HRVATSKA KONFERENCIJA O PROCJENI RIZIKA PODRIJETLOM IZ HRANE

Osijek, 16.-17. listopada 2017.

Alergije porijeklom iz hrane – trenutno stanje i izazovi za budućnost

Izv.prof. dr. sc. M.Turkalj

Dječja bolnica Srebrnjak, Zagreb,

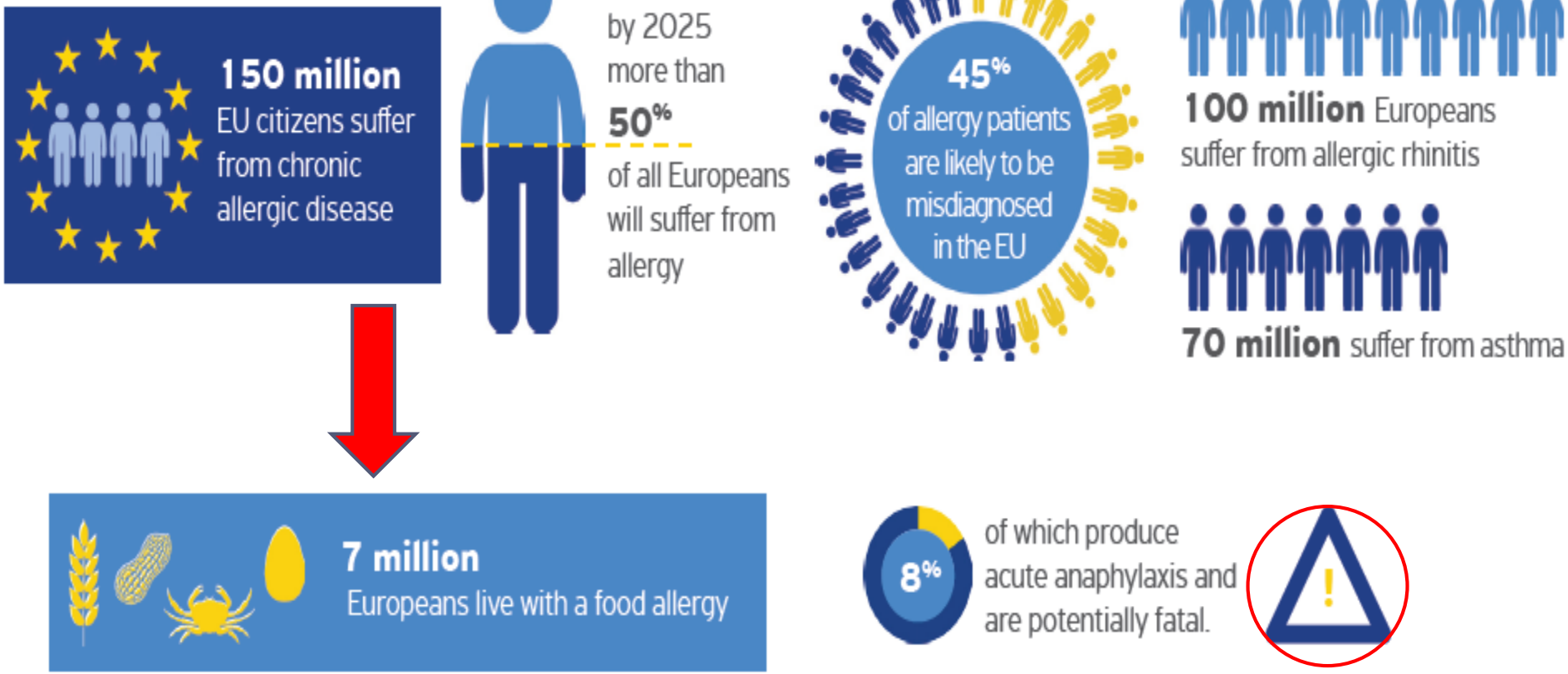
Medicinski fakultet Sveučilišta J.J.Strossmayer, Osijek

Hrvatsko katoličko sveučilište, Zagreb

Sadržaj:

- Učestalost alergija porijeklom iz hrane
- Što je alergija na hranu?
- Zašto i kada se javljaju alergijske reakcije na hranu?
- Alergeni porijeklom iz hrane
- Klinička slika
- Dijagnostika
- Liječenje
- Izazovi za budućnost

Alergije u Europi

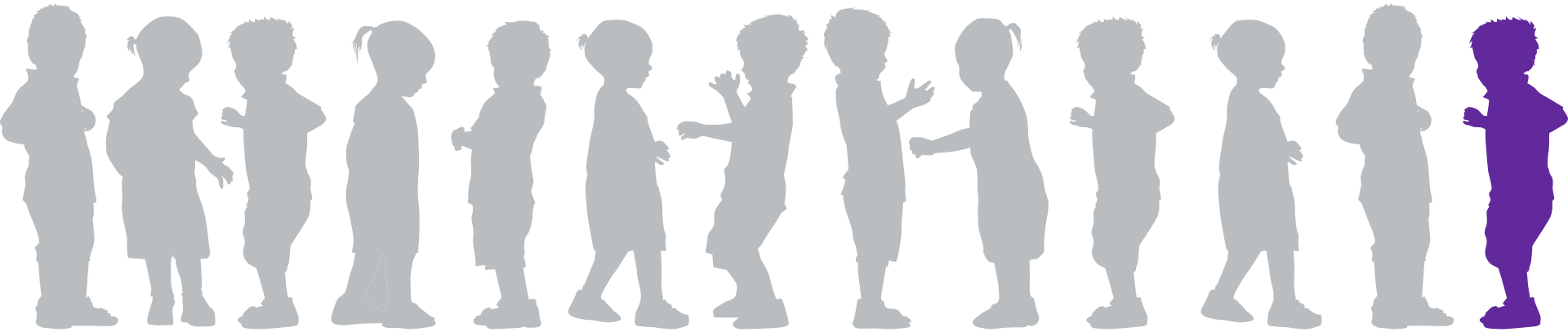


Alergija na hranu u djece u SAD-u

includes

5.9 million

children (1 in 13)



Porast alergije na hranu posebno u djece

- Porast alergije na hranu za 50% 1997 and 2011.[1]

- 1 od 3 djece s alergijom na hranu imaju alergiju na više alergena porijeklom iz hrane (multipla senzibilizacija)

[1] Jackson, K., Howie, L, Akinbami, L. Trends in Allergic Conditions Among Children: United States, 1997-2011. *National Center for Health Statistics Data Brief* . 2013. Retrieved from www.cdc.gov/nchs/data/databriefs/db121.pdf.

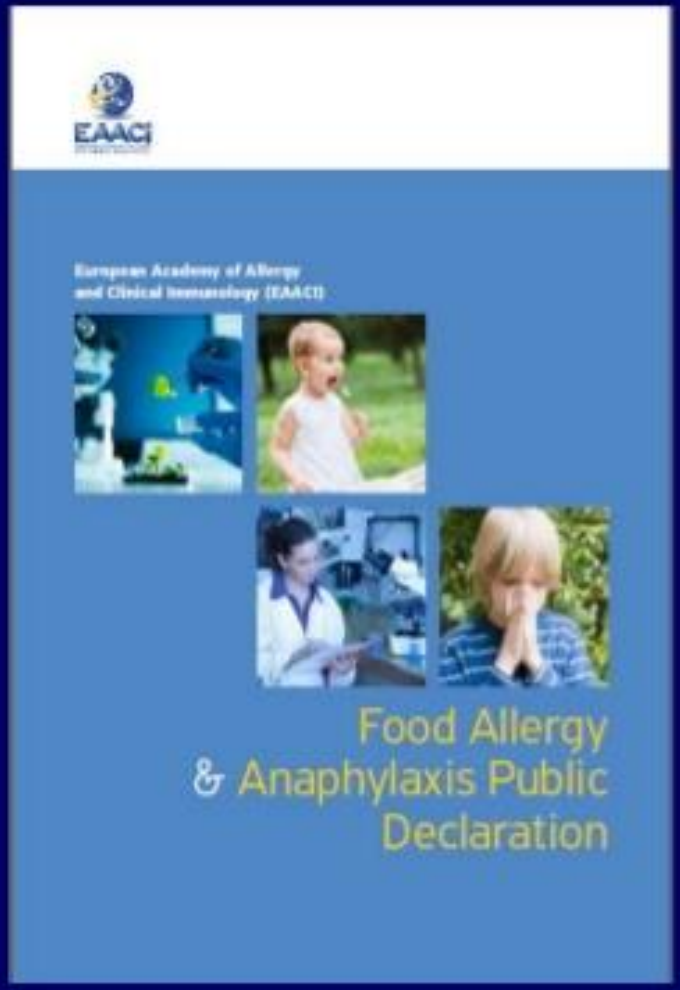
[2] Gupta RS, Springston, MR, Warrier BS, Rajesh K, Pongracic J, Holl JL. The prevalence, severity, and distribution of childhood food allergy in the United States. J Pediatr.2011; 128.doi: 10.1542/peds.2011-0204.

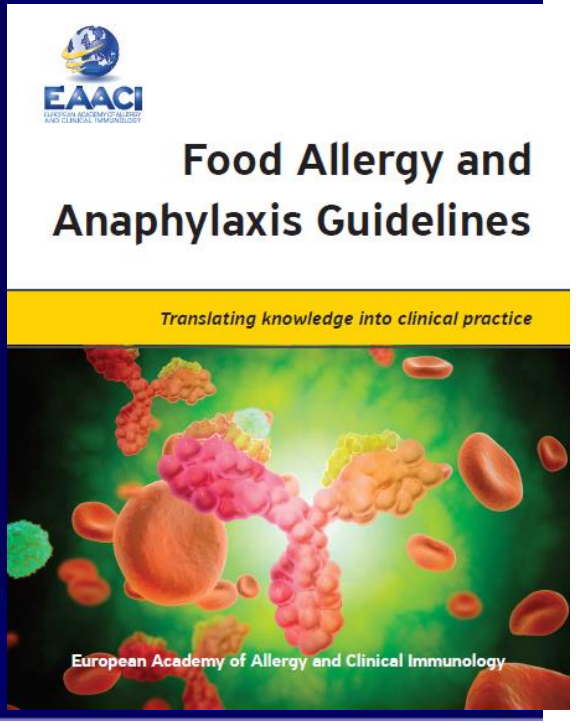
FOOD ALLERGY AWARENESS

HOUSING & FOOD SERVICES
UNIVERSITY of WASHINGTON
Division of Student Life

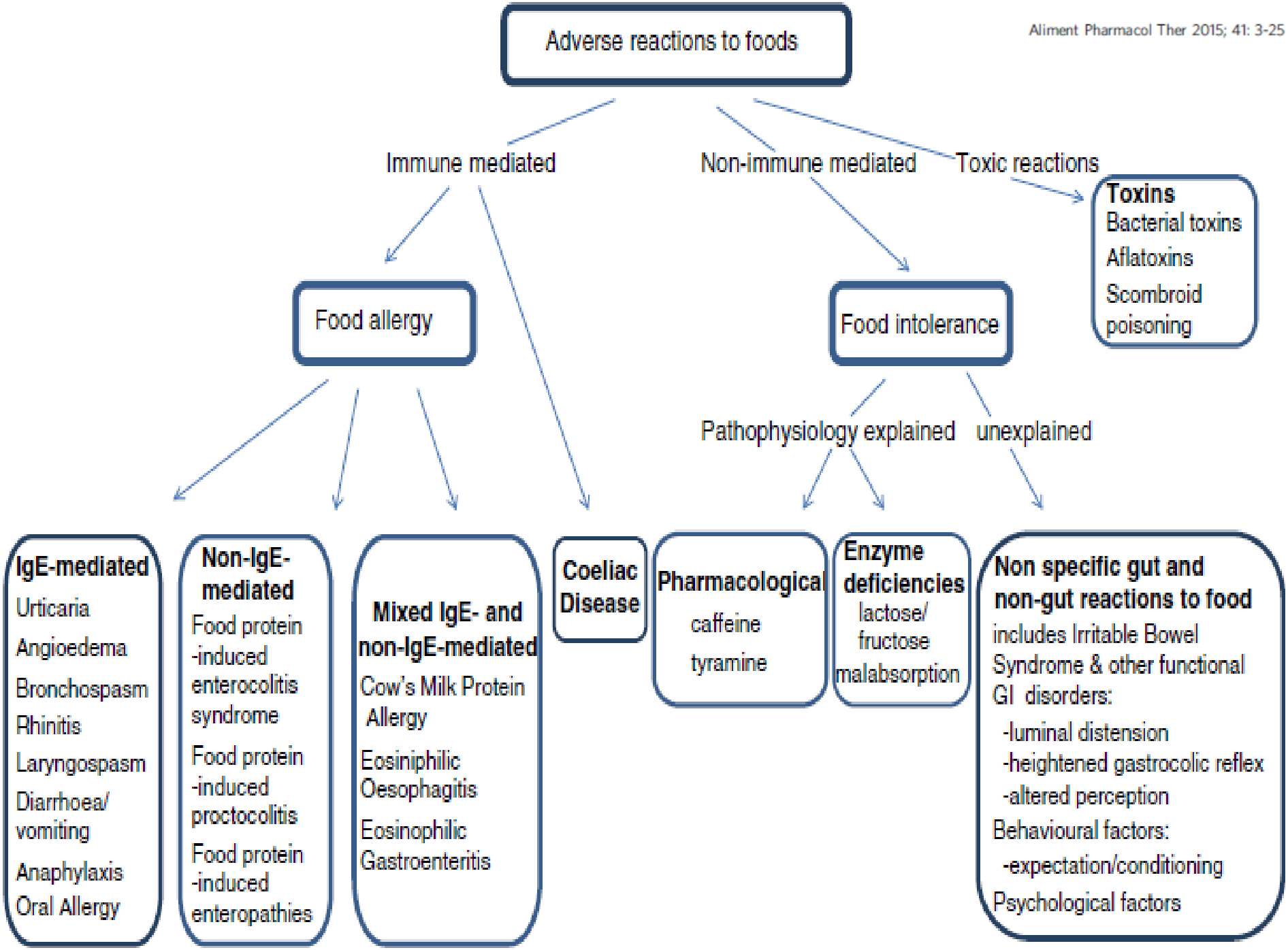
PUBLIC DECLARATION

www.eaaci.net





Aliment Pharmacol Ther 2015; 41: 3-25



Difference

Food Allergy

Immune system reaction

Food Intolerance

Inability to digest a food

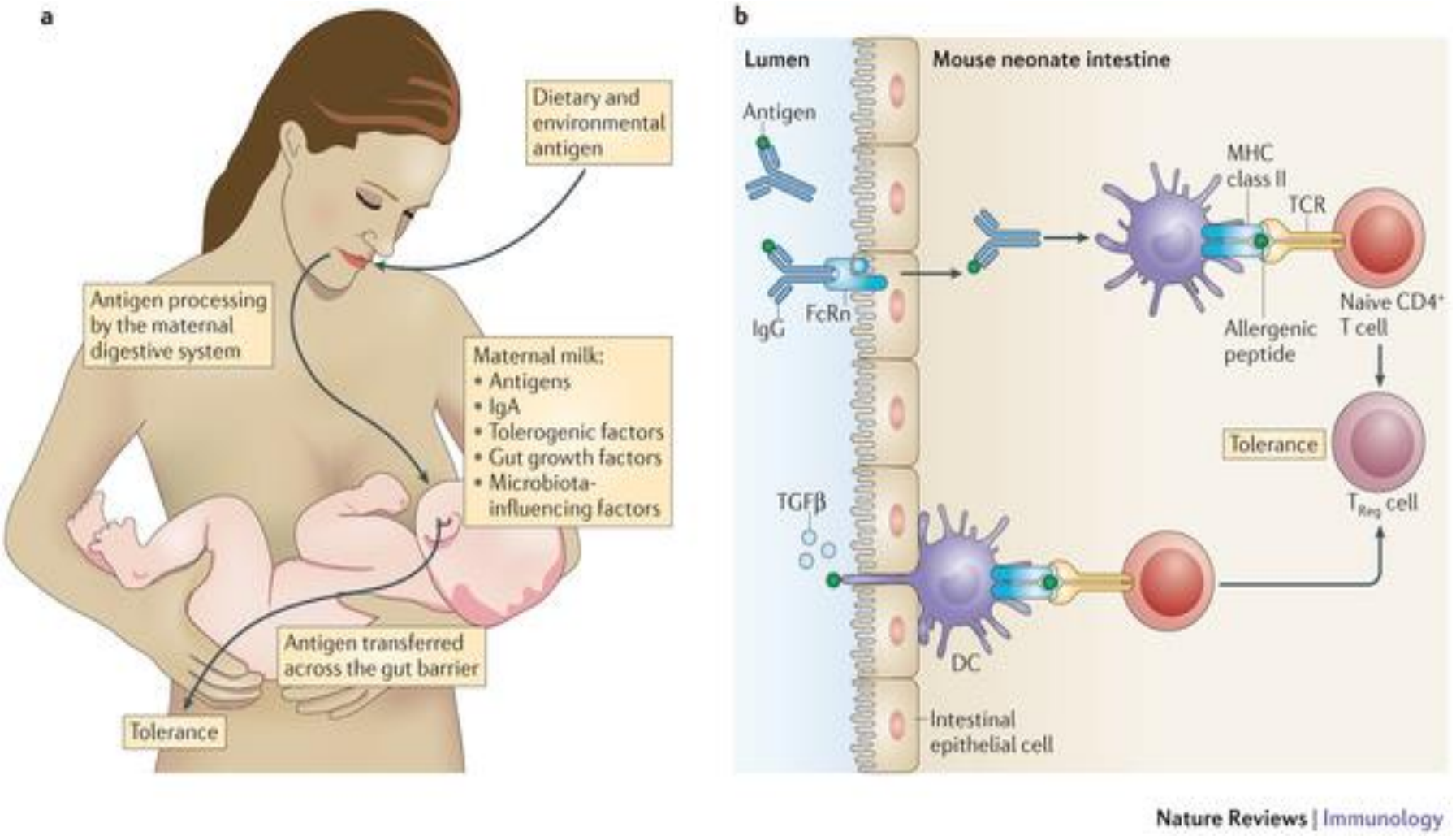
Alergija i intolerancija hrane

- *Alergija*
- Patomehanizam – aktivacija imunološkog sustava
- Jače reakcije, po život opasne
- Nagli razvoj simptoma
- Na proteinske komponente u hrani
- senzibilizacija
- Male količine Ag – nisu ovisne o dozi
- naslijeđe

