Differences in epitome response in peanut-allergic subjects treated with different immunotherapy preparations

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Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

Type	Company
Employment full time / part time	DBV Technologies (part time), University of Sydney/Children's Hospital at Westmead, Sydney Australia (part time)
Research Grant (P.I., collaborator or consultant; pending and received grants)	National Health and Medical Research Council of Australia (NHMRC), Allergy and Immunology Foundation of Australasia, Nestle Health Sciences
Other research support	Sydney Children's Hospitals Foundation, Phadia Laboratory Systems
Speakers Bureau / Honoraria	None
Ownership interest (stock, stock-options, patent or intellectual property	DBV stock options
Consultant / advisory board	Allergenis, Westmead Fertility Centre

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

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1 Background and Aims

BACKGROUND

- Epitopes represent each single, small fragment of allergen to which an allergic individual can produce an antibody
- Each allergenic food, such as peanut, has many epitopes
- The summation of the repertoire of antibodies produced in response to an allergen by each individual can be considered their **epitome** - **fingerprints of an individual's humoral response to an allergen**

AIMS

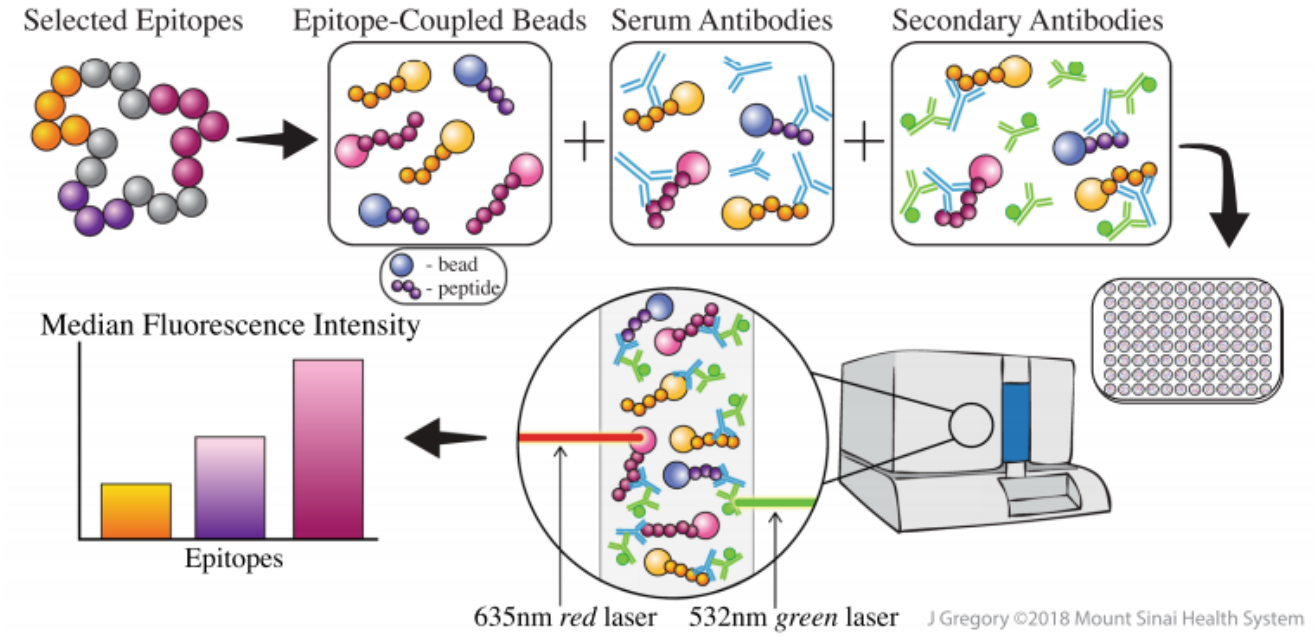
- To understand how the epitome is modulated during peanut immunotherapy (P-IT), the epitome of individuals participating in three P-IT clinical trials was examined:
    1. POISED: Oral Immunotherapy (OIT) with roasted peanut
    2. BOPI: OIT with initial boiled peanut, transitioning to roasted peanut
    3. PEPITES: Epicutaneous immunotherapy (EPIT) with peanut protein

