

Biomarkers of desensitization / tolerance in food allergy AIT

Carmen Riggioni MD, MSc, PhD student
JM EAACI Immunotherapy Group



SJD

Sant Joan de Déu
Barcelona · Hospital

Disclosure

In relation to this presentation, I declare no real or perceived conflicts of interest

Funding

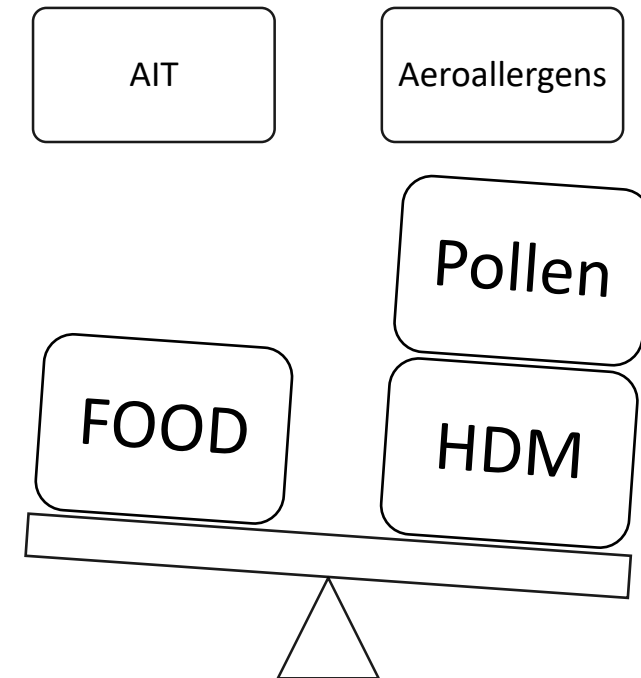
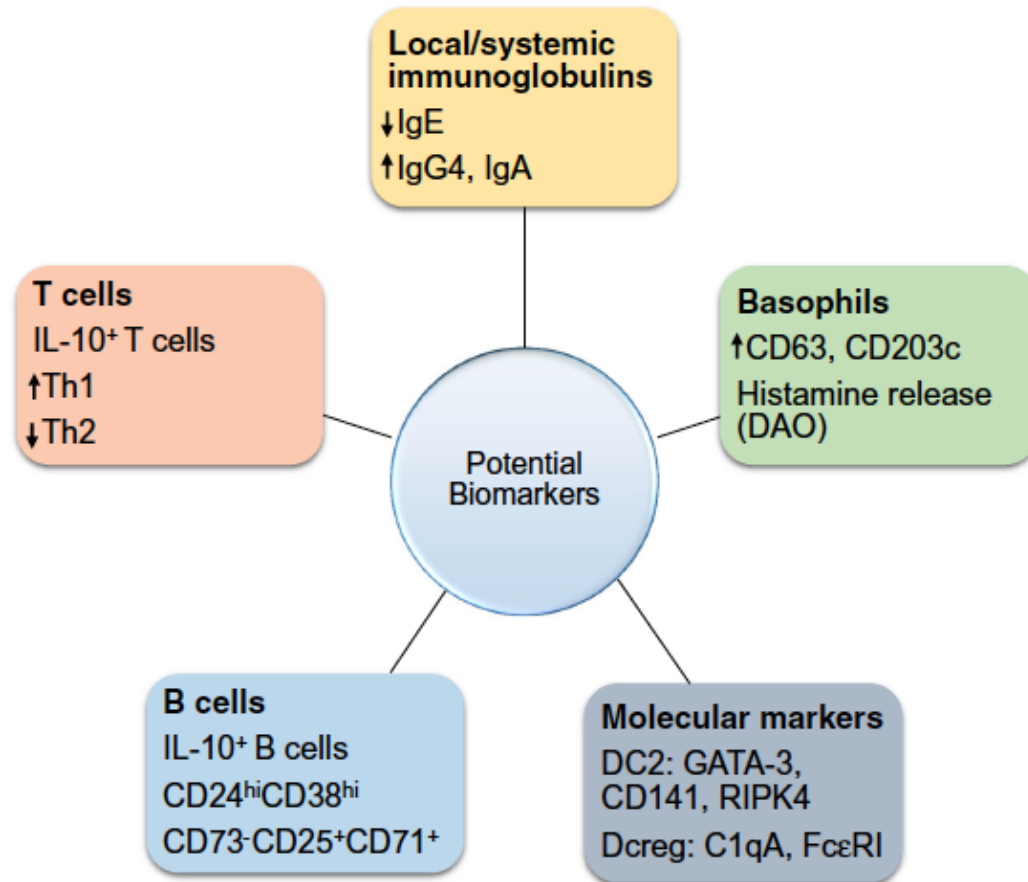
- EAACI research fellowship
- SEICAP grant

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation.

Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (e.g. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.



Biomarkers in FA-AIT



Importance of Biomarkers

- Distinguish patients with the highest likelihood of responding to AIT.
- Guidance regarding when to discontinue AIT.
- Predicting symptomatic relapse or adverse events.
- Stratify the patient in a protocol that they can realistically follow.
- The type of maintenance the patient should undertake.

Definitions:

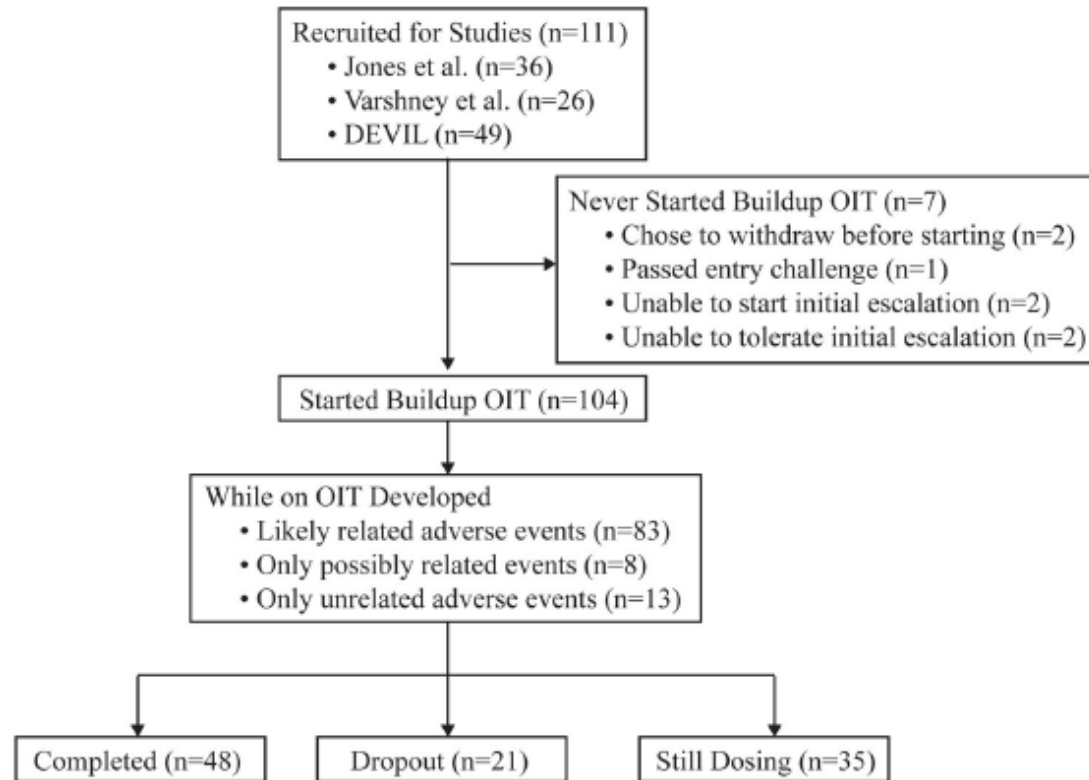
Desensitization

- Effectiveness during treatment
- The ability to safely consume foods containing the culprit allergen while on allergen immunotherapy.

