Corso di Laurea Magistrale in Biotecnologie Mediche
Università degli Studi di Napoli Federico II
Corso Integrato di Basi molecolari di patologie immunitarie e neurologiche

Allergen Specific Immunotherapy (SIT)

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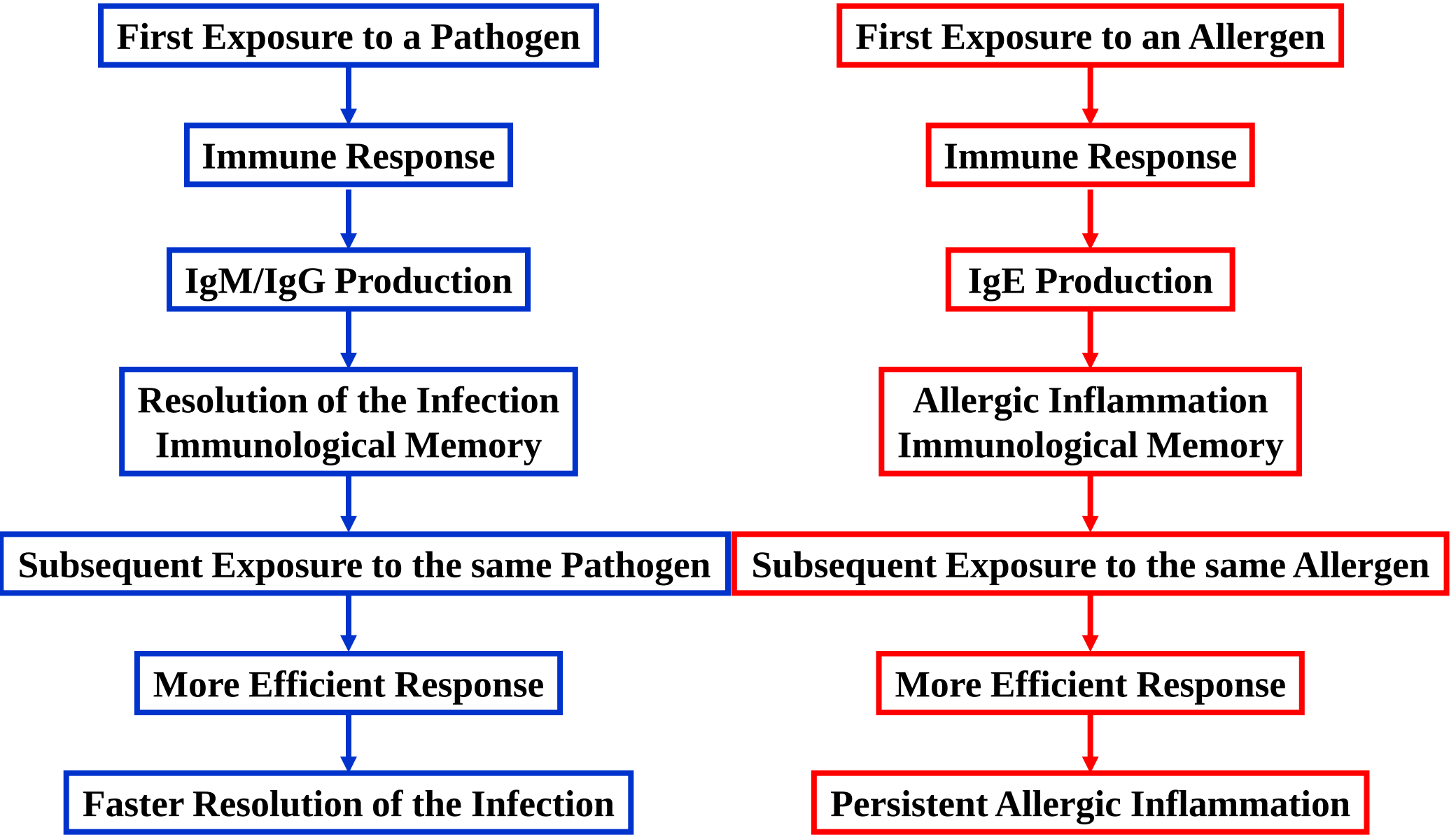
The “Allergy March”

Of 100 allergic patients:

- **> 75 worsen** → Symptoms worsening and new clinical manifestations appearance
- **≈ 20 stable disease** → No change of symptoms compared to the beginning
- **< 5 improve** → Symptoms improvement

The evolution of allergic diseases is associated to the intrinsic characteristic of immune responses



Available fighting tools against the “Allergic March”

The therapeutic strategy for the IgE-mediated allergic disease:

1. **To avoid allergen exposure**
2. **Symptomatic drugs**
3. **Immune system modulation by allergen specific immunotherapy (SIT)**
4. **Biological Therapy with anti-IgE antibodies**

SIT is the only therapeutic strategy able to modify the natural history of IgE-mediated allergic diseases!!!

Allergen Specific Immunotherapy (SIT): definition

Allergen specific immunotherapy (SIT) consists in the administration of increasing doses of allergen extracts to patients with allergic conditions to induce immunological tolerance and then modify/abolish symptoms.

