

Moscow 12.03.13

Carbamylated monomeric allergoid for respiratory allergy: the advantages of LAIS®

E. Compalati



*-Allergy & Respiratory Diseasec Clinic
University of Genoa. Italy*

*-Lofarma Spa, Milan. Italy
Medical Scientific Department*



WHO position paper 1998

- SIT is indicated for *inhalants* and *venom* allergy
- SIT is positioned as the only treatment able to modify the natural course of allergy

 Risk/benefit

Other routes



SLIT..from the literature

- No fatal reactions ever reported
- No difference in the incidence between children and adults
- Most reaction mild and localized in the oral mucosa or gastrointestinal tract (incidence **≈40-75%**)
- Very few systemic serious reactions reported (0.26%)



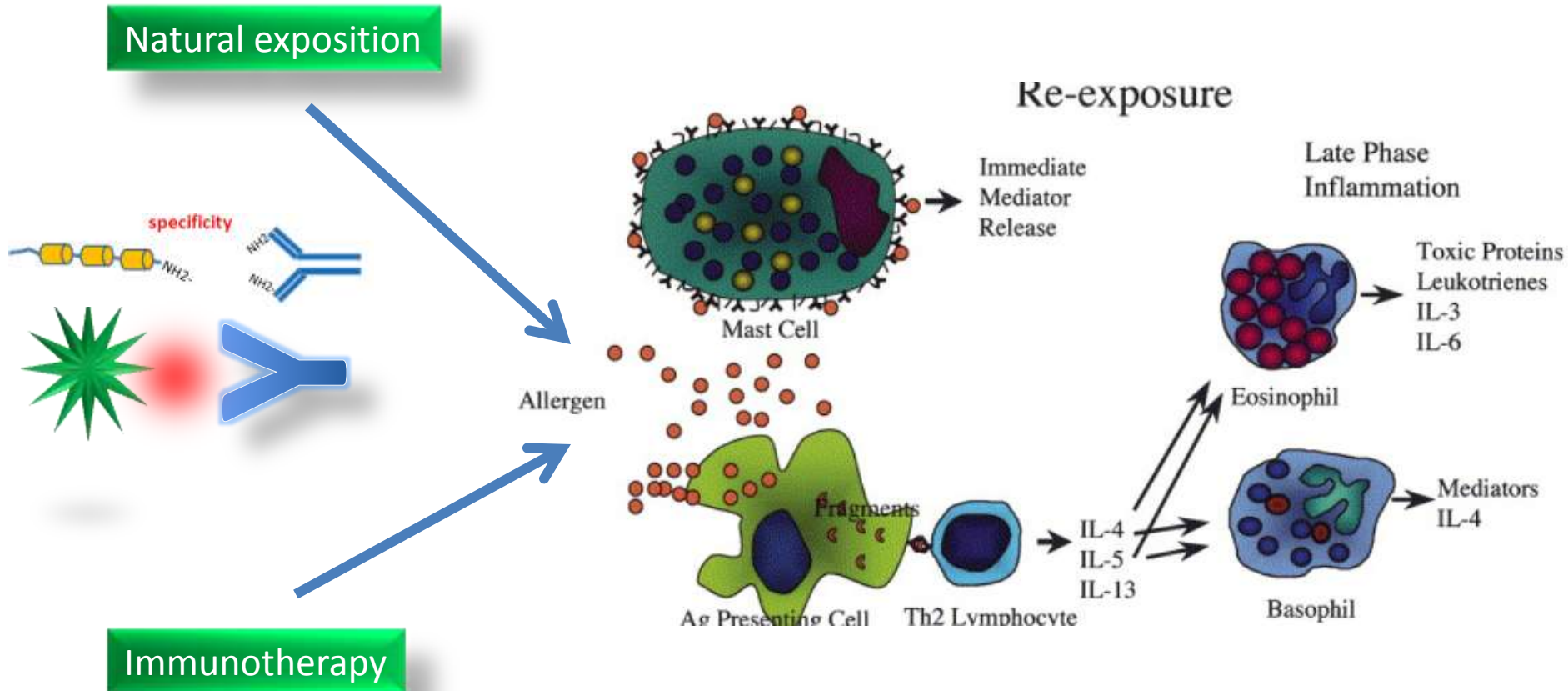
Cox LS et al. JACI 2006
Radulovic S et al. Allergy 2011
Passalacqua G. et al. Curr Drug Saf 2007
Ibañez MD et al. Pediatr Allergy Immunol 2007

Anaphylaxis to SLIT

Report	Age- sex	Allergen	Manufacturer
Antico 2006 - Italy	36 y-woman	Latex	ALK-Abellò
Dunsky 2006 -USA	31 y- woman	Mix	Greer
Eifan 2007 - Turkey	11 y-girl	Mites, 5 grass	Stallergenes
Blazowski 2008 - Poland	16 y-girl	Mites	Stallergenes
Rodreguez- Perez 2008-Mexico	27 y-woman	Mix	unknown
Rodreguez- Perez 2008-Mexico	7 y-girl	Mites, Tree	unknown
Rodreguez- Perez 2008-Mexico	11 y-boy	Mites	unknown
De Groot 2009 - Netherland	13 y-boy	Grass	ALK-Abellò
De Groot 2009 - Netherland	27 y-woman	Grass	ALK-Abellò
Buyukozturk 2010 - Turkey	adult	Latex	ALK-Abellò
Buyukozturk 2010 - Turkey	adult	Latex	ALK-Abellò

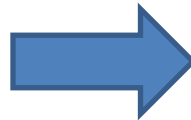
1/100 millions administrations

Immunotherapy: adverse events



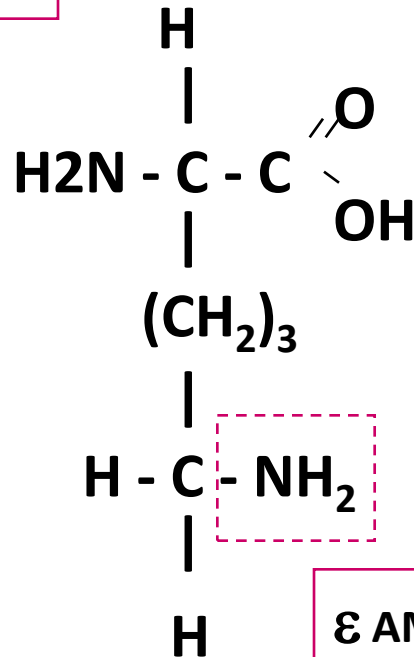
LAIS[®]

from ALLERGEN...to ALLERGOID



Lais[®] is a modified allergen with a specific reaction with potassium-cyanate

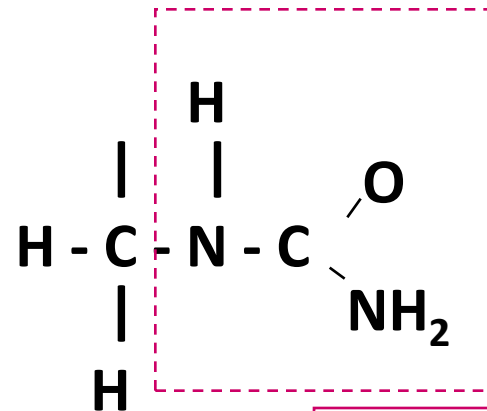
LYSINE:



ε AMINIC
GROUP



HOMOCITRULLINE:



UREIDIC
GROUP

“carbamylation”

Consequences of chemical modification



1

PRESERVATION
of molecular sizes
-monomericity-

2

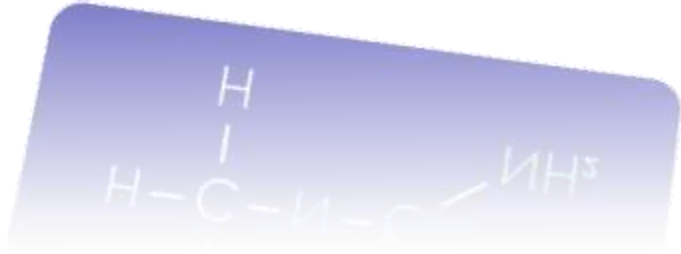
Dramatic REDUCTION
of specific IgE linking
-reduced allergenicity-

3

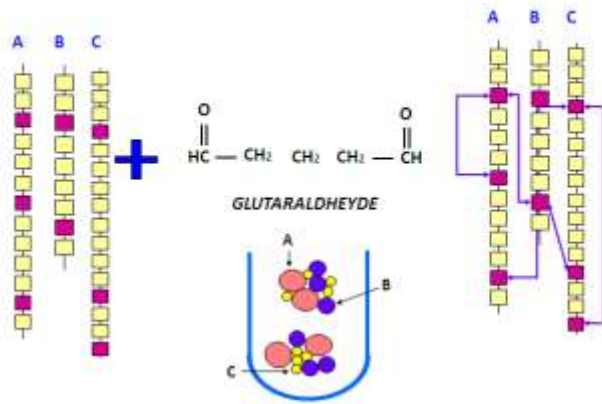
NO
alteration of T-epitopes
-preserved immunogenicity-

4

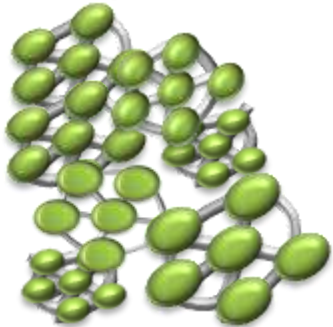
RESISTENCE
to enzymatic degradation
-high bioavailability-



