut” challenge (31/33)
- Important to recognized immunodominant nuts in the dyads
 - Cashew
 - Walnut
- Wasserman et al Letters Ann Allergy Asthma Immunol 127 (2021)

Clinical Cross Reactivity: tree nuts

- NutCRACKER Study

- Assess co-desensitization to pecan, hazelnut, and cashew with walnut-only OIT
- Pecan: 100% (46/46) of pecan allergic patients were desensitized with walnut OIT (passed 4000mg challenge)
- Hazelnut: 53% (8/15) of patients with concomitant hazelnut allergy were fully desensitized with walnut OIT, though 93% (14/15) had a partial response (tolerance of 1000mg protein or 10x increase from baseline)
- No significant cross desensitization observed to cashew with walnut OIT
- Elizur et al, Lancet Child/Adolescent 2019

Tree nut Take Home guidance

- Strong evidence to support that desensitization to walnut will co-desensitize to pecan
- Similarly, desensitization to cashew will desensitize to pistachio.
- There is likely at least partial desensitization to hazelnut with walnut OIT
- Thus, you only need
 - Cashew for cashew/pistachio
 - Walnut for walnut/pecan

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Legume: peanut and everything else

- Peanut is NOT commonly associated with other clinical legume allergy
- Peanut allergy is commonly associated with soy sensitization but rarely soy allergy
 - 10/32 peanut-allergic patients sensitized on SPT
 - 1/32 peanut allergic patients clinically allergic to soy
- Legume triad:
 - Lentil, Green pea, Chickpea have a high rate of clinical cross reactivity
 - 64% of patients with at least one of the above reacted to the other two
 - By contrast, low rate of allergy in this group to green bean, white bean or soy (or peanut)
 - Chan et al, JACI Pract 2019
 - Sicherer et al JACI Pract 2020

Legume Take Home Message

- Peanut allergy is not highly associated with other legume allergy
- Chickpea, lentil and pea have a fairly high degree of co-allergy (legume triad)
- Reasonable to consider in the legume triad that there would be co-desensitization but there is no published data
- Think about lupin

Lupin

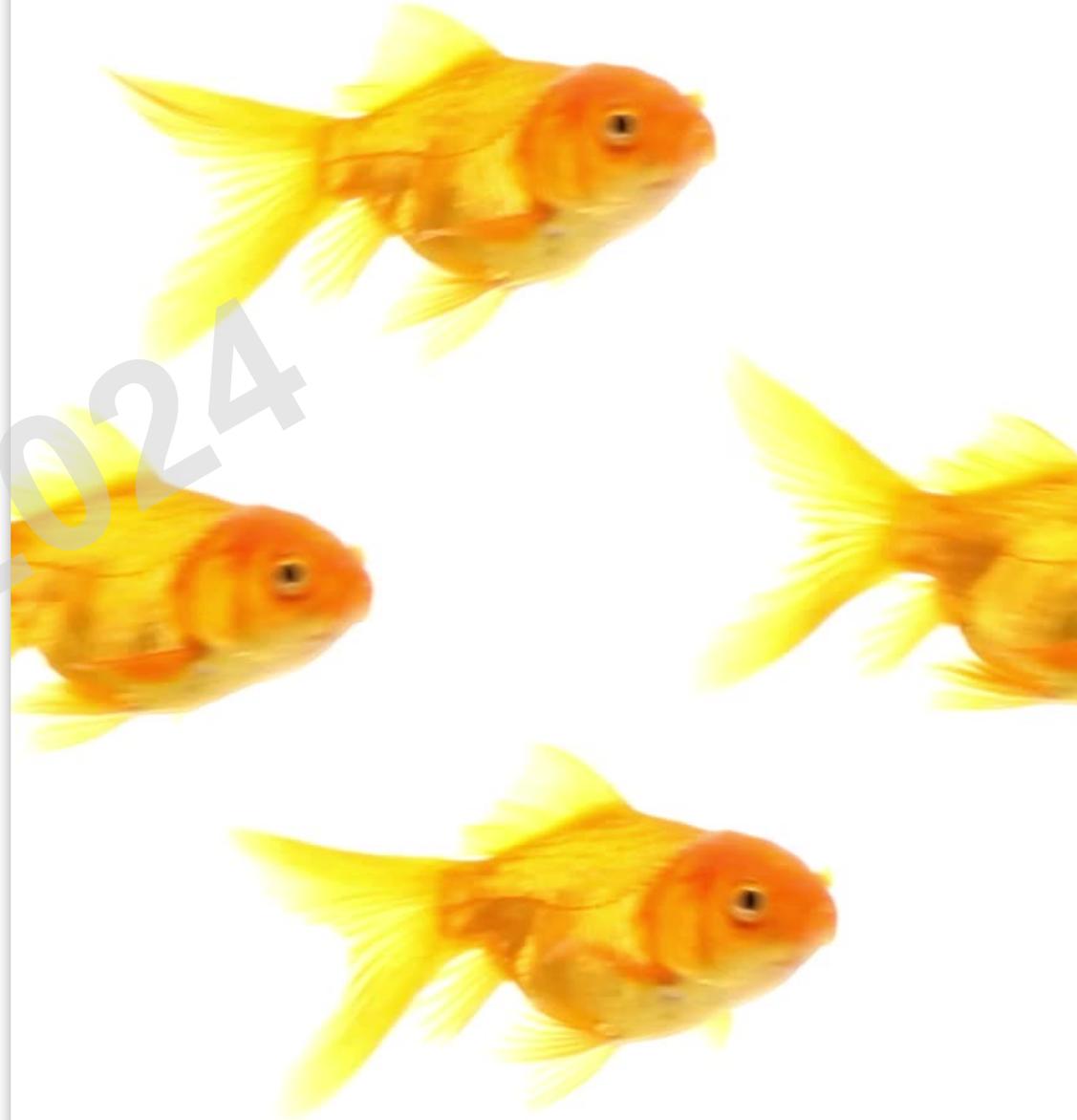
- Lupin is an emerging legume allergen in the US, though more recognized in Europe
- Lupine flour commonly found in pasta, baked goods and as gluten replacer
- Rate of peanut/lupin co-allergy appears higher than peanut and other legumes
 - 34-44% co-sensitization
 - True co-allergy estimates highly variable based on limited challenge data, but ranging from 10-80%
 - Sicherer JACI Pract 2020