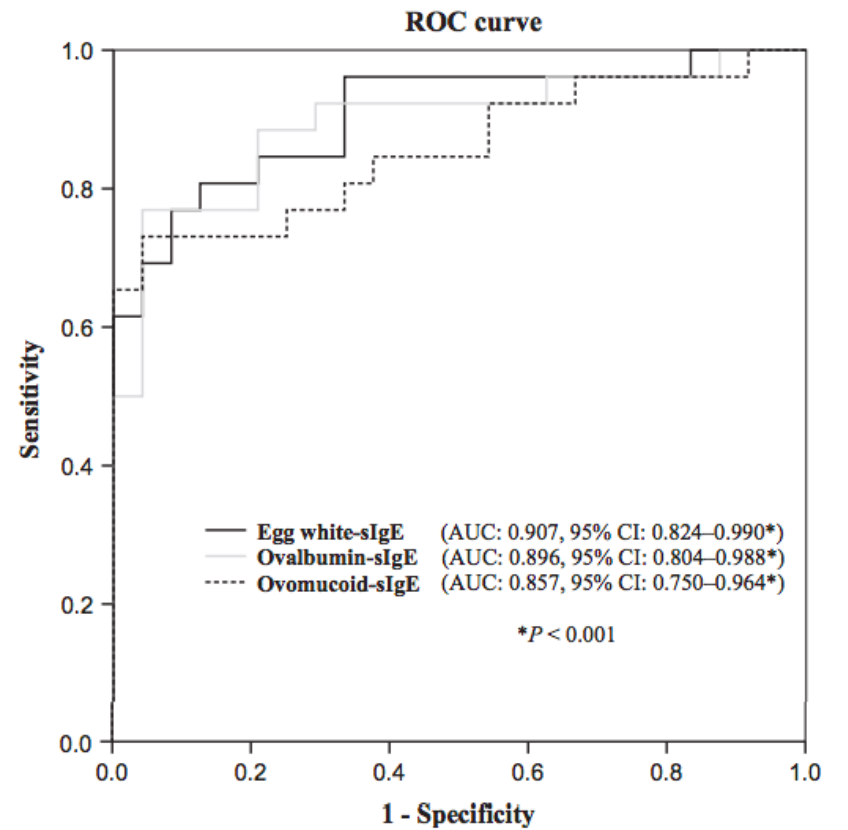
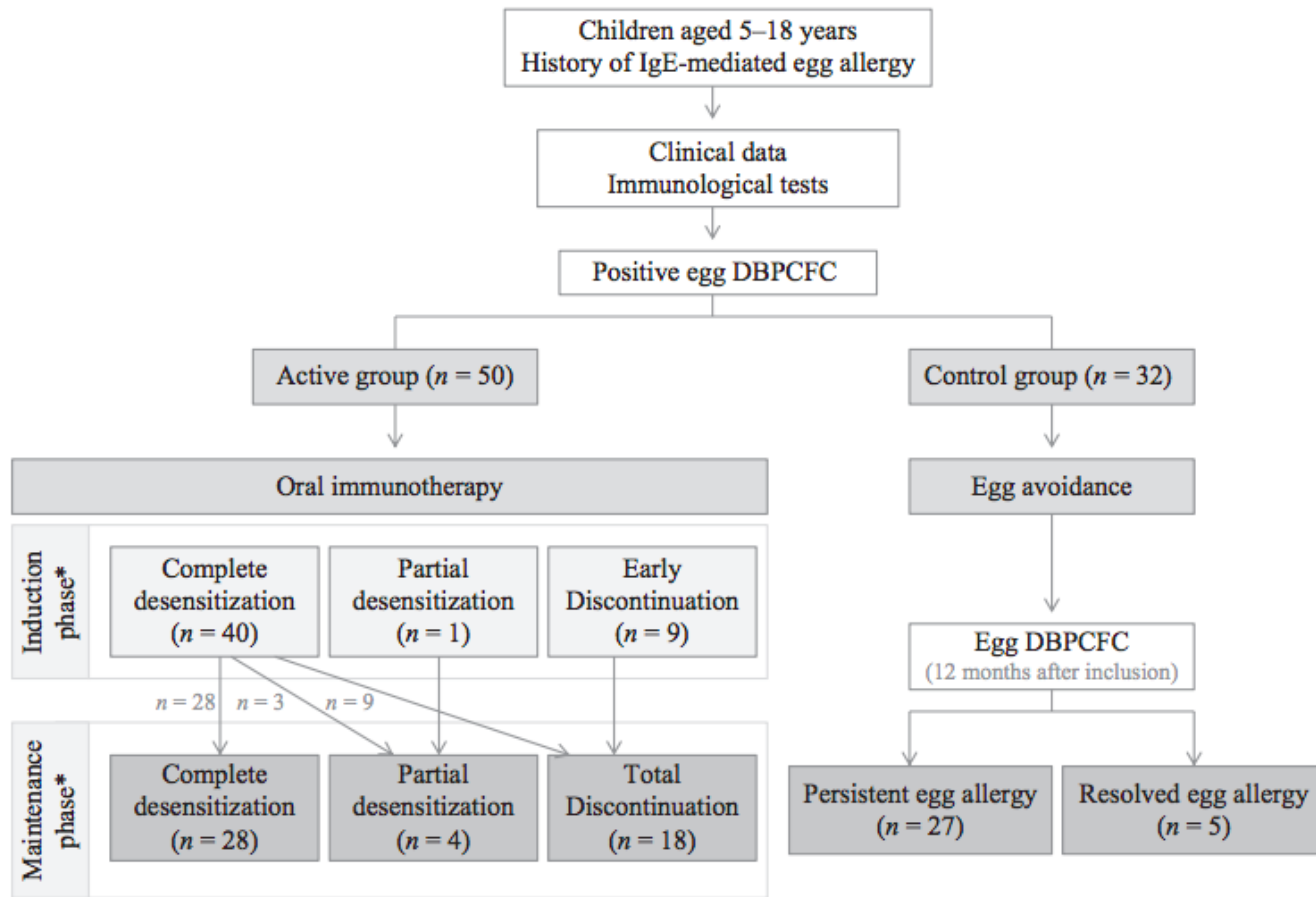
Tolerance

