

The Induction of Allergen-specific Antibodies in Allergy and Oral Tolerance



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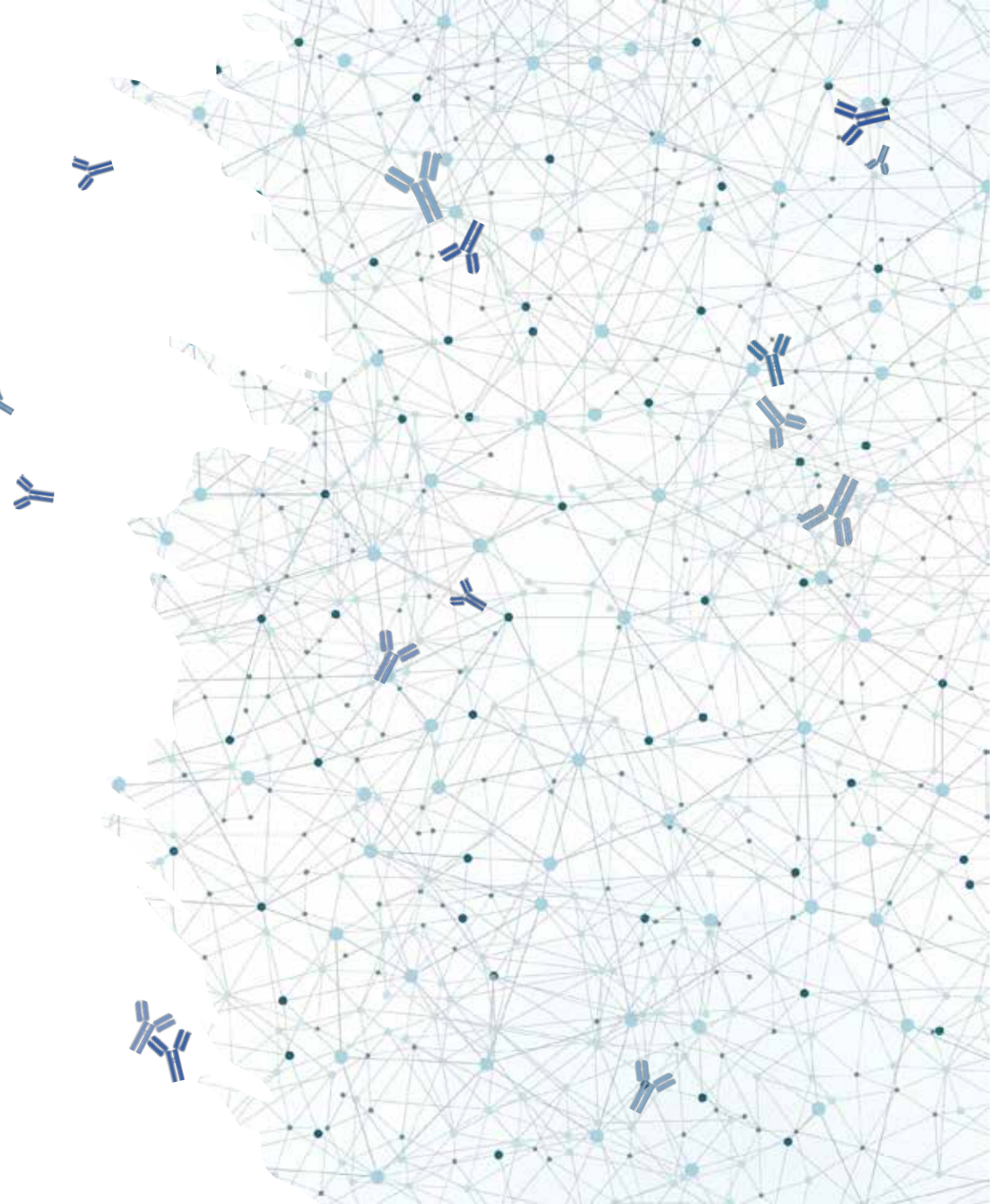


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Massachusetts General Hospital

Harvard Medical School

PATIL
LAB



THE FOOD ALLERGY EPIDEMIC

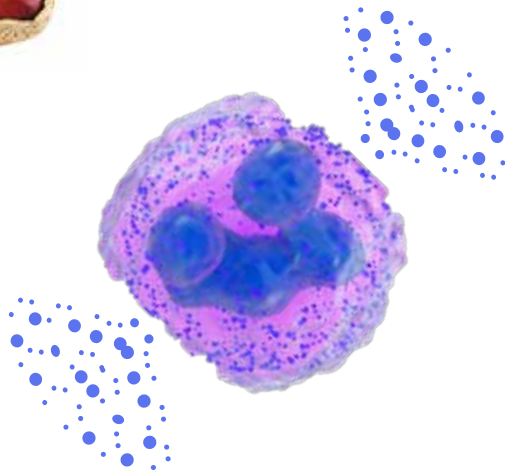


Claim lines with diagnoses of anaphylactic food reactions increased 377 percent between 2007 and 2016.

Every three minutes
a food allergy reaction sends
someone to the emergency room

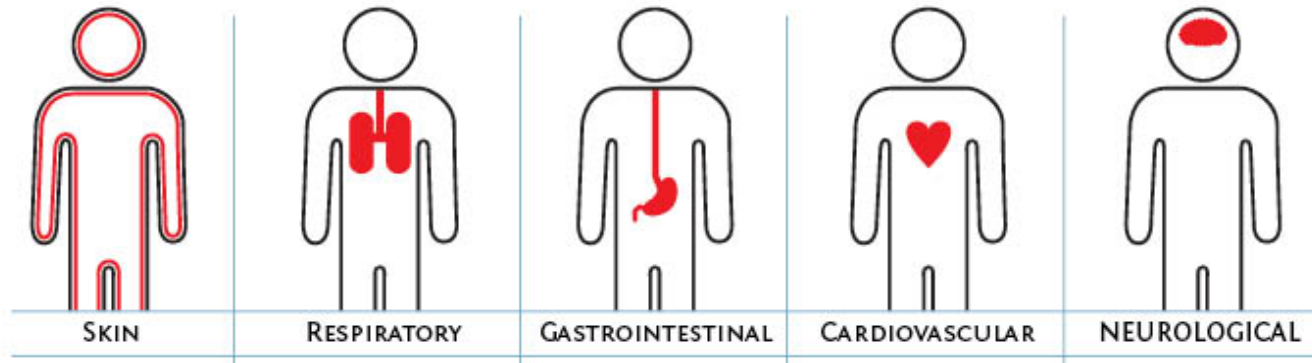
Affects 10%
2 kids per class

IgE-mediated food allergies



Surface IgE cross-linking on allergen effector cells, mast cells and basophils

Anaphylaxis



SKIN

RESPIRATORY

GASTROINTESTINAL

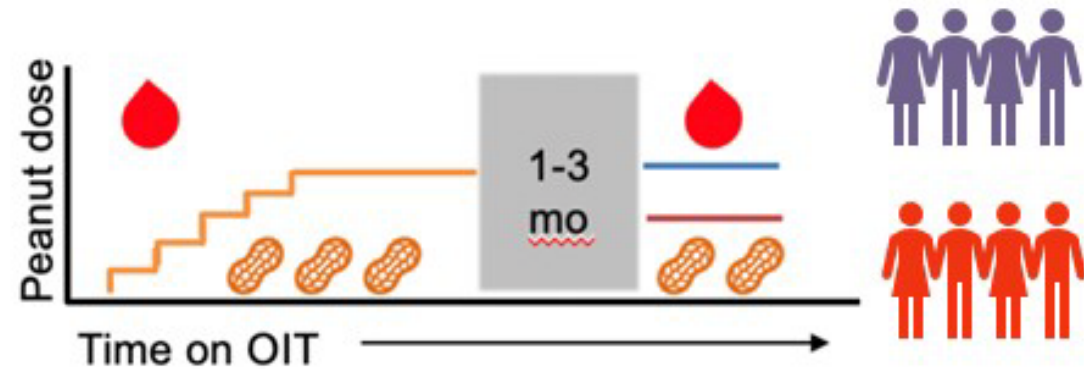
CARDIOVASCULAR

NEUROLOGICAL

Peanut Oral Immunotherapy (OIT)



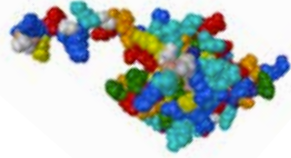
Golden peanut flour,
medium roast



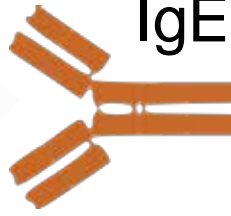
- Increasing doses of peanut, daily ingestion
 - Modified rush
 - Build-up
 - Maintenance dosing
- FDA approval of first commercial product
- Problem: Adverse events, anaphylaxis, sustained efficacy

Allergen-specific IgG antibodies in immunotherapy

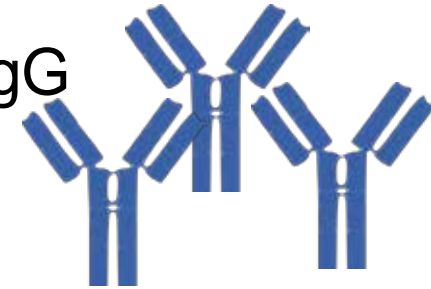
Allergen



IgE



IgG



Affinity

Clonality

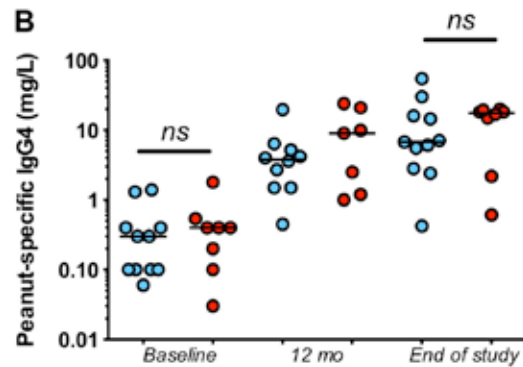
Diversity

Epitope recognition

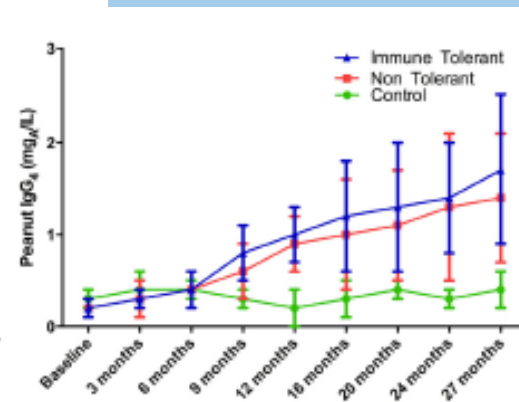
Fc receptor binding

Quality over Quantity

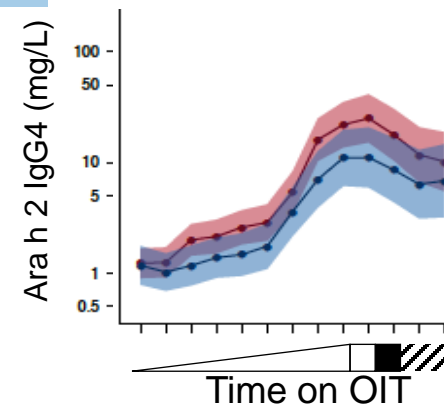
- Transient Desensitization (TD)
- Sustained Unresponsiveness (SU)



Vickery, et.al. 2014, JACI.

