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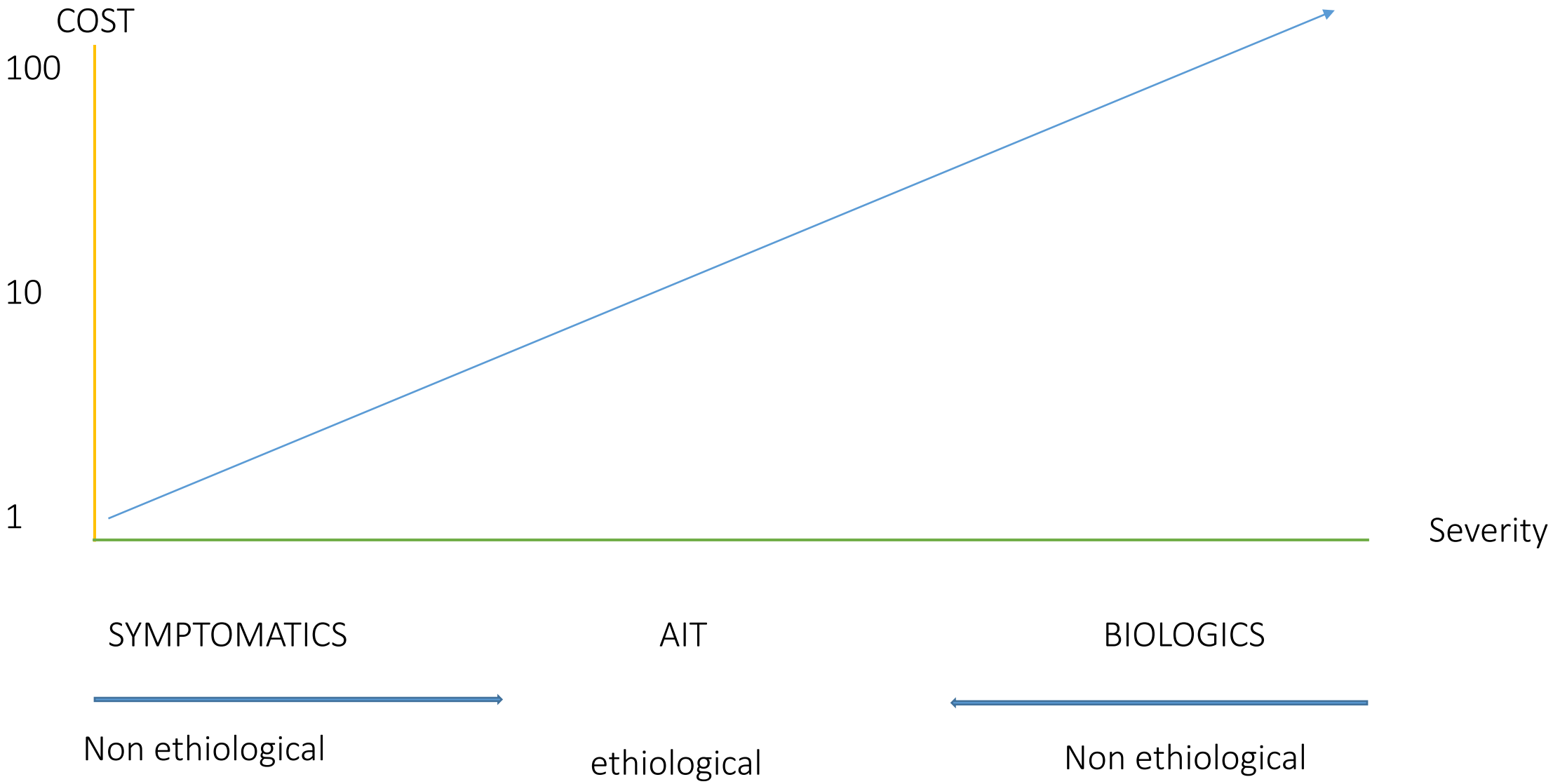
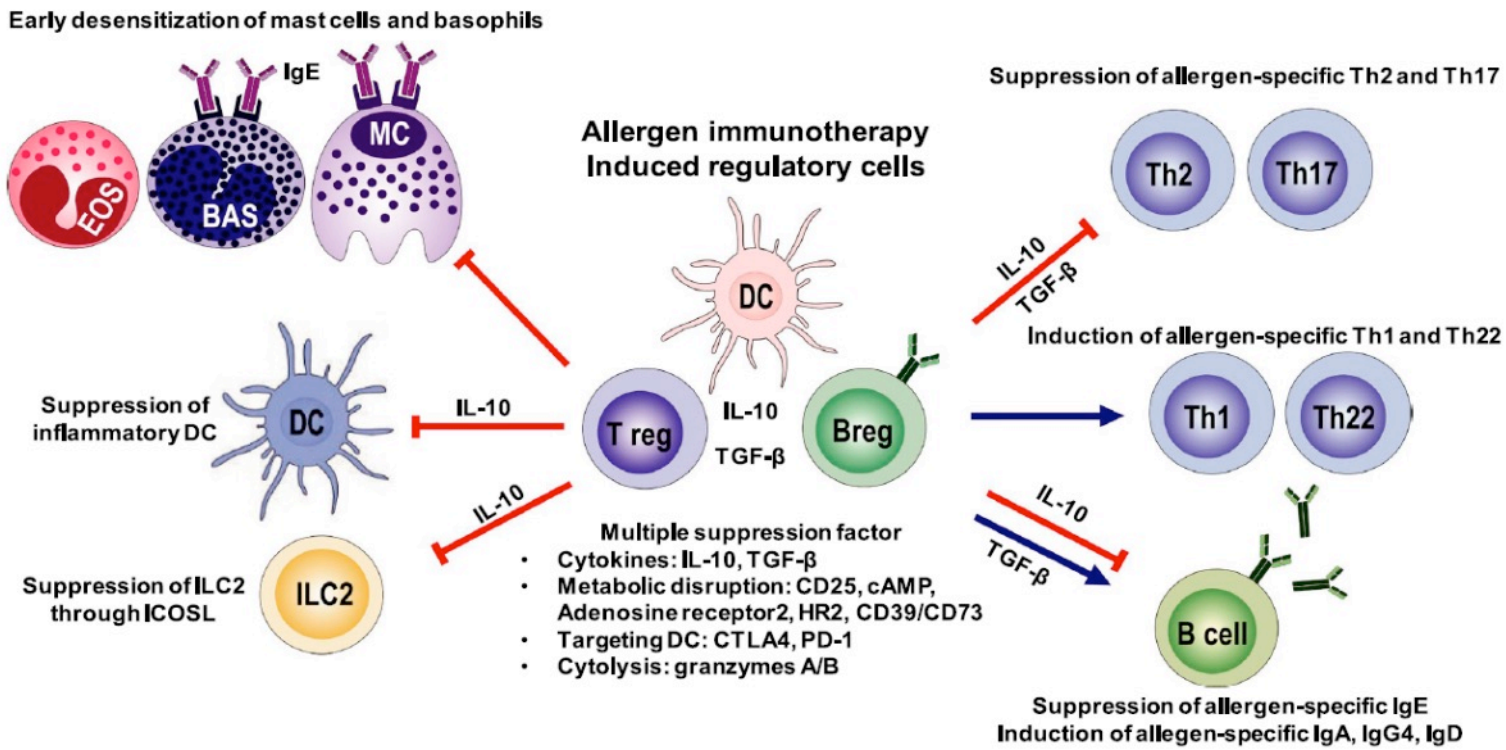
Unmet needs in immunological mechanisms in AIT: key cellular players

Domingo Barber
Universidad CEU San Pablo

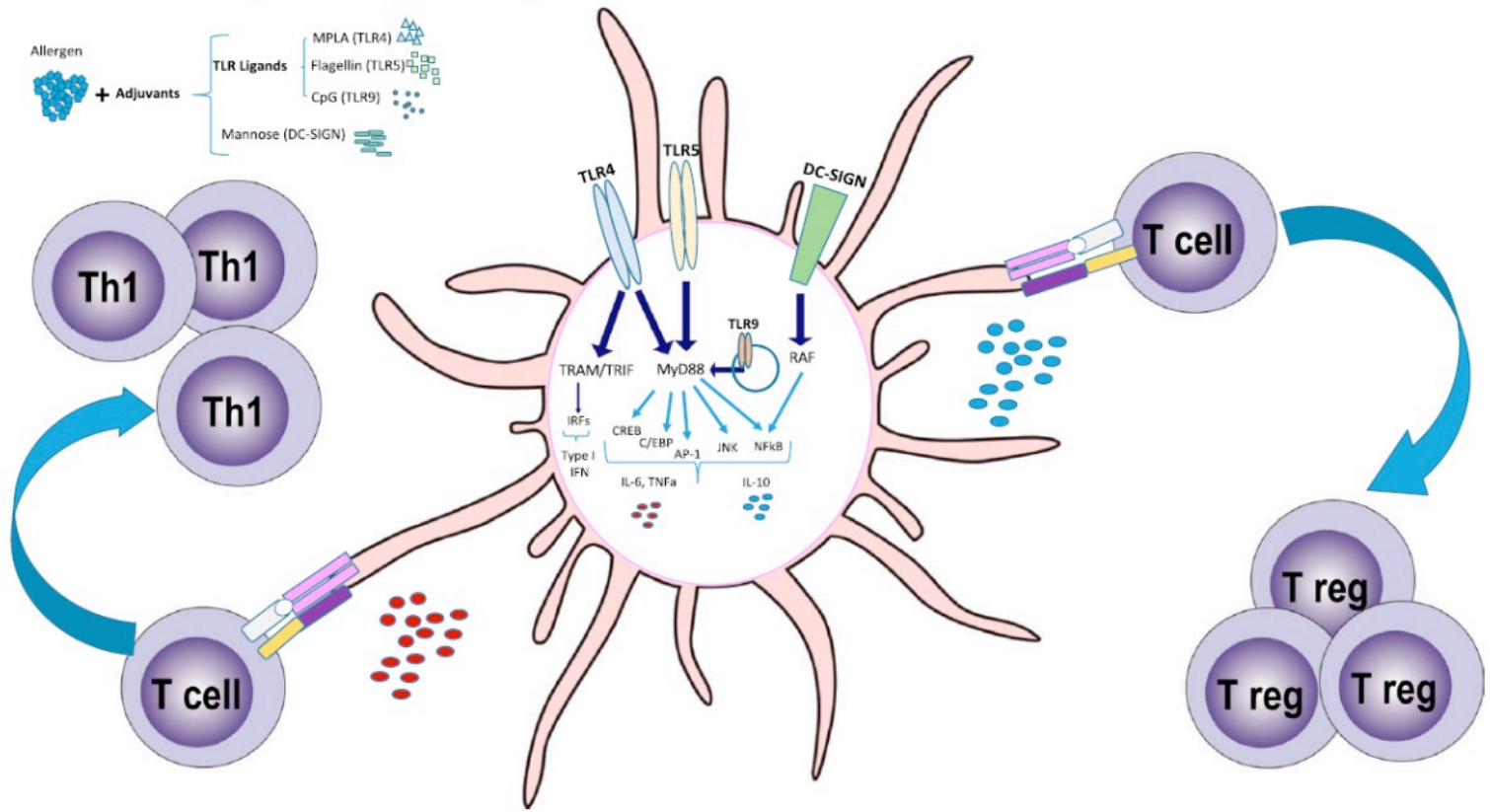
Ethiological management of allergy





Allergen-specific immunotherapy: power of adjuvants and novel predictive biomarkers