- Sustained unresponsiveness.
- Post-discontinuation effectiveness
- The ability to safely consume a normal serving of food containing the trigger allergen despite a period of absence of exposure

Novel Baseline Predictors of Allergic Side Effects During Peanut Oral Immunotherapy



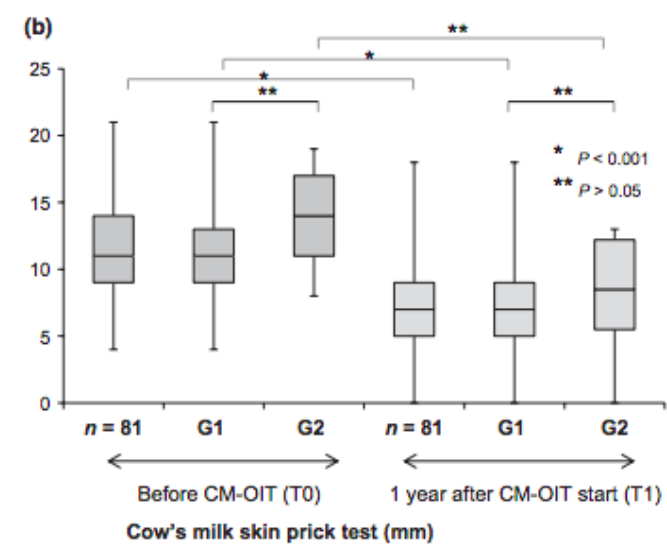
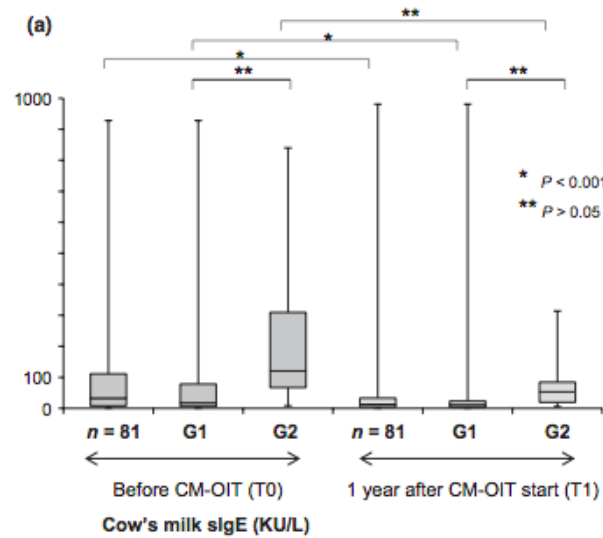
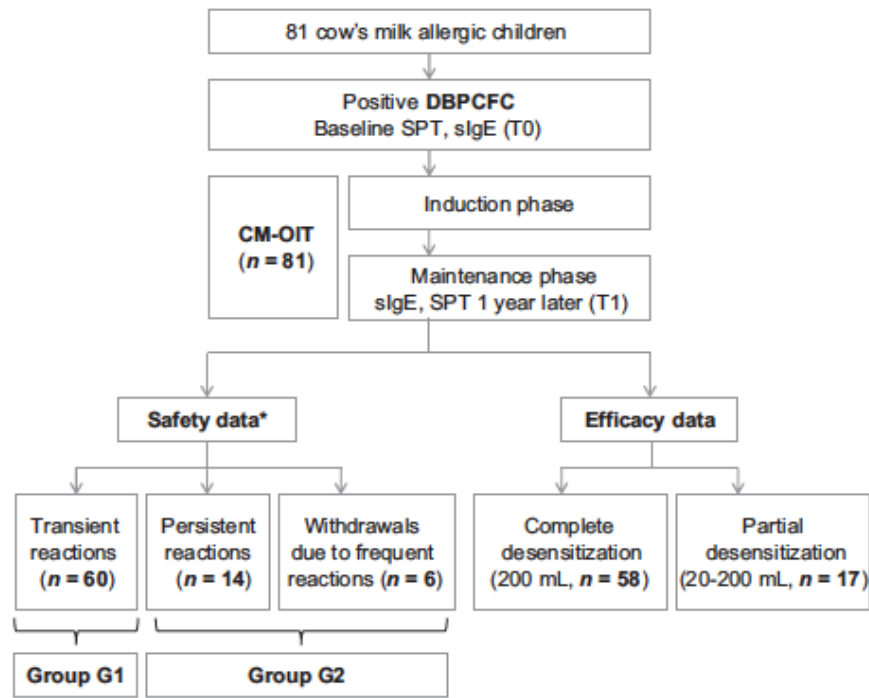
- 80% presented adverse events
 - 72% build-up
 - 47% maintenance
- 42% experienced systemic reactions
 - Predictors: baseline allergic rhinitis, asthma
 - 2.9-fold higher
- 49% experienced gastrointestinal symptoms
 - Peanut SPT predicted increased gastrointestinal sx
 - 1.4-fold for every 5 mm
- 20% of subjects dropped out, half due to persistent gastrointestinal symptoms