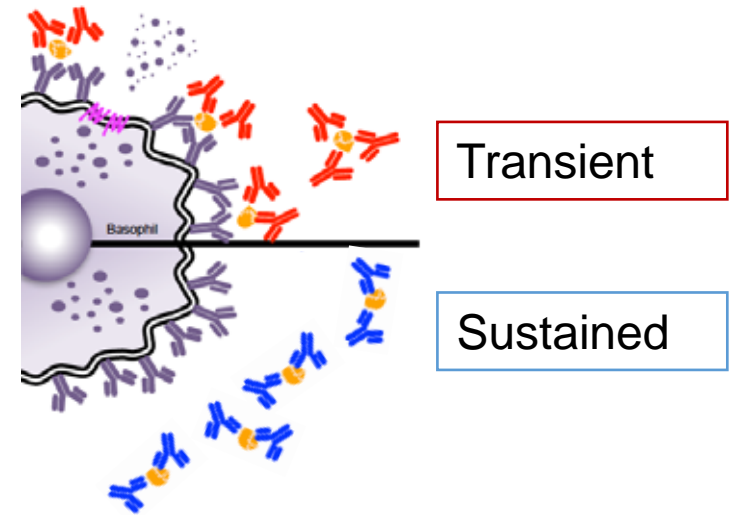
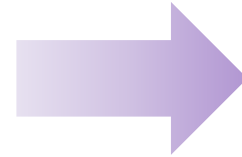
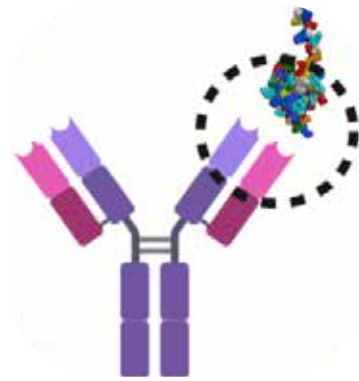
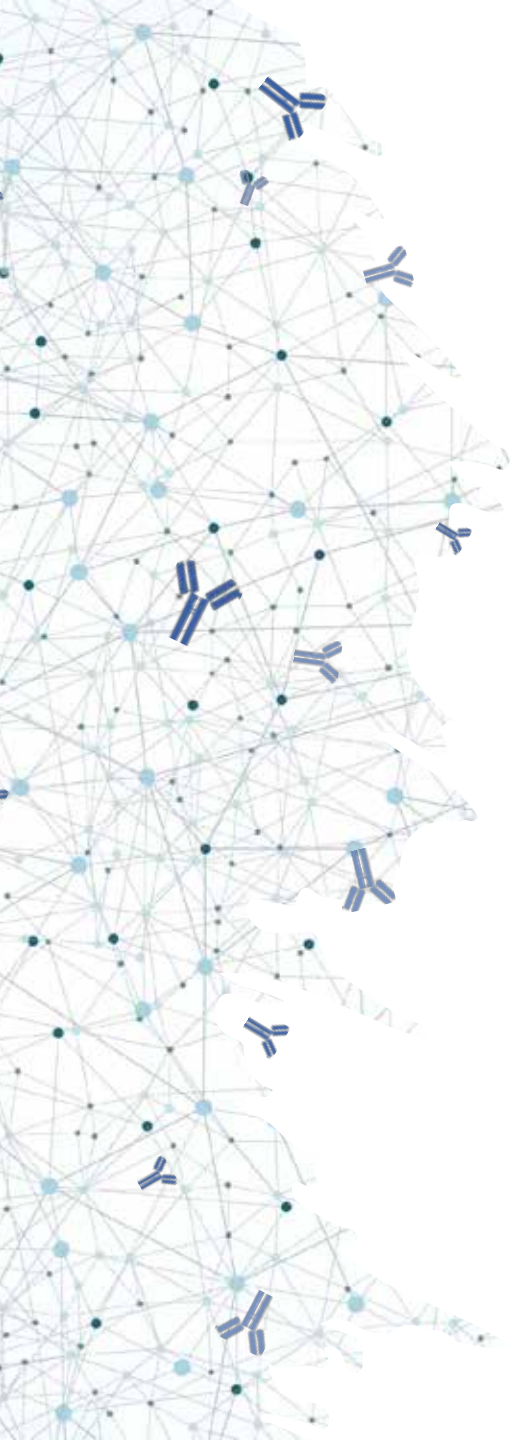


Syed, et.al. 2014, JACI.



Patil, et.al. 2019, JACI.

What characteristics of OIT-induced antibodies drive durability of clinical response to OIT?

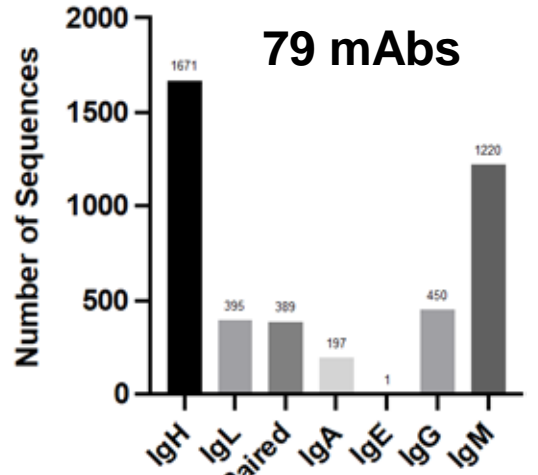
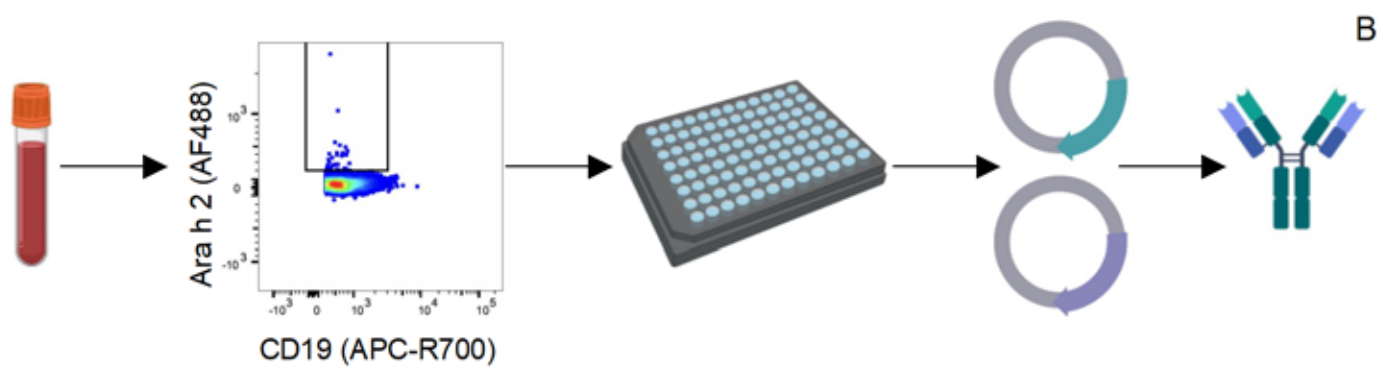
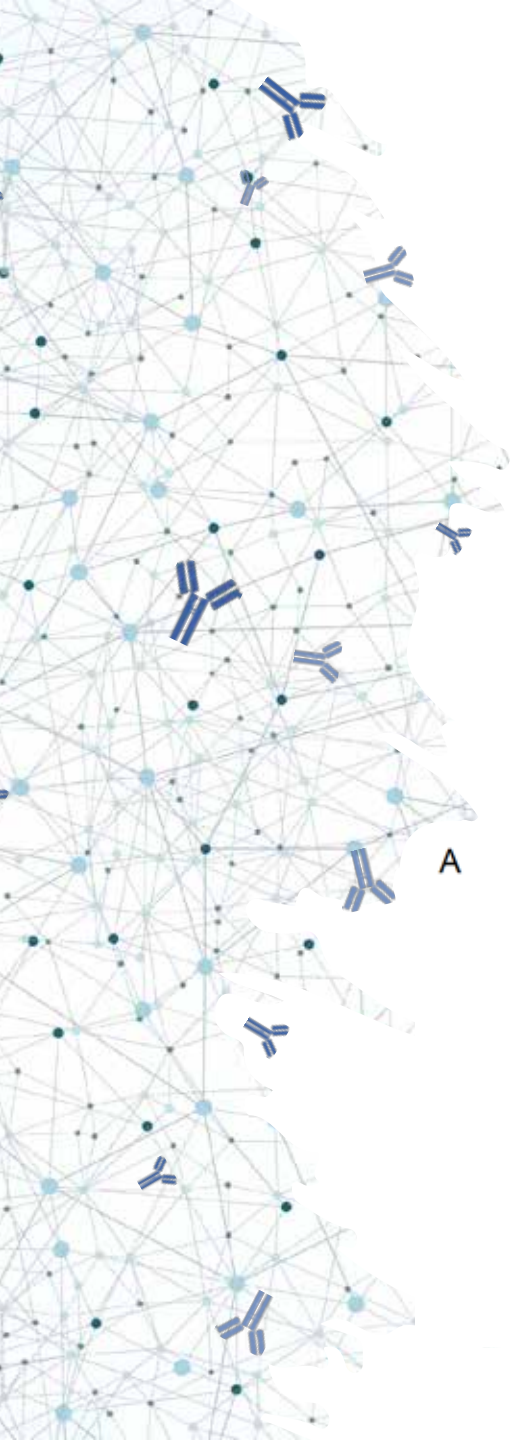
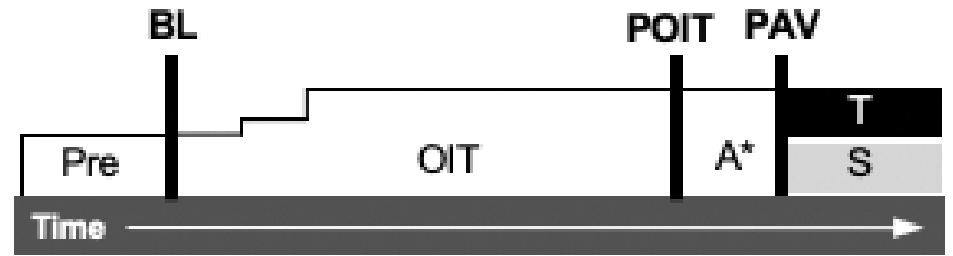
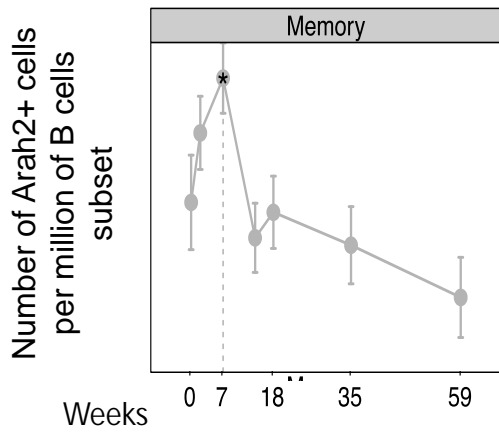