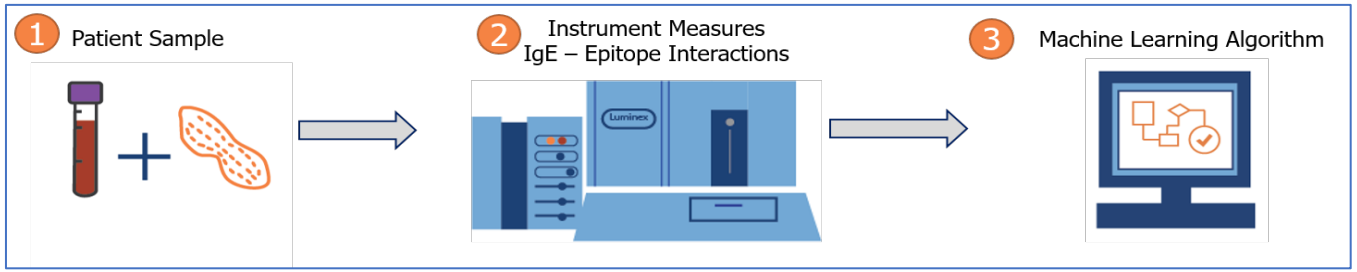
The specific **Objectives** of the study were to:

1. Identify similarities and dissimilarities in peanut epitome modulation across studies
2. Identify potential epitopes that may be biomarkers of treatment response

2 Methods: BBEA Technology

- A Bead-Based Epitope Assay (BBEA) platform[1] was used to monitor the reactivity of IgE and IgG4 in patient serum to 64 linear epitopes from Ara h 1, Ara h 2 and Ara h 3