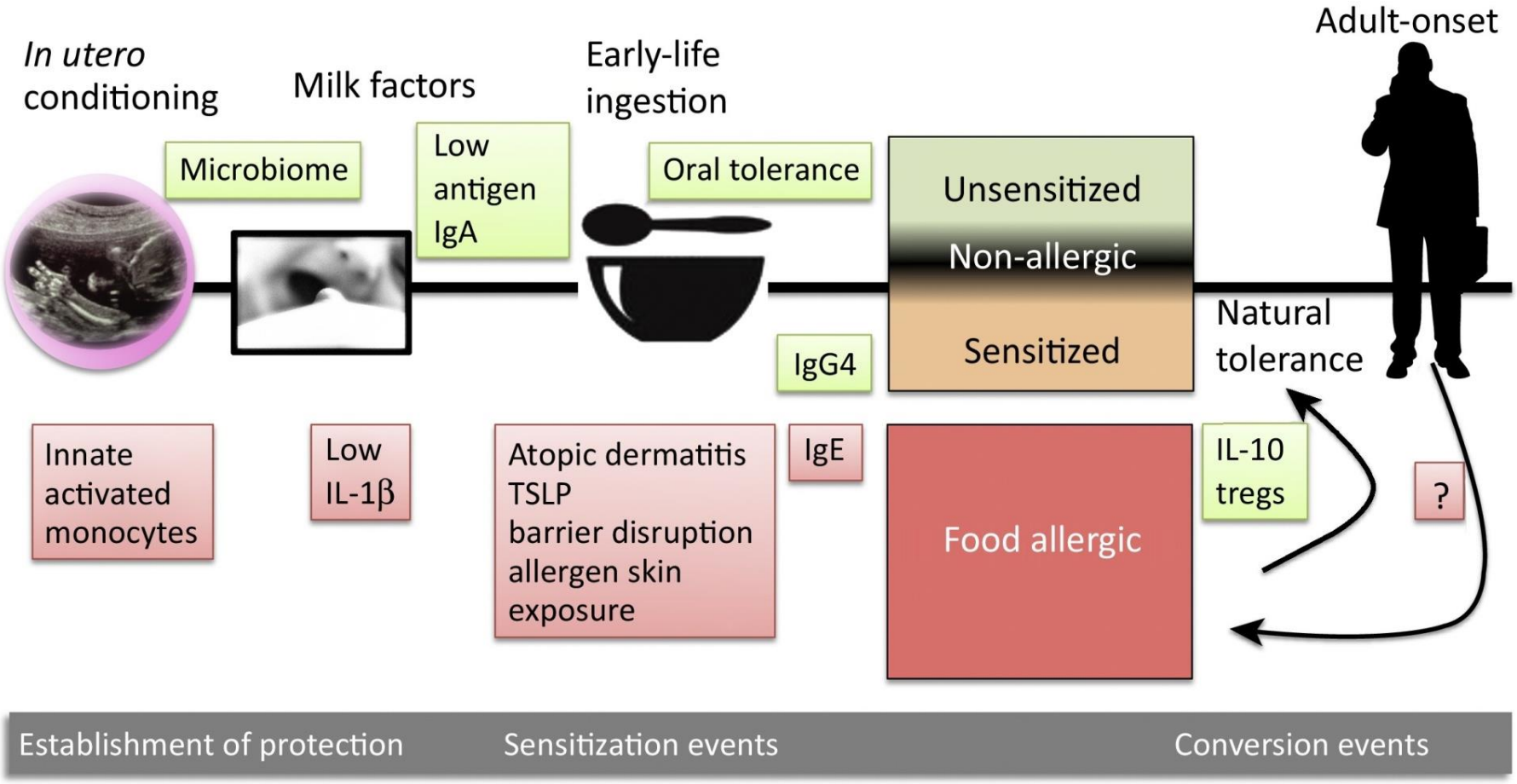
- *Intolerancija*
- Enzimski deficit, farmakološki čimbenici
- Blaže reakcije, nisu po život opasne
- Sporiji razvoj simptoma
- Ovisne o količini i učestalosti konzumiranja
- Stečene
- najčešće naslijedni čimbenici nisu važni

Kako i zašto se javlja alergija na hranu?