Structural characterization
of the antibody binding
interaction with antigen

Functional ability to
suppress allergic effector
cell activation related to
clinical efficacy of OIT

Durability of OIT response

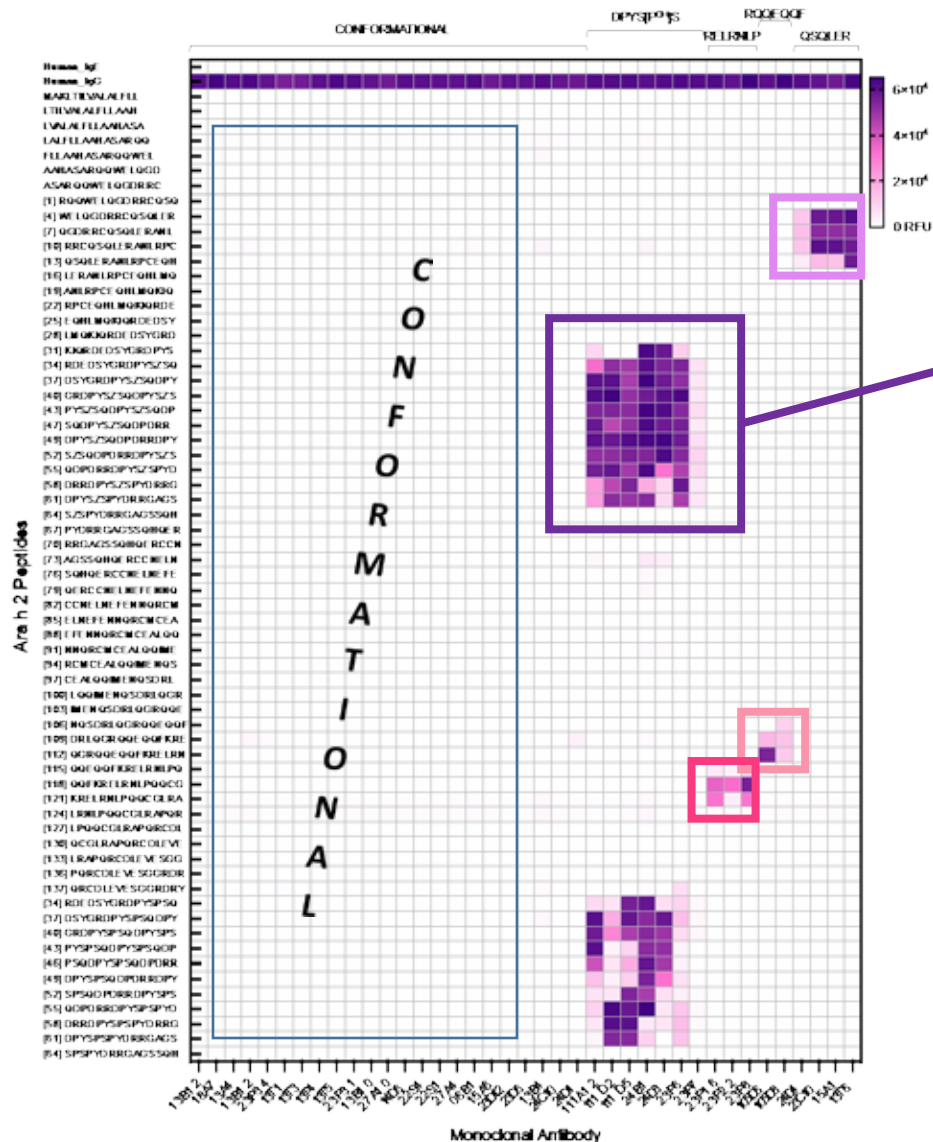
Study	Sustained	Transient
Pediatric	5	5
Adult	5	3



Patil, et.al. 2015, JACI.

LaHood*, Min *...Patil, J Clin Investigation, 2023.

Sequential Ara h 2 epitopes of OIT-induced mAB



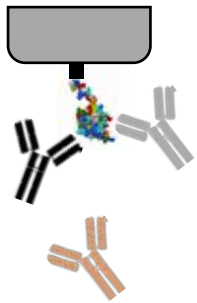
Sequential epitopes (by frequency)

DPYSP⁰HS
 KRELRLNPQQ
 QGRQQEQQF
 DRRCQSOLER

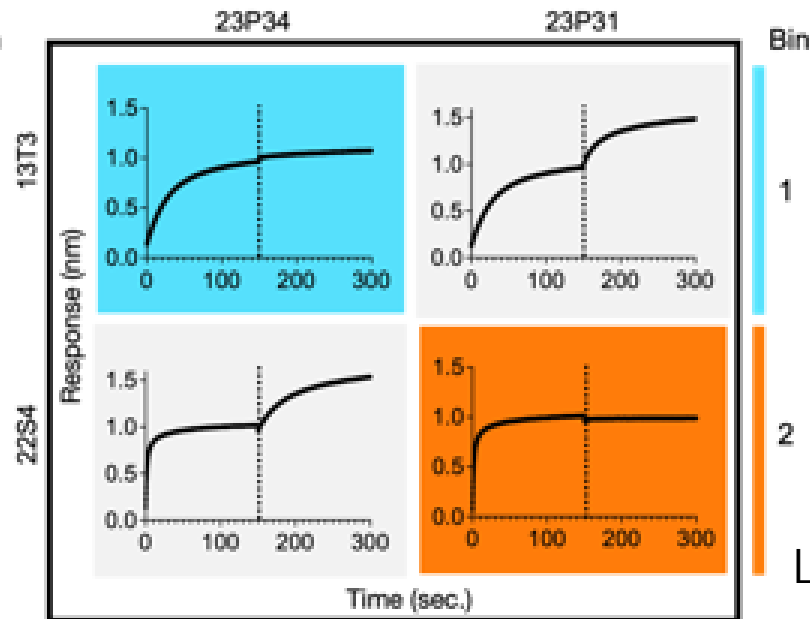
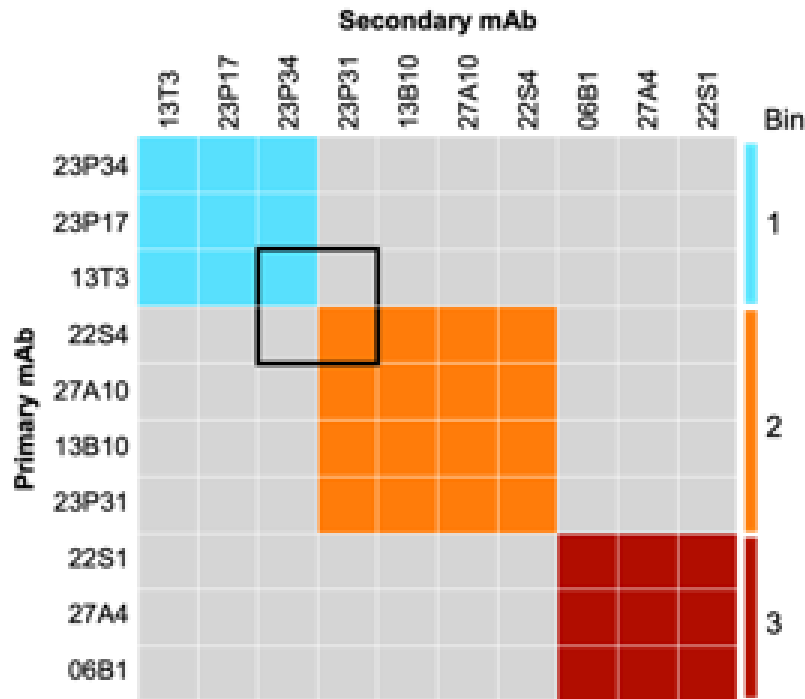
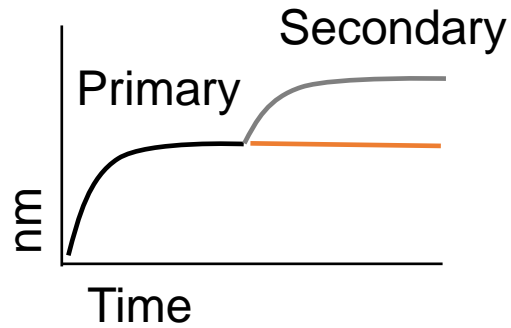
LaHood*, Min *...Patil, JCI, 2023.



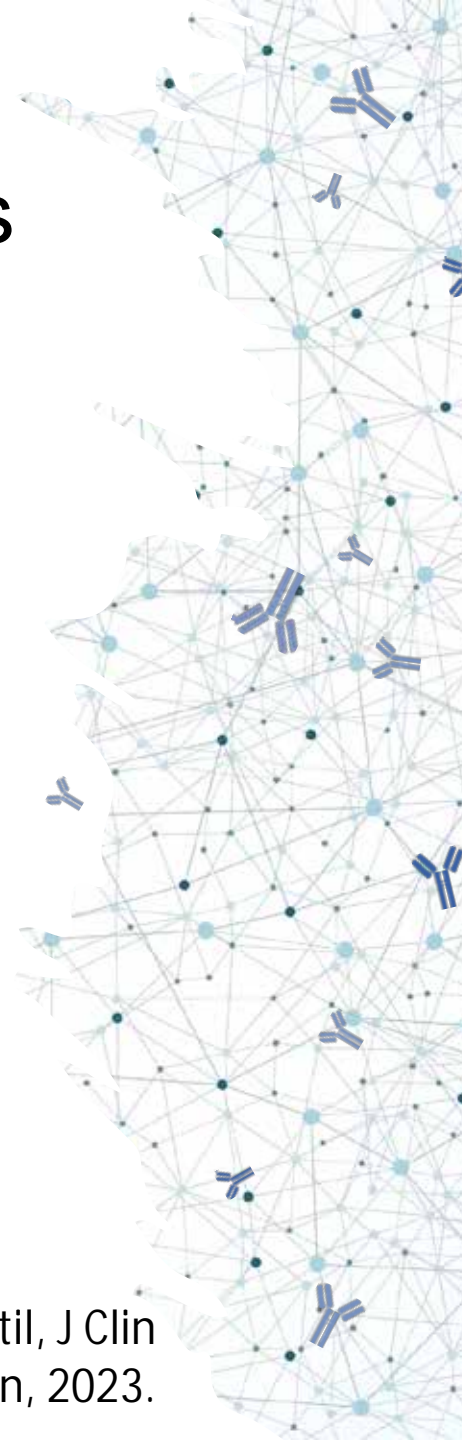
Epitope binning identifies 3 conformational epitopes



