Nuevos tratamientos: el futuro es hoy

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FUNDACION CIDEA

Nuevos tratamientos

- Nuevas estrategias de uso de terapeuticas conocidas : Tratamiento intermitente , Suplementar Vitamina D
- Nuevas terapeuticas
  - Nuevos farmacos
  - Biólogicos
  - Inmunoterapia
  - Por que y para quien
- Rol de la Inflamometría / biomarcadores para el tratamiento personalizado
- Microbioma y asma

FUNDACION CIDEA

Tratamiento continuo vs Intermitente

Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults (Review)

Chauhan BF, Chartrand C, Ducharme FM

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 2

FUNDACION CIDEA

Tratamiento continuo vs Intermitente

- No significant difference in the number of asthma attacks of moderate severity
- Not enough information to conclude to that the two approaches were equivalent.
- ***Inhaled corticosteroids everyday*** : better asthma control, better lung function, less use of reliever medication and more symptom-free days.
- Children grew slightly less (0.41 cm/y) with daily inhaled budesonide and beclomethasone

FUNDACION CIDEA

The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: A systematic review and meta-analysis of randomized controlled trials

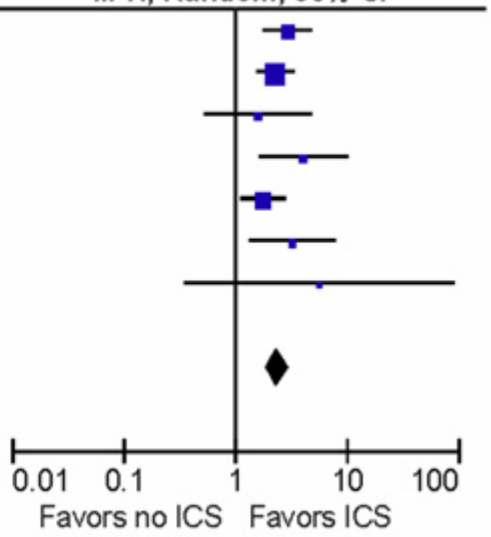
Matthew A. Rank, MD,[a] John B. Hagan, MD,[a] Miguel A. Park, MD,[a] Jenna C. Podjasek, MD,[a] Shefali A. Samant, MD,[a] Gerald W. Volcheck, MD,[a] Patricia J. Erwin, MLS,[b] and Colin P. West, MD, PhD[c,d] *Rochester, Minn*

(J Allergy Clin Immunol 2013;131:724-9.)

Study or Subgroup	Stopped ICS Events	Stopped ICS Total	Continued ICS Events	Continued ICS Total	Weight	Risk Ratio M-H, Random, 95% CI
Berger 2010	55	150	18	144	21.0%	2.93 [1.81, 4.74]
Condemi 1997	57	95	27	101	36.9%	2.24 [1.56, 3.22]
Hahhtela 1994	6	18	4	19	4.1%	1.58 [0.53, 4.70]
Lazaurs 2001	21	56	5	54	6.0%	4.05 [1.65, 9.97]
Martinez 2011	36	74	20	72	25.0%	1.75 [1.13, 2.72]
Papi 2007	21	119	6	110	6.4%	3.24 [1.36, 7.72]
Waalkens 1993	6	20	0	8	0.6%	5.57 [0.35, 88.77]
Total (95% CI)		**532**		**508**	**100.0%**	**2.35 [1.88, 2.92]**
Total events	202		80			

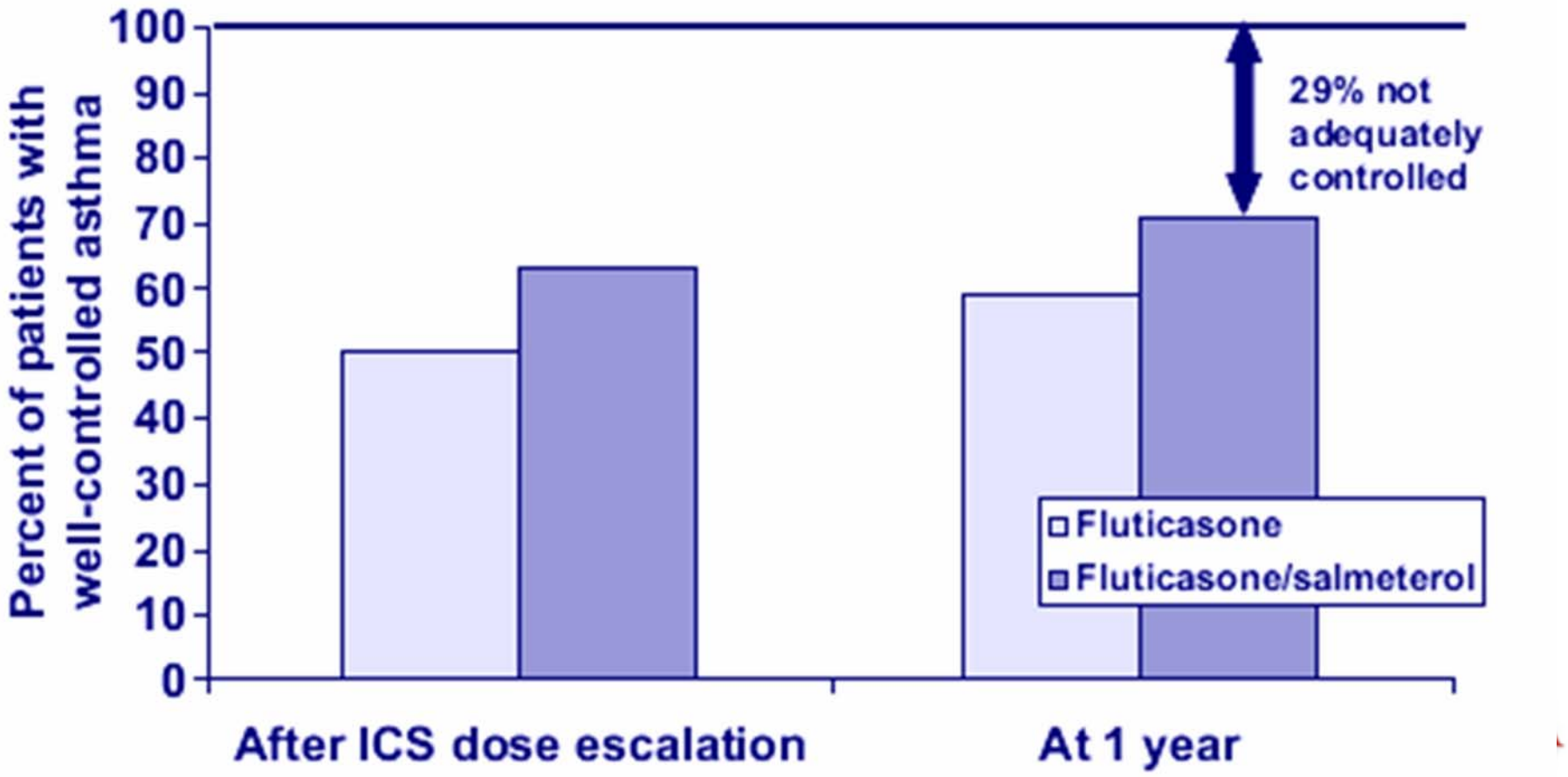
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.59$, df = 6 (P = 0.47); $I^2 = 0\%$

Test for overall effect: Z = 7.59 (P < 0.00001)

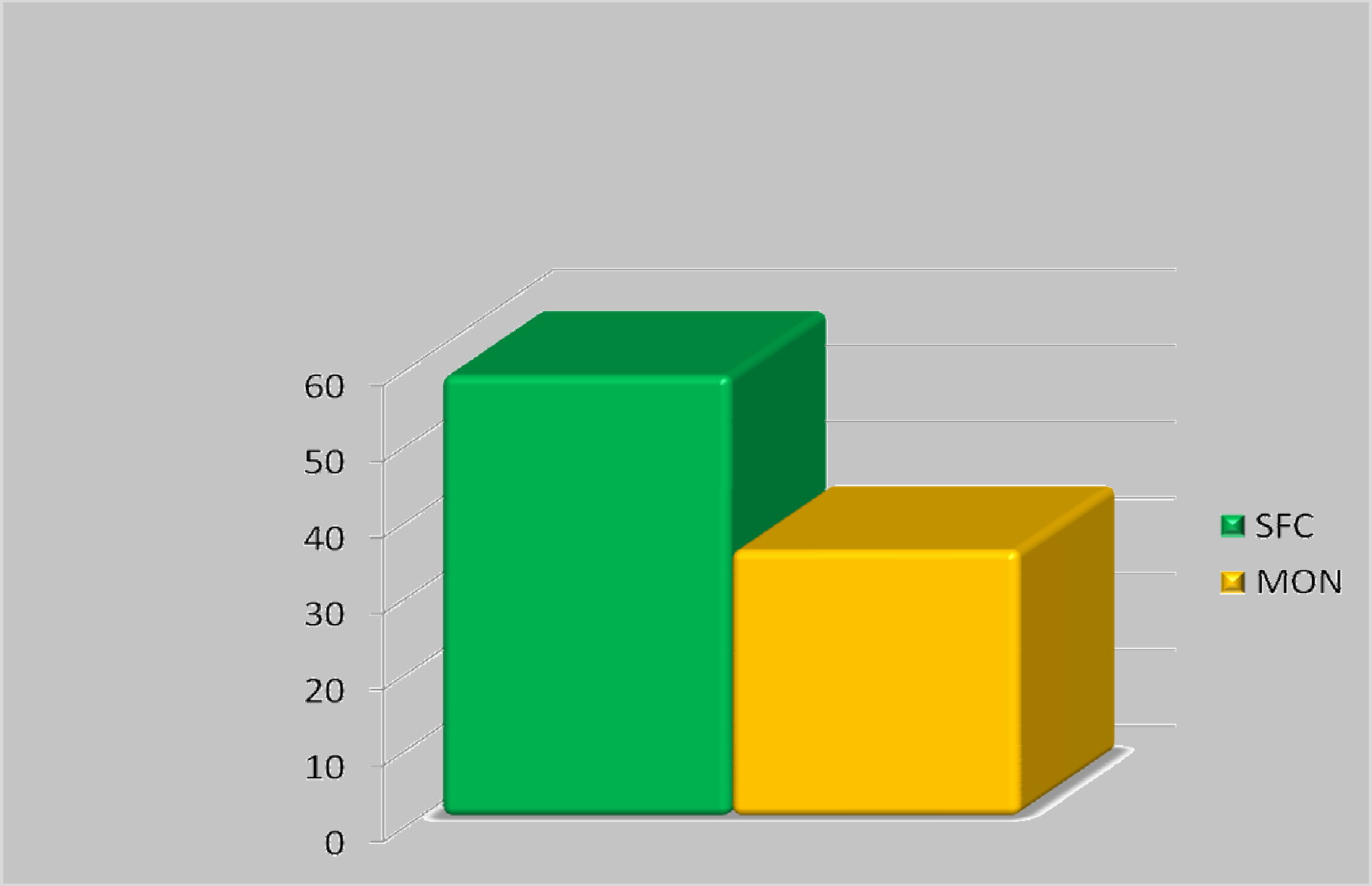


Clinical implications: For every 4 patients with stable asthma who stop low-dose ICSs, 1 will have an exacerbation in the next 6 months that is attributable to stopping the ICS.

Proportion of patients with well-controlled asthma in the Gaining Optimal Asthma ControL study at the end of ICS dose escalation and after 1 year of treatment



Proportion and Distribution of Patients Achieving Well-Controlled Asthma over Treatment



Søren Pedersen, Jorge Maspero, Nadeem Gul,and Raj Sharma, Pediatric Pulmonology 2011

Current therapies for asthma and allergy are relatively safe and effective at controlling symptoms

BUT

- Do not change the chronic course of disease or natural history of asthma
- Do not prevent asthma and allergy
- Do not control of the severe forms
- Are not curative therapies.

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Ultra long-acting β_2 agonists under development

Vilanterol

Olodaterol

Abediterol (LAS-100977)

AZD3199

PF-610355 (?)

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(Ultra) LABA/ICS combinations in clinical development for pediatrics and adults

- Formoterol + mometasone (Dulera)
- Formoterol + fluticasone propionate (Flutiform)
- Formoterol + ciclesonide
- Indacaterol + mometasone (QMF-149)
- Indacaterol + QAE-397
- Vilanterol + fluticasone furoate (Relovair)
- GS-424020 (novel mutual prodrug of salmeterol and desisobutrylciclesonide)

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Programs in development for novel bronchodilators

- Finding new classes of bronchodilators has proved difficult.
- Research groups have sought to improve the existing classes of bronchodilator drugs.
- The majority of programs are focused on developing new ligands that interact with β_2-adrenoceptors and/or muscarinic receptors in a manner that
  - enhances their bronchodilator effectiveness
  - duration of action,
  - allows only one administration per day.

Novel classes of bronchodilators

- Selective phosphodiesterase inhibitors
- K^+ channel openers
- Vasoactive intestinal peptide analogs
- Rho kinase inhibitors
- Brain natriuretic peptide and analogs
- Nitrix oxide donors
- E-prostanoid receptor 4 agonists
- Bitter taste receptor agonists

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Cazzola et al, *Pharmacol Rev* 2012

Long-acting antimuscarinic agents

Glycopyrronium (NVA-237)
Umeclidinium (GSK-573719)
Aclidinium
TD-4208
CHF 5407
QAT370
BEA-2180BR
Trospium
Dexpirronium
AZD8683
PF-3715455 or PF-3635659

- **COPD?=>Adult Asthma ??=> adolescent & pediatric asthma ???**

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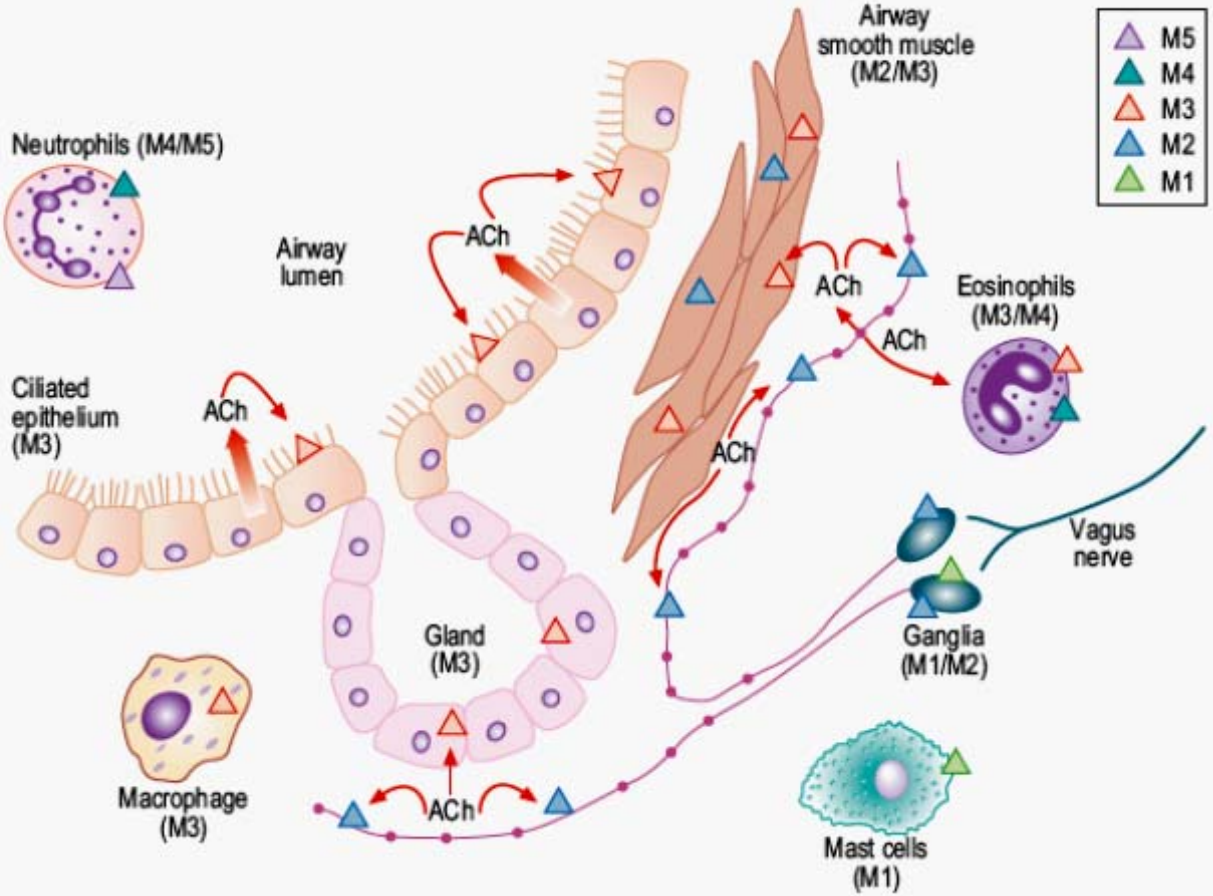
Cholinergic system & lungs

- In airways, acetylcholine is principal parasympathetic neurotransmitter.
- Acetylcholine acts upon two types of receptors
  1. nicotinic
  2. muscarinic
     - 5 subtypes, classified as M1-M5.
- Different M receptor subtypes are located on different airway structures, and their activation can lead to different downstream effects.

FUNDACION CIDEA



- airway smooth muscle (M3/M2)
- epithelium (M3), glands (M3), parasympathetic ganglia (M1/M2), parasympathetic nerve endings (M2)
- in inflammatory cells: mast cells (M1), macrophages (M3), neutrophils (M4/M5, and eos (M3/M4)

- M1, M3, M5 receptors have *stimulatory* effect on target tissue
- M2 and M4 subtypes are *inhibitory*
- Ideal anticholinergic drug for obstructive airway disease (effect on smooth muscle) should antagonize M3 receptor, with little affinity for M2 receptor.

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Anticholinergic Agents as Bronchodilators

- Compete with acetylcholine at M3 receptors on airway smooth muscle which $\Rightarrow$
  - decreases intracellular concentration of cGMP
  - inhibits tonic cholinergic activity.
  - bronchodilation (primarily a local, site-specific effect).

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Ipratropium bromide

- Nonselective antagonist of M1, M2, and M3
- Blockade of M2 receptor allows further release of presynaptic acetylcholine, may antagonize bronchodilatory effect of blocking M3

Tiotropium bromide

- 6–20-fold higher affinity for muscarinic receptors than ipratropium.
- Has functional relative selectivity for M3
  - Although tiotropium binds to both M2 and M3 receptors, dissociates much faster from M2, which results in a more selective antagonist action for M1

Tiotropium bromide

- Prolonged pharmacologic activity is result of its slow dissociation from M1 and M3 receptors.
- Half-life of the drug-M3 receptor complex is

  ~ 35 h for tiotropium

  ~0.3 h for ipratropium
- Currently in development as add on for adult and pediatric asthma

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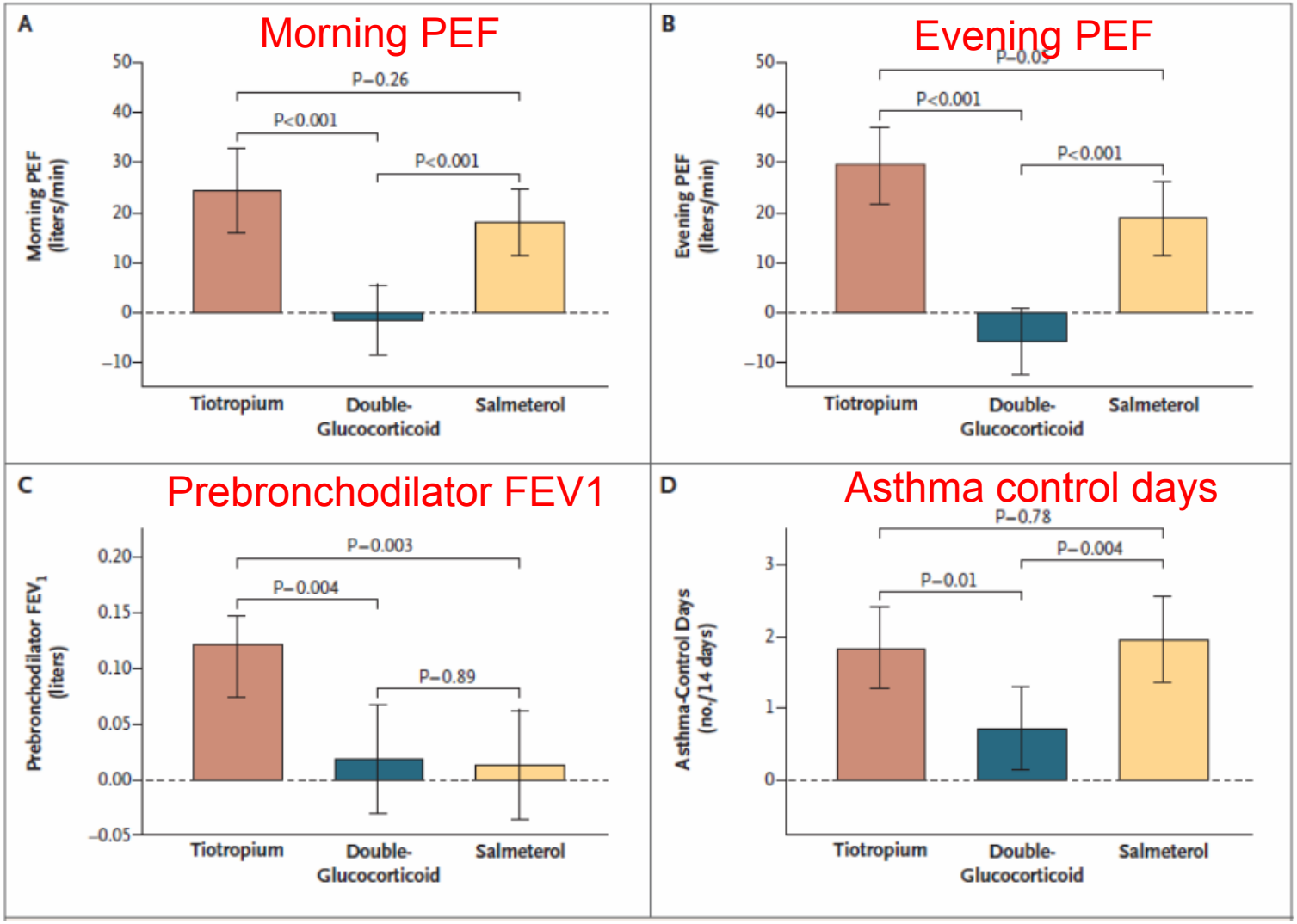
a) TIO superior to double ICS dose for



b) non inferior to salmeterol for for all outcomes, [superior for pre-BD FEV1]

Peters,NEJM 2010

Bifunctional muscarinic antagonists and β_2-adrenergic agonists (MABAs)

GSK-961081

AZD2115

LAS190792

PROPOSED Indications :

