Immunoterapia specifica: alla ricerca del dosaggio ottimale

XXX CONGRESSO NAZIONALE

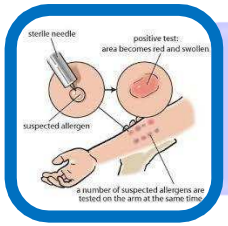
SIAAIC

Società Italiana di Allergologia, Asma ed Immunologia Clinica

FIRENZE 6/9 APRILE 2017 | WWW.SIAAIC2017.ORG

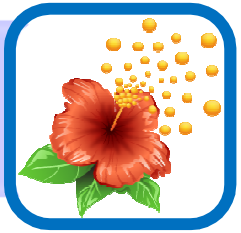
STALLERGENES GREER

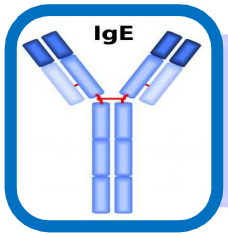
SE AVESSIMO UN PAZIENTE IDEALE...



Monosensibile

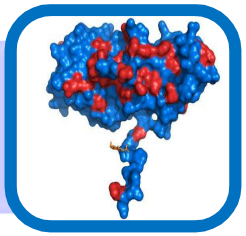
Con chiara manifestazione di sintomi dopo esposizione all'allergene causale

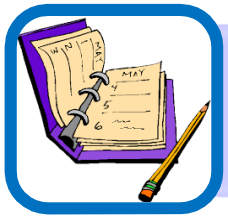




Con conferma di SPT positivo e livelli di IgE specifiche

Con IgE per allergeni maggiori





Compliante e preciso nella compilazione di un diario

In linea con criteri inclusione/esclusione AIT

…sarebbe facile prescrivere AIT?

QUALE AIT?

Efficace e sicura per il paziente

Via di somministrazione ideale per il paziente

Sostenibile e accessibile

Elevata qualità dell'estratto

QUALITY IS THE TRUE ESSENCE

PER LA PRODUZIONE BIOLOGICA IL PRODOTTO È IL PROCESSO

- COME FARMACI BIOLOGICI, LA PRODUZIONE DEGLI ALLERGENI È INTRINSECAMENTE IMPEGNATIVA E COMPLESSA RISPETTO AI FARMACI CHIMICI TRADIZIONALI[1]

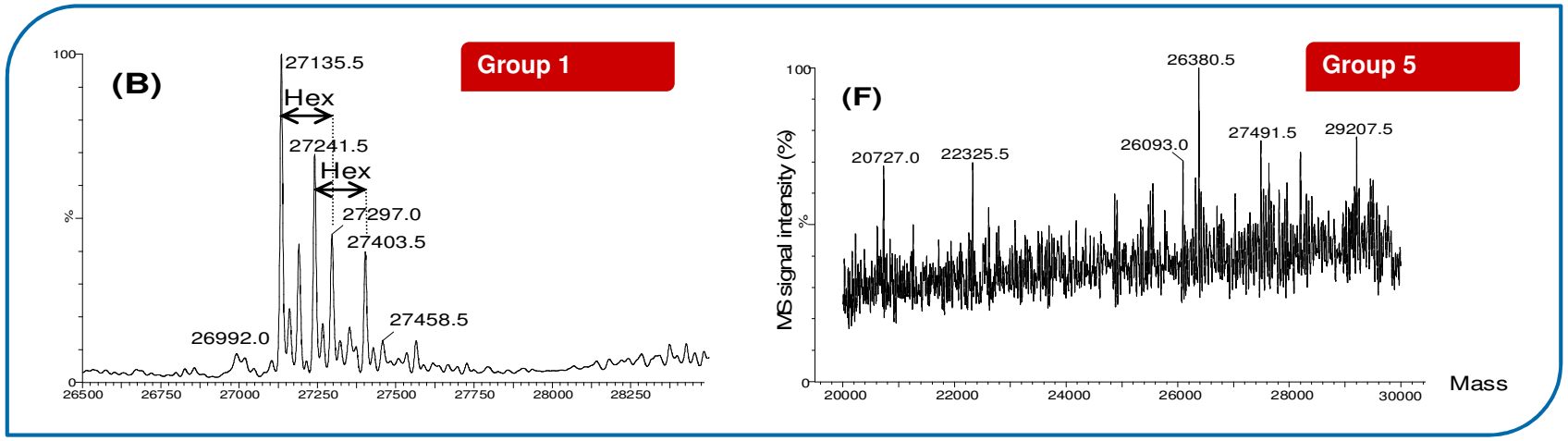
- I MEDICINALI BIOLOGICI SONO CARATTERIZZATI DA UNA VARIABILITÀ INTRINSECA[1]

FARMACI CHIMICI[1]	FARMACI BIOLOGICI[1]
• Prodotti per sintesi chimica = strutture chimiche **ben definite**	• Prodotti in un **sistema vivente**
• In larga parte **indipendenti dai processi**	• Solitamente **molecole** molto **grandi e complesse** o mix eterogenei di molecole
• Solitamente possono essere analizzati per determinare i loro vari componenti	• **Fortemente dipendenti dal processo.** Anche cambiamenti minimi nel processo produttivo possono comportare cambiamenti significativi nell'efficacia o nell'immunogenicità
• Legame diretto tra il peso e l'attività	• **Difficili da caratterizzare e da controllare dalla materia prima al principio attivo finale**
• **1 prodotto = 1 farmaco = 1 struttura chimica**	

1. Declerk PJ. Biologicals and biosimilars: a review of the science and its implications. GaBI J 2012;1:13-6.

THE INTRINSIC VARIABILITY OF ALLERGENS

MASS SPECTROMETRY-BASED ANALYSES OF GRASS POLLEN ALLERGENS



- **Numbers of main isoforms:**
  - → Group 1 (grass) 5-10
  - → Group 5 (grass) 30-50
  - → Bet v 1: 27
  - → Der p 1: 24
  - → Der p 2: 15
  - → Der f 1: 10
  - → Der f 2: 17

As components of living organisms, allergens consist in heterogeneous mixtures of molecules (in contrast to chemical drugs)

PRODUCTS FOR ALLERGY IMMUNOTHERAPY: A COMPLEX DEVELOPMENT

PRODUCT DESIGN

Documented scientific rationale

MANUFACTURING PROCESS DEV.

Raw materials → Drug substance → Drug product

- Allergen extraction, purification, formulation, yield cost, robustness, scaling up

PRODUCT CHARACTERIZATION

Raw materials → Drug substance → Drug product

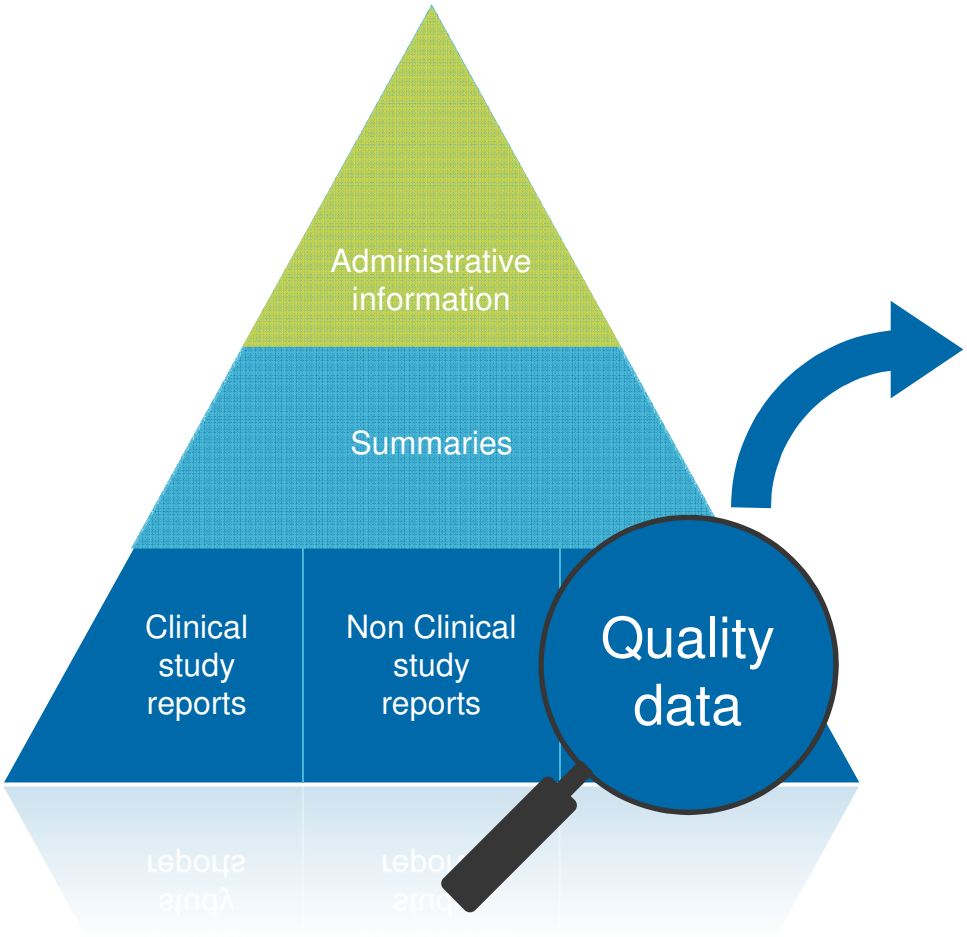
- Development and implementation of analytical methods for identity, purity, consistency, stability