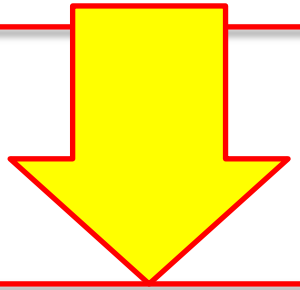
SCIT

SLIT

Immunotherapy: Restoring Long-term, Clinical Immune Tolerance to Allergens

Immunologic goals

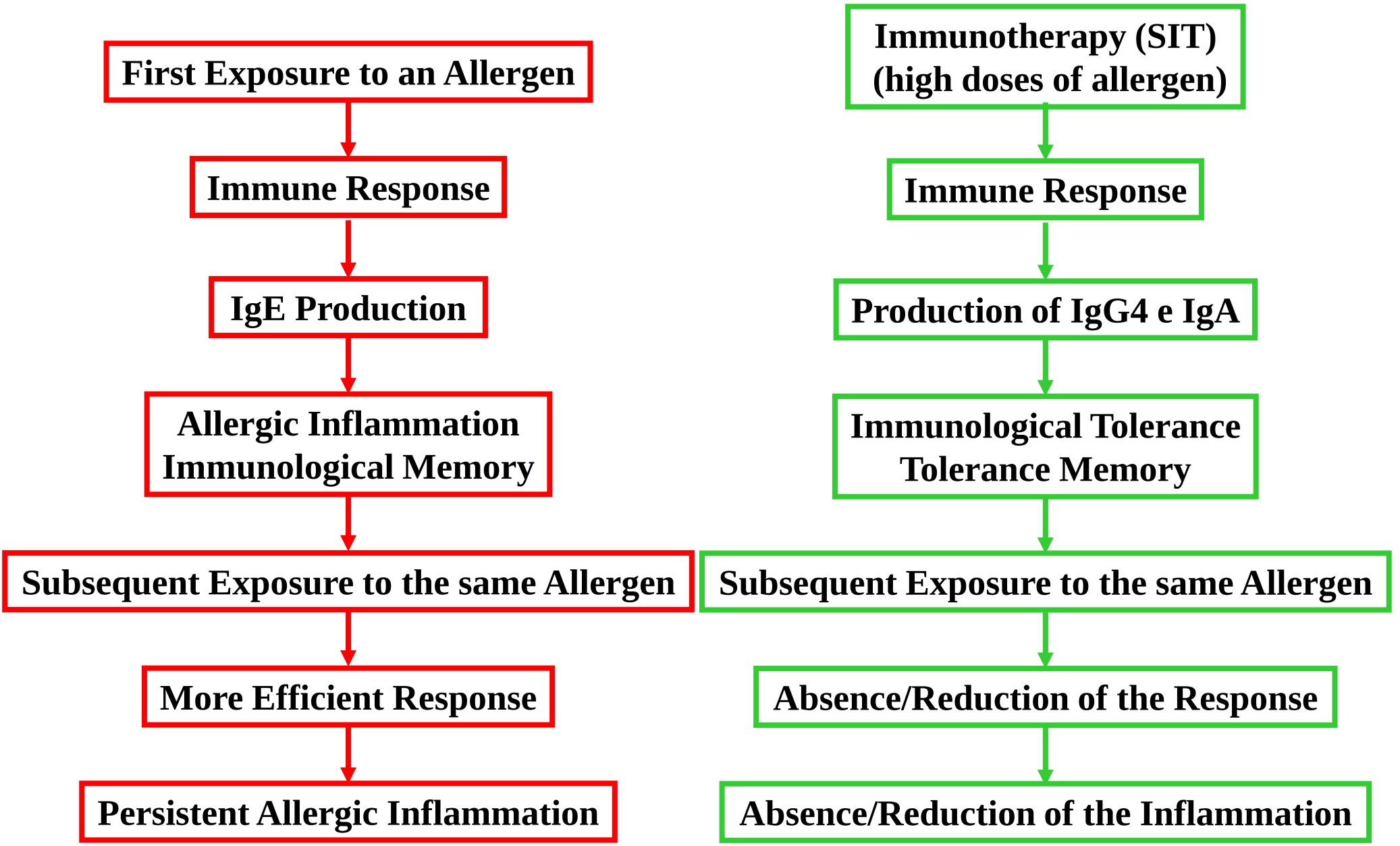
Changes in memory-type, allergen-specific T- and B-cell responses, as well as in mast cell and basophil activation thresholds such that they will not cause allergic symptoms.



Clinical goals

Prevention of new allergen sensitizations and of the progression to more severe disease, such as development of asthma after allergic rhinitis or development of systemic anaphylaxis.