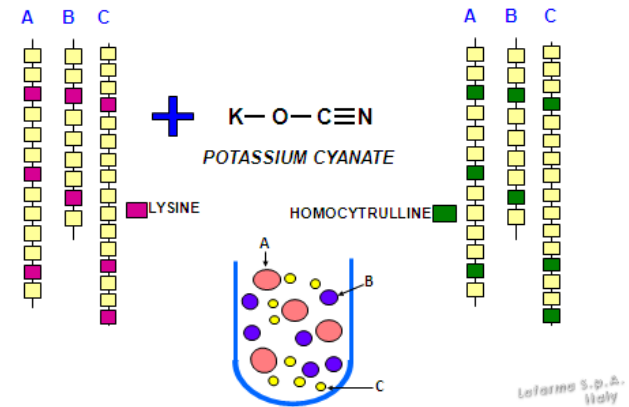
Traditional Polymeric Allergoids



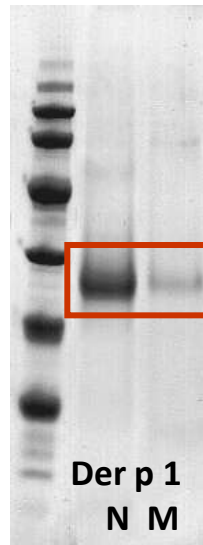
polymeric >1000 kda



Monomeric Allergoid



monomeric ~40 kda



Consequences of chemical modification



1

PRESERVATION
of molecular sizes
-monomericity-

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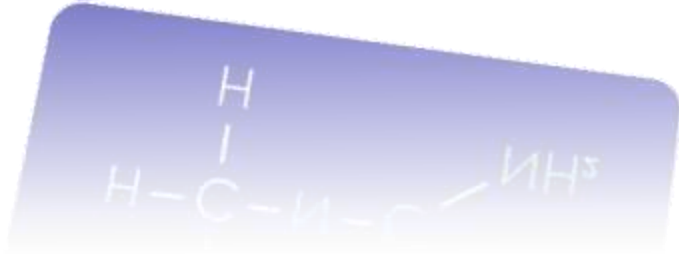
Dramatic REDUCTION
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-preserved immunogenicity-

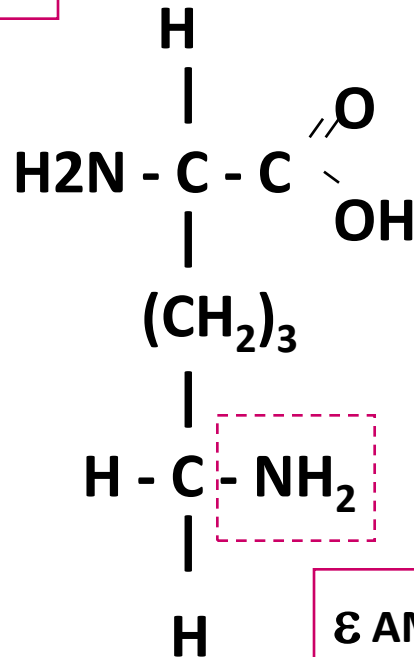
4

RESISTENCE
to enzymatic degradation
-high bioavailability-



NATIVE ALLERGEN

LYSINE:

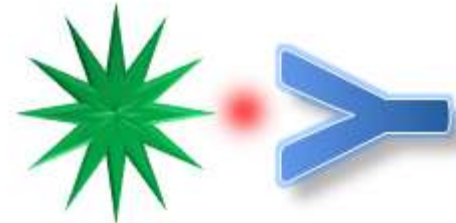


ε AMINIC
GROUP

IgE-binding



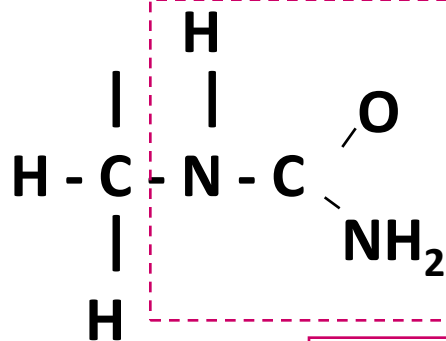
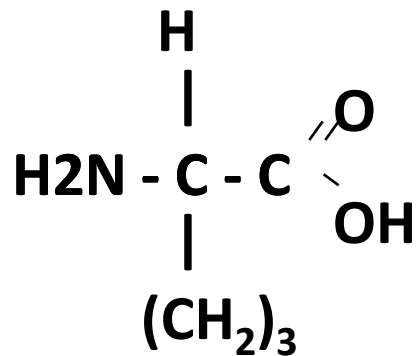
Allergen – Antibody



Side effects

MODIFIED ALLERGEN - LAIS[®]

HOMOCITRULLINE:



UREIDIC
GROUP

NO IgE-binding



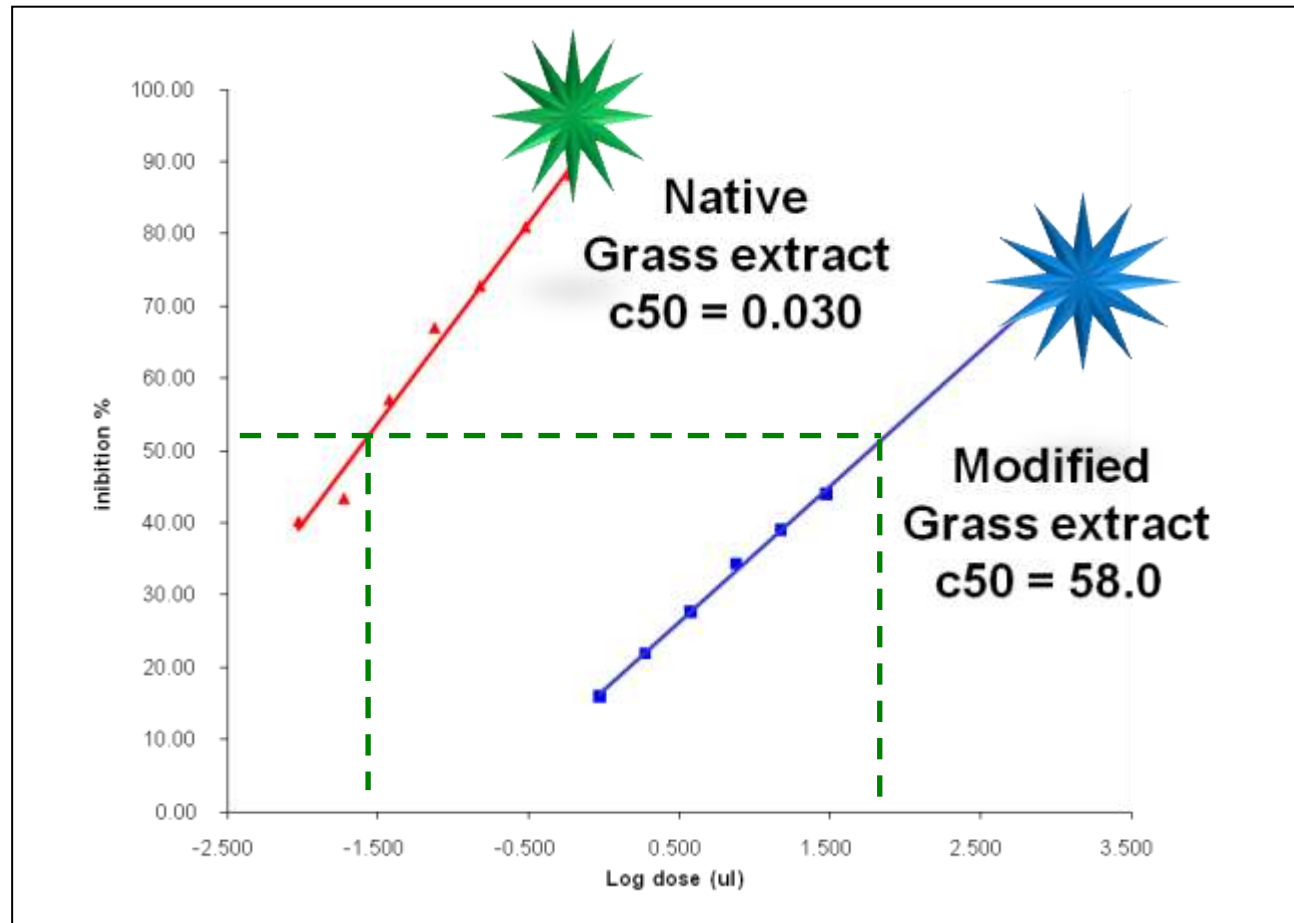
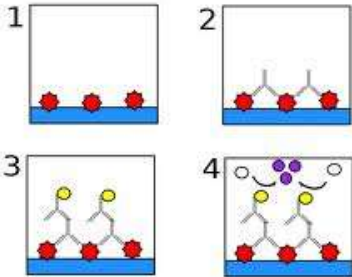
Allergen – Antibody