CLINICAL DEVELOPMENT

Preclinical → Phase I → Phase II → Phase III

- Safety, dosing, efficacy

COMMON TECHNICAL DOCUMENT



- **Manufacturing process** (development, validation, critical steps)
- **Control and characterization** (specifications, analytical methods, batch analysis, impurities)
- **Reference standards**
- **Container closure system**
- **Stability studies**

WELL CONTROLLED SOURCE MATERIALS

Pollen harvesting machine

- Harvesting and processing of pollens from cultured grasses

Synthetic culture medium of mites

- Development of a synthetic cultured medium free from proteins of animal origin (Stalmite™)

Batard *et al.* Allergy, 2016;71:220

TERRENO DI COLTURA DI GRADO FARMACEUTICO

2013

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2013;161:285–286
DOI: 10.1159/000347045

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Accepted after revision: January 10, 2013
Published online: March 15, 2013

Quality Control of House Dust Mite Extracts for Allergen Immunotherapy

Philippe Moingeon[a] Thierry Batard[a] Emmanuel Nony[a] Maud Hrabina[a] Franco Frati[b]

[a]Stallergènes SA, Antony, France; [b]Stallergenes, Milan, Italy

To ensure extract consistency, source materials are obtained from cultures of each of the two mite species in a well-controlled medium combining wheat germ, yeast and synthetic amino acids (the latter in proportions which recapitulate the composition of the human stratum corneum) [6]. Those culture conditions have been rigorously established for each of the mite species to support optimal growth as well as high allergenic activity and major allergen content [6]. Our source materials are

QUALITY CONTROL ALL ALONG THE MANUFACTURING CHAIN

Robust manufacturing process

- **Source materials**

- **Drug products**

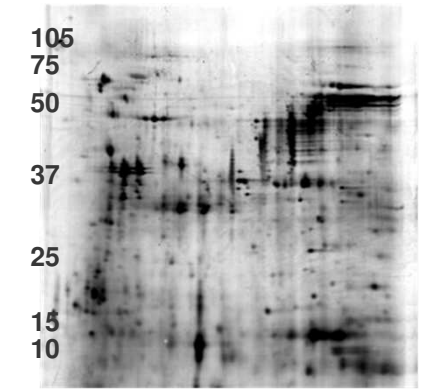
Extraction, concentration, purification, freeze drying

QUALITY CONTROL

→ Allergenic activity
→ Major allergen content
→ Presence of minor allergens
→ Protein profile
→ Stability studies

Formulation, packaging

ALLERGEN EXTRACTS
(DRUG SUBSTANCES)

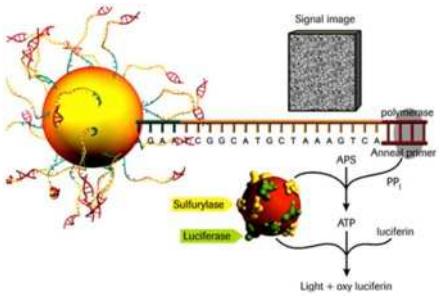


STALLERGENES GREER™

COMPREHENSIVE CHARACTERIZATION OF ALLERGEN EXTRACTS USING STATE OF THE ART TECHNOLOGIES (OMICS)

TRANSCRIPTOME

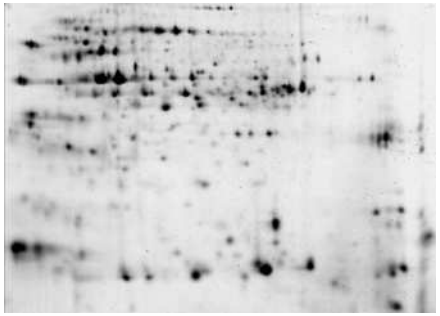
de *novo* sequencing



+

PROTEOME

MS analyses



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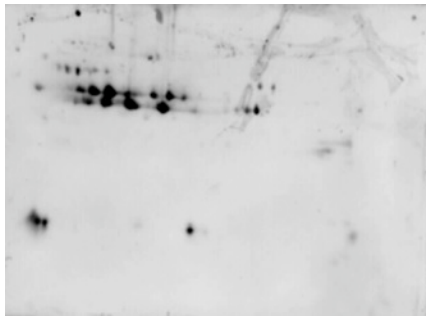
ALLERGOME

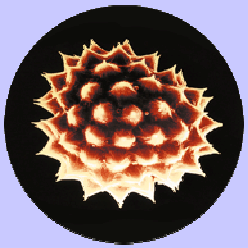
IgE reactivities



- **OUTPUTS:**
  - → 2D proteome/allergome maps
  - → Comprehensive characterization of allergenic extracts

House dust mites

→ Confirmation of the presence of all known allergen groups



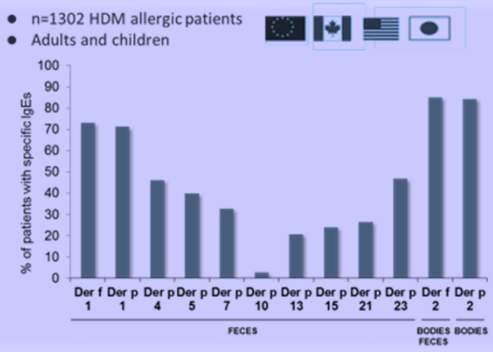
Ragweed

→ **Amb a 11** identified as a new major allergen

- Batard T. *et al.* (2016). Allergy *71*, 220-229.
- Bouley J. *et al.* (2015). J Allergy Clin Immunol *136*, 1055-1064
- Groeme R. *et al.* (2016). J Biol Chem. 10.1074/jbc.M115.702001
- Bordas-Le Floch V. *et al.* (2015). PLoS One *10*, e0136258

THE RIGHT PRODUCT FOR THE RIGHT PATIENT

- **Patient characterization**



→ e.g. HDM allergic patients are sensitized to allergens present in both bodies and feces

Batard *et al.* Allergy, 2016;71:220

- **Product characterization**

→ All mite allergens listed by IUIS are present in HDM extracts

QUALI GRAMINACEE

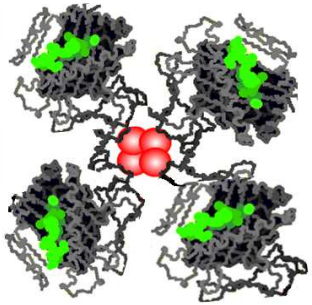
Grass-specific CD4$^+$ T-cells exhibit varying degrees of cross-reactivity, implications for allergen-specific immunotherapy

L. D. Archila[1], J. H. DeLong[1], E. Wambre[1], E. A. James[1], D. M. Robinson[2] and W. W. Kwok[1,3]

[1]Benaroya Research Institute at Virginia Mason, Seattle, WA, USA, [2]Virginia Mason Medical Center, Seattle, WA, USA and [3]Department of Medicine, University of Washington, Seattle, WA, USA

The reorientation of grass pollen-specific CD4+ T cells from a Th2 to a Th1/T Reg profile is central to AIT efficacy