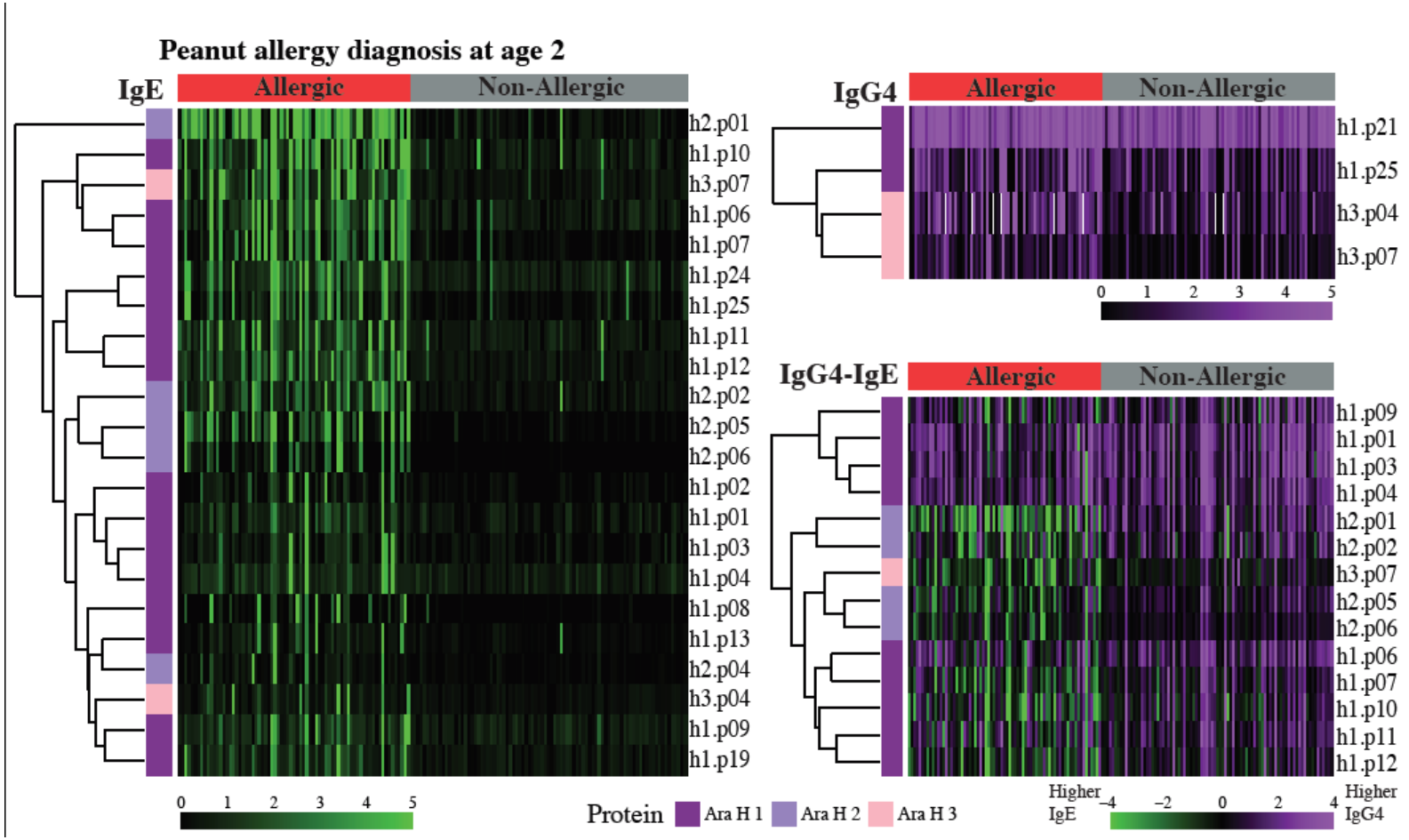




- The BBEA methodology enables simultaneous quantification of antibodies binding to sequential epitopes
- Epitopes are covalently coupled to unique fluorescent microspheres (Luminex)
- Epitope-labelled beads are mixed to form a master library
- Patient plasma and a secondary fluorophore-labeled antibody are then incubated with the beads
- The Luminex instrument uses dual-lasers for quantification (red for beads, green for secondary antibodies)
- For each epitope, the signal is quantified as a median fluorescence intensity (MFI)

1. Suprun M, et al. *Sci Rep.* 2019;9:18425. doi.org/10.1038/s41598-019-54868-7.

2 Methods: What does an epitome look like?



1. Suprun M, et al. *Sci Rep.* 2019;9:18425. doi.org/10.1038/s41598-019-54868-7.

2 Methods: Peanut IT Cohorts

	POISED	BOPI	PEPITES
Route	OIT	OIT	EPIT
RCT	YES	YES	YES
Age Group (years)	7-49	8-17	4-11
Key inclusion criteria	Peanut SPT >5 mm Baseline CRD ≤500 mg	CRD at baseline ≤1.44 g Tolerates ≥1/8 boiled peanut	Baseline ED ≤300 mg peanut protein Peanut s-IgE >0.7kU$_A$/L Peanut SPT ≥6mm/8mm
Age, median (years)*	11	12	8
Peanut IT form	Defatted roasted peanut flour	Boiled peanut for up-dosing, transitioning to roasted whole peanut	Lyophilized peanut extract
Maintenance regimen	Daily 4000 mg PN protein (PNP) as defatted flour, orally	Daily, 4 roasted peanuts (~1000 mg PNP), orally	Daily, 250 µg PNP via epicutaneous route
Primary Outcome	Tolerant to cumulative PNP dose of 4g at Week 117 DBPCFC (following 3 months off OIT)	Desensitization to >1.4 g at Month 12 DBPCFC	ED ≥300 mg (if baseline ED ≤10 mg) ED ≥1000 mg (if baseline ED >10 mg) at Month 12 DBPCFC
No. of responders / No. placebo subjects analyzed†	31/8	35/0	14/19

OIT=oral immunotherapy; EPIT=epicutaneous immunotherapy; RCT=randomized controlled trial; CRD=cumulative reactive dose; ED=eliciting dose; SPT=skin prick test; PN=peanut; IT=immunotherapy; DBPCFC=double-blind, placebo-controlled food challenge.