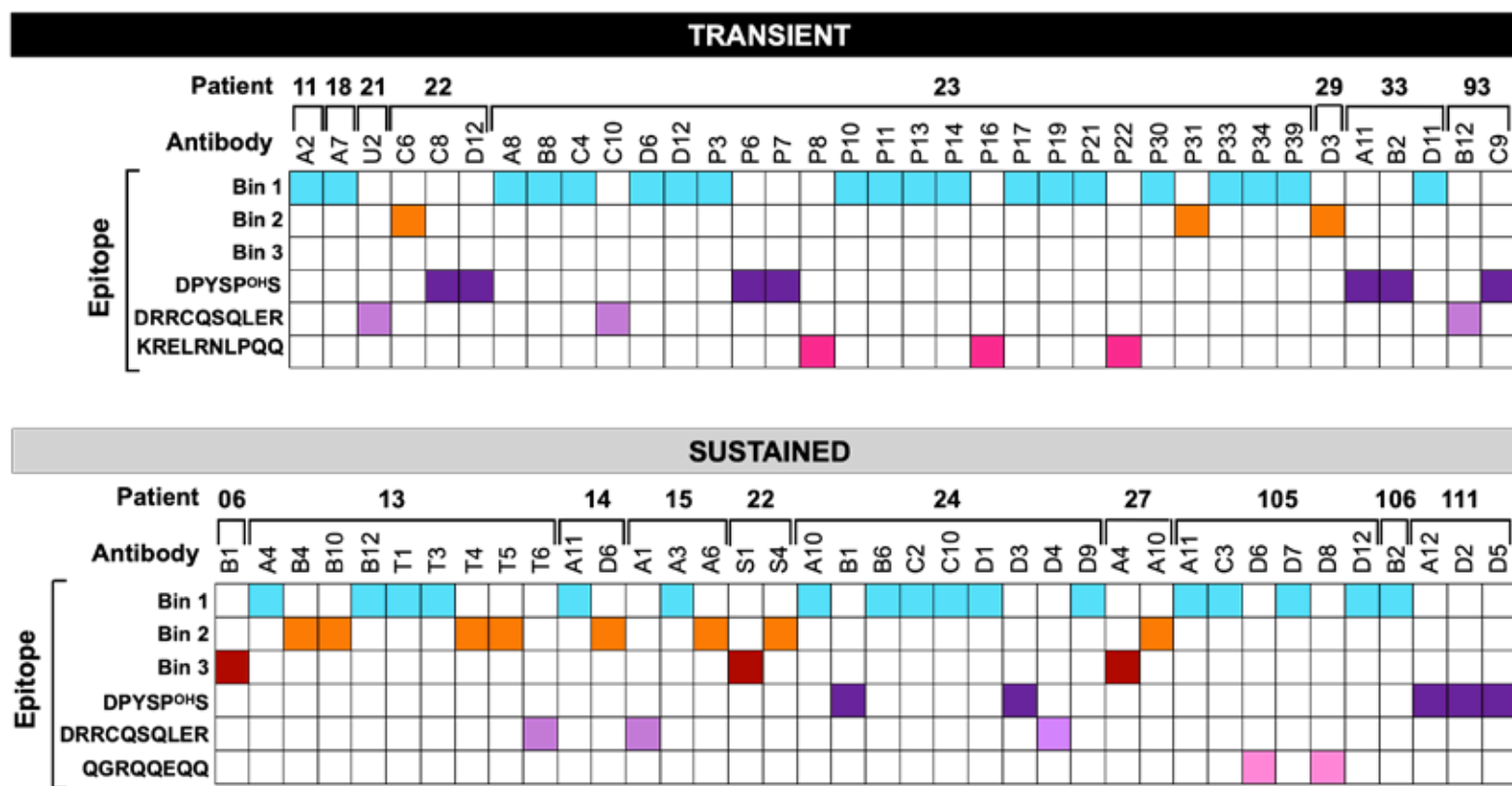
Sensor
Ara h 2



LaHood*, Min *...Patil, J Clin Investigation, 2023.



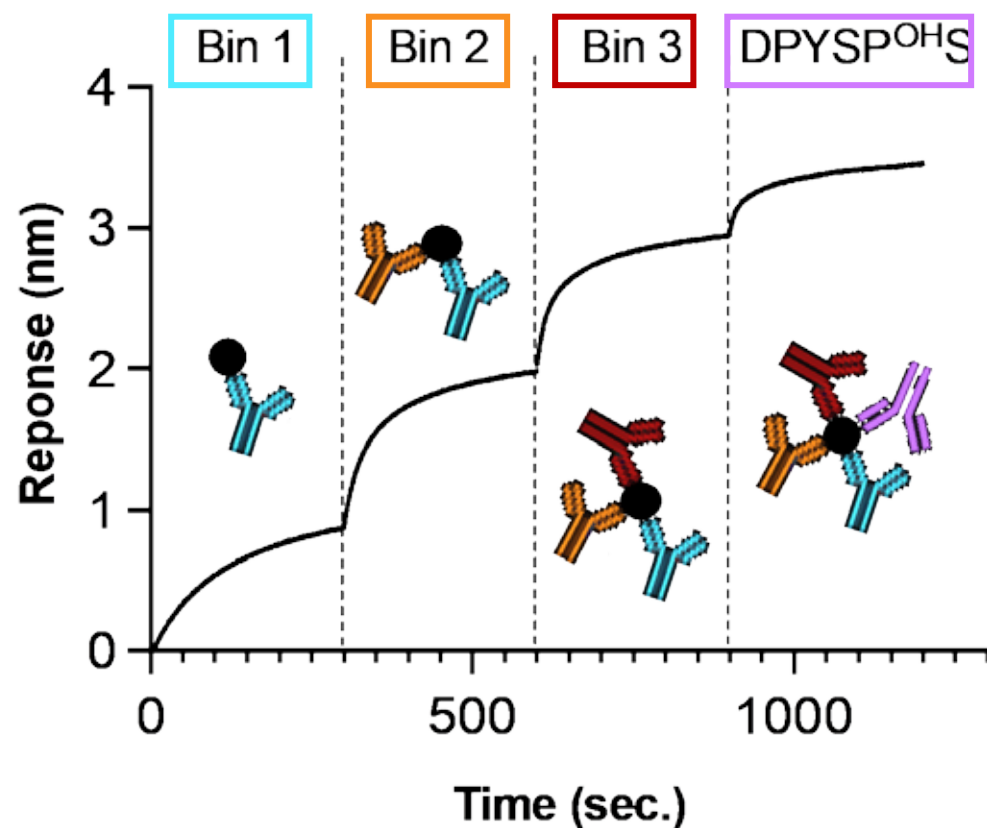
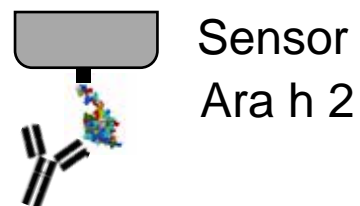
Epitope-specificity in sustained and transient responses to OIT



LaHood*, Min *...Patil, J Clin Investigation, 2023.



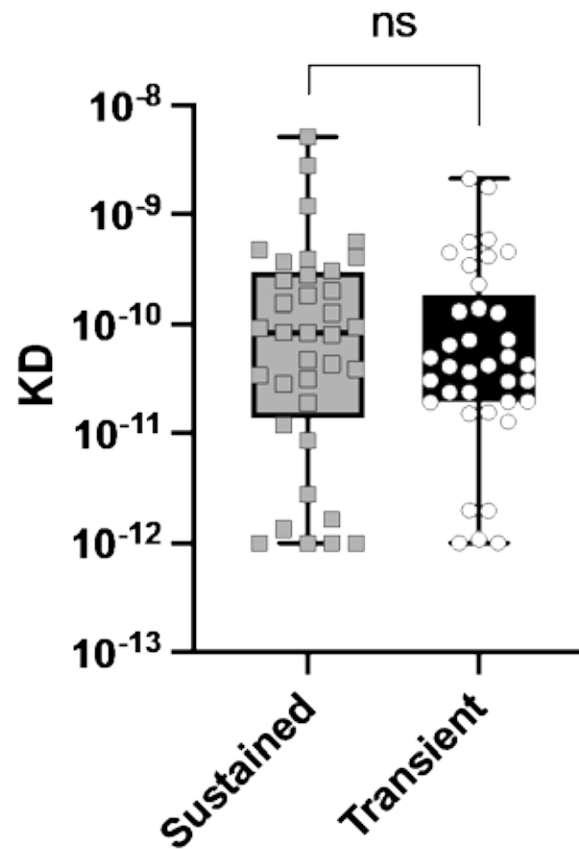
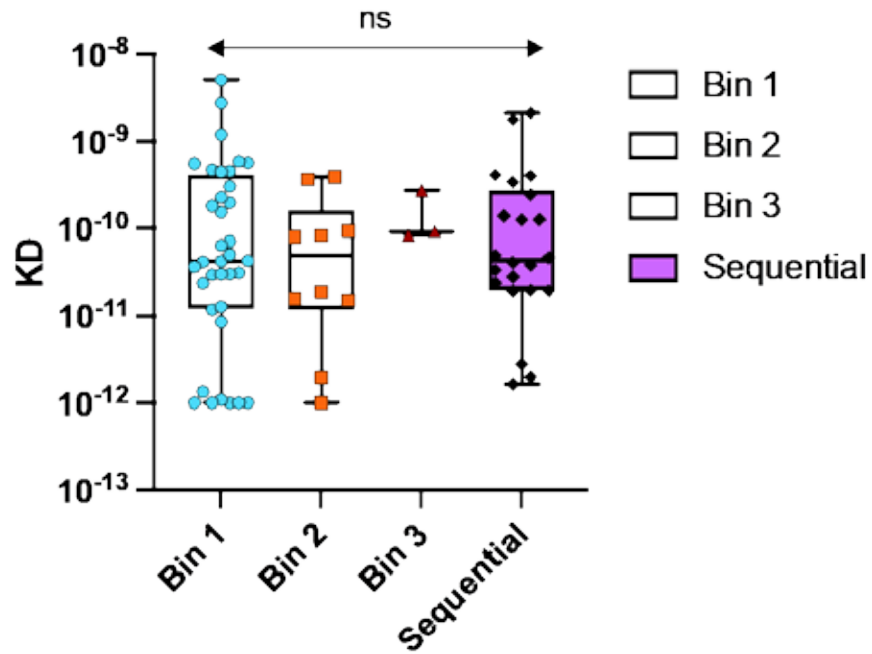
3 conformational epitopes do not overlap with immunodominant sequential epitope



LaHood*, Min *...Patil, J Clin Investigation, 2023.