Mechanisms of action of SIT



Mechanisms of SIT

Ig class switch

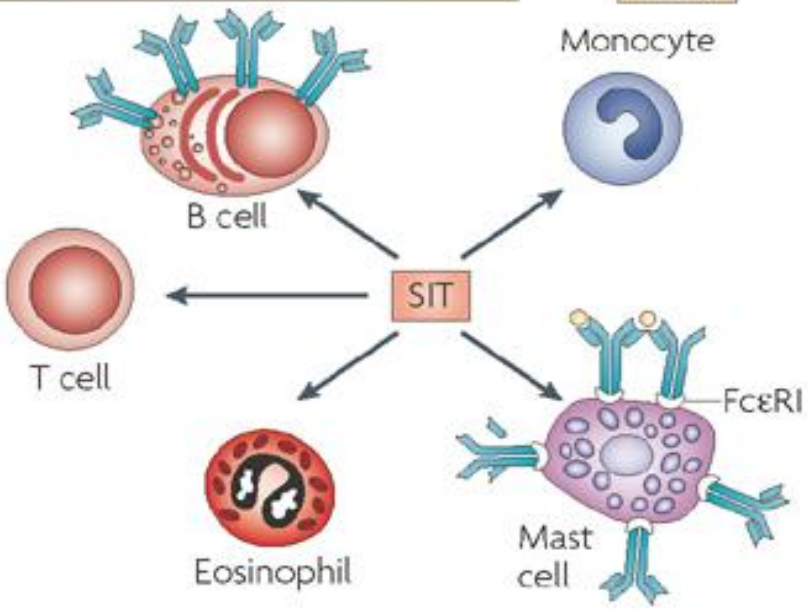
↓ Allergen-specific IgE
↓ Seasonal increases in IgE
↑ Blocking antibodies: IgG1, IgG4 and IgA
↑ IL-10

Immunomodulatory cytokines

↑ IL-10 and TGF-β

Immunodeviation & Immunoregulation

↓ Allergen-specific proliferation
↓ Tissue numbers in late-phase reactions
↓ T_H2-cell cytokines in tissues
↑ T_H1-cell cytokines in tissues
↑ T_{Reg} cells, IL-10 and TGFβ