Milena Sokolowska[1], Tadech Boonpiyathad[2], Maria M. Escribese[3,5], Domingo Barber[4,5]



Allergen-specific immunotherapy: power of adjuvants and novel predictive biomarkers

Milena Sokolowska[1], Tadech Boonpiyathad[2], Maria M. Escribese[3,5], Domingo Barber[4,5]

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Vaccines formulation complexity

-Each product is unique

-The same product administered in different ways has different effects

Review

Vaccine adjuvants: Understanding the structure and mechanism of adjuvanticity

Shuting Shi [a,b,1], Haoru Zhu [a,b,1], Xinyu Xia [a,b,1], Zhihui Liang [a,b], Xuehu Ma [a,b], Bingbing Sun [a,b,*]

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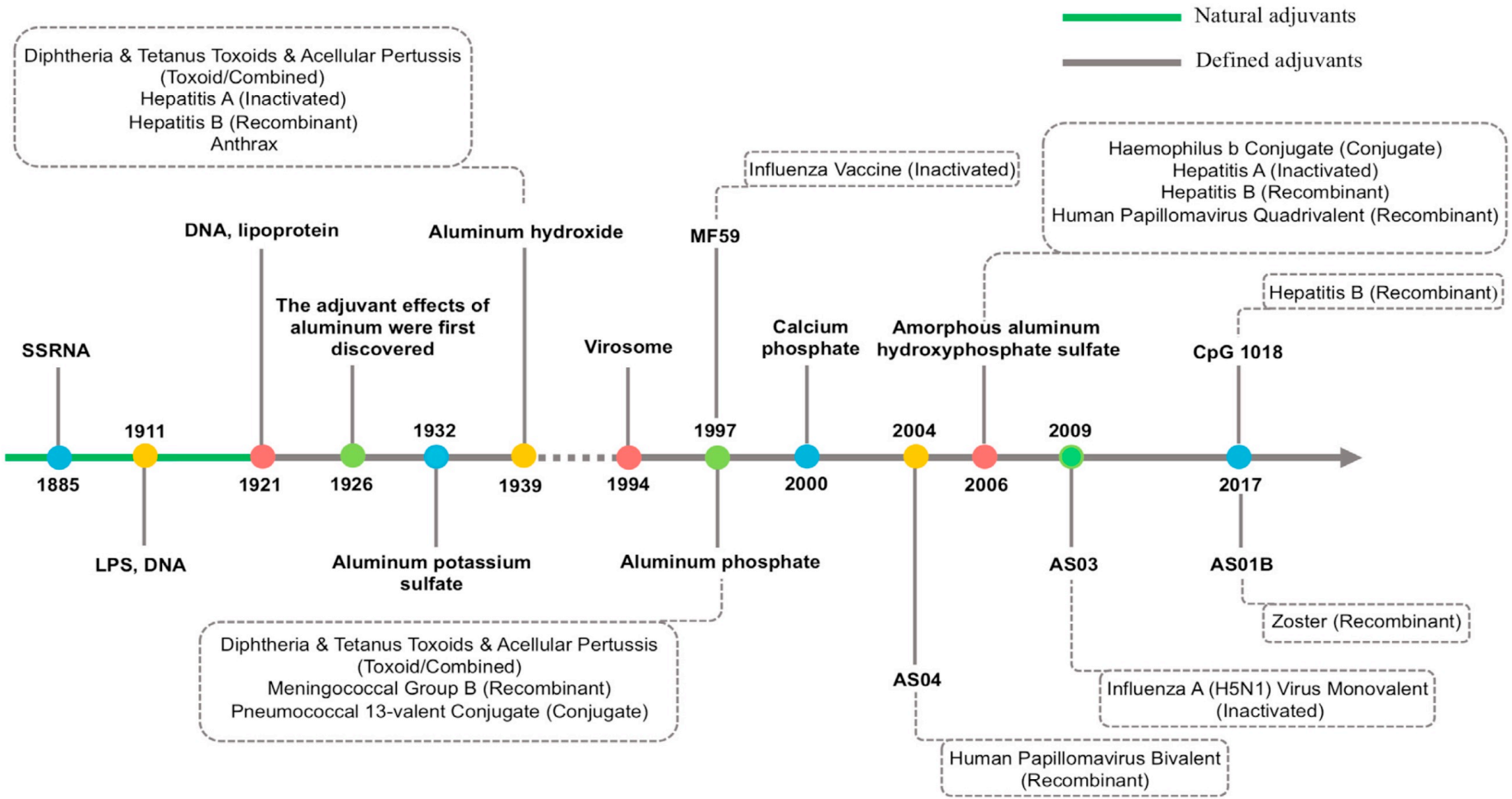
[b] School of Chemical Engineering, Dalian University of Technology, 2 Linggong Road, 116024 Dalian, China

Vaccine 37 (2019) 3167–3178



De Gregorio et al.
Eur J Immunol. (2008)38;2068-71.

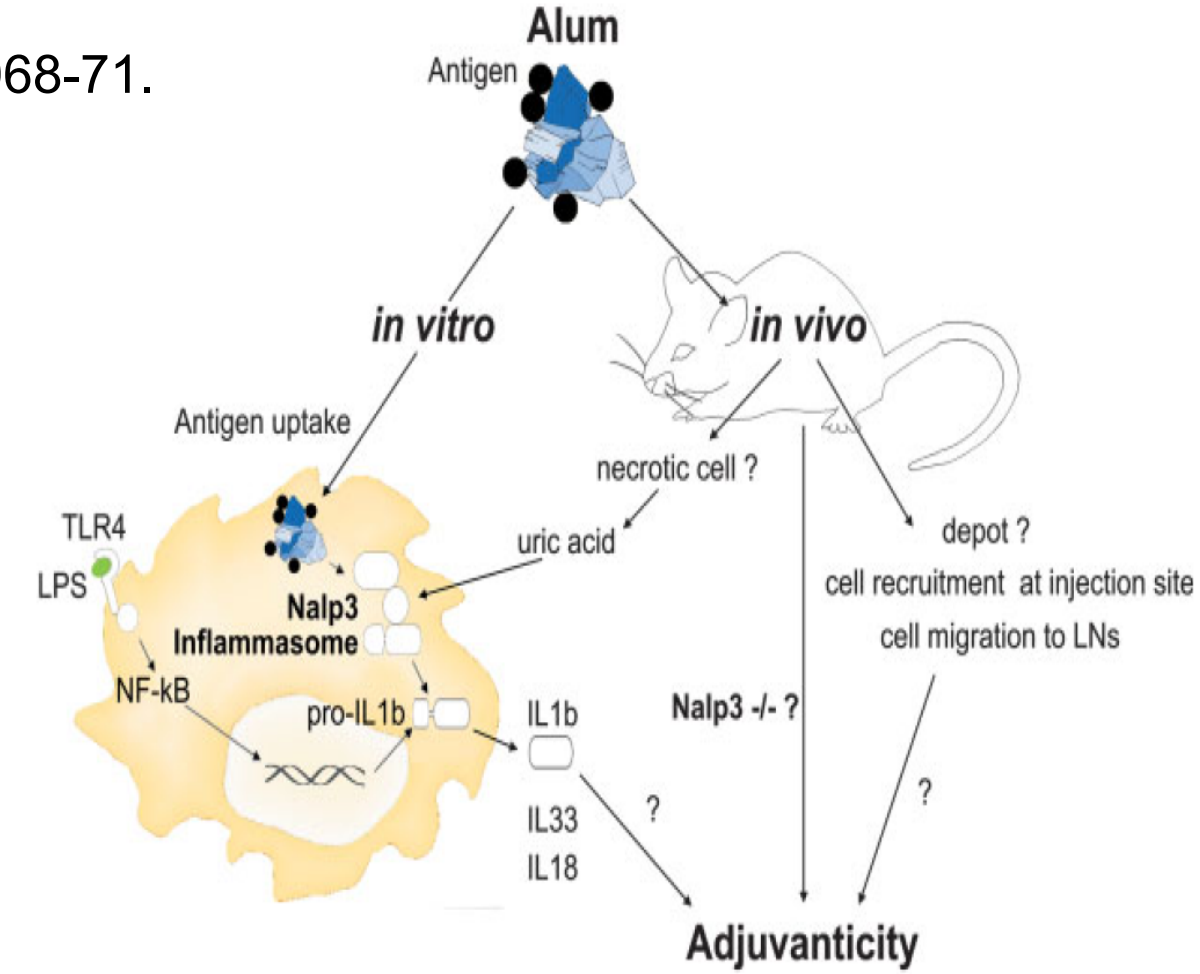


Figure 2. Proposed mechanisms of action of alum *in vitro* and *in vivo* and their possible contributions to adjuvanticity. *In vitro*, alum complexed with antigen increases antigen uptake by APC. In addition, alum induces direct activation of Nlrp3 (Nalp3) inflammasome complex and synergizes with LPS stimulation of TLR4 for the secretion pro-inflammatory cytokines such as IL-1β, IL-18 and IL-33. *In vivo*, alum induces necrosis in unidentified target cells resulting in production of uric acid, which has the potential to stimulate Nlrp3. Alum also stimulates local recruitment of APC and migration of APC to the draining lymph nodes. It has been proposed that alum may also enhance local antigen persistency ("depot" effect). The contribution of all these activities to alum adjuvanticity and the requirement of Nlrp3 are not yet fully understood.

Eur. J. Immunol. 2008. 38: 2085–2089 DOI 10.1002/eji.200838549 HIGHLIGHTS

European Journal of Immunology

The Nlrp3 inflammasome is critical for aluminium hydroxide-mediated IL-1β secretion but dispensable for adjuvant activity

Luigi Franchi and Gabriel Núñez

Department of Pathology and Comprehensive Cancer Center, The University of Michigan Medical School, Ann Arbor, MI, USA

DOI: 10.1111/all.13982

LETTER TO THE EDITOR

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

Aluminium from adjuvanted subcutaneous allergen immunotherapeutics in rats is mainly detected in bone

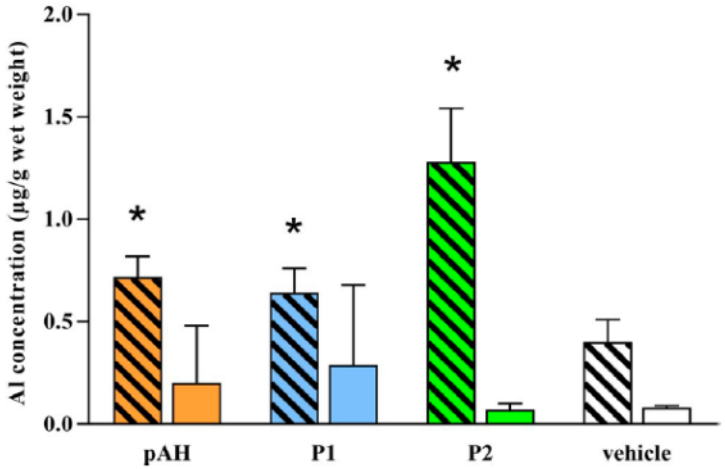


FIGURE 2 Mean (+SD) Al concentration in bone (striped bars) and brain (unfilled bars) of rats on day 80 after SC injection of plain AH adjuvant (pAH), adjuvanted SCIT products P1 or P2, or vehicle. *$P < .05$ (ANOVA compared with vehicle) [Colour figure can be viewed at wileyonlinelibrary.com]