COPD

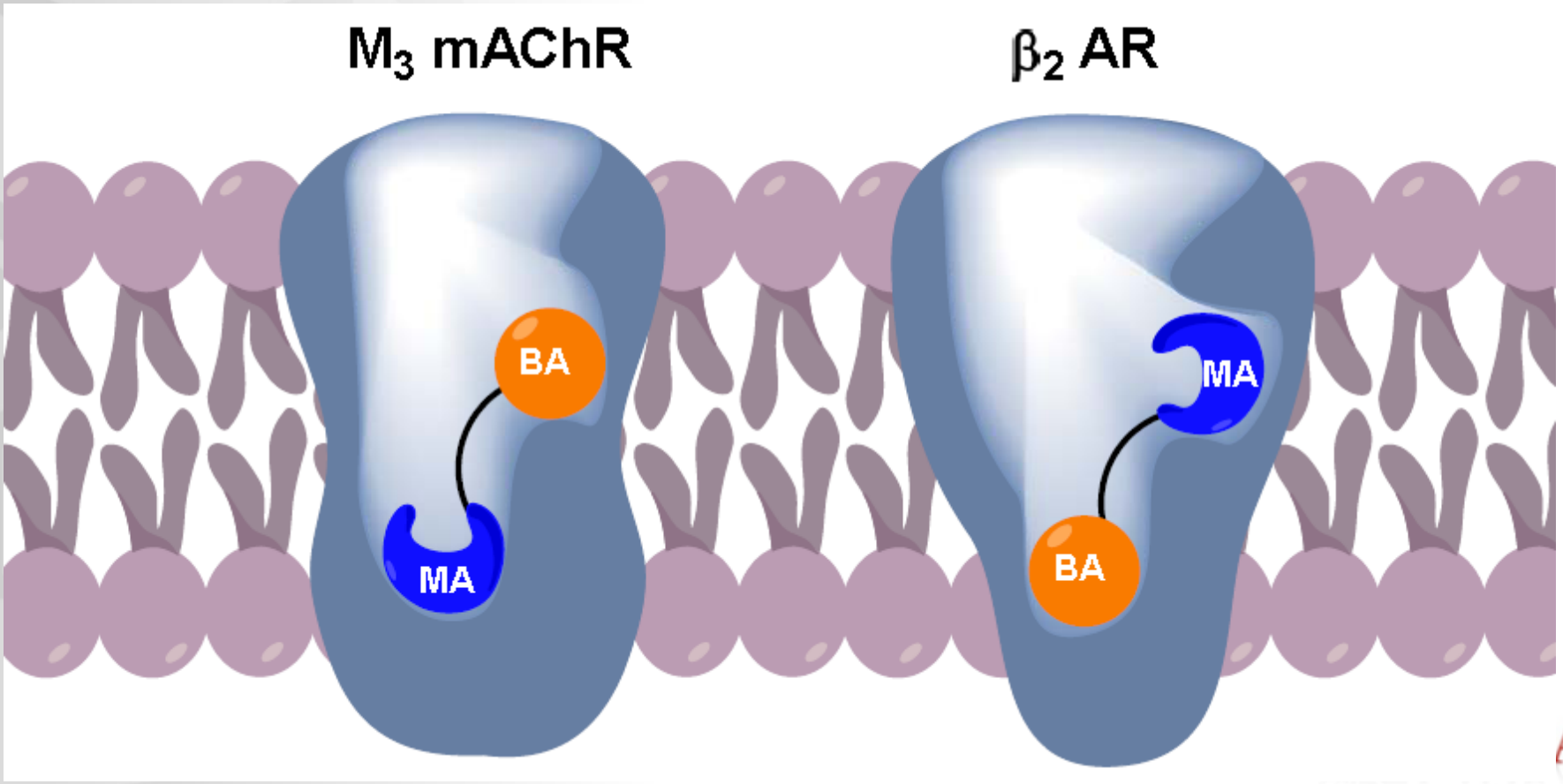
ASTHMA

COPD + ASTHMA

Development has regulatory challenges

Proposed bimodal orientation of a MABA in the respective binding sites

The BA fragment acts as a secondary binding group in the M_3 receptor to provide increased affinity over the MA fragment alone. When the same compound binds in the β_2 receptor, the roles of the MA and BA fragments are reversed



Editorials

Asthma: The paradox of heterogeneity

Jeffrey M. Drazen, MD *Boston, Mass*

JACI MAY 2012

- After years of treating patients with asthma, you know that this syndromic label means many different things.
- Asthma is a heterogeneous condition that, for the sake of first-line treatment, we have made homogenous.
- This is the paradox of heterogeneity.

The need for new therapies

- ***More efficacious treatments which may***
  - Alter the course of the disease
  - Pointed towards a cure.
  - Target remodelling
  - Dominate theraphy resistant asthma

BUT

- **Only for subsets of patients**
- **Phenotype or <u>Endotype</u> oriented : <u>*BIOMARKER S NEEDED !!*</u>**
- Risk /Benefit balance and Benefit/Costs for health service

Problems in drug development for the treatment of asthma

- Complexity of the whole disease spectrum
- Complexity of molecular mechanisms
- Limited biomarkers for subgrouping and endotyping
- Limited information on how to improve on existing therapies (
- Low patient adherence
- Small animal models are poorly predictive. Most drugs that are effective in mouse models have failed in clinical trials
- Individual outcomes are different, and different outcomes cannot be distinguished using a bulk approach
- It is not possible to study the combination of two new biologicals that may potentiate each other until one of them is approved (however, biologicals are unlikely to be effective when used alone)

Personalised medicine:
to get the right drug
to the right person
at the right time.

Need to ensure a more accurate diagnosis of disease and to better predict an individual's response to pharmacological therapy

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PERSONALIZED MEDICINE

Utilize individual gene-biologic information to understand the unique requirements for:

1. OPTIMAL TREATMENT
2. HEALTH MAINTENEANCE
3. DISEASE PREVENTION

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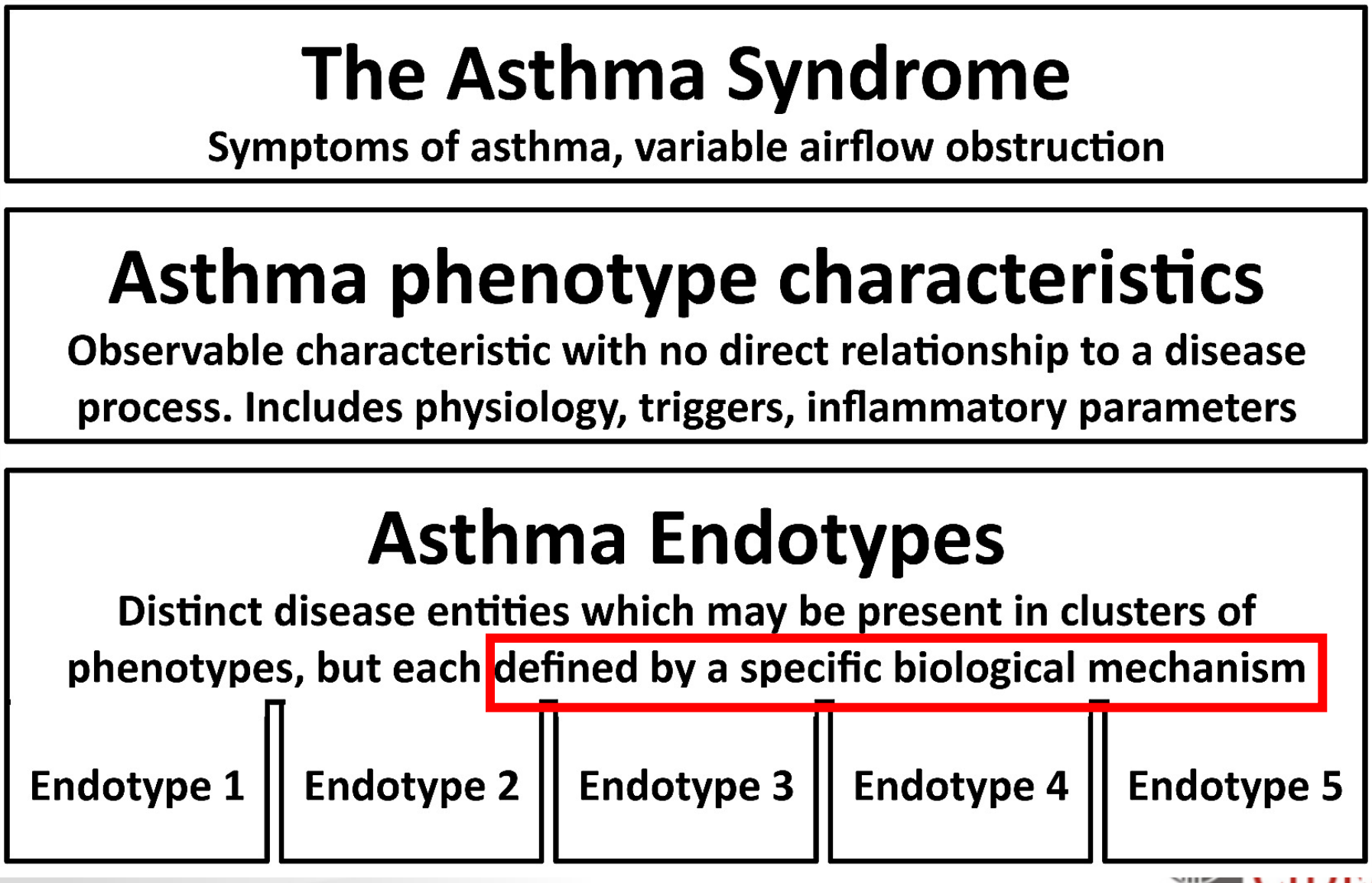
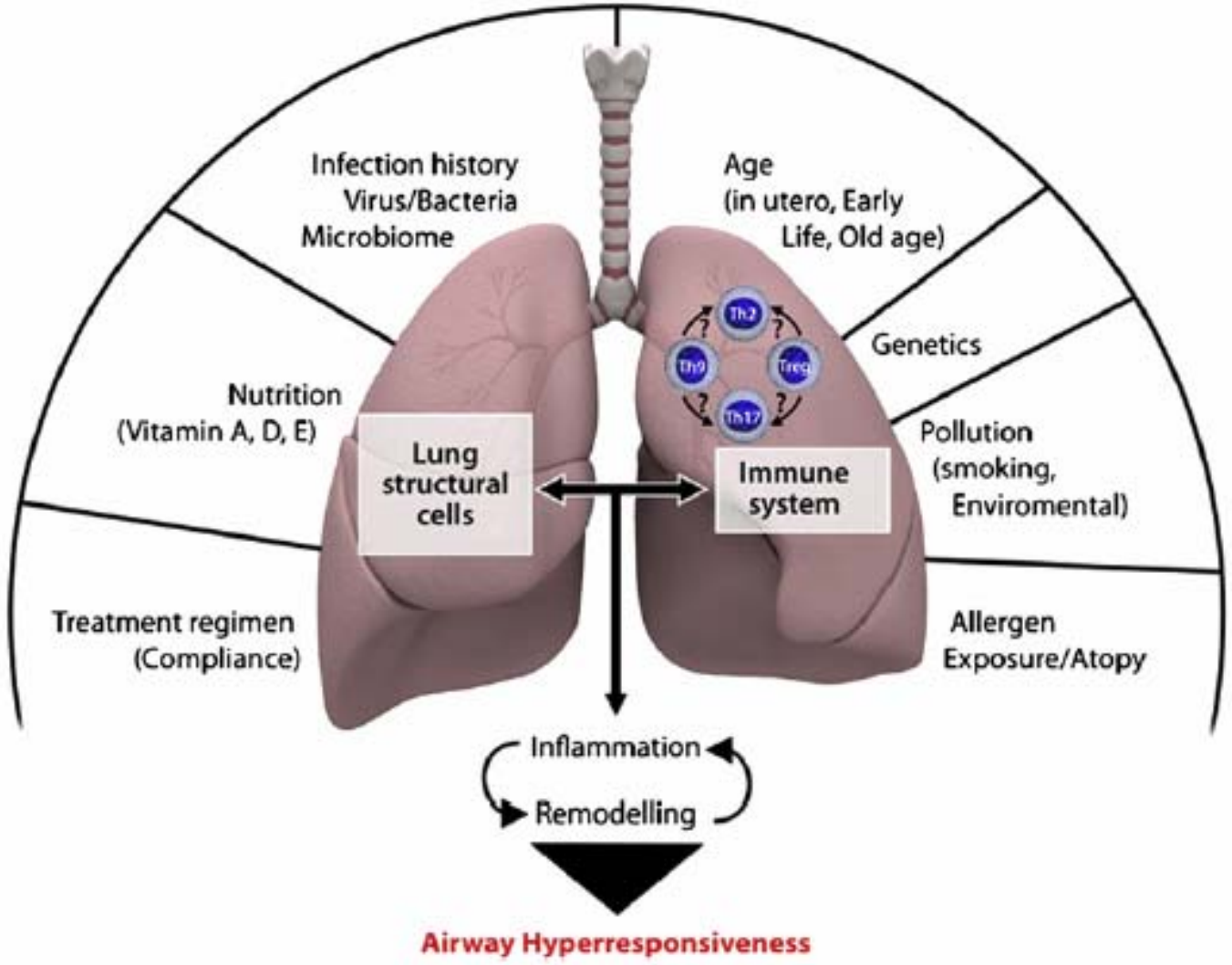
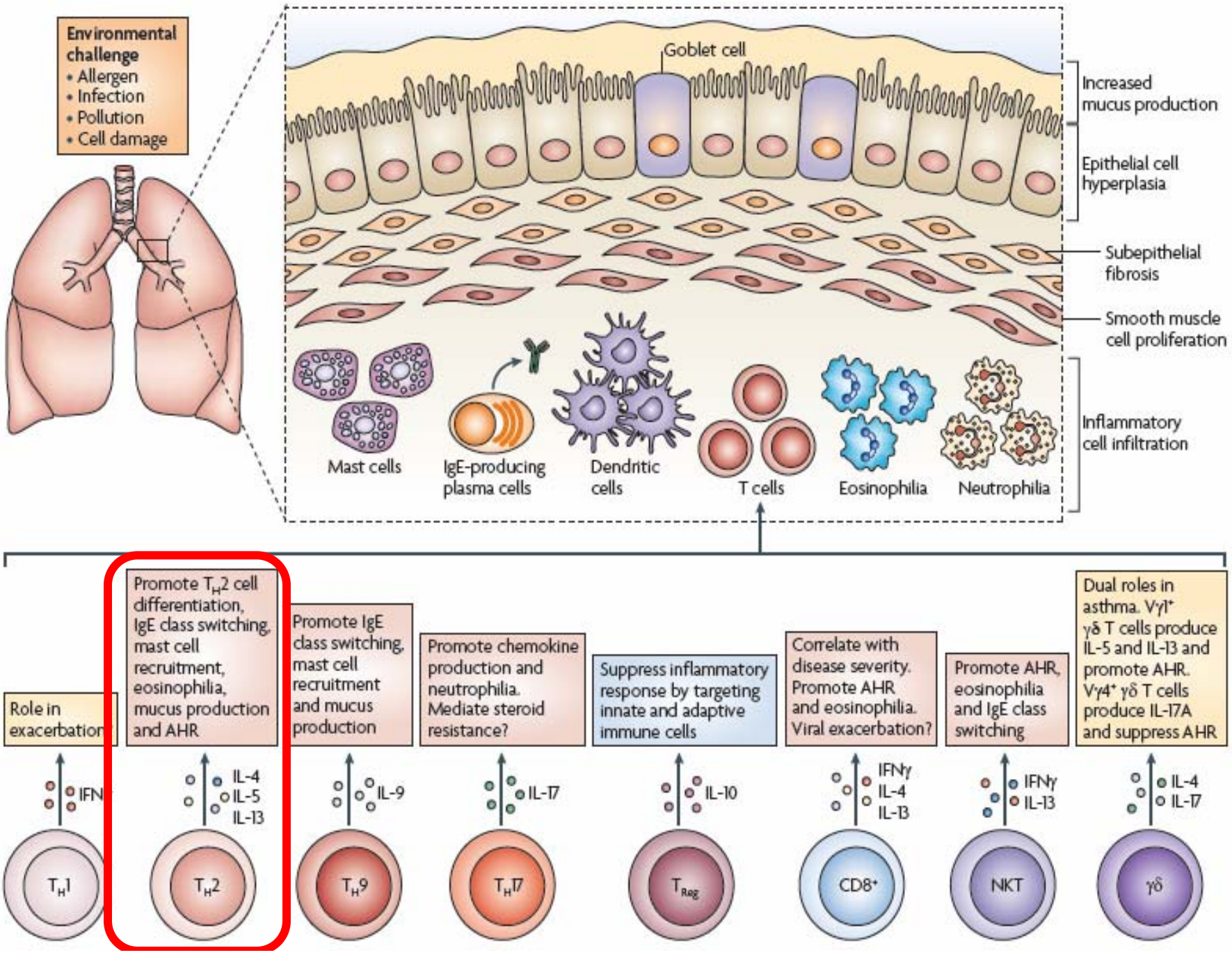
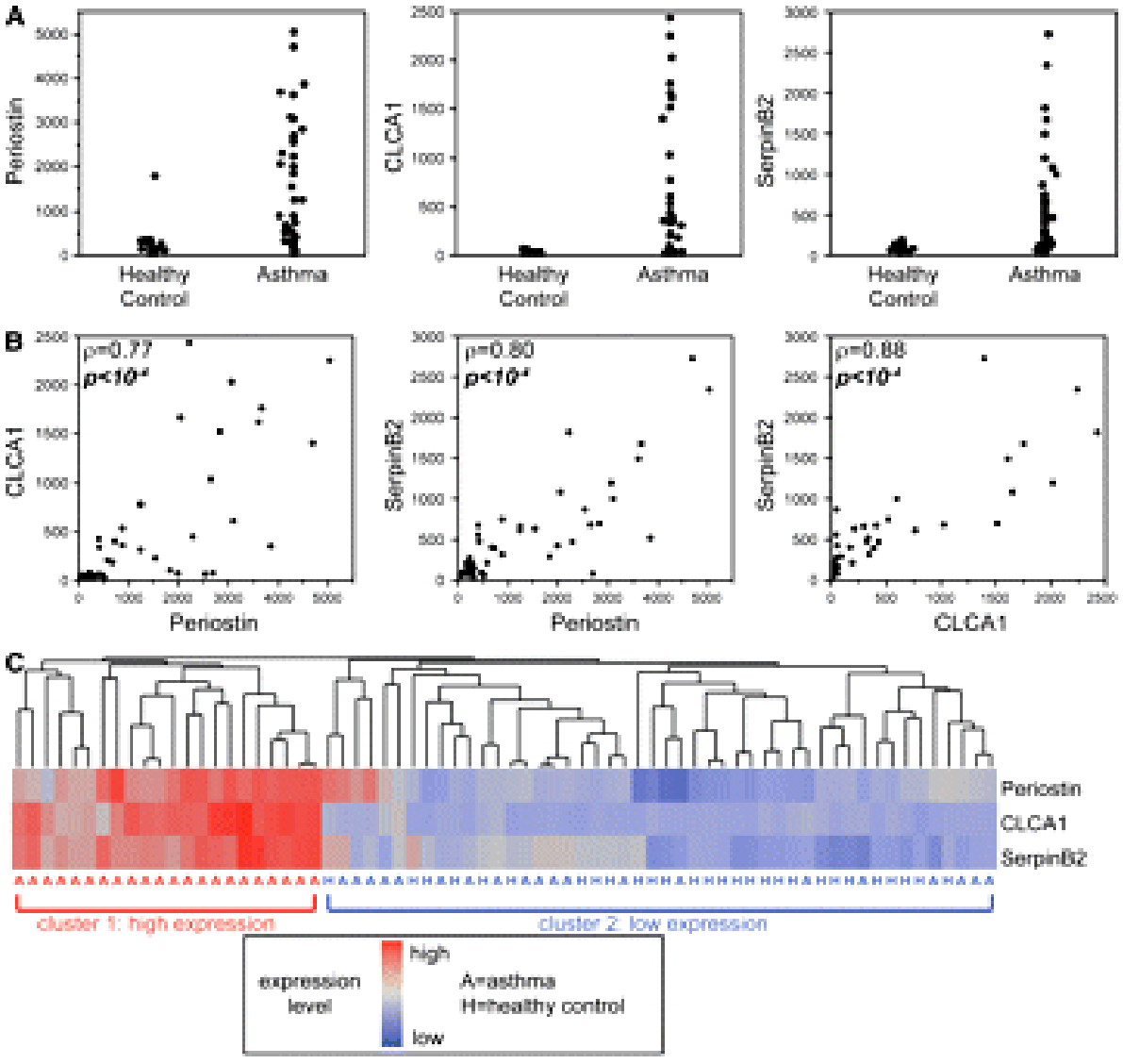


Source: Journal of Allergy and Clinical Immunology 2011; 127:355-360 (DOI:10.1016/j.jaci.2010.11.037)

The interplay between environmental exposures, lung structural cells, and immune cells in determining asthma pathophysiology.