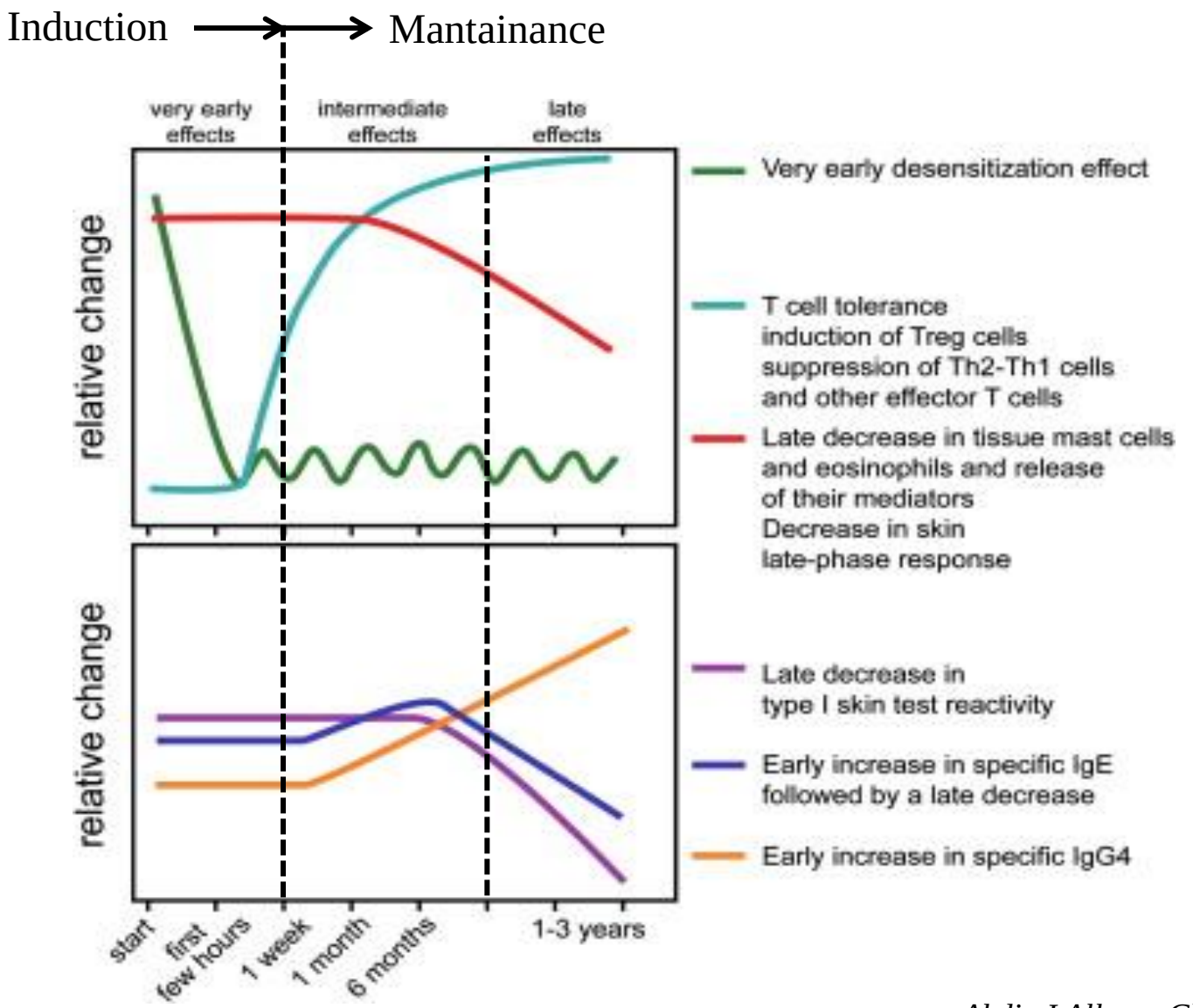


↓ Tissue numbers
↓ Mediator release

Mast cell number and effector functions
Inflammatory cell recruitment

*Holgate and Polosa Nature Reviews Immunology 2008;**8**:218-230*

Immunologic changes during SIT

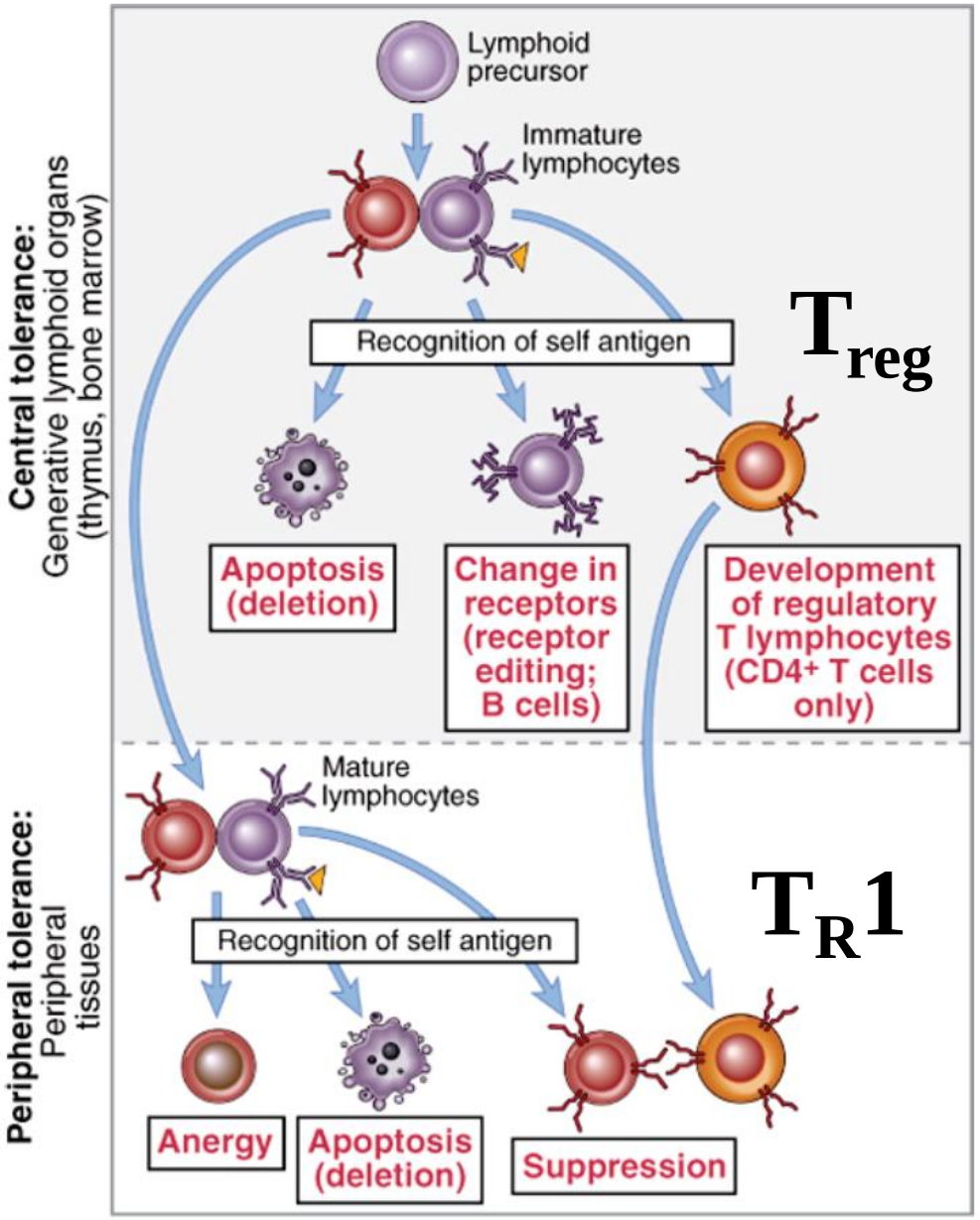


Akdis J Allergy Clin Immunol 2011;127(1):18–27

Immunological Tolerance

- Immunological Tolerance is the lack of response to an antigen due to a previous exposure to the same antigen
- When a lymphocyte encounter an antigen, it can be activated and gives rise to a specific immune response (immunogen antigen) or undergo anergy, giving rise to to immunological tolerance (tolerogenic antigen).
- The tolerance to self-antigens is induced in self-reactive immature T cells in primary lymphoid organs (thymus, Central Tolerance) or in mature lymphocytes at specific sites (lymphnodes, peripheral tolerance).
- The tolerance to exogenous antigens occurs through peripheral tolerance mechanisms. Low doses of exogenous antigens presented together with adjuvant molecules favor the induction of the immune response. High doses of antigens, by contrast, induce tolerance.