Furthermore, our data indicate that Al-adjuvanted SCIT products do not behave uniformly: we observed a remarkable difference in the degree of systemic Al availability at day 80 between two

Safety of rush subcutaneous immunotherapy administered in real life using an infusion pump

Letters / Ann Allergy Asthma Immunol 115 (2015) 523–535

Silvia Antonieta Uriarte Obando, MD[*]
Joaquín Sastre Domínguez, MD, PhD[*,†]
[*]*Allergy Department*
Jiménez Díaz Foundation
Madrid, Spain

Table 1
Schedule of rush immunotherapy

Extract	Week	Vial	Dose, mL	SQ[a] or STU,[b] μg per dose	Administration
Avanz	0	B	0.1	3000 SQ	IP
	2	B	0.2	6000 SQ	IP
	4	B	0.5	15,000 SQ	IP
	6	B	0.5	15,000 SQ	IP
	8	B	0.5	15,000 SQ	Without IP
	10	B	0.5	15,000 SQ	Without IP
Pangramin	0	B	0.1	100 STU	IP
	2	B	0.2	200 STU	IP
	4	B	0.8	800 STU	IP
	6	B	0.8	800 STU	IP
	10	B	0.8	800 STU	Without IP
	14	B	0.8	800 STU	Without IP
Alutard	0	4	0.1	10,000 SQ	IP
	1	4	0.5	50,000 SQ	IP
	2	4	1	100,000 SQ	IP
	4	4	1	100,000 SQ	IP
	8	4	1	100,000 SQ	Without IP
	12	4	1	100,000 SQ	Without IP
Pharmalgen	0	4	0.1	5 μg	IP
	1	4	0.5	50 μg	IP
	2	4	1	100 μg	IP
	4	4	1	100 μg	IP
	8	4	1	100 μg	Without IP
	12	4	1	100 μg	Without IP

Abbreviations: IP, infusion pump; STU, skin test unit; SQ, standard quality unit.
[a]Equivalent maximum dose: 100,000 SQ of approximatelv 14.6 μg/mL for Fel d 1 and approximately 8 μg/mL for Can f 1.
[b]Equivalent maximum dose: 1000 STU of approxima

Table 2
Description of doses and adverse reactions

Extract	Patients	All doses	Doses with IP	LRs, No. (%)				SRs, No. (%)				Grading[a]			Time of onset	
				All LRs		LRs with IP		All SRs		SRs with IP						
				Patients	Doses	Patients	Doses	Patients	Doses	Patients	Doses	1	2	3	I	D
Avanz	20	96	78	4 (20)	11 (11.5)	4 (20)	10 (12.8)	3 (15)	4 (4.2)	3 (15)	4 (5.1)	3	1	0	2	2
Pangramin	6	30	25	2 (33.3)	6 (20)	2 (33.3)	6 (24)	0 (0)	0 (0)	0 (0)	0 (0)	0	0	0	0	0
Alutard	81	390	345	12 (14.8)	17 (4.4)	12 (14.8)	17 (4.9)	10 (12.3)	21 (5.4)	9 (11.1)	18 (5.2)	10	8	0	15	3
Pharmalgen	5	27	22	3 (60)	7 (25.9)	3 (60)	7 (31.8)	1 (20)	1 (3.7)	1 (20)	1 (4.5)	1	0	0	0	1
Total	112	543	470	21 (18.8)	41 (7.5)	21 (18.8)	40 (8.5)	14 (12.5)	26 (4.8)	13 (11.6)	23 (4.9)	14	9	0	17	6

Published in final edited form as:

JAMA. 2017 February 14; 317(6): 615–625. doi:10.1001/jama.2016.21040.

Effect of Two Years of Treatment with Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at Three Years among Patients with Moderate to Severe Seasonal Allergic Rhinitis: A Randomized Clinical Trial:

The GRASS Randomized Clinical Trial

CONSORT - Enrollment, Randomization, Treatment, and Follow-up.

231 patients were assessed for eligibility

125 were not eligible for inclusion in the study

105 did not meet inclusion criteria

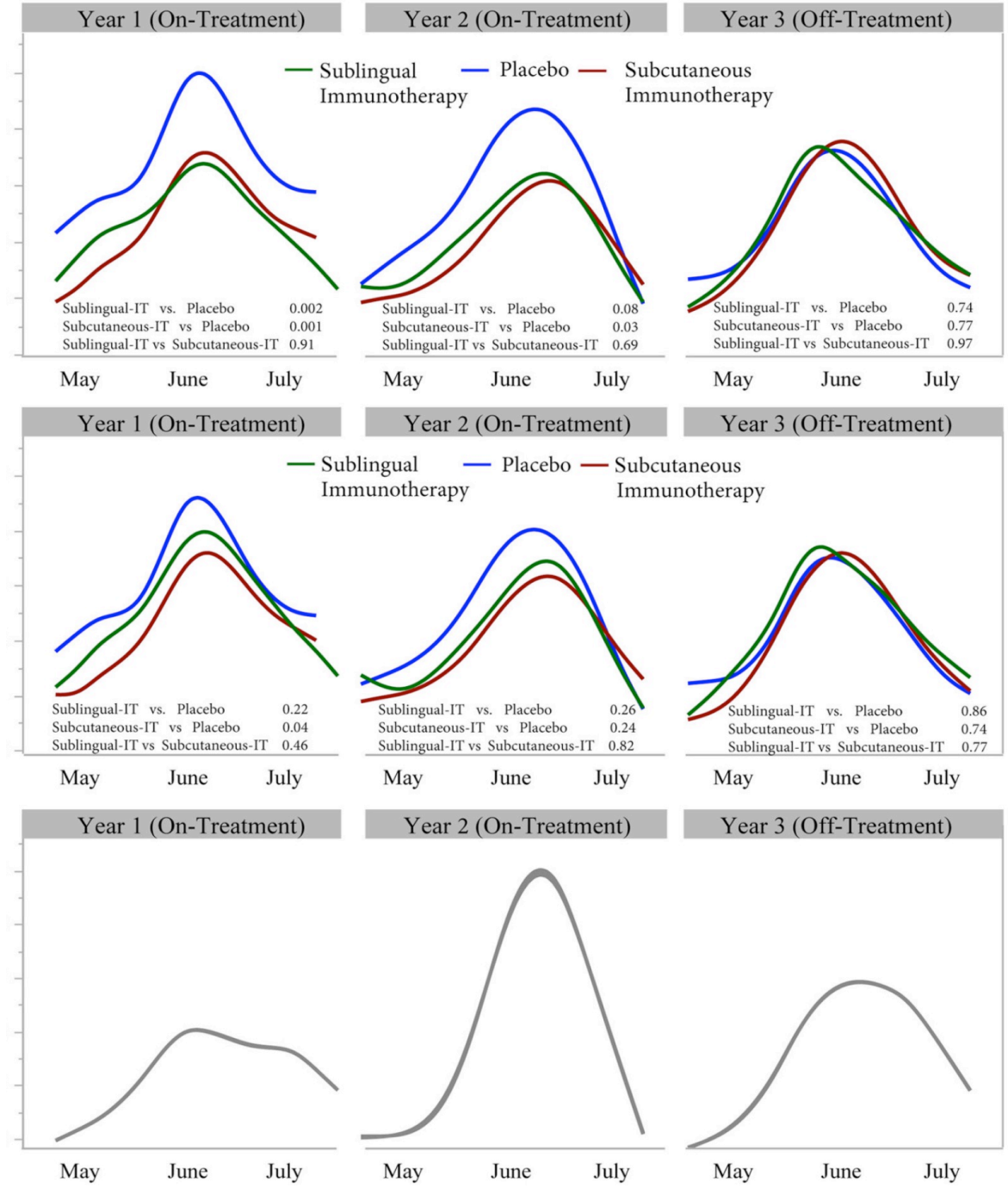
- 29 Had negative grass Skin Prick Tests and/or sIgE to grass
- 35 Had moderate to severe symptoms due to tree pollen allergy
- 14 Had allergic rhinitis symptoms due to other inhaled allergens
- 13 Met exclusionary medical conditions
- 5 Had persistent asthma requiring regular ICS outside of the pollen season
- 9 Met other exclusionary criteria