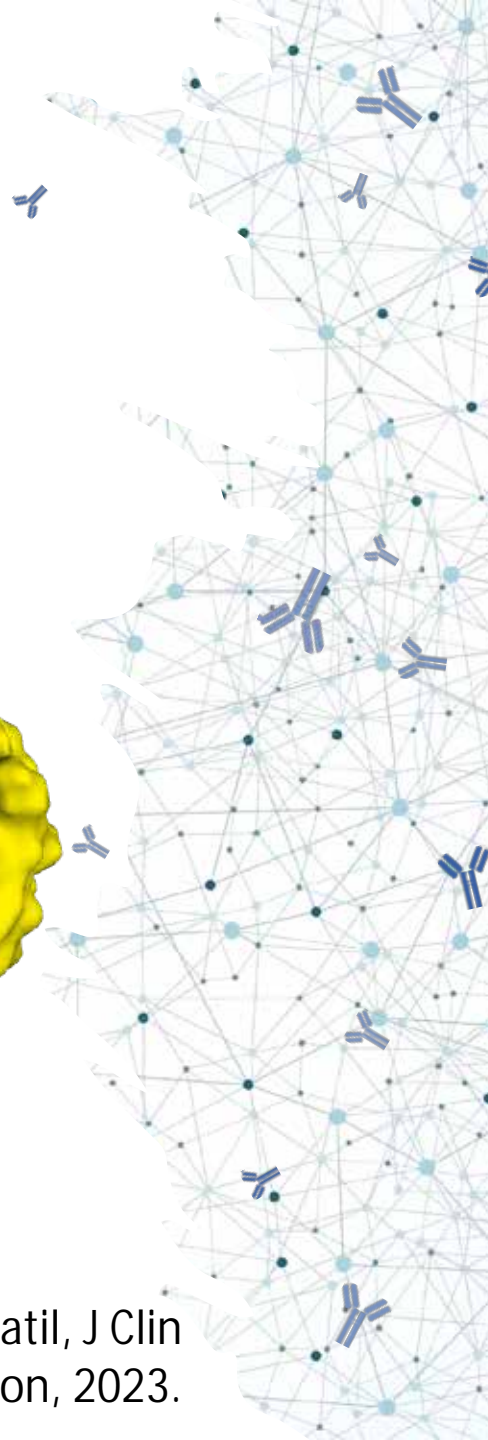
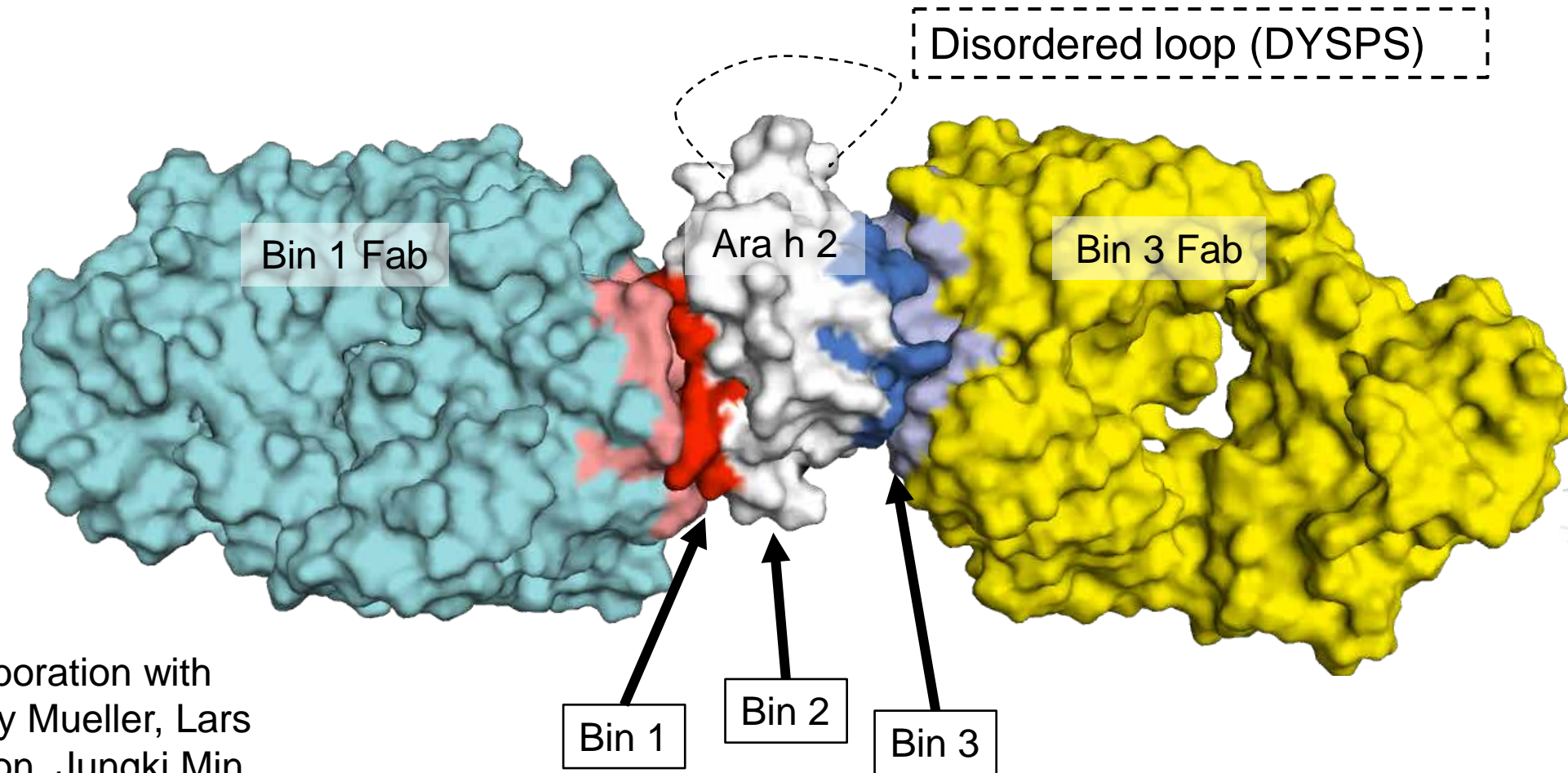
Affinity to Ara h 2 does not correlate with durable efficacy of OIT



LaHood*, Min *...Patil, J Clin Investigation, 2023.



Defining Bins 1 and 3 using X-ray crystallography



In collaboration with
Geoffrey Mueller, Lars
Pederson, Jungki Min
(NIEHS) and Anna
Pomes (InBio)

LaHood*, Min *...Patil, J Clin
Investigation, 2023.

Conformational antibody epitopes of Ara h 2

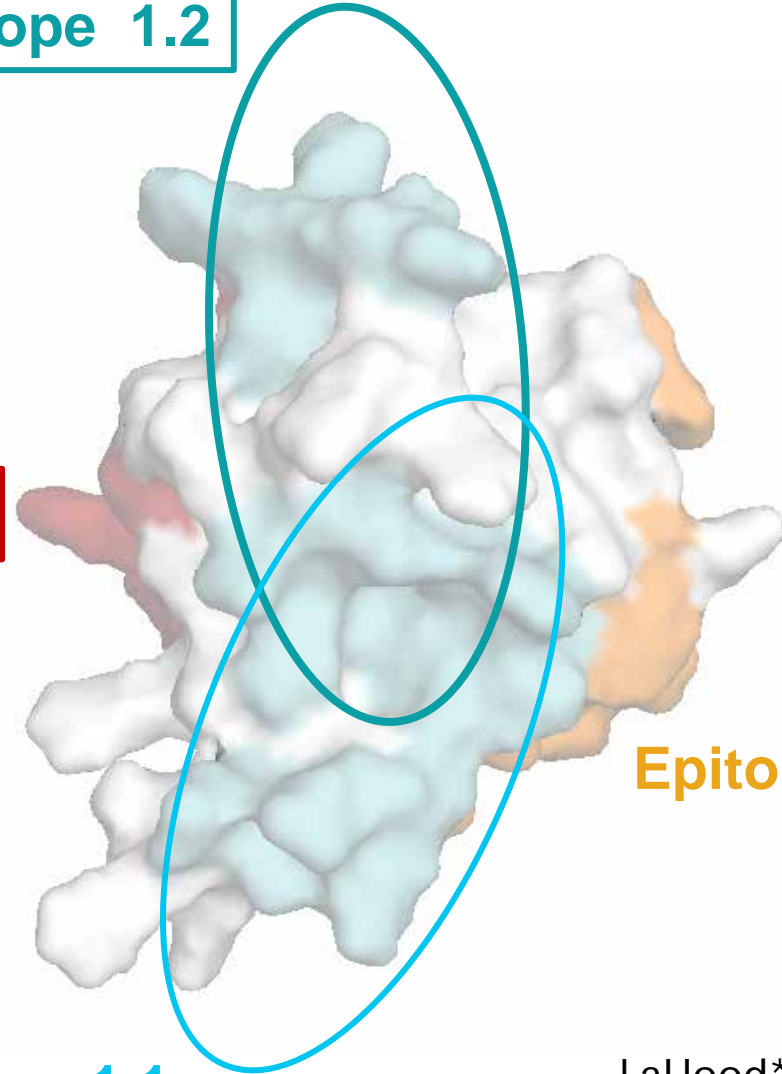
Epitopes associated with sustained responses

Epitope 1.2

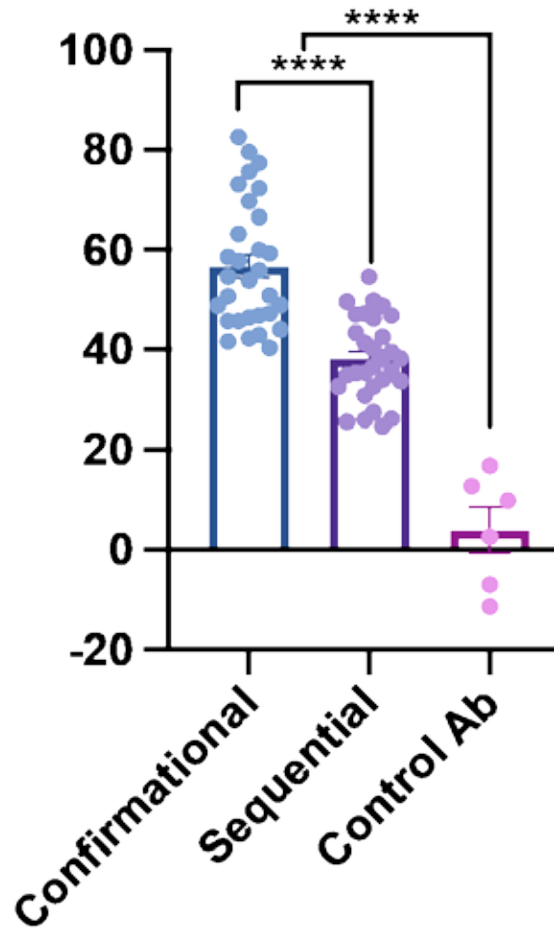
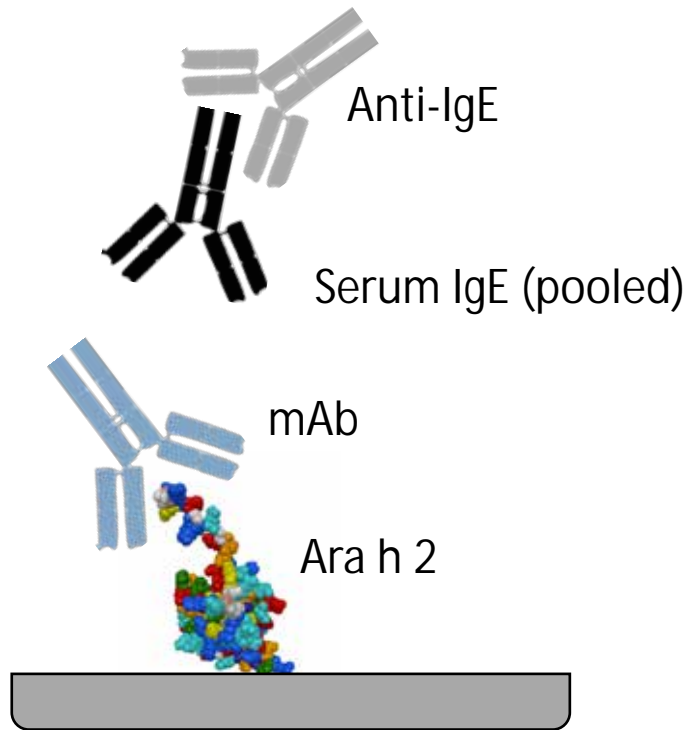
Epitope 3