IgE Optimal cut-off

- Egg white 9.41kU/L
- Ovalbumin 6.49 kU/L
- Ovomuroid 8.85 kU/L

CM IgE ≥ 50 kU/L
CM-SPT ≥ 9 mm
Anaphylaxis OFC





Characteristics at baseline of successful patients

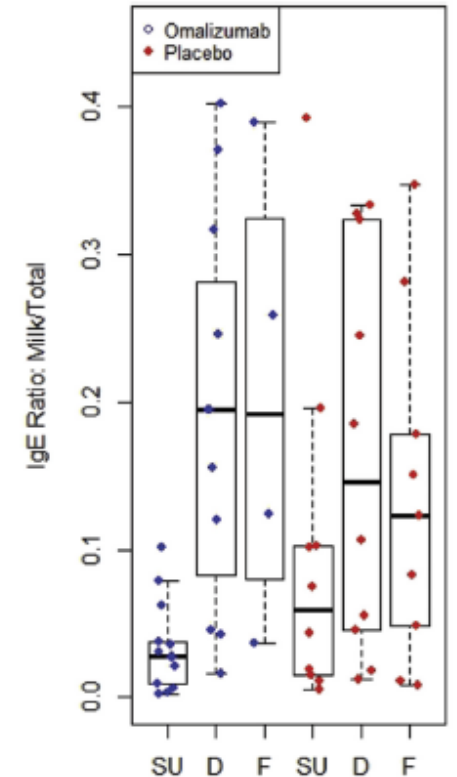
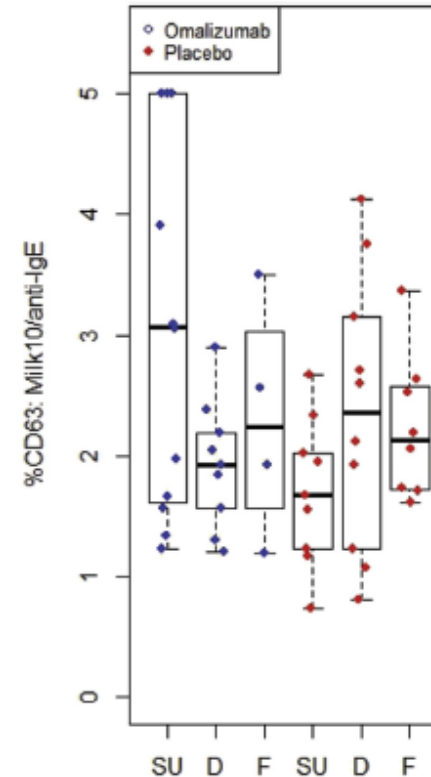
- Smaller baseline SPT to milk ($p=0.012$)
- Smaller baseline end point titration SPT to milk ($p=0.11$)
- Lower median milk-specific IgE
- Log_{10} casein-specific IgE ($p=0.012$)
- Greater baseline casein-specific IgG4/IgE ratio ($p=0.007$)
- No change in BAT

Sustained unresponsiveness

- The addition of omalizumab to OIT markedly improves safety with no significant effects on efficacy.
- With or without omalizumab, most subjects could be desensitized to a high dose (10g) of milk protein over a 24 month period, but half had increased reactivity after an 8 week period of avoidance.

Mechanistic correlates of clinical responses to OMZ in the setting of CM-OIT

- Investigate mechanisms by which OMZ modulates immunity in the context of OIT to identify baseline biomarkers.
- Pre-OIT basophil reactivity positively associated with occurrence of symptoms during OIT.
- Baseline milk IgE/total IgE ratio correlated with the likelihood of achieving sustained unresponsiveness.
- Combining omalizumab therapy with milk OIT led to distinct alterations in basophil reactivity but not T-cell responses.