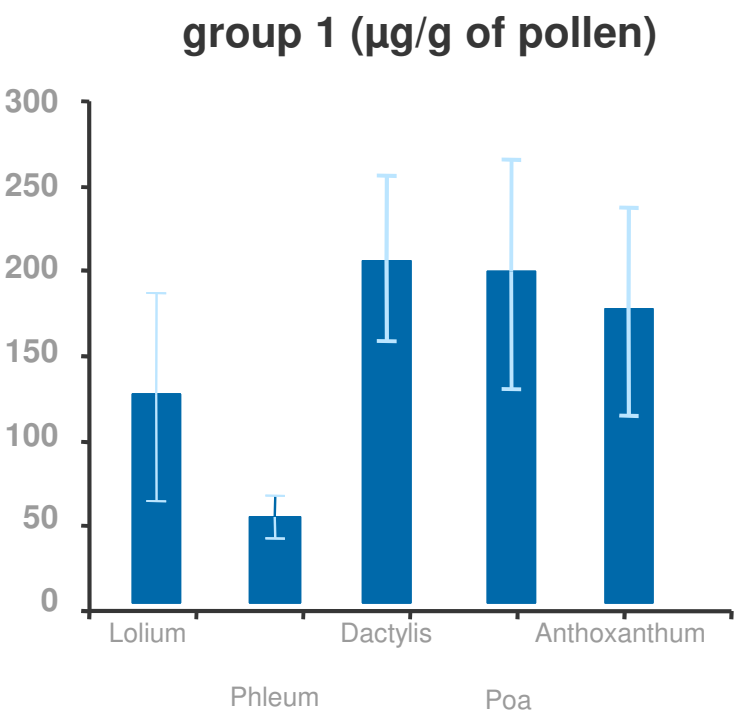
- ✓ Patients allergic to grass pollens have Th2 cells in their blood directed to both cross reactive and non-cross reactive T cell epitopes
- ✓ These Th2 cells specific for non cross-reactive T cell epitopes contribute to allergic inflammation

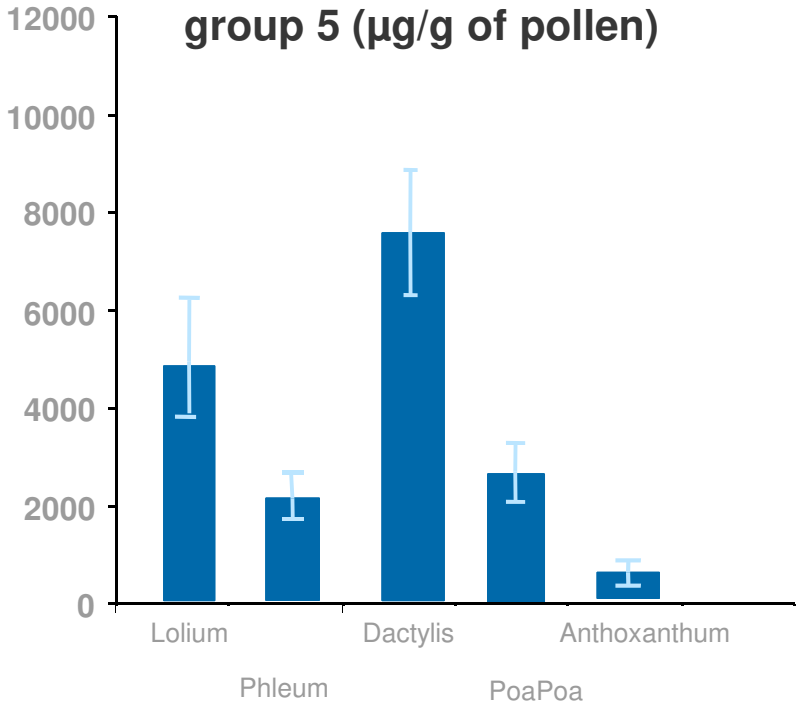


Multiple grass-pollen-species immunotherapy should be more beneficial than single species immunotherapy

Archila LD, et al. Clin Exp Allergy 2014;44(7):986-98.

