The Journal of Allergy and Clinical Immunology:
In Practice

# Expert Roundtable on Sublingual Immunotherapy

# FACULTY

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Professor of Medicine, University of South Florida

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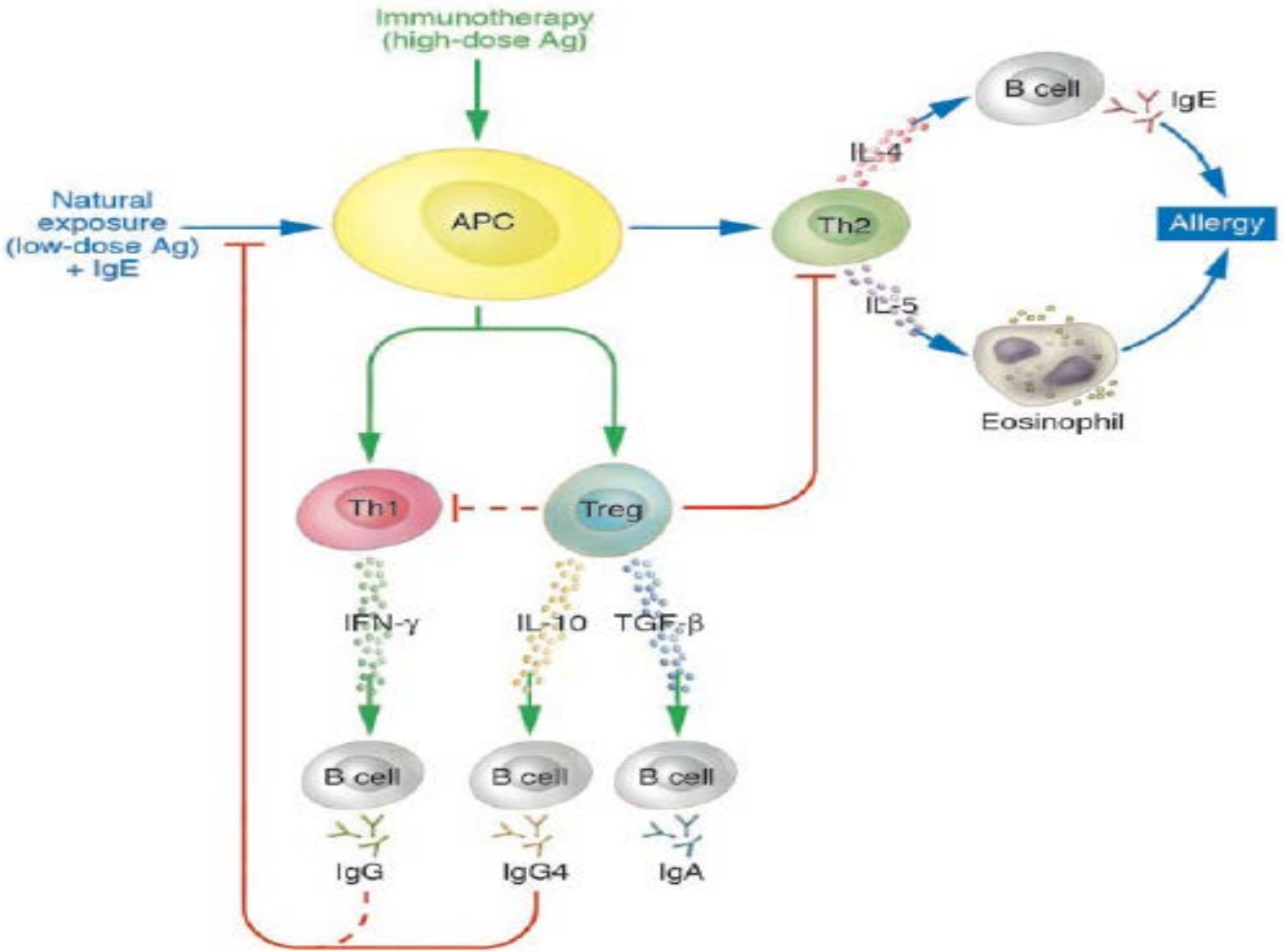
# Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or asthma

- Patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens.

Decision depends on:

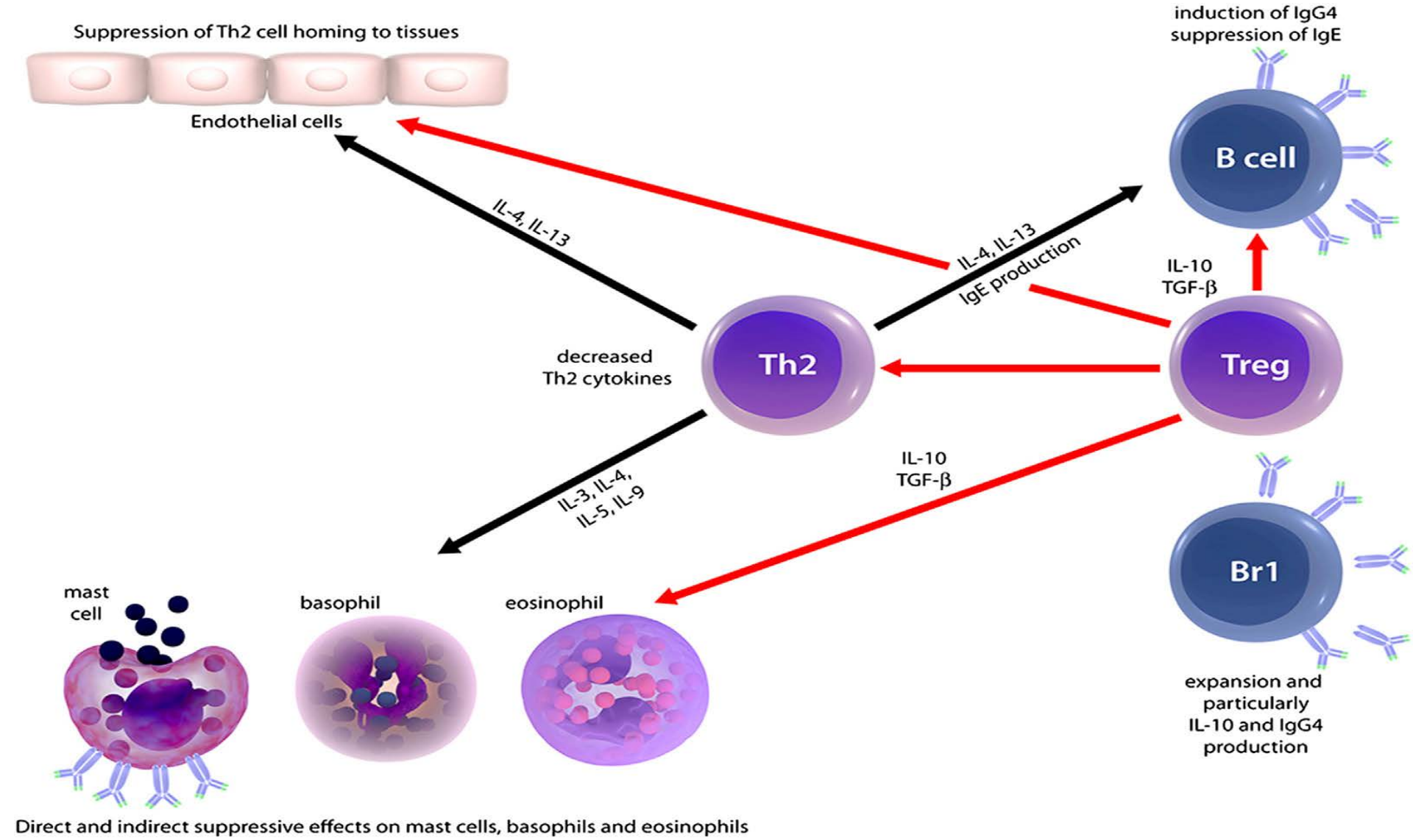
- The patient's preference/acceptability;
- Adherence;
- Medication requirements;
- Response to avoidance measures;
- Adverse effects of medications;

Cox, Nelson, Lockey, et al. *J Allergy Clin Immunol*. 2011;127(1 Suppl):S1-55.