Environmental challenge
• Allergen
• Infection
• Pollution
• Cell damage
Goblet cell
Increased mucus production
Epithelial cell hyperplasia
Subepithelial fibrosis
Smooth muscle cell proliferation
Inflammatory cell infiltration
Mast cells
IgE-producing plasma cells
Dendritic cells
T cells
Eosinophilia
Neutrophilia
Role in exacerbation
Promote TH2 cell differentiation, IgE class switching, mast cell recruitment, eosinophilia, mucus production and AHR
Promote IgE class switching, mast cell recruitment and mucus production
Promote chemokine production and neutrophilia. Mediate steroid resistance?
Suppress inflammatory response by targeting innate and adaptive immune cells
Correlate with disease severity. Promote AHR and eosinophilia. Viral exacerbation?
Promote AHR, eosinophilia and IgE class switching
Dual roles in asthma. Vγ1+ γδ T cells produce IL-5 and IL-13 and promote AHR. Vγ4+ γδ T cells produce IL-17A and suppress AHR
IFN
IL-4
IL-5
IL-13
IL-9
IL-17
IL-10
IFNγ
IL-4
IL-13
IFNγ
IL-13
IL-4
IL-17
TH1
TH2
TH9
TH17
TReg
CD8+
NKT
γδ



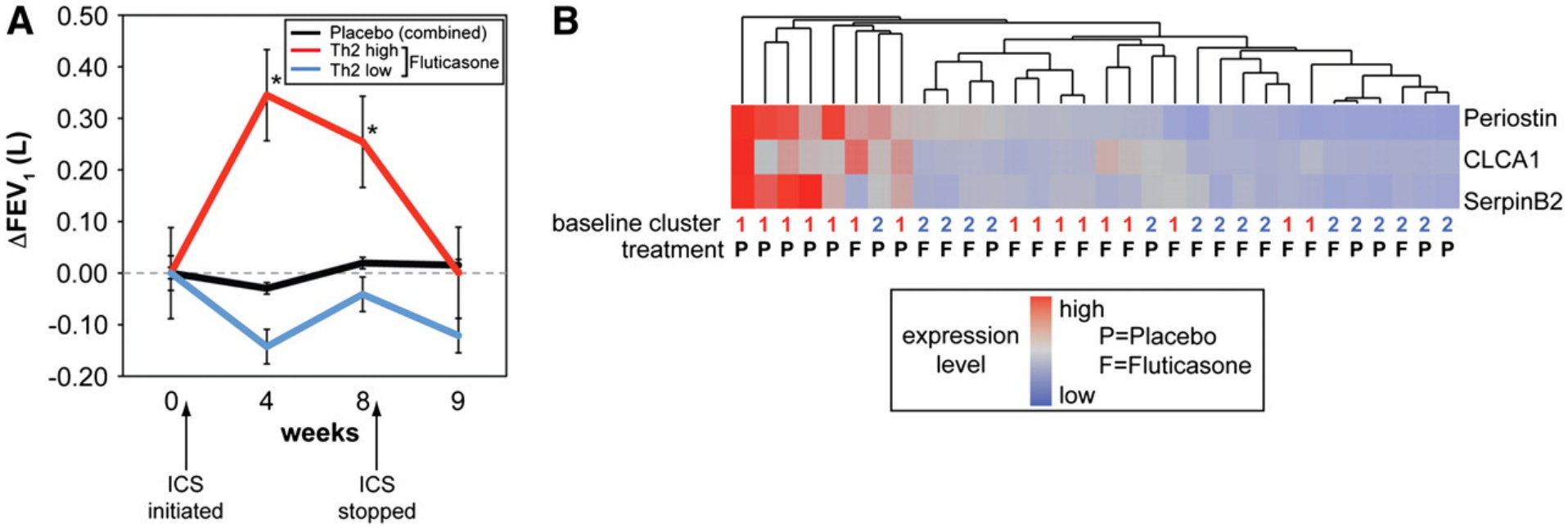
	Spearman ρ	p-value
IL-13 vs. IL-5	**0.58**	**<10⁻⁴**
IL-13 vs. IL-4	0.13	0.38
IL-4 vs. IL-5	0.14	0.36

TH2 HIGH & LOW

Expression levels of three IL-13 induced genes in the airway define two subgroups of patients with asthma

Am. J. Respir. Crit. Care Med. September 1, 2009 vol. 180 no. 5 388-395

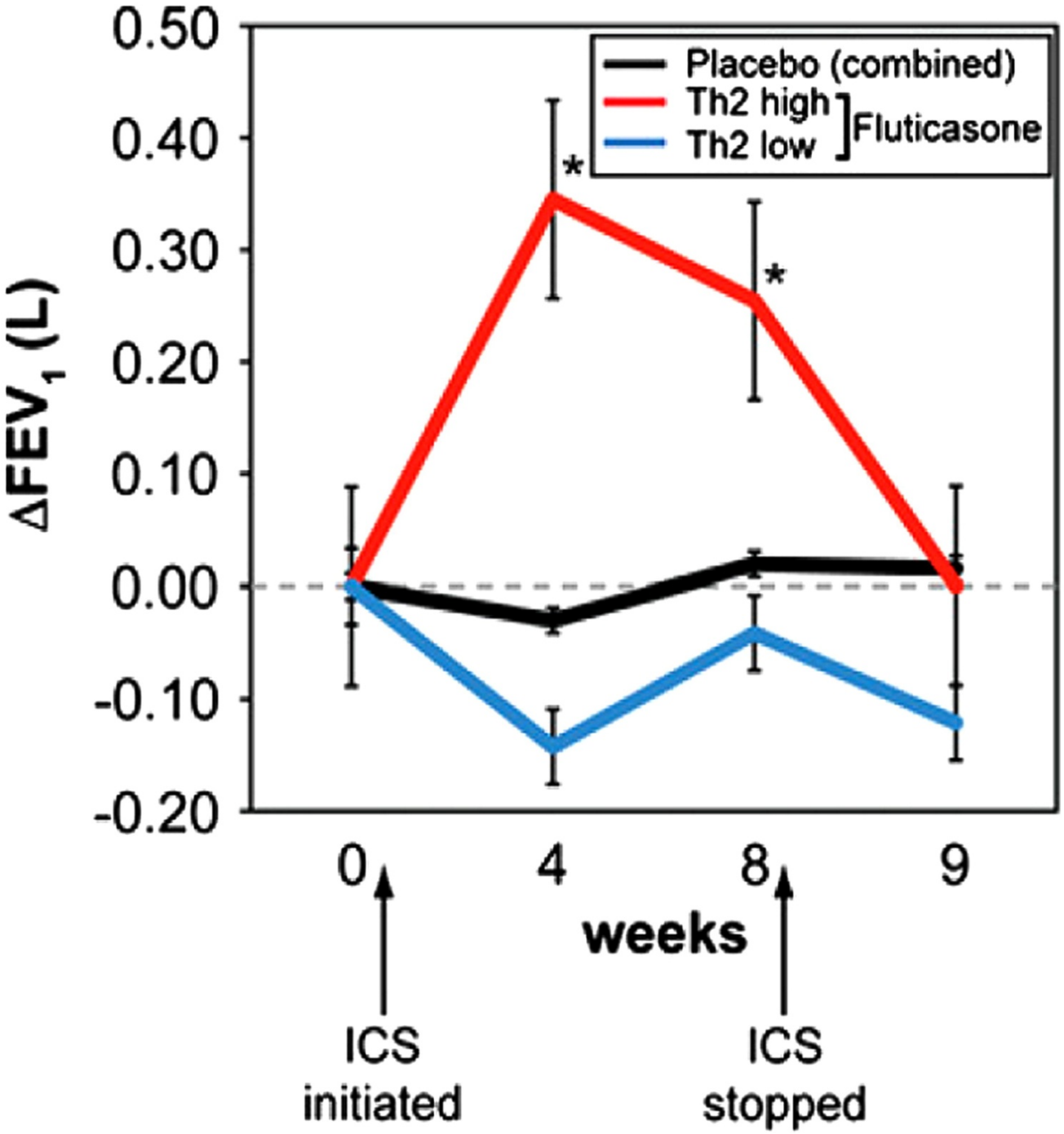
Responsiveness of Th2-high asthma to inhaled steroids and reproducibility of phenotypic markers after placebo in a randomized controlled trial

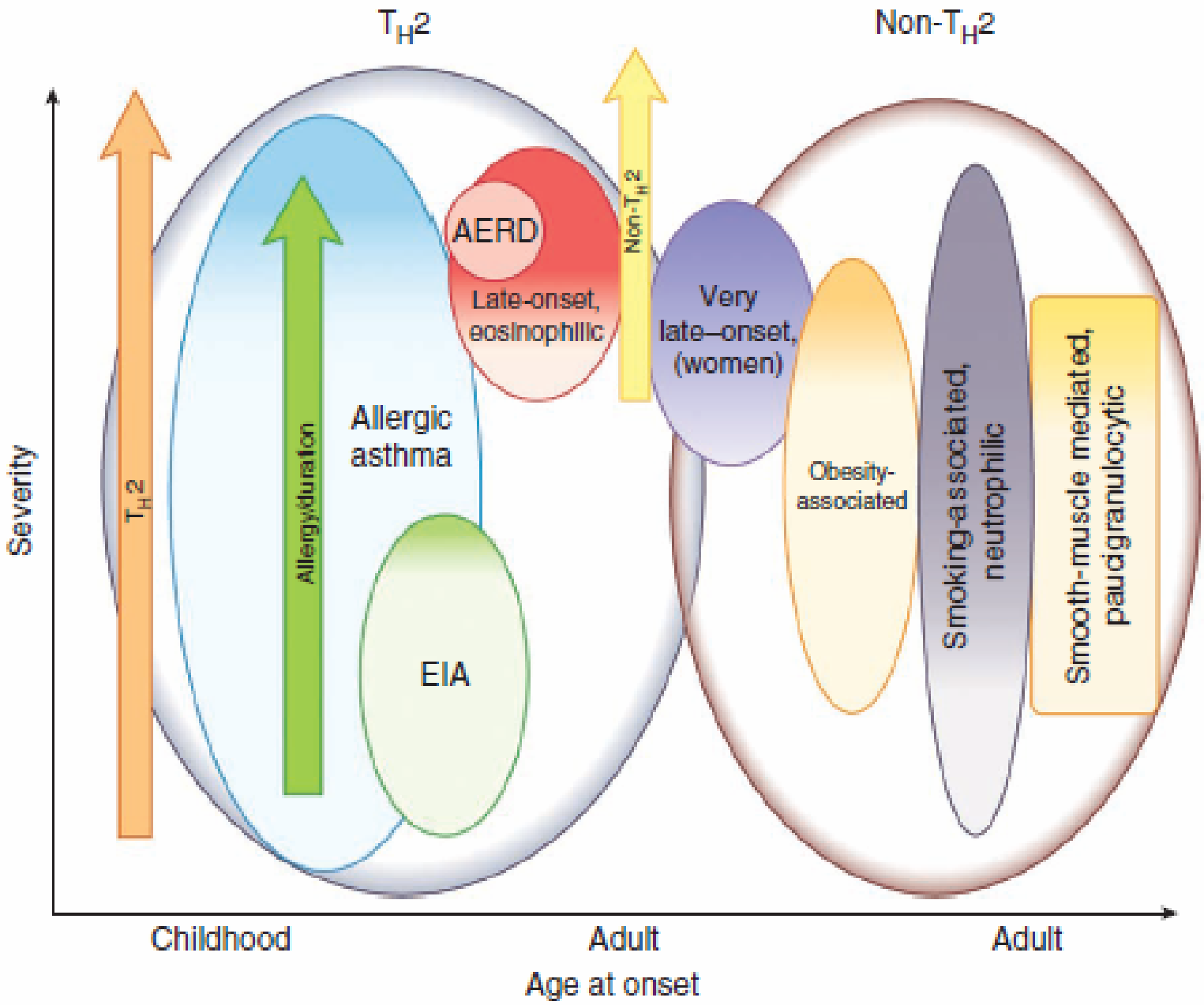


Am. J. Respir. Crit. Care Med. September 1, 2009 vol. 180 no. 5 388-395

Responsiveness of patients with TH2-high asthma to inhaled steroids.

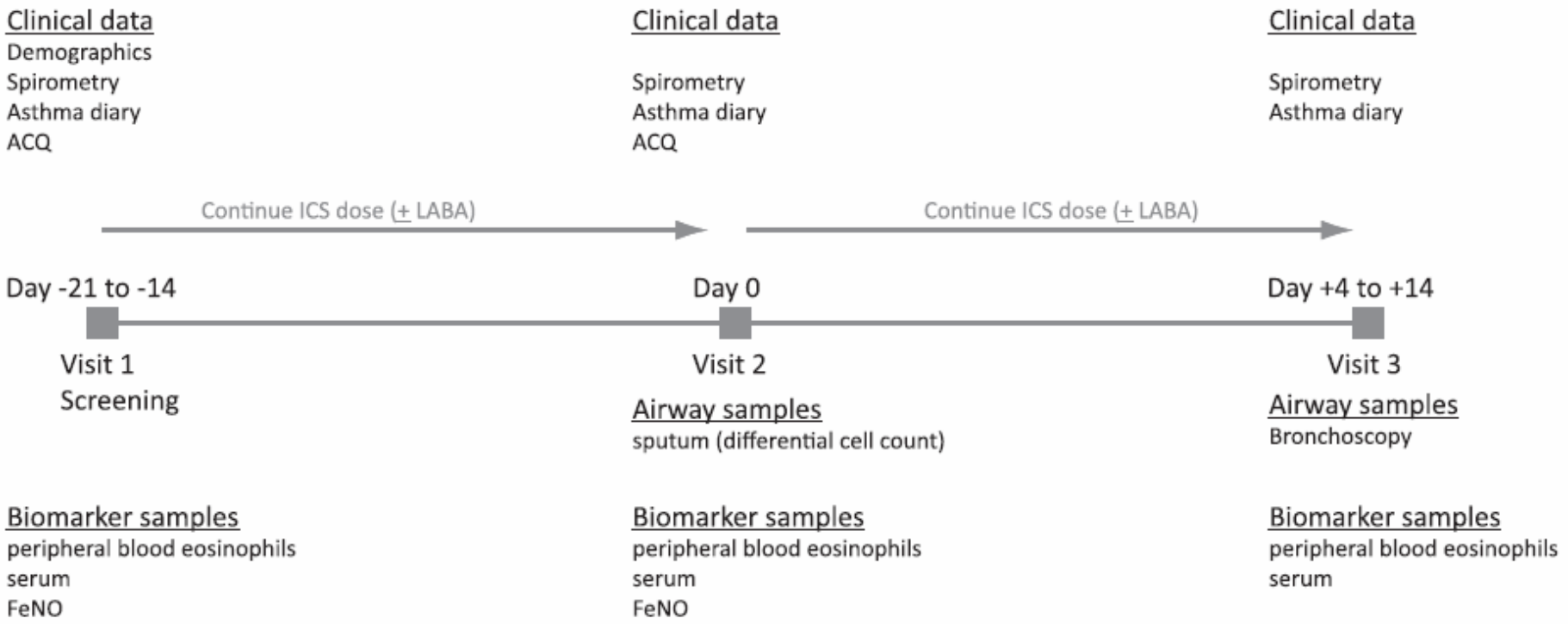
Am J Respir Crit Care Med Vol 180. pp 388–395, 2009





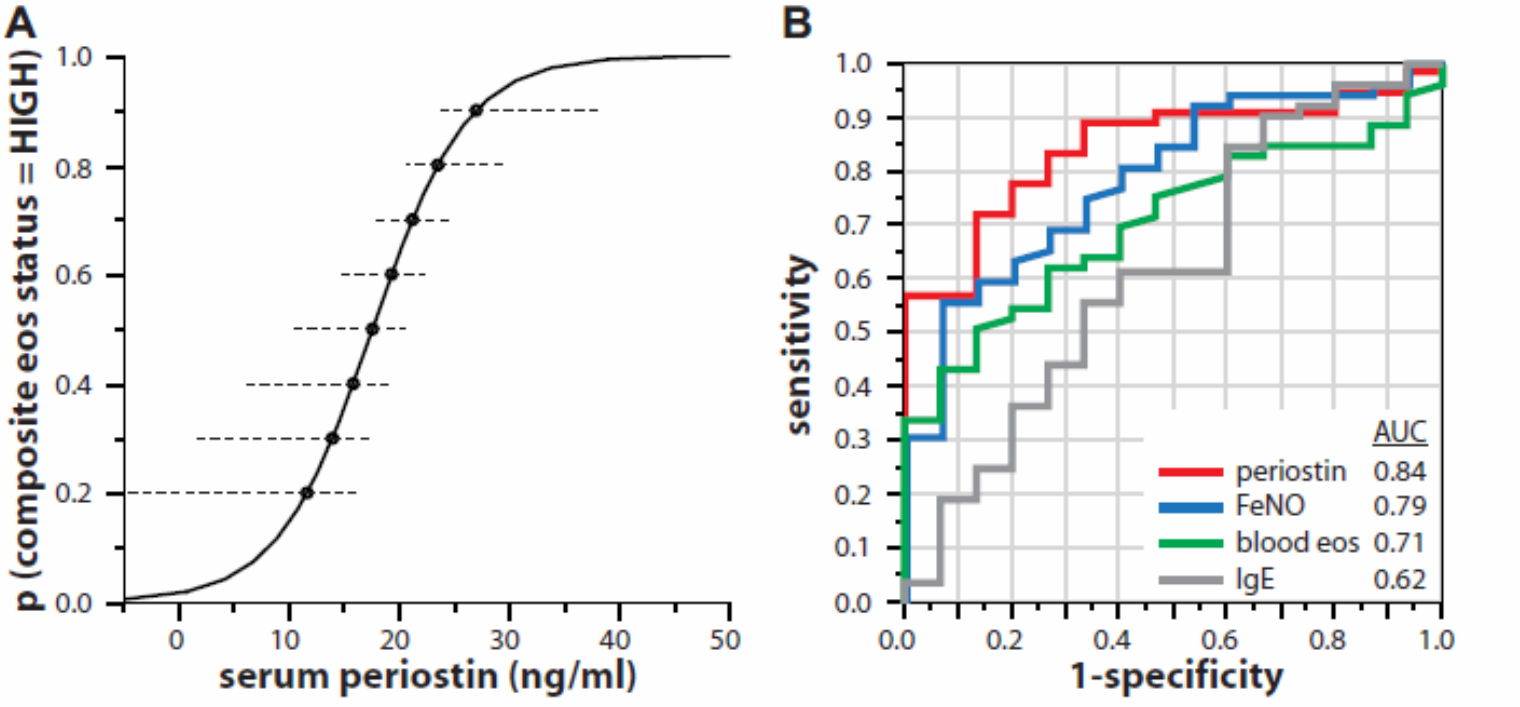
Wenzel S, nature medicine VOLUME 18 | NUMBER 5 | MAY 2012

Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients



JACI 2012

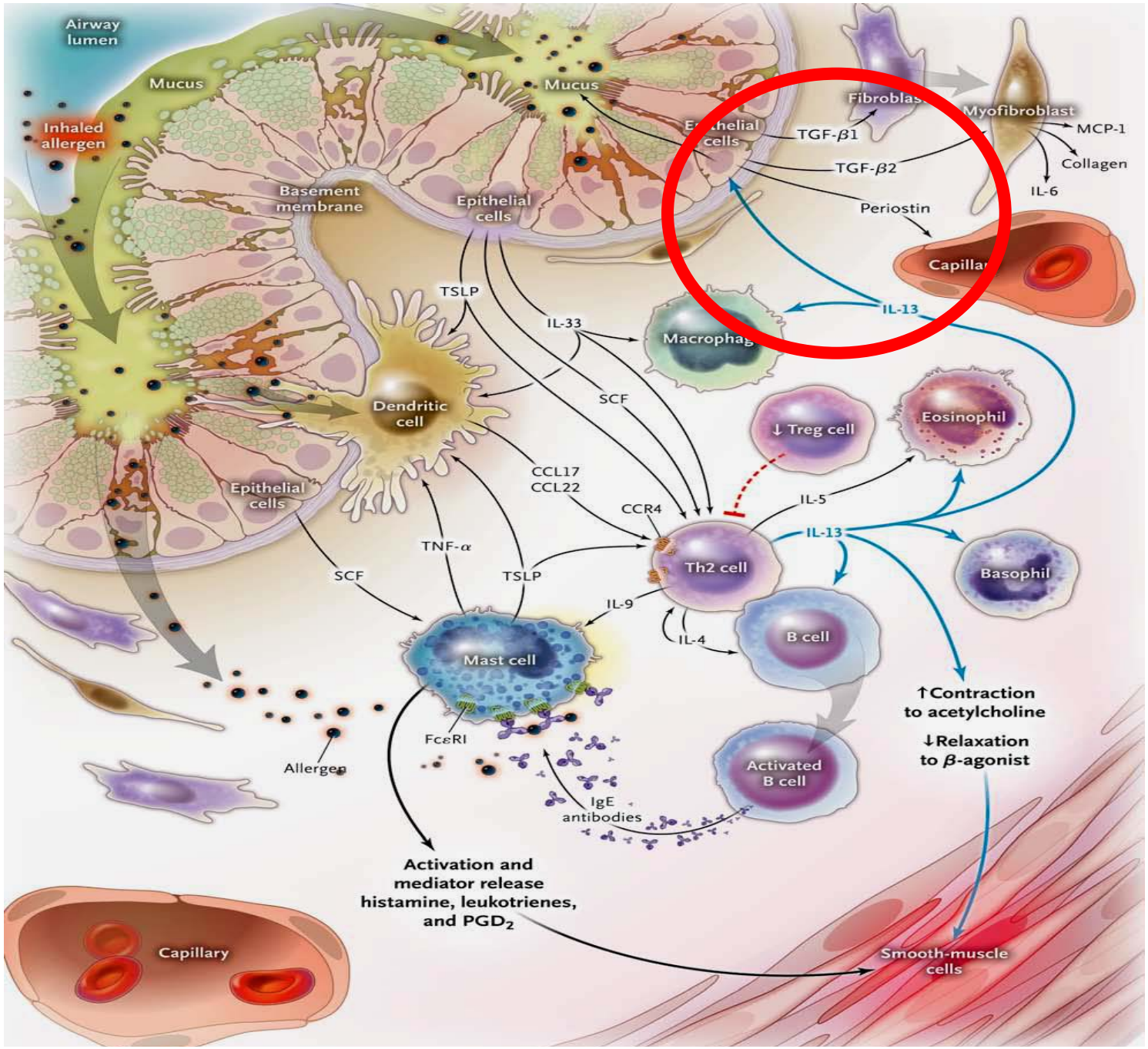
Sensitivity of biomarkers for eosinophilic airway inflammation



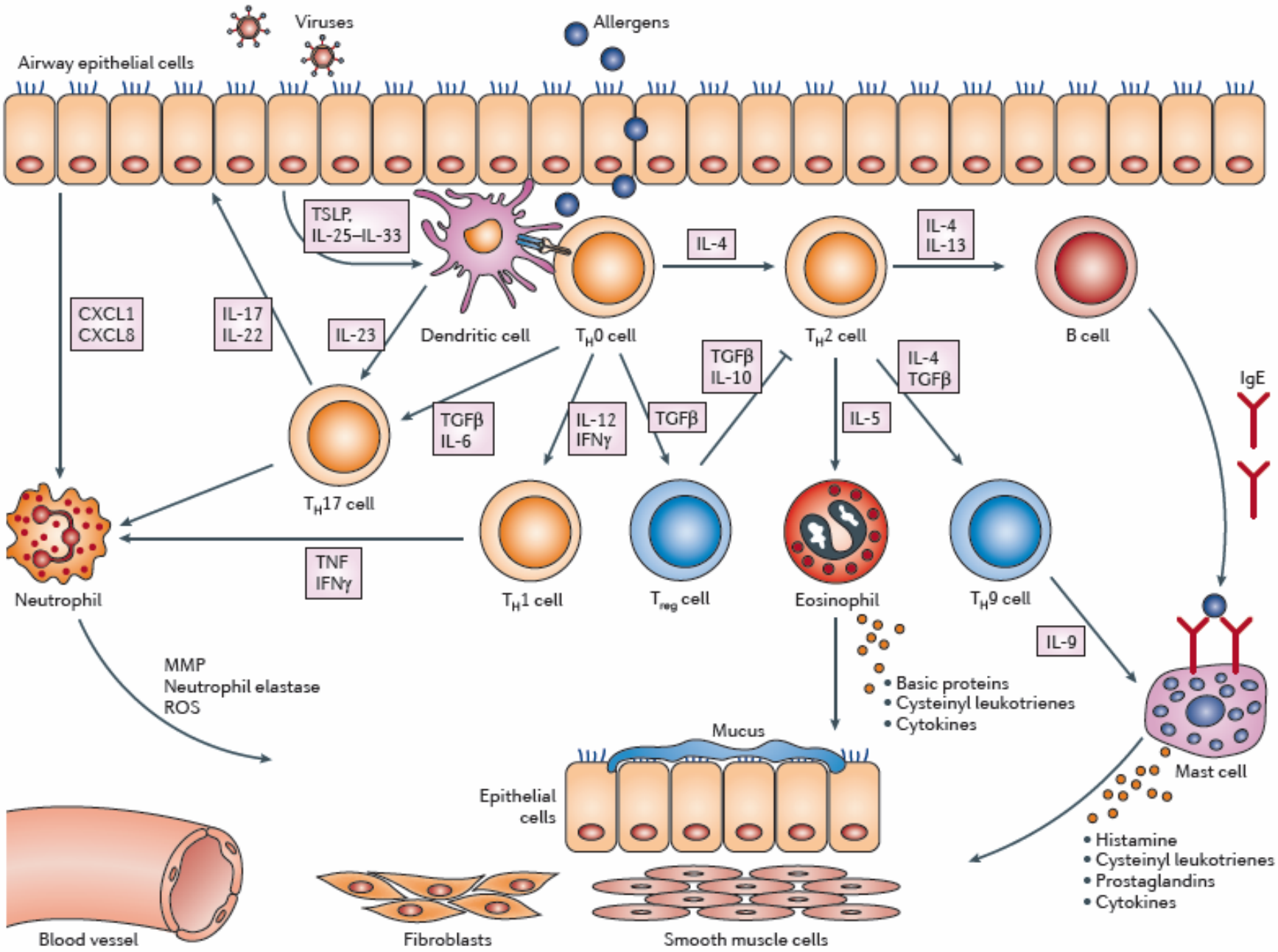
Periostin levels in peripheral blood identify asthmatic patients with increased airway eosinophil numbers and therefore might be a clinically useful biomarker to select patients for TH2-targeted asthma therapies