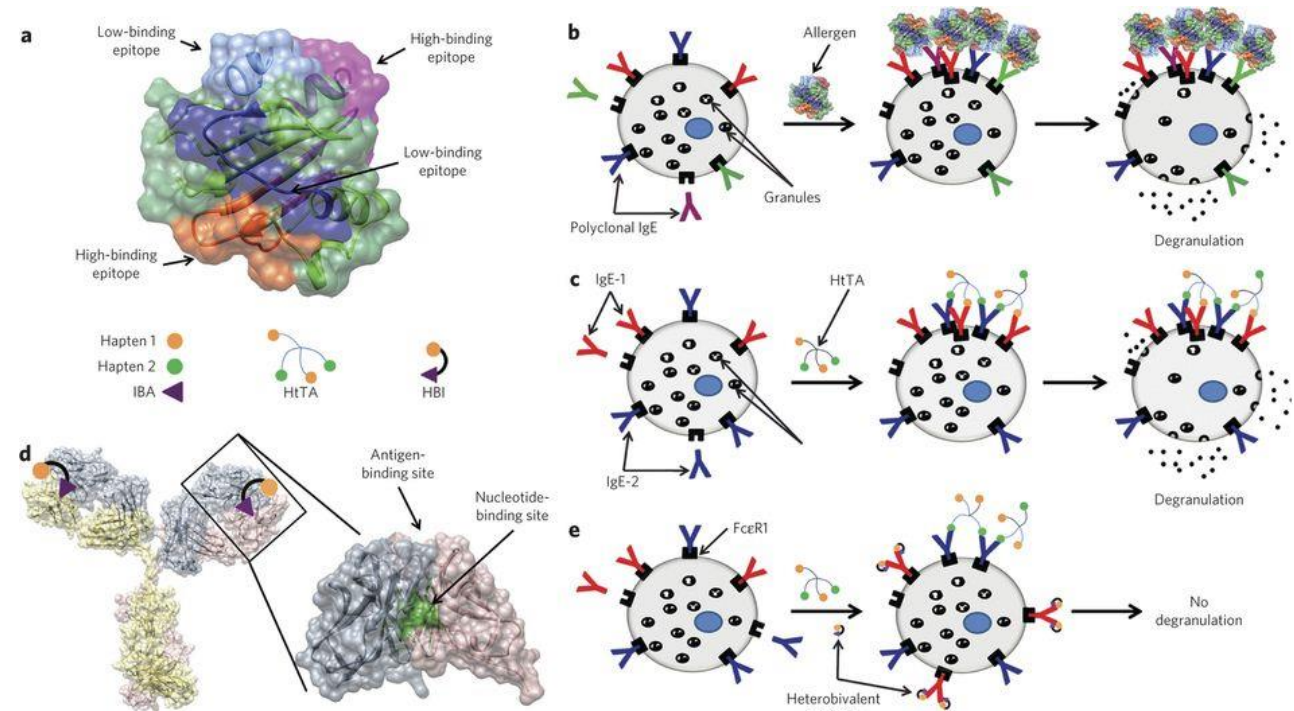
Treg biomarkers might be useful in predicting immune tolerance in peanut OIT

- 23 peanut-allergic patients underwent peanut OIT vs. 20 peanut-allergic controls.
- Antibody and basophil activation measurements did not statistically differentiate between peanut OIT and controls.
- T-cell function and demethylation of *FOXP3* CpG sites in antigen-induced Treg were significantly different between tolerant and non-tolerant participants.
- Modifications at the DNA level of antigen-induced T-cell subsets may be predictive of sustained unresponsiveness during peanut OIT.