*Median age subjects with samples included in the analysis.

†A random sample of subjects on placebo or treatment were selected for analysis from POISED and PEPITES; all subjects on active treatment from BOPI were analyzed.

2 Methods: Analysis

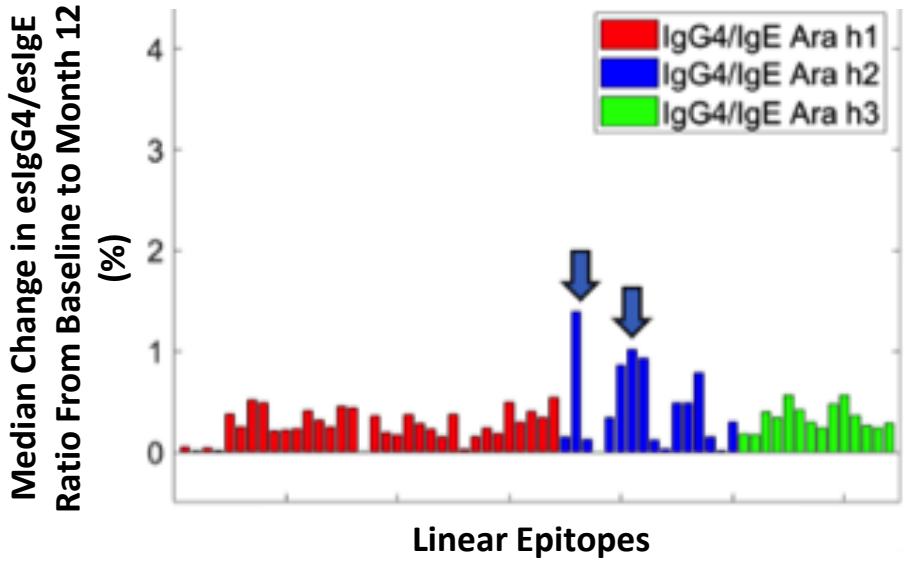
- The BBEA method was applied under SOPs to all subjects in triplicate and randomized across plates
- IgE and IgG4 reactivity to 64 linear epitopes from Ara h 1, Ara h 2 and Ara h 3 was measured
  - denoted epitope specific (es); esIgE and esIgG4
- Raw data was processed: noise removal, log normalized, triplicates merged
- For each study, responders were defined as those subjects with an eliciting dose of 1000 mg or greater based on a DBPCFC after 12 months of P-IT
- The median change across each cohort from baseline to 12 months for each epitope ratio of esIgG4 reactivity to esIgE reactivity (esIgG4/esIgE) was assessed

BBEA=bead-based epitope assay; SOP=standard operating procedure; Ig=immunoglobulin; P-IT=peanut immunotherapy.

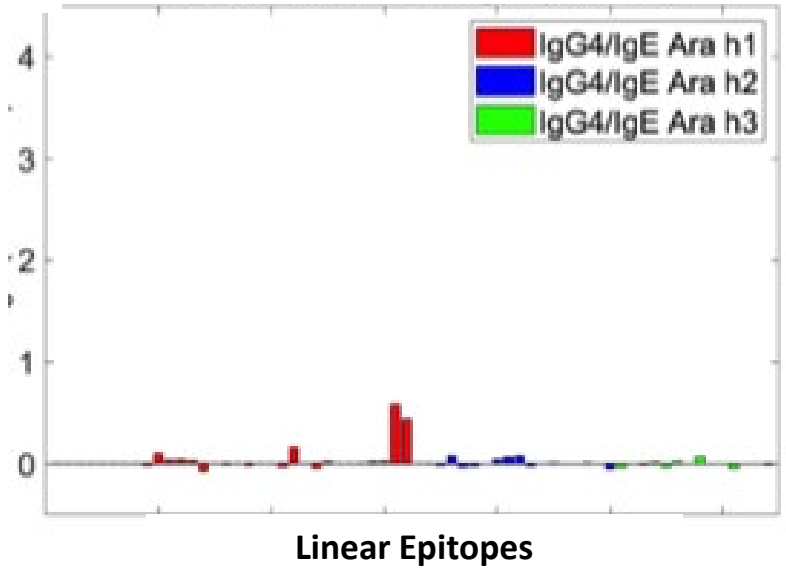
3 Results: Identification of Informative Epitopes (POISED)