THE QUANTITY OF GROUP 1 AND GROUP 5 MAJOR ALLERGENS VARIES BETWEEN GRASS SPECIES



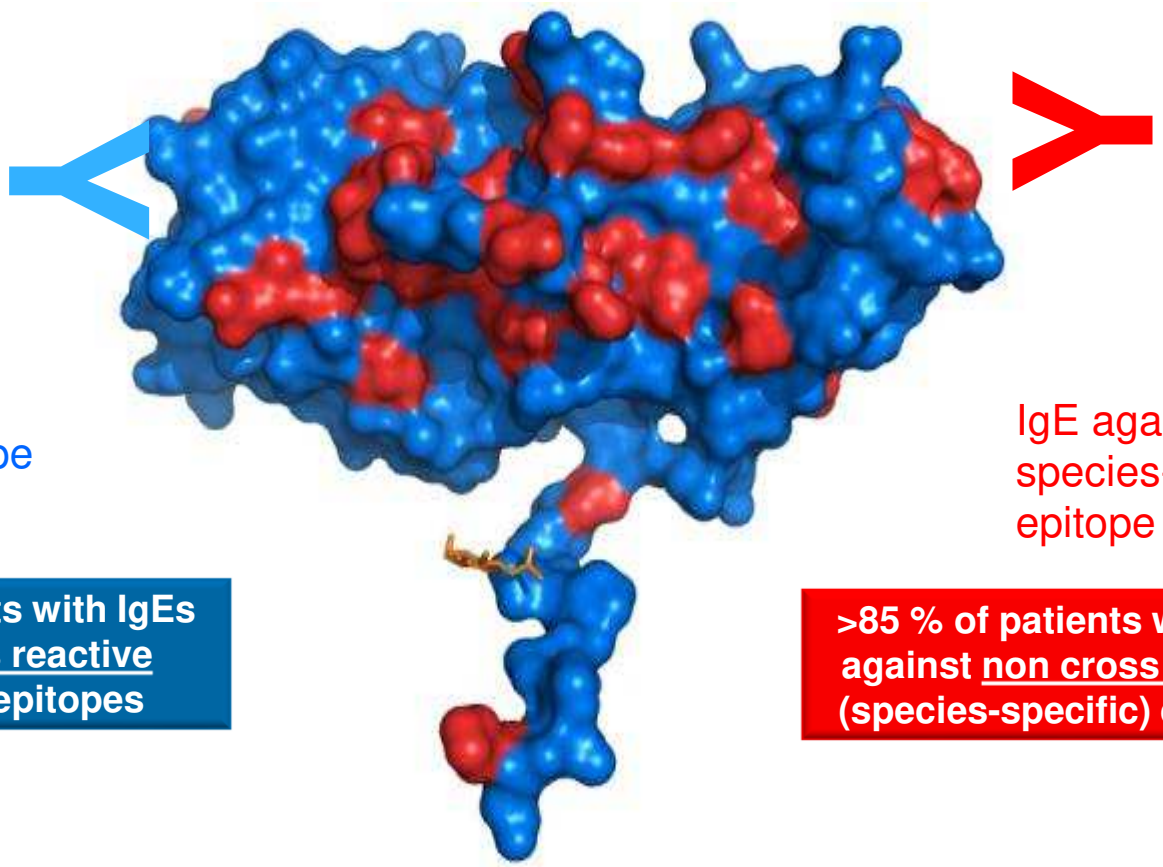


Moingeon P, et al. *Int Arch Allergy Immunol. 2008;146(4):338-42. 97*

STALLERGENES GREER™

RELEVANCE TO PATIENT SENSITIZATION: ANALYSIS OF IGE RESPONSES TO GRASS POLLEN ALLERGENS

Group 1 allergen: variable aminoacids shown in red



IgE against conserved epitope

100 % of patients with IgEs against cross reactive (conserved) epitopes

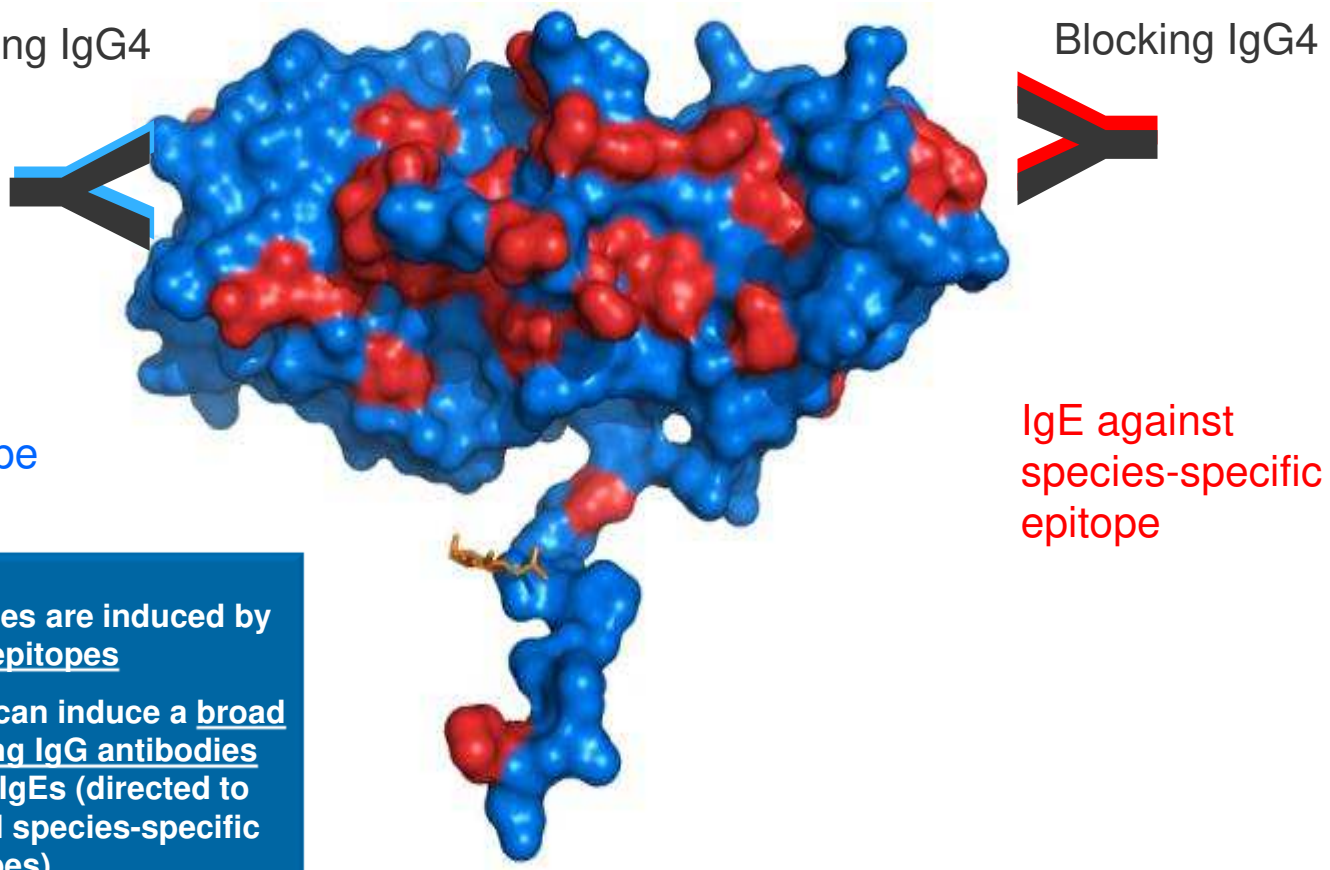
IgE against species-specific epitope

>85 % of patients with IgEs against non cross reactive (species-specific) epitopes

Chabre H, et al. Clin Exp Allergy 2010; 40: 505-19.

RELEVANCE TO IMMUNOTHERAPY: INDUCTION OF BLOCKING IGG4 ANTIBODIES

Group 1 allergen: variable aminoacids shown in red



IgG and IgE antibodies are induced by the same epitopes

A 5 grass pollen mix can induce a broad spectrum of blocking IgG antibodies competing with all IgEs (directed to both conserved and species-specific epitopes)

Chabre H, et al. Clin Exp Allergy 2010; 40: 505-19.

MOLECOLE DI ACARI

Table 1. Allergens identified in *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* species.

Allergen groups	Biological function/activity	MW (kDa)	Presence reported in mite species		Sequence homology between the two species	Prevalence of IgE recognition	Location within mites
1	Cysteine protease	24–27	Dp	Df	81%, 24 isoforms for Der p 1 and 10 isoforms for Der f 1	60–80%	Feces
2	Nieman Pick C2 homolog	15	Dp	Df	88%, 15 isoforms for Der p 2 and 17 isoforms for Der f 2	≥70%	Body
3	Trypsin	25–30	Dp	Df	81%	10–15%	Body (Df)
4	α-amylase	56–63	Dp		?	10–25%	Feces
5	Unknown	14	Dp		?	10–40%	Feces
6	Chymotrypsin	25	Dp	Df	75%	41–65%	
7	Unknown	26–31	Dp	Df	86%	20–40%	Feces
8	Glutathione-S-transferase	25–27	Dp	Df	?	10–40%	Feces
9	Collagenolytic serine protease	24–29	Dp		?	?	Feces
10	Tropomyosin	33–37	Dp	Df	98%	5–10%	
11	Paramyosin	98–103	Dp	Df	97%	65–80%	
13	Fatty acid binding protein	15		Df	?	<25%	Feces
14	Apolipophorin	177	Dp	Df	>80%	20–60%	Body
15	Chitinase	98–105	Dp	Df	90%	15–30%	
16	Gelsolin/villin	53–55		Df	?	35–47%	
17	Calcium-binding protein	53		Df	?	35%	
18	Chitin-binding protein	49–60	Dp	Df	88%	30–40%	
20	Arginine kinase	40	Dp		?	5–20%	Body
21	Unknown	14	Dp	Df	?	15–30%	Feces
22	Unknown	67		Df	?	?	Feces
23	Peritrophin-like protein domain	14	Dp		?	30–60%	Feces

Allergen groups 12 and 19 were reported in *Blomia*, but not in *Dermatophagoides* mite species.
Df: *Dermatophagoides farinae*; Dp: *Dermatophagoides pteronyssinus*; MW: Molecular weight.
From [30](WHO/International Union of Immunological Societies site providing the official list of registered allergens and their isoforms). Prevalence of IgE recognition was obtained from [4,15,30,35,36] and [PM, Unpublished Data].

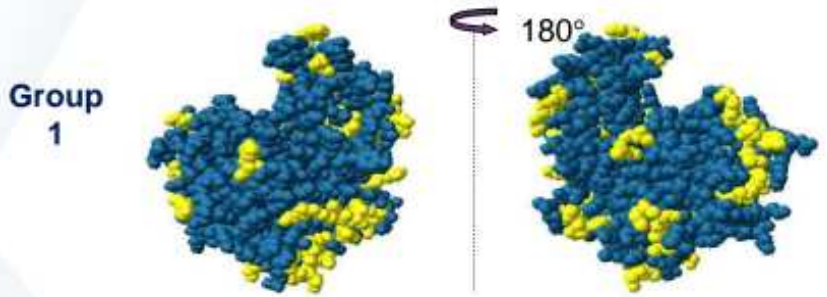
Razionale all'utilizzo

di entrambi gli estratti

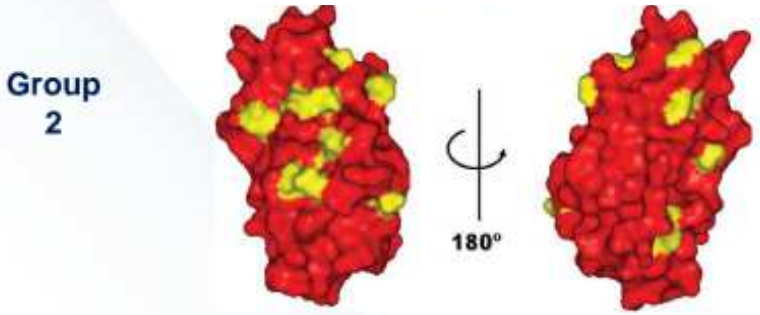
- *D. pteronyssinus* and *D. farinae,* some differences exist (80-85% amino acid sequence homology)
- *D. pteronyssinus* and *D. farinae* extracts was consistently more efficacious than single extracts