Immunotherapy
(high-dose Ag)
Natural
exposure
(low-dose Ag)
+ IgE
APC
B cell
IgE
IL-4
Th2
Allergy
IL-5
Eosinophil
Th1
Treg
IFN-γ
IL-10
TGF-β
B cell
B cell
B cell
IgG
IgG4
IgA

S Durham

# AIT Mechanisms




Direct and indirect suppressive effects on mast cells, basophils and eosinophils

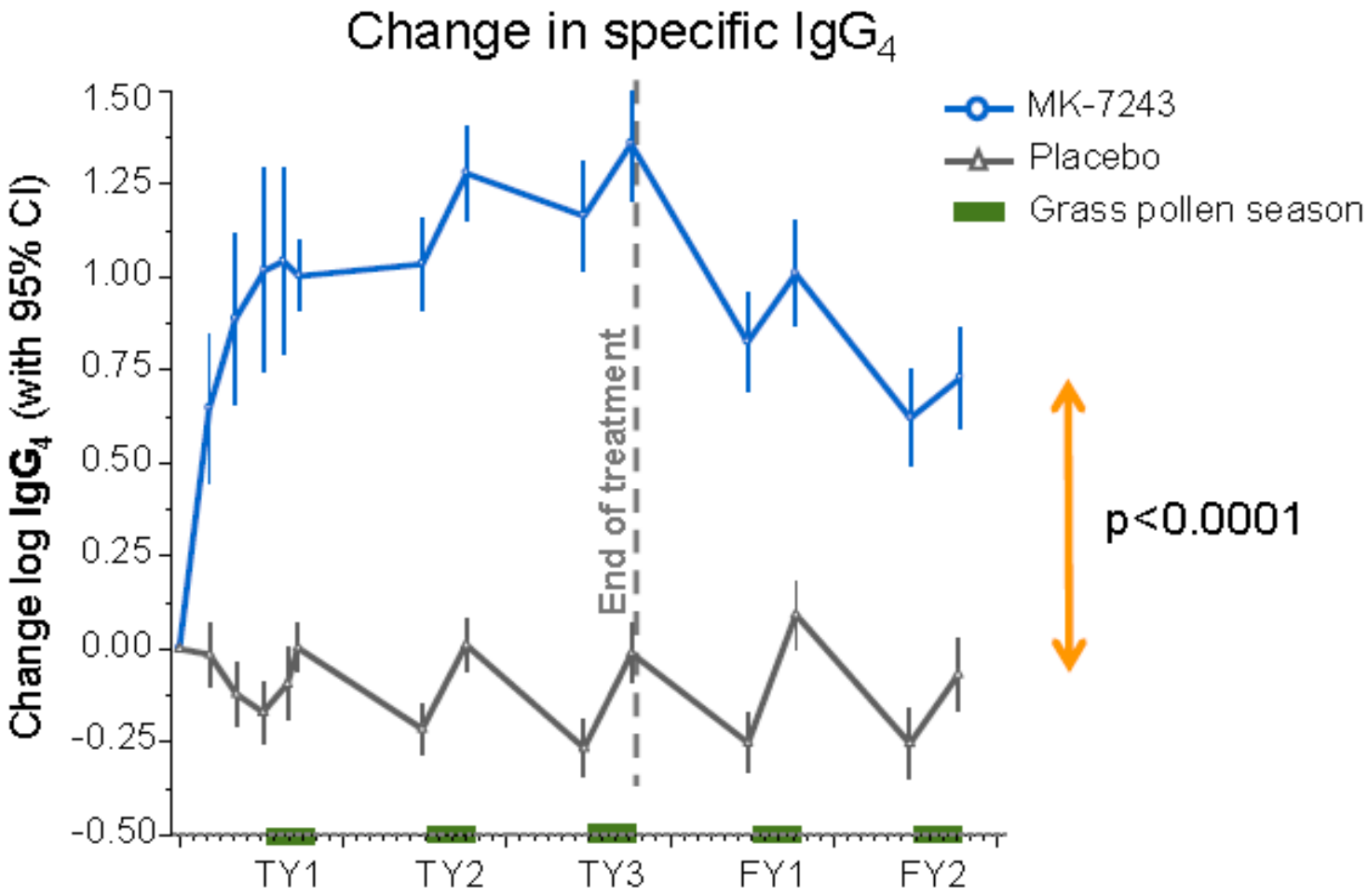
M Akdis and C Akdis. J Allergy Clin Immunol 2014;133:621-31.