- Overall, the majority of epitope ratios (esIgG4/esIgE) increased 25%-50% indicating that IgG4 levels are generally increasing due to therapy
- This is evident when compared to Placebo group where effectively no change is observed over the same time period
- Of interest are two Ara h 2 epitopes, marked by the blue arrows, that demonstrate >100% change, which is considered highly informative epitopes for response in this population

POISED Epitome Change in Responders (N=31)



POISED Epitome Change in Placebo (N=9)

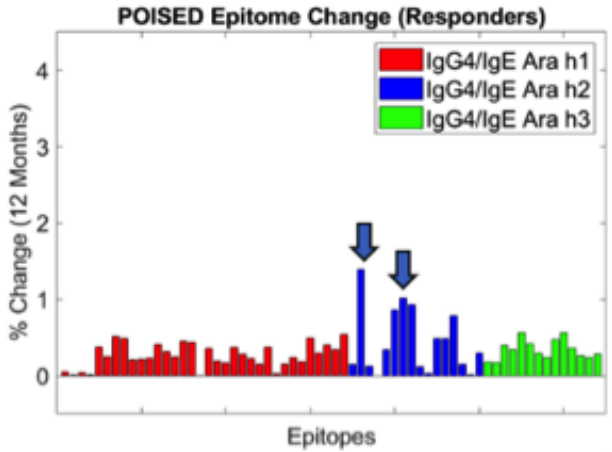


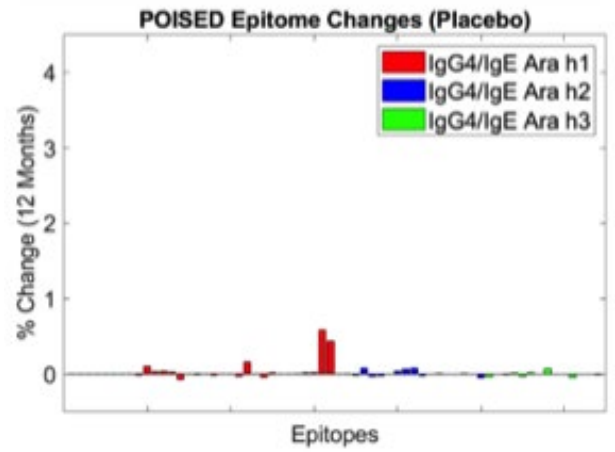
- 64 epitopes are arranged in order from Ara h 1 through to Ara h 3
- Each bar represents the median of all subjects esIgG4/esIgE to a single linear epitope

3 Results: Cohort Comparisons

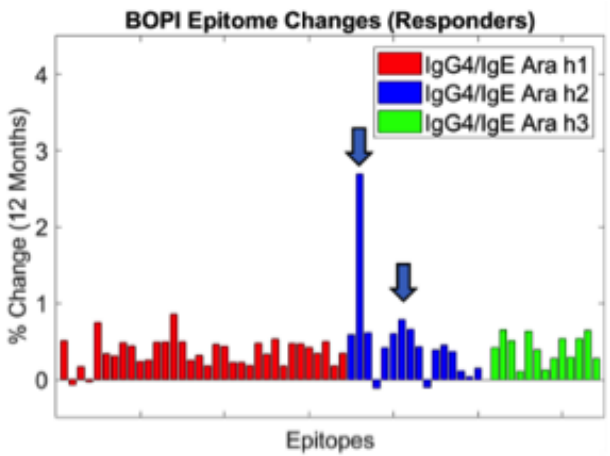
- The same two Ara h 2 epitopes modulated by P-IT therapy in POISED are also modulated in BOPI and PEPITES
- These same two Ara h 2 epitopes have also been validated on two independent cohorts to diagnose peanut allergy with 95% accuracy as compared to DBPCFC (see Thematic Poster Session 11)
- Importantly, there are additional epitopes uniquely modified by P-EPIT in PEPITES compared to P-OIT