17 withdrew informed consent

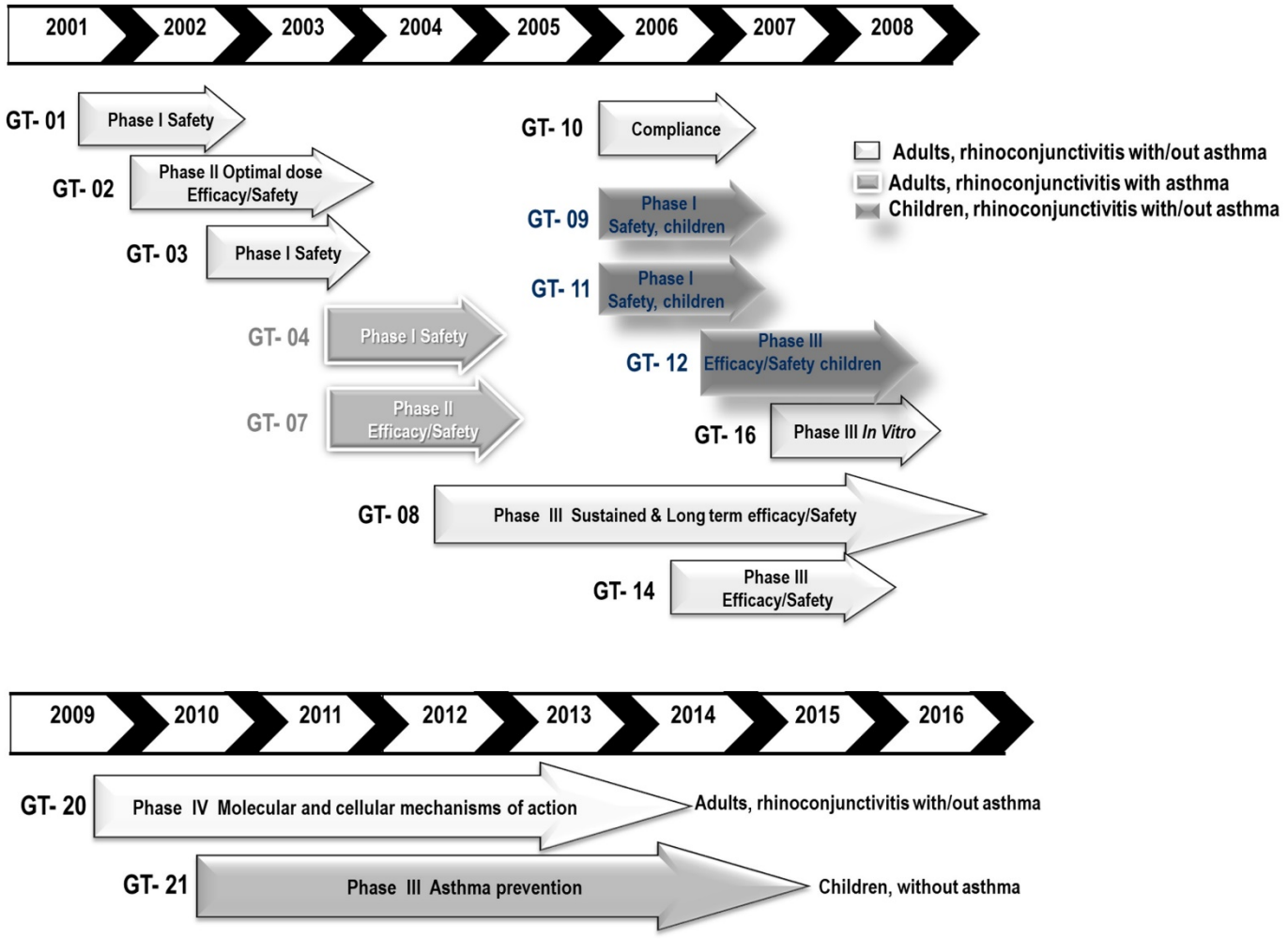
3 lost to follow-up

106 underwent baseline assessments and randomization

	36 were assigned to SLIT	**34 were assigned to Placebo**	**36 were assigned to SCIT**
Treatment Yr-1	**33 completed 1-yr assessments** 2 withdrew consent due to time commitment 1 lost to contact	**33 completed 1-yr assessments** 1 terminated due to medical condition unrelated to study treatment	**34 completed 1-yr assessments** 1 lost to contact 1 withdrew consent due to SCIT-related adverse reaction
Treatment Yr-2	**31 completed yr-2 assessments** 1 moved abroad 1 withdrew consent due to time commitment	**32 completed yr-2 assessments** 1 withdrew consent due to time commitment	**32 completed yr-2 assessments** 1 terminated due to adverse event unrelated to study treatment 1 lost to contact
Follow-up	**30 completed yr-3 assessments (30)** 1 terminated due to pregnancy	**31 completed yr-3 assessments** 1 lost to contact	**31 completed yr-3 assessments** 1 withdrew consent due to time commitment
	30 were included in the modified intent-to-treat population 27 were included in the per-protocol population	31 were included in the modified intent-to-treat population 30 were included in the per-protocol population	31 were included in the modified intent-to-treat population 27 were included in the per-protocol population



AIT GRASS-TABLETS: Summary of clinical trials performed in Europe.



Barber et al. Human Vaccines & Immunotherapeutics 2019. In press

SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial

Stephen R. Durham, MD,[a] Waltraud Emminger, MD,[b] Alexander Kapp, MD, PhD,[c] Jan G. R. de Monchy, MD,[d] Sabina Rak, MD,[e] Glenis K. Scadding, MD, FRCP,[f] Peter A. Wurtzen, PhD,[g] Jens S. Andersen, PhD,[g] Bente Tholstrup, MSc,[g] Bente Riis, PhD,[g] and Ronald Dahl, MD[h] *London, United Kingdom, Vienna, Austria, Hannover, Germany, Groningen, The Netherlands, Gothenburg, Sweden, and Hørsholm and Aarhus, Denmark*

J ALLERGY CLIN IMMUNOL
MARCH 2012

-Early Effect
-Sustained Effect

-Long-term effect
-Preventive effect

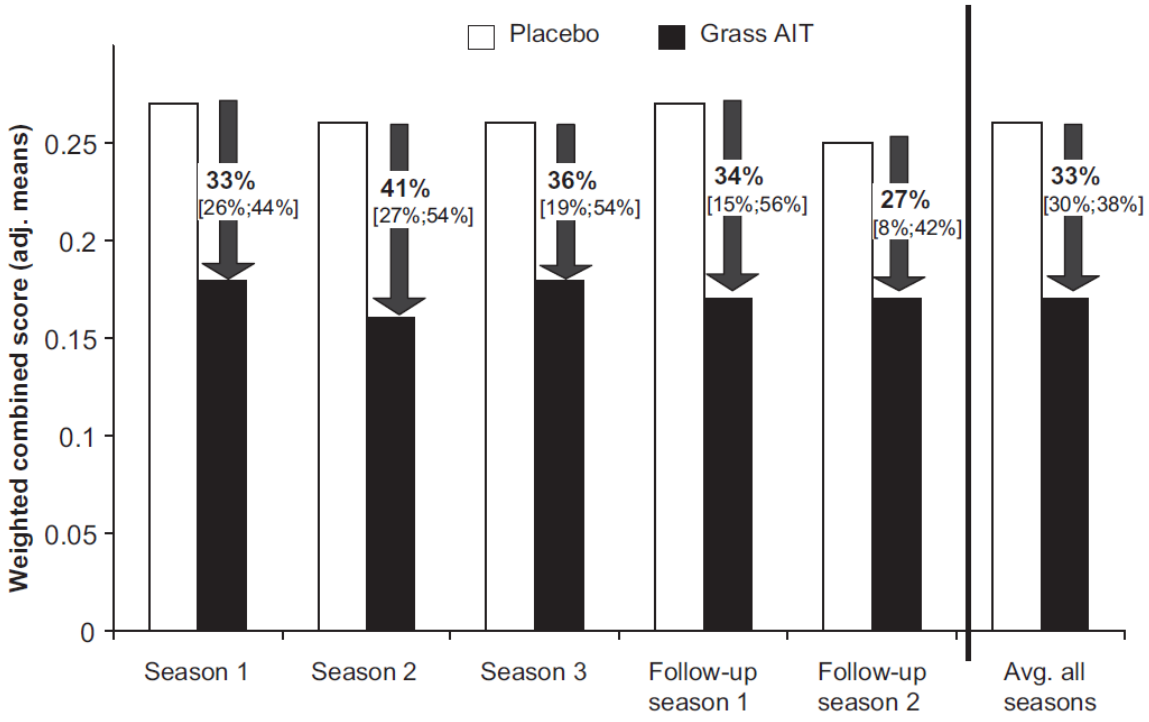


FIG 1. Weighted rhinoconjunctivitis combined symptom and medication score for the 5 grass pollen seasons of the trial and averaged over all seasons with relative differences between groups and 95% CI. All relative differences were statistically significant. *Adj.*, Adjusted; *avg.*, averaged.

Allergy 2007: 62: 958–961

DOI: 10.1111/j.1398-9995.2007.01416.x

Short communication

Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy

M. A. Calderon[1], A. O. Birk[2], J. S. Andersen[2], S. R. Durham[1]

[1]Imperial College, National Heart and Lung Institute, London, UK; [2]ALK-Abelló, Hørsholm, Denmark

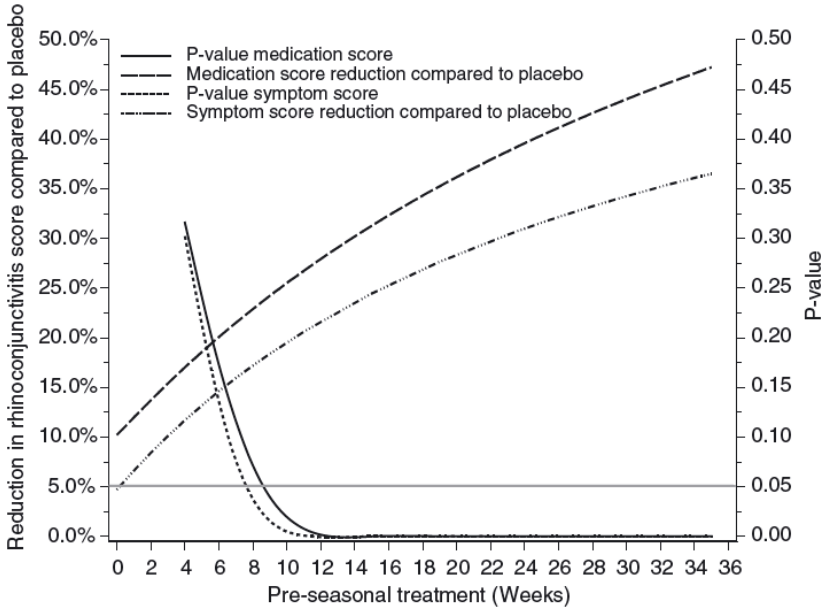


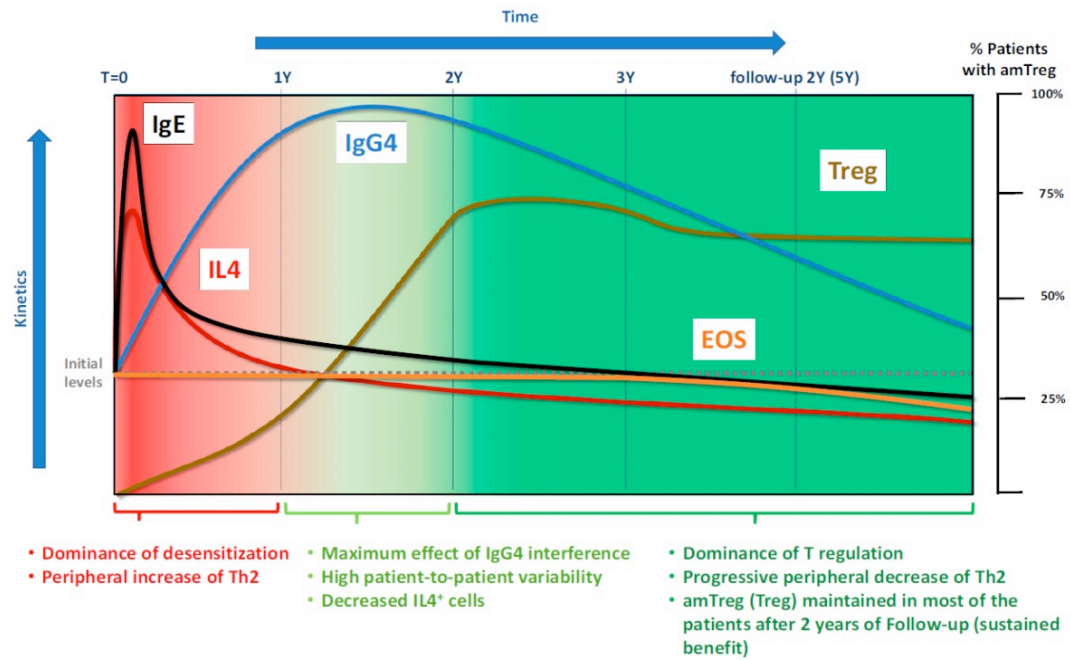
Figure 1. Duration of preseasonal treatment in relation to average symptom and medication score reductions in the grass pollen season.

Persistent regulatory T-cell response 2 years after 3 years of grass tablet SLIT: Links to reduced eosinophil counts, sIgE levels, and clinical benefit

Allergy. 2019;74:349–360.