AIT ACARI, RAZIONALE PER IL MIX DI DUE ACARI

AMINO ACID SEQUENCE DIFFERENCES BETWEEN DER P AND DER F ALLERGENS



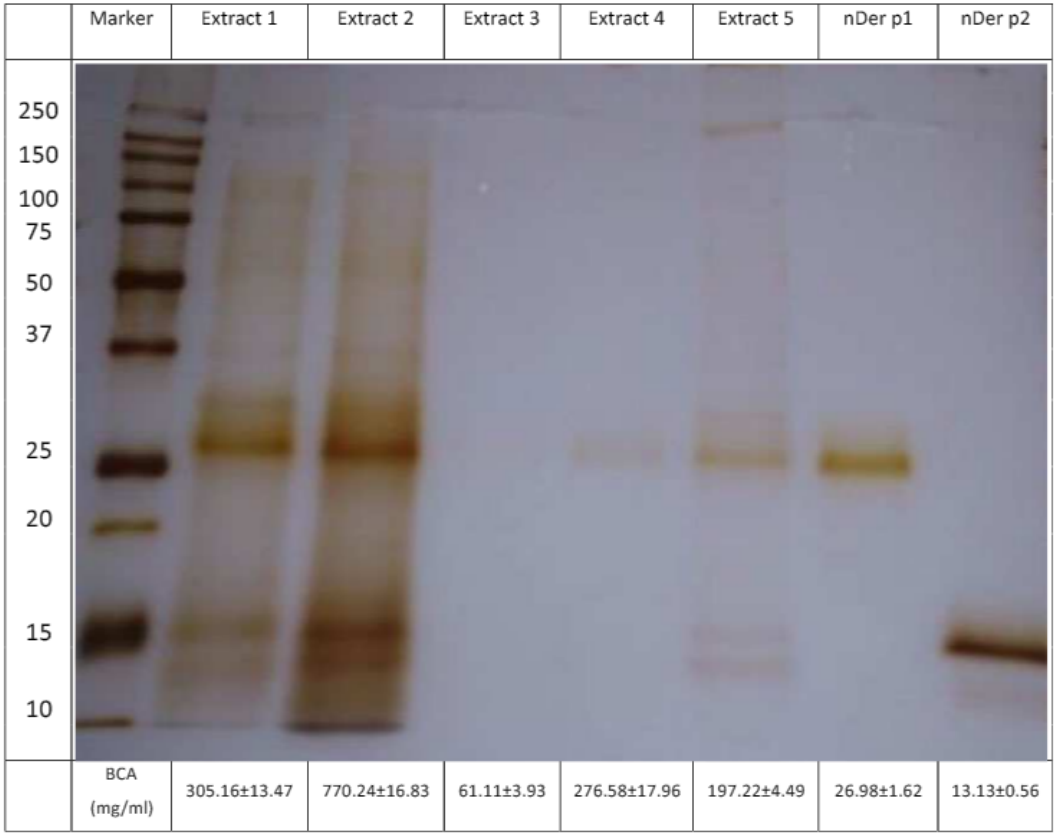
Varying aminoacids are indicated in yellow



For a given allergen, existence of species-specific epitopes recognized by IgEs and IgGs

Moingeon P, Expert Rev Vaccines, 2014; 13: 1463-73

ACARI: ESTRATTI IN COMMERCIO



	Marker	Extract 1	Extract 2	Extract 3	Extract 4	Extract 5	nDer p1	nDer p2
BCA (mg/ml)		305.16±13.47	770.24±16.83	61.11±3.93	276.58±17.96	197.22±4.49	26.98±1.62	13.13±0.56

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Allergy

ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Variation in allergen content in sublingual allergen immunotherapy with house dust mites

F. Moreno Benítez[1,2], M. Espinazo Romeu[1,2], A. Letrán Camacho[1,2], S. Mas[3], F. J. García-Cózar[2,4] & A. I. Tabar[5,6]

[1]Lobaton Clinic, S.L.P, Cadiz; [2]"Immunology and Allergy" UCA-AICS, University of Cadiz, Cadiz; [3]Universitat Pompeu Fabra, Barcelona; [4]Department of Biomedicine, Biotechnology and Public Health (Immunology), School of Medicine, University of Cadiz and Puerto Real University Hospital Research Unit, Cadiz; [5]Allergy Department, Complejo Universitario de Navarra, Pamplona, Spain; [6]IdiSNA, Navarra Institute for Health Research, Pamplona, Spain

ALLERGEN STANDARDIZATION IS CRITICAL TO GUARANTEE BATCH TO BATCH CONSISTENCY

Commercial extracts are released after comparing their biological activity with a corresponding standard

In vivo calibration (skin tests)

In vitro characterization

IN HOUSE REFERENCE PREPARATION (IHRP)

COMPARISON

- **Protein content**
- **Allergen content**
- **Biological activity (ELISA inhibition)**

Index of Reactivity (IR)

COMMERCIAL ALLERGEN EXTRACTS

IN PROCESS QUALITY CONTROL

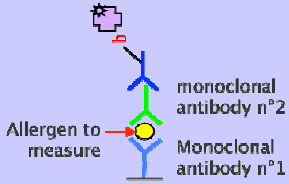
ADJUSTMENT

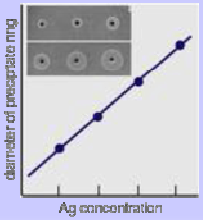
QUALITY CONTROL FOR RELEASE

STALLERGENES GREER™

QUANTITATIVE MEASUREMENT OF MAJOR ALLERGENS

- **ELISA sandwich**
  - → Monoclonal or polyclonal specific antibodies
  - → e.g. EU create project (Bet v 1)





- **Radial Immuno-Diffusion (RID)**
  - → e.g. Amb a 1, Fel d 1
  - → Specific polyclonal antibodies in the gel

- **Mass-spectrometry**
  - → Measurement after ionization of the mass of specific peptides
  - → Identification
  - → Quantification of all allergen variants

PRODUZIONE DI LIVELLO FARMACEUTICO

International Archives of Allergy and Immunology

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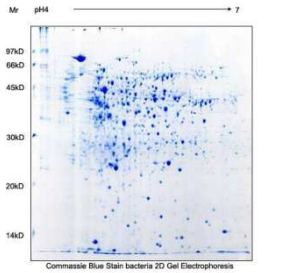
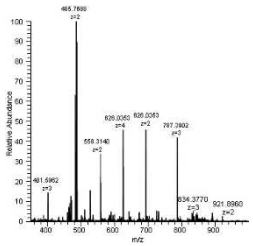
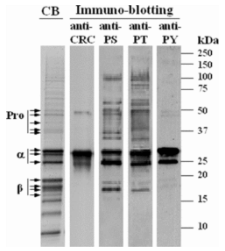


Commassie Blue Stain bacteria 2D Gel Electrophoresis





2D gel analysis

+

Mass spectrometry

+

Immunoblotting

cles. The rationale supporting this approach is to obtain extracts whose allergen composition and content mimick natural exposure conditions. The characterization of such *D. pteronyssinus* and *D. farinae* source materials using a combination of proteomic approaches (i.e. 2D gel analysis and mass spectrometry-based protein sequencing, as well as immunoblotting with allergen-specific antibodies) confirmed unambiguously the presence of a broad spectrum of both major and minor allergens in these cultures (table 1). On a quan-

ESTRATTO OTTIMALE

- **La qualità dell'estratto allergenico è essenziale per una diagnosi accurata e un trattamento sicuro ed efficace**

- **L'estratto ideale copre tutti i profili di sensibilizzazione dei pazienti allergici «mimando» la naturale esposizione:**
  - ✓ Deve contenere gli allergeni maggiori quantificati
  - ✓ Deve contenere tutti gli epitopi e non contenere altre sostanze a basso peso (es istamina)
  - ✓ Deve essere standardizzato: potenza allergenica nota e riproducibile
  - ✓ I mix (dello stesso gruppo omologo) hanno lo scopo di avere repertorio completo proveniente da specie

LA SCELTA DELLA DOSE OTTIMALE

Demoly *et al. Clin Transl Allergy (2015) 5:44*
DOI 10.1186/s13601-015-0088-1

Clinical and Translational Allergy

REVIEW Open Access

Choosing the optimal dose in sublingual immunotherapy: Rationale for the 300 index of reactivity dose

Pascal Demoly[1*], Gianni Passalacqua[2], Moises A. Calderon[3] and Tarik Yalaoui[4]