Mechanisms of Immunological Tolerance



Regulatory T cell subsets

Treg ⇒ Thymus ⇒ Central Tolerance

T_R1 ⇒ Lymphnodes ⇒ Peripheral Tolerance

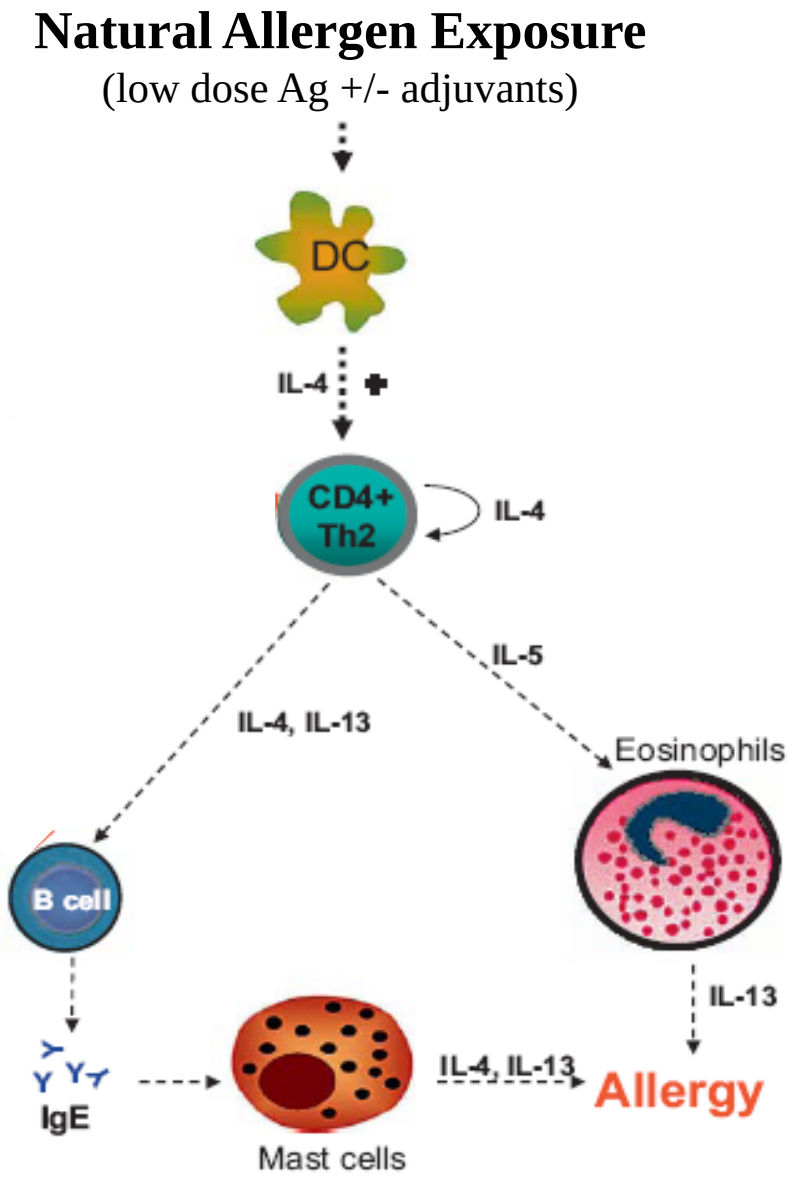
Expression of CD25 (α chain of IL-2R)

Expression of FoxP3 (Transcription Factor)

IL-10 and TGF-β production

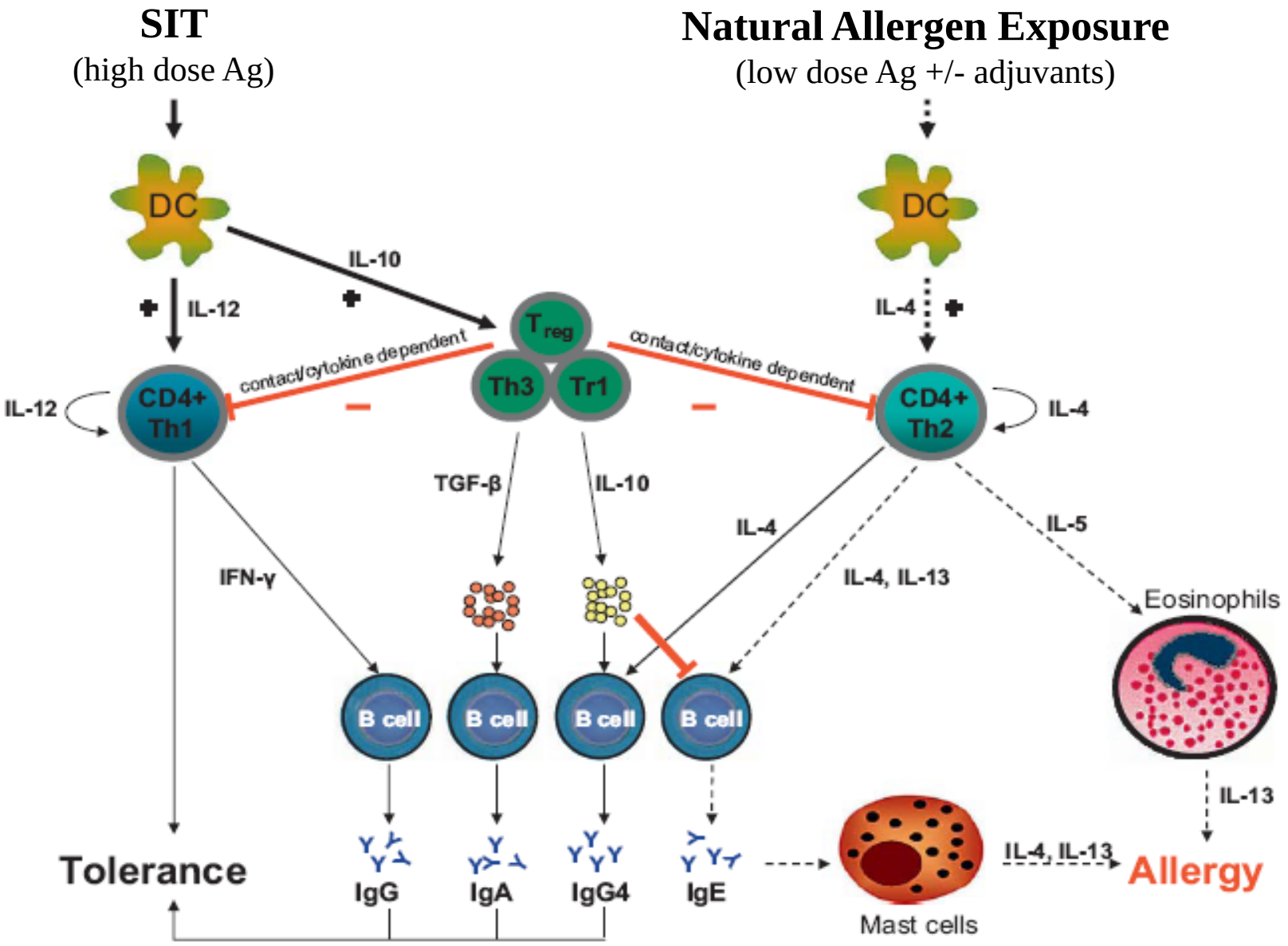
Peripheral tolerance to exogenous antigens occurs through the induction of T_R1 cells