No Side effects

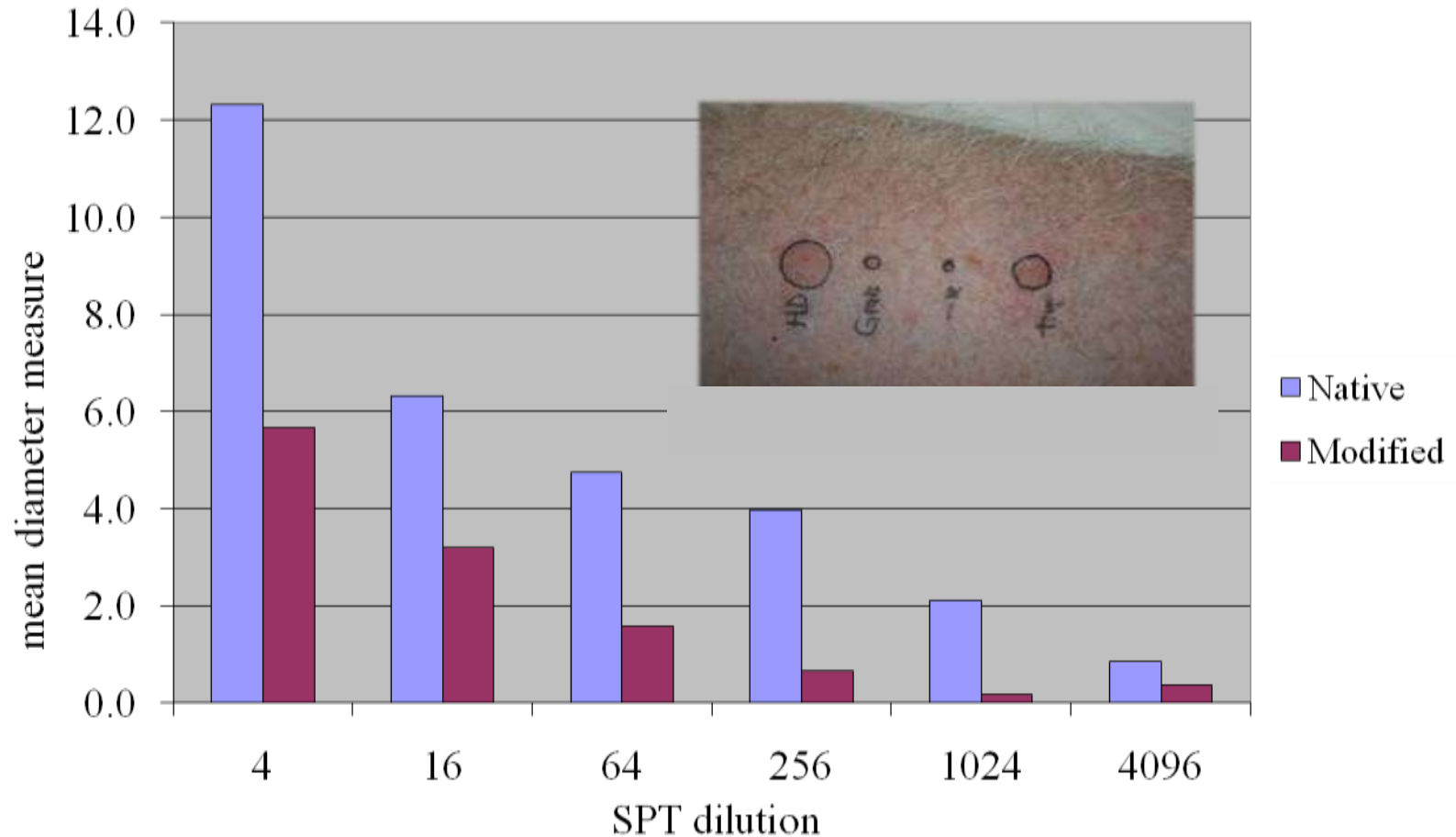


REDUCED REACTIVITY with IgE of LAIS demonstrated *in-vitro* (comparison between native and modified grass extract by EAST-inhibition)



REDUCED REACTIVITY with IgE of LAIS *demonstrated in-vivo*

(comparison between native and modified
grass extract by SPT)



Tolerability from literature



SLIT with
Traditional
allergens

Incidence of side
effects:

Local: **40-70%**

Systemic: **<5%**



SLIT with
LAIS[®]

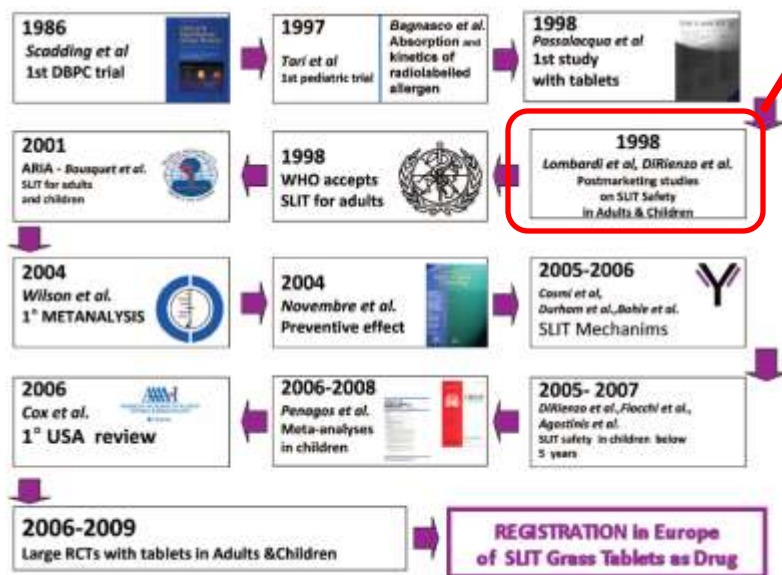
Incidence of side
effects:

Local: **sporadic**

Systemic: **sporadic**

No serious events ever reported

The WORLD ALLERGY ORGANIZATION SLIT position paper 2009



SLIDE 1. History of sublingual immunotherapy.

Safety of SLIT with
monomeric allergoid LAIS® in
adults: multicenter post-
marketing surveillance study



C. Lombardi et al. 2001

198 patients

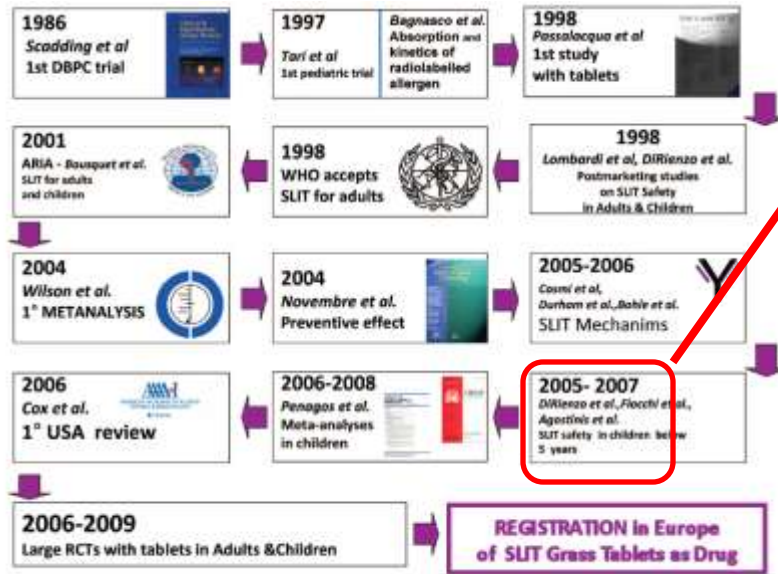
32800 doses

Follow-up : 3 years

Pollen, mites LAIS®

Percentage of Adverse Events : **<7.5%**
(17 episodes – 15 mild, 2 moderate)

The WORLD ALLERGY ORGANIZATION SLIT position paper 2009



SLIDE 1. History of sublingual immunotherapy.

Age range: 1,5 - 3,5 y

Safety of SLIT with a monomeric carbamylated allergoid in very young children

F. Agostinis et al. 2005



33 children

Follow-up : 2 years

Mite (19), grass (17) LAIS®

Aqueous LAIS® drops - Oral intake

Parents's diary card for 22.2 months follow-up

Adverse events: 5% of patients
(0.071 per 1000 doses)

Table I

Immunotherapy protocol of patients treated with 4000 AU of a chemically modified allergen extract (monomeric allergoid). Tablets had to be kept under the tongue for at least two minutes before swallowing

Time (min)	Dose of monomeric allergoid in orosoluble tablets (AU)
0	100
5	300
10	600
15	1,000
20	2,000

AU: allergenic units.

Demographic characteristics of subjects

	Asthma Intermittent/mild persistent		Rhinitis Intermittent/persistent	
	Children (n = 10)	Adults (n = 31)	Children (n = 18)	Adults (n = 46)
Sex, M/F	9/1	17/14	11/7	12/34
Age (\pm SD)	12 \pm 0	34.1 \pm 7.8	13.1 \pm 2.1	35.07 \pm 11.1
HDM positive	3	23	8	22
Parietaria positive	2	7	5	20
Grass positive	5	1	5	4

Data are expressed as mean \pm SD unless otherwise indicated.