# What Is Known About How SLIT Works

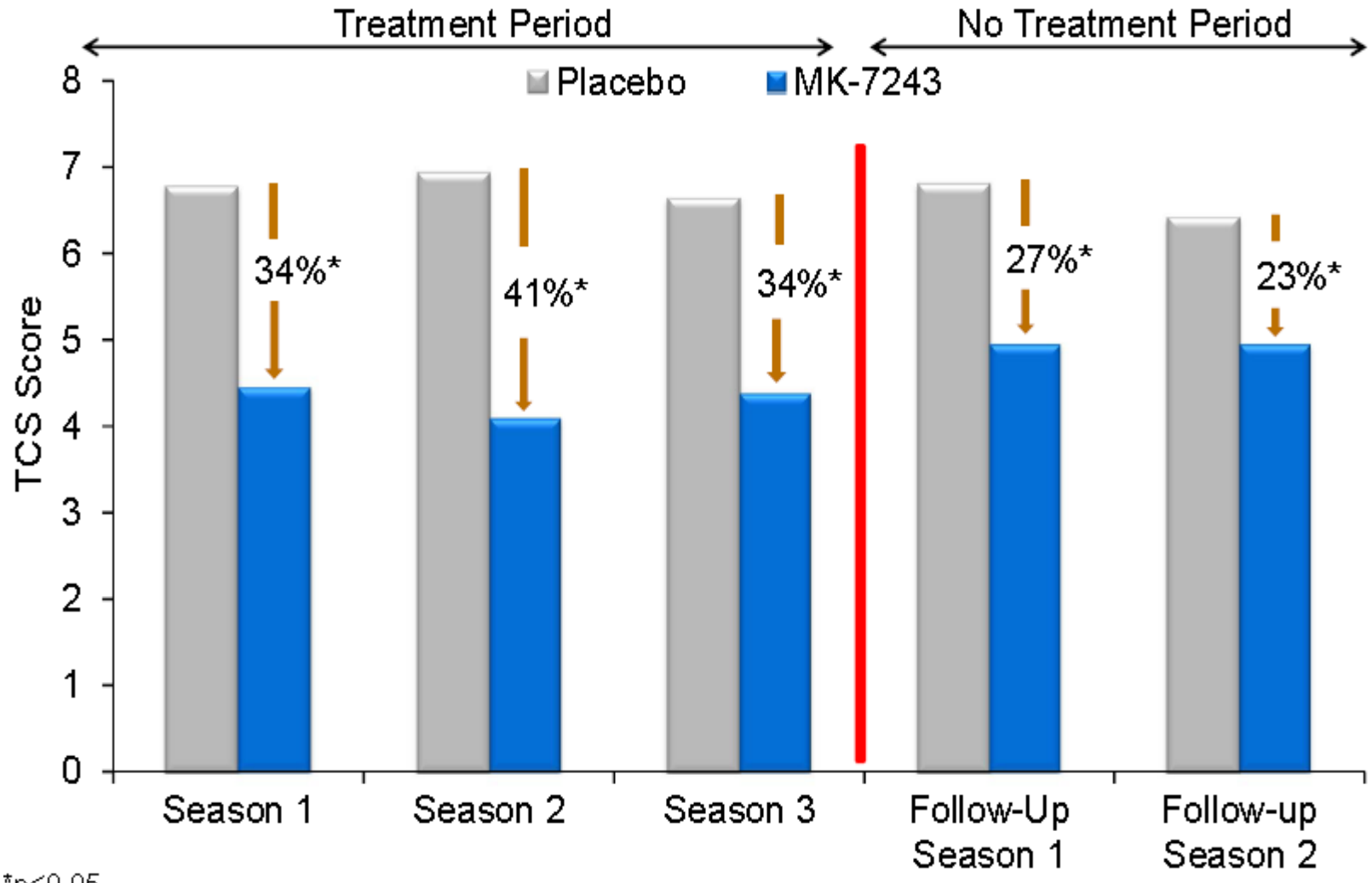
- The mechanisms of action of SLIT are less well established than those for SCIT
- Various subsets of DCs are present in the oral cavity that could be important to the induction of tolerance.
- Some studies show increased IL-10 and TGFβ mRNA
- IgG4 and IgA levels increase, but IgE levels remain stable
- ECP and serum IL-13 levels are decreased
- Nasal tryptase secretion after nasal allergen challenge tests decreased

M Akdis and C Akdis. J Allergy Clin Immunol 2014;133:621-31.

# Grazax Sustained Immunologic Effects



# Grazax Long-Term Clinical Effects




*p<0.05

# Biomarker predictors of effective immunotherapy?

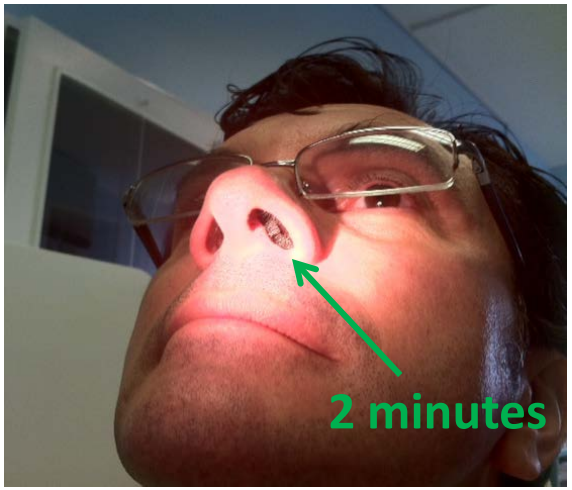
- History of *symptoms* on *exposure* to a *clinically relevant* allergen with objective confirmation of *IgE sensitivity* (SPT/Sp IgE)

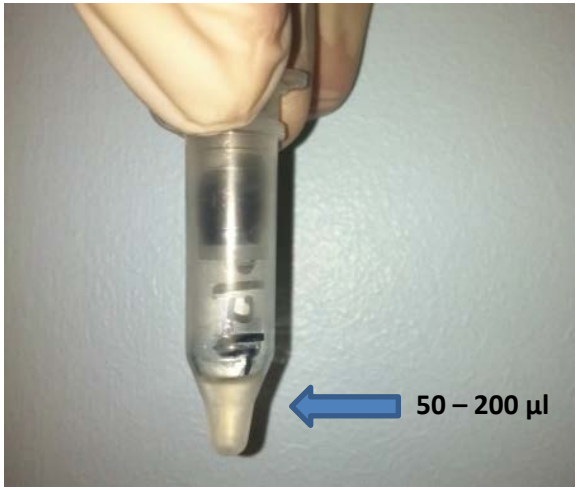
- Ideal biomarker:
  - feasible and accessible
  - predict disease severity
  - predict responsiveness to treatment
  - Monitor progress

# Biomarker predictors of effective Immunotherapy

- Nasal allergen challenge
- Local nasal mediators, cytokines, antibodies
- Serum antibodies
  - IgG, IgG4, IgE, IgA
  - 'Blocking antibodies'
    - IgE-FAB inhibition
    - Basophil activation inhibition
- Peripheral cellular responses
  - Basophils

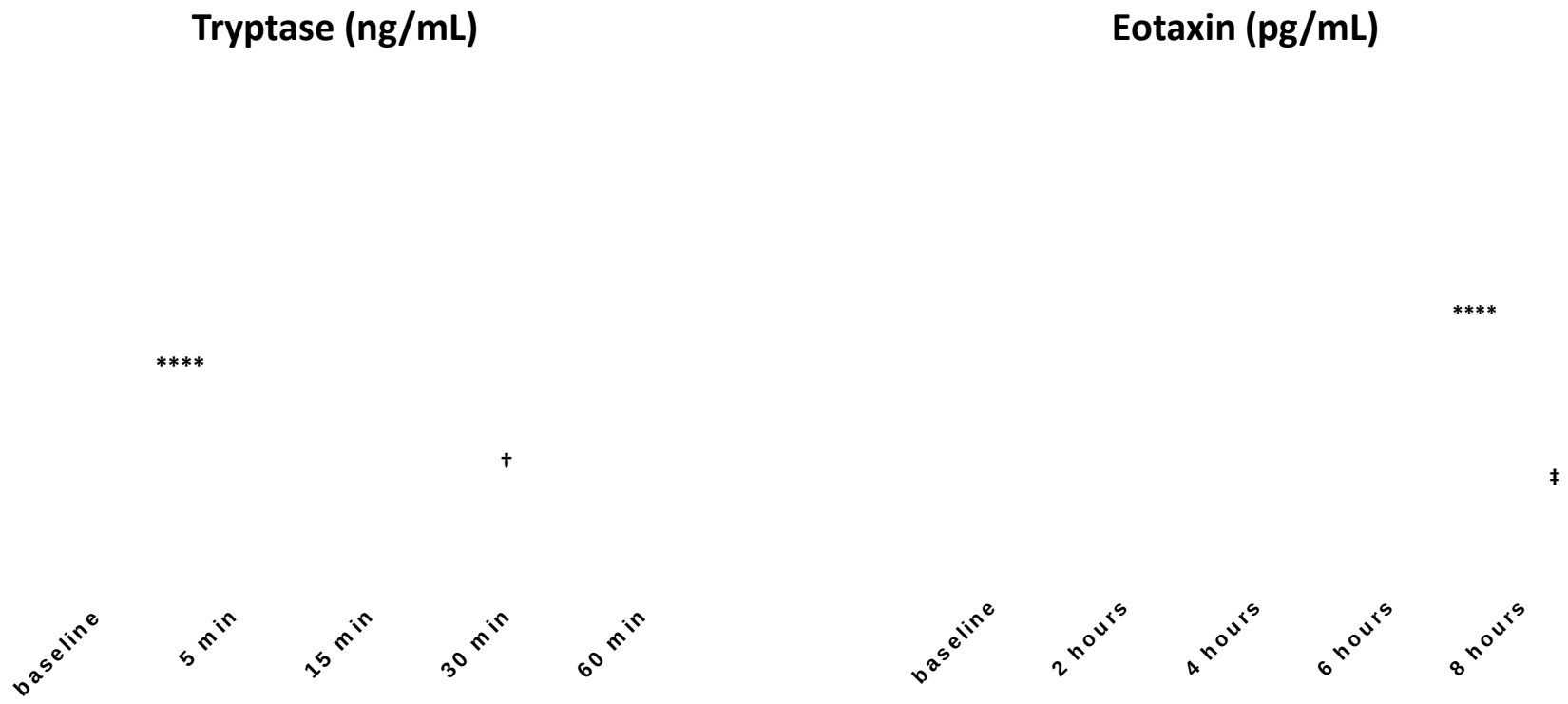
# Nasal allergen challenge: fluid collection