JACI 2012

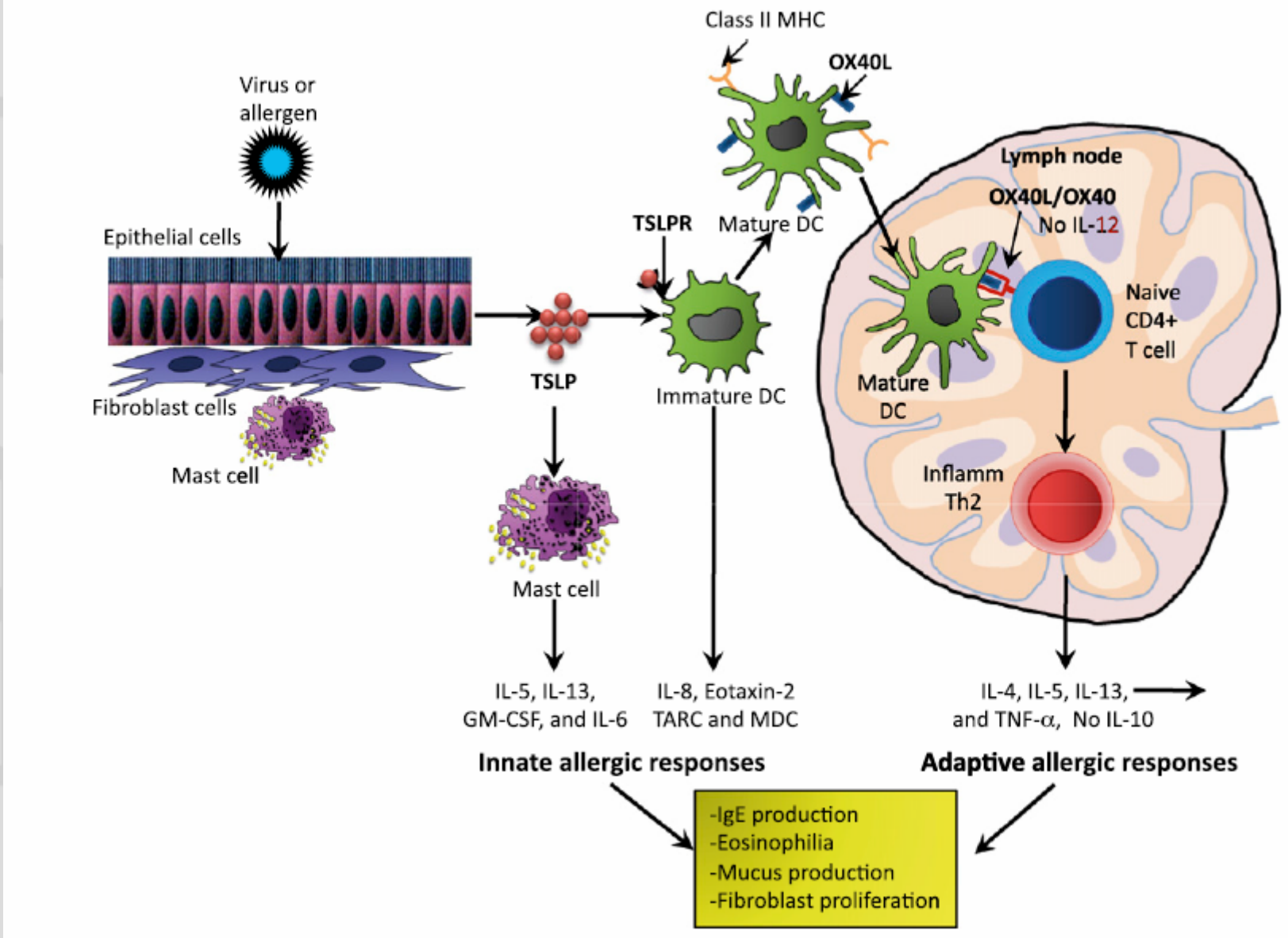
Interleukin-13 and Non–Interleukin- 13 Inflammatory Pathways in Asthma.



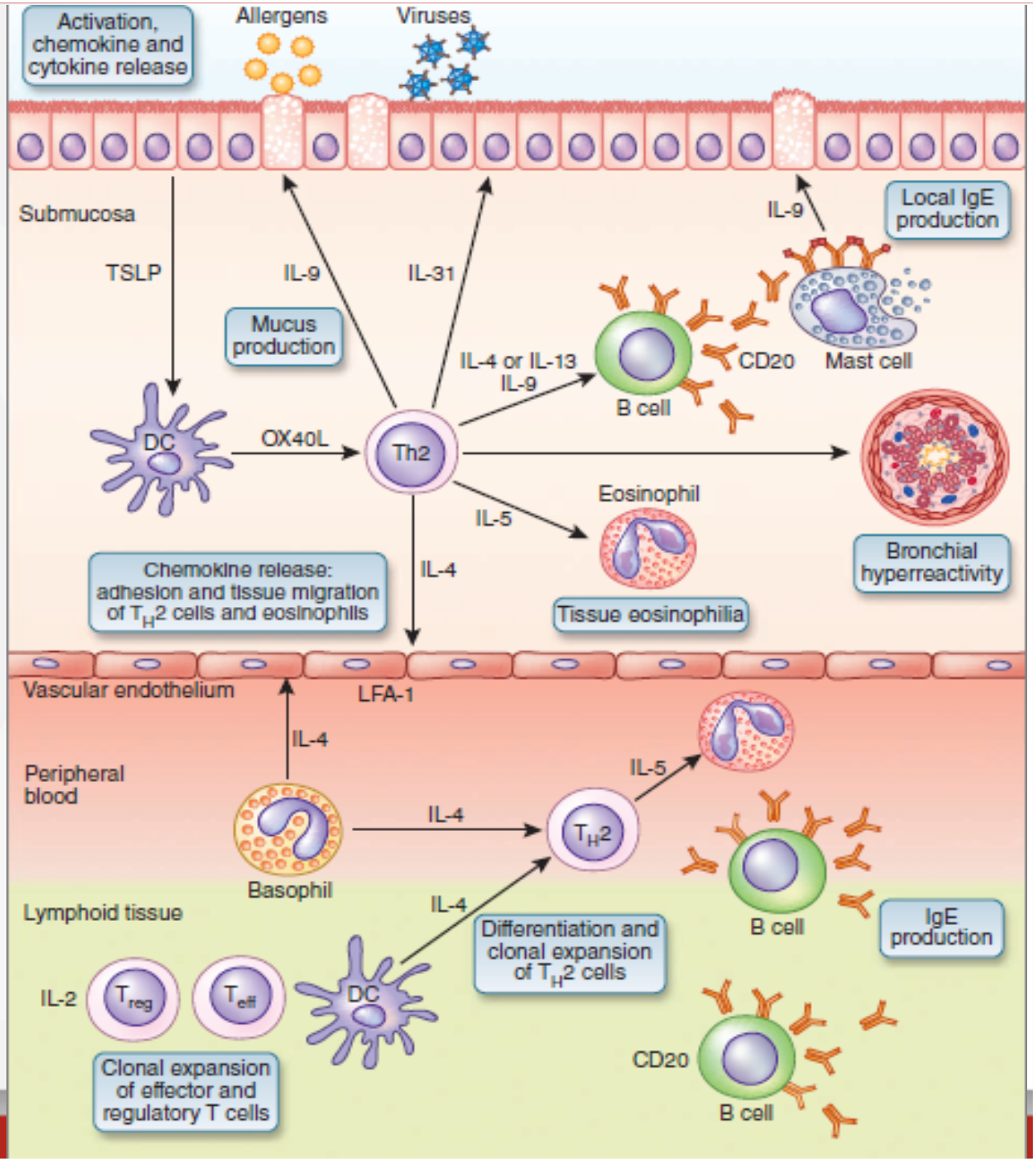
Pathobiology of asthma



Pathophysiologic characteristics of OX40/OX40L and TSLP in allergic inflammation



Targets for new immunomodulatory drugs in asthma



Targets for new immunomodulatory drugs in asthma

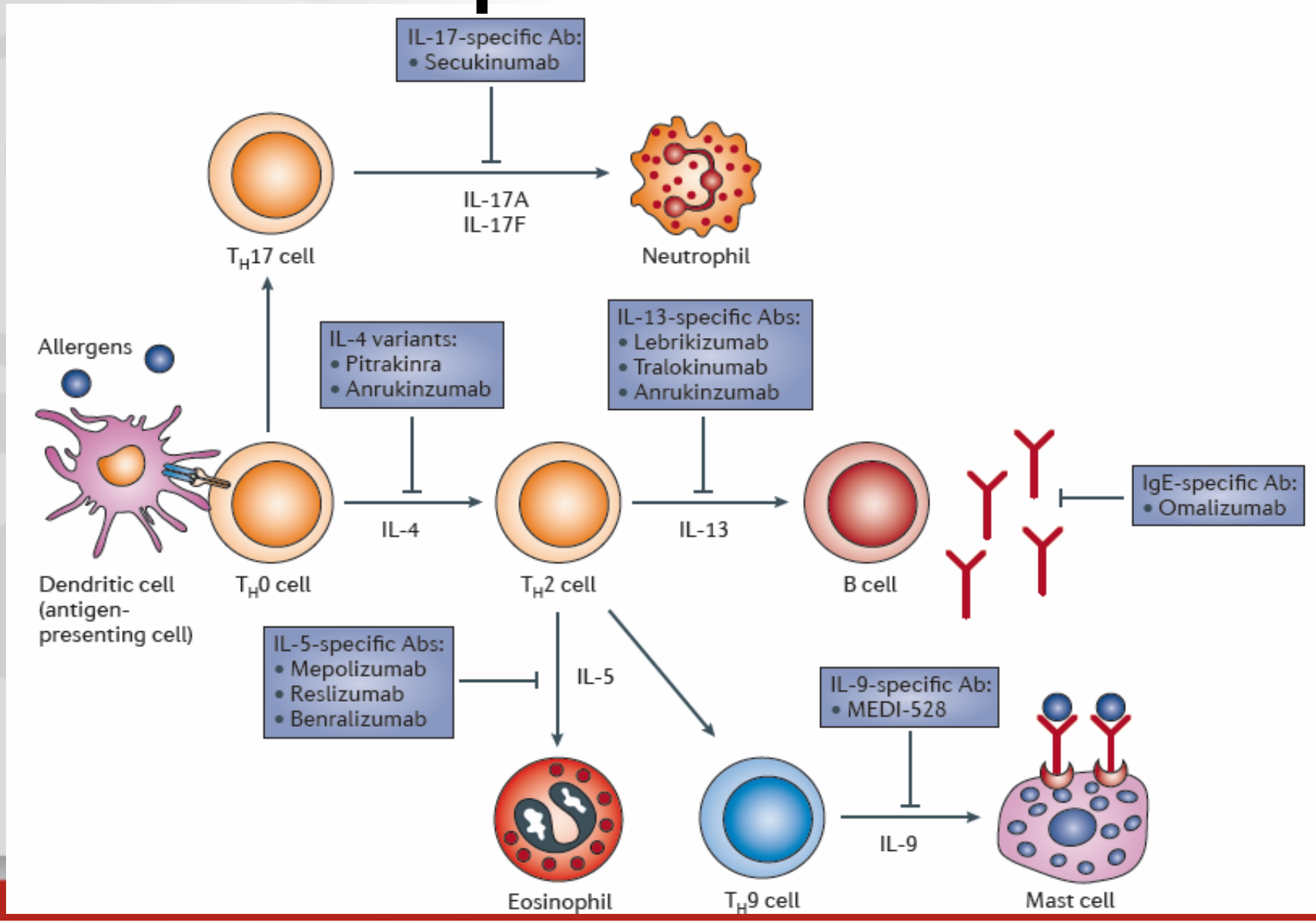
- **Epithelial cell activation** and their proinflammatory cytokines and chemokines which induce inflammation and TH2 responses: TNF-α, IL-13, TSLP and IL-31, IL-33
- **Epithelial apoptosis** and shedding in eczema and asthma
- **The TH2 response**: IL-4, IL-5, IL-9, IL-13, IL-25 and IL-33
- **Eosinophilia**: IL-5, IL-25 and IL-33
- **Local and systemic IgE production**: IL-4, IL-13, CD20 and IgE

FUNDACION CIDEA

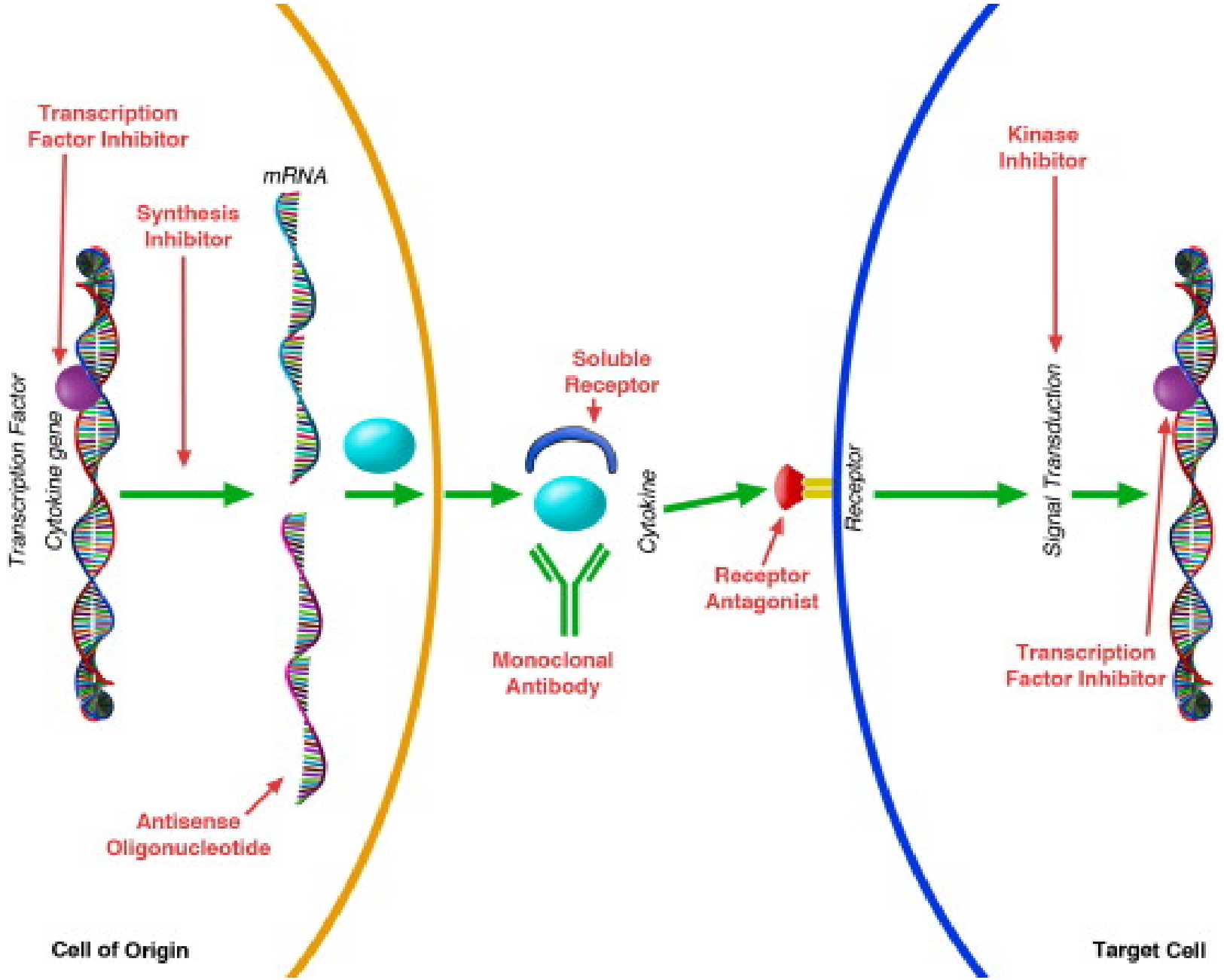
Targets for new immunomodulatory drugs in asthma

- **Crosslinking of IgE receptor FcεRI** of mast cells /basophils and their degranulation
- **Smooth muscle and myofibroblast** activation and bronchial hyperreactivity: IL-4, IL-9, IL-13, IL-25, IL-33
- **Survival and reactivation of migrating inflammatory cells** and their interaction with resident cells and inflammatory cells: IL-2, IL-4
- **Cell migration and chemokines**
- Other **effector T cell subsets**, as TH9, TH17 and TH22 cells

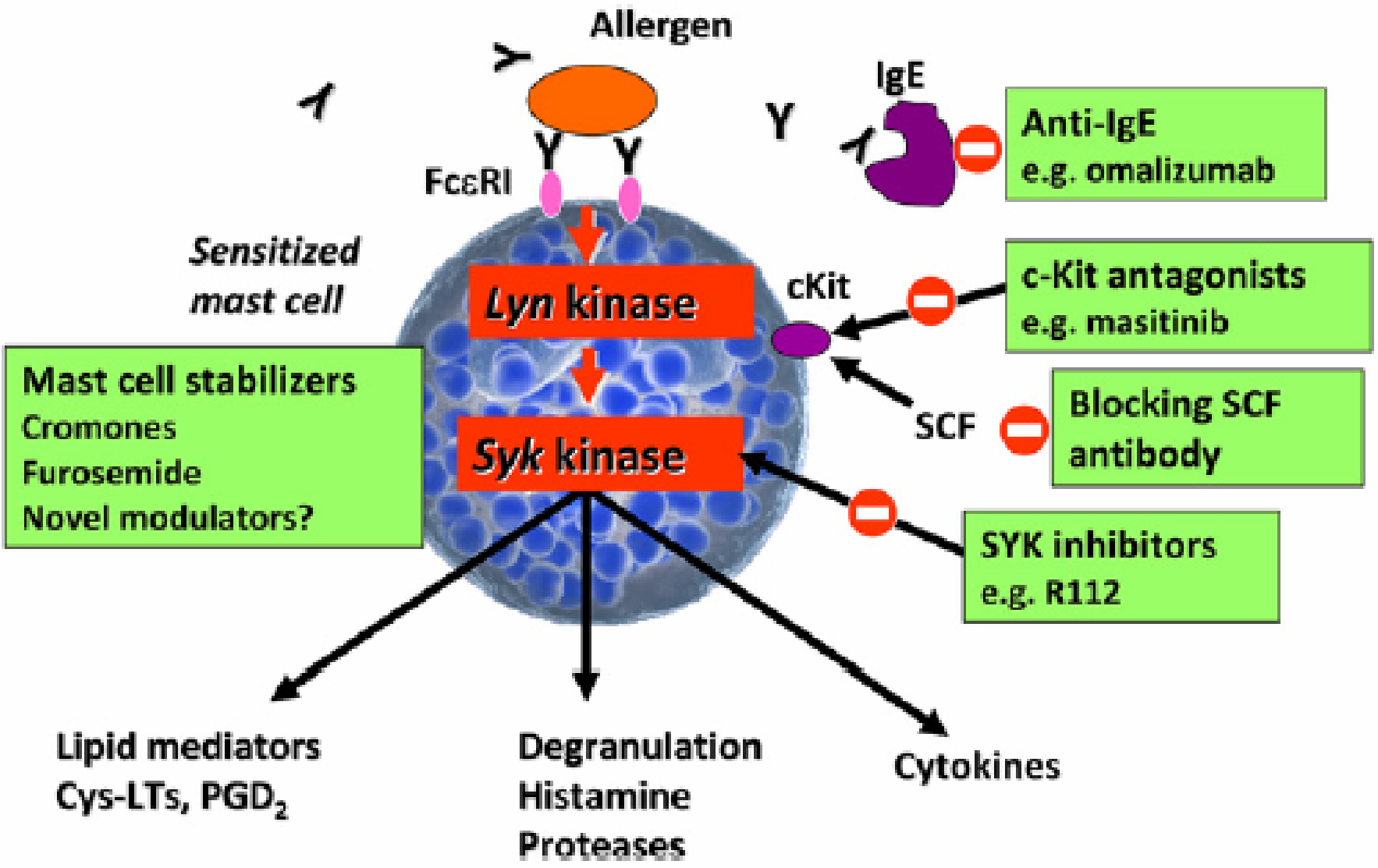
Mechanism of action of biological therapies for asthma.