Rosa Varona[1] | Tania Ramos[2] | Maria Marta Escribese[3,4,5] | Lucia Jimeno[6] | Agustin Galán[6] | Peter A. Würtzen[7] | Francisco Vega[2] | Alicia Marín[6] | Santiago Martín[6] | Ana C. Carrera[1] | Carlos Blanco[2,5] | Domingo Barber[3,5]

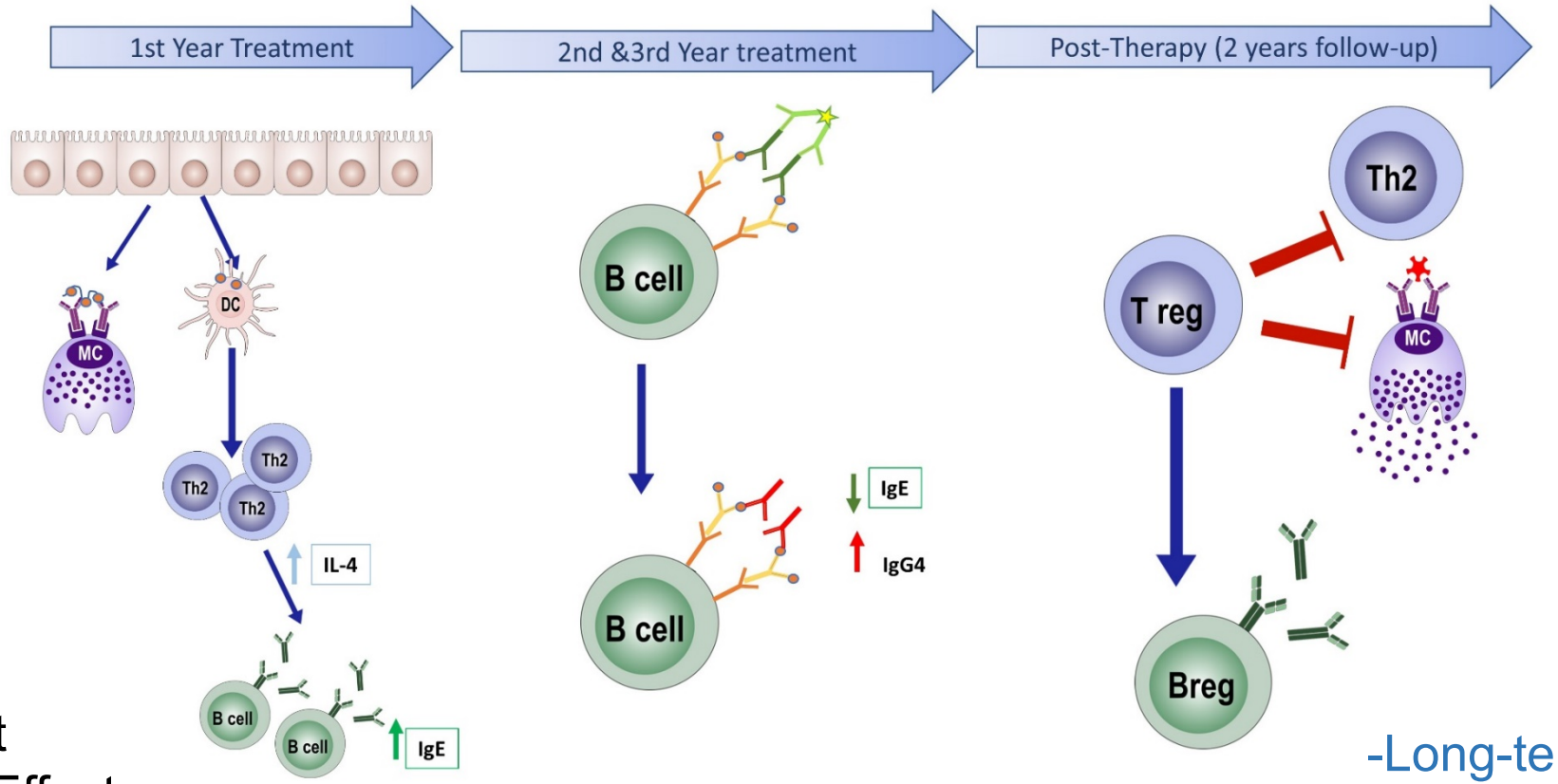
Changes in humoral and cellular immune responses during grass pollen SLIT over a five-year period (3+2 follow-up)



GRAPHICAL ABSTRACT

Early effect is governed by effector cell desensitization. SIgG4 interference is generated a few months after SIT initiation and is maximum in the first two treatment years. amT regulatory response is consolidated after 3 continuous treatment years and is key for sustained benefit two years after SIT cessation.

AIT : Three concerted mechanisms with different kinetics and high patient to patient variability



-Early Effect
-Sustained Effect

-Long-term effect
-Preventive effect

Barber et al. Human Vaccines & Immunotherapeutics 2019.

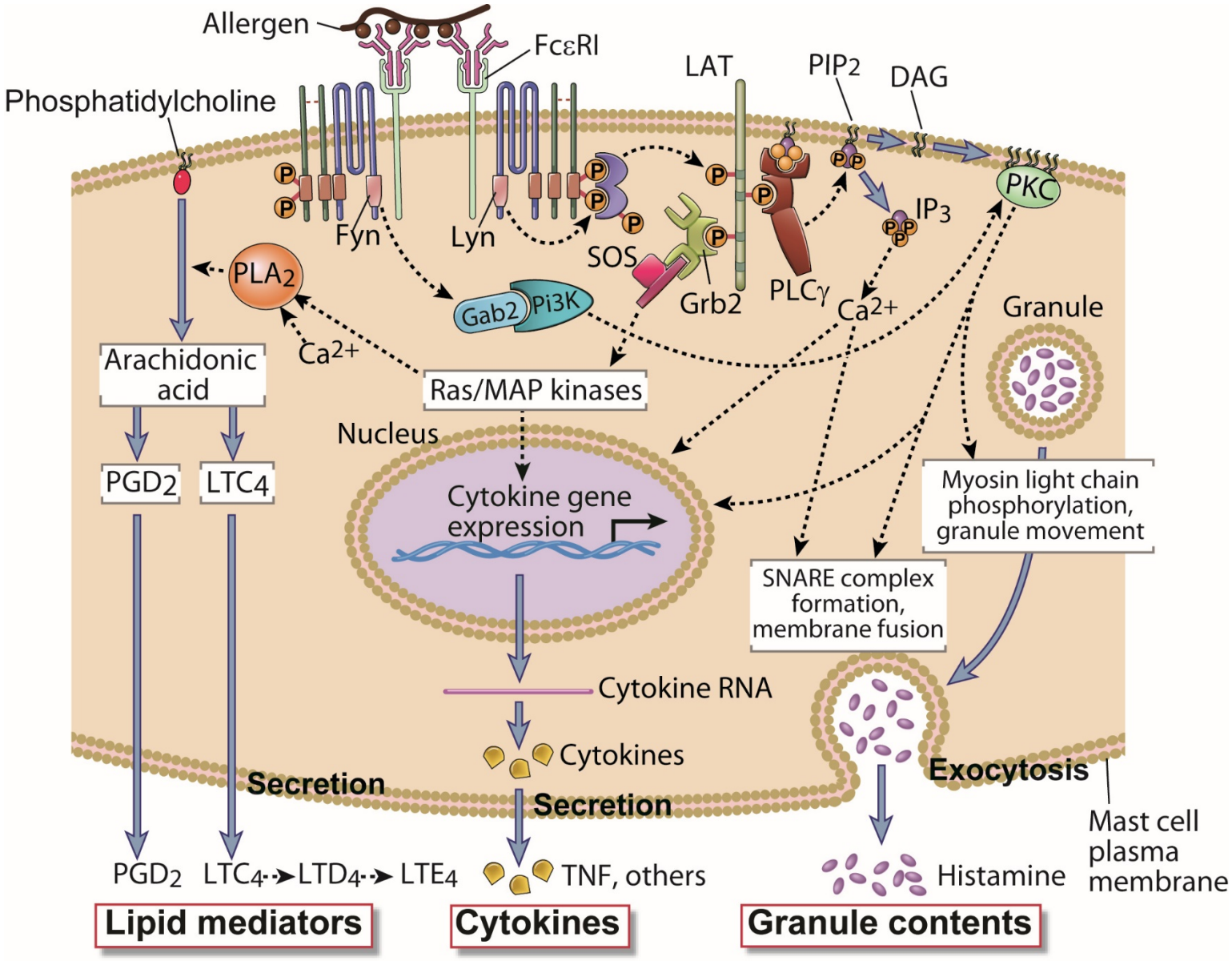
Sustained Successful Peanut Oral Immunotherapy Associated with Low Basophil Activation and Peanut-Specific IgE

Mindy Tsai, DMSc[1,2*], Kaori Mukai, PhD[1,2*], R. Sharon Chinthrajah, MD[1,2], Kari C. Nadeau, MD, PhD[1,2,] Stephen J. Galli, MD[1,2,3,]

PII: S0091-6749(19)31620-3
DOI: https://doi.org/10.1016/j.jaci.2019.10.038
Reference: YMAI 14285

To appear in: *Journal of Allergy and Clinical Immunology*

Biochemical Events of Mast Cell Activation



Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy

Erkka Valovirta, MD,[a,b] Thomas H. Petersen, MD,[c] Teresa Piotrowska, MD,[d] Mette K. Laursen, MSc,[e] Jens S. Andersen, MSc, PhD,[e] Helle F. Sørensen, MSc, PhD,[e] and Rabih Klink, MD,[f] on behalf of the GAP investigators*

Turku, Finland, Kolding and Hørsholm, Denmark, Białystok, Poland, and Laon, France

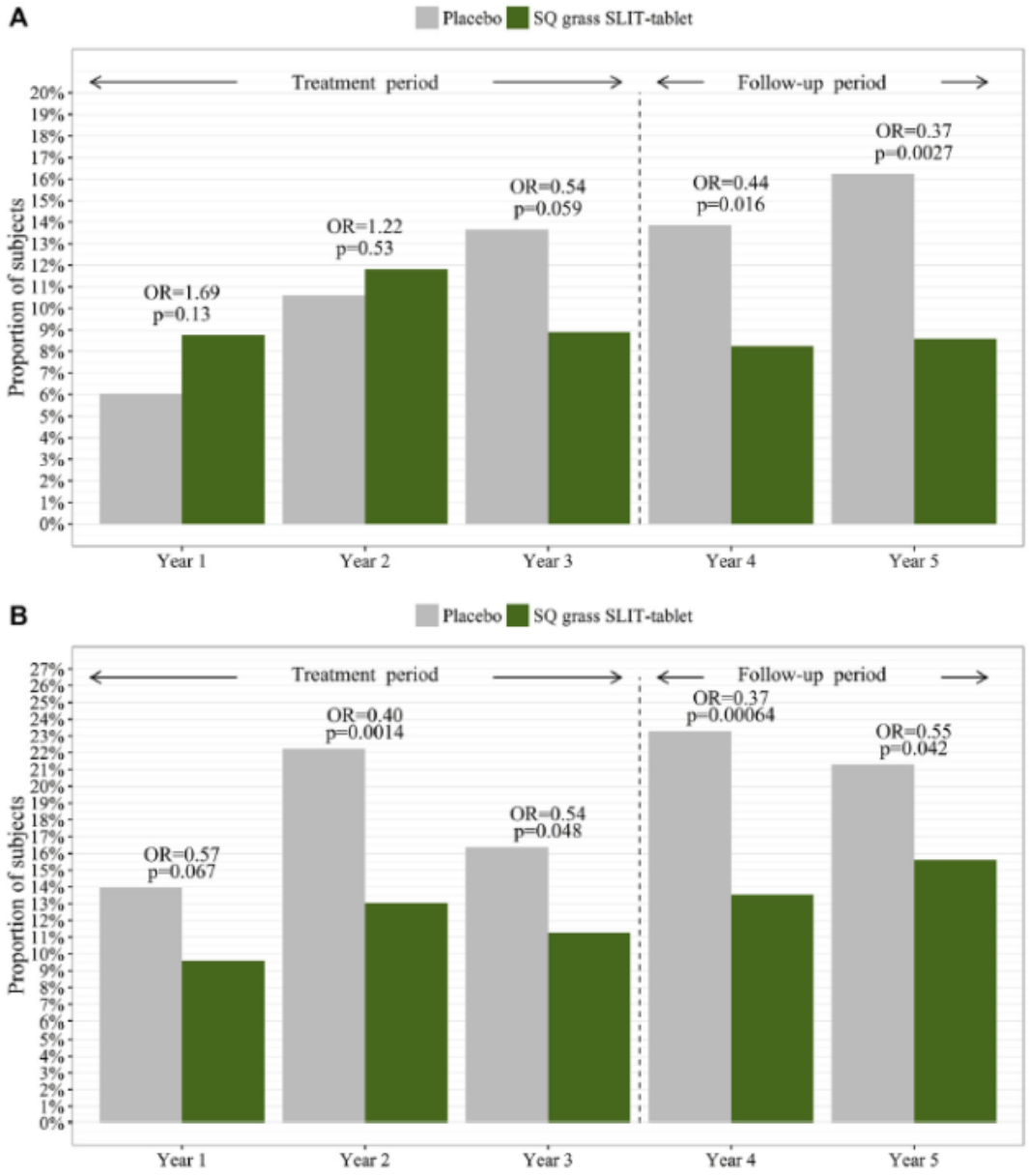


FIG 2. Proportion of subjects experiencing asthma symptoms or asthma medication use reported at winter visits (**A**) and summer visits (**B**).