Scadding GW, Calderon MA, Hansel T, Wurtzen PJ et al. *J Immunol Methods.* 2012;384:25-32.

# Tryptase and eotaxin in nasal fluid




Median, IQR, range
Comparisons by Mann-Whitney test
**** non-allergic vs untreated allergic (p=0.0001)
†untreated allergic vs SIT (p=0.05)
‡untreated allergic vs SIT-completed (p=0.05)

Scadding G, Eifan A, Shamji M et al. AAAAI 2014

# SEROLOGICAL EVIDENCE OF IMMUNITY WITH COEXISTING SENSITIZATION IN A TYPE OF HUMAN ALLERGY (HAY FEVER)*

By ROBERT A. COOKE, M.D., JAMES H. BARNARD, M.D., SELIAN HEBALD, M.D., and ARTHUR STULL, Ph.D.

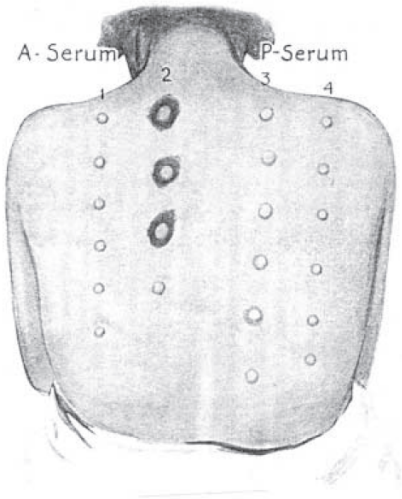
(*From the Department of Medicine of New York Hospital and Cornell University Medical College, and the Department of Allergy of The Roosevelt Hospital, New York*)

J Exp Med 1935; 62: 733-50

Robert RA Cooke

Using ragweed hay fever as an example of a type of allergy we record serological studies which were undertaken to explain the protection resulting from pollen injections. The results have indicated to us the production of an inhibiting or immune type of substance that prevented the allergen from reacting with the sensitized cell, and they have also demonstrated the coexistence of both sensitizing and immune antibodies in the specifically treated patients.

# Passive transfer of ragweed allergy with pre-IT serum A and inhibition with post-IT serum B ( Cooke R et al)




| | A-serum | | | | P-serum | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | Ragweed pollen extract units | Ragweed pollen extract units | 3 | 4 | |
| 1:10 | ○ | ○ | 50 | 150 | ○ | ○ | 1:10 |
| 1:100 | ○ | ○ | 100 | 300 | ○ | ○ | 1:100 |
| 1:200 | ○ | ○ | 150 | 500 | ○ | ○ | 1:200 |
| 1:300 | ○ | ○ | Saline control | 700 | ○ | ○ | 1:300 |
| 1:400 | ○ | | | 1000 | ○ | ○ | 1:400 |
| 1:500 | ○ | | | Saline control | ○ | ○ | 1:500 |

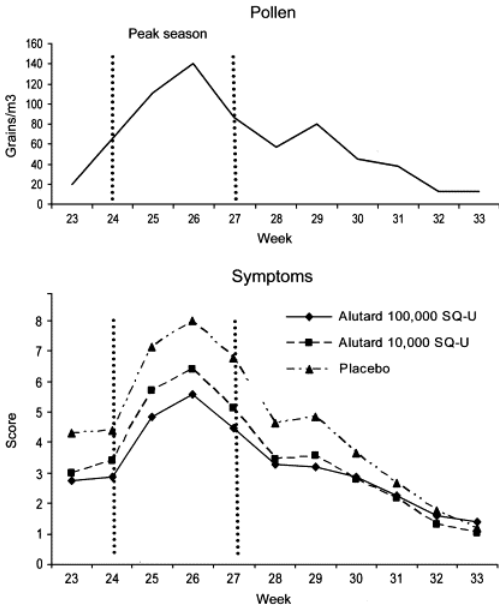
Courtesy of Flicker S, Valenta R. *Int Arch Allergy Immunol*. 2003;132:13-24.

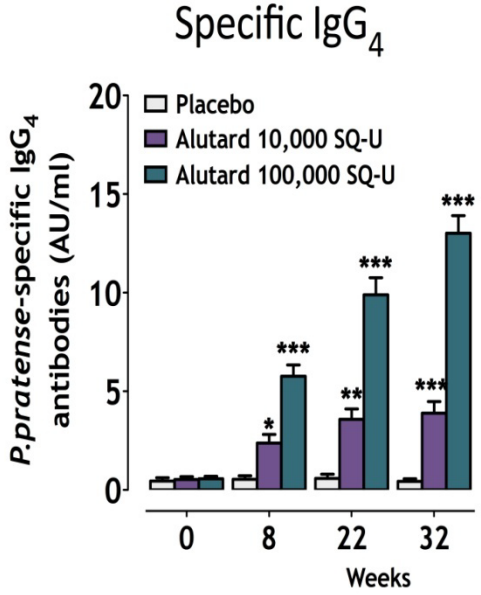
ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

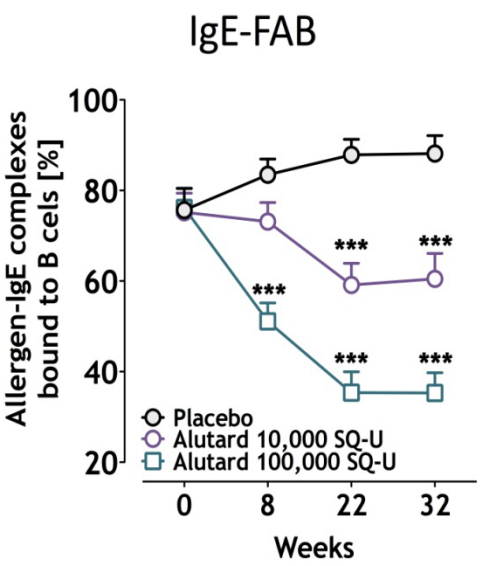
# Functional rather than immunoreactive levels of $IgG_4$ correlate closely with clinical response to grass pollen immunotherapy

M. H. Shamji[1], C. Ljørring[2], J. N. Francis[1], M. A. Calderon[1], M. Larché[3], I. Kimber[4], A. J. Frew[5], H. Ipsen[2], K. Lund[2], P. A. Würtzen[2] & S. R. Durham[1]

Allergy 2012 ;67:217-26.