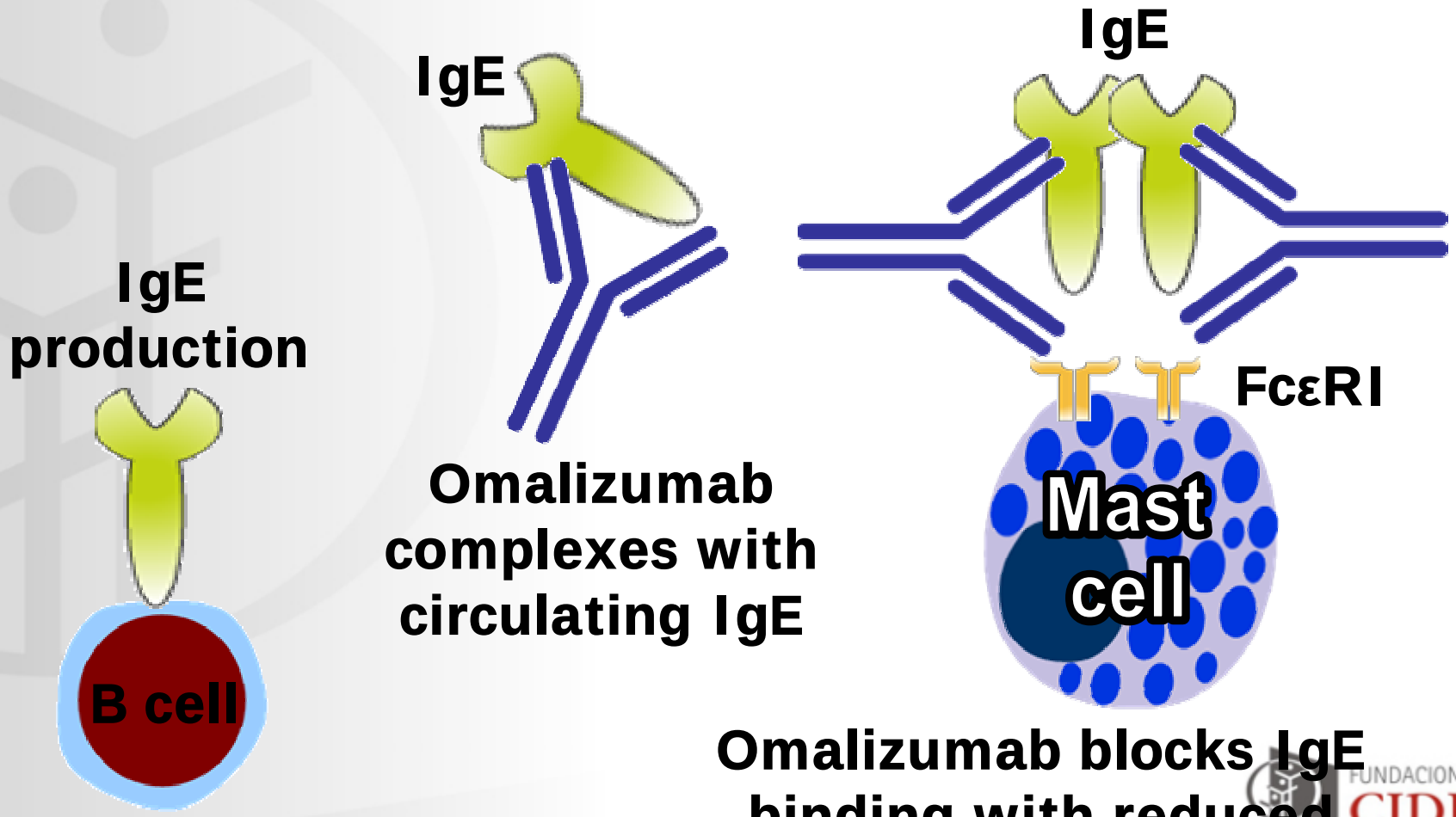
Mechanistic strategies to inhibit cytokine-induced effects



MAST CELL INHIBITION



IgE: a worthy therapeutic target



FUNDACION CIDEA

EFFICACY AND SAFETY OF SUBCUTANEOUS OMALIZUMAB VERSUS PLACEBO AS ADD ON THERAPY TO CORTICOSTEROIDS FOR CHILDREN AND ADULTS WITH ASTHMA: A SYSTEMATIC REVIEW

Gustavo J. Rodrigo, Hugo Neffen and José A. Castro-Rodriguez

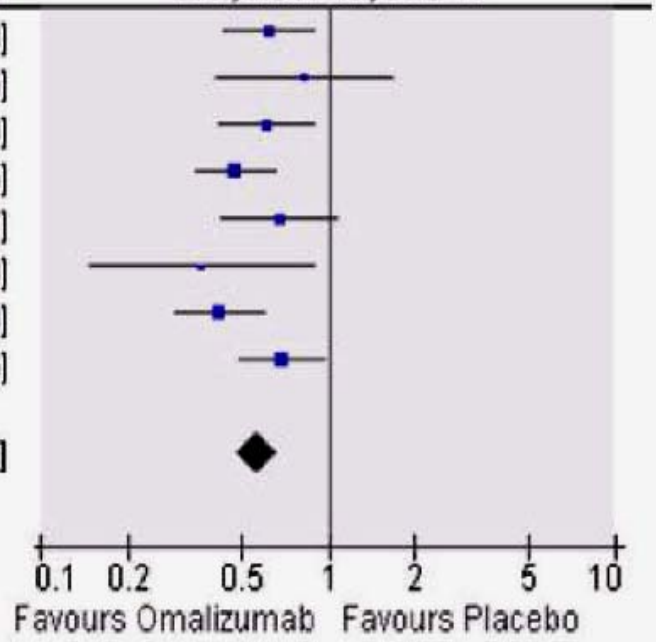
Chest; Prepublished online August 5, 2010;
DOI 10.1378/chest.10-1194

This information is current as of August 10, 2010

Study or Subgroup	Omalizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Busse 2001	39	268	60	257	15.5%	0.62 [0.43, 0.90]
Holgate 2004	13	126	15	120	4.8%	0.83 [0.41, 1.66]
Humbert 2005	35	246	55	236	14.2%	0.61 [0.42, 0.90]
Lanier 2009	56	384	59	192	18.9%	0.47 [0.34, 0.65]
Milgrom 2001	35	225	25	109	10.4%	0.68 [0.43, 1.07]
Ohta 2009	6	151	18	164	3.0%	0.36 [0.15, 0.89]
Soler 2001	35	274	83	272	16.0%	0.42 [0.29, 0.60]
Vignola 2004	43	209	59	196	17.2%	0.68 [0.49, 0.96]
Total (95% CI)		**1883**		**1546**	**100.0%**	**0.57 [0.48, 0.66]**
Total events	262		374			

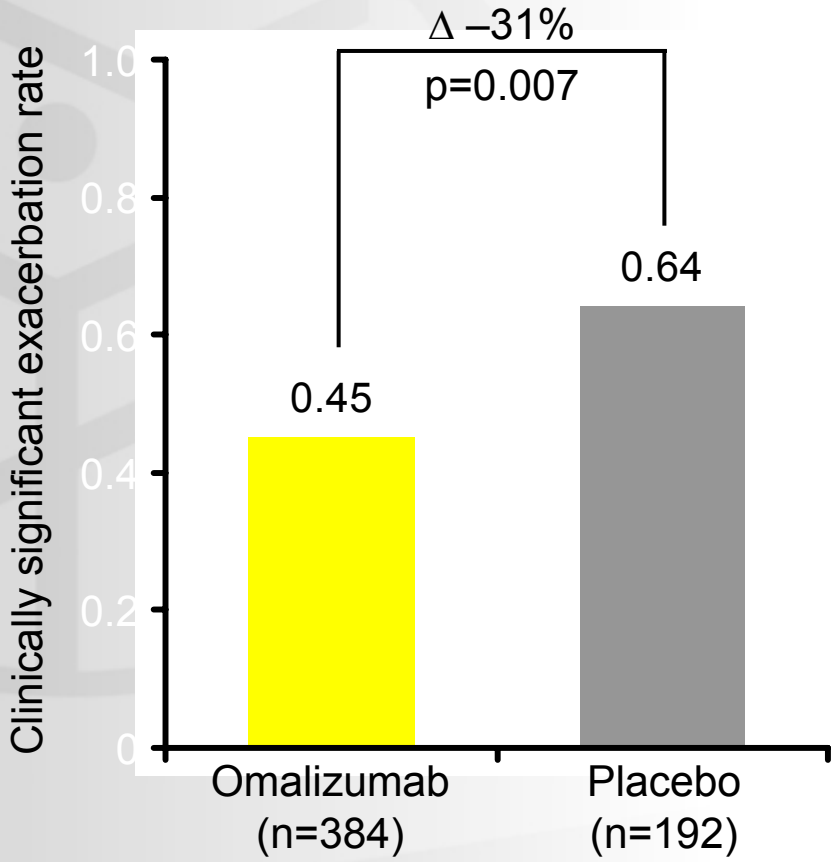
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.15$, $df = 7$ ($P = 0.32$); $I^2 = 14\%$

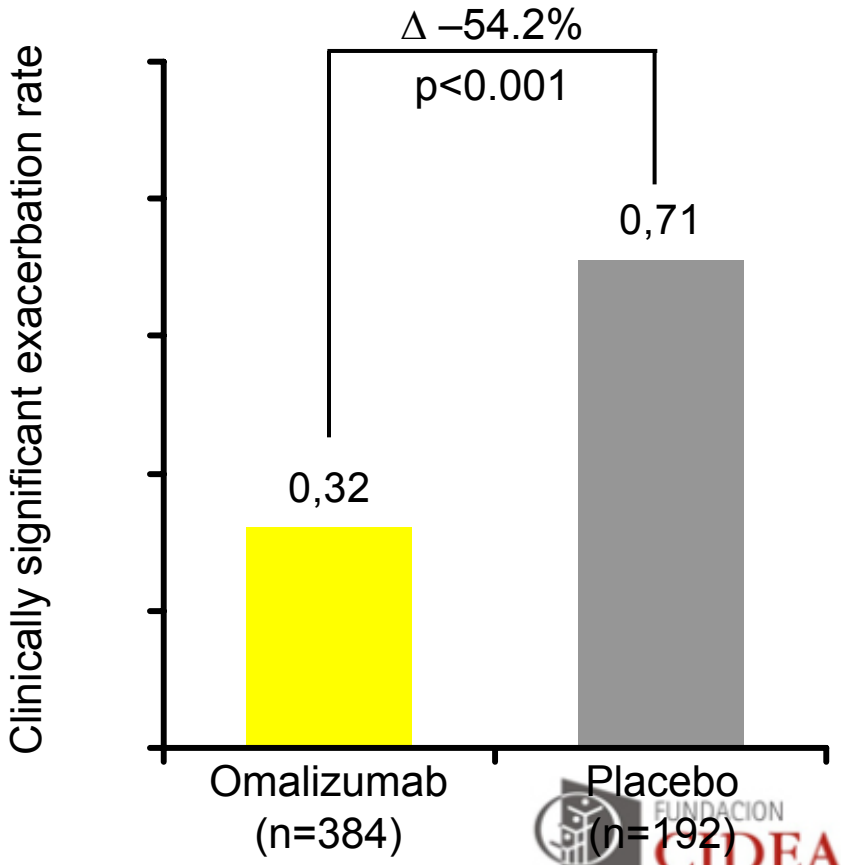
Test for overall effect: $Z = 7.06$ ($P < 0.00001$)



Exacerbations are reduced and efficacy is maintained over time

1st 24 weeks – primary a





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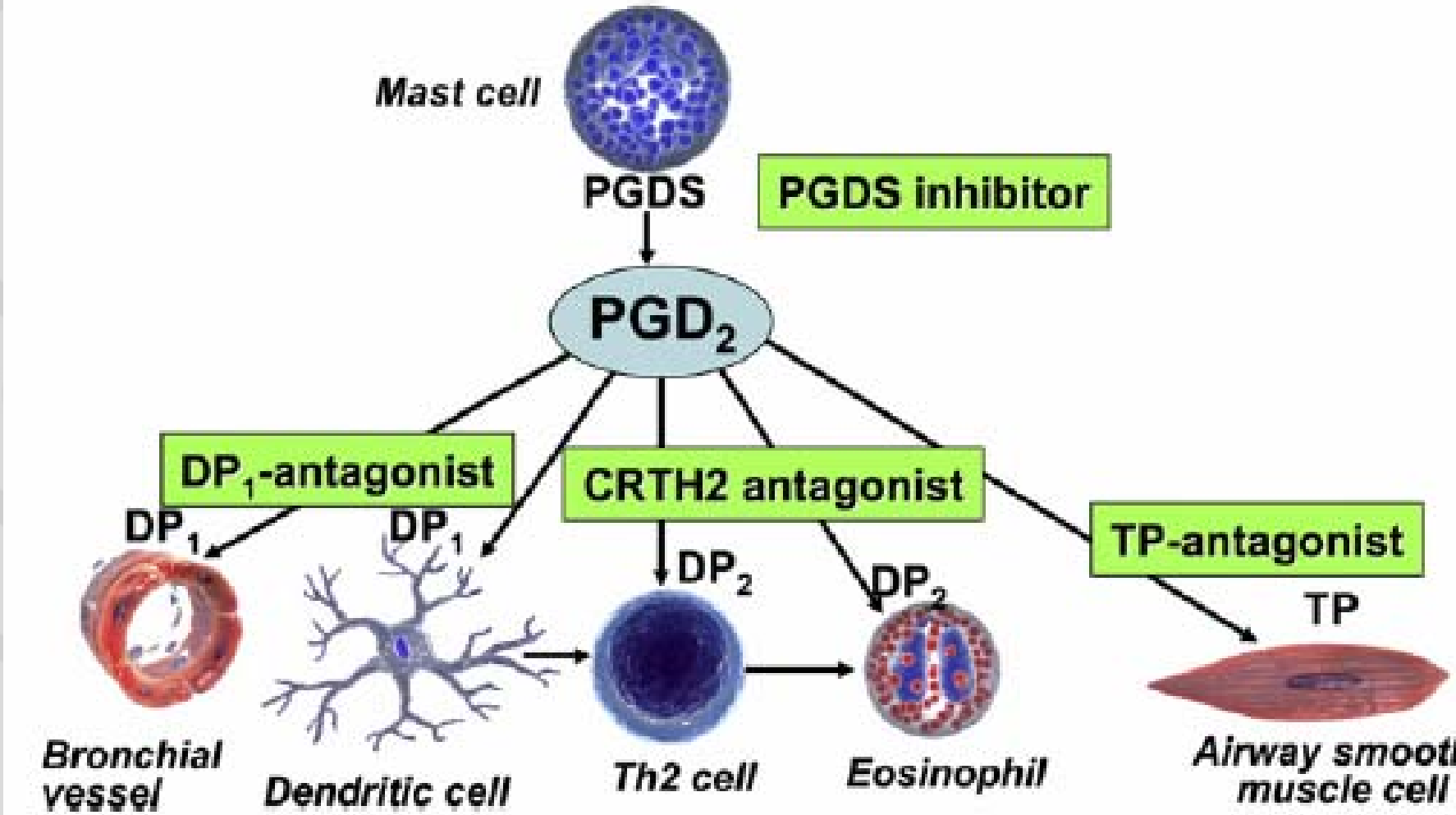
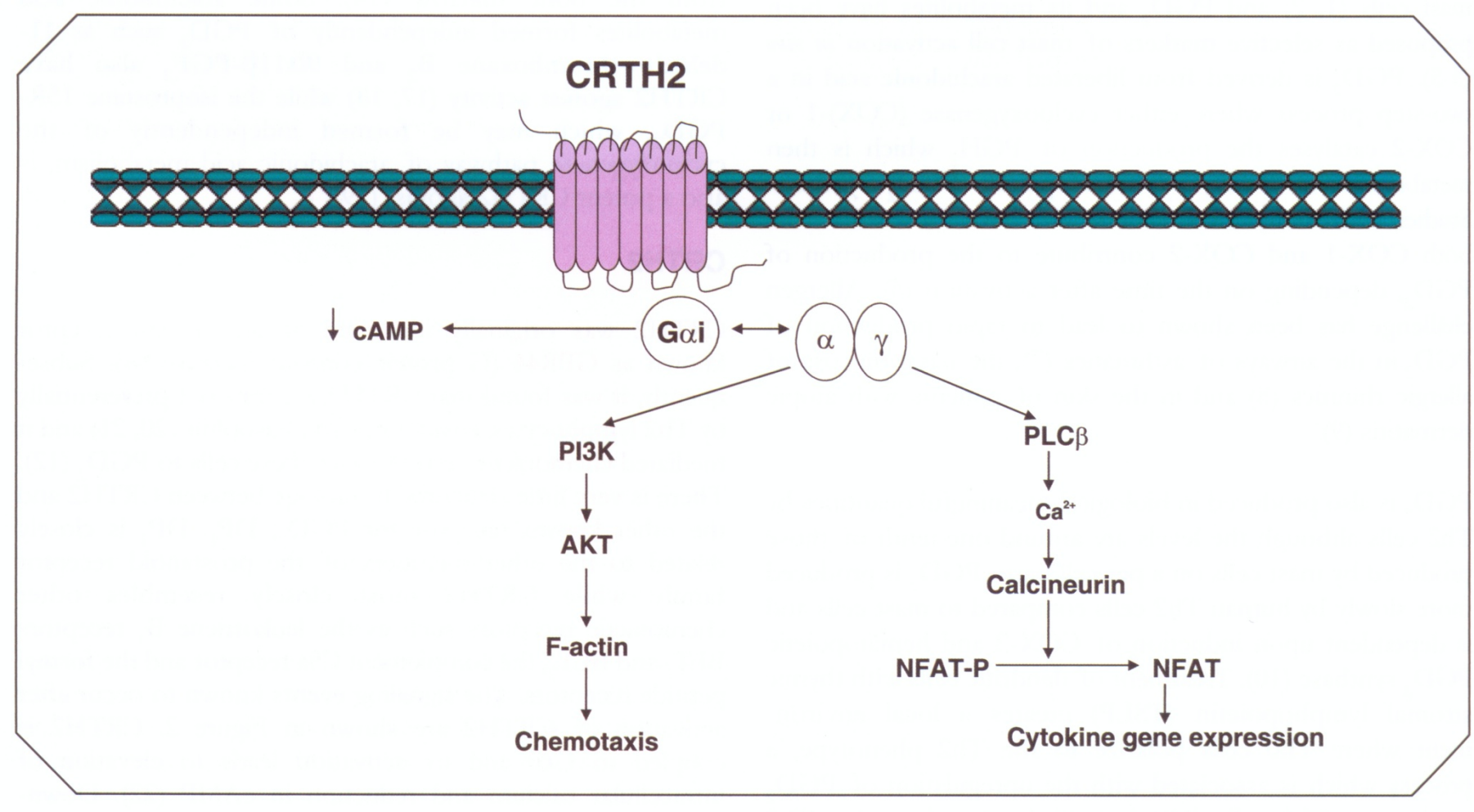
Lanier B, et al. ACAAI 2008 (poster)


Mast cell
PGDS
PGDS inhibitor
PGD2
DP1-antagonist
CRTH2 antagonist
TP-antagonist
DP1
DP1
DP2
DP2
TP
Bronchial vessel
Dendritic cell
Th2 cell
Eosinophil
Airway smooth muscle cell

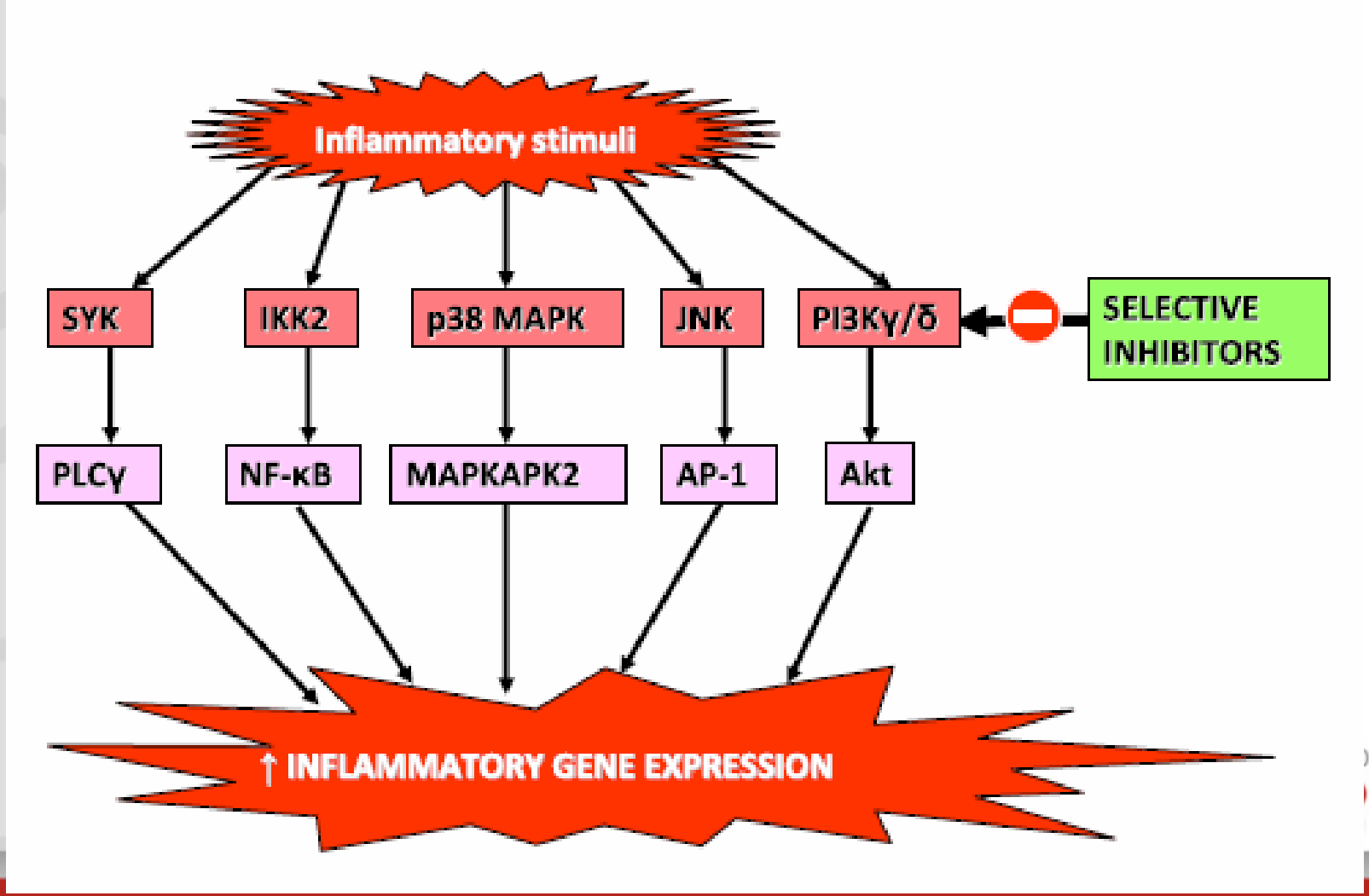
CRTH2 BLOCKERS : RAMATROBANT AND OTHERS



Intracellular signalling pathways

- **Kinase inhibitors :**
  - Kinases have a critical role in the expression and activation of inflammatory mediators in the airway, in both resident and infiltrating cell function and airway remodelling
  - Different kinase pathways can activate specific downstream transcription factors, there is considerable cross-talk between pathways
  - ***Changes in kinase activation status reported in all asthmatic patients, particularly in those with severe asthma where in association with reduced glucocorticoid responsiveness***