IR per diagnosi e trattamento

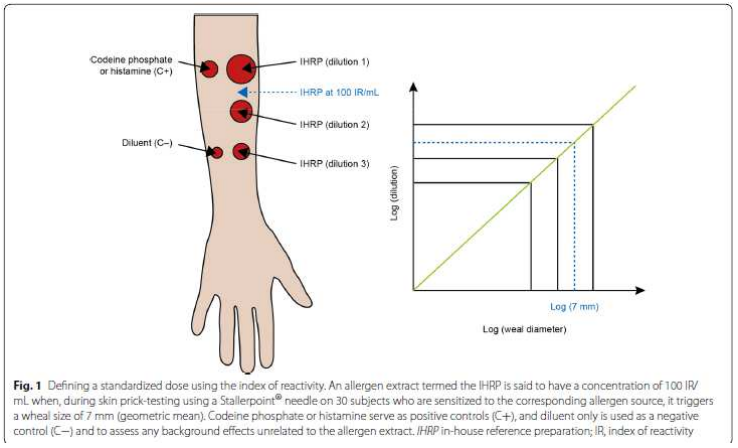
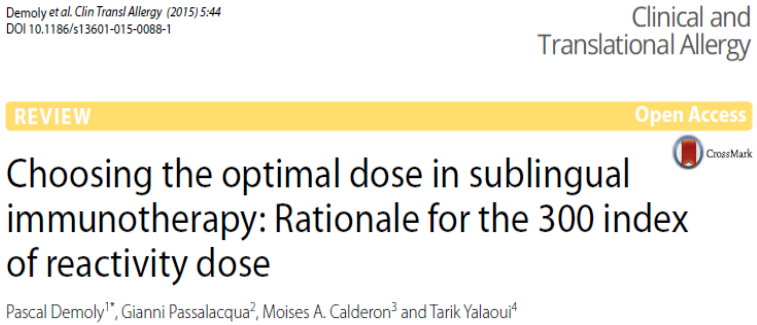


Fig. 1 Defining a standardized dose using the index of reactivity. An allergen extract termed the IHRP is said to have a concentration of 100 IR/mL when, during skin prick-testing using a Stallerpoint® needle on 30 subjects who are sensitized to the corresponding allergen source, it triggers a wheal size of 7 mm (geometric mean). Codeine phosphate or histamine serve as positive controls (C+), and diluent only is used as a negative control (C–) and to assess any background effects unrelated to the allergen extract. *IHRP* in-house reference preparation; IR, index of reactivity

LA SCELTA DELLA DOSE OTTIMALE



Demoly *et al. Clin Transl Allergy (2015) 5:44*
DOI 10.1186/s13601-015-0088-1

Clinical and Translational Allergy

REVIEW Open Access

Choosing the optimal dose in sublingual immunotherapy: Rationale for the 300 index of reactivity dose

Pascal Demoly[1*], Gianni Passalacqua[2], Moises A. Calderon[3] and Tarik Yalaoui[4]

Formulazioni della SLIT:

- **Compresse** (SLIT tablets)
- **Estratto glicerinato** (SLIT drops)

- **Evidenze: esiste un rapporto dose-risposta ed è fondamentale l'utilizzo della dose dimostratasi clinicamente efficace**
- **Gli studi relativi a graminacee e HDM compresse o graminacee, betulla o HDM drops per il trattamento delle allergie respiratorie hanno confermato che la dose 300 IR fornisce l'efficacia e la tollerabilità ottimali**

FDA richiede la concentrazione in BAU
Per le graminacee 300 IR corrispondono a 9,000 BAU

UN ESEMPIO DI 300IR DOSE OTTIMALE

Worm *et al. Clinical and Translational Allergy* 2014, **4**:7
http://www.ctajournal.com/content/4/1/7

Clinical and Translational Allergy

RESEARCH Open Access

Sustained efficacy and safety of a 300IR daily dose of a sublingual solution of birch pollen allergen extract in adults with allergic rhinoconjunctivitis: results of a double-blind, placebo-controlled study

Margitta Worm[1*†], Sabina Rak[2†], Frédéric de Blay[3], Hans-Jorgen Malling[4], Michel Melac[5], Véronique Cadic[5] and Robert K Zeldin[5]

RISULTATI CLINICI DELL'AIT CON UN ESTRATTO A DOSE OTTIMALE

- ✓ Efficace in poche settimane
- ✓ Efficacia già al primo ciclo di trattamento
- ✓ Efficacia che perdura nel tempo
- ✓ Efficacia dopo la sospensione

AIT GRAMINACEE

EXPERT REVIEWS

Five-grass-pollen sublingual immunotherapy tablet for the treatment of grass-pollen-induced allergic rhinoconjunctivitis: 5 years of experience

Expert Rev. Clin. Immunol. 10(10), 1309–1324 (2014)

Drug Profile — Didier, Wahn, Horak & Cox

Table 2. Summary of 5-grass-pollen sublingual immunotherapy tablet efficacy from five Phase I–III clinical trials.

Study Phase	Primary end point	Treatment	Primary analysis set (n)	LS mean	LS mean difference vs placebo		p-value vs placebo[†]	Ref.
					Absolute point estimate (95% CI)	*Relative point estimate (%)*		
VO34.04 EU study in adults IIb/III	ARTSS	500 IR (4M) 300 IR (4M) 100 IR (4M) Placebo	143 136 142 148	3.74 3.58 4.72 4.93	-1.22 (-1.91, -0.53) -1.39 (-2.09, -0.69) -0.26 (-0.95, 0.43)	-24.7 -28.2 -5.3	0.0006 0.0001 0.4606	[46]
VO56.07A Allergen-exposure chamber study in adults I	ARTSS	300 IR Placebo	45 44	4.85 6.87	-1.97 (-2.99, -0.94)	-29.3	0.0003	[49]
VO52.06 EU pediatric study III	ARTSS	300 IR (4M) Placebo	131 135	3.25 4.51	-1.13 (-1.80, -0.46)	-25.5	0.0010	[50]
VO53.06[*] Long-term efficacy study in adults III	AAdSS	300 IR (4M) 300 IR (2M) Placebo	149 147 165	3.39 3.25 5.21	-1.82 (-2.61, -1.02) -1.96 (-2.76, -1.16)	-34.9 -37.6	<0.0001 <0.0001	[28,51]
VO61.08 US study in adults III	Daily CS[§]	300 IR (4M) Placebo	208 228	0.32 0.45	-0.13 (-0.19, -0.06)	-28.2	0.0003	[52]

2M or 4M, patients received active treatment starting 2 or 4 months, respectively, before the pollen season.
[†]Based on absolute point estimate of LS mean difference.
[*]Year 3 results are presented.
[§]Daily CS is derived from the RTSS and RMS and gives equal weight to symptoms and medication use. This score is conventionally expressed on a scale from 0 to 3 and calculated per day for each patient as: daily CS = (daily RTSS/6 + daily RMS)/2.
AAdSS: Average Adjusted Symptom Score; ARC: Allergic rhinoconjunctivitis; ARTSS: Average rhinoconjunctivitis Total Symptom Score; CS: Combined Score; IR: Index of reactivity; LS: Least squares; RMS: Rescue Medication Score; RTSS: Rhinoconjunctivitis Total Symptom Score; SLIT: Sublingual immunotherapy.

AIT GRAMINACEE

Main paper

Rhinitis, sinusitis, and upper airway disease

Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen–induced rhinoconjunctivitis

Alain Didier, MD,[a] Margitta Worm, MD,[c] Friedrich Horak, MD,[d] Gordon Sussman, MD,[e] Olivier de Beaumont, MD,[f] Martine Le Gall,[f] Michel Melac, MD,[f] and Hans-Jorgen Malling, MD[b] *Toulouse and Antony, France, Copenhagen, Denmark, Berlin, Germany, Vienna, Austria, and Toronto, Ontario, Canada*

Year 4
(1 year post treatment)

Year 5
(2 years post treatment)

doi: 10.1111/cea.12100 *Clinical & Experimental Allergy*, **43**, 568–577

ORIGINAL ARTICLE Clinical Allergy

Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen–induced allergic rhinoconjunctivitis

A. Didier[1], H.-J. Malling[2], M. Worm[3], F. Horak[4], G. Sussman[5], M. Melac[6], S. Soulié[6] and R. K. Zeldin[6]
[1]*Respiratory Diseases Department, Rangueil-Larrey Hospital, Toulouse, France,* [2]*Allergy Clinic, Gentofte University Hospital, Copenhagen, Denmark,* [3]*Department of Dermatology and Allergy, Allergy Center Charité, CCM, Charité - Universitätsmedizin Berlin, Berlin, Germany,* [4]*Allergy Center Vienna West, Vienna, Austria,* [5]*The University of Toronto, Toronto, ON, Canada and* [6]*Global Clinical Development, Stallergenes S.A., Antony, France*