Gammeri. Allergologia et Immunopathologia 2005

1 case of stomach upset in 105 patients (0.9%)

**Safety and tolerability
of ultra-rush regimen and high dose**

Carbamylated monomeric allergoid has:

1) SAFETY 

Consequences of chemical modification



1

PRESERVATION
of molecular sizes
-monomericity-

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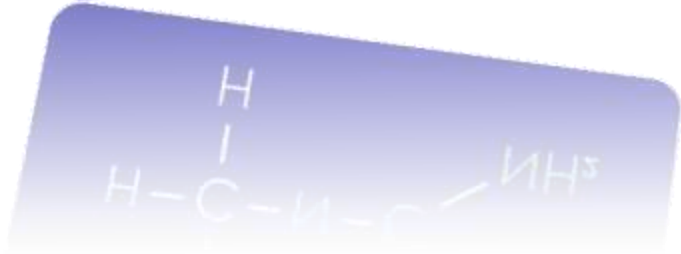
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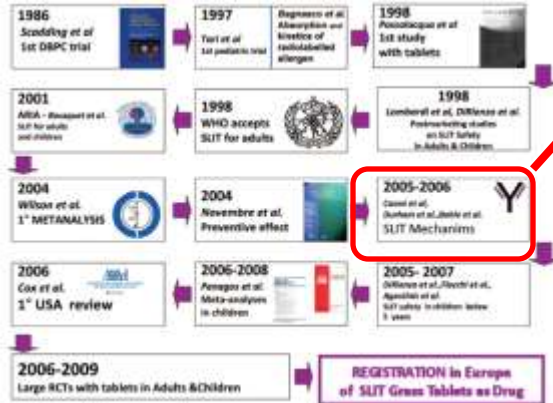
NO
alteration of T-epitopes
-preserved immunogenicity-

4

RESISTENCE
to enzymatic degradation
-high bioavailability-



The WAO SLIT position paper 2009



doi: 10.1111/j.1365-2222

Cosmi - Maggi - Romagnani . Clin Exp Allergy 2006

ORIGINAL PAPER

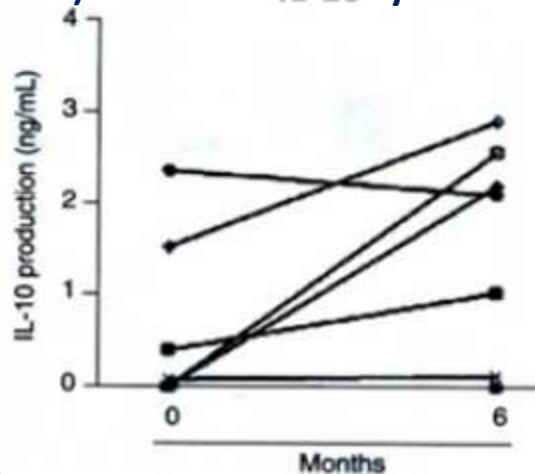
Sublingual immunotherapy with *Dermatophagoides* monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon- γ - and interleukin-10-production

L. Cosmi¹*, V. Santarlasci¹*, R. Angelini¹, F. Liotta¹*, L. Maggi¹*, F. Frosali¹, O. Rossi¹, P. Falagiani¹, G. Riva¹, S. Romagnani¹, F. Annunziato¹ and E. Maggi¹*

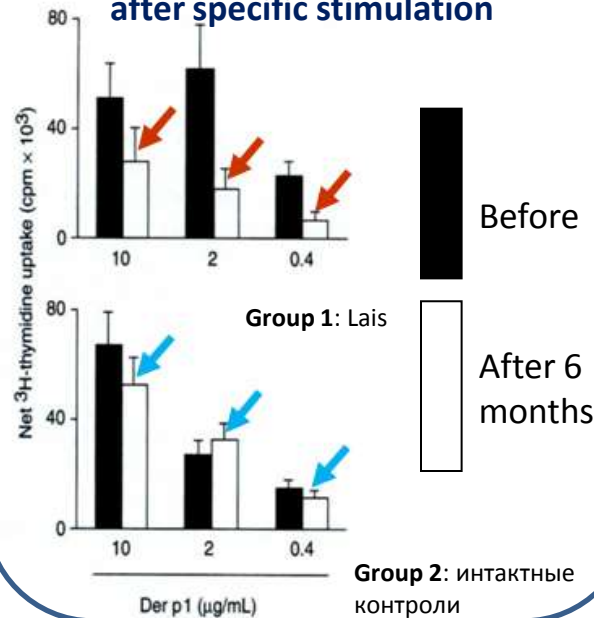
¹Center of Research, Transfer, High Education 'DENOTE', University of Florence, Firenze and ²Loforma Allergeni, SpA, Milano, Italy

SLIDE 1. History of sublingual immunotherapy.

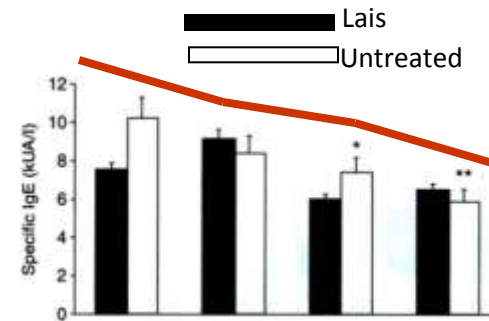
1) increased IL-10 cytokine



2) reduced lymphocytes proliferative capacity after specific stimulation

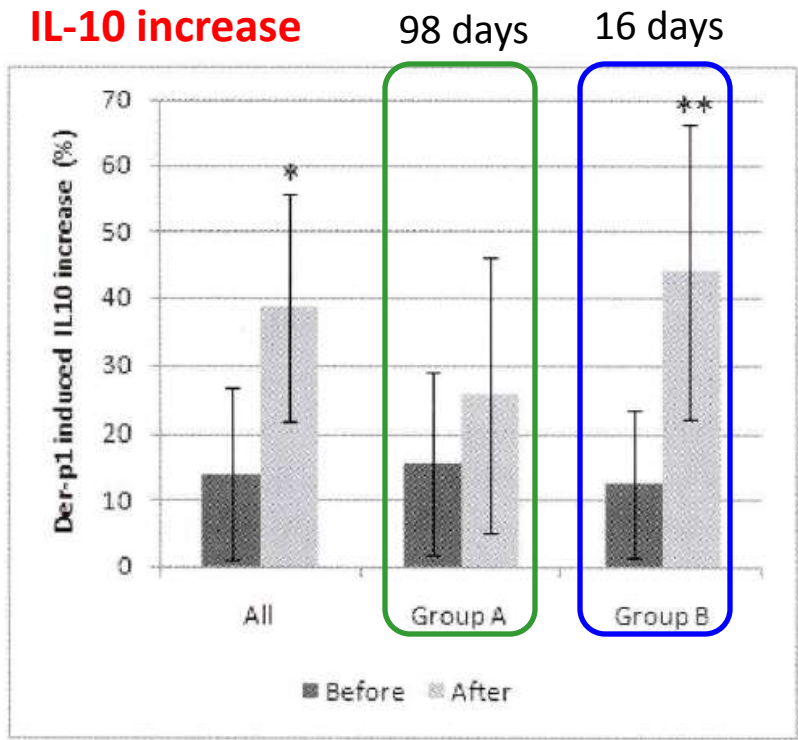
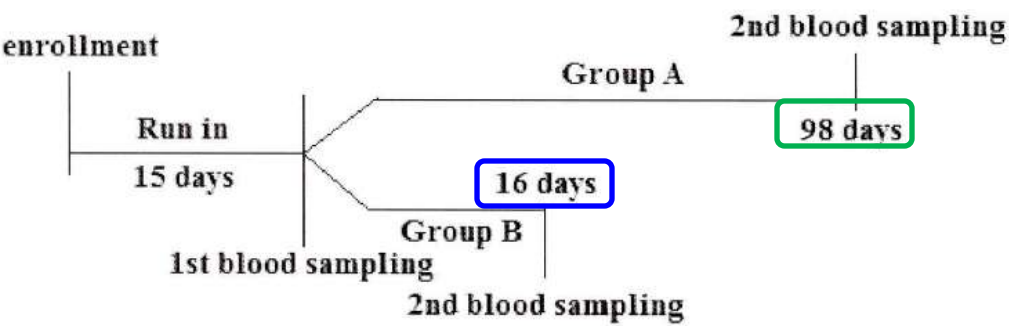


3) No early IgE peak



EARLY CYTOKINE MODULATION AFTER THE RAPID INDUCTION PHASE OF
SUBLINGUAL IMMUNOTHERAPY WITH MITE MONOMERIC ALLERGOIDS

M. DI GIOACCHINO, A. PERRONE, C. PETRARCA, F. DI CLAUDIO,
G. MISTRELLO¹, P. FALAGIANI¹, V. DADORANTE², N. VERNA, M. BRAGA³,
E. BALLONE⁴ and E. CAVALLUCCI



F. AGOSTINIS¹, C. FOGLIA¹, M.E. BRUNO², P. FALAGIANI²

Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen



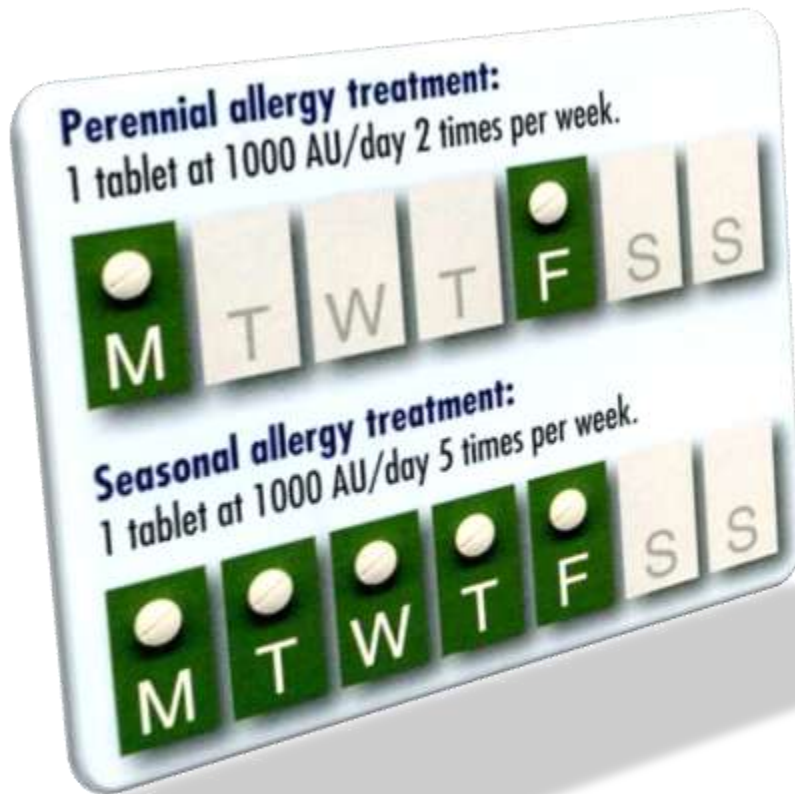
¹ Pediatric Division, Ospedali Riuniti, Bergamo; ² Scientific Direction, Lofarma S.p.A., Milano

- prospective, open-label, randomized study
- 1000 AU five times a week without any up-dosing Vs pharmacotherapy
- pre/co-seasonally for 12 weeks/year for 2 consecutive years.
- 40 allergic children (16 with rhinitis and 24 with rhinitis and asthma)
- range 4-16 years

no systemic , no local adverse events



Carbamylated monomeric allergoid: doses & schedule



Grass

Holcus lanatus, Phleum pratense, Poa pratensis

Pellitory

Parietaria judaica , Parietaria officinalis

Ragweed

Ambrosia artemisiifolia

Olive

Olea europea

Birch

Alnus incana, Betula pendula

Mugwort

Artemisia vulgaris

Cat

Felis domesticus

Mites

Dermatophagoides p, Der f

Dosages

300 -1,000 Allergenic Units (AU)/tablet.