Epitope 2

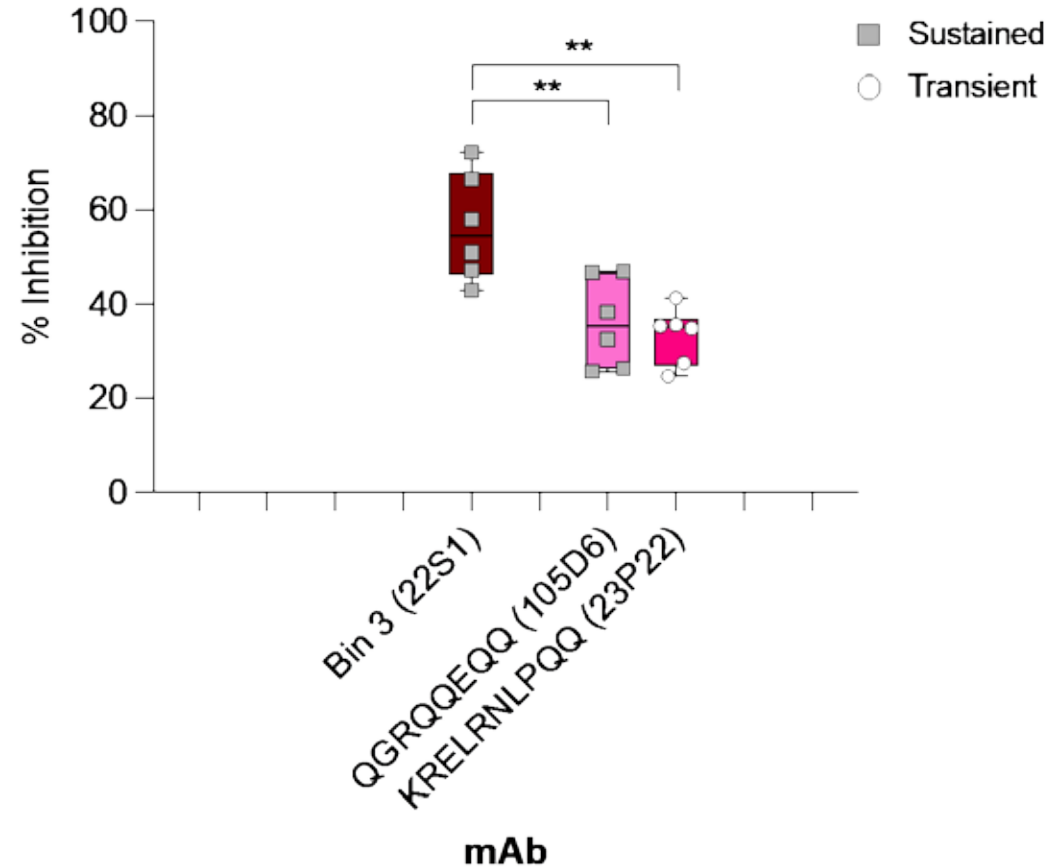
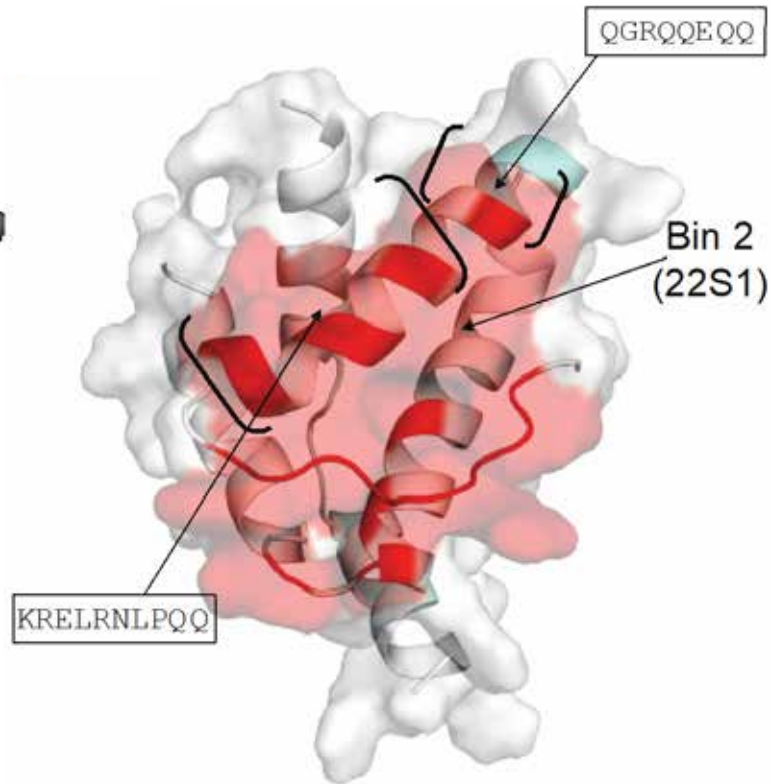
Epitope 1.1



Functional inhibition of IgE binding

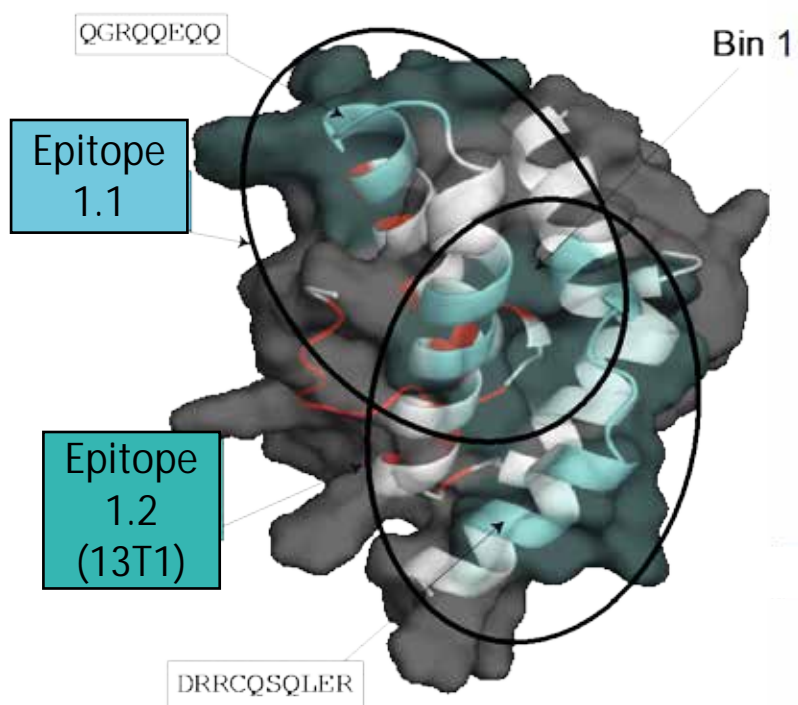


Functional inhibition of IgE binding

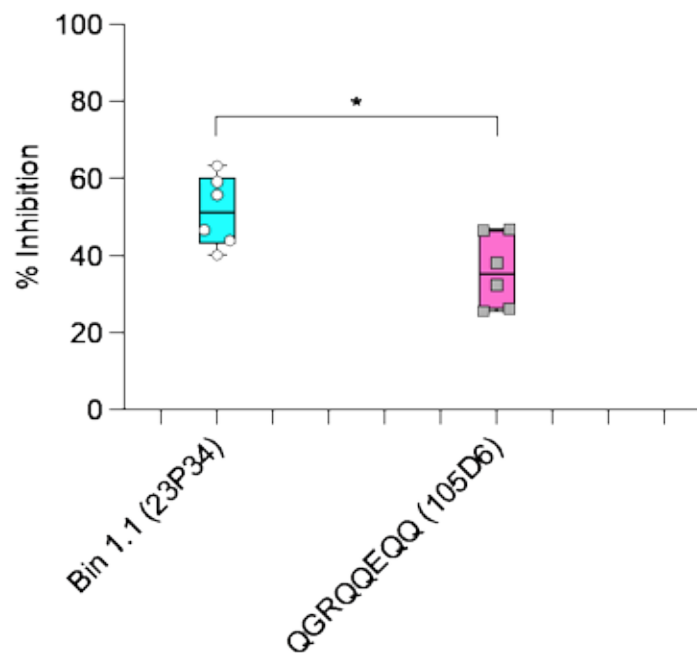


LaHood*, Min *...Patil, J Clin Investigation, 2023.