POISED

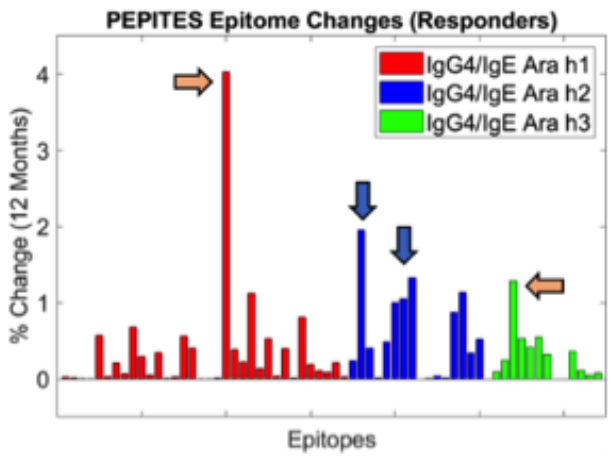


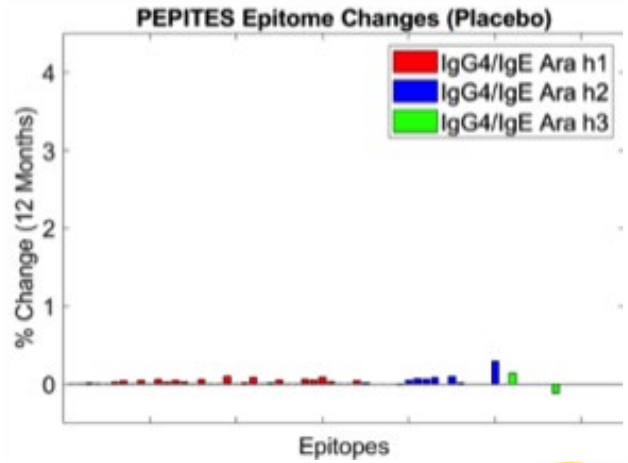


BOPI



PEPITES





P-IT=peanut immunotherapy; EPIT=epicutaneous immunotherapy; OIT=oral immunotherapy; DBPCFC=double-blind, placebo-controlled food challenge.

4 Summary and Future Directions

- We have identified key peanut epitopes which are highly correlated with response to P-IT
- Different forms of P-IT promote both shared and unique fingerprints - likely related to the route of delivery, and perhaps also regimen and dose
- There appear to be key epitopes in Ara h 2 which are consistent across all three studied cohorts, and their evolution over the treatment period is associated with clinical response to therapy
- Differences between BOPI and POISED suggest that different processing of peanut (boiled vs roasted), even though both are via OIT, may influence the epitope response
- Differences between EPIT and OIT studies, particularly in the recruitment of informative epitopes from Ara h 1 and h 3 highlight the potential differences in response using different routes and doses (ultra low dose vs high dose)
- Analyses are ongoing to understand whether there are any potential epitome fingerprints earlier in the course of IT or at baseline that are associated with/predictive of:
  - Future response to IT
  - Sustained unresponsiveness
- Analyses are ongoing to understand whether epitome fingerprints can assess degree of desensitization on treatment

5 Acknowledgements

Kearney P.[1], Getts R.[1], Hayward C.[1], Porter A.[1], Sampson H. A.[2,7], Chinthrajah S.[3], Galli S. J.[3], Nadeau K. C.[3], Turner P. J.[4,6], Campbell D.[5-7]

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