Inhibition of proinflammatory kinase pathways for severe asthma



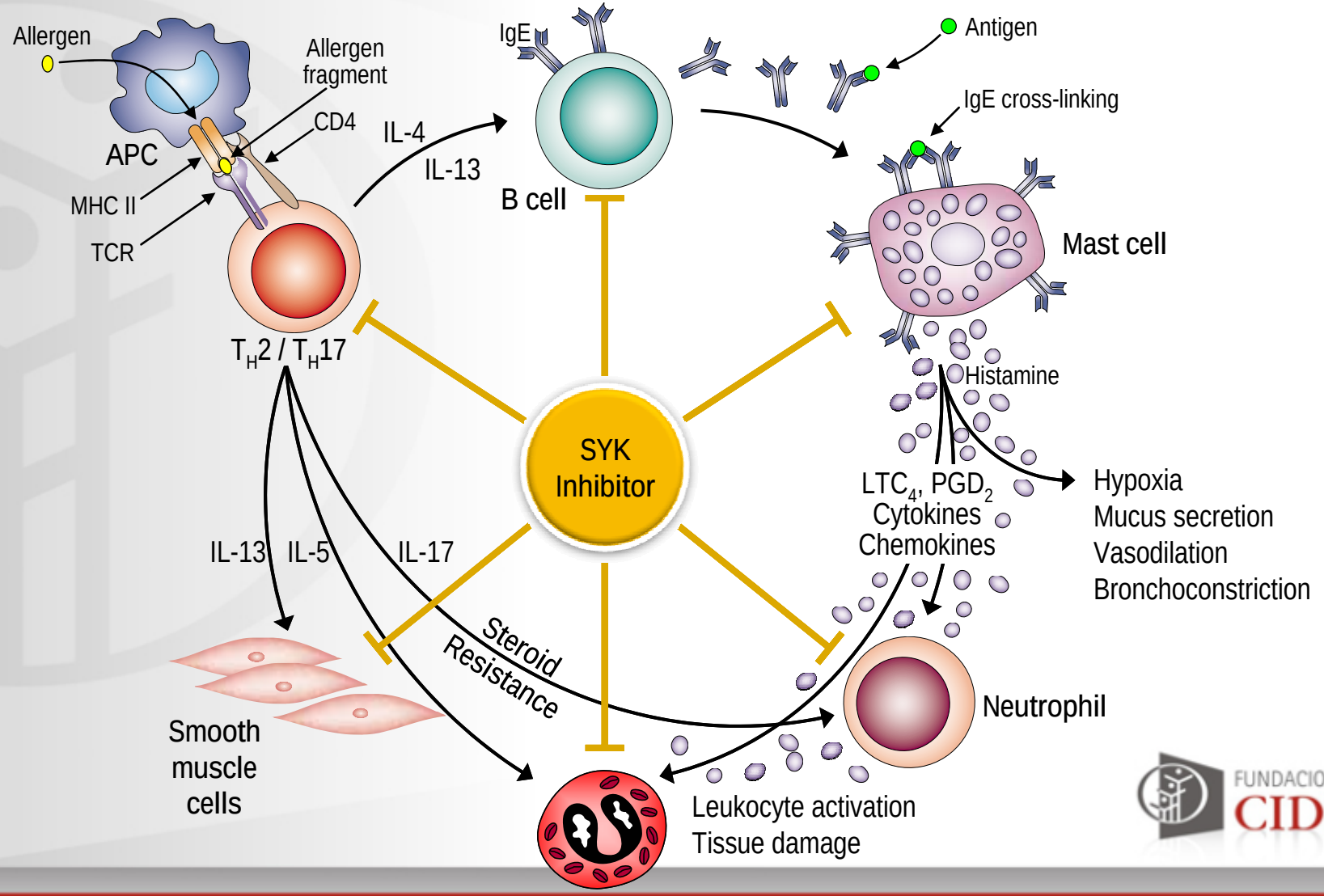
Masitinib is tyrosine kinase inhibitor which effectively and specifically ***inhibits c-kit and PDGF***

- Antagonism of the SCF/c-kit pathway leads to a reduction in mast cells,histamine levels, eosinophil infiltration, IL-4 synthesis and BHR
- PDGF inhibition may decrease remodeling
- In a clinical trial in severe steroid dependant asthma (Humbert , Allergy 2009) allowed improved ACQ, reduced rescue medication and exacerbations
- Side effects were edema , skin rash, nausea
- Concerns: neutropenia and cardiotoxicity

FUNDACION CIDEA

SYK is a Compelling Anti-Inflammatory Target

Spleen tyrosine kinase is an enzyme critical for Fc receptor signaling in cell types integral in asthma

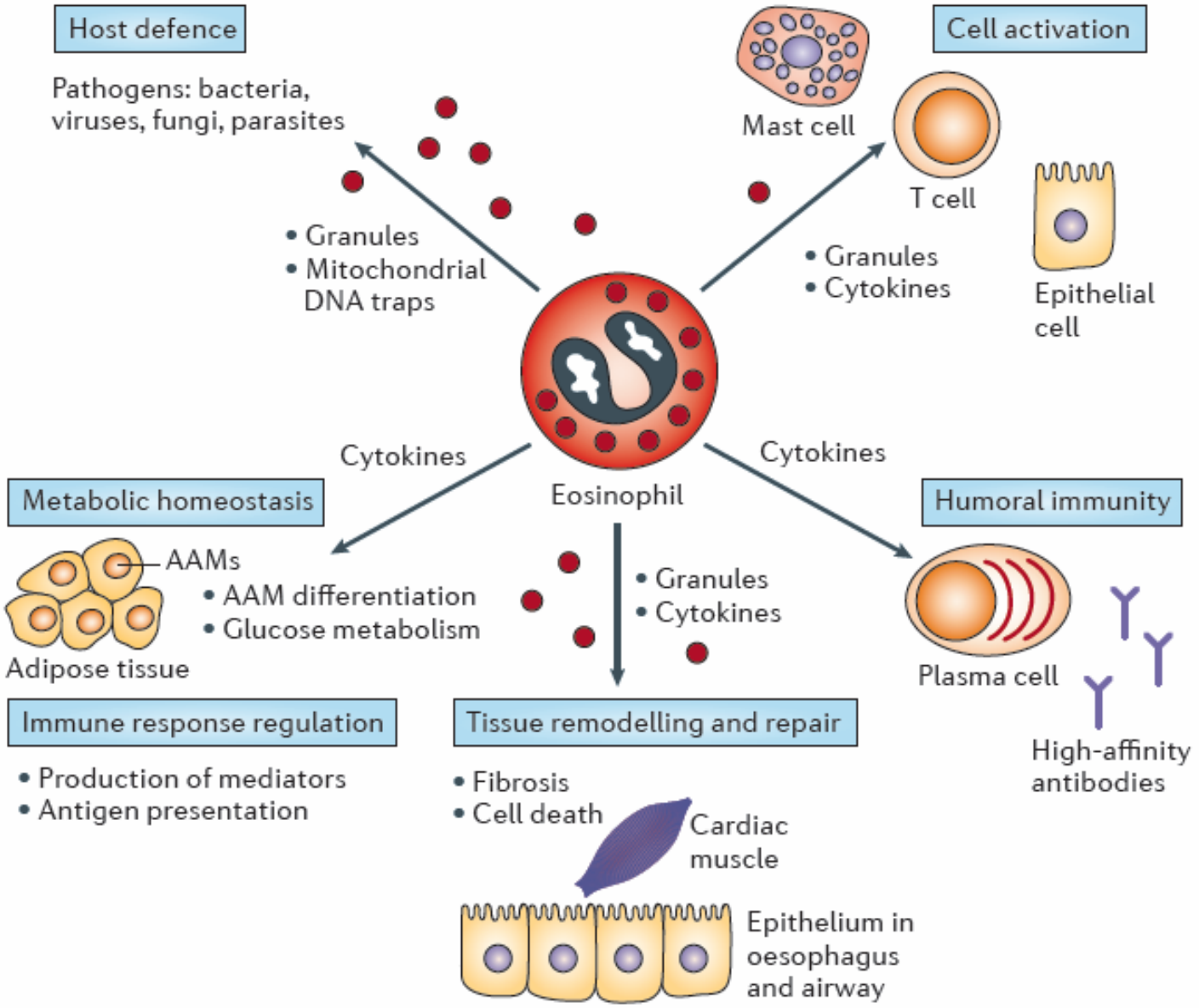


FUNDACION CIDEA

Syk kinase inhibitors

- Syk kinase is an intracellular protein tyrosine kinase that plays an important role in both ***mast cell and basophil activation and the release of mast cell mediators***, including important cytokines.
- Inhibition of Syk kinase is a potential therapeutic modality for allergic inflammation.
- R112, a Syk kinase inhibitor administered intranasally to patients with seasonal allergic rhinitis, demonstrated improvement in symptom scores over placebo with a duration of action exceeding 4 hours.
- No significant adverse events were reported.
- R-343, a Syk kinase inhibitor, is under development for intrapulmonary delivery for the therapy of allergic asthma

Effector functions of eosinophils



FUNDACION CIDEA

Role of eosinophils and IL-5 in asthma

- Eosinophils maturation, migration,survival and activation influenced by: IL-3, IL-5, GM-CSF, CC chemokines, and PAF.
- Eosinophil infiltration and degranulation in pulmonary tissue implicated in pathophysiology of asthma
- IL-5 expression elevated in bronchoalveolar lavage fluid and bronchial biopsies in patients with asthma
- Level of IL-5 in BALF and bronchial mucosa correlates with disease activity
- IL-5 mRNA upregulated in mucosa post-allergen challenge

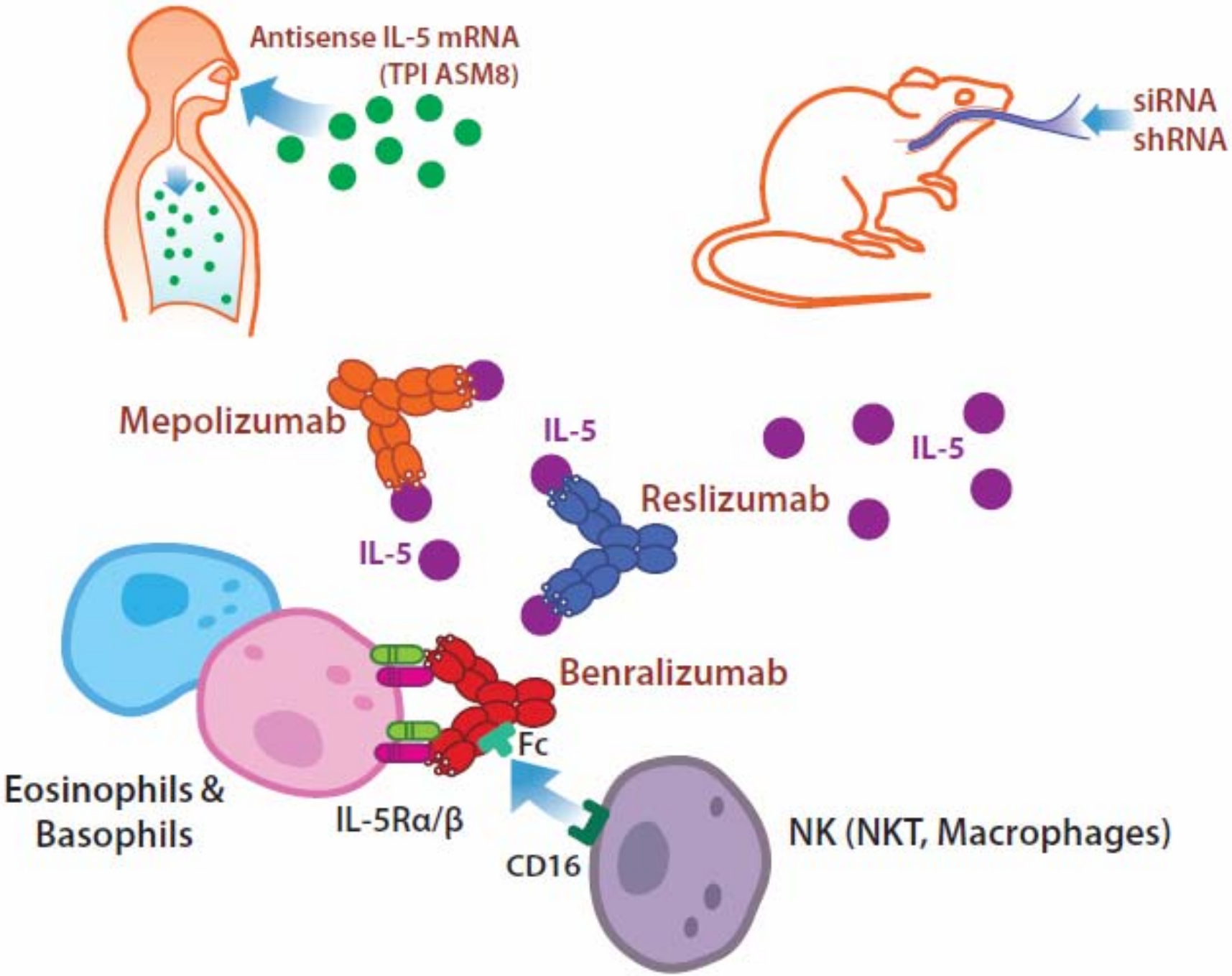
Bousquet J et al. *N Engl J Med* 1990;323:1033-9
Hamid Q et al. *J Clin Invest* 1991;87:1541-6
Humbert M et al. *AJRCCM* 1997;156:704-8
Robinson D et al. *JACI* 1993;92:313-24

Eosinophils and asthma exacerbations

Green RH et al. Lancet. 2002; 360:1715-21

Al presente esta estrategia no ha demostrado funcionar en pacientes pediatricos

- A rise in counts measured longitudinally predicts subsequent loss of asthma control (Green 2002, *Jatakanon 2006, Deykin 2004)*
- Tighter control of sputum eosinophils leads to a reduction in exacerbations


Antisense IL-5 mRNA
(TPI ASM8)
siRNA
shRNA
Mepolizumab
IL-5
IL-5
Reslizumab
IL-5
Benralizumab
Fc
Eosinophils &
Basophils
IL-5Rα/β
CD16
NK (NKT, Macrophages)

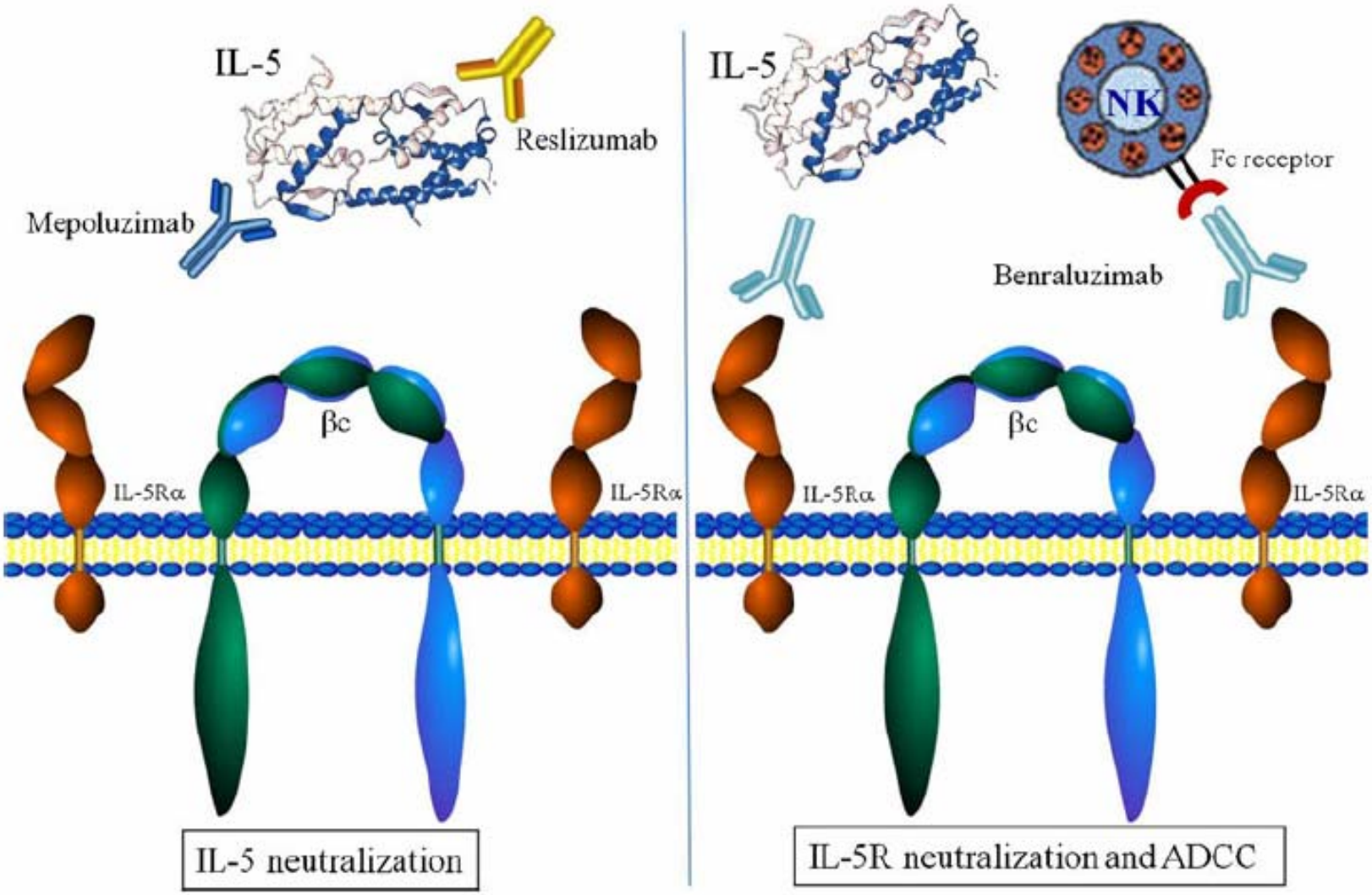

IL-5
Reslizumab
Mepoluzimab
βc
IL-5Rα
IL-5Rα
IL-5 neutralization
IL-5
NK
Fc receptor
Benraluzimab
βc
IL-5Rα
IL-5Rα
IL-5R neutralization and ADCC

Table 1 Targeting IL-5 and the IL-5R

Target Sites	Drug	Other Names	Isotype	Mechanism	Human Uses
IL-5	Mepolizumab (GSK)	SB-240563	IgG1k	Neutralizing antibody	(Phase 2) Asthma
					(Phase 2) Adult eosinophilic esophagitis
		Bosatria			(Phase 2) Pediatric eosinophilic esophagitis
					(Phase 2) Churg Strauss syndrome
					(Phase 2) Nasal polyposis
					(Phase 3) Hypereosinophilic syndromes
					(Phase 3) Pediatric eosinophilic esophagitis
					(Phase 3) Rhinovirus induced asthma
					(Phase 3) COPD
	Reslizumab (Cephalon)	SCH55700	IgG4k	Neutralizing antibody	(Phase 3) Asthma
		Cinquil			(Phase 2) Hypereosinophilic syndromes
					(Phase 3) Pediatric eosinophilic esophagitis
					(Phase 2) Loiasis
IL-5R α	Benralizumab (MedImmune)	MEDI-563	IgG1k	ADCC, competitive inhibition	(Phase 2) Asthma
					(Phase 2) COPD
βc & Eotaxin	TPI ASM8 (Pharmaxis)			Antisense gene target	(Phase 2) Asthma

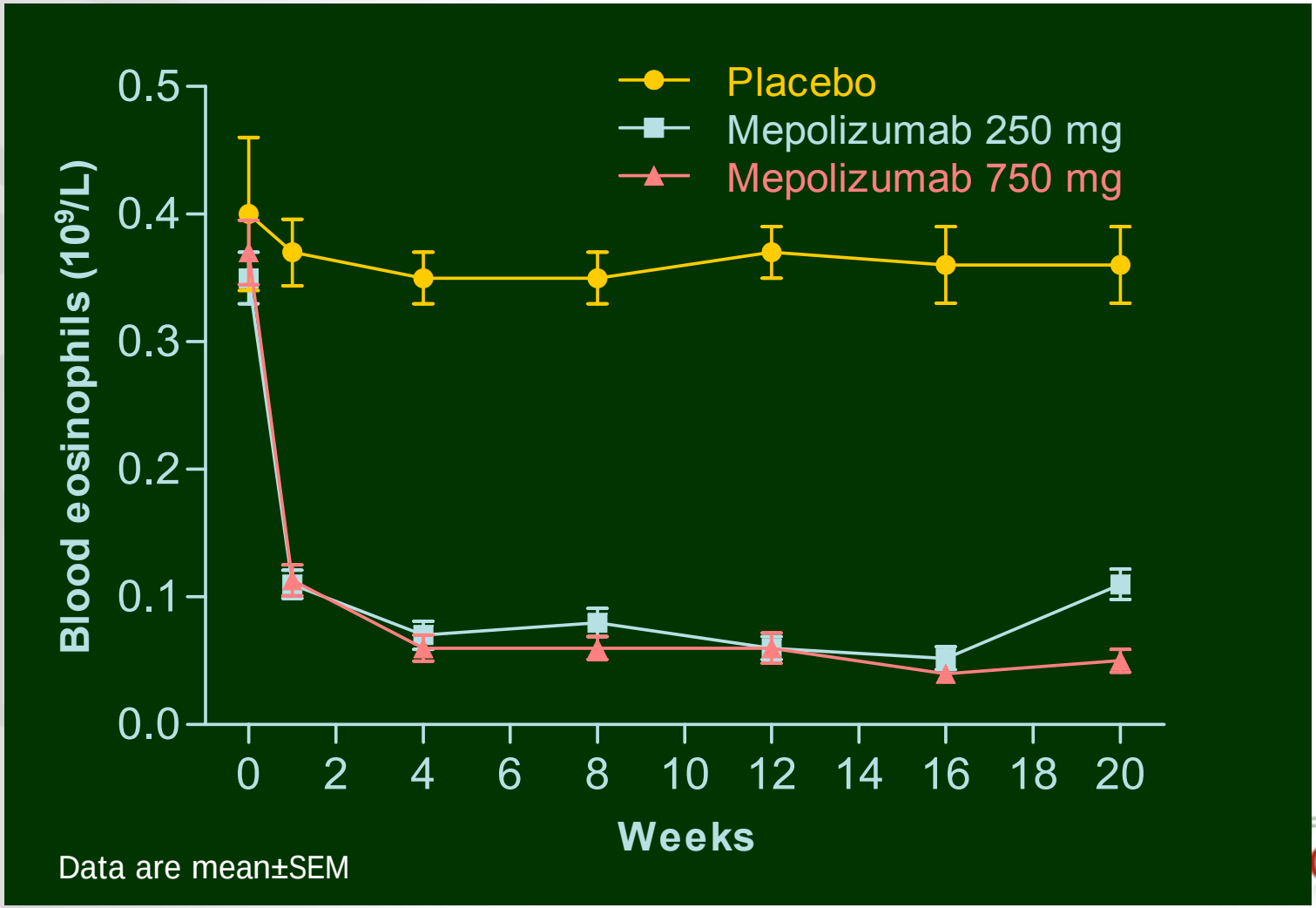
Mepolizumab (mepo)

- Mepolizumab is a humanised monoclonal antibody (IgG1 kappa) against human IL-5
- Intention is to develop mepo for:
  - Severe refractory asthma patients
- Has been studied in hypereosinophilic syndrome (HES) and paediatric eosinophilic esophagitis (EE), Atopic dermatitis
- Nasal polyposis also being explored