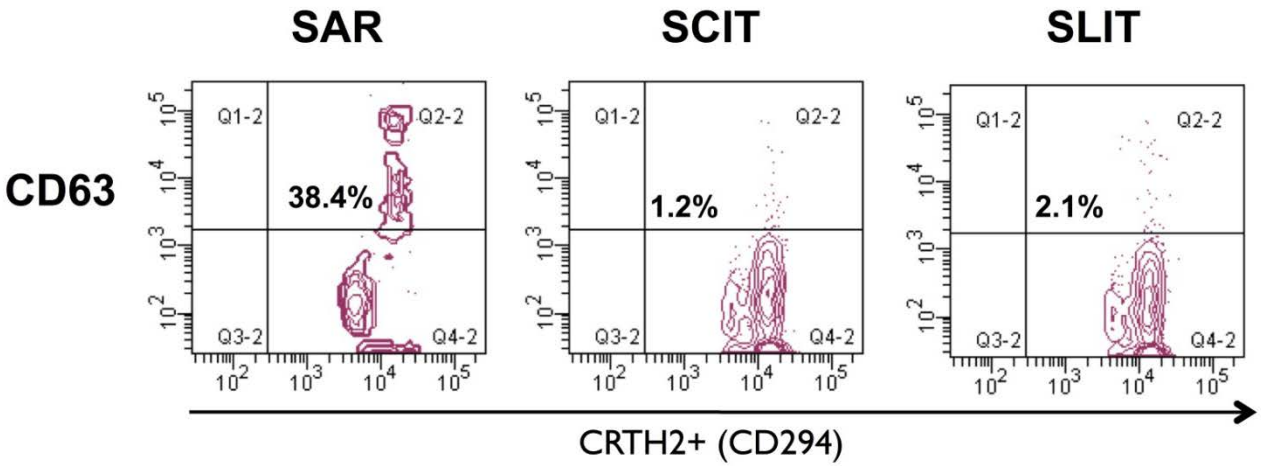


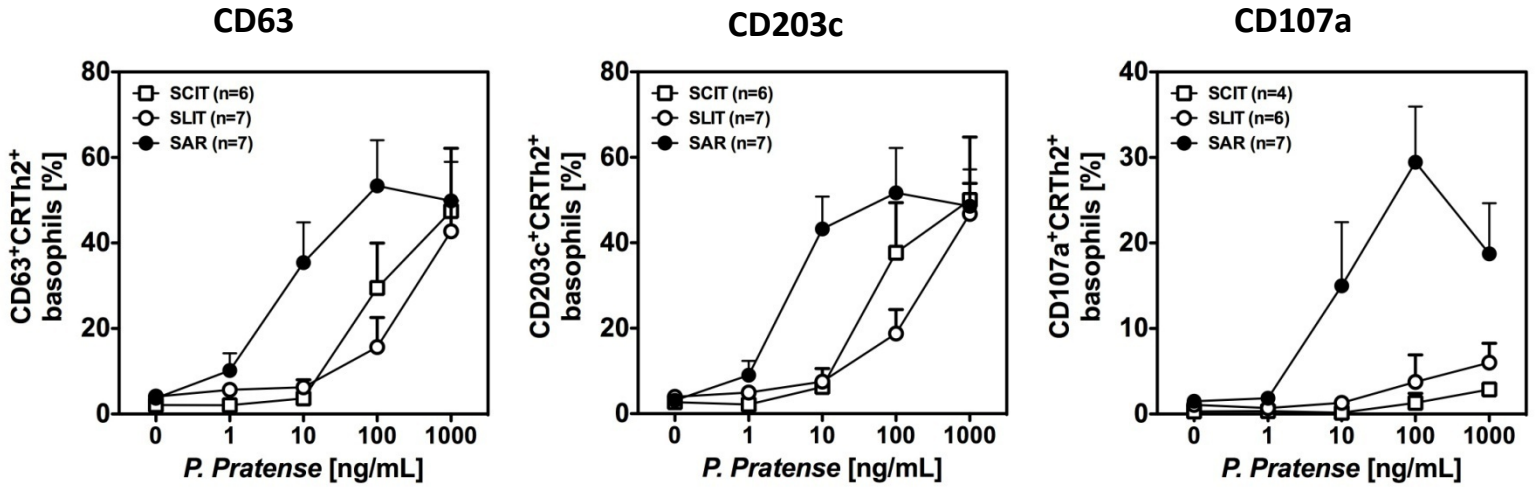




**Frew AJ et al, JACI 2006;117: 319-25**
**SCIT Grass pollen extract (n=410)**

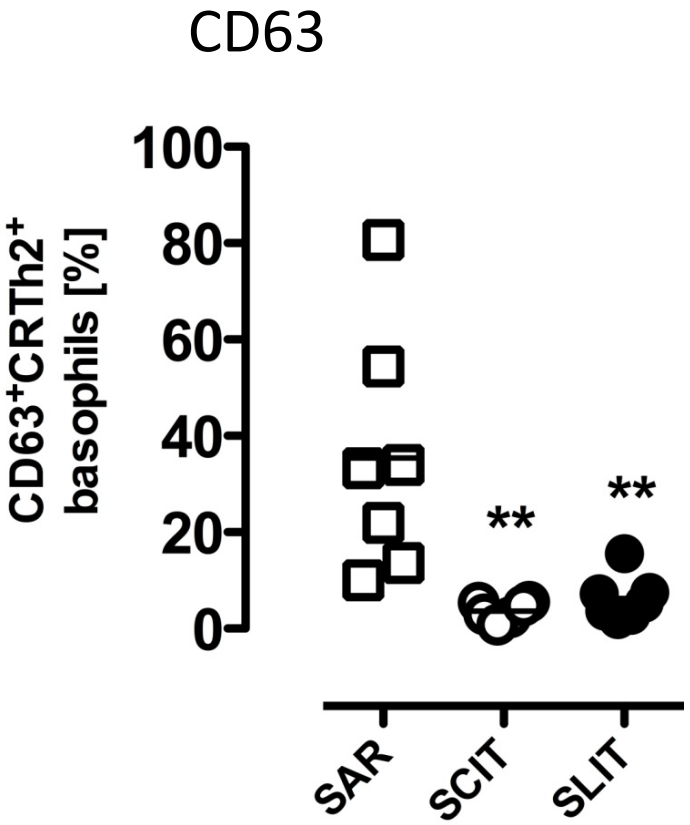
# Grass pollen-specific immunotherapy decreases *ex vivo* allergen-induced basophil reactivity