Winter asthma symptoms only improve in the third winter an reach the highest improvement two years after AIT cessation

Understanding severity:

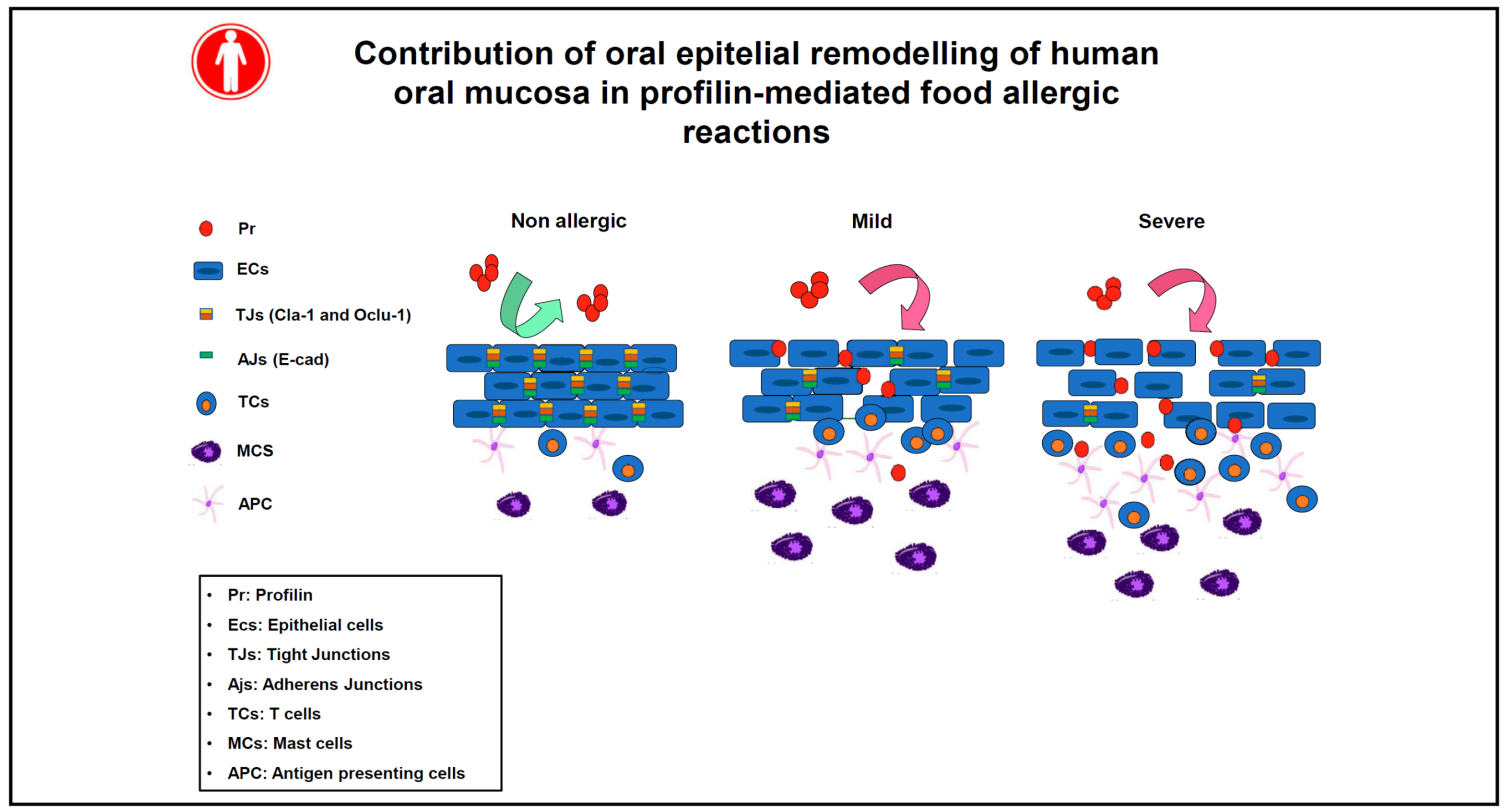
1. Severe reactors to profilin

Profilin-mediated food-induced allergic reactions are associated with oral epithelia remodeling

J ALLERGY CLIN IMMUNOL
FEBRUARY 2019

Domenico Rosace, MSc,[a] Cristina Gomez-Casado, PhD,[a] Paloma Fernandez, PhD,[a] Marina Perez-Gordo, PhD,[b] María del Carmen Dominguez, MD,[c] Angel Vega, MD,[c] María Teresa Belver, MD,[d] Tania Ramos, MD,[d] Francisco Vega, MD,[d] Guadalupe Marco, MD, PhD,[e] Manuel de Pedro, MD,[e] Leticia Sanchez, MD,[e] María de las Mercedes Arnas, MD, PhD,[f] Marcela Santaolalla, MD, PhD,[f] Miguel Ángel Saez, MD,[g] Sara Benedé, PhD,[h] Montserrat Fernandez-Rivas, MD, PhD,[e] Carlos Blanco, MD, PhD,[d] Maria Isabel Alvarado, MD, PhD,[c] María M. Escribese, PhD,[a,b] and Domingo Barber, PhD[a] *Madrid and Cáceres, Spain*

GRAPHICAL ABSTRACT



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DOI: 10.1111/all.13563

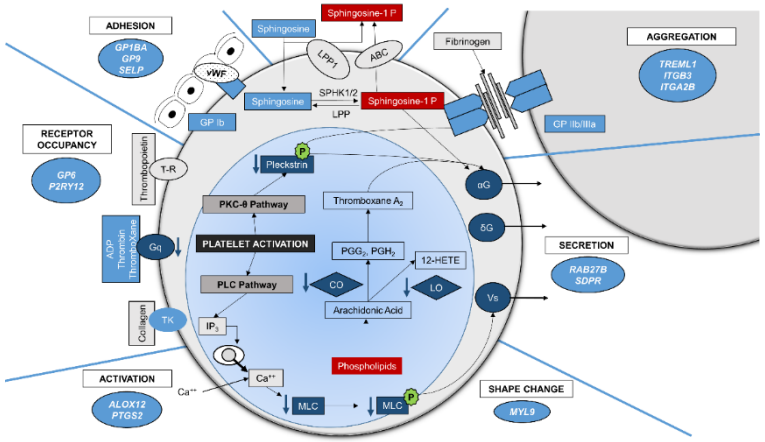
ORIGINAL ARTICLE

Experimental Allergy and Immunology

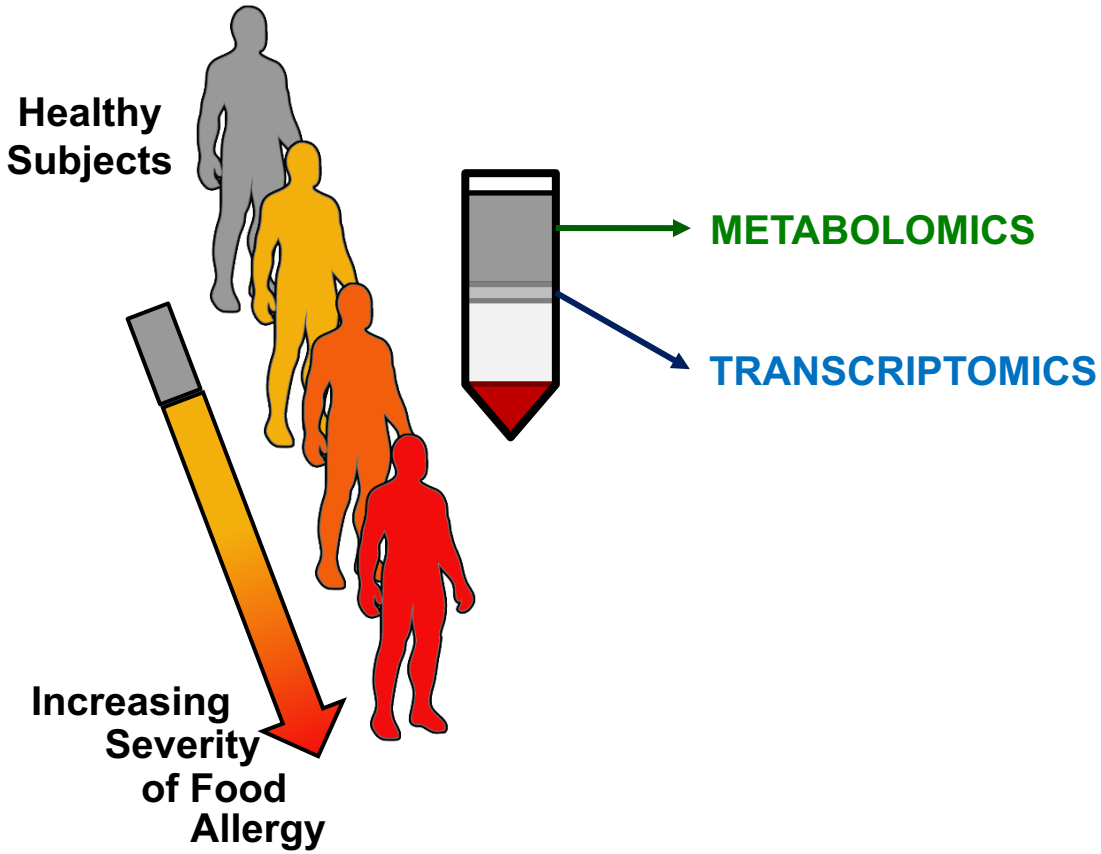
WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Multi-omics analysis points to altered platelet functions in severe food-associated respiratory allergy