Rana senzibilizacija/tolerancija na antigene porijeklom iz hrane

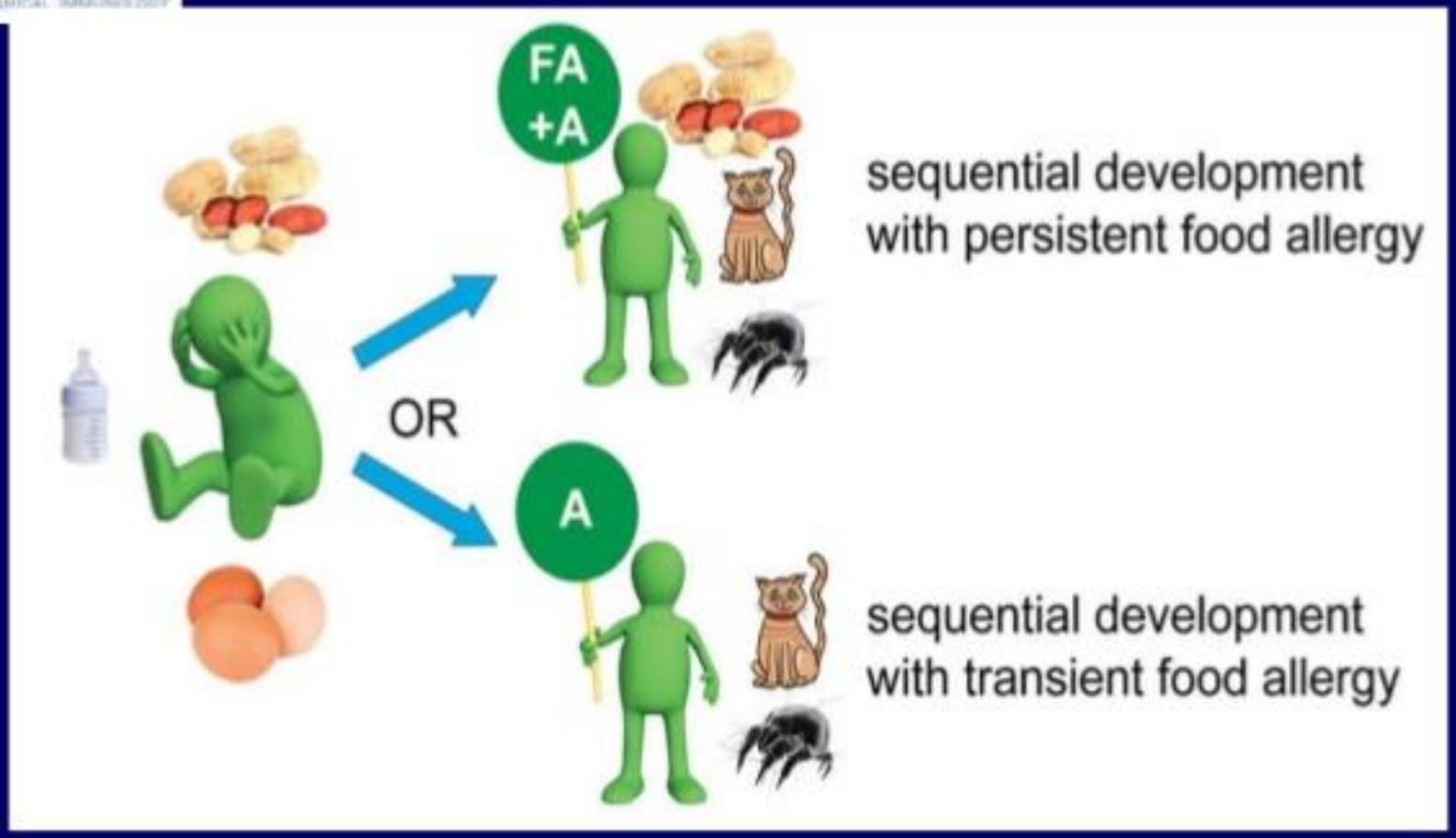


Alergija – tolerancija na hranu



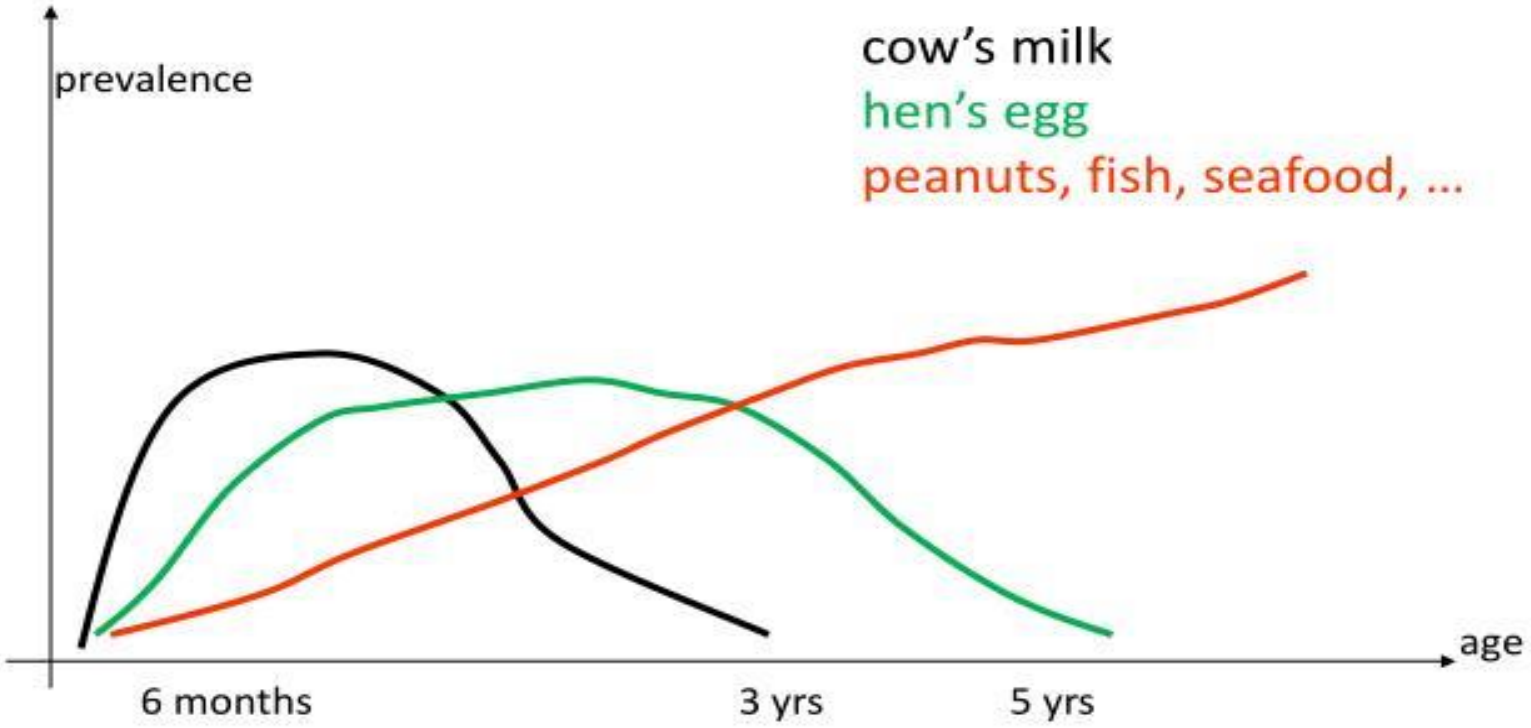
Trends in Immunology

Food Allergy as an antecedent to Asthma
the Atopic March



EAACI Global Atlas on Asthma 2013

Every food has its own story…



Food allergy and Asthma
increased risk for anaphylaxis

Food allergy and Pollen Allergic Rhinitis

Cross reactivity

Ekspozicija i senzibilizacija na nutritivne alergene

Oralna

Inhalacijom

kožni kontakt

Ekspozicija alergenima u hrani ”skriveni” alergeni, kros-kontaminacija

Alergeni porijeklom iz hrane

Glavni alergeni porijeklom iz hrane

ICON-14 glavnih nutritivnih alergena

14 major allergens

Crustaceans

Eggs

Fish

Peanuts

Soya

Milk

Tree Nuts

Celery

Mustard

Sesame

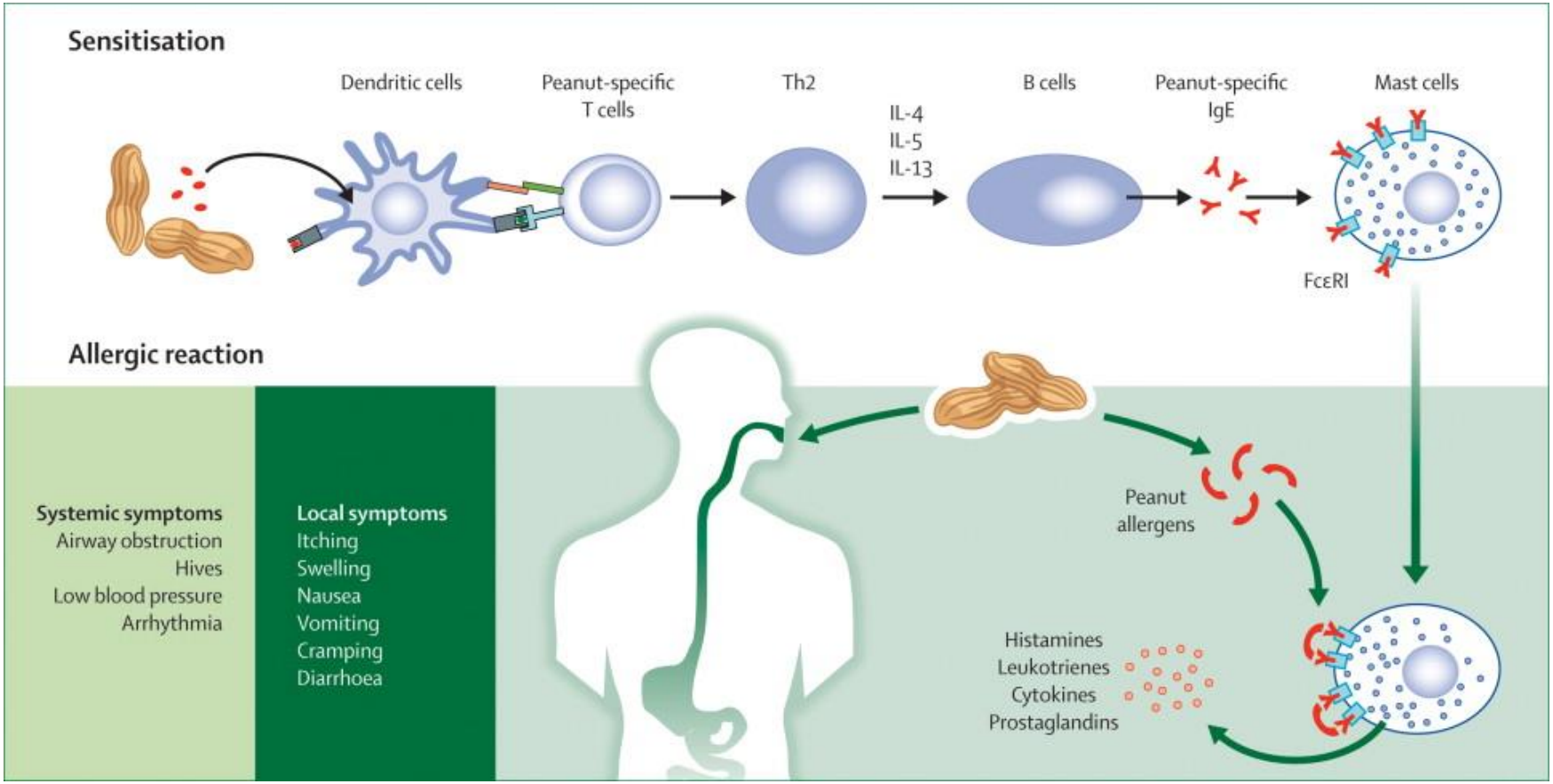
Sulphites

Lupin

Molluscs

Gluten

Osnovni patomehanizam alergije na hranu

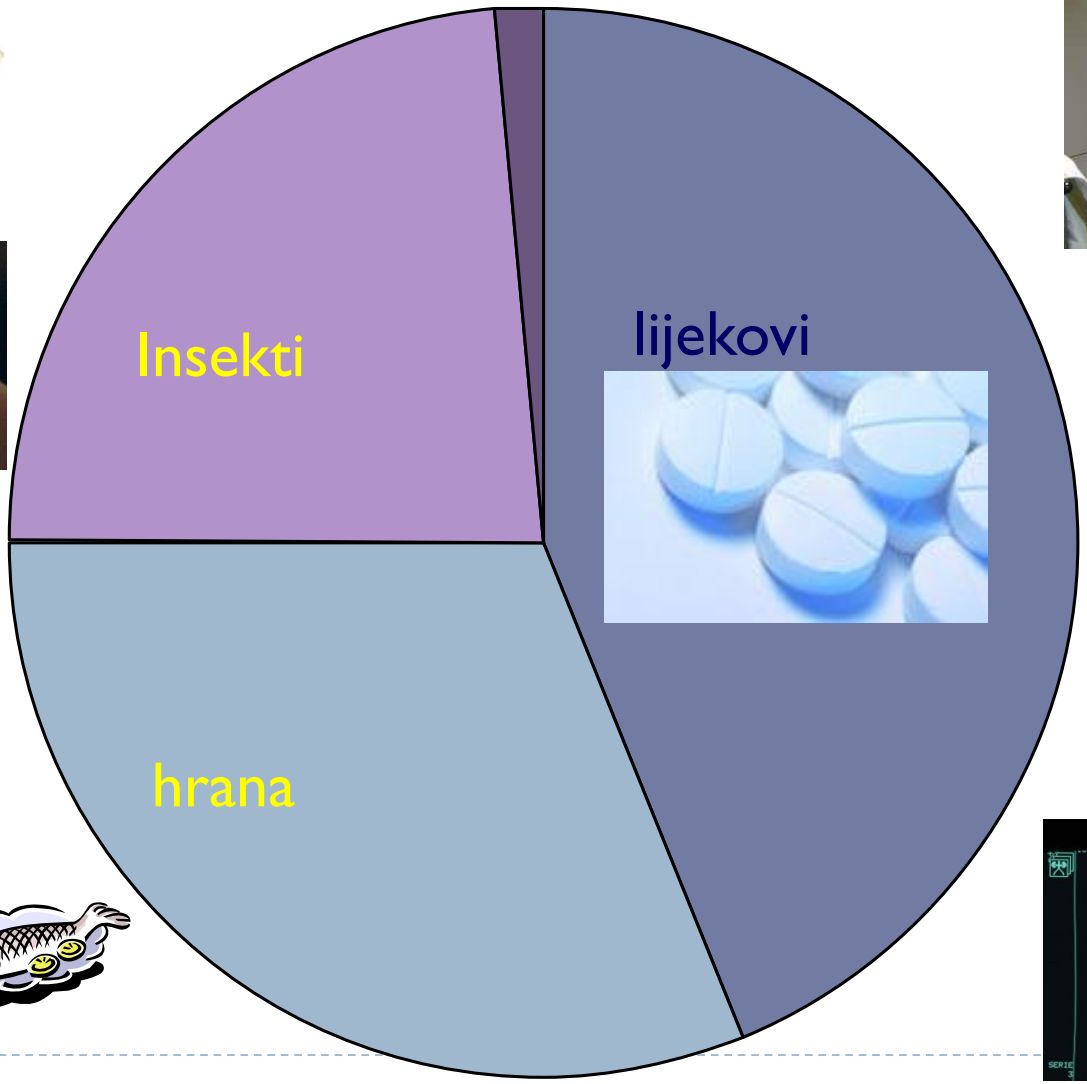


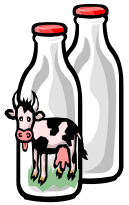
Cutaneous Manifestations of Food Allergy






Uzroci letalne anafilaksije





Anafilaksija u naporu povezana s hranom

Napor

žitarice

Temperatura

Gastrin

Oslobađanje medijatora
- Histamin
- dr. (LTD4,PAF, itd.)

ANAFILAKSIJA

Triggering Mechanisms

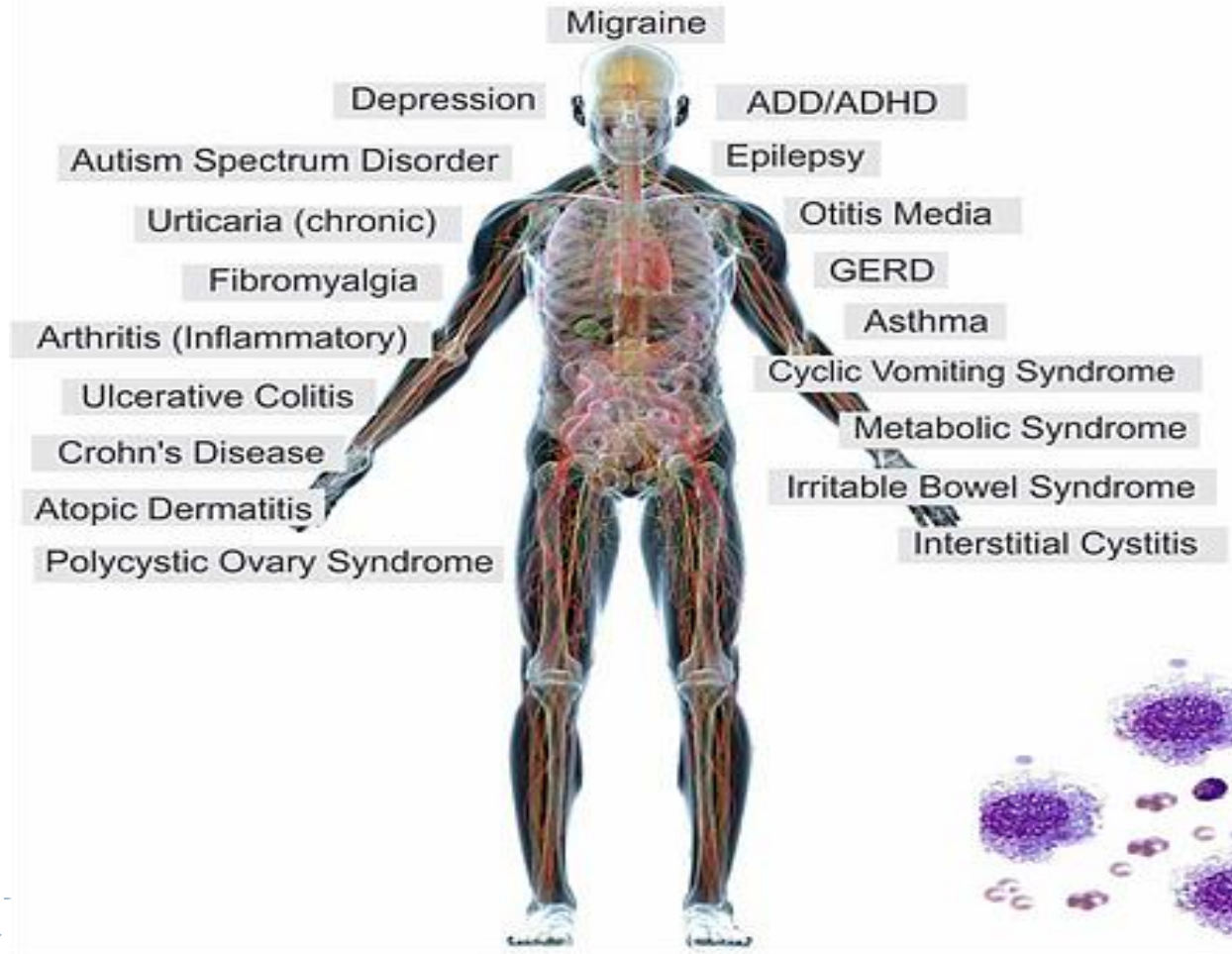
- Food antigens
- Food chemicals
  - Haptens
  - Amines
  - Pharmacologic
- Immune Complexes
  - IgG
  - IgA
  - IgM
- Lectins

Cellular Activation

- Lymphocytes
  - Sensitized T-cells
  - T-Cells
  - NK Cells
  - K Cells
- Eosinophils
- Basophils
- Monocytes
- Neutrophils

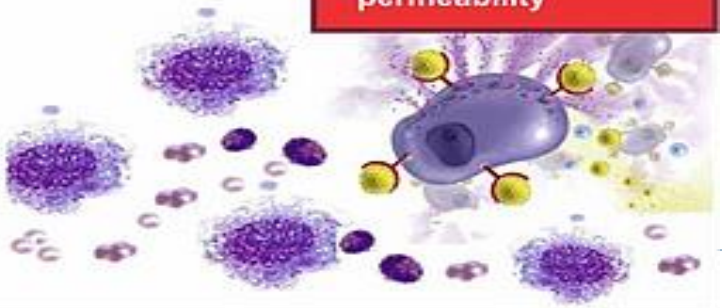
Mediator Release

- Cytokines
  - Interleukins
  - Chemokines
  - TNFs
  - Interferons
- Leukotrienes
- Histamine
- ECP, MPE, Amines
- Prostaglandins
- Others

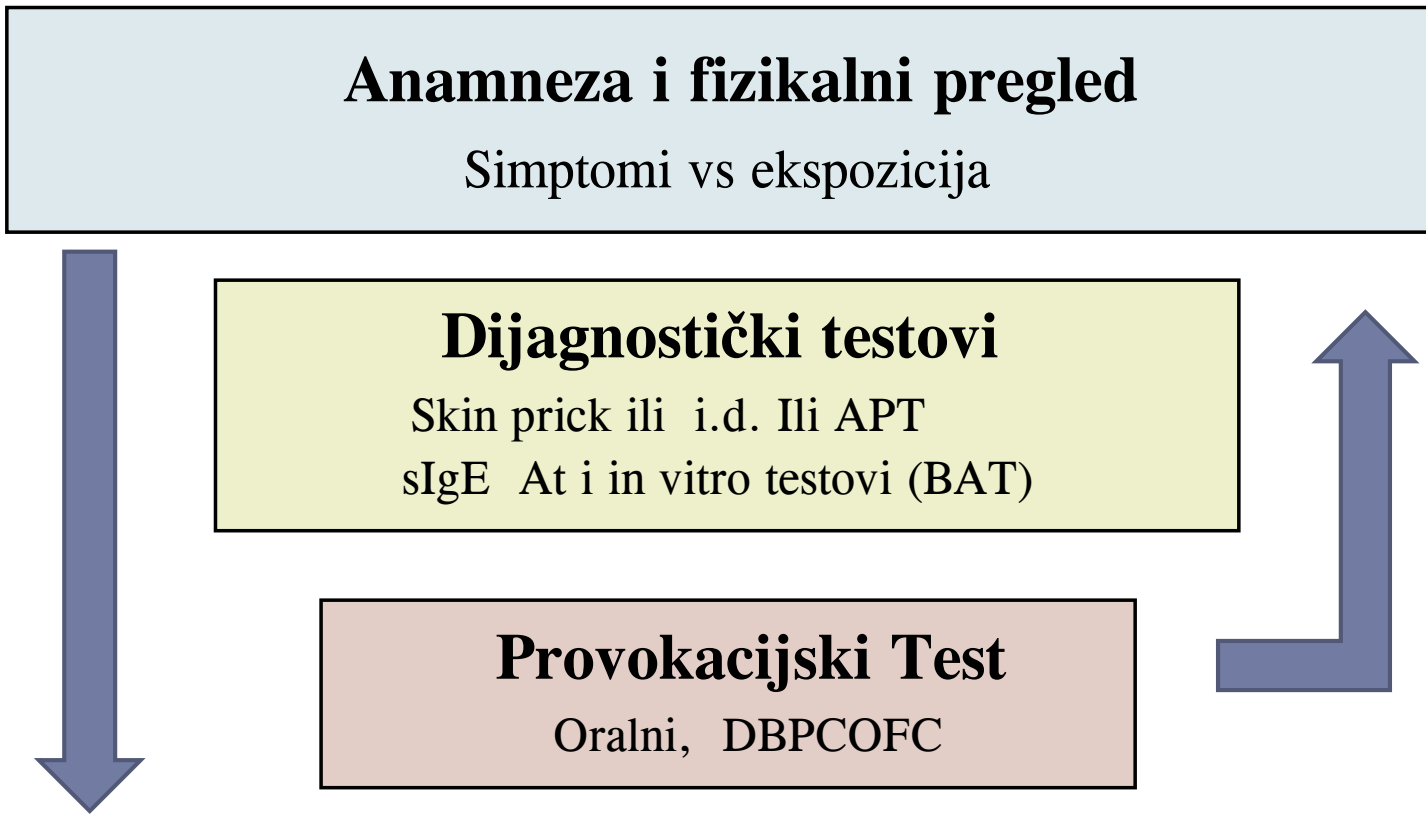


Pathophysiologic Effects

- Inflammation
  - Subclinical
  - Clinical
- Tissue damage
- Pain receptor activation
- Smooth muscle contraction
- Edema
- Excess mucous
- Neurological
- Endocrine
- Increased gut permeability



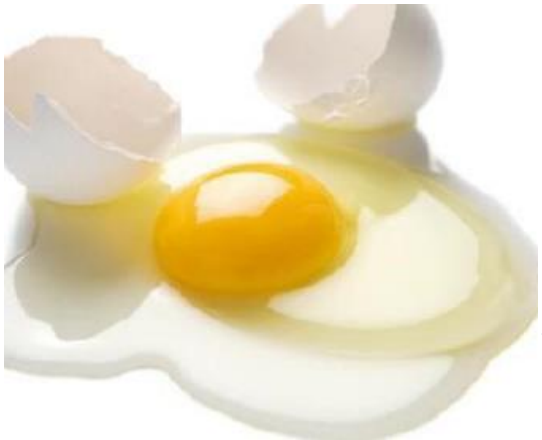
Glavne komponente u dg. alergije na hranu



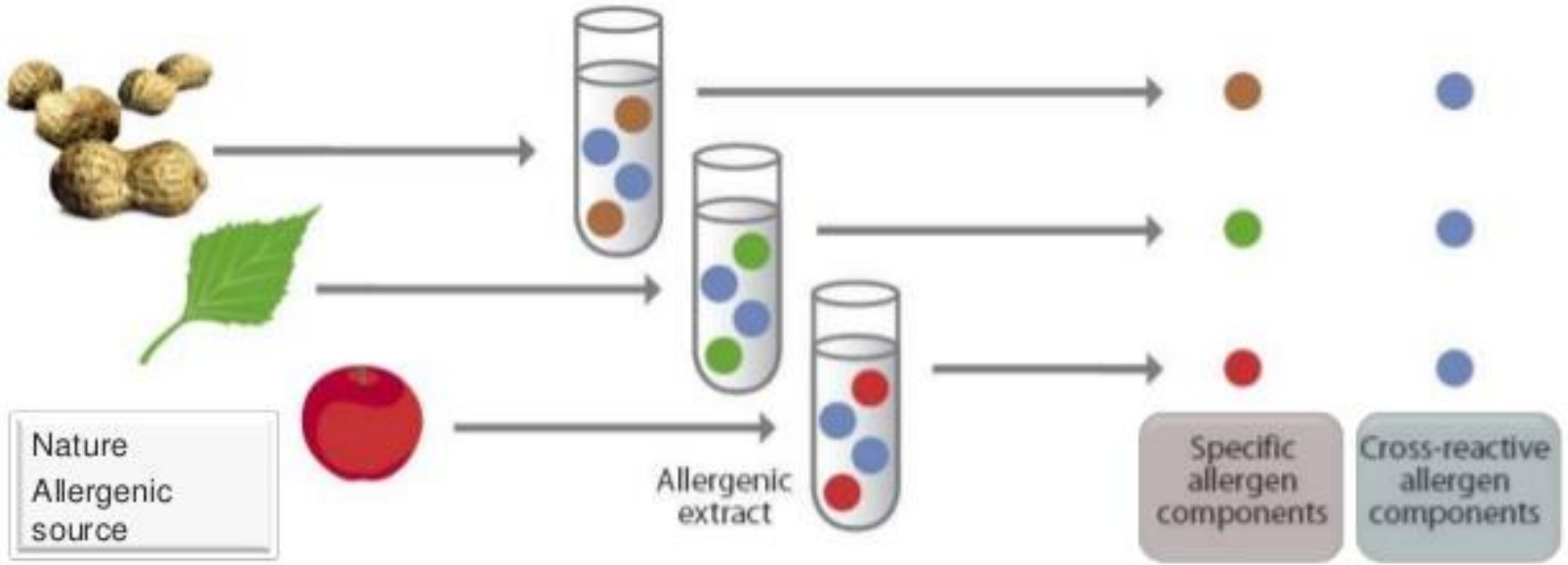
In vivo dijagnostika alergije na hranu

Provokacijski testovi na hranu

- Dvostruko slijepi
- Jednostruko slijepi
- Otvoreni
- Dvostruko-slijepi placebo kontrolirani test (DBPCFC)
- Napor + oralni provokacijski test
- Inhalacijski provokacijski test