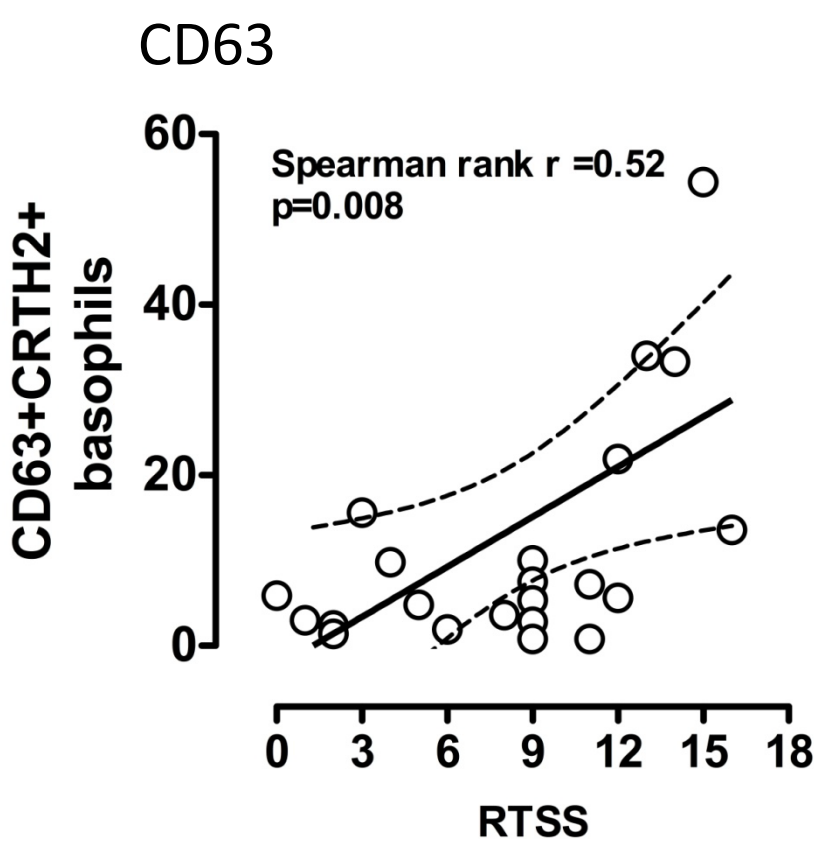



Shamji, Durham et al.

# CD63+ basophils are suppressed after SIT and correlate with seasonal symptom severity



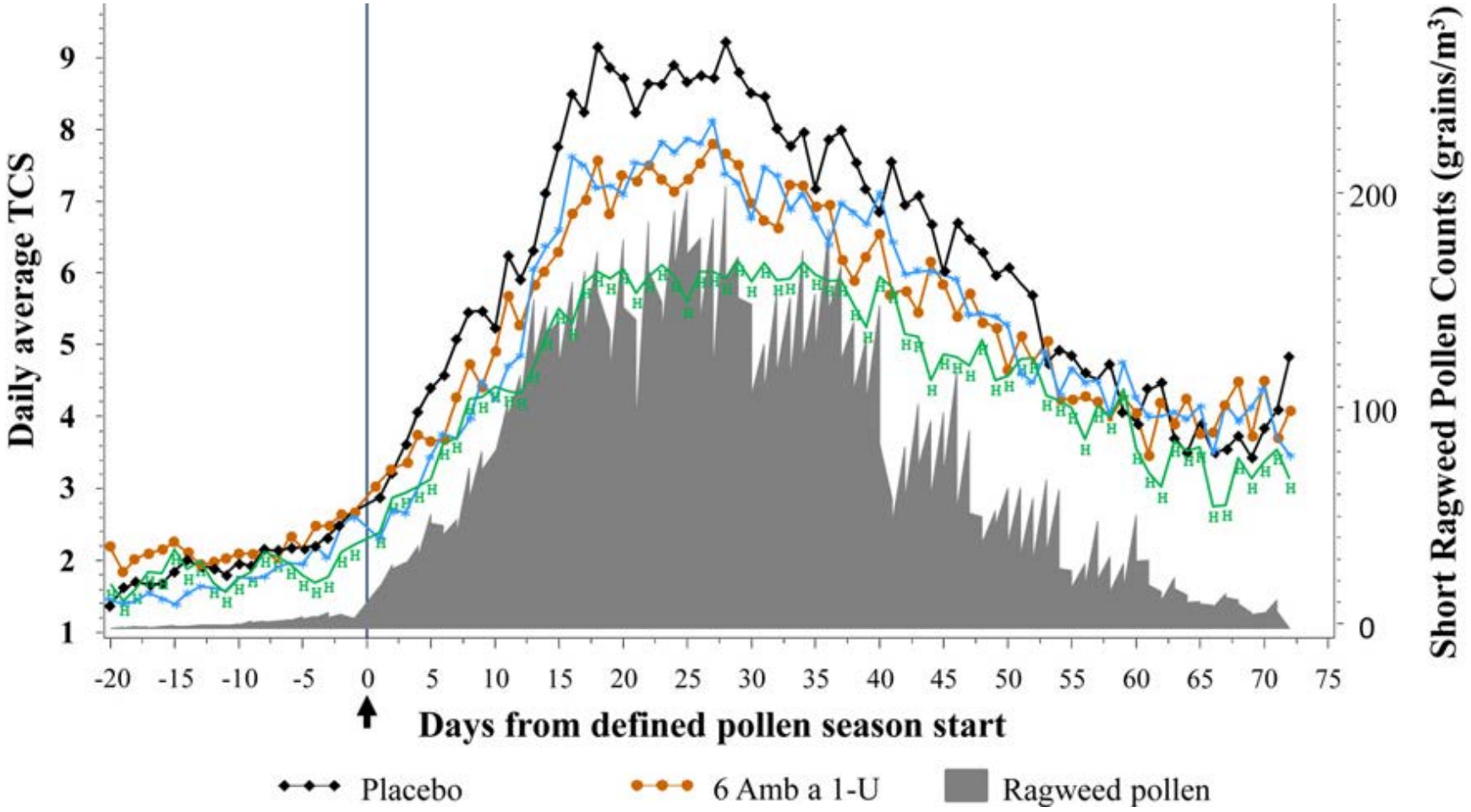




Shamji, Durham et al.

# Biomarker predictors of effective immunotherapy?

- History of *symptoms* on *exposure* to a *clinically relevant* allergen with objective confirmation of *IgE sensitivity* (SPT/Sp IgE)
- *Possible* Biomarker candidates:
  - Nasal allergen challenge (PNIF, AUC 0-60 min)
  - Nasal Th2 cytokines (Tryptase, IL-9 at 8hrs)
  - Serum blocking antibodies (IgE-FAB inhibition)
  - Basophil activation tests

# Total combined score plotted against pollen count (averaged across all regions)




Creticos, Maloney et al. *J Allergy Clin Immunol*. 2013;131:1342-1349.