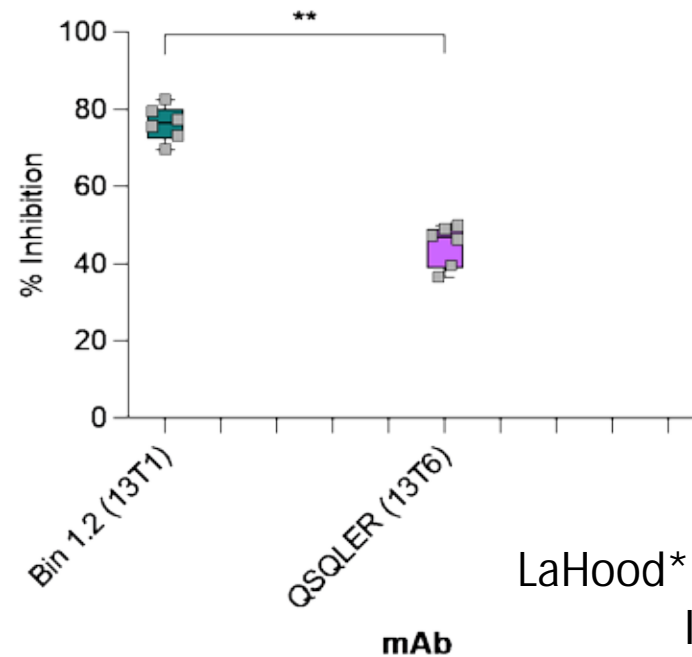




Epitopes 1.1 and 1.2



■ Sustained
○ Transient

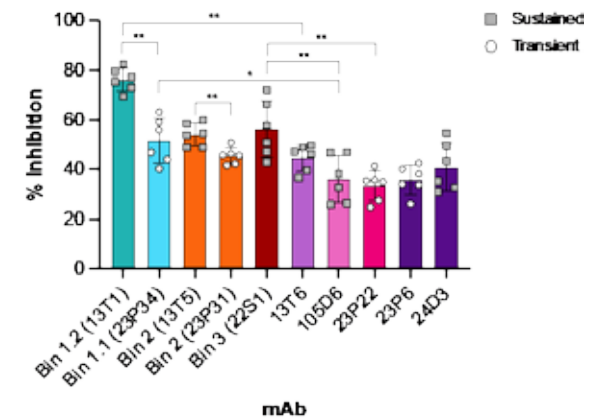
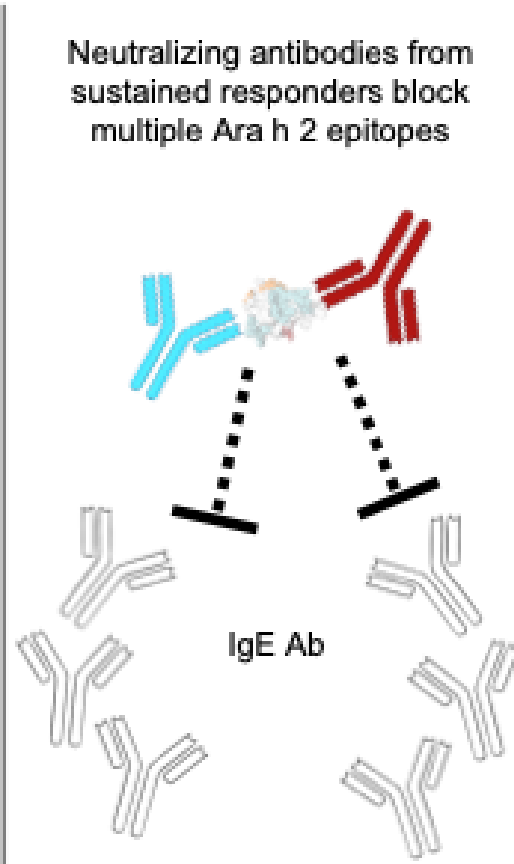
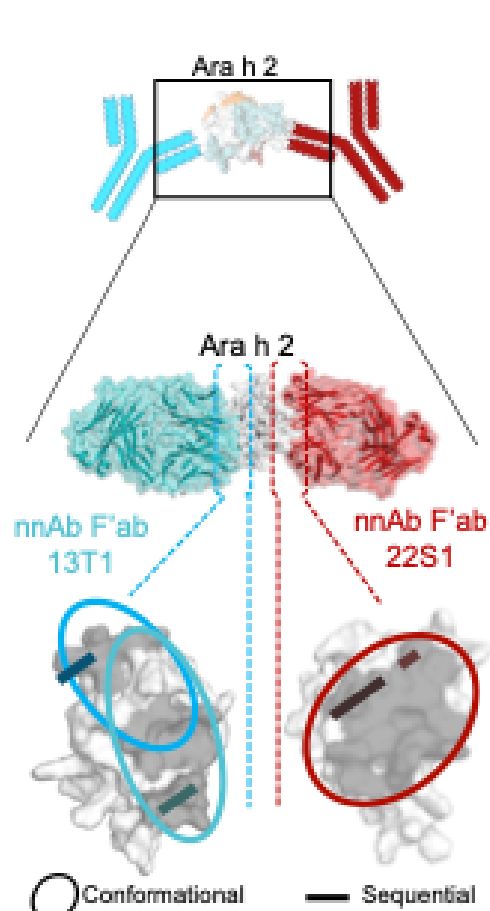
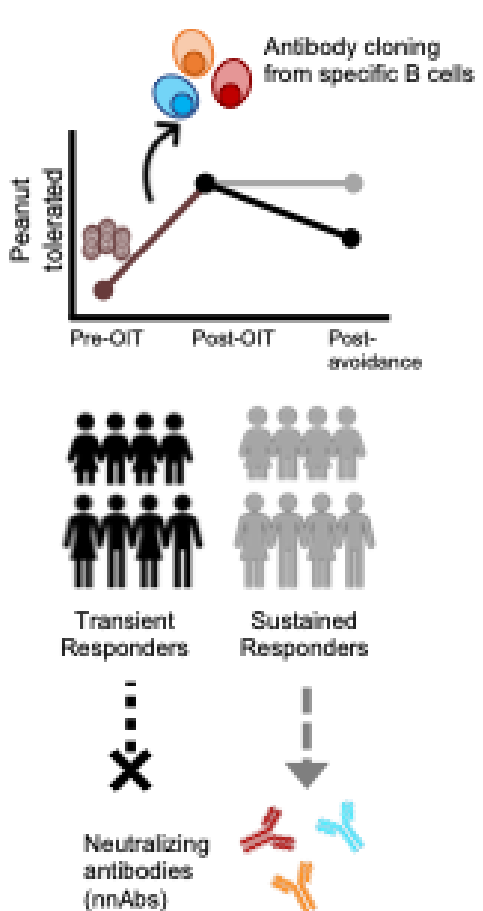
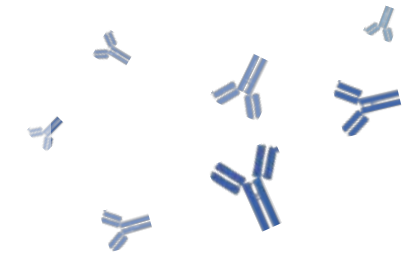


■ Sustained
○ Transient

LaHood*, Min *...Patil, J Clin Investigation, 2023.



Neutralizing antibodies in durability of clinical tolerance after OIT



LaHood*, Min *...Patil, J Clin Investigation, 2023.

Convergent antibodies and public repertoires

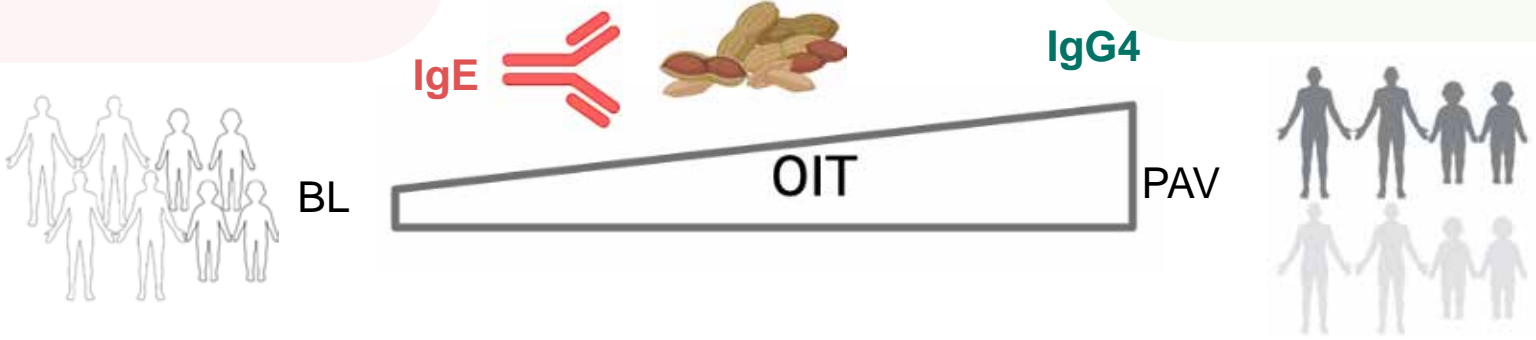
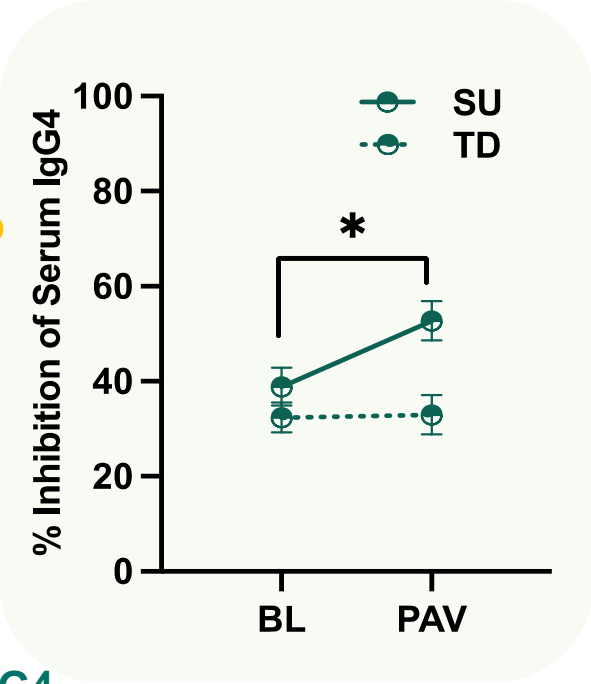
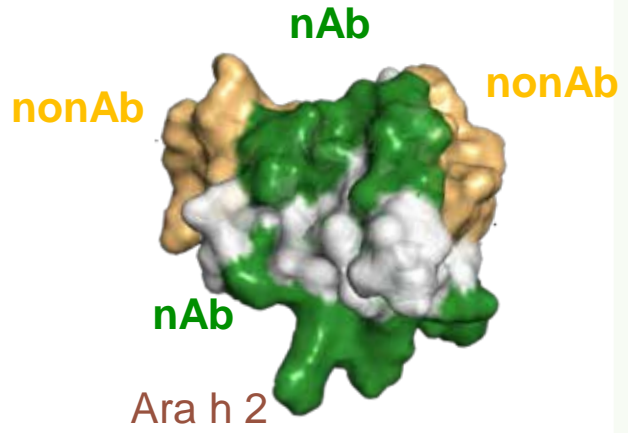
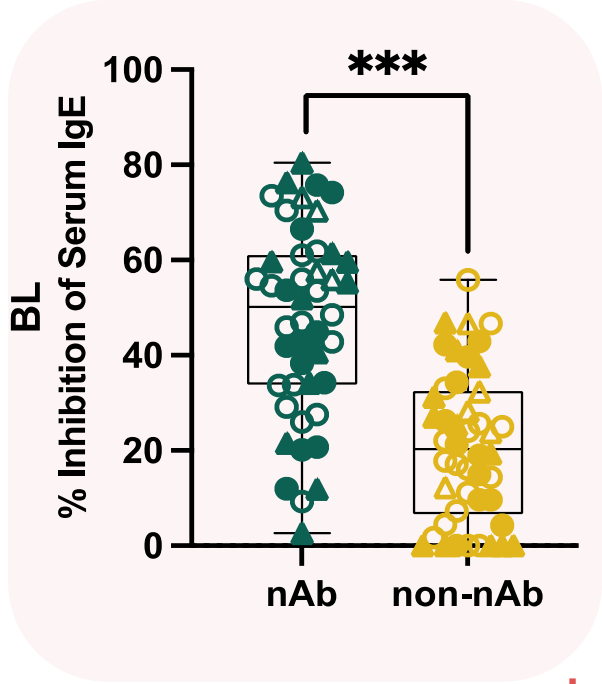
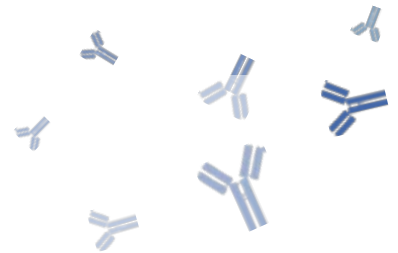
	VKDNGLRSFDS	MQALQTPWT
23P10	VKDNGLRSFDS	MQALQTPWT
23D12	AKDNGLRSFDS	MQALQTPWT
23P13	AKDSGLRSFEV	MQAQTPWT
23P14	VKDTGLRSFHS	MQALQT.WT
23P3	VKDNGYRAFDL	MQSLQT.WT
23P19	VKDNGYRAFDL	MQSLQT.WT
23P17	VKDGGLRYFDY	MQSLQT.FT
23D6	VKDGGLRYFDY	MQSLQT.FT
23P33	VKDGGLRYFDS	MQSLQT.FT
23P34	VKDGGLRYFDS	MQSLQT.FT
23B8	VKDGGLRYXQH	MQSLKS.FT
23C4	VKDGGLRYFQY	MQSLET.FT
11A2	VKDNGWRSFAY	MQALQA.FT
23P11	VKDSGLRYFNL	MQALQS.WT
23P21	VKDSGLRAFEI	MQALQR.WT
23P39	VKDSGLRSLQY	MQAQQS.WT
24C10	VKDTGLRSFDS	HQYYSTPHS
24C2	VKDTGLRSFDS	MQALQT.WT
24A10	VKDTGLRSFDS	MQALQS.WT
24D1	VKDTGLRSFDS	MQALQS.WT
105A11	AKDIGLRSLDS	MQALQG.WT