Double-blind, placebo-controlled randomized studies

Passalacqua 1998	Mites	adults	2 years	↓ symptoms/EOS/ICAM1
Caffarelli 2000	Grass	kids	1 season	↓ symptoms/drugs
Passalacqua 2006	Mites	adults	3 years	↓ symptoms/drugs
Palma-Carlos 2006	Grass	adults	2 years	↓ symptoms/drugs
Ariano 1998	Pellitory	adults	2 years	↓ symptoms/drugs
Mezei 1996	Ragweed	adults+kids	1 season	↓ symptoms/drugs
Bordignon 1994	Grass	adults	1+2 years	↓ symptoms/drugs
Cavagni 1996	Grass	kids	1+1 years	↓ symptoms/drugs



SYSTEMATIC REVIEW

Carbamylated monomeric allergoids as a therapeutic option for sublingual immunotherapy of dust mite- and grass pollen-induced allergic rhinoconjunctivitis: a systematic review of published trials with a meta-analysis of treatment using Lais[®] tablets

R. Mösges, B. Ritter, G. Kayoko, and S. Allekotte

Grass Vs placebo:

Difference: -34% in symptoms reduction

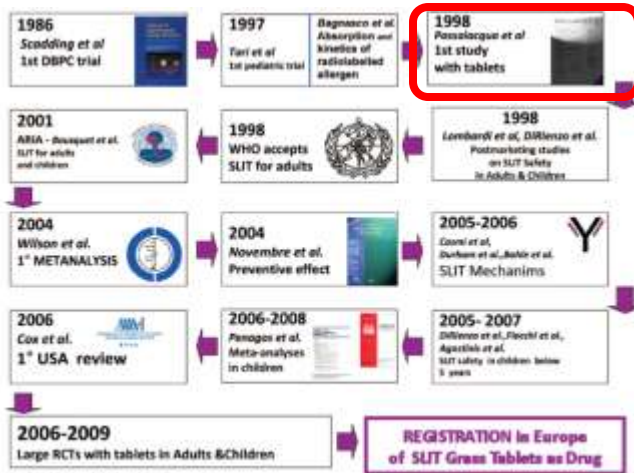
Difference: -48% in medication use reduction

Mites Vs placebo:

Difference: -22% in symptoms reduction

Difference: -24% in medication use reduction

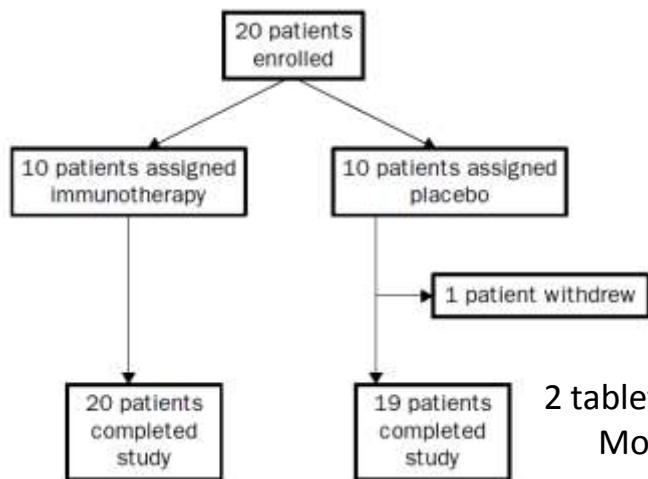
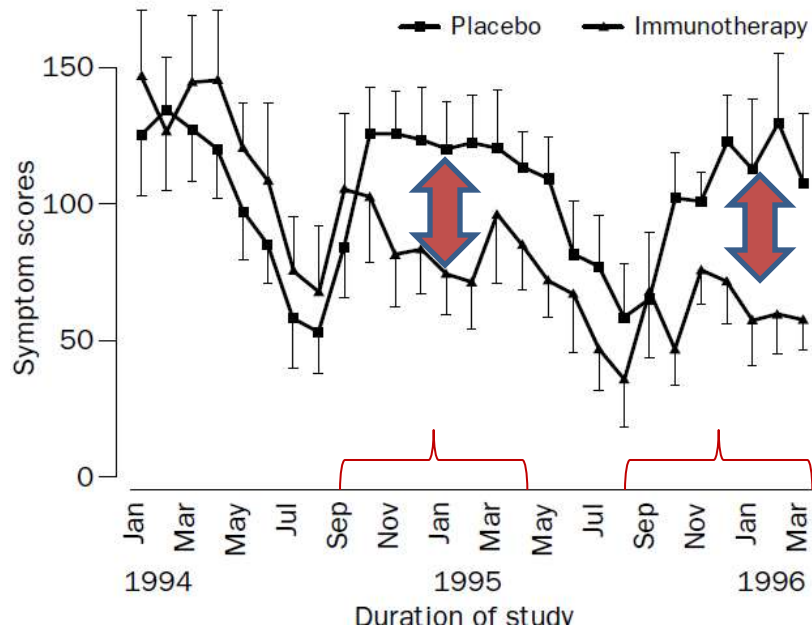
The WAO SLIT position paper 2009



Double-blind randomized placebo-controlled trial (DB PC RCT) with **TABLET**

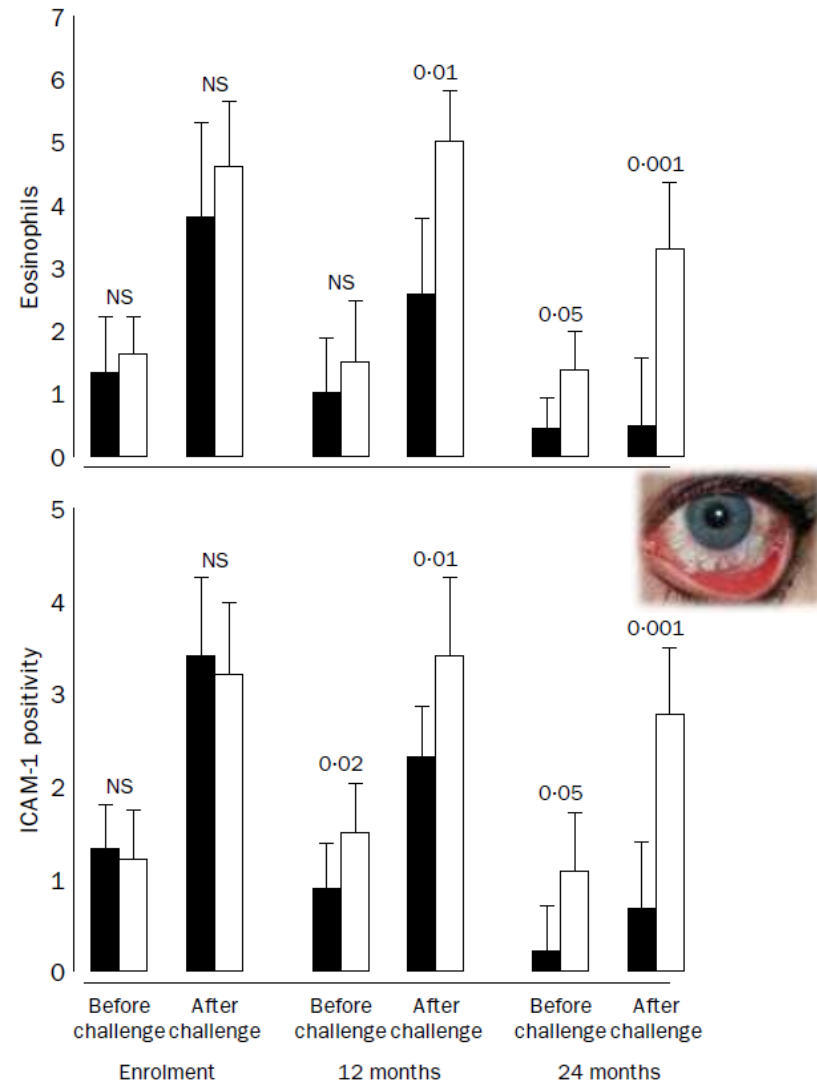
Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis

Giovanni Passalacqua, Monica Albano, Laura Fregonese, Annamaria Riccio, Caterina Pronzato, Giuseppe Sandro Mela, Giorgio Walter Canonica



2 tablet 1000AU x 2 / week
 Monosensitized patients
 2 years of study

Conjunctival provocation Test



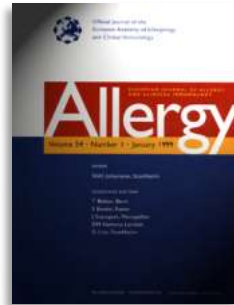
Passalacqua. Lancet 1998

Original article

Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial

C. Caffarelli

Pediatric Department, Parma



Allergy. 2000;
55(12):1142-7.