# Mean TCS during the entire ragweed pollen season

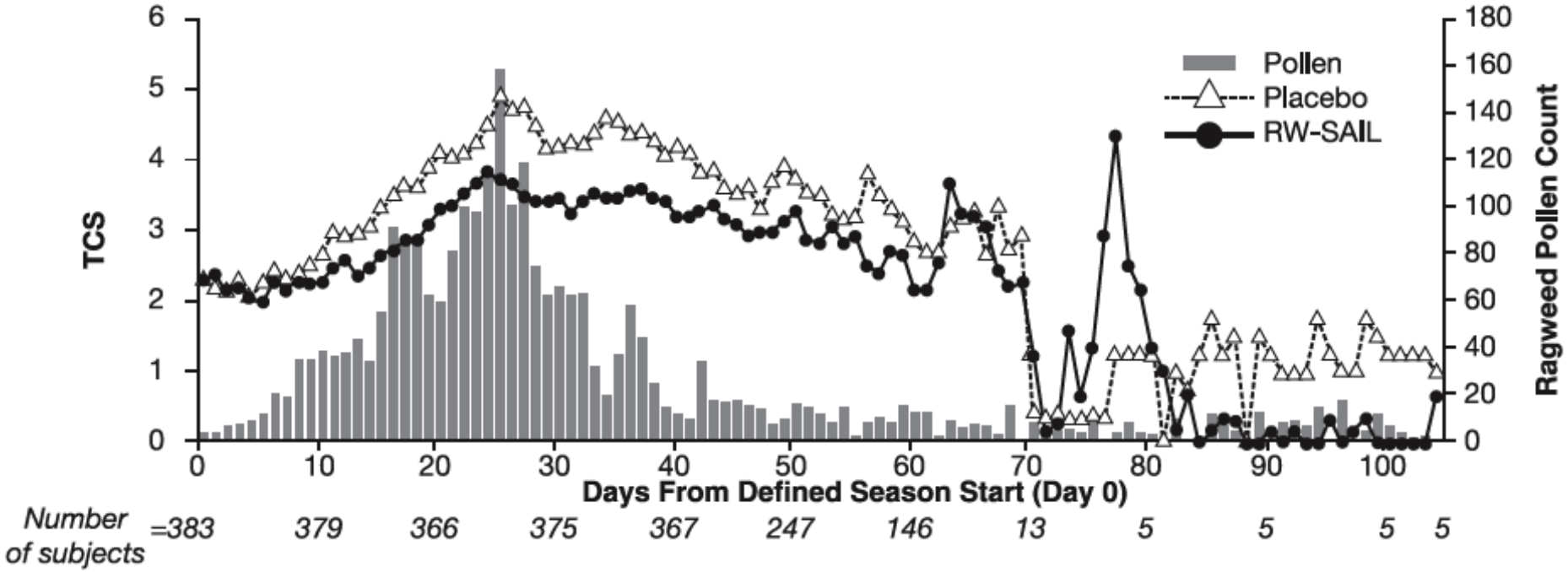



**FIG 3.** Mean TCS during the entire ragweed pollen season. Days 72-104 of the graph display data from only 3 centers (with data from only 4-13 subjects; only 1 center continued to supply data after day 77). The uptick in TCS seen in the RW-SAIL arm of the study on days 76-79 comprises data from only 3-6 subjects who recorded symptoms.

Creticos et al. *J Allergy Clin Immunol*. 2014;133:751-758.

## Summary of RW-SAIL and placebo in average daily total combined symptom and medication scores and daily symptom scores during the ragweed pollen season

| | Total combined score | | | Daily symptom score | | |
|---|---|---|---|---|---|---|
| | Placebo | RW-SAIL | *P* value* | Placebo | RW-SAIL | *P* value* |
| Entire pollen season, no. patients | 211 | 218 | | 193 | 196 | |
| Score, mean (SD) | 1.44 ± 2.40 | 0.82 ± 1.64 | <.001 | 1.37 ± 2.29 | 0.79 ± 1.56 | <.001 |
| Peak pollen season, no. patients | 196 | 196 | | 193 | 196 | |
| Score, mean (SD) | 2.02 ± 3.20 | 1.17 ± 2.10 | .002 | 1.90 ± 3.01 | 1.12 ± 1.99 | .002 |

**P* values designate difference in LS means.

Creticos et al. *J Allergy Clin Immunol*. 2014;133:751-758.

# SLIT Safety


- Majority of SLIT AEs are local reactions: oromucosal
  - occur in beginning of treatment
  - resolve within a few days or weeks without any medication intervention
- Dose-response relationship with AEs in some studies but not consistent in collective
- No apparent relationship with updosing schedule and AEs
  - More recent studies had no updosing or ‘ultra- rush’
- No reported differences in AE in discontinuous vs. continuous

**WARNING: SEVERE ALLERGIC REACTIONS**

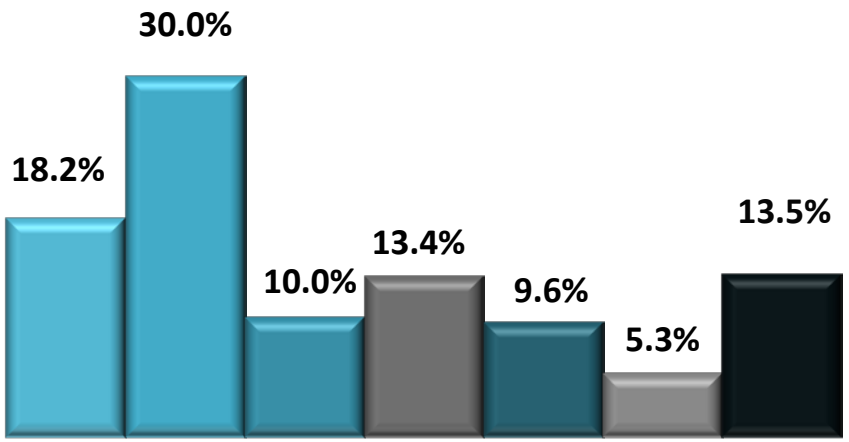
See full prescribing information for complete boxed warning.

- GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer GRASTEK to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- GRASTEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- GRASTEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

# Florida Medicaid Retrospective Claims
# 12 years; 7.5 million enrollees; 4151 received SCIT

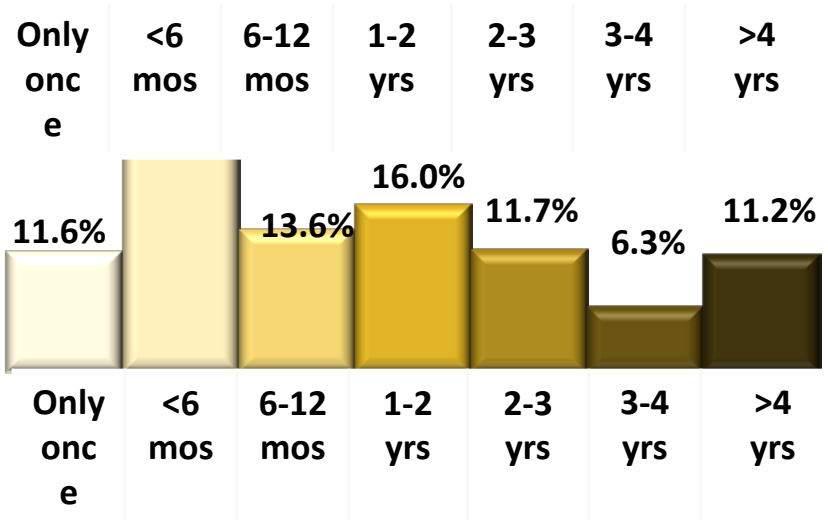
## SCIT Duration

**Adults (N=1,265)**




*Only 18.8% of adults completed a 3-year course of SCIT*

**Children (N=2,886)**




*Only 17.5% of children completed a 3-year course of SCIT*

*From Hankin AAAAAI 2011; Hankin et al, *J Allergy Clin Immunol*. 2008;121(1):227-32.