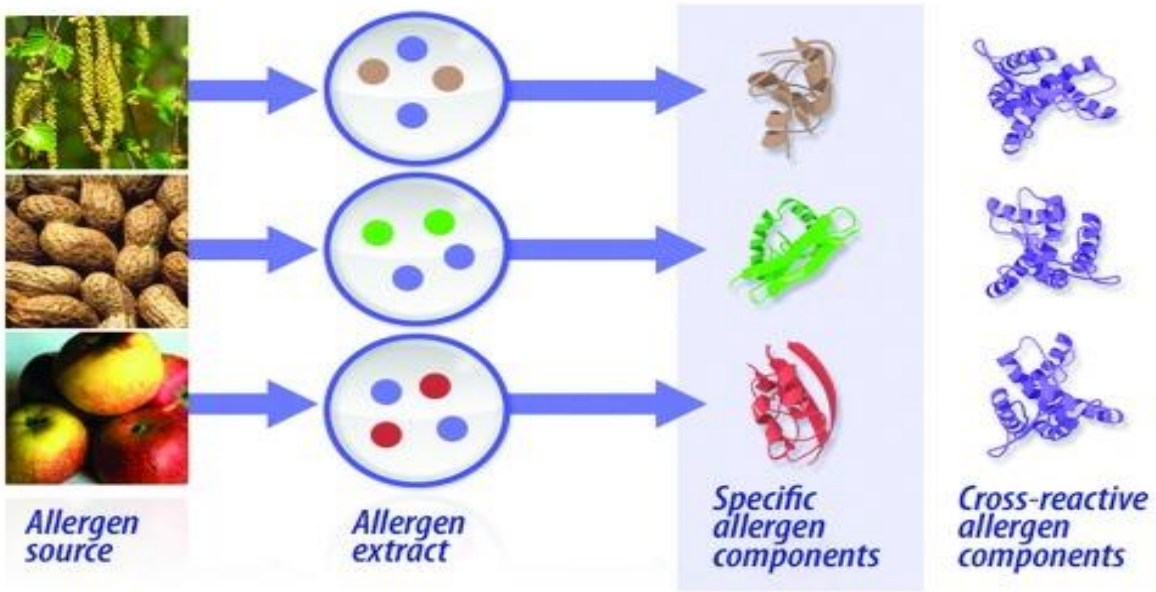


Currently available tests detect only sensitization, not clinical allergy, cannot predict prognosis and severity



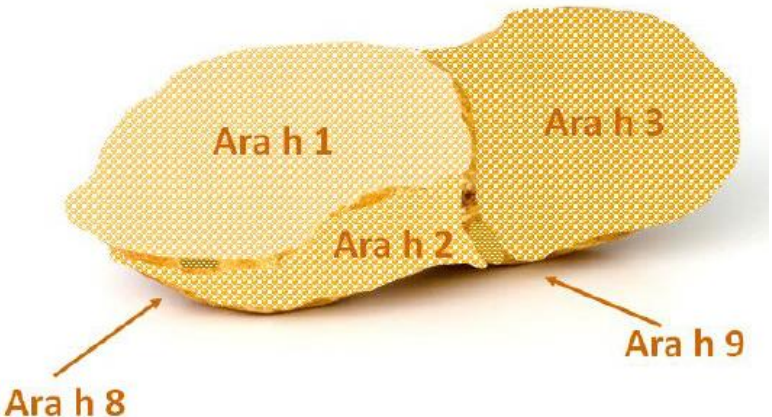
contain a mixture of allergenic and non-allergenic molecules

Alergenski ekstrakti- *in vitro* dijagnostika

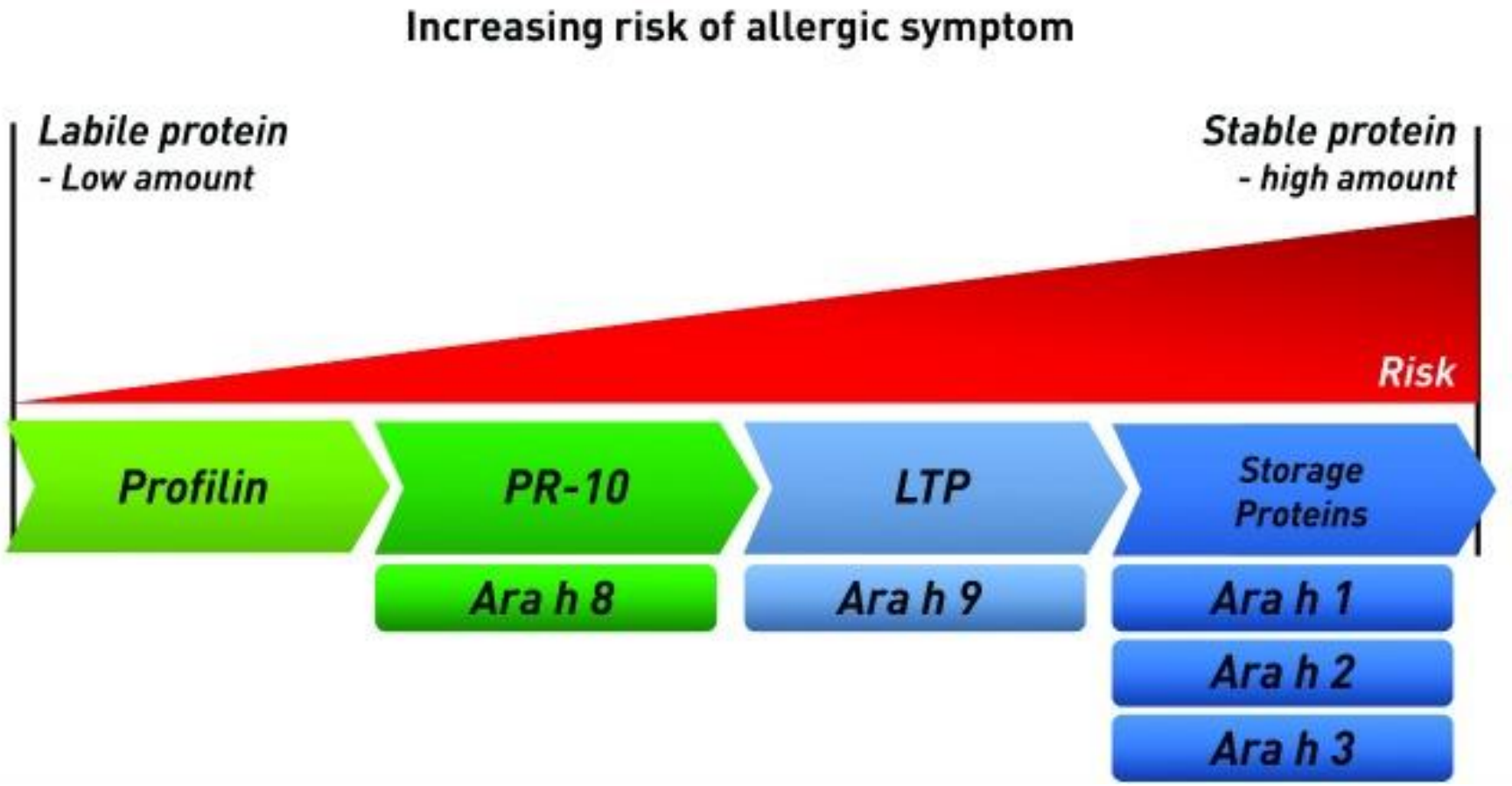


Uloga molekularne dijagnostike – primjer alergije na kikiriki

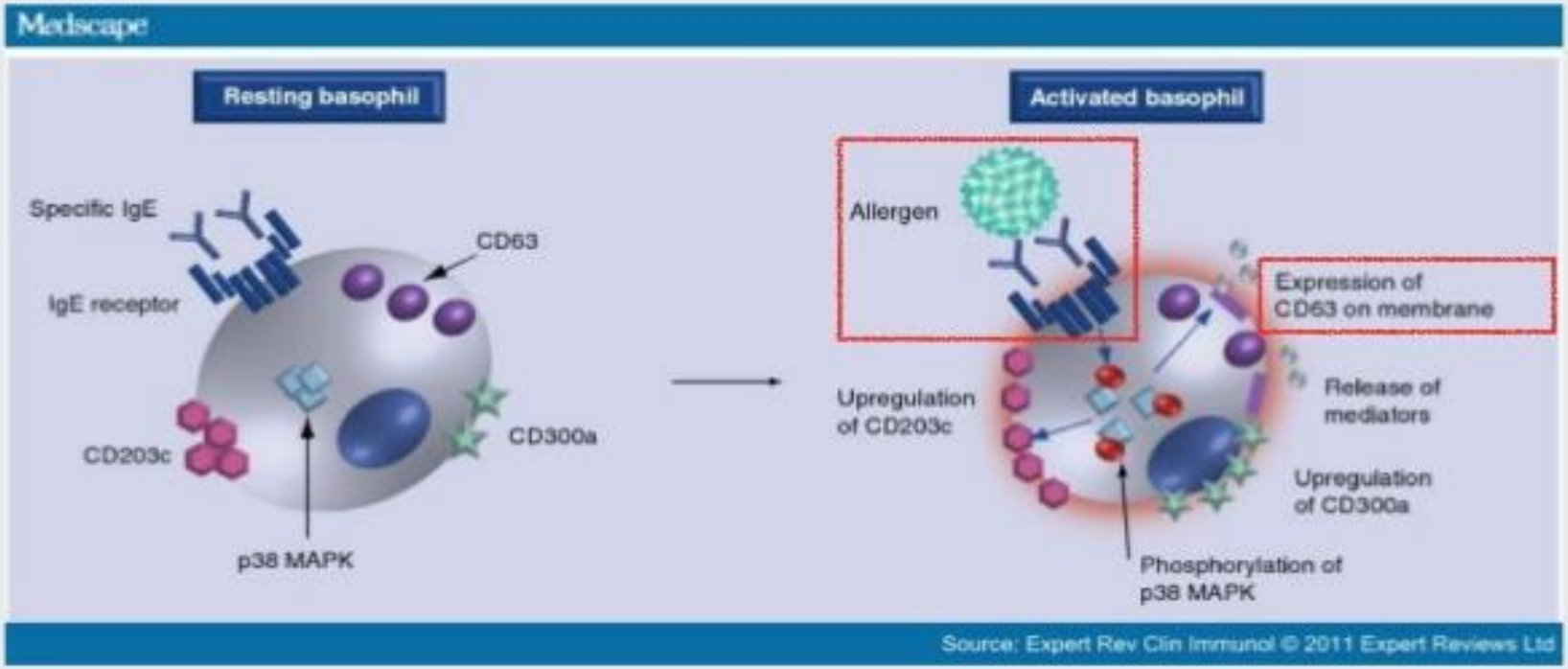
- Cca 10% djece senzibilizirano na kikiriki
- Samo 1-2% alergično (simptomi +)
- Od njih samo dio ima rizik za pojavu anafilaksije
- Rizik ovisan o alergiji na komponente kikirikija
- Alergija na "stabilne" komponente (Ara h 1, 2, 3) – veći rizik od anafilaksije



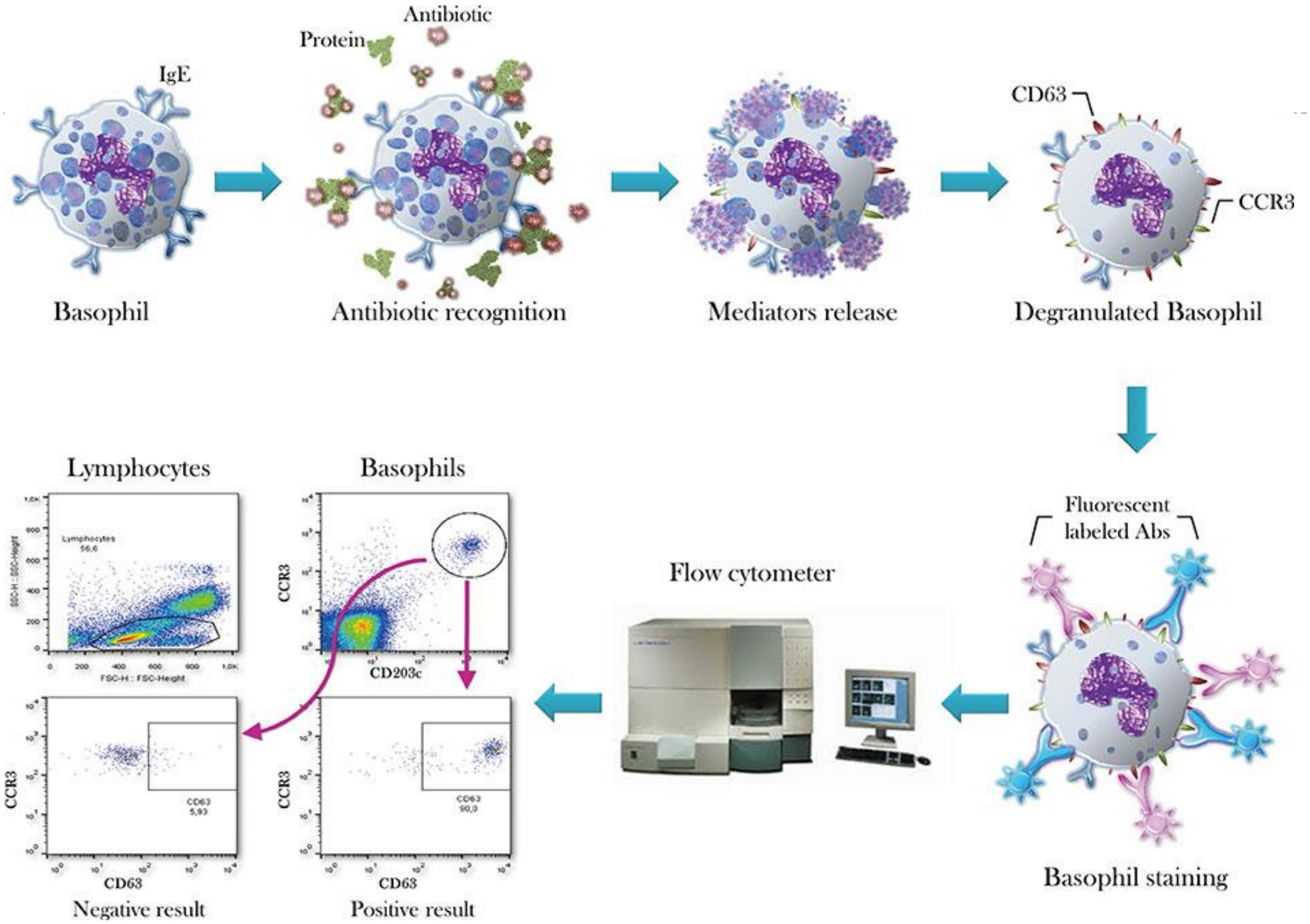
Alergija na kikiriki



Basophil activation test (BAT)



Before test : Basophil > 50 cells


IgE
Antibiotic
Protein
CD63
CCR3
Basophil
Antibiotic recognition
Mediators release
Degranulated Basophil
Fluorescent
labeled Abs
Basophil staining
Flow cytometer
Lymphocytes
Basophils
Lymphocytes
56,6
FSC-H : FSC-Height
SSC-H : SSC-Height
CCR3
CD203c
CD63
5,93
CD63
90,9
Negative result
Positive result

Liječenje alergija na hranu

Liječenje alergijskih reakcija na hranu

- Nema učinkovite, etiološke terapije
  - (od FDA ili EMA odobrene th.)

- Eliminacijska dijeta je jedina mjera prevencija alergijskih reakcija
- Epinefrin je ključni u liječenju teških alergijski reakcija

- Nova th. – AIT
  - SCIT
  - oralna
  - sublingualna
  - epikutana
  - rektalna
- .

Several promising Approaches for the Allergen-specific Immunotherapy in Food Allergy

subcutaneous

sublingual

rectal

oral

epicutaneous

Subkutana imunoterapija u liječenju alergije na hranu

FDA; No licensed immunotherapy products are available for the treatment of food allergy!

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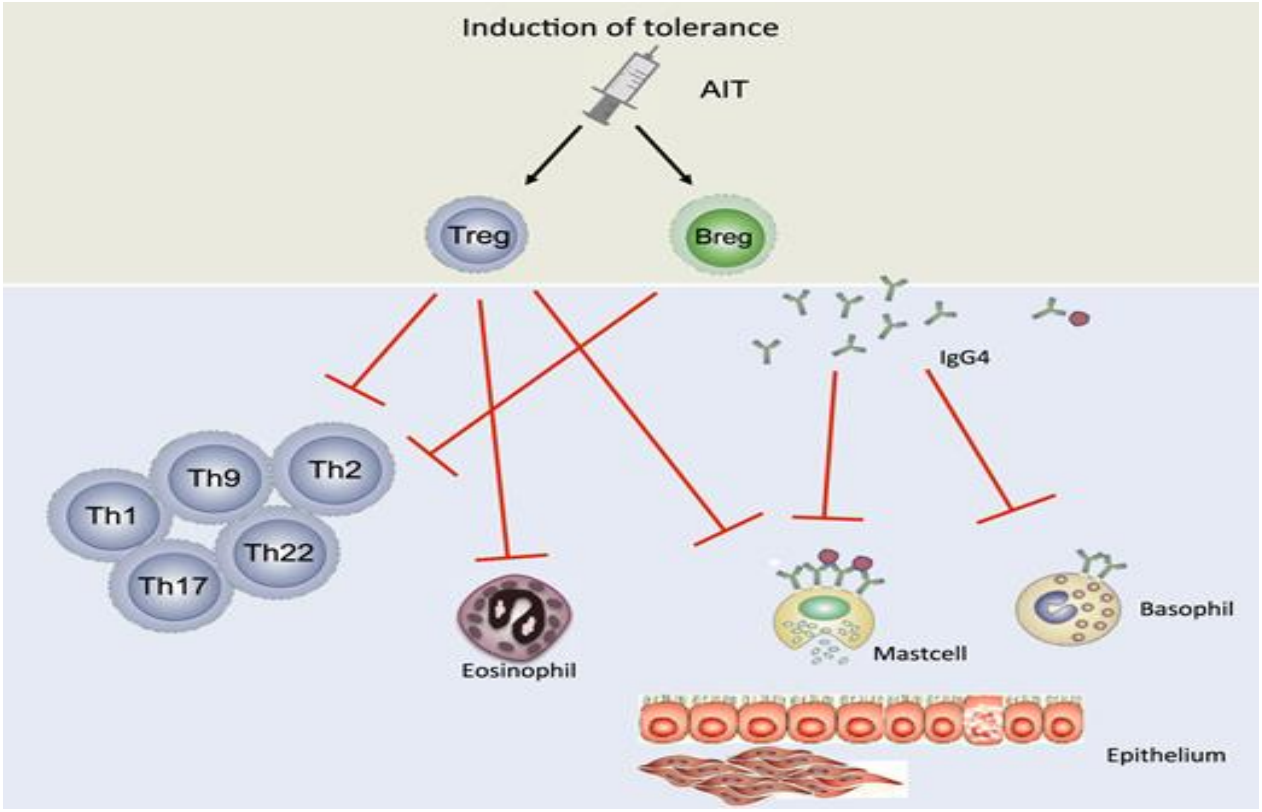
SCIT- učinkovitost oko 50%, nuspojave - opasne !