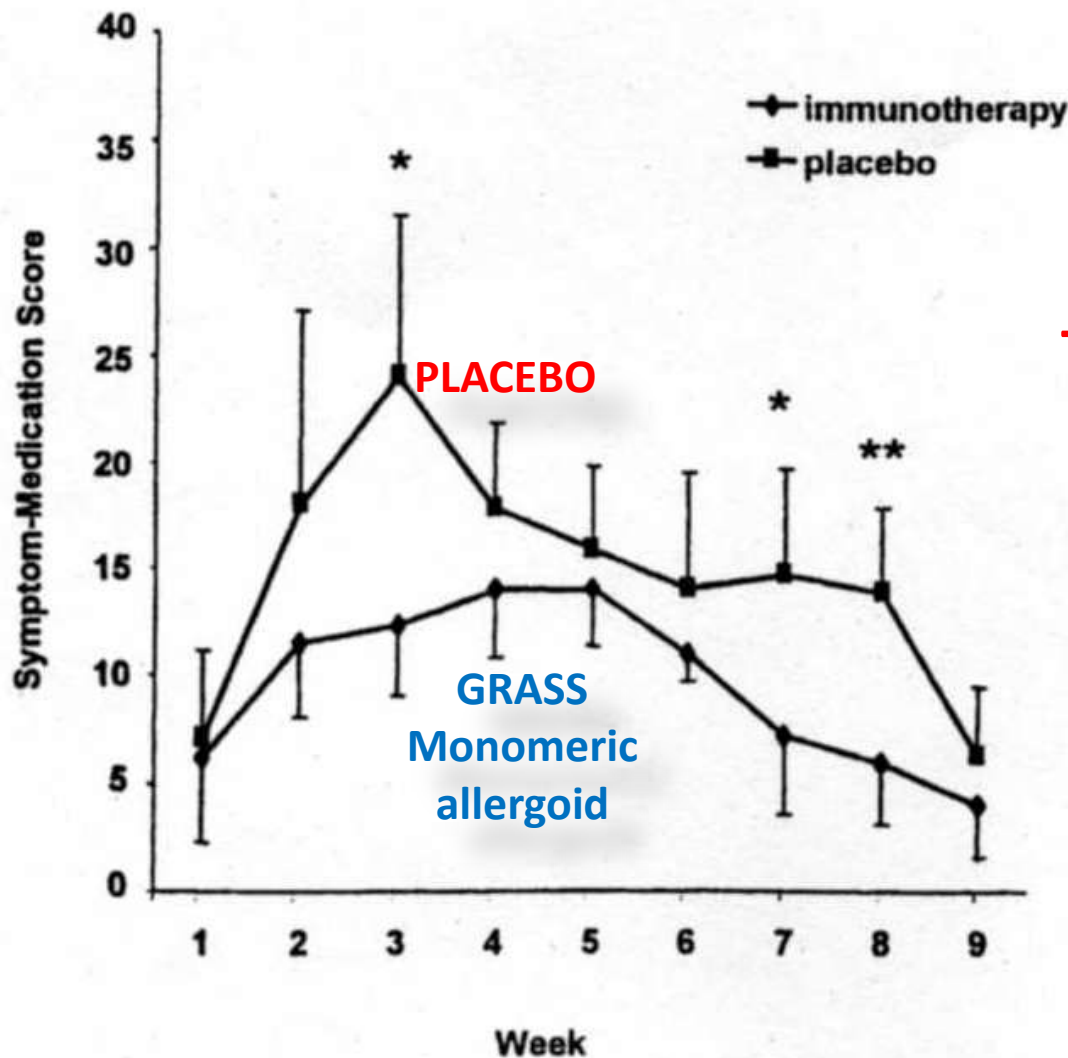


DB PC RCT
with tablets *in children*

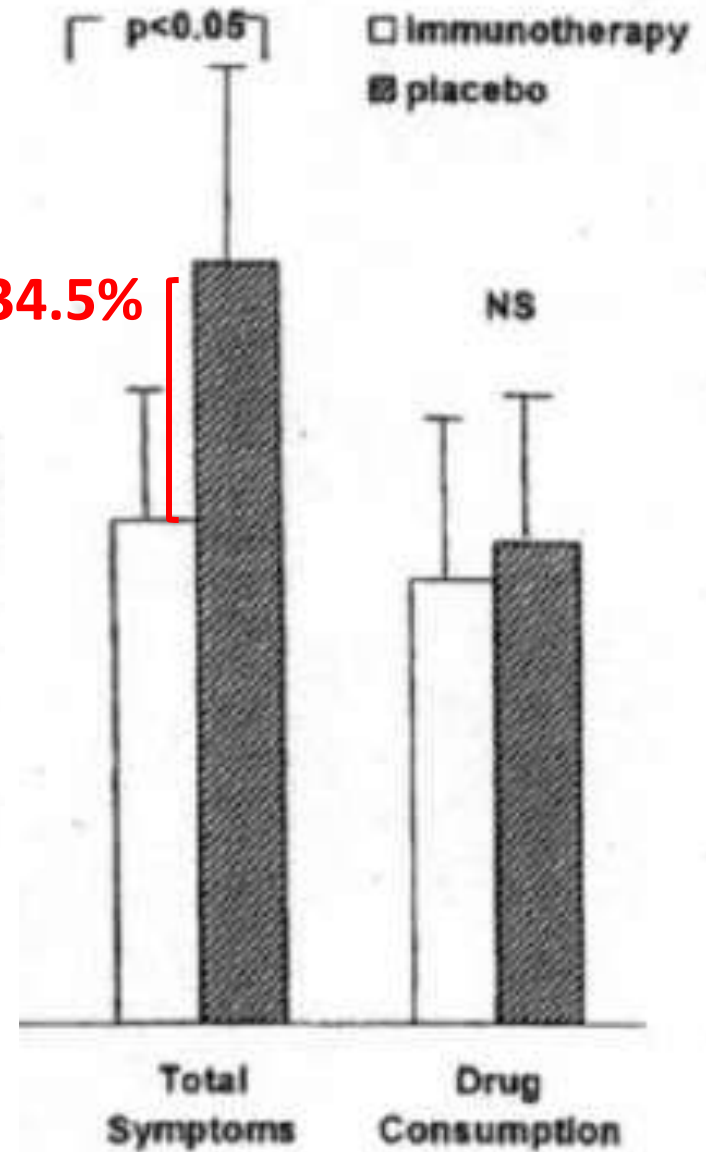
44 subjects with asthma/rhinitis/conjunctivitis

Pre-seasonal grass pollen tablet (3 months)





-34.5%



Symptoms + medications

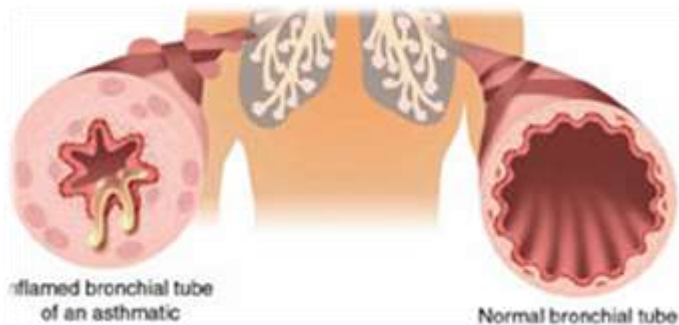
Caffarelli. Allergy 2000

Controlled Study of Preseasonal Immunotherapy with Grass Pollen Extract in Tablets: Effect on Bronchial Hyperreactivity



Table 2. PD20 (μg) at the MCh test in the two groups at baseline and after 3 years

Patients	IT group		Controls	
	Before	After	Before	After
1	450	750	300	450
2	600	1200	450	600
3	750	900	600	600
4	1200	1800	1200	1200
5	1500	1800	450	450
6	450	900	900	750
7	300	450	900	600
8	450	450	450	1500
9	600	1200	600	1800
10	750	1500	450	600
11	1200	1800	600	750
12	1200	900	750	750
13	1350	1800	1200	1200
14	1500	1800	1500	1800
15	450	750	450	450
16	600	1200	600	750
17	750	1200	1500	1800
18	900	900	1200	1200
19	1200	1500		
20	750	950		
Mean	848	1188	800	958
SD	381	454	368	488
P (t test)	.01		NS	



Lombardi et al. JIACI 1999

Carbamylated monomeric allergoid has:

1) SAFETY ✓

2) EFFICACY ✓

Long lasting effect

International Archives of
**Allergy and
Immunology**

Int Arch Allergy Immunol. **2007**;142(1):70-8.



Long-Lasting Effects of Sublingual Immunotherapy for House Dust Mites in Allergic Rhinitis with Bronchial Hyperreactivity: A Long-Term (13-Year) Retrospective Study in Real Life

Maurizio Marogna^a Marco Bruno^b Alessandro Massolo^c Paolo Falagiani^b

4 years

7-8 years

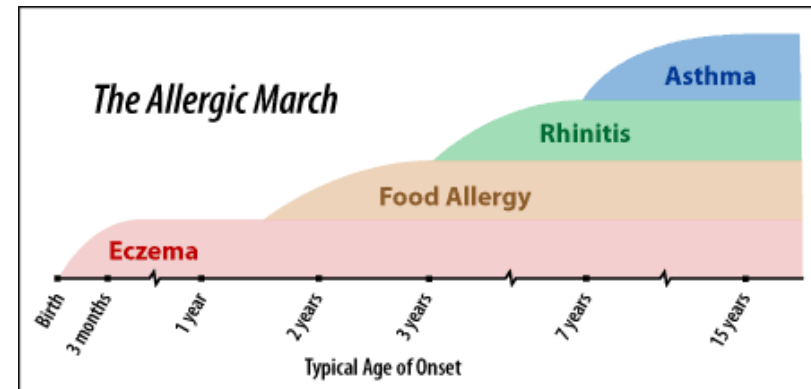
Prevention asthma & new sensitizations

Sublingual immunotherapy in the context of a clinical practice improvement program in the allergological setting: results of a long-term observational study.