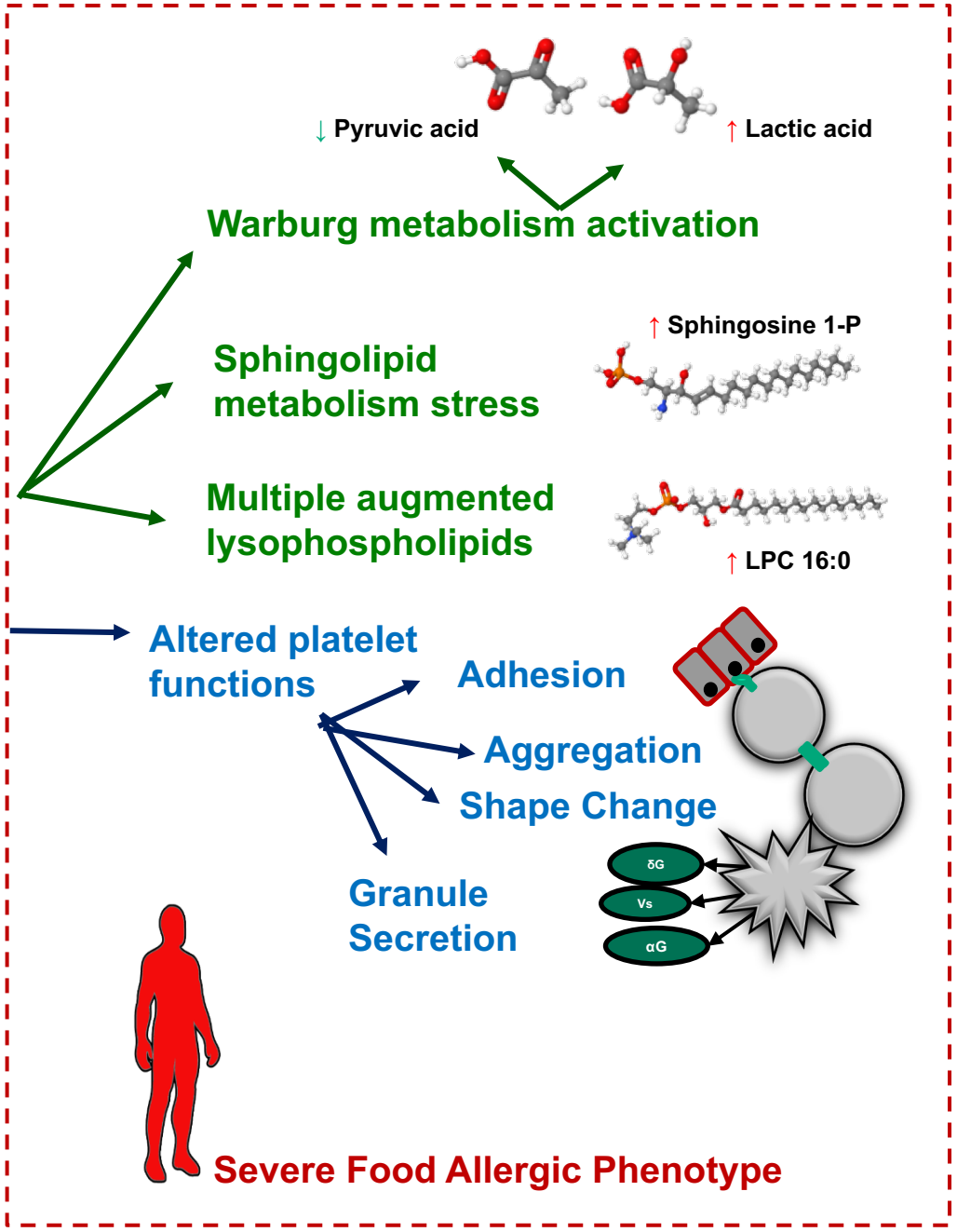
David Obeso[1,2] | Leticia Mera-Berriatua[1] | Juan Rodríguez-Coira[1,2] | Domenico Rosace[1] | Paloma Fernández[1] | Isabel Adoración Martín-Antoniano[1,3] | Marcela Santaolalla[4] | Guadalupe Marco Martín[5] | Tomás Chivato[1,3] | Montserrat Fernández-Rivas[5] | Tania Ramos[6] | Carlos Blanco[6] | María I. Alvarado[7] | Carmen Domínguez[7] | Santiago Angulo[8] | Coral Barbas[2] | Domingo Barber[1] | Alma Villaseñor[1] | María M. Escribese[1,9]



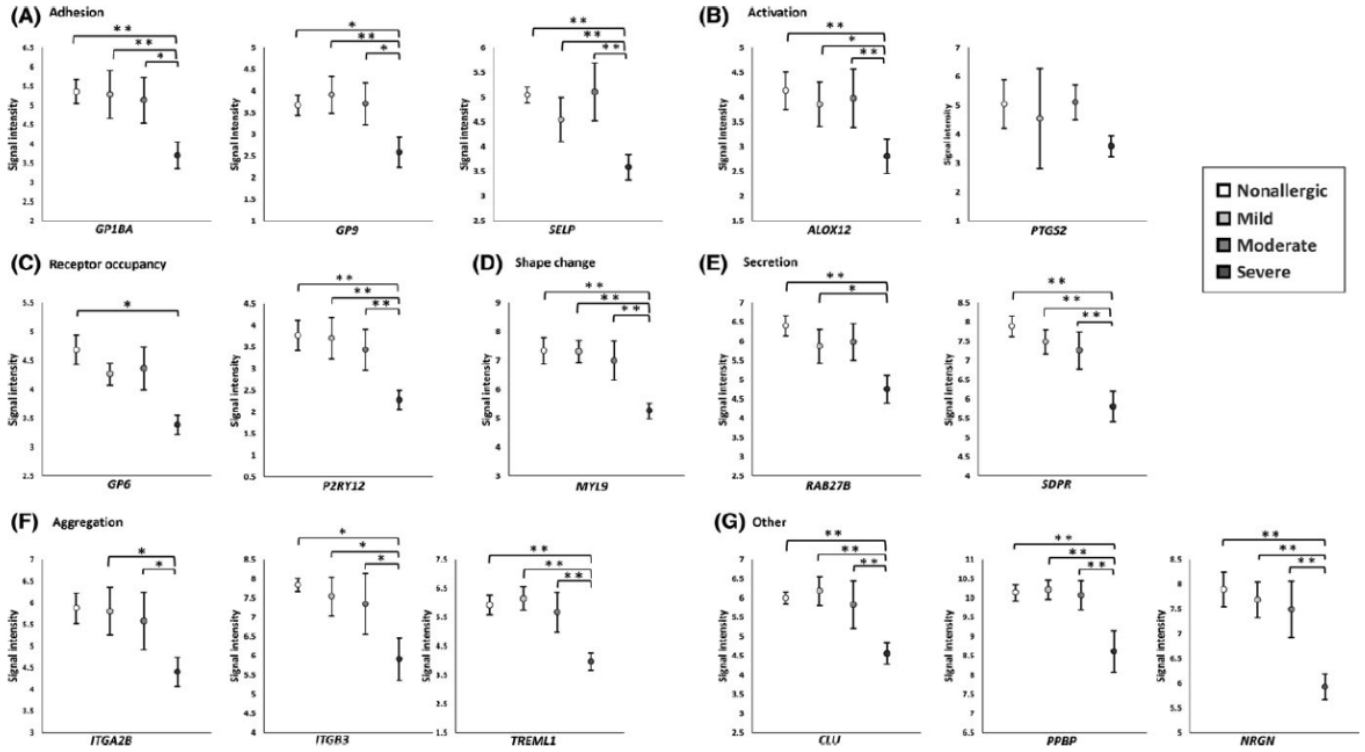
SIGNATURES LINKED TO SEVERE PHENOTYPE



Obeso et al Allergy. 2018



PLATELETS



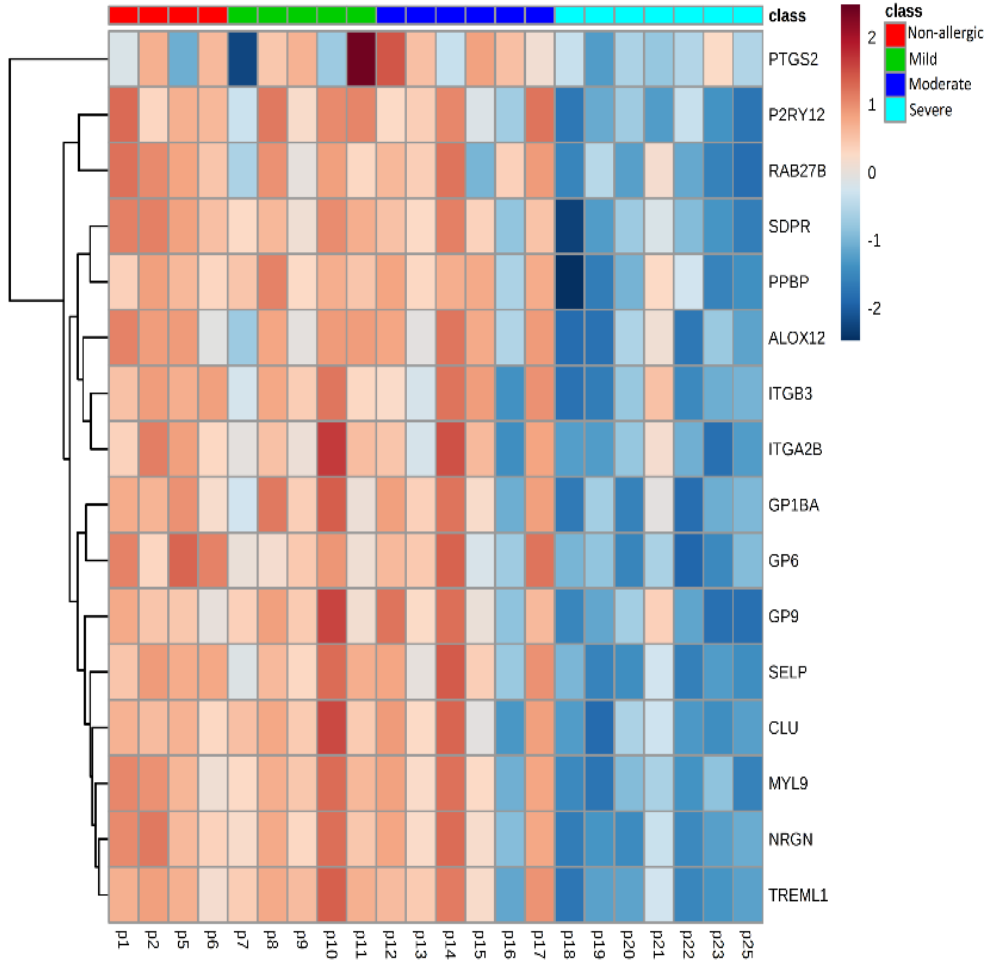
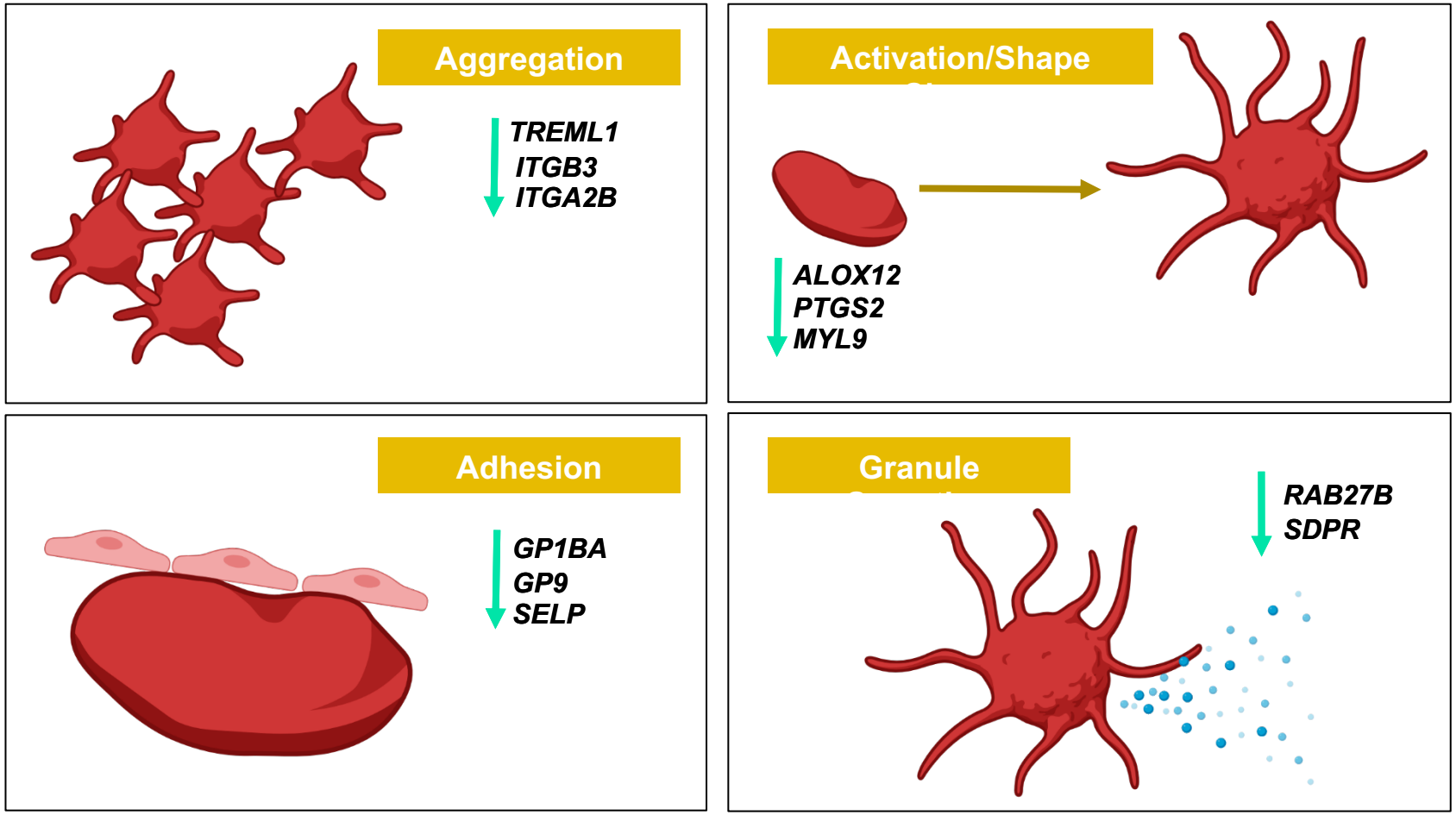