Epitope 1.1

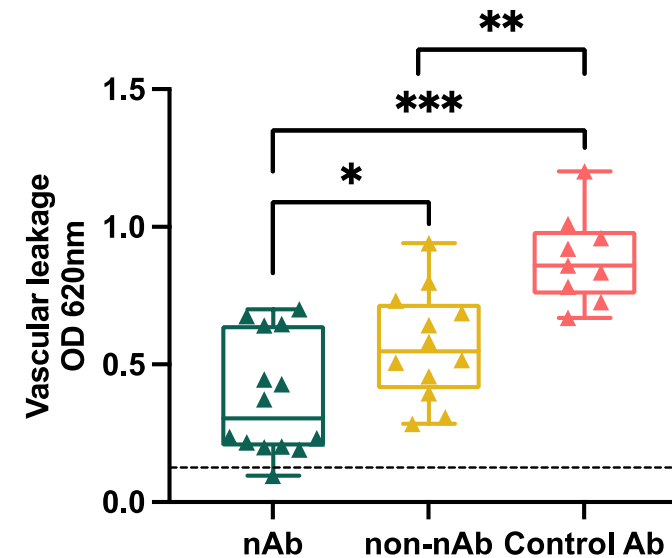
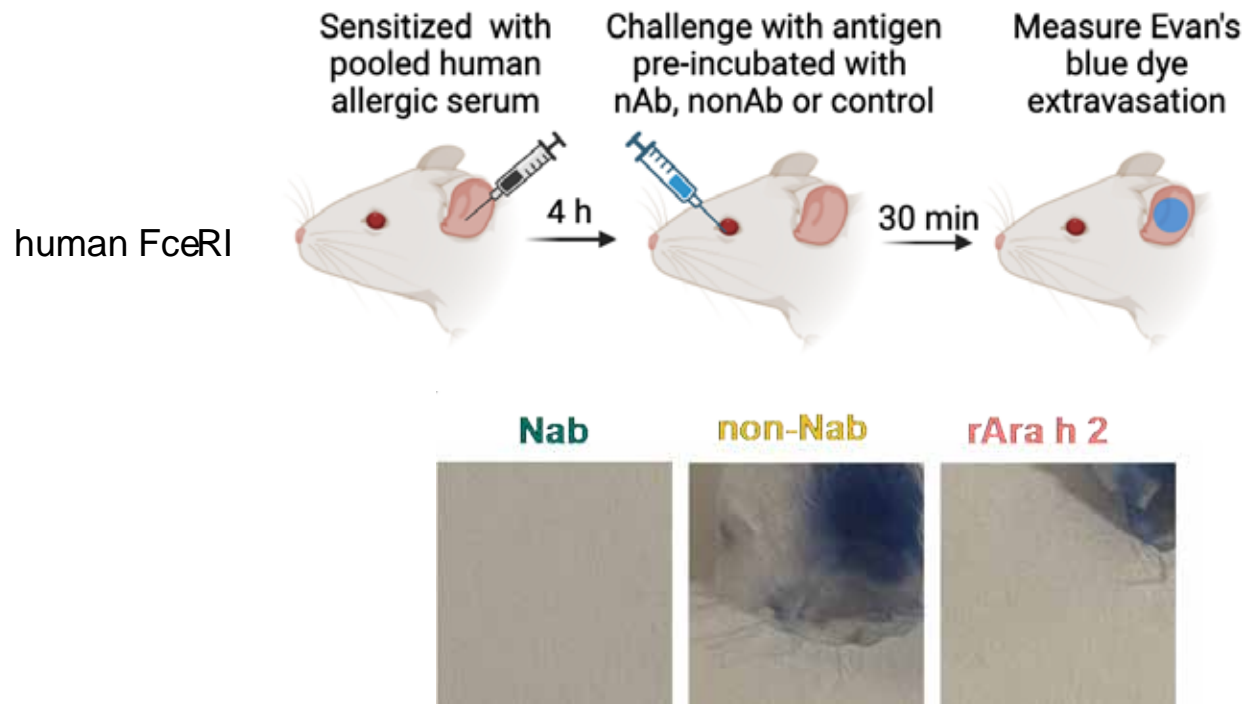
- X Asp, Glu
- X Arg, Lys, His
- X Phe, Tyr, Trp
- X Ala, Gly
- X Cys, Met
- X Ser, Thr
- X Asn, Gln
- X Leu, Val, Ile
- X Pro



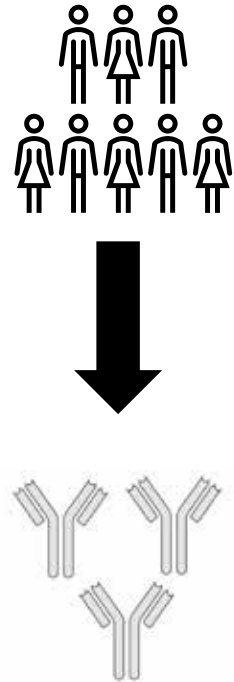
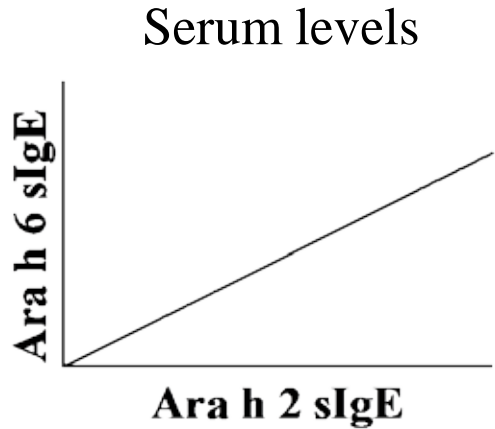
IgG4 nAbs in OIT



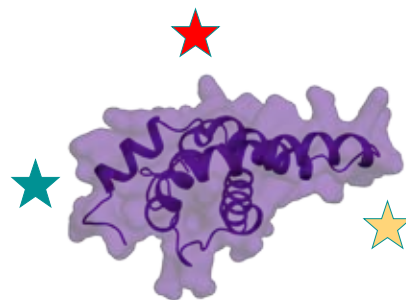
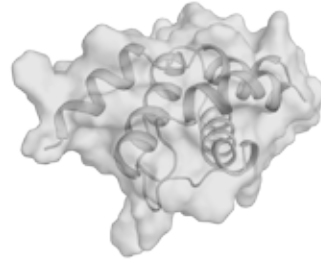
nAbs inhibit murine IgE in murine model of passive cutaneous anaphylaxis more than non-nAbs



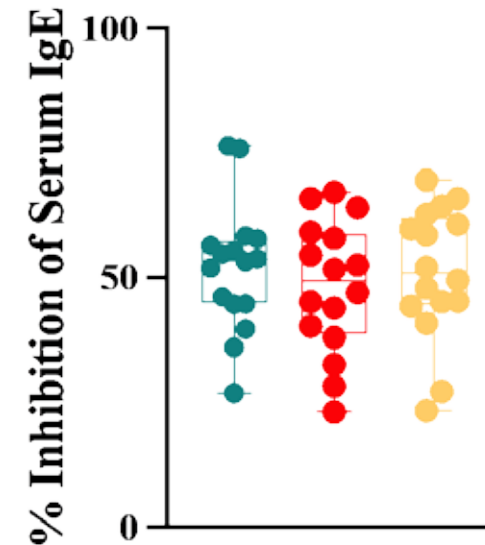
Epitope-specific cross-reactivity of 2S albumin specific IgE



Ara h 2



Ara h 6



Allergen-specific antibodies in peanut allergy



- Neutralizing IgG4 induced in OIT underlie sustained clinical tolerance
 - Epitope-specific allergen-specific antibodies to immunodominant allergen Ara h 2
 - Neutralization defined as the ability to block multiple IgE epitopes
 - Polyclonal serum identifies these antibodies to be increased during OIT only in those with sustained responses to OIT
- Cross-reactivity of 2S albumins
 - Ara h 2 is immunodominant over Ara h 6, with a larger number of epitopes
 - Affinity is higher to Ara h 2 due to the rigidity of epitope-paratope interactions
- 2S albumin recognition occurs similarly across many patients due to convergent evolution
 - Suggests this is a fundamental property of the human antibody repertoire.

Structural-functional molecular determinants of allergenicity



Epitopes

- Localization
- Cross-reactivity

Paratopes

- Public antibodies
- Evolution of allergenic recognition

Functionality

- Allergic activation
- Neutralization

Acknowledgements

FOOD ALLERGY CENTER



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GENERAL HOSPITAL



MassGeneral Hospital
for Children



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Kwasi Amoako

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Dr. Herve Bernard

Anna Pomes (InBio)

Shreffler Lab (MGH)

Love Lab (MIT)



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Thank you!