RESEARCH Open Access

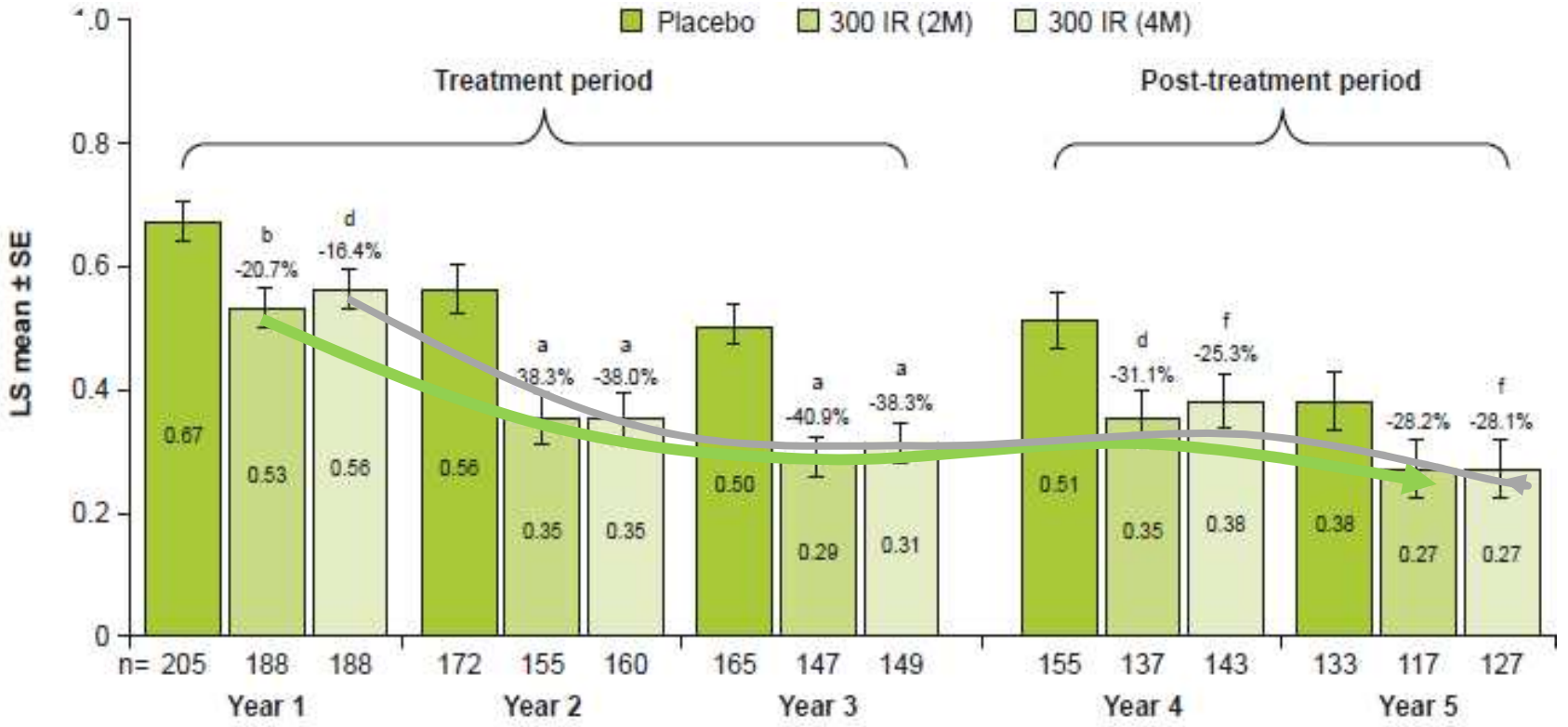
Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score

Alain Didier[1*], Hans-Jørgen Malling[2], Margitta Worm[3], Friedrich Horak[4] and Gordon L Sussman[5]

Didier et al., J Allergy Clin Immunol. 2011 Sep;128(3):559-66
Didier et al., Clin Exp Allergy. 2013 May;43(5):568-77
Didier A, Abstract EAACI 2014
Didier A et Al Clin Transl Allergy. 2015 May 22;5:12

EFFICACIA A LUNGO TERMINE – DOPO LA SOSPENSIONE

Daily Combined Score



5-Grass pollen tablet 2 months and 4 months absolute value are stable from year 2 to year 5

[a]p < 0.0001, [b]p < 0.0005, [c]p < 0.001, [d]p < 0.005, [e]p < 0.01, [f]p < 0.05 for comparison vs placebo

STALLERGENES GREER™

Didier A et Al Clin Transl Allergy. 2015 May 22;5:12

AIT ACARI – EFFICACE ANCHE NELL'ASMA
EFFICACE AL PRIMO ANNO E ALLA SOSPENSIONE

SLIT drops


ORIGINAL ARTICLE — AIRWAY DISEASES

House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma

L. Wang[1], J. Yin[1], R. Fadel[2], A. Montagut[2], O. de Beaumont[2] & P. Devillier[3]

[1]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [2]Stallergenes S.A., Antony; [3]UPRES EA 220, Foch Hospital, Suresnes, France

HDM tablets


Rhinitis, sinusitis, and upper airway disease

Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis

Karl-Christian Bergmann, MD,[a] Pascal Demoly, MD, PhD,[b] Margitta Worm, MD,[a] Wytske J. Fokkens, MD, PhD,[c] Teresa Carrillo, MD, PhD,[d] Ana I. Tabar, MD, PhD,[e] Hélène Nguyen, PharmD,[f] Armelle Montagut,[f] and Robert K. Zeldin, MD[f] *Berlin, Germany, Montpellier and Antony, France, Amsterdam, The Netherlands, and Las Palmas de Gran Canaria and Pamplona, Spain*


Allergy

ORIGINAL ARTICLE — EXPERIMENTAL ALLERGY AND IMMUNOLOGY

House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis

Y. Okamoto[1], S. Fujieda[2], M. Okano[3], Y. Yoshida[4], S. Kaisuda[5] & K. Masuyama[6]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba; [2]Department of Otorhinolaryngology-Head and Neck Surgery, University of Fukui, Fukui; [3]Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama; [4]Biostatistics Department, Shinogi & Co., Ltd., Osaka; [5]Clinical Development Department, Shinogi & Co., Ltd., Osaka; [6]Department of Otorhinolaryngology-Head and Neck Surgery, Graduate School of Medical Science, University of Yamanashi, Yamanashi, Japan


Rhinitis, sinusitis, and upper airway disease

Efficacy and safety of sublingual tablets of house dust mite allergen extracts: Results of a dose-ranging study in an environmental exposure chamber

CrossMark

Michel Roux, MD,[a] Philippe Devillier, MD, PhD,[b] William H. Yang, MD,[c] Armelle Montagut, MSc,[a] Kathy Abiteboul, PharmD,[a] Agnès Viatte, MSc,[a] and Robert K. Zeldin, MD[a] *Antony and Suresnes, France, and Ottawa, Ontario, Canada*

Wang et al., Allergy 2014 Sep;69(9):1181-8
Bergman et al., JACI 2014;133:1608-14
Roux et al, JACI 2016; 138:451-8
Okamoto A et, Allergy 2016;72(3):435-443

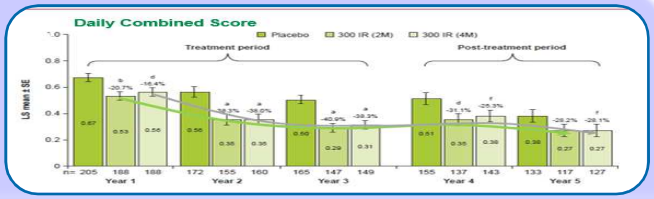
LA SCELTA DELLA FORMULAZIONE OTTIMALE

La scelta diventa soggettiva quando sono garantiti:

✓ **Qualità dell'estratto (standardizzazione e riproducibilità)**

✓ **Dose ottimale**

✓ **Efficacia e sicurezza dimostrate**



FARMACOECONOMIA: VANTAGGI DELL'AIT

Clin Drug Investig
DOI 10.1007/s40261-013-0067-z

ORIGINAL RESEARCH ARTICLE

Economic Evaluation of 5-Grass Pollen Tablets Versus Placebo in the Treatment of Allergic Rhinitis in Adults