Metode alergen specif. imunoterapije u liječenju nutritivne alergije

- **Oralna IT (OIT)**
  - Guta se s hranom
  - Otvorene ili "slijepe" studije
  - mg – g hrane

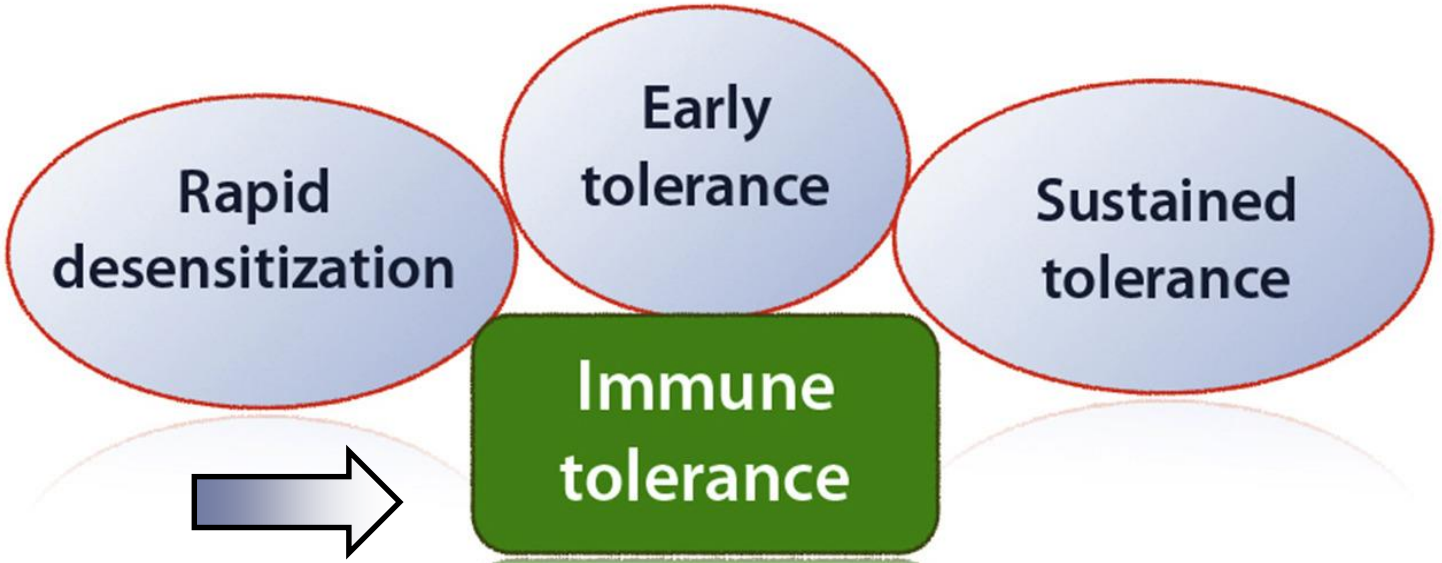
Sublingvalna imunoterapija

- Male doze
- Sigurnija, manje nuspojava
- Nije jednako učinkovita kao OIT

- Ufazi istraživanja
  - Kl. studije faze 2.

- Mlijeko, kikiriki, lješnjak, breskva, kivi

Mechanisms of AIT

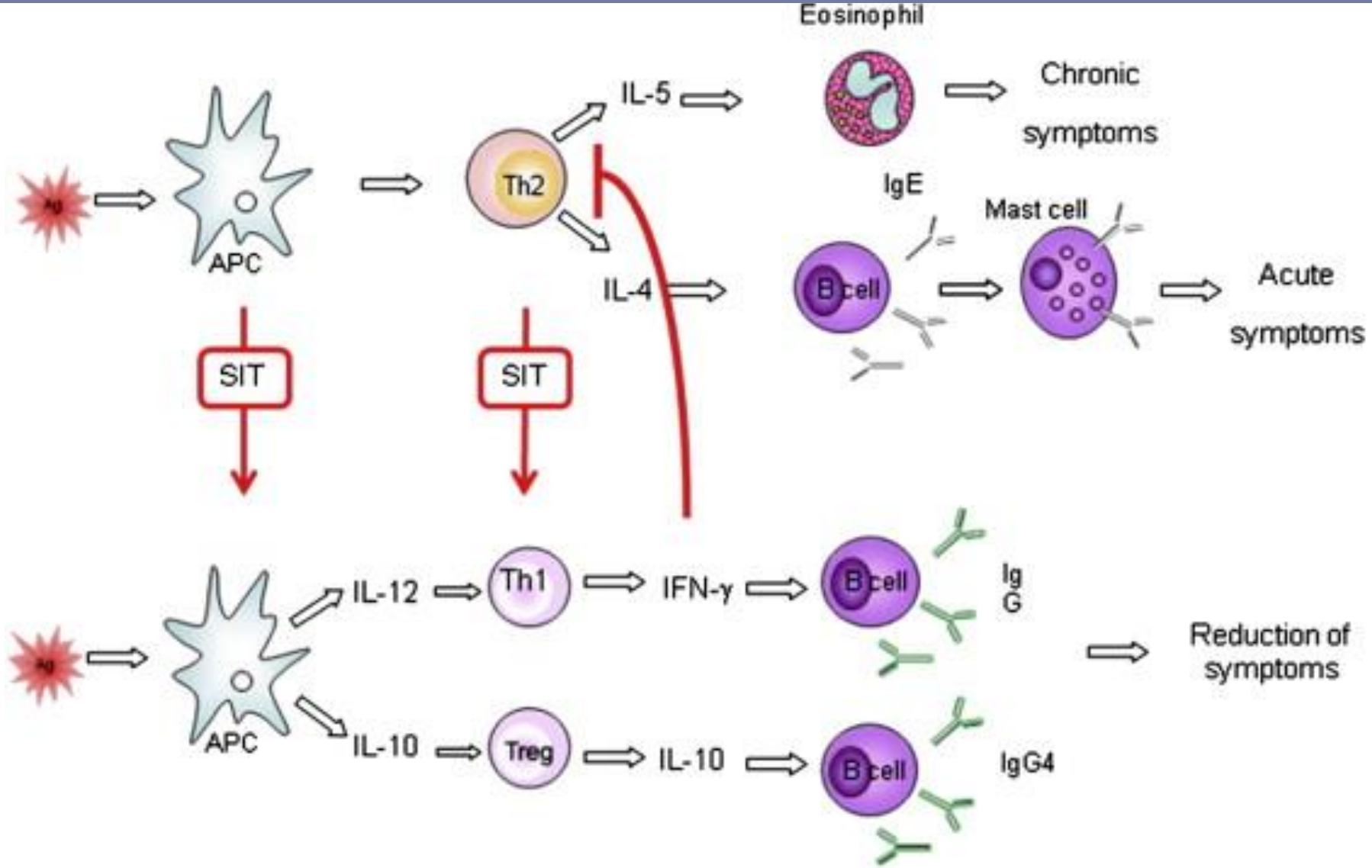


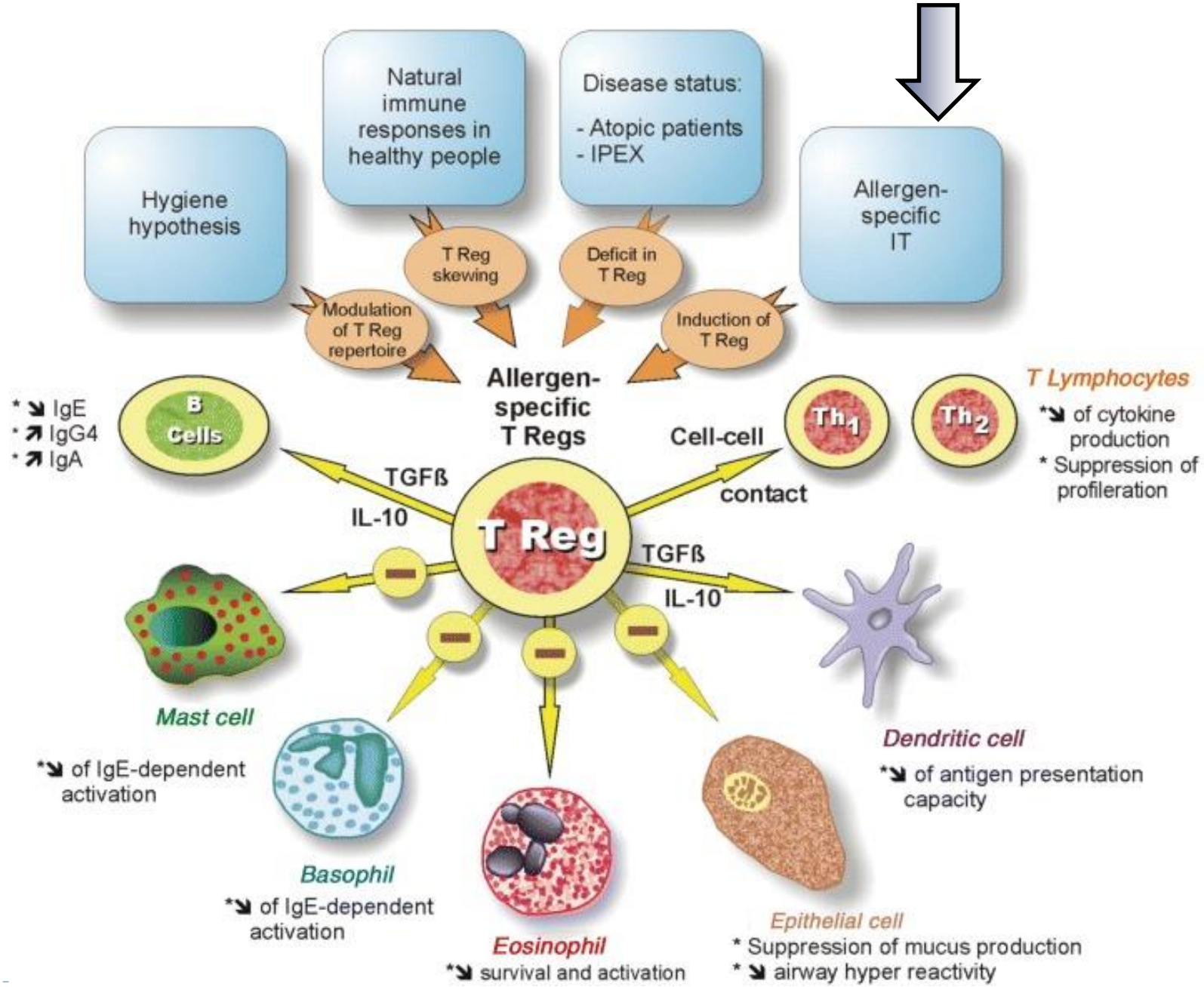
Effector cell desensitization
- IgE
- Mast cell and Basophil
- Mediators - Histamine signal

Increased Treg/Breg cells
Increased Th1/Th2
Increased IgG4 >
Decreased IgE
Decresed tissue inflammation
Decreased mast cells and eosinophils and their mediators in tissues

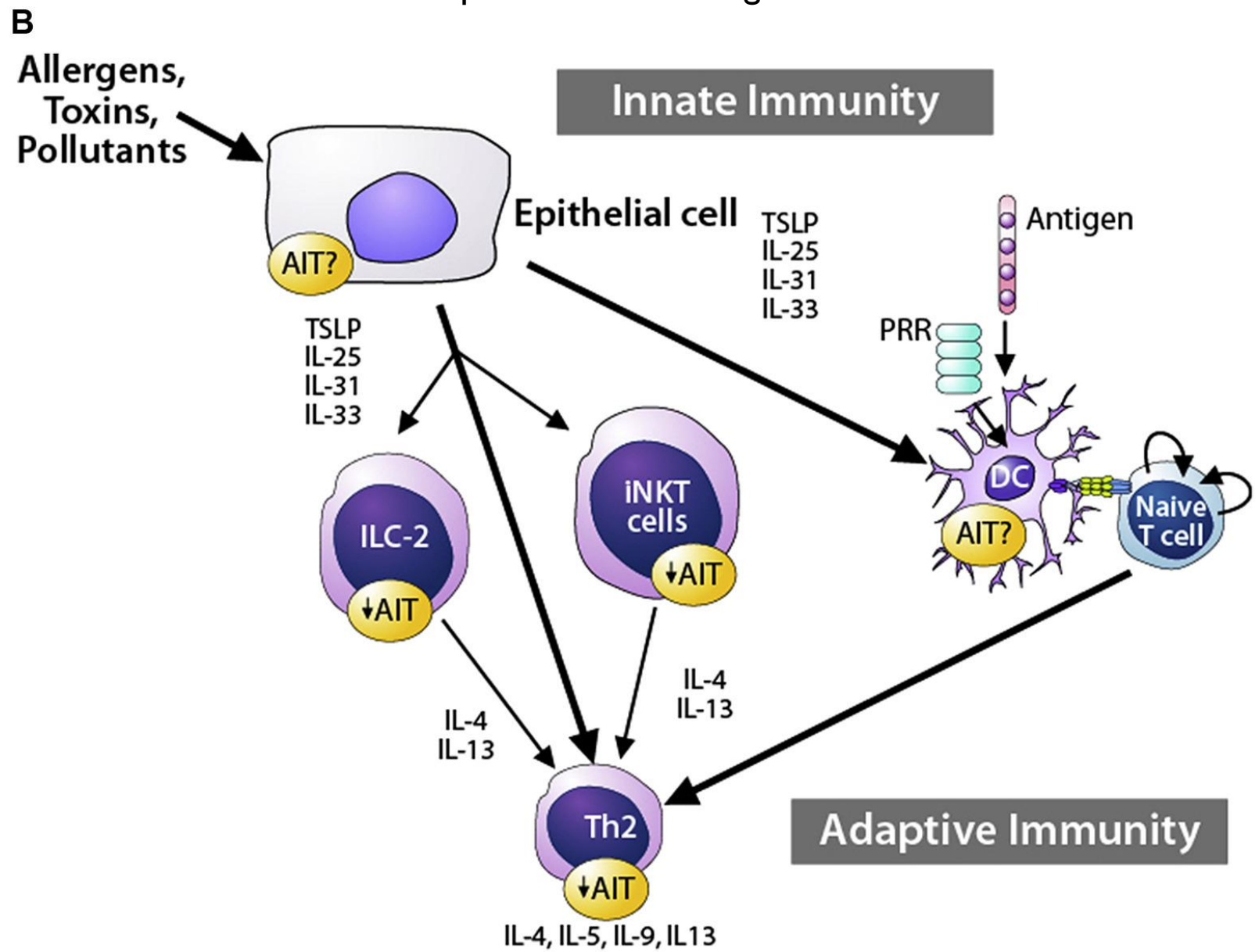
Journal of Allergy and Clinical Immunology 2016 137, 358-368DOI: (10.1016/j.jaci.2015.12.1300)

Osnovni patomehanizam AIT-a




Natural immune responses in healthy people
Disease status:
- Atopic patients
- IPEX
Hygiene hypothesis
Allergen-specific IT
T Reg skewing
Deficit in T Reg
Modulation of T Reg repertoire
Induction of T Reg
Allergen-specific T Regs
* ↘ IgE
* ↗ IgG4
* ↗ IgA
B Cells
Cell-cell contact
Th1
Th2
T Lymphocytes
*↘ of cytokine production
* Suppression of profileration
TGFß
IL-10
T Reg
TGFß
IL-10
Mast cell
*↘ of IgE-dependent activation
Basophil
*↘ of IgE-dependent activation
Eosinophil
*↘ survival and activation
Dendritic cell
*↘ of antigen presentation capacity
Epithelial cell
* Suppression of mucus production
* ↘ airway hyper reactivity