Marogna M, Massolo A.

Eur Ann Allergy Clin Immunol. 2003 Apr;35(4):133-40.

From	to	SLIT		CONTROL		χ^2	df	p value (two tailed)
		n	%	n	%			
RHINITIS	N	48	100.0	33	51.5	32.148	1	$p < 0.001$
	H	0	0.0	14	21.9	12.000	1	$p = 0.001$
	A	0	0.0	17	26.6	15.132	1	$p < 0.001$
	Sub-total	48	100	64	100	-	-	-
HYPER-REACTIVITY	N	19	85.4	23	45.1	10.712	1	$p = 0.002$
	H	2	9.1	18	35.3	5.305	1	NS ($p = 0.024$)
	A	1	4.5	10	19.6	2.725	1	NS ($p = 0.156$)
	Sub-total	22	100	51	100	-	-	-
ASTHMA	N	28	77.8	19	34.6	16.284	1	$p < 0.001$
	H	4	11.1	12	21.8	1.721	1	NS ($p = 0.263$)
	A	4	11.1	24	43.6	10.806	1	$p = 0.001$
	Sub-total	36	100	55	100	-	-	-



After 36 months treatment

BASELINE	n	New sensitisations		χ^2	df	p value (two tailed)
		n	%			
SLIT	106	3	2.8	47.021	2	$p < 0.001$
CONTROL	170	64	37.6			

Carbamylated monomeric allergoid has:

1) SAFETY ✓

2) EFFICACY ✓

3) PREVENTIVE EFFECTS ✓

Consequences of chemical modification



1

PRESERVATION
of molecular sizes
-monomericity-

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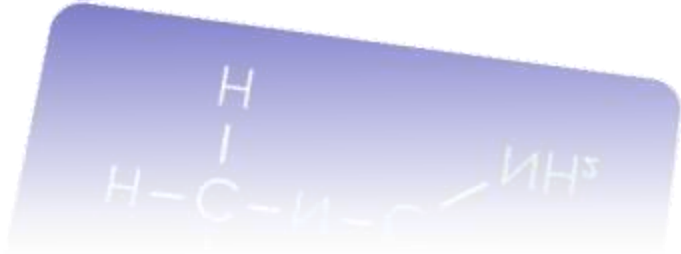
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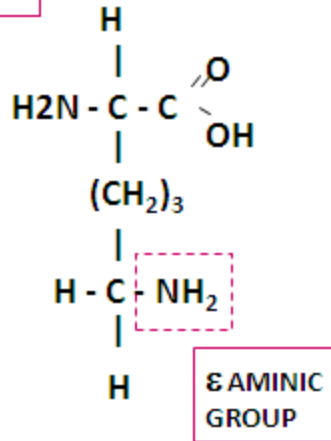
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to enzymatic degradation
-high bioavailability-



NATIVE ALLERGEN

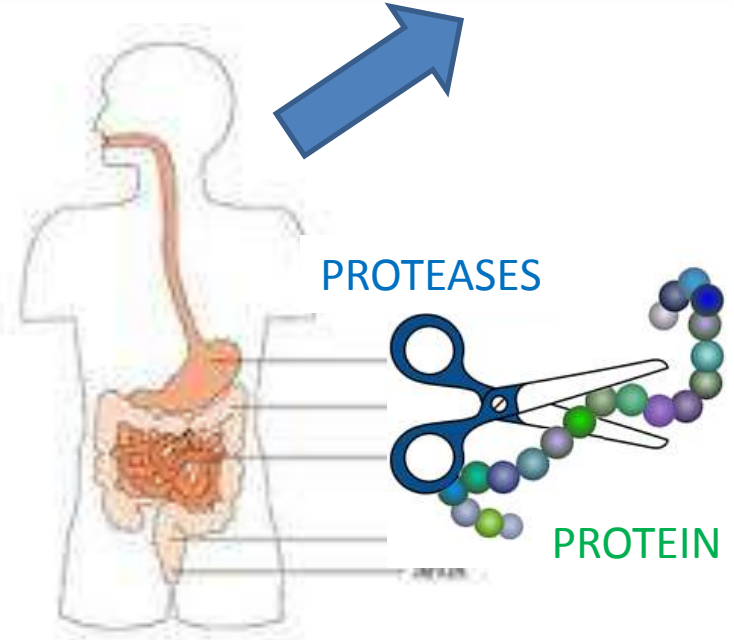


LYSINE:



Enzymatic degradation

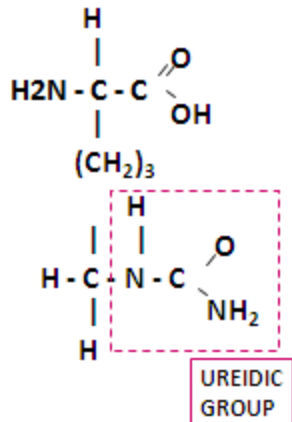
Reduced bioavailability
High doses needed



MODIFIED ALLERGEN - LAIS®



HOMOCITRULLINE:



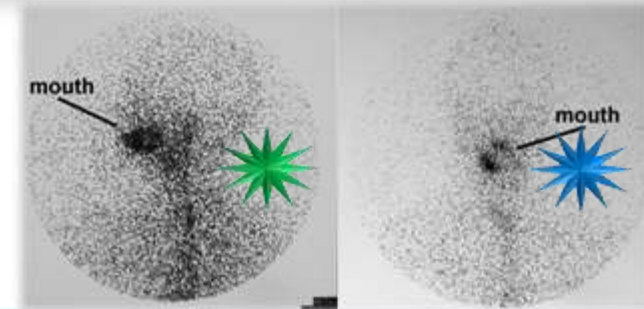
NO Enzymatic degradation

High bioavailability
Efficient dose



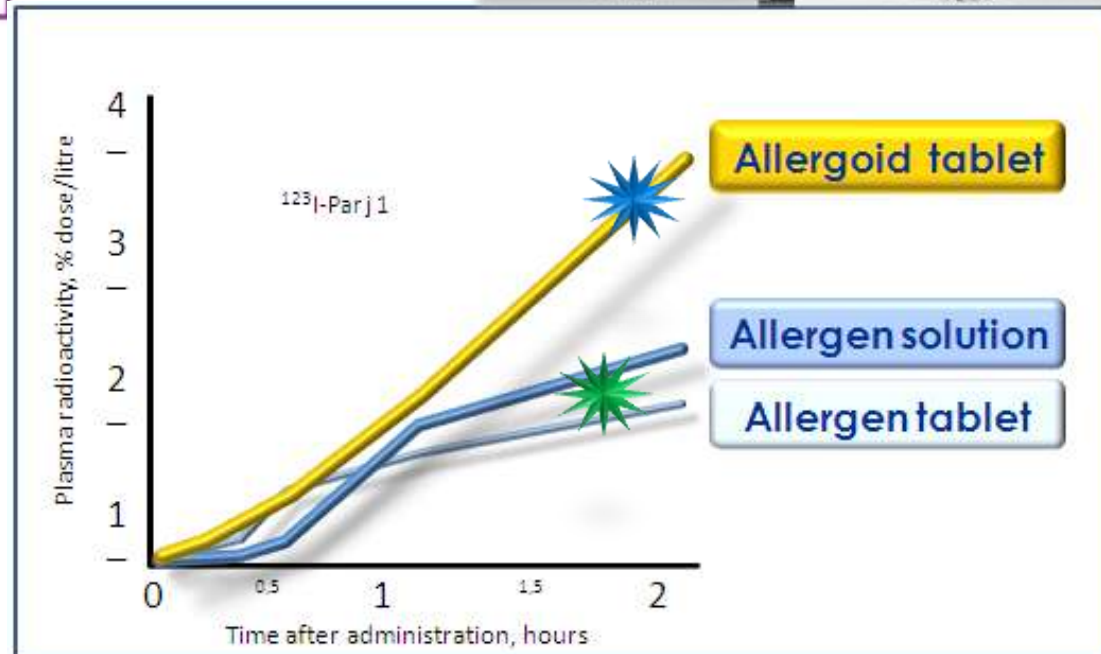
Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers.

Bagnasco M, Passalacqua G, Villa G, Augeri C, Flamigni G, Borini E, Falagiani P, Mistrello G, Canonica GW, Mariani G. Allergy and Clinical Immunology, Department of Internal Medicine, Genoa, Italy.
Comment in: *Clin Exp Allergy*. 2001 Jan;31(1):8-10.