Immunological Network in Allergen Immunotherapy (SIT)



Möbs C. *et al.* Int. Arch. Allergy Immunol. 147: 171, 2008

Immunological Network in Allergen Immunotherapy (SIT)



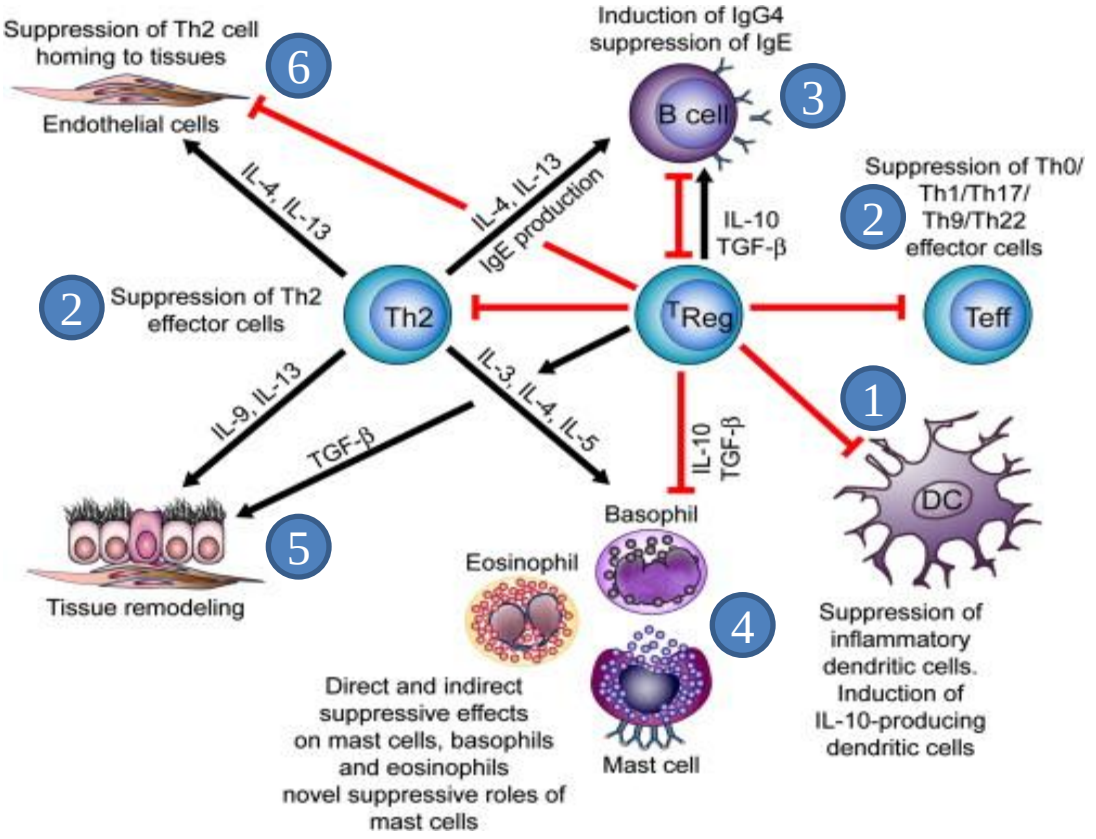
Möbs C. *et al.* Int. Arch. Allergy Immunol. 147: 171, 2008

Peripheral Tolerance in SIT is Mediated by Inducible T Regulatory Cells

- Natural: $FOXP3^+CD4^+CD25^+$ (T_{Reg})
- Thymus, present at birth

- Inducible: T_R1 cells
- Periphery, develop in tolerogenic conditions

1. Suppression of dendritic cells that support the generation of effector T cells
2. Suppression of T_H2 and other effector T cells
3. Suppression of allergen-specific IgE and induction of IgG4, IgA
4. Suppression of mast cells, basophils, and eosinophils
5. Interaction with resident tissue cells and remodeling
6. Suppression of effector T-cell and inflammatory cell migration to tissues.