FUNDACION CIDEA

SB-240563/006: Effect on blood eosinophil counts in moderate asthma

Blood eosinophil counts decreased with mepolizumab, but not placebo

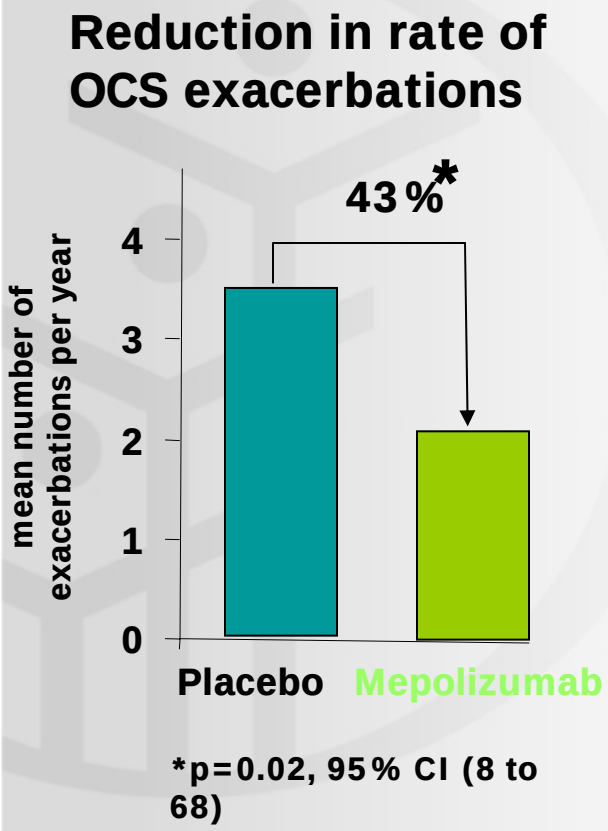


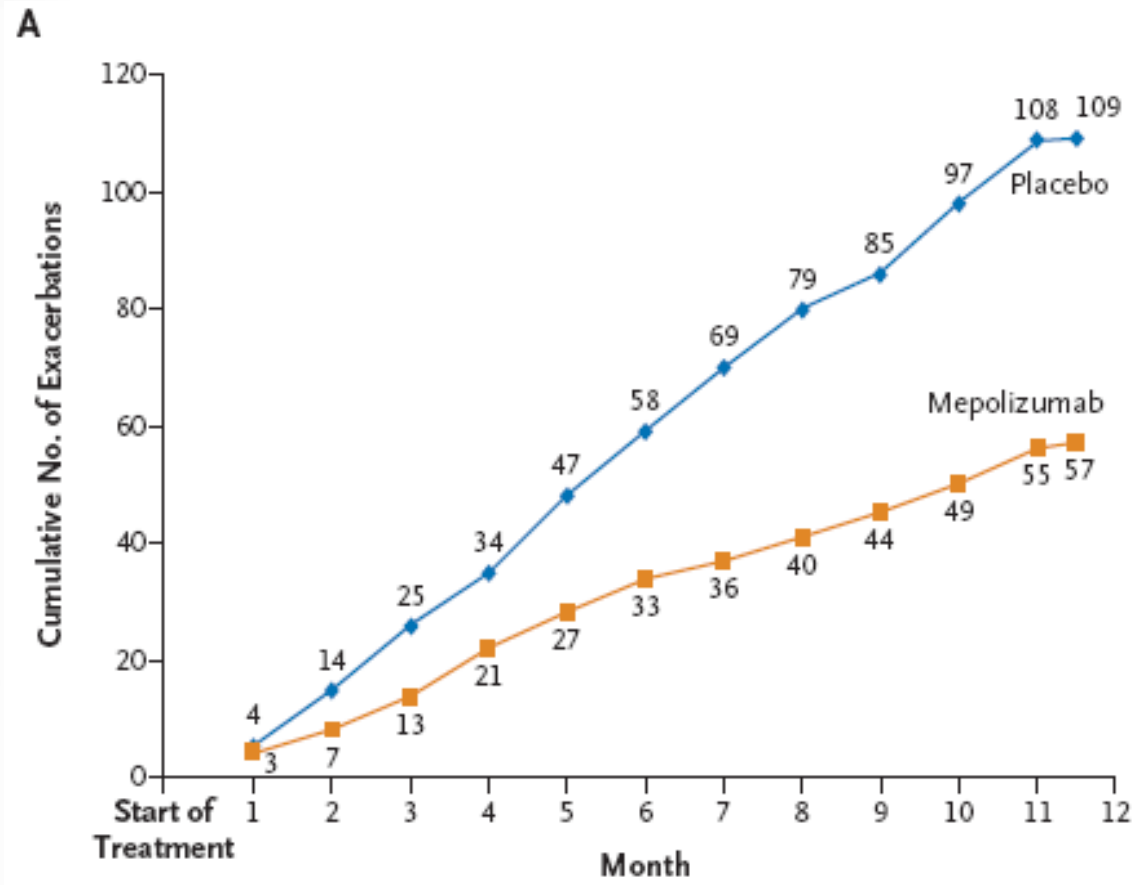
FUNDACION CIDEA

Flood-Page P *et al.* Am J Resp Crit Care 2007

Flood-Page P et al. *AJRCCM* 2007;176:1062-71

Results: significant reduction in exacerbations

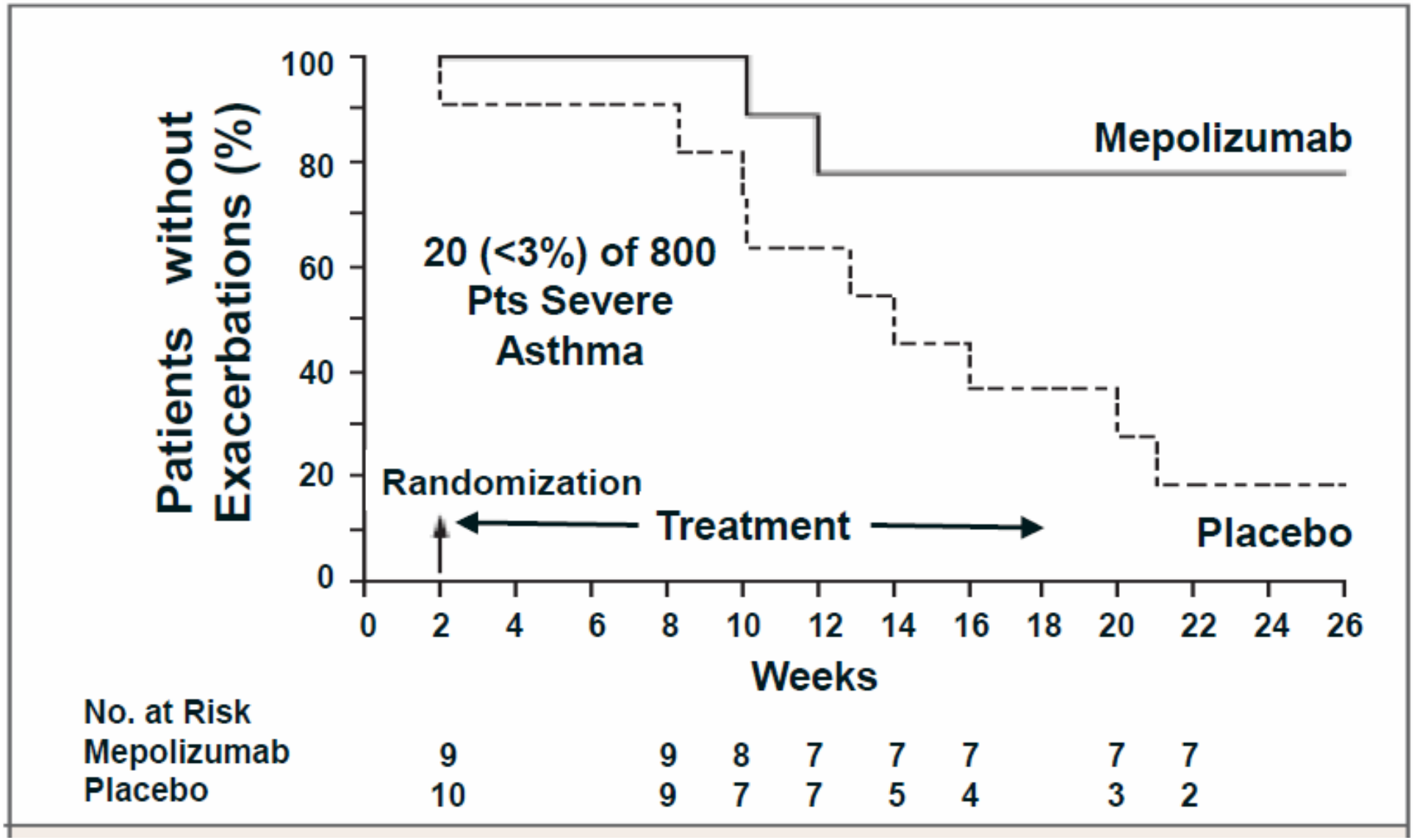


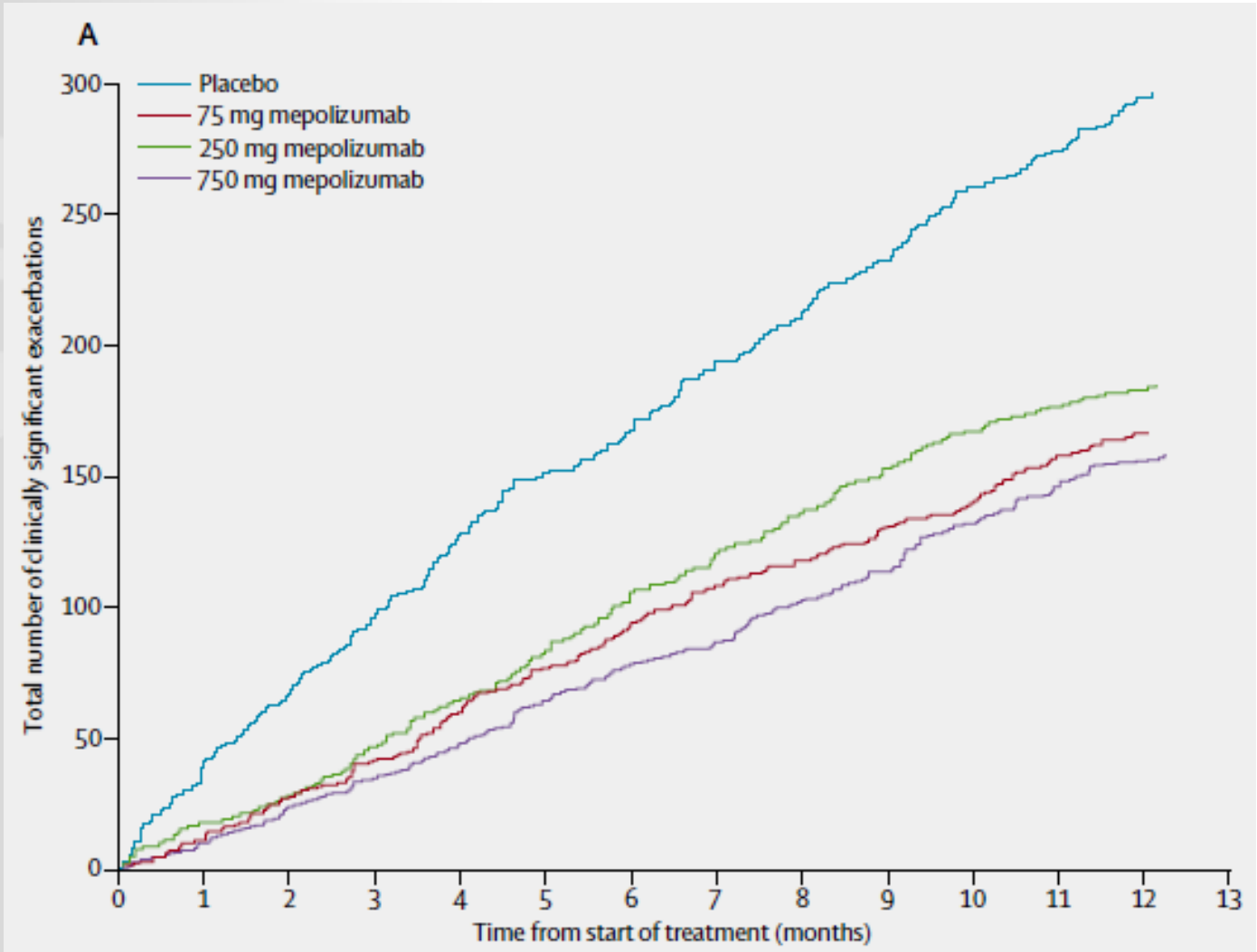


FUNDACION CIDEA

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Nair, et al. NEJM 2009; 360:985-993





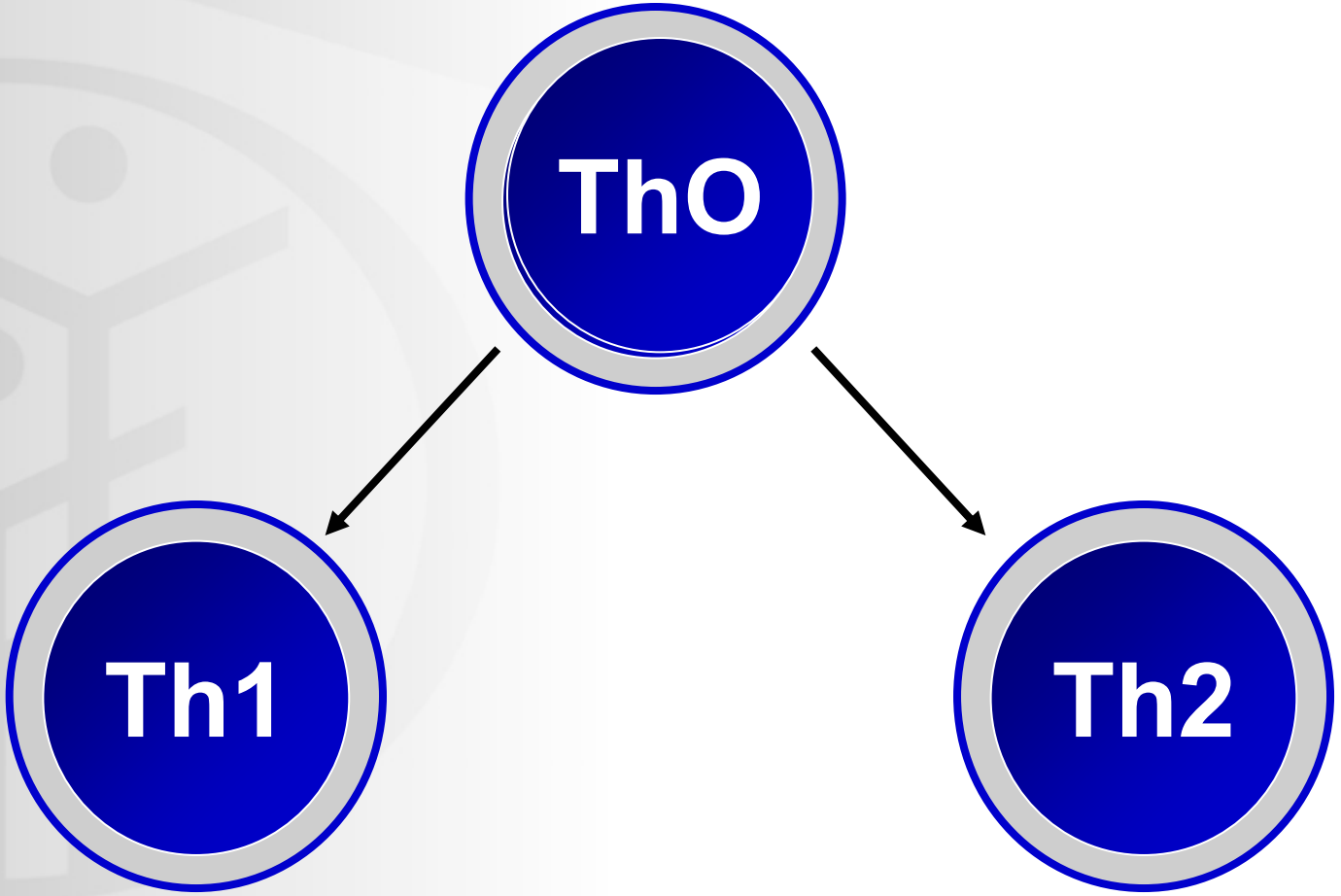
The rate of clinically significant exacerbations was 2·40 per patient per year in the placebo group, 1·24 in the 75 mg mepolizumab group (48% reduction, 95% CI 31–61%; p<0·0001), 1·46 in the 250 mg mepolizumab group (39% reduction, 19–54%; p=0·0005), and 1·15 in the 750 mg mepolizumab group (52% reduction, 36–64%; p<0·0001**).**

Mepolizumab in Asthma: Overall Efficacy Conclusions

- **Persistent and dose-dependent reduction in blood eosinophil counts**
- **Significant reductions in sputum, bronchial mucosa, and bone marrow eosinophils**
- **Significant reduction in severe exacerbation frequency in refractory eosinophilic asthma**
- **Positive effect on Asthma Quality of Life**
- **No clinically significant effect on functional parameters**
  - **late asthmatic response to allergen challenge**
  - **airway hyperresponsiveness**
  - **PEFR**
  - **FEV_1**
  - **β_2-agonist use**