Seafood (fish and shellfish) Allergy

- No significant overlap between finned fish and shellfish allergy on a molecular basis and rare to see a patient allergic to both (2-7%)

Two distinct dominant allergens

- Tropomyosin (Met e 1): shellfish
- Parvalbumins (finned fish)



Finned fish homology

- Within finned fish, about 85% homology of parvalbumin among common fish (tuna, trout, salmon)
- However, there are some outliers with lesser homology: swordfish, sole, tilapia. Allergies to these fish may be more isolated to reflect minor non-parvalbumin allergy
- Tuna tends to be the lowest parvalbumin content, so some patients who react even to multiple other finned fish might tolerate tuna
- Heating/canned fish can reduce parvalbumin allergenicity by 20-60% and might results in clinical tolerance for some patients



Finned Fish OIT

- Limited data but a few case reports
- 20 yo Japanese patient desensitized with 12mg of parvalbumin protein (mackerel)
- At the end of 2 years of OIT, she was able to tolerate a fillet with 66 mg parvalbumin protein
- Very different low/slow protocol

Yokozeki et al, Allergology Intl 2021

Shellfish Homology

- High degree homology among crustacean tropomyosin (95%), so most patients who are clinically allergic to one crustacean will react to all (crab, shrimp, lobster)... crawfish?
- Less homology among crustacean and mollusk (oysters, clams) tropomyosin (55-65%)
- Estimates vary but only a minority of shellfish allergic patients are allergic to both crustacean and mollusk families (14%)
- Evolutionary conservation between tropomyosin of arthropod (dust mite and cockroach) and shellfish. There are oral allergy variants

Shellfish OIT

One small study

- 3 patients desensitized to 300mg of shrimp protein
- Notably this was also in the context of omalizumab
- 2/3 tolerated 12 grams of shrimp challenge at 36 weeks.
- No cross crustacean challenges performed.

Take Home Messages

- Cashew/Pistachio and walnut/pecan have strong clinical co-allergy
- Desensitization to immunodominant allergen (cashew or walnut) is adequate for desensitization to both members of dyad in almost cases
- Peanut is not associated with high degree of other legume allergy, though lupin is on the rise
- Chickpea/lentil/pea can be thought of as a legume triad with a high degree of clinical co-allergy
- Tuna has low parvalbumin and may be tolerated when other fish are not
- Crustaceans have a high allergen homology and rate of co-allergy
- Parvalbumin content is important to define degree of allergenicity of finned fish

Cross reactivity table

- Sicherer JACI in Practice 2020

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