Peripheral T-cell tolerance is initiated by increased autocrine action of allergen-specific T_{Reg} cells producing high levels of IL-10 and TGF-β

Akdis J Allergy Clin Immunol 2011;127(1):18–27

Allergic diseases evolution with and without SIT

Natural history

On 100 allergic patients:

> 75 worsen
(Symptoms worsening and new clinical manifestations appearance)

- 50

≈ 20 stable
(No change of symptoms compared to the beginning)

- 15

< 5 improve
(Symptoms improvement)

+ 65

With SIT

On 100 allergic patients:

< 25 worsen
(Symptoms worsening and new clinical manifestations appearance)

≈ 5 stable
(No change of symptoms compared to the beginning)

>70 improve
(Symptoms improvement)

Peculiar aspects of SIT

- Resolution or significant improvement of symptoms in allergic rhinitis and asthma patients
- Prevention of asthma development in rhinitis patients (70% risk reduction)
- Limitation in the acquisition of new allergic sensitization (90% risk reduction)
- Prevention of anaphylactic reactions in patients allergic to hymenoptera venom
- Two different SIT administration routes:
    1) Subcutaneous Immunotherapy (SCIT)
    2) Sublingual Immunotherapy (SLIT)

Sub-cutaneous immunotherapy (SCIT)

- Patients receive a course of injections, starting with a very low dose of allergen and building up gradually until a plateau or maintenance dose is achieved
- Maintenance dose injections are then given at 4-8-week intervals for 3 to 5 years
- Standard protocol: the updosing phase is generally given as a series of weekly injections
- Cluster protocol: giving several doses on each day and then waiting a week before giving a further series of injections
- Rush protocol: giving the whole series of incremental injections in a single day
- The major limiting factor in SCIT is anaphylactic side-effects, which vary in incidence from 0.1-5% of individuals depending on severity

Sub-lingual Immunotherapy (SLIT)

- High-dose topical immunotherapy regimen: 20 to 400 times the total dose given by SCIT
- Treatment regimens involve a rapid build-up phase followed by treatment given either daily or 3 times per week with rapidly dissolving tablets containing allergen extracts. Some preparations are supplied in liquid form, with a calibrated dropper
- Oral mucosal tissue has a natural tolerogenic character without inflammatory cells around mucosal tissue in spite of high bacterial colonization, high permeability for allergens, and rapid wound healing without scar development
- In meta-analyses, systemic side effects were relatively rare and mild, and none of the side effects were judged to be life-threatening

SCIT versus SLIT

TABLE 1

Meta-analyses of SCIT and SLIT: Calculation of effect strengths

	SCIT (10) SMD (95% CI)	SLIT (11) SMD (95% CI)
Symptoms	−0.73 (−0.97 to −0.5)	−0.49 (−0.64 to −0.34)
Medications	−0.57 (−0.82 to −0.33)	–0.32 (−0.43 to −0.21)

SMD, standardized mean difference; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; CI, confidence interval

Dtsch Arztebl Int 2013; 110(9): 148−58

SCIT versus SLIT

	SCIT	SLIT
Efficacy	++++	+++
Safety	+++	++++
Costs	30-40 Euro/month	35-45 Euro/month
Advantages	Well-known rapidity and efficacy	Self-administration Safety
Disvantages	Potential adverse systemic reactions (0.5% of patients)	Higher doses and more time to achieve the final benefit

SIT Clinical Indications

Disease	**Indications**	**Documented Effects**
Venom hypersensitivity	Stage 3 (Urticaria, Dyspnea, Dysphagia, Dysphonia) Stage 4 (Anaphylaxis)	SIT is the only therapy to prevent the risk of anaphylaxis on subsequent sting (30%-70% risk in patients with a previous systemic reaction) Duration: at least 3 years
Allergic Rhinitis	ARIA guidelines: from moderate-intermittent to severe-persistent	Clinical efficacy (reduction in symptom score and medication use) Effective also in multiple allergic sensitization patients Duration: at least 3 years
Allergic bronchial asthma	GINA guidelines: from Step 2 to Step 4 (high dose ICS+LABA)	Clinical efficacy (reduction in symptom score and medication use) Nonspecific bronchial reactivity improvement Duration: at least 3 years

Documented Effects of Immunotherapy

Insect sting allergy: SIT is the only preventive treatment for anaphylaxis

Allergic rhinitis and asthma: symptom improvement and/or reduction of medication use

Change in natural history of allergic disease

- **prevention of the onset of new sensitizations**
- **prevention of the onset of asthma in rhinitic children**

Long-lasting effect once discontinued

Long-Lasting Efficacy of Subcutaneous IT: Controlled Trials

Study	Allergen	Duration
Hedlin, 1995	Cat/dog	3 yrs
Ariano, 1999	Parietaria	4 yrs
Durham, 2000	Grass	5 yrs
Eng, 2002	Grass	3 yrs