Matteo Ruggeri · Marco Oradei · Franco Frati · Paola Puccinelli · Cristina Romao · Ilaria Dell'Albani · Cristoforo Incorvaia · Americo Cicchetti

Verheggen et al. Clinical and Translational Allergy (2015) 5:1
DOI 10.1186/s13601-015-0045-z

Clinical and Translational Allergy

RESEARCH Open Access

Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany

Bram G Verheggen[1*], Kirsten Y Westerhout[1], Carl H Schreder[2] and Matthias Augustin[3]

Original article

Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany

K.Y. Westerhout
B.G. Verheggen
Pharmerit International, Rotterdam, The Netherlands

Abstract

Objectives:

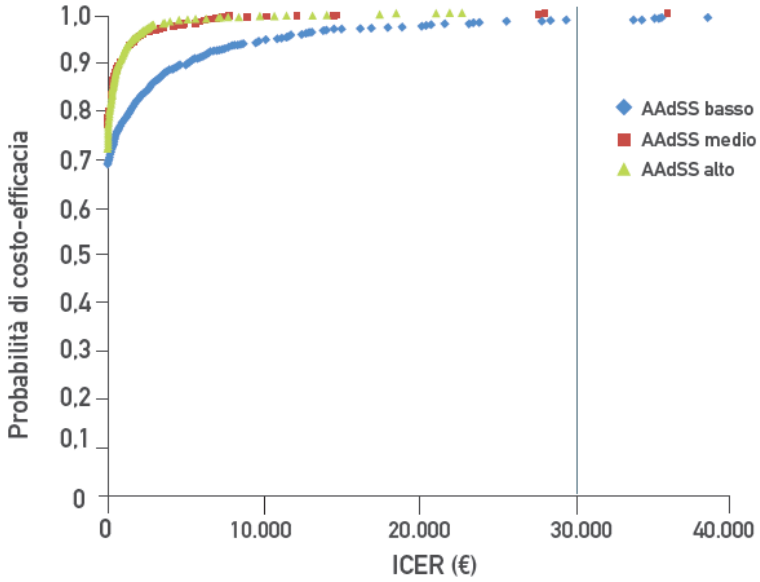
Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost

George Dranitsaris BPharm PhD[1] and Anne K. Ellis MD MS[2,3]

[1]Health Services Research Consultant, Augmentium Pharma Consulting, Toronto, Ontario, Canada
[2]Associate Professor and Chair, Division of Allergy, Department of Medicine, Queen's University, Kingston, Ontario, Canada
[3]Director, Allergy Research Unit, Kingston General Hospital, Kingston, Ontario, Canada

FARMACOECONOMIA: VANTAGGI DELL'AIT

- ✓ **Nei pazienti con rinite moderata grave l'ICER è estremamente positivo**
- ✓ **Le comprese di 5 graminacee hanno un buon rapporto costo-efficacia nel trattamento della RA da graminacee in pazienti adulti rispetto al trattamento farmacologico tradizionale**
- ✓ **Le 5 graminacee economicamente sono vantaggiose verso altre SLIT e SCIT**
- ✓ **Le 5 graminacee sono economicamente vantaggiose vs i sintomatici (in press)**

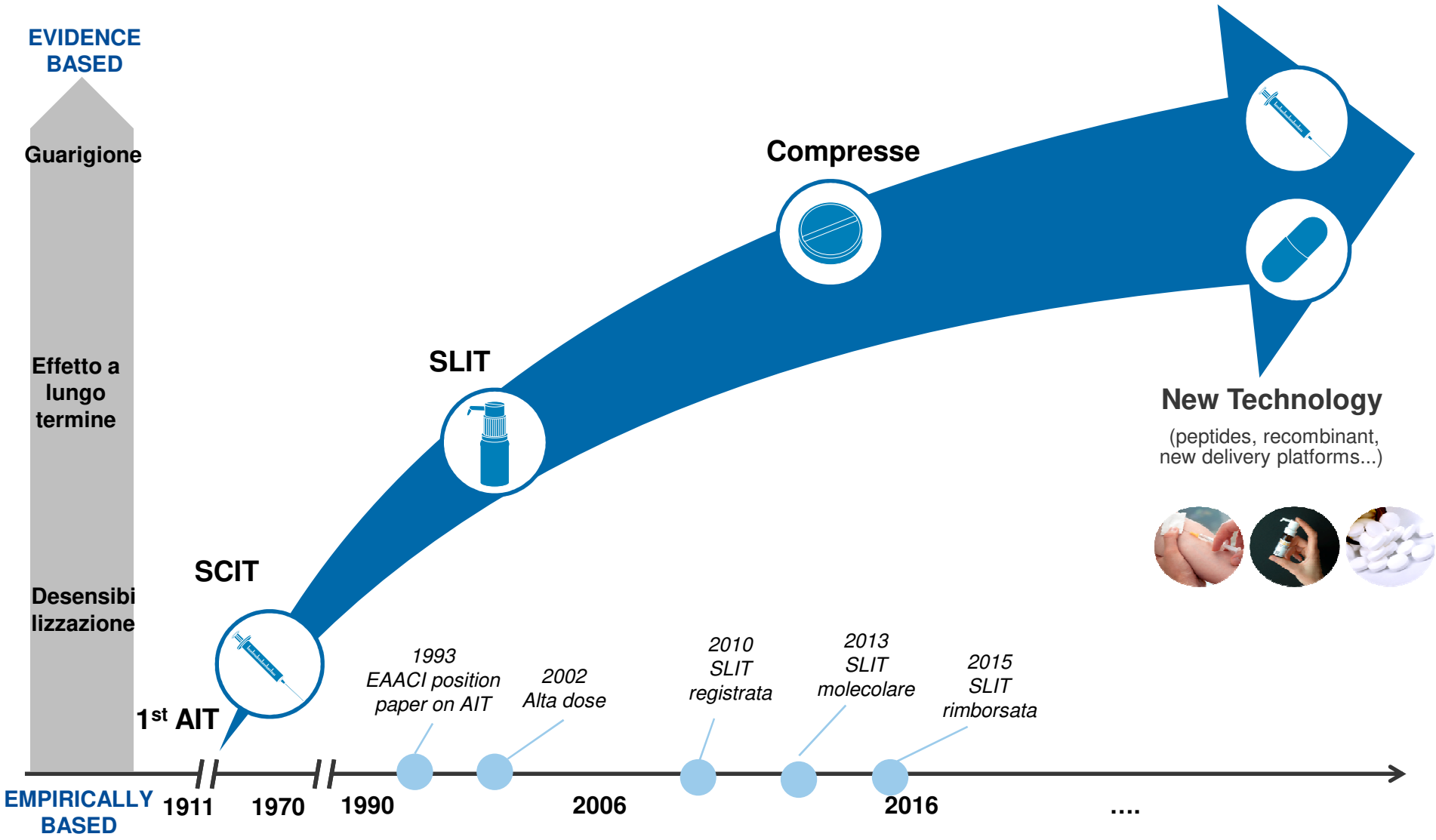


Curva di accettabilità del rapporto costo-efficacia.
Il valore soglia di 30.000 €/ QALY rappresenta la massima disponibilità a pagare considerata sostenibile sulla base delle recenti decisioni delle più importanti agenzie regolatorie internazionali.

AAdSS: *Average Adjusted Symptom Score*
ICER: *Incremental Cost-effectiveness Ratio*

Grafico elaborato dall'articolo Ruggeri et al, Clin Drug Investig 2013

CONCLUSIONI: L'EVOLUZIONE DELL'AIT



CONCLUSIONI

Se cerchiamo l'AIT ottimale:

L'estratto deve essere di qualità certificata	✓ Qualità della materia prima, del processo produttivo e controlli quali-quantitativi ✓ Tutti gli epitopi al quale il paziente è esposto e al quale è risultato positivo
Deve essere efficace e sicura	✓ Dose ottimale ✓ Efficacia e sicurezza dimostrate da studi in doppio-cieco
Deve essere vantaggiosa economicamente	✓ Cost-effectiveness dimostrata da studi di farmaco-economia

XXX CONGRESSO NAZIONALE

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Società Italiana di Allergologia,
Asma ed Immunologia Clinica

FIRENZE 6/9 APRILE 2017 | WWW.SIAAIC2017.ORG

Grazie dell'attenzione

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