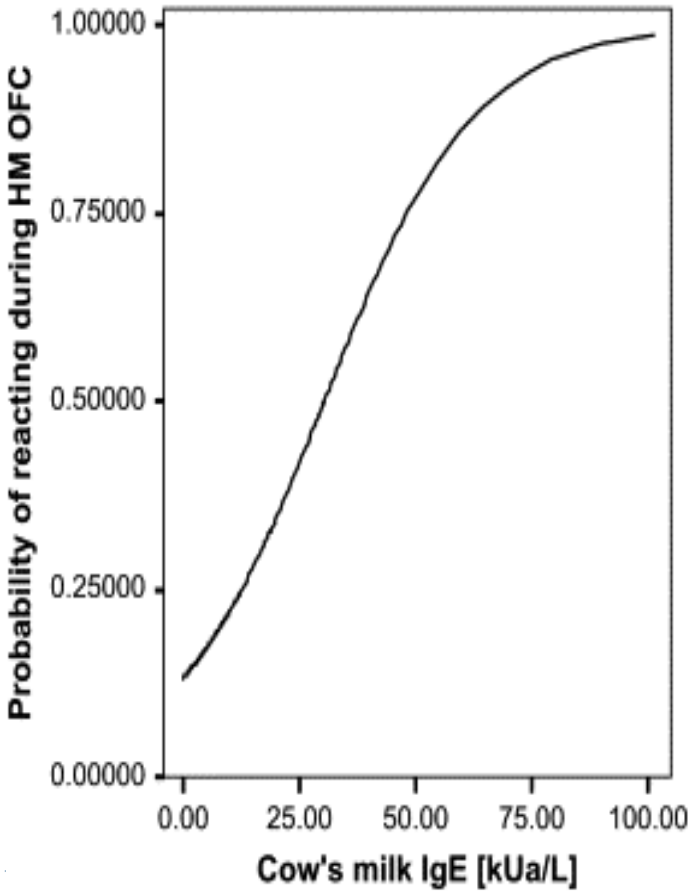
AIT i prirođeni imuni odgovor



Journal of Allergy and Clinical Immunology 2016 137, 358-368DOI: (10.1016/j.jaci.2015.12.1300)

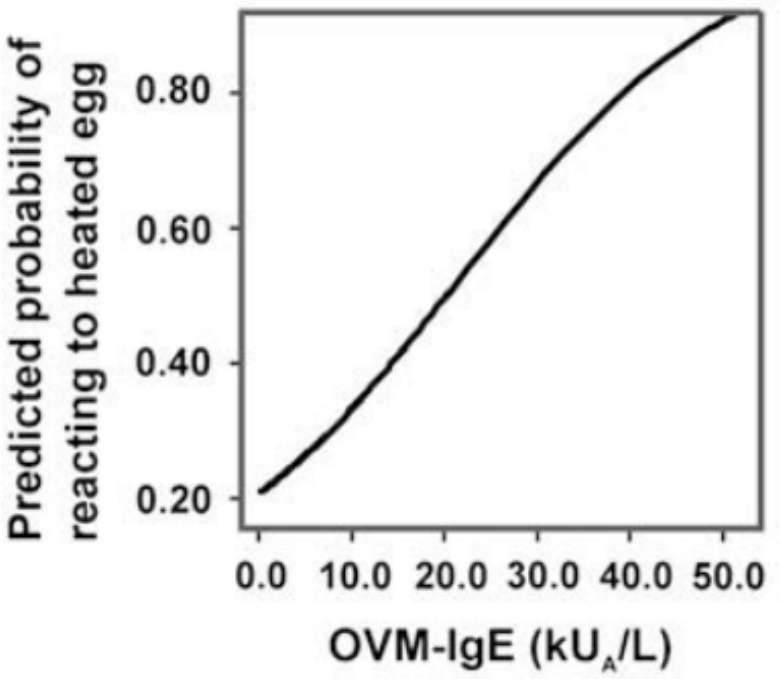
Desenzibilizacija na KM/jaja

¾ djece alergične na KM toleriraju kuhano KM



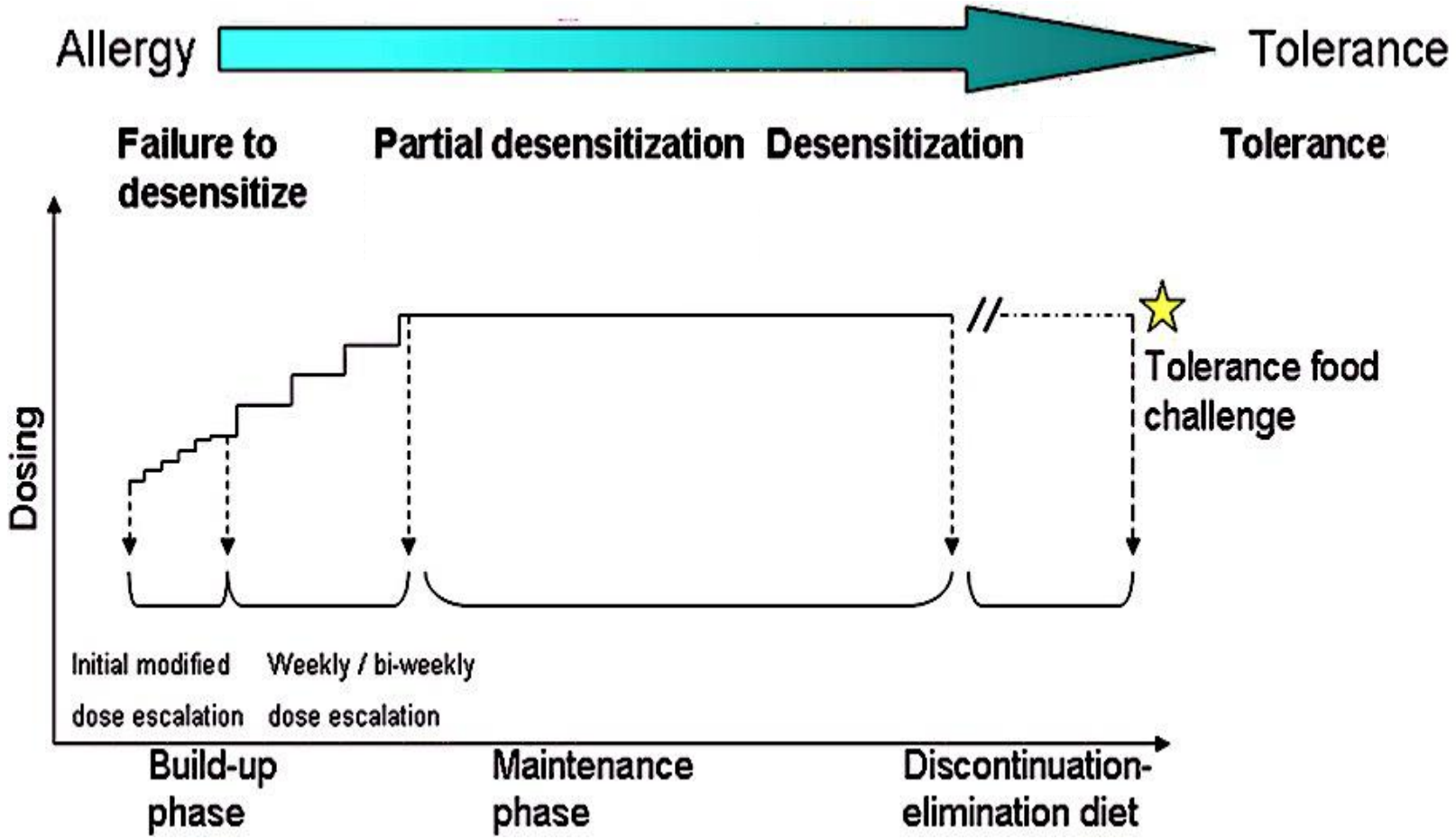
Nowak-Wegrzyn et al. JACI. 2008: 122:342-7.

Preko ½ djece alergičnoa na jaja toleriraju pečeno jaje



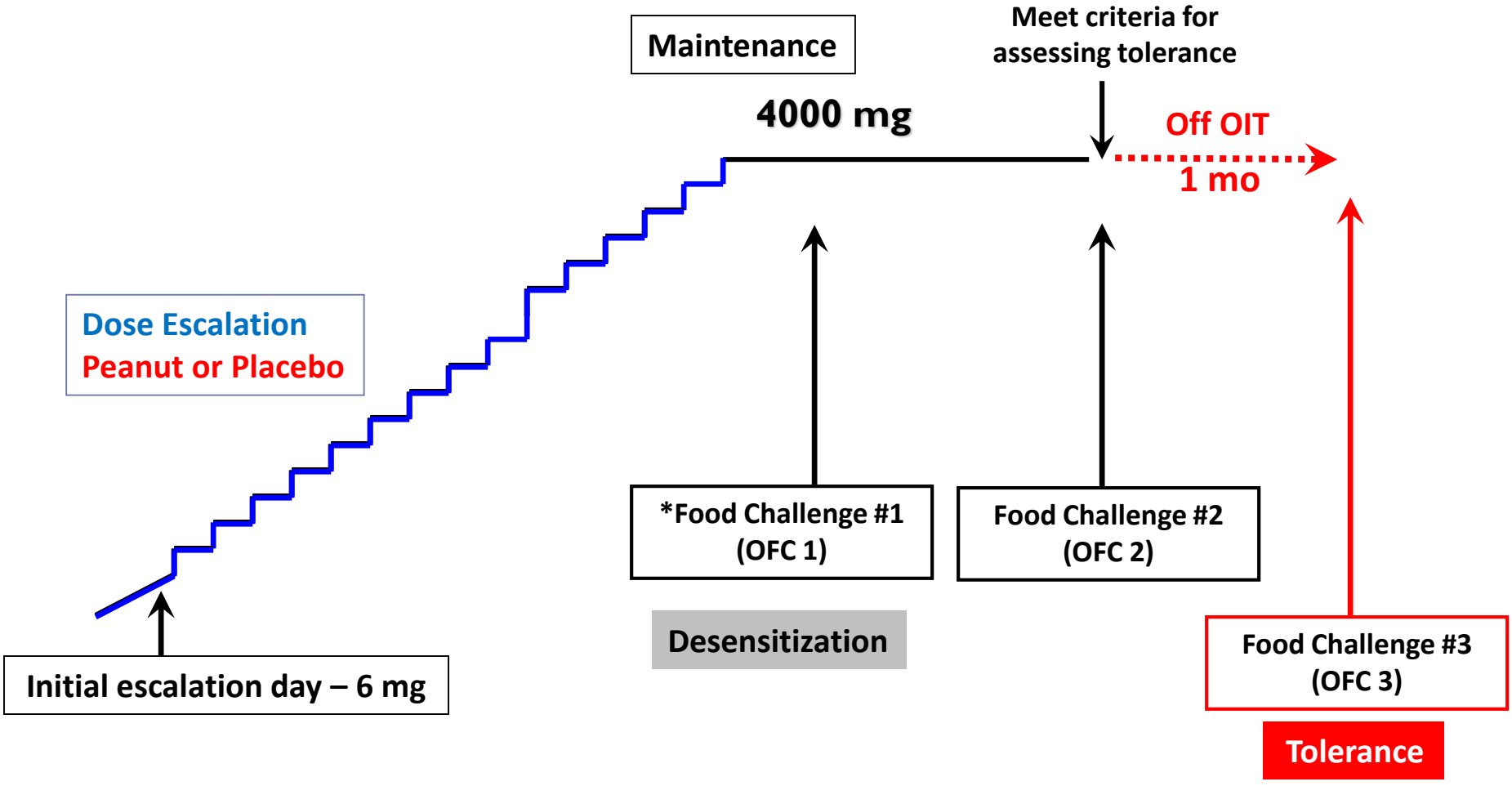
Lemon-Mulé et al. JACI. 2008:977-85

Način primjene **OIT**



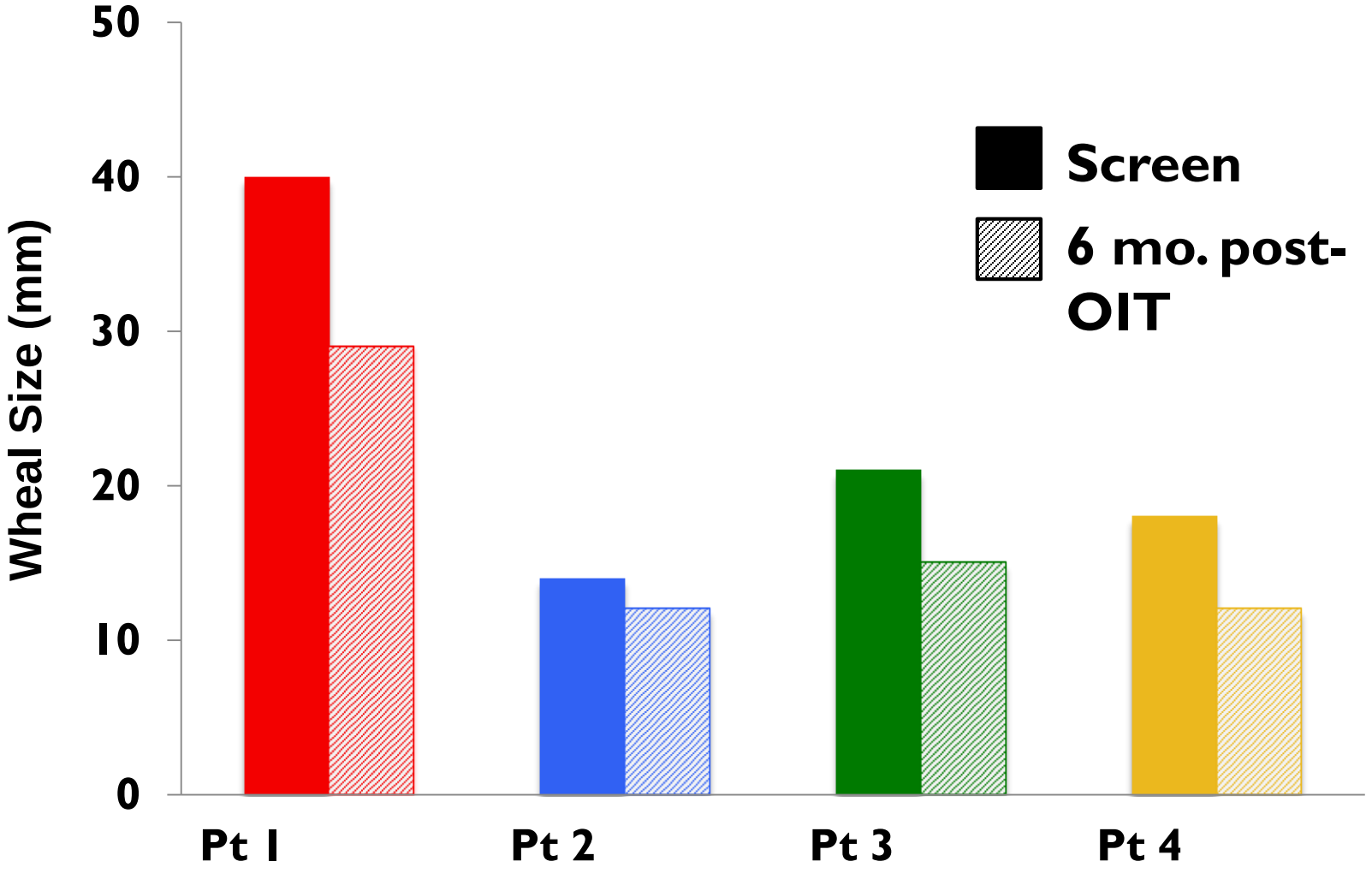
Nowak-Wegrzyn JACI March 2011

Dizaj studije: DBRCT- OIT s kikirikijem Duke and Arkansas



Varshney et al. JACI March 2011

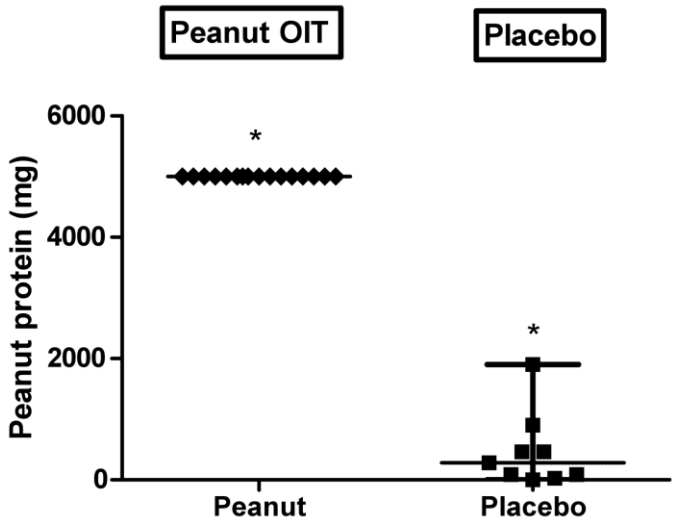
OIT - kikiriki
Rezultati SPT-a



OIT-kikiriki – klinički značajna desensitizacija i supresija aktivacije mastocita

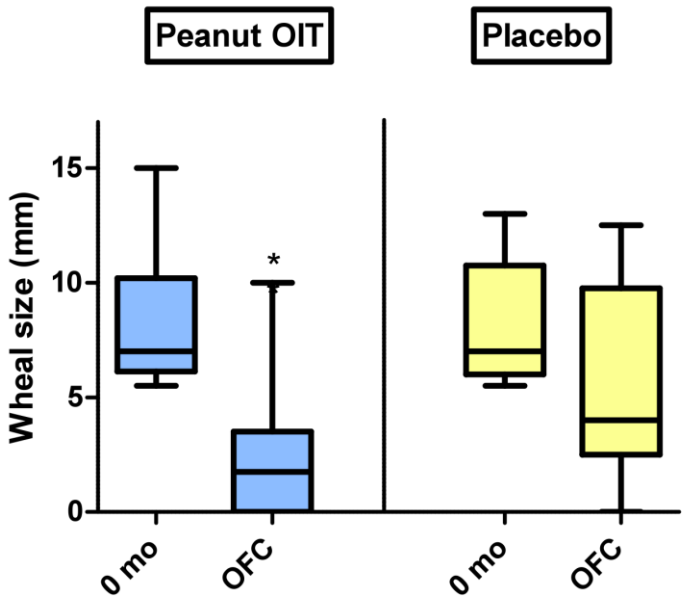
- **25 subjects** – 16 - active treatment; 9 – placebo (3 withdrew)
  - Any peanut-allergic subject – unless accompanied by significant hypotension
  - All subjects - maximum dose of 6 mg (initial day); 4000 mg during build-up