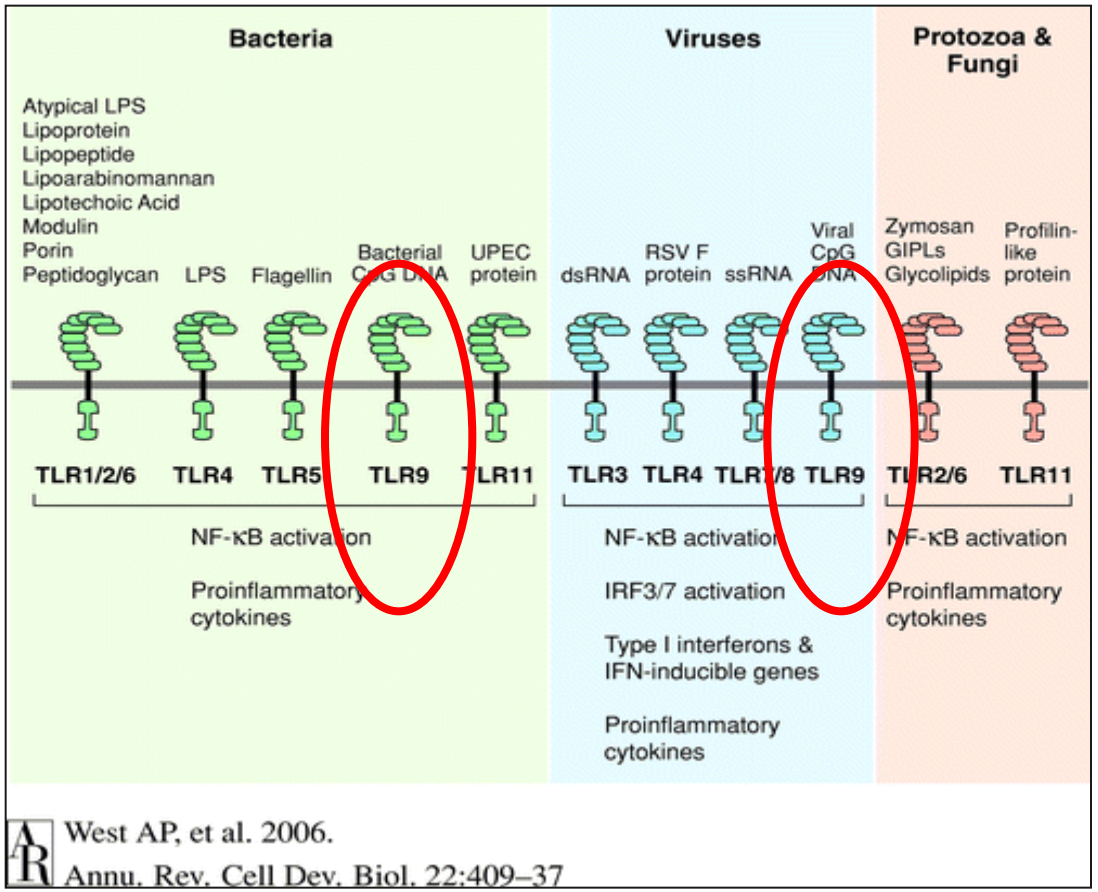
Disvantages of Natural Extract based SIT

- Contain a number of components and some of them could promote adverse reactions and/or limit the efficacy of the SIT
- Difficult to increase the concentration of components important for the therapeutic efficacy
- Variable efficacy
- No modifications to adapt to patients
- Could induce new sensitizations
- No standardization among the various products

SIT Future Directions

- **Recombinant allergens**
  - allergen extracts contain multiple allergens. Most patients react to the "major allergens" (recognized by > 50% of sera from a pool of patients with that specific sensitization). Some patients only recognize allergens that are not in that pool and might not respond to standard extracts.
  - With recombinant allergens for SIT available, the range of sensitivities can lead to patient-tailored products.
  - Clinical trials have confirmed the efficacy of recombinant allergen cocktails but have not yet shown superiority to conventional vaccines.
- **Peptide immunotherapy (PIT)**
  - the epitopes recognized by IgE molecules are usually 3-dimensional, whereas T-cell epitopes are short linear peptide fragments of the antigen; it should be possible to use peptide fragments of allergens to modulate T cells without risking anaphylaxis.
  - either large doses of natural sequence peptides are given, deceiving the T cell into high-dose tolerance, or else an altered peptide ligand can be given.
  - To date, synthetic peptide-based vaccines from Fel d 1 and Api m 1 have been clinically evaluated, and evidence for the induction of peripheral T-cell tolerance to a whole allergen has been demonstrated
  - Early studies of cat-allergen PIT showed modest clinical efficacy and reported frequent adverse events
- **Recombinant bioengineered molecules (Hypoallergenic allergens)**
  - A potential barrier to PIT of allergy is the complexity of epitope usage in the allergen-specific T-cell response.
  - recombinant hybrid molecules that span the whole T-cell repertoire, but do not bind IgE, have been developed for several allergens , characterized by misfolded conformational B-cell epitopes, but intact T-cell epitopes

Immunomodulatory Adjuvants as Improved IT Strategy



West AP, et al. 2006.
Annu. Rev. Cell Dev. Biol. 22:409–37

A new class of adjuvants ("immune response modifiers") acts on APC through Toll-like Receptors (TLRs), which recognize pathogen-associated molecular patterns (PAMPs) on microorganisms.

Two main approaches considered for SIT: the administration of **CpG oligodeoxynucleotides alone**, **or coupled to the allergenic protein**, which enhance immunogenicity by eliciting a T_H1-type response to the allergen and stimulating T_H1 cytokine expression in cultured human PBMCs.

Modified from Akdis Nat Rev Drug Discovery 2009;8:645-660