WAO SLIT POSITION PAPER

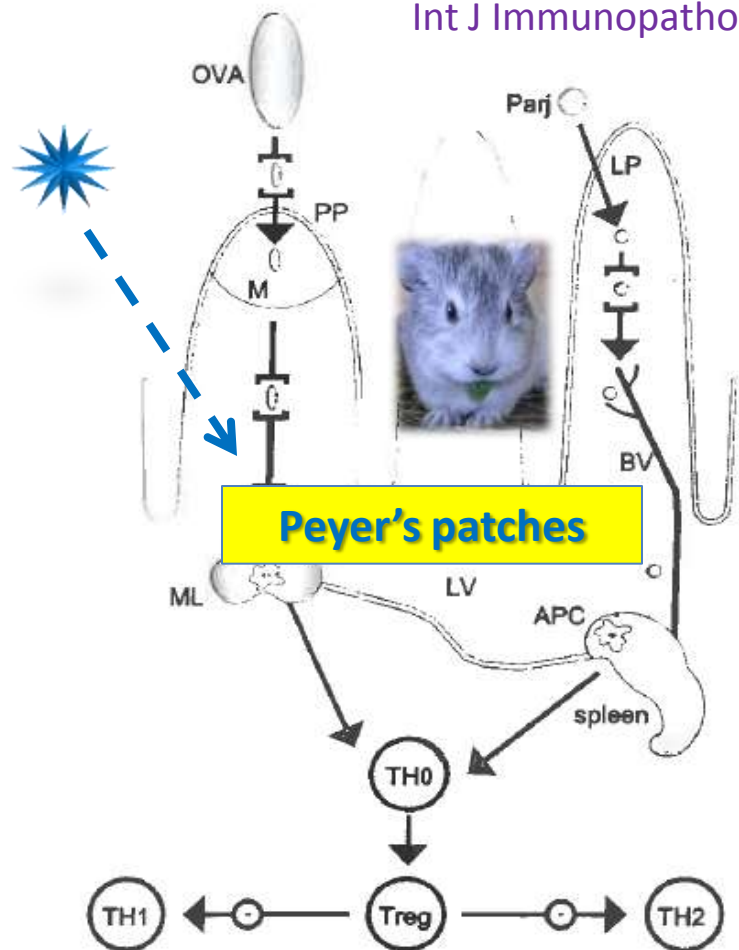
Increased biodistribution



MONOMERIC ALLERGOID INTRAGASTRIC ADMINISTRATION INDUCES LOCAL AND SYSTEMIC TOLEROGENIC RESPONSE INVOLVING IL-10-PRODUCING CD4⁺CD25⁺ T REGULATORY CELLS IN MICE

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Int J Immunopathol Pharmacol. 2010; 23 (4): 1021-1031.



Lais[®]: Systemic effects:

Serum
PBMC

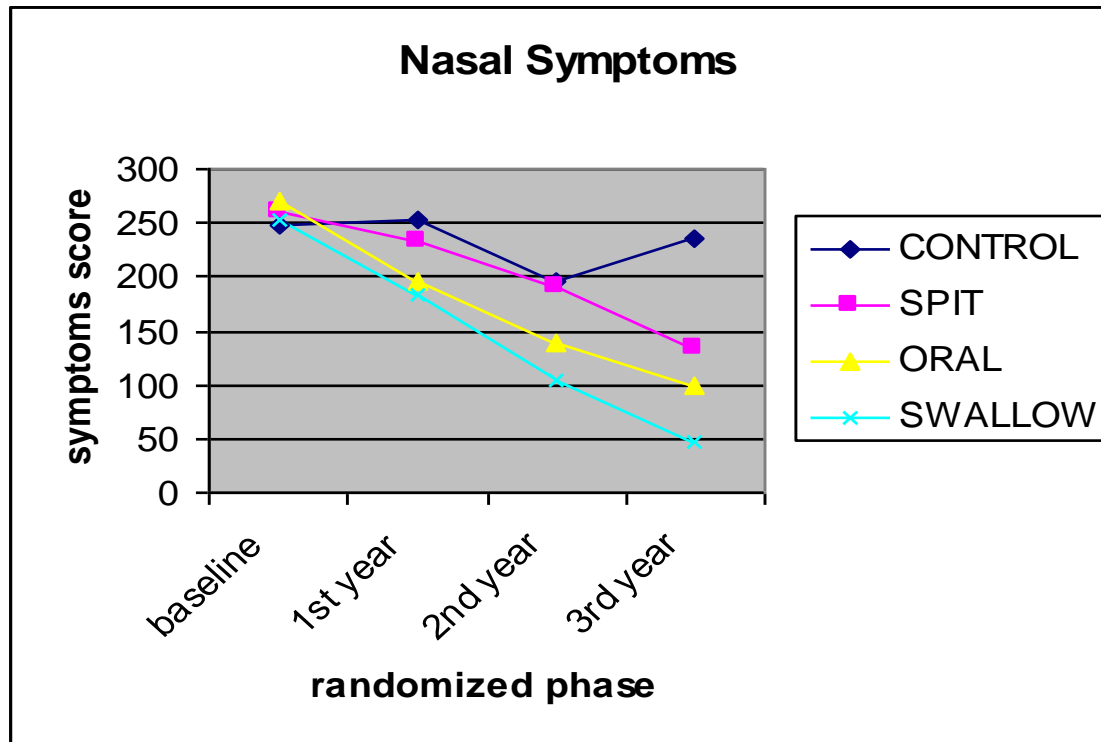
IgE
IL4

Peyers'

CD4+CD25+ T reg



Monomeric allergoid: oral ingestion provides clinical effects



Prospective
randomized open
controlled study
HDM – monomeric
allergoid (1000 AU
tw/w)
87 adults with
AR±AA
september-
february
assessment

Absorption:

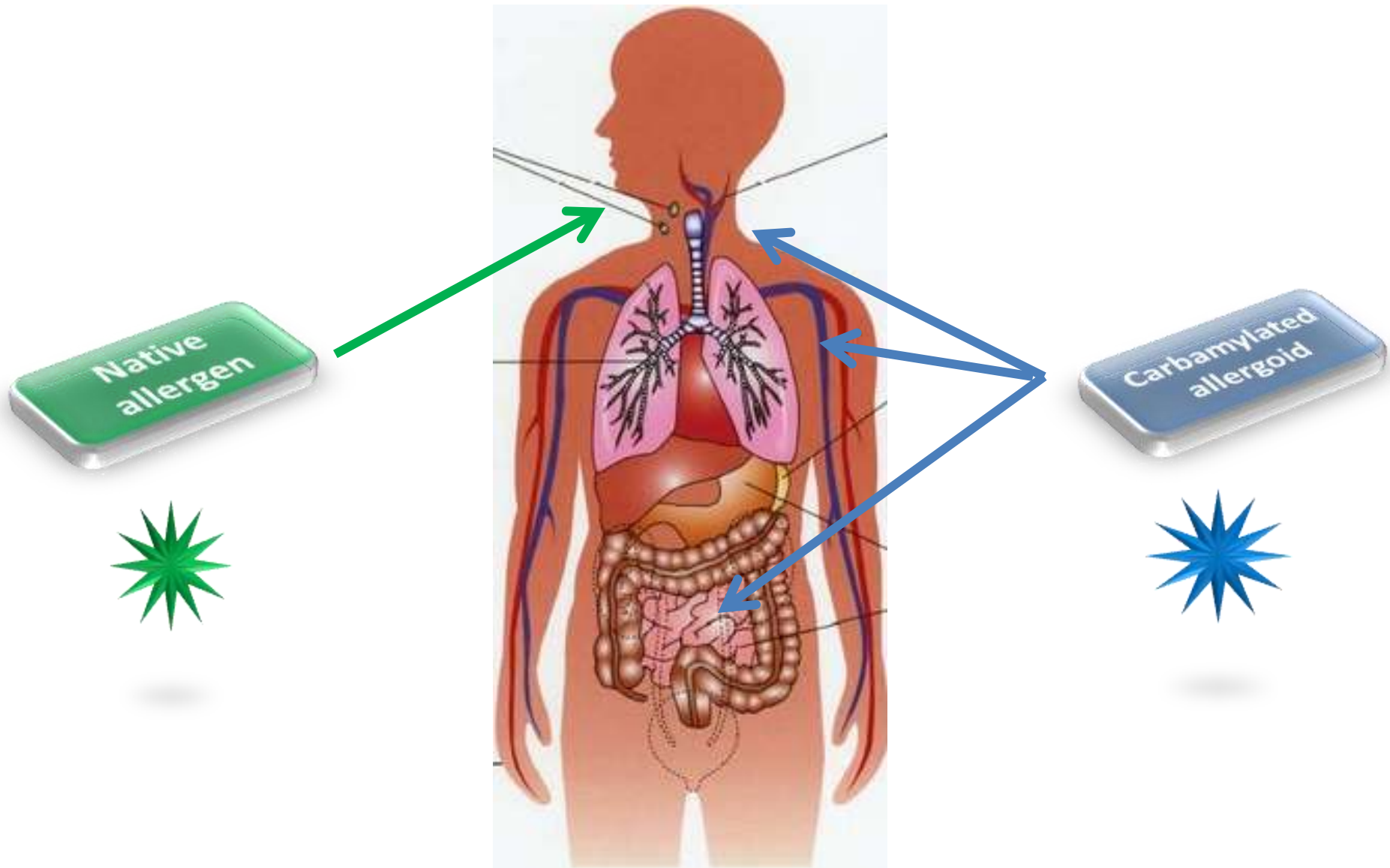
Oromucosal

Enteric

Oromucosal + enteric

Marogna et al. EAACI 2013

Biologically active dose



Carbamylated monomeric allergoid has:

1) SAFETY ✓

2) EFFICACY ✓

3) PREVENTIVE EFFECTS ✓

4) EFFICIENCY ✓

EFFECTIVENESS IN REAL LIFE



SAFETY



**EFFICACY/
PREVENTION**



EFFICIENCY



...to center the target

Thank you

SUMMARY:

Carbamylated monomeric allergoid
(Lais[®])

1. preserved molecular size = sublingual
2. reduced allergenic activity = well tolerated
3. retained immunological activity = effective
4. High bioavailability = high efficient dose



Milan, Italy