Peanut OFC I



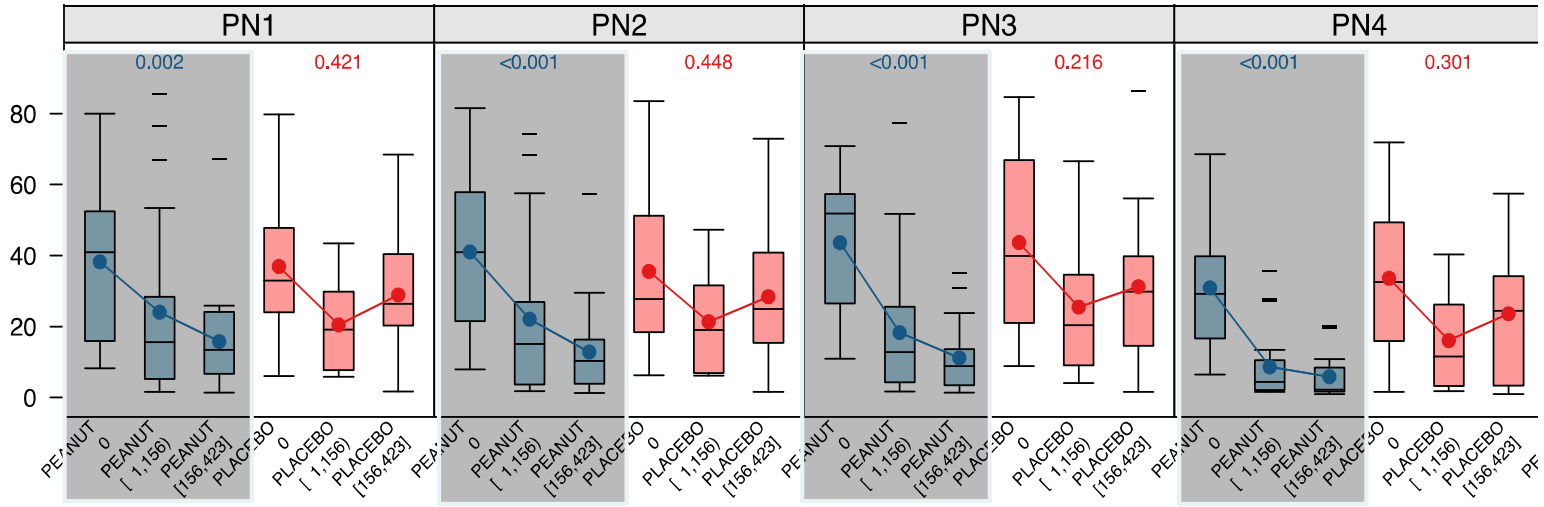
* P=.008

Peanut SPT



Varshney et al. JACI March 2011

Antigen specifična supresija aktivacije
Bazofila – CD63% Hi



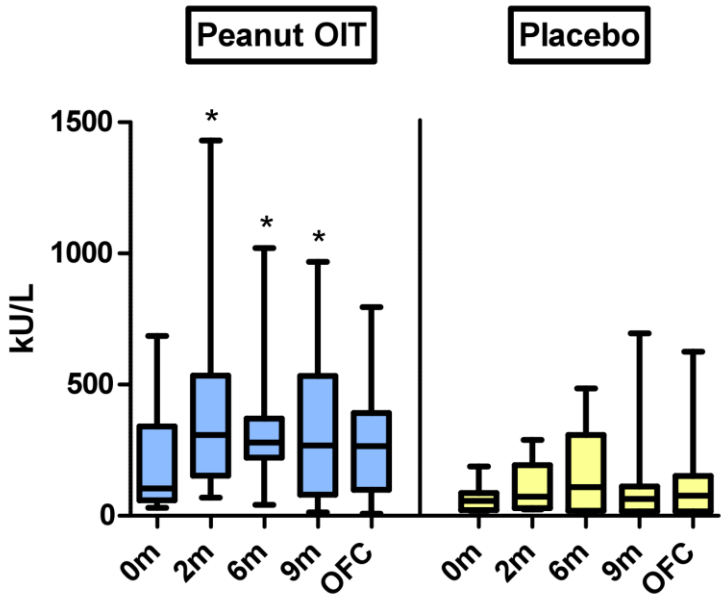
- 4 concentrations of peanut cultured with subject's cells at each time point – 0, 6 and 12 months (PN1, PN2, PN3, PN4)

Thyagarajan, Shreffler et al. AAAAI 2009

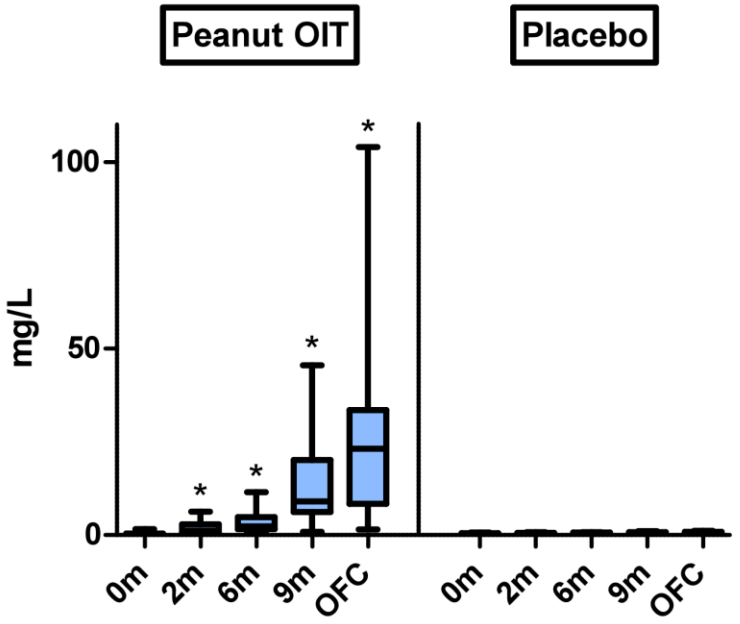
- Significant change in basophils – CD63% over time on OIT

Kikiriki sIgE and sIgG4 u serumu tijekom OIT

Peanut IgE



Peanut IgG4



Varshney et al. JACI March 2011

ImmunoCAP-FEIA (Phadia)

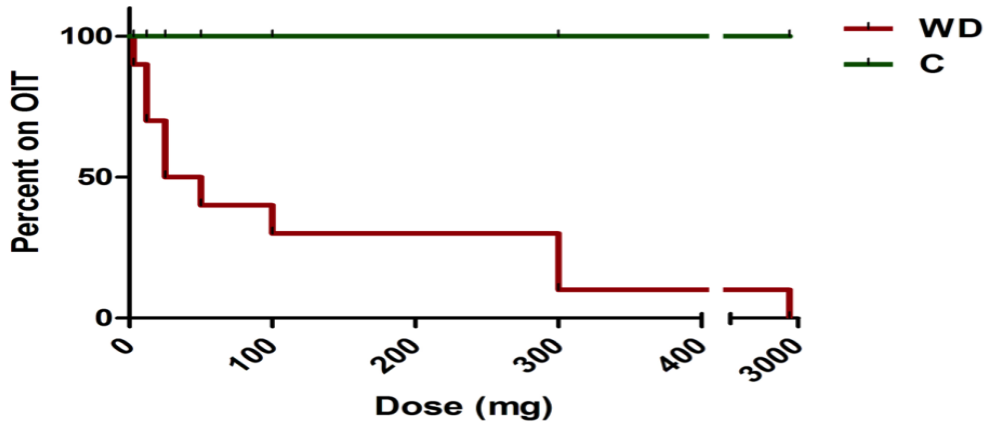
Sigurnost OIT

- Čimbenici rizika za pojavu rekacija tijekom OIT
  - febrilitet, virusna infekcija, napor, menses (Varshney JACI 2009)

- Pojava simptoma tijekom prvih ~15-25% doze alergena
  - Uglavnom blagi, orofaringealni
  - <1% doze– umjereni do jaki simptomi

- Primjena epinefrina
  - <1% dose

- Gastrointestinalni simptomi su rani i limitirajući
    - Prekid (odustajanje) ~10-20%

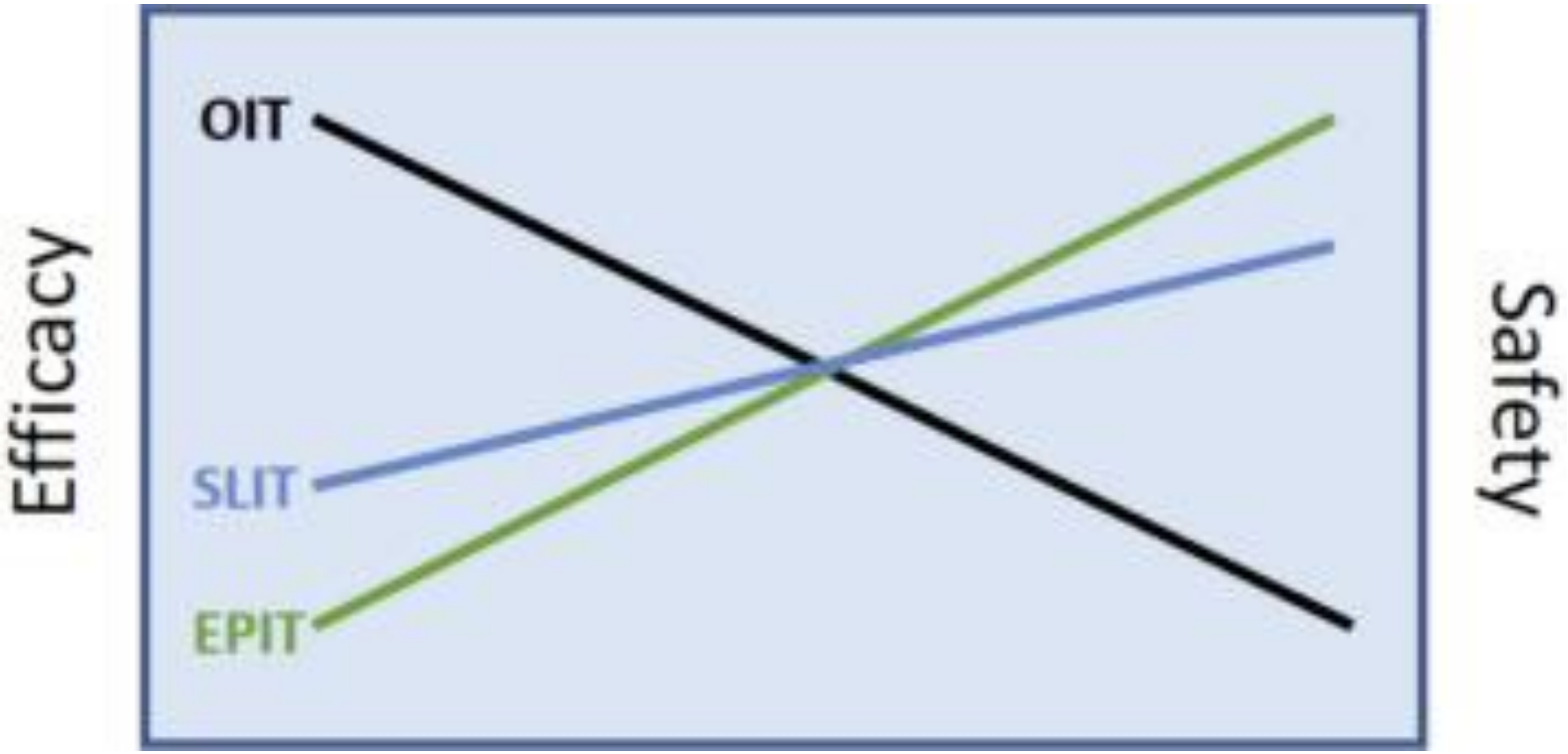


Epikutana imunoterapija (Patch)

- Povišen je prag za alergene u animalnom (mišjem) modelu
- Siguran u ljudi
- Preliminarne studije su pokazale učinkovitost u ljudi (250mcg/dozi)
- Faza III kl. studije u tijeku (PEPITES)

DuPont et al. JACI. 2014
DuPont et al. JACI. 2010

Alergen-specifična imunoterapija u liječenju alergije na hranu



PRESTO Studija

(Prospective, Randomized Study to evaluate the Effectiveness of Synbiotics on Cow's Milk Allergy Tolerance)

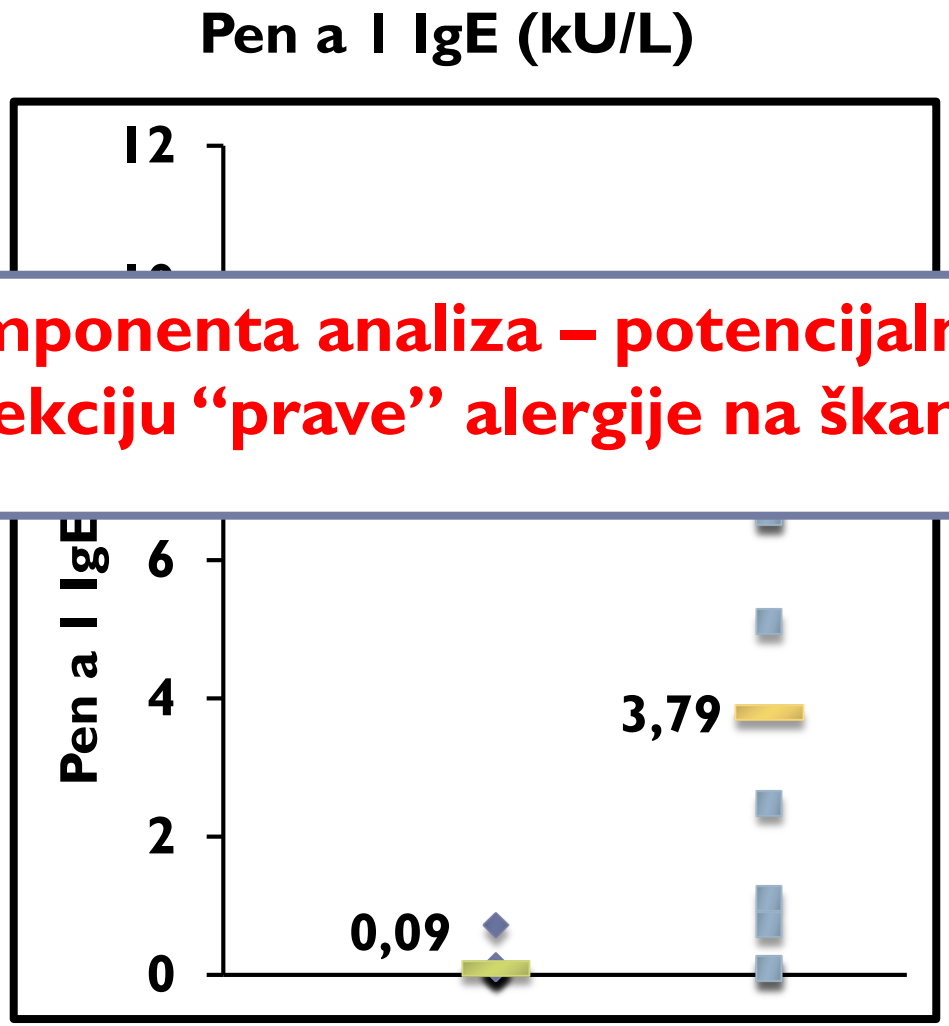
Cilj: odrediti da li simbiotska formula dovodi do ranije tolerancije na KM i smanjuje senzibilizaciju na druge alergene

Kriteriji:

1. Diagnoza alergije na KM
2. Dob < 13 mj. starosti

PRESTO

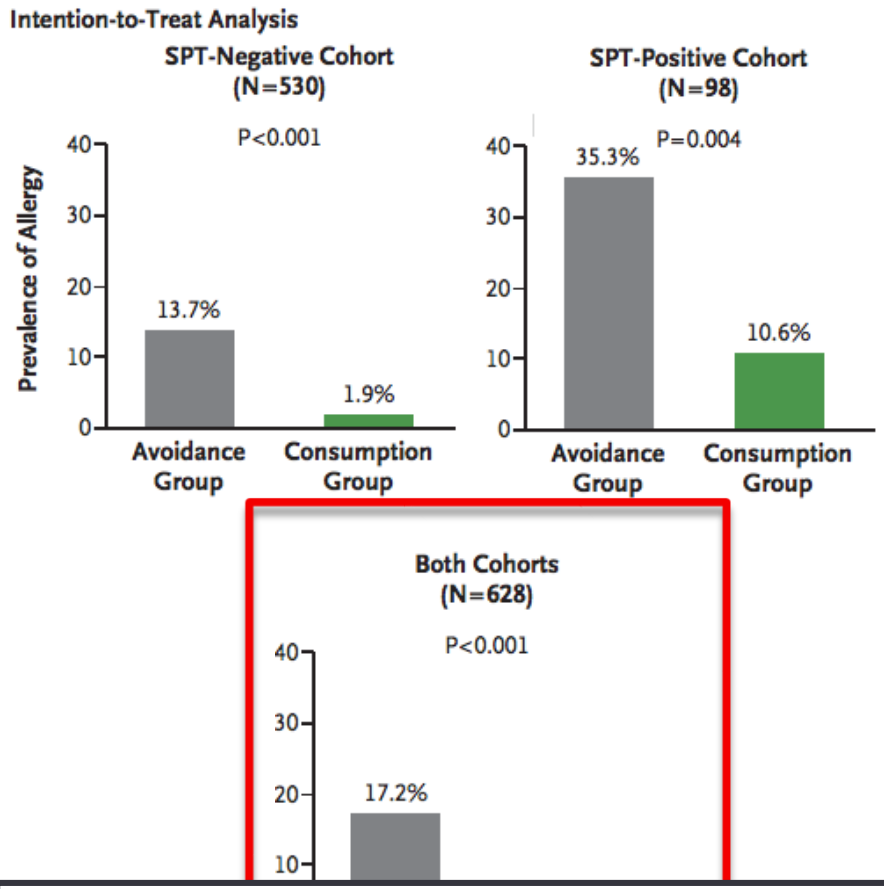
Praćenje imunološkog odgovora u bolesnika alergičnih na škampe



***Pen a 1*, komponenta analiza – potencijalni marker za detekciju "prave" alergije na škampe**

Tuano et al, In preparation

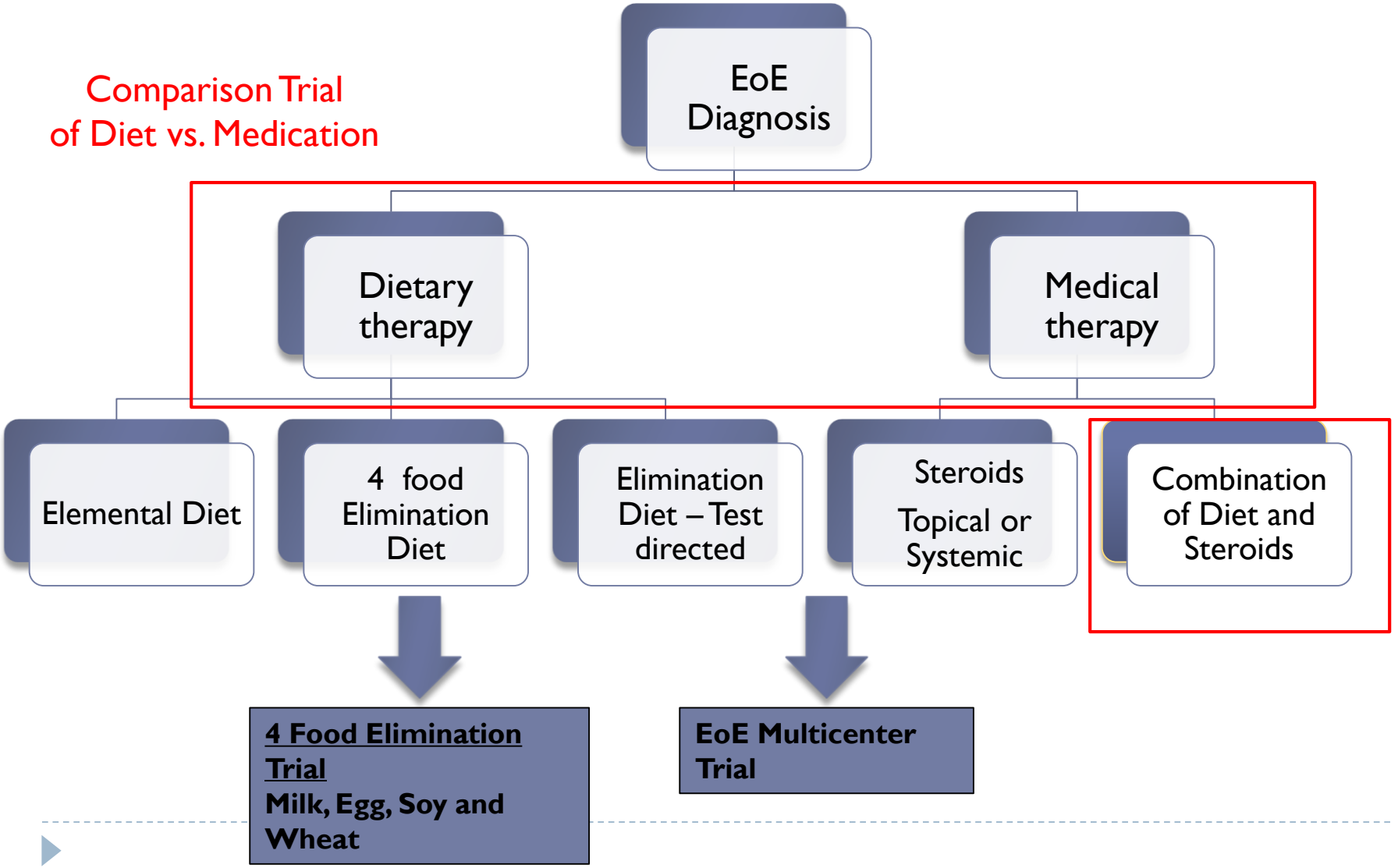
LEAP Studija



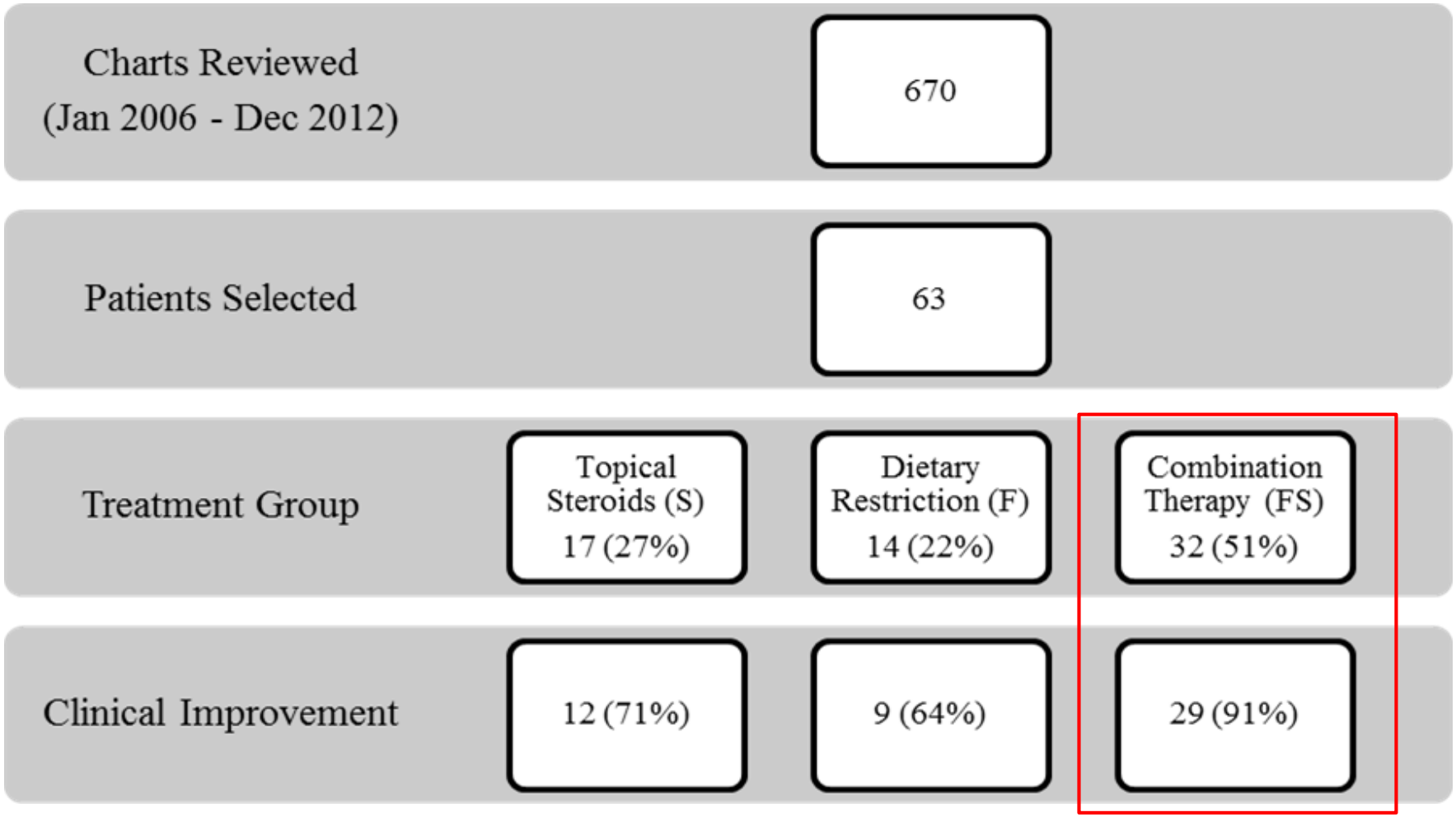
- **Cilj:**
  - Pratiti učinak ranog uvođenja kikirikija na prevenciju alergije na kikiriki
- **Metoda:**
  - Visoko rizična dojenčad (jaki *eczem +/- alergija na jaja*) 4-11 mj. stara
    - Pozitivan kožni test (≤4mm)
    - Negativan kožni test
  - Randomizirani u (2) grupe kroz 5 god:
    - Djeca koja su jela kikiriki
    - Djeca koja nisu jela kikiriki

Alergija na kikiriki se 5x više razvila u djece koja su izbjegavala kikiriki

Standardni EoE - shema liječenja



EoE Kombinacijska terapija



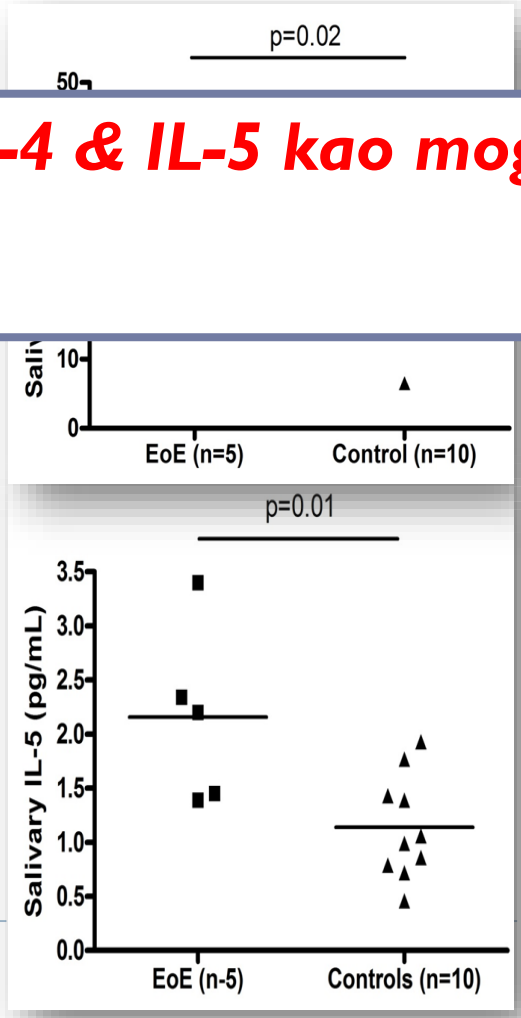
Seth N, Chokshi N et al. Submitted

Citokini iz sline u **EoE**

Određivanje citokina u EoE

Metodom "magnetic high-sensitivity human multiplex assays" (EMD Millipore, MA)

IL-4 & IL-5 kao mogući markeri EoE – mjereni u uzorcima sline



IL-4 (pg/mL)	37.3 ± 4.0	24.3 ± 3.0	0.02
IL-5 (pg/mL)	2.1 ± 0.3	1.1 ± 0.1	0.01
IL-13 (pg/mL)	4.7 ± 0.9	4.3 ± 0.6	0.75
Eotaxin 3 (pg/mL)	52.2 ± 3.4	45.1 ± 1.8	0.07
TSLP (pg/mL)	7.3 ± 0.1	7.0 ± 0.1	0.15

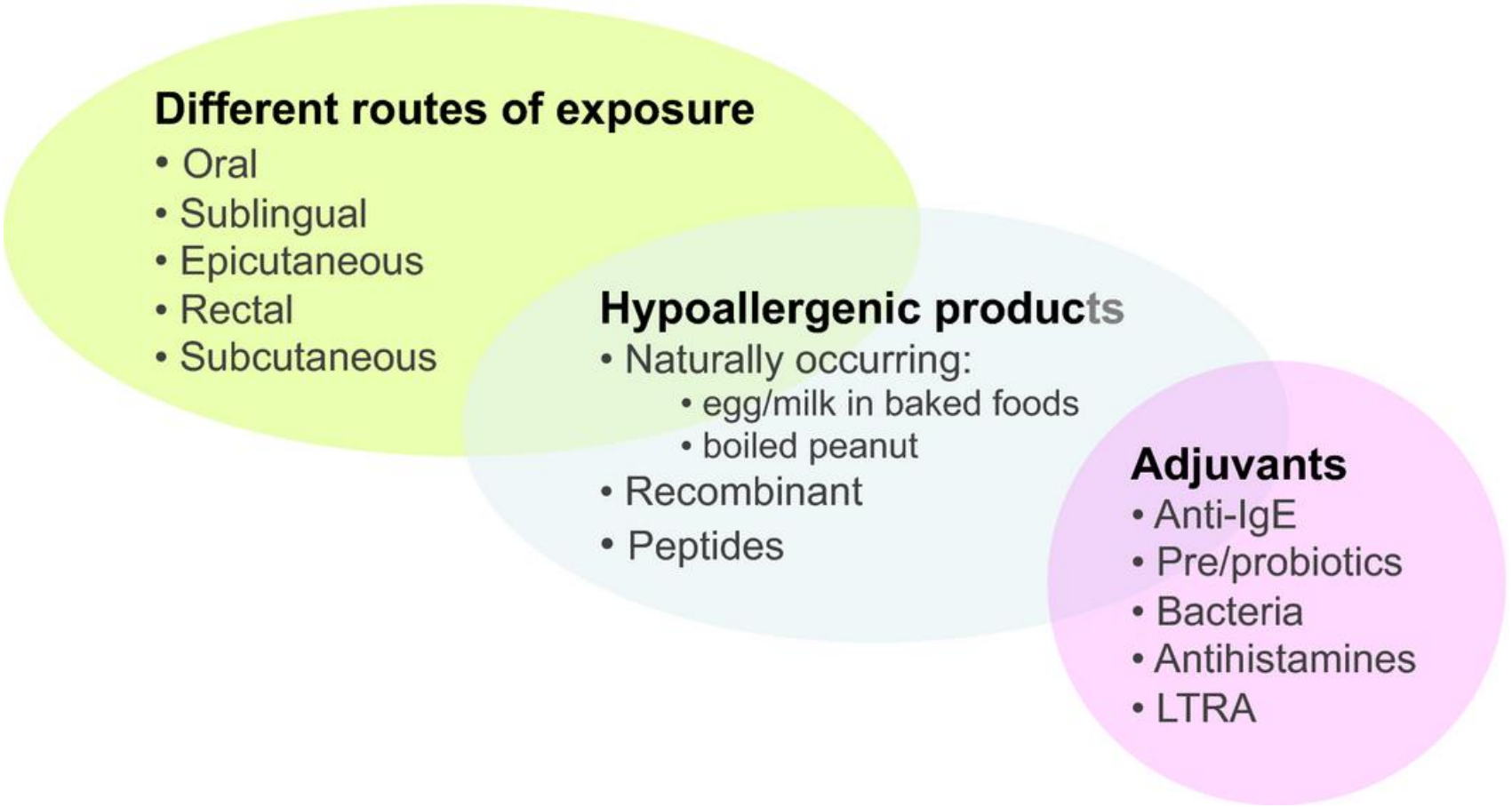
Hiremath et al., Ann Allergy Asthma Immunol, 2015

Prijavljene kliničke studije

- Jednogodišnja, privremena analiza OIT kikirikijem nakon oralnog provokacijskog testa
- Faza 3 – OIT kikirikijem
- Faza 3 - Epikutana "patch" imunoterapija
- Faza 1 – OIT škampima
- Faza 1 – OIT orahom
- Faza 1 – "Multi-Food" OIT

FARE
CLINICAL NETWORK
MEMBER

Kako poboljšati sigurnost OIT u alergiji na hranu?



Pediatric Allergy and Immunology
Volume 27, Issue 2, pages 117-125, 22 DEC 2015 DOI: 10.1111/pai.12510
http://onlinelibrary.wiley.com/doi/10.1111/pai.12510/full#pai12510-fig-0001

Zaključak

- Alergije porijeklom iz hrane su u porastu (globalni problem)
- Razlozi porasta alergijskih bolesti nisu poznati
- Alergijske reakcije na hranu su po život opasne (anafilaksija)
- Dijagnostički testovi se usavršavaju (zlatni standard je DBPCOFCT)
- U liječenju osim eliminacijske dijete sve više istraživanja vezana uz alergen-specifičnu imunoterapiju (OIT)

Zaključak?

Hvala na pozornosti!
Pitanja?