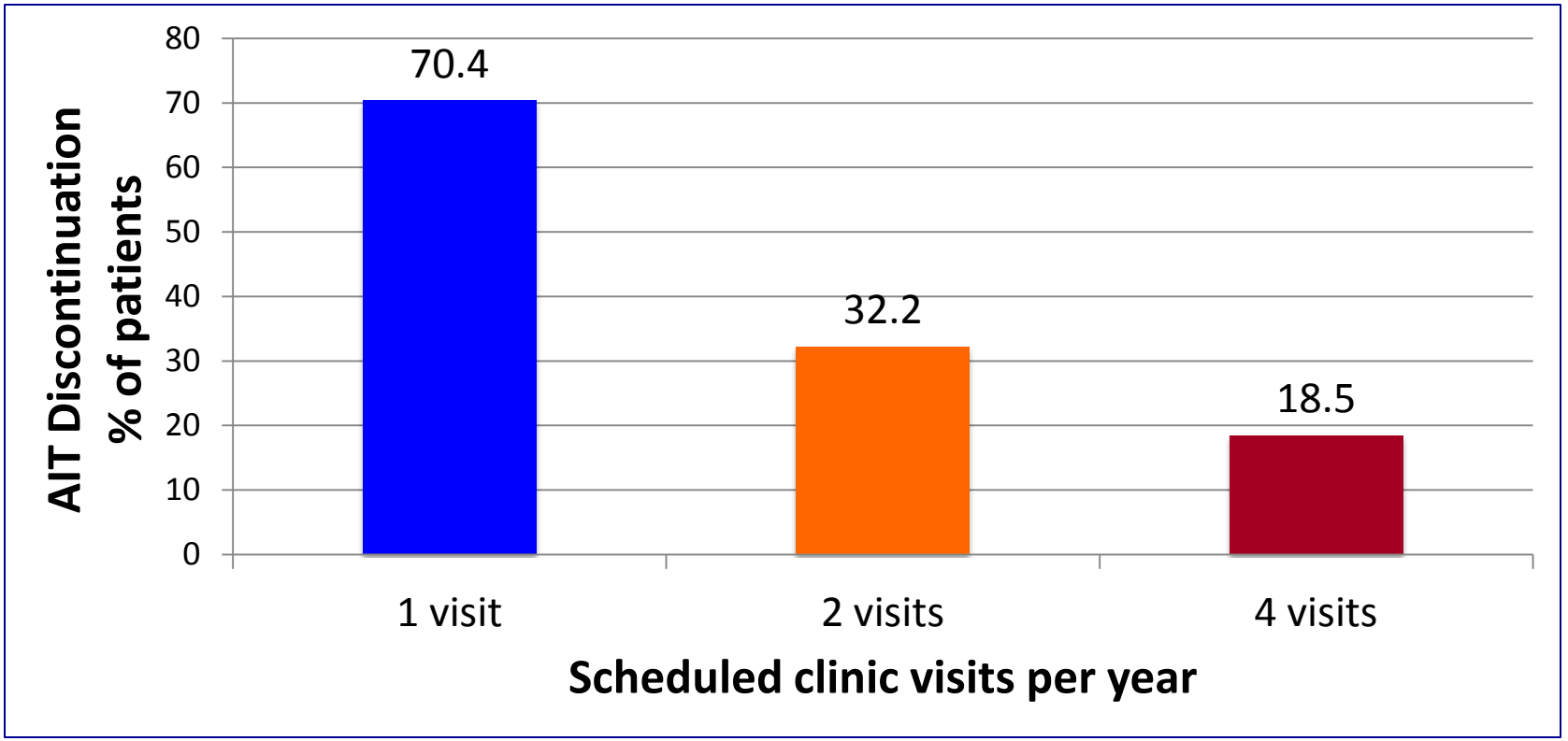
# Most Commonly Cited Reasons for AIT Discontinuation

*Among top 2 reasons listed for AIT discontinuation/nonadherence*

| SCIT (9 studies) | SLIT (7 studies) |
|---|---|
| Inconvenience (8) | Cost (4) |
| Concurrent illness (3) | Inability to take medication according to schedule/time consuming (3) |
| Cost (3) | Ineffectiveness (3) |
| Ineffectiveness (3) | Adverse reactions (3) |

Cox L, et *al* *J Allergy Clin: In Practice* 2014; March/April 2014 issue: Volume 2, (2).

# Significantly Improved SLIT Adherence with More Frequent Clinical Monitoring

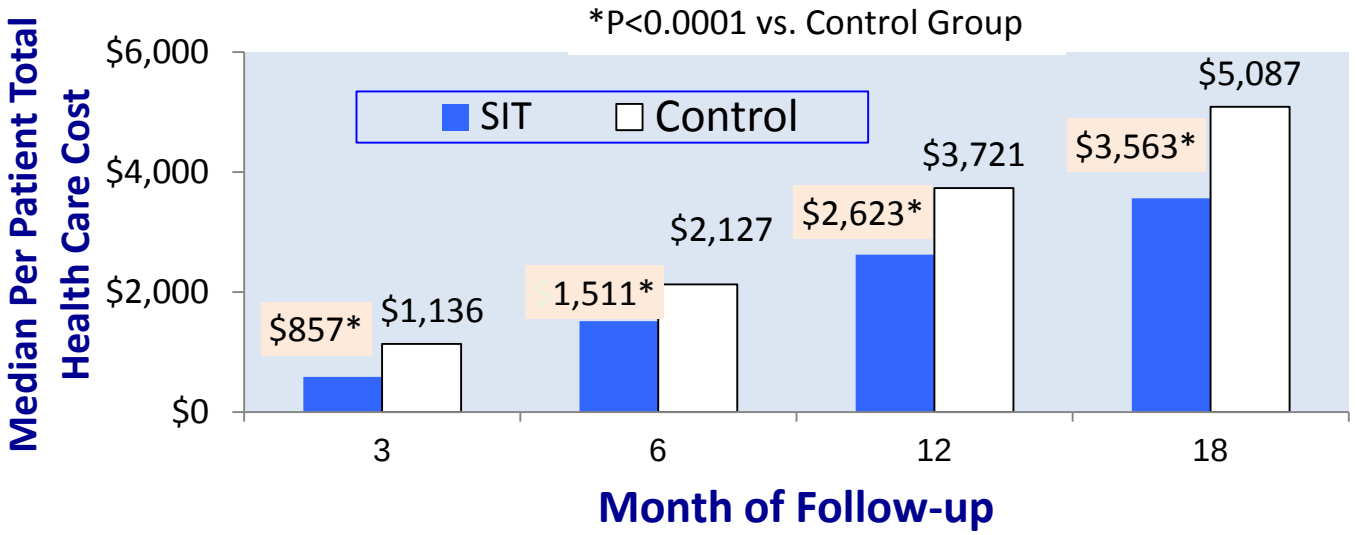



**Study:** 300 children 6-16 yrs prescribed SLIT and randomized to 3 scheduled clinic visit follow-up groups: 1, 2 and 4 visits per year (100 each). Non-compliance defined as stopped before 2 years.

Vita D, Caminiti L, Ruggeri P, et al. *Allergy*. 2010;65(5):668-9.

# 38% reduction in 18-month total health care costs in AR patients treated with SCIT vs. matched controls

- **Results:** Significant 18-month total healthcare cost reduction in SCIT group compared with match control who did not receive SCIT
  - **42% children**
  - **30% adults**
- **Significant savings seen beginning at 3 months**
- **Significant reductions in inpatient, outpatient and pharmacy costs**




Hankin *J Allergy Clin Immunol* 2013;131:1084-91.