FIGURE 4 Trajectories of significant transcripts associated with platelet functions. (A) Adhesion, (B) Activation, (C) Receptor Occupancy, (D) Shape Change, (E) Secretion, (F) Aggregation, (G) Other (Key: "nonallergic": white square, "mild": light gray square, "moderate": gray square, "severe": dark gray square), 95% confidence interval limits for the mean (central circle) of each experimental group are indicated ** ANOVA p-value < 0.001. *ANOVA p-value < 0.05.

Obeso et al Allergy. 2018

Platelet functionality might be compromised in severe patients



LETTER

108 | NATURE | VOL 544 | 6 APRIL 2017

The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors

Emma Lefrançais[1]*, Guadalupe Ortiz-Muñoz[1]*, Axelle Caudrillier[1], Beñat Mallavia[1], Fengchun Liu[1], David M. Sayah[2], Emily E. Thornton[3], Mark B. Headley[3], Tovo David[4], Shaun R. Coughlin[4], Matthew F. Krummel[3], Andrew D. Leavitt[1], Emmanuelle Passegué[1] & Mark R. Looney[1,5]

karyocytes per hour in an imaged lung volume of 0.07 mm^3 (Fig. 1g and Supplementary Video 5). When extrapolated to the entire lung volume, this equals more than 10 million platelets produced per hour from the lungs (Fig. 1h, Methods and Extended Data Table 1). Overall, when adjusted for platelet lifespan and splenic sequestration, we estimate that the lung is responsible for approximately 50% of total platelet production in the mouse (Fig. 1i, Methods and Extended Data Table 1). Blood platelet counts were unchanged after 2PIVM (Extended Data

Our results provide direct evidence that the lungs are a major site of platelet biogenesis, which involves a distinct mechanism of proplatelet release from intravascular megakaryocytes (of extrapulmonary origin) in the lung microcirculation (Extended Data Fig. 9a). These results open new lines of investigation to improve our approach to treating thrombocytopenia, which affects millions of patients worldwide and causes substantial morbidity and mortality. We propose that the lungs are an ideal bioreactor for the production of mature platelets from megakaryocytes, and could advance studies of the treatment of thrombocytopenia with cell-based therapies[16]. Beyond the mechanical forces that

International Journal of
Molecular Sciences

MDPI

Review

Understanding Platelets in Infectious and Allergic Lung Diseases

Int. J. Mol. Sci. **2019**, *20*, 1730; doi:10.3390/ijms20071730

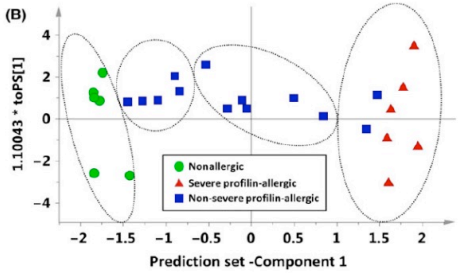
Cristina Gomez-Casado [1,*], Alma Villaseñor [1], Alba Rodriguez-Nogales [2], Jose Luis Bueno [3], Domingo Barber [1] and Maria M. Escribese [1]

Table 1. *Cont.*

Produced Metabolites		
No.	**Molecule**	**Immune/Inflammatory Role**
1	Thromboxane	Eicosanoid: T-cell differentiation, monocyte activation
2	Nitric oxide	Reactive oxygen species: anti-inflammatory and antithrombotic
3	GPIbα	Adhesion molecule: binds Mac-1 on leukocytes
4	TXA2	Mediator that enhance platelet activation
5	S1P	Active metabolite which activate platelets and stimulate mitogenesis
6	PAF	Bioactive lipid: induce endothelial migration
7	Chrondroitin sulfate	Metabolite released by platelets after trigger complement activation
8	LPA	Lipid: ligand of G protein-coupled receptors
Membrane Receptors		
No.	**Molecule**	**Immune/Inflammatory Role**
1	TLR1, TLR2, TLR4, TLR6, TRL8 and TLR9	Receptors that recognize pathogen-associated molecular patterns and mediate inflammatory events
2	CD40, CD40L	Receptor: Mediator of interactions between lymphocytes and antigen presenting cells
3	GPIa, GPIIb/IIIa, GPIc-IIa (VLA-6)	Platelet glycoprotein: adhesion molecules
4	GPVI	Collagen receptor: induces powerful platelet activation
5	P2X1	Receptor is involved in platelet shape change and in activation by collagen
6	P2Y1, P2Y12	G-protein receptors: sustain platelet activation in response to ADP
7	PAR-1, PAR-4	Thrombin activates platelets through proteolytic cleavage of PAR receptors
8	ICAM-2,	Adhesion molecule
10	JAM-A,	Protects from thrombosis by suppressing integrin αIIbβ3

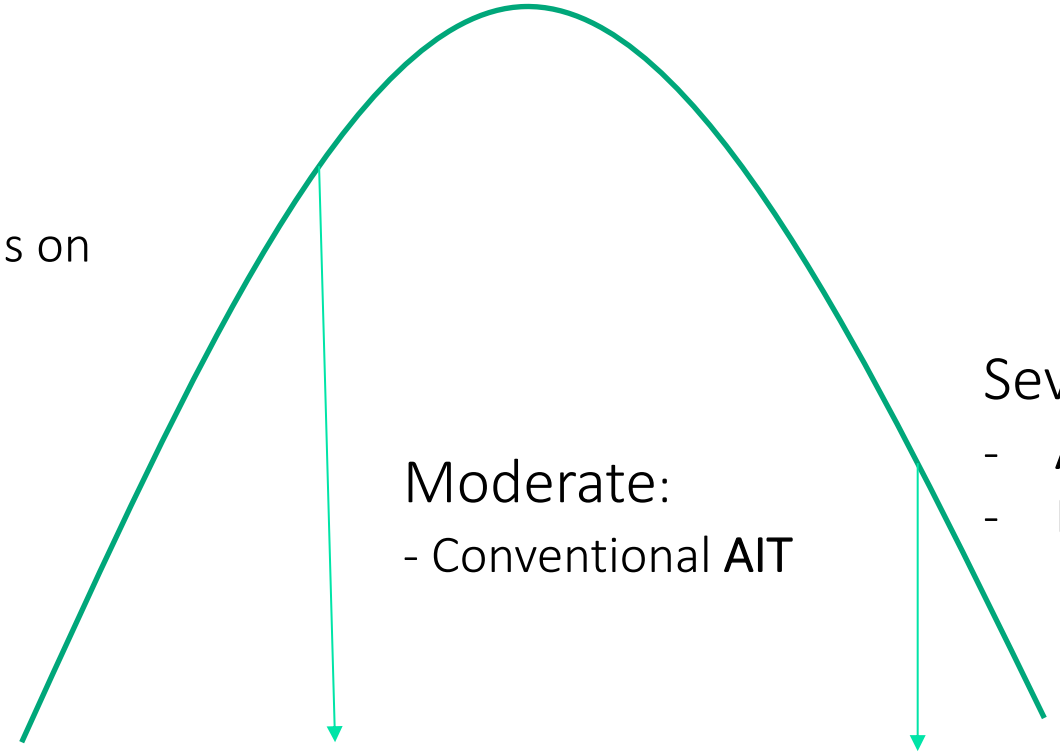
NOTE: ADP, adenosine 5′-diphosphate; CD40L, CD40 ligand; DC, dendritic cell; GPIba, glycoprotein Iba; 5-HT, 5-hydroxytryptamin; IL, interleukin; LPA, lysophosphatydic acid; MIP, macrophage-inflammatory protein; MMP, metalloproteinase; NAP, neutrophil-activating peptide; PAFR, platelet-activating factor receptor; PAR, protease-activated receptors; PDGF, platelet-derived growth factor; PF4, platelet factor 4; PMN, neutrophil; ppbp, proplatelet basic protein; SDF, stromal cell–derived factor; SP1, sphingosine-1-phosphate; TGF, transforming growth factor; Th, T helper; TLR, toll-like receptor; TNF, tumor necrosis factor; TxA2, Thromboxane A2; VEGF, vascular endothelial growth factor; VWF, von Willebrand factor.

Ethiological approach should be centric in allergy disease management



Mild

-**AIT** with Focus on Prevention



Moderate:

- Conventional **AIT**

Severe:

- **AIT poor risk/benefit**
- Biologics(stabilization/reversion)?

Reflections

-Effector cell down-regualtion either by direct desensitization (short-term) or by global immune regulation (long-term) is key for clinical benefit.

-Understanding mechanisms associated to allergen specifc desensitation is critical (neurological mechanisms?)

-Barriers and repair related systems are critical players to be monitored before and during AIT intervention

-Omics allow a better understanding of allergy disease progression and intervention possibilities, including AIT

-It might be possible to define a combination of biomarkers to classify patients in base to severity.

-This classifiction could be used to decide AIT intervention strategies and to monitor effect, specially long-term effect

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