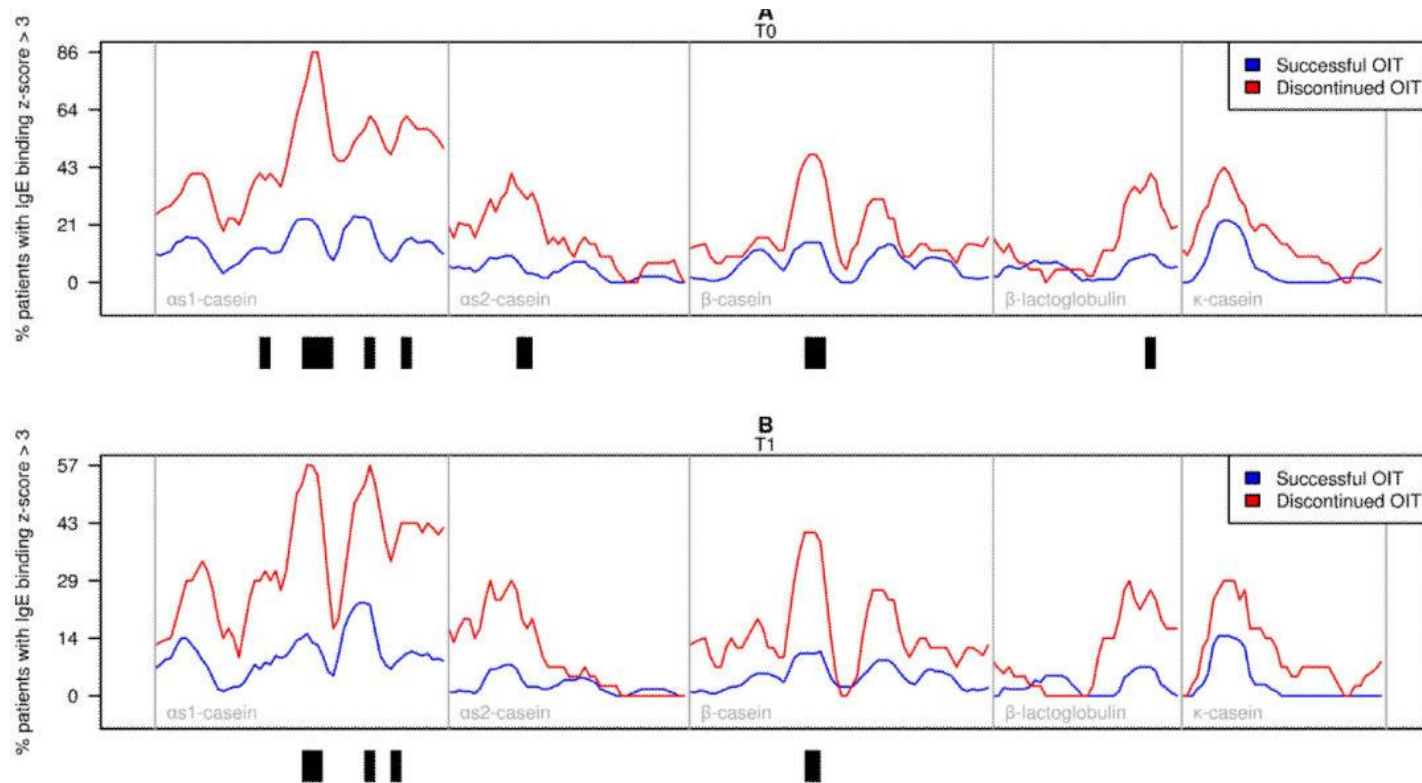
Epitope binding

The number and types of epitopes bound by patients' IgE and IgG4 antibodies associated with:

- Type of adverse events in OIT
- Efficacy of OIT



Epitope binding



Comparison of the two patient groups:

- Children who discontinued CM-OIT due to adverse reactions (red, n=6)
- Children who successfully completed OIT (blue, n=26)

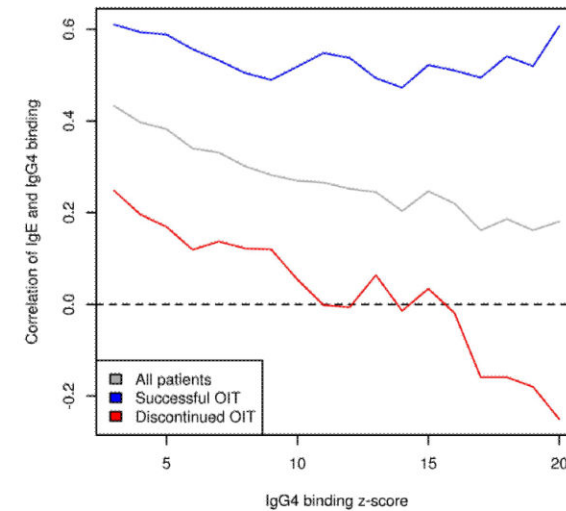
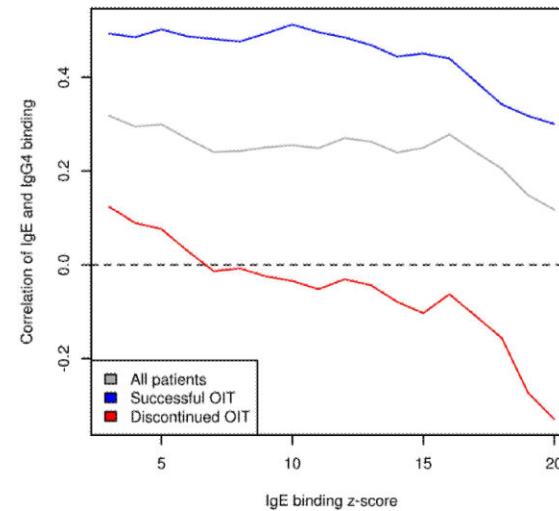
Epitope binding

COMPLETED OIT

- IgE binding decreased and IgG4 binding increased significantly from the initiation to completion of OIT.
- Had IgE and IgG4 antibodies that more often recognized the same epitopes.

DISCONTINUED OIT

- Had IgE and IgG4 antibodies that bound to CM peptides with greater intensity, broader diversity and greater affinity.