FUNDACION CIDEA

IL-4 and IL-13 of Th2 cells

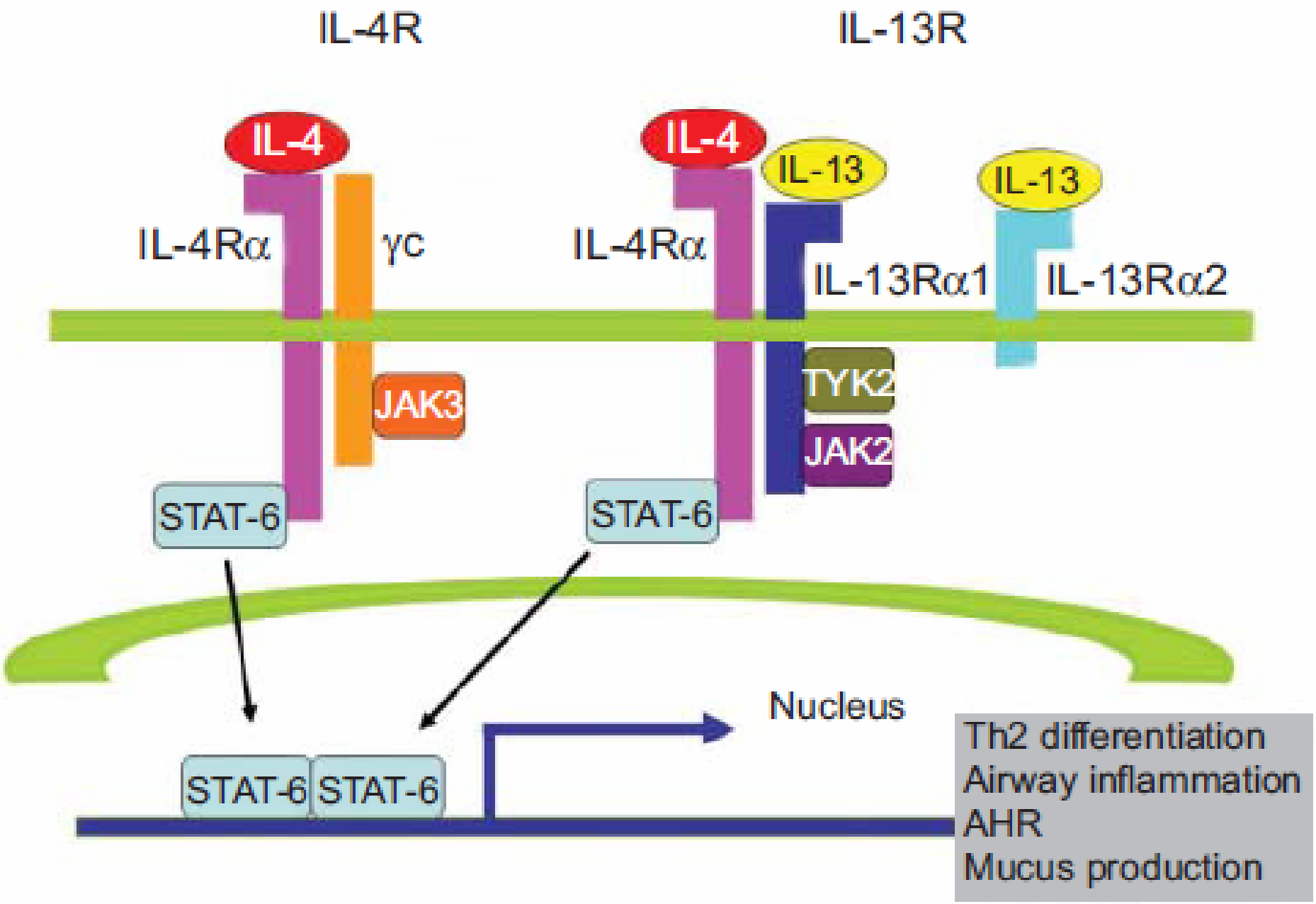


IFN-γ

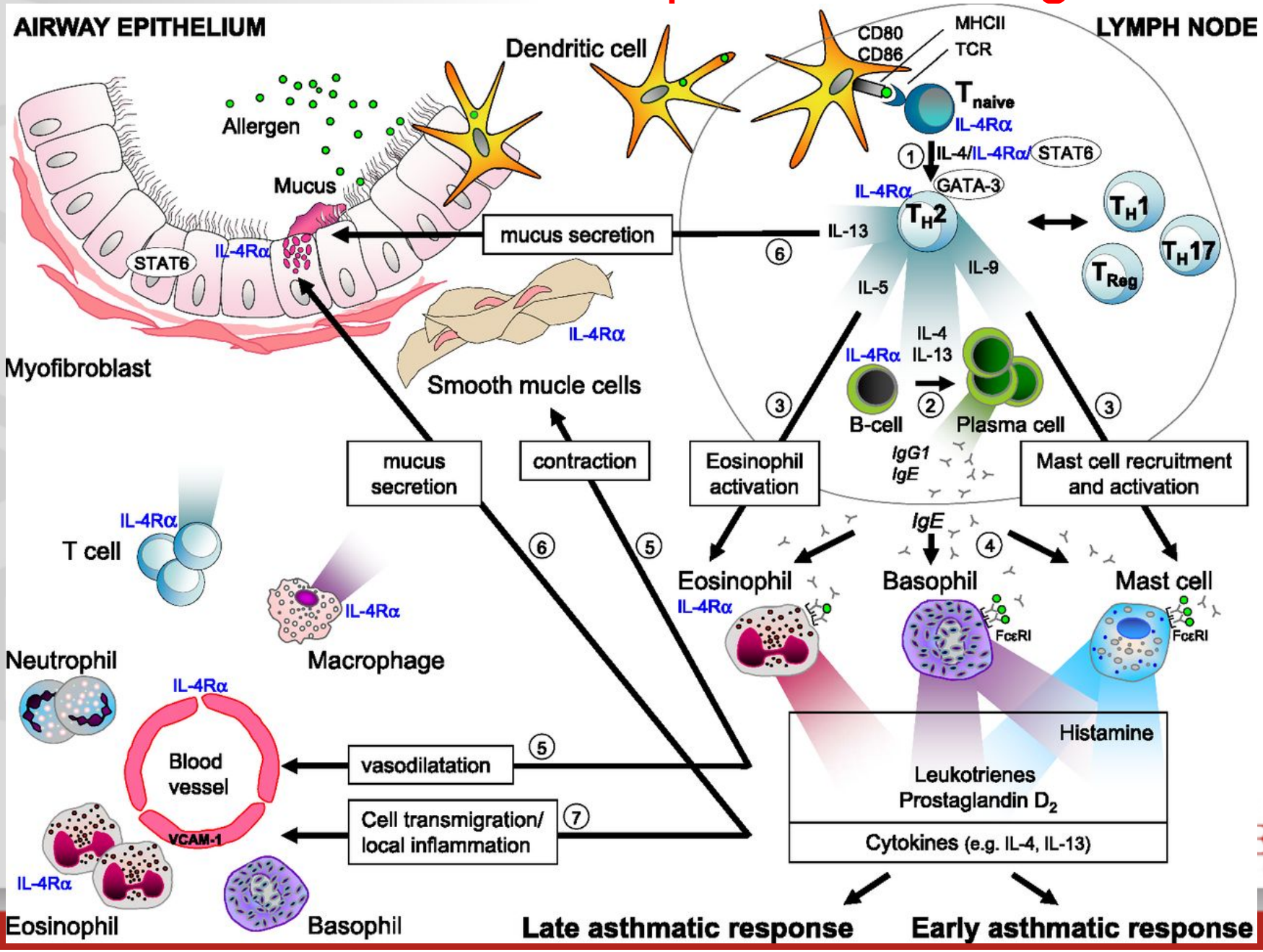
IL-4, IL-5, IL-13

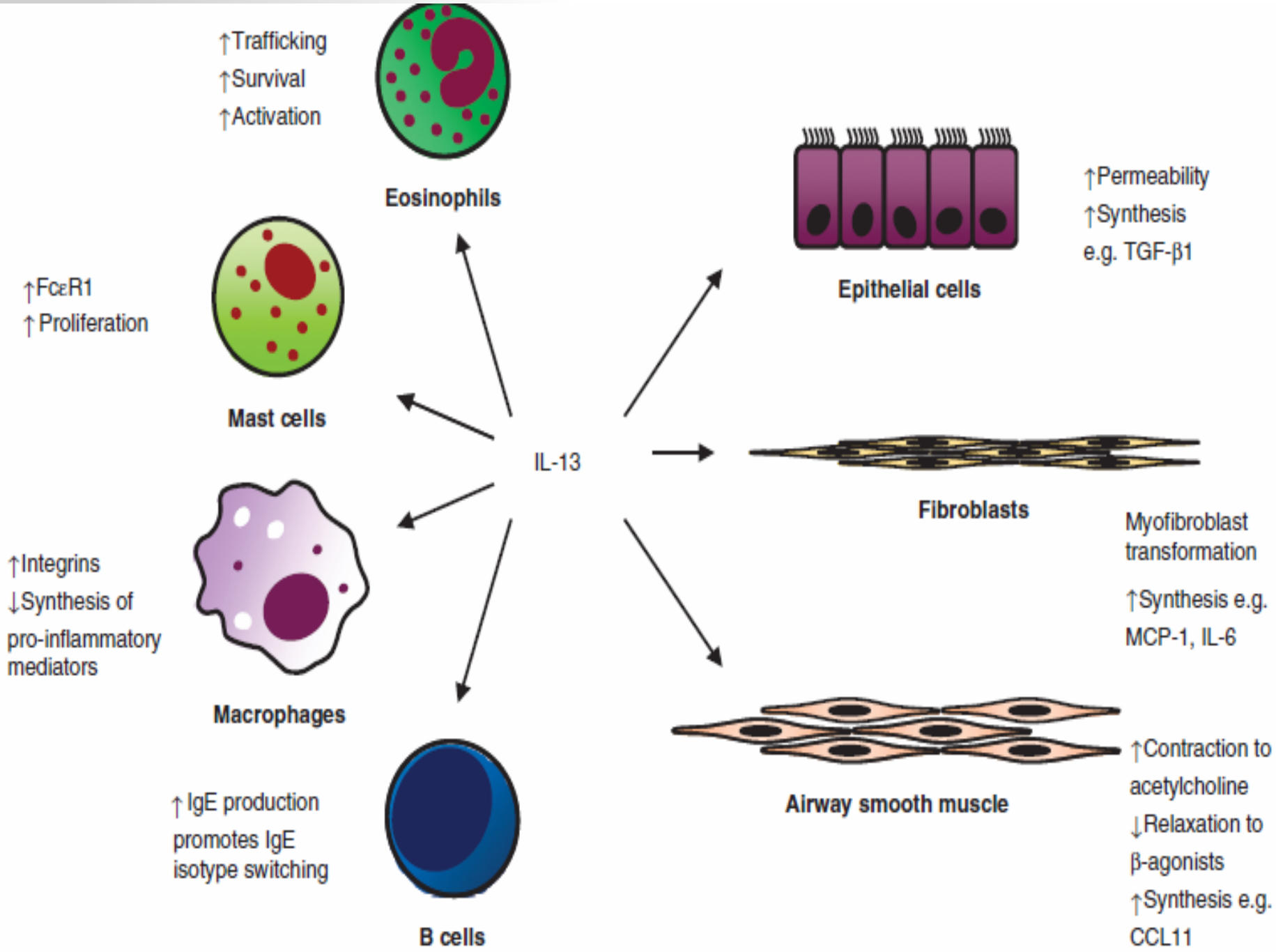
cell-mediated immunity

allergy/asthma

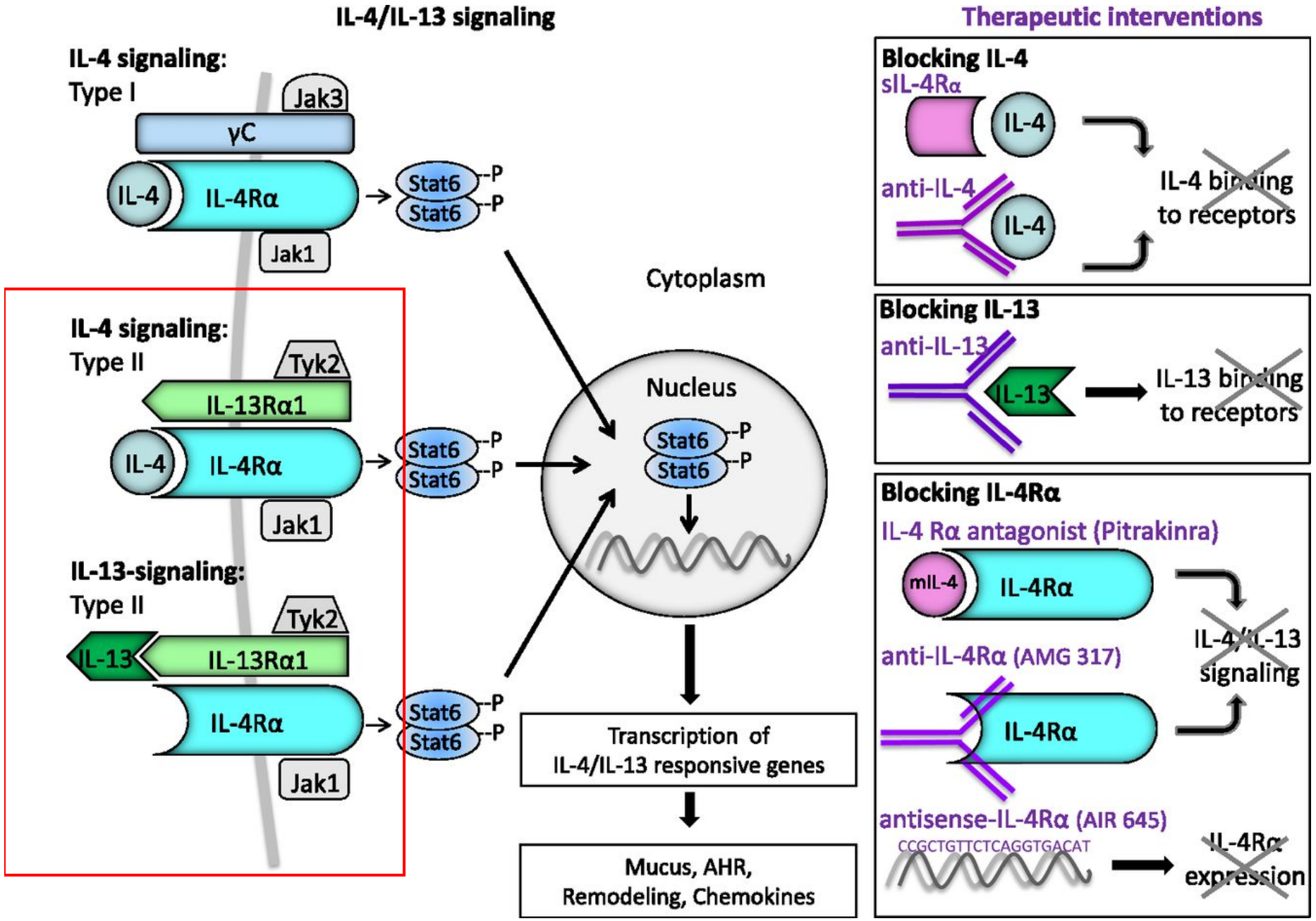

IL-4R
IL-13R
IL-4
IL-4Rα
γc
JAK3
STAT-6
IL-4
IL-13
IL-13
IL-4Rα
IL-13Rα1
IL-13Rα2
TYK2
JAK2
STAT-6
Nucleus
STAT-6
STAT-6
Th2 differentiation
Airway inflammation
AHR
Mucus production

Role of IL-4 in the development of allergic asthma




↑Trafficking
↑Survival
↑Activation
Eosinophils
↑FcεR1
↑ Proliferation
Mast cells
↑Integrins
↓Synthesis of
pro-inflammatory
mediators
Macrophages
↑ IgE production
promotes IgE
isotype switching
B cells
IL-13
Epithelial cells
↑Permeability
↑Synthesis
e.g. TGF-β1
Fibroblasts
Myofibroblast
transformation
↑Synthesis e.g.
MCP-1, IL-6
Airway smooth muscle
↑Contraction to
acetylcholine
↓Relaxation to
β-agonists
↑Synthesis e.g.
CCL11

IL-4/IL-13 signaling and therapeutic interventions to treat allergic asthma.



A wide range of biologic agents against these targets has been developed

- anti–IL-13 mAb
  - (IMA-026, IMA-638 (anrukinzumab), QAX576, CAT-354,MILR 1444A)
- anti–IL-4Ra mAb
- anti–IL-13Ra1 mAb,
- IL-4Ra/IL-13Ra1 fusion protein,
- IL-4/IL-13 vaccines,
- antisense and small interfering RNA
- IL-4 double mutein

FUNDACION CIDEA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohen, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.

ABSTRACT

BACKGROUND

Many patients with asthma have uncontrolled disease despite treatment with inhaled glucocorticoids. One potential cause of the variability in response to treatment is heterogeneity in the role of interleukin-13 expression in the clinical asthma phenotype. We hypothesized that anti–interleukin-13 therapy would benefit patients

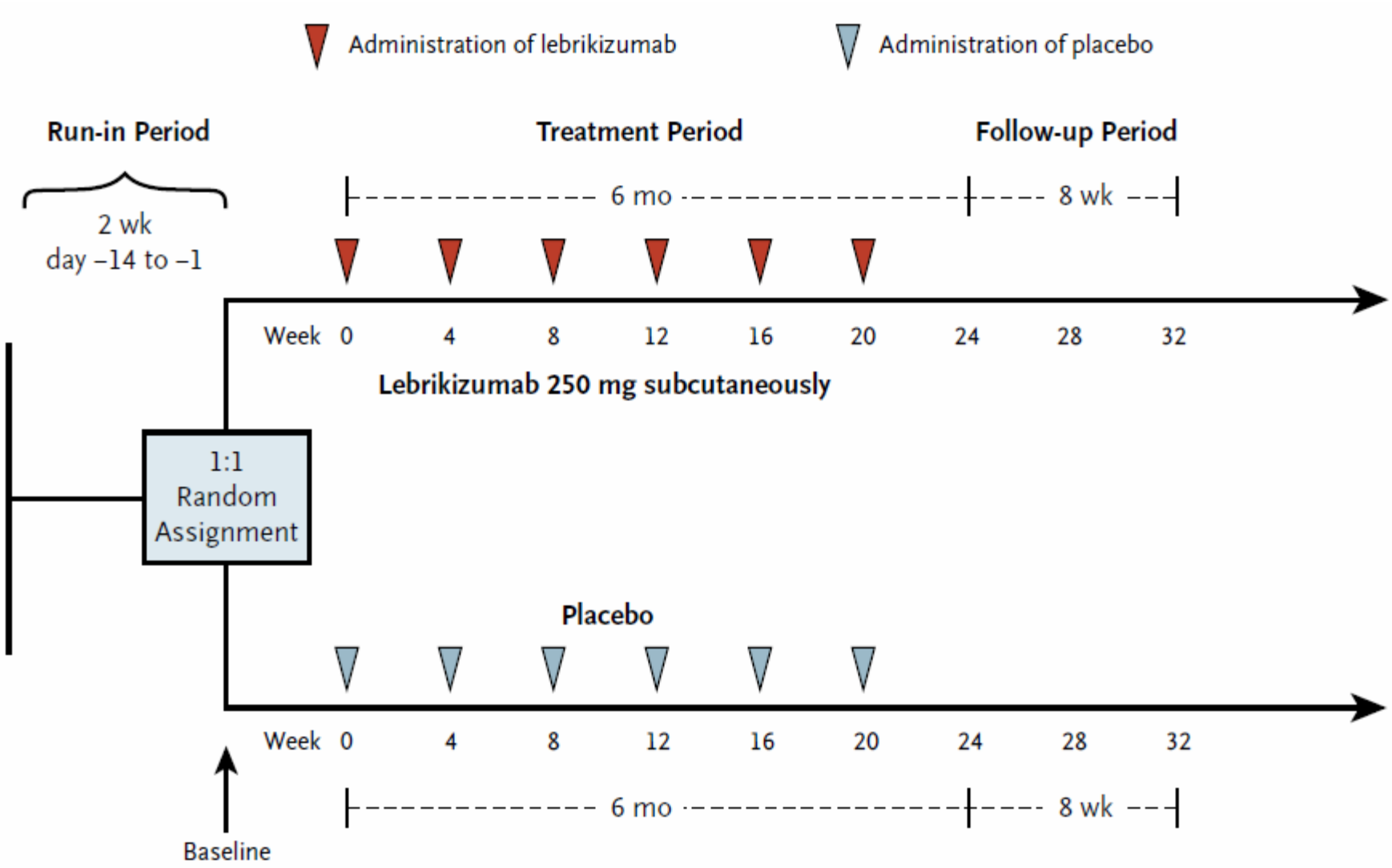
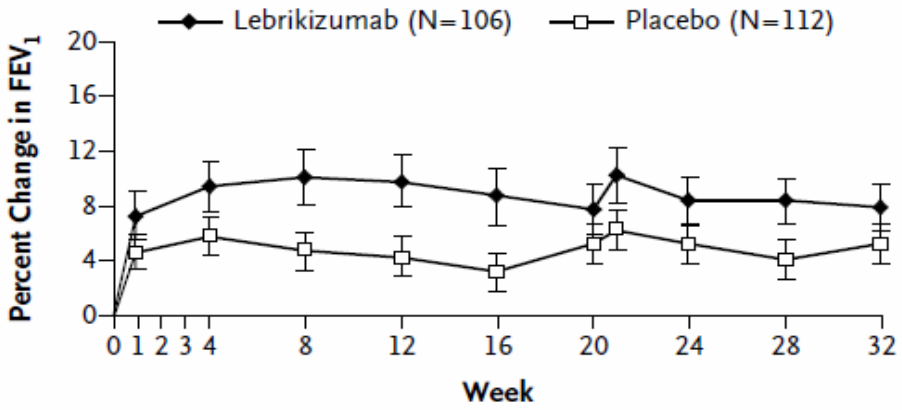


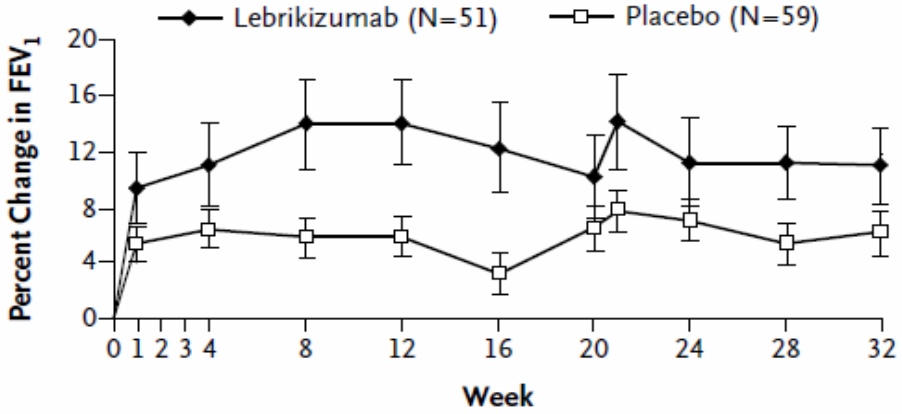
Figure 1. Schematic Representation of the Study Design.

Eligibility of the patients was established during a 2-week run-in period. This period was followed by a double-blind, randomized, placebo-controlled treatment period (day 1 to week 24) during which patients recorded their peak expiratory flow twice a day, as well as symptoms of asthma once a day. At monthly study visits through week 24, assessments included spirometry, safety evaluation, blood testing, measurement of FE_{NO}, and outcome questionnaires; at the visits through week 20, the study drug was also administered. Safety and efficacy continued to be monitored during the follow-up period (week 24 to week 32).

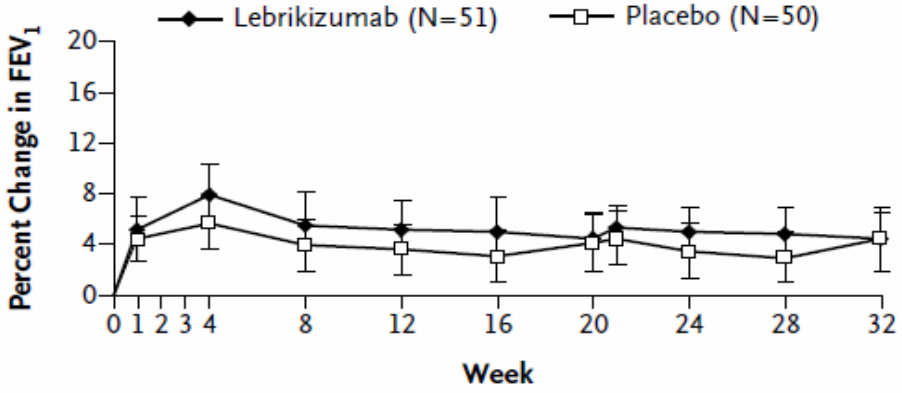
A Total Cohort



B High-Periostin Subgroup



C Low-Periostin Subgroup



FUNDACION CIDEA

QAX576

- Fully human IgG/κ monoclonal antibody
- Highly potent and specific inhibitor of human interleukin (IL) 13
- Once QAX576 has bound to IL-13, the dissociation is very slow.
- IL-13 inhibition has a profound effect on airway hyperreactivity and inflammation within the allergic lung

FUNDACION CIDEA

IL-4 Modifiers

Altrakincept	Solubilized IL-4 receptor fragment, neutralizes IL-4	Failed to show efficacy in large phase 3 trial. Adcock et al (2008)
Pascolizumab	Monoclonal Ab against IL- 4	Phase 2 study of pascolizumab discontinued because of inefficacy. Hart et al (2002)
Pitrakinra	IL-4 mutant protein. Binds to α subunit of IL-4 receptor, antagonizes both IL-4 & IL-13/ STAT-6	Improved pulmonary function, ⇓ FENO; IL-4 R α polymorphisms predict response Wenzel et al. Lancet 2007;370:1422 Slager RE et al. AJRCCM 2011; 183:A6178 Slager RE et al. JACI 2010; 126:875

IL-4 variant : Pitrakinra

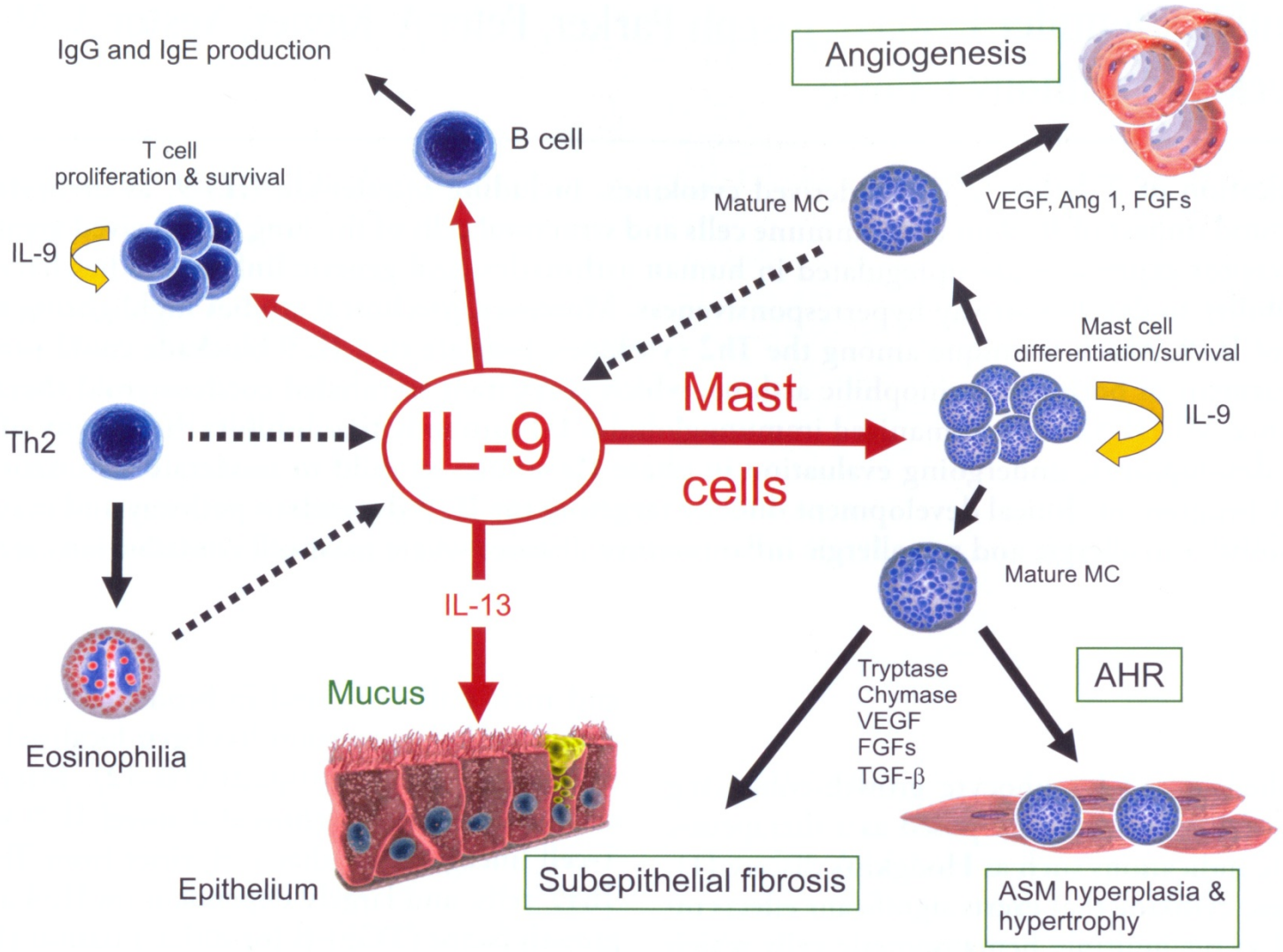
- AMG-317 is a fully human antagonist to the IL-4Ra receptor subunit
- Daily sc injections for 4 weeks (15 ug)
- Nebulizations twice daily 60 ug
- Higher dose inhibits LAR after antigen challenge (4 vs 16% fall in FEV1)
- Interpretation : Local treatment, targeted at inhibition of interleukins 4 and 13 in the lung, could substantially diminish the symptoms of asthma.

Wenzel S et al. Lancet 20.10.07; 370: 1422-31

FUNDACION CIDEA