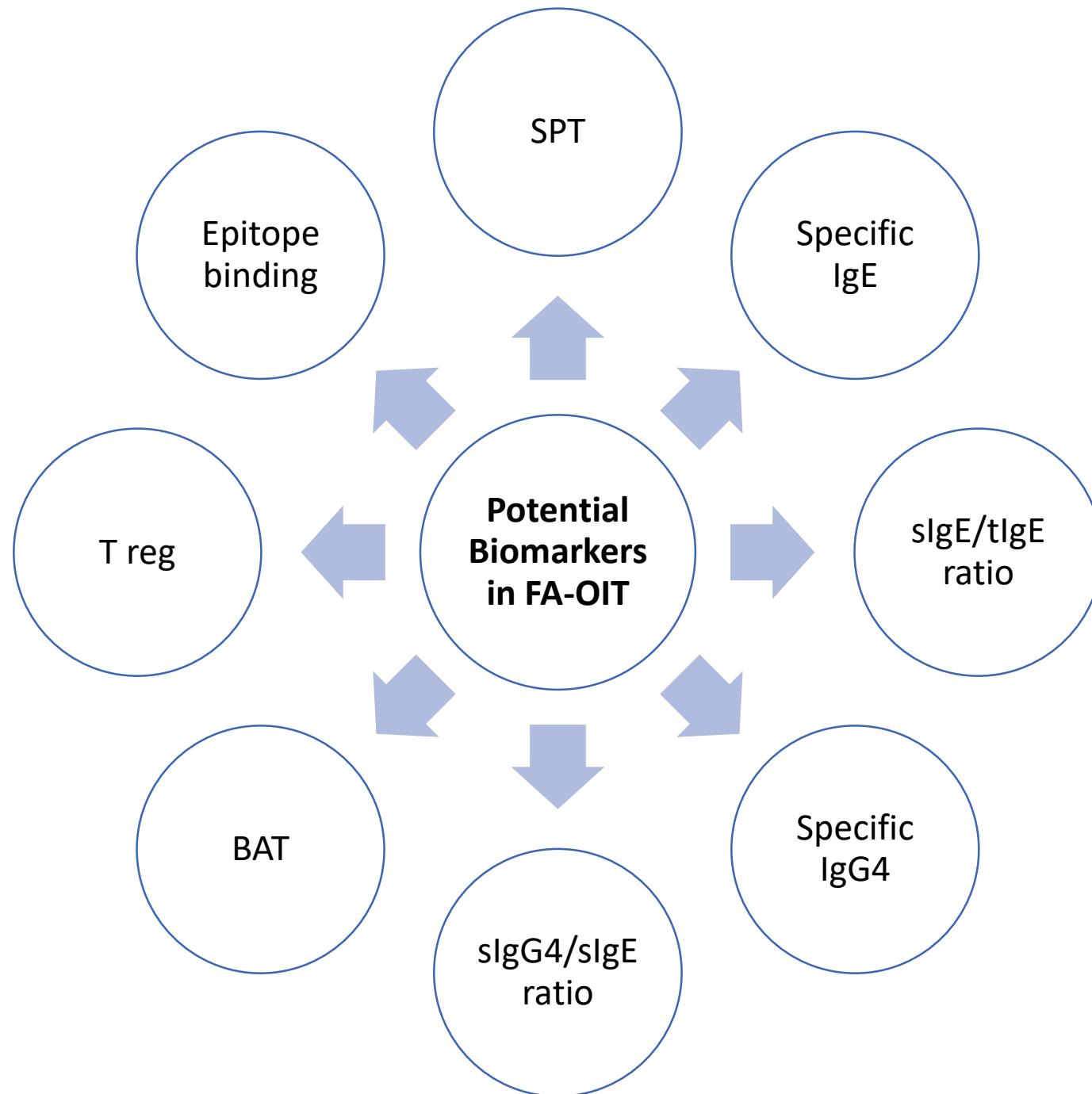


Epitope binding

- In children with high IgE binding to CM epitopes, lower antibody affinity may discriminate those who will complete OIT successfully from those who will have to discontinue therapy.
- Combining measurements of IgE and IgG4 binding intensity and affinity to the CM epitopes distinguishes the two patient groups better than any single traditional parameter.

Innate Lymphoid Cells

- Specific studies targeting ILC2 response during immunotherapy for food allergy is presently lacking, with additional studies needed to evaluate its use in predicting clinical outcome.



Can biomarkers replace OFC ?

- The standard of assessing long term efficacy is through OFC
- Reliable biomarkers could help eliminate the need for OFC and provide a safer and more convenient alternative to these challenges.

REALITY :

- **FEW AND NOT PERFECT ALTERNATIVES**
- **WEAK TRANSLATION TO CLINICAL PRACTICE**

TAKE HOME MESSAGES

- There are no ideal biomarkers that can determine tolerance and desensitization to date.
- More homogeneity in FA-AIT trials is needed to come up with useful and robust clinical tools.
- It is important to consider each patients' individual profile before starting FA-AIT, plus the families' commitment and adherence.
- Set realistic goals for your patient and their families prioritizing, safety and education.
- Remember FA-AIT is a long term commitment for both families and physicians and should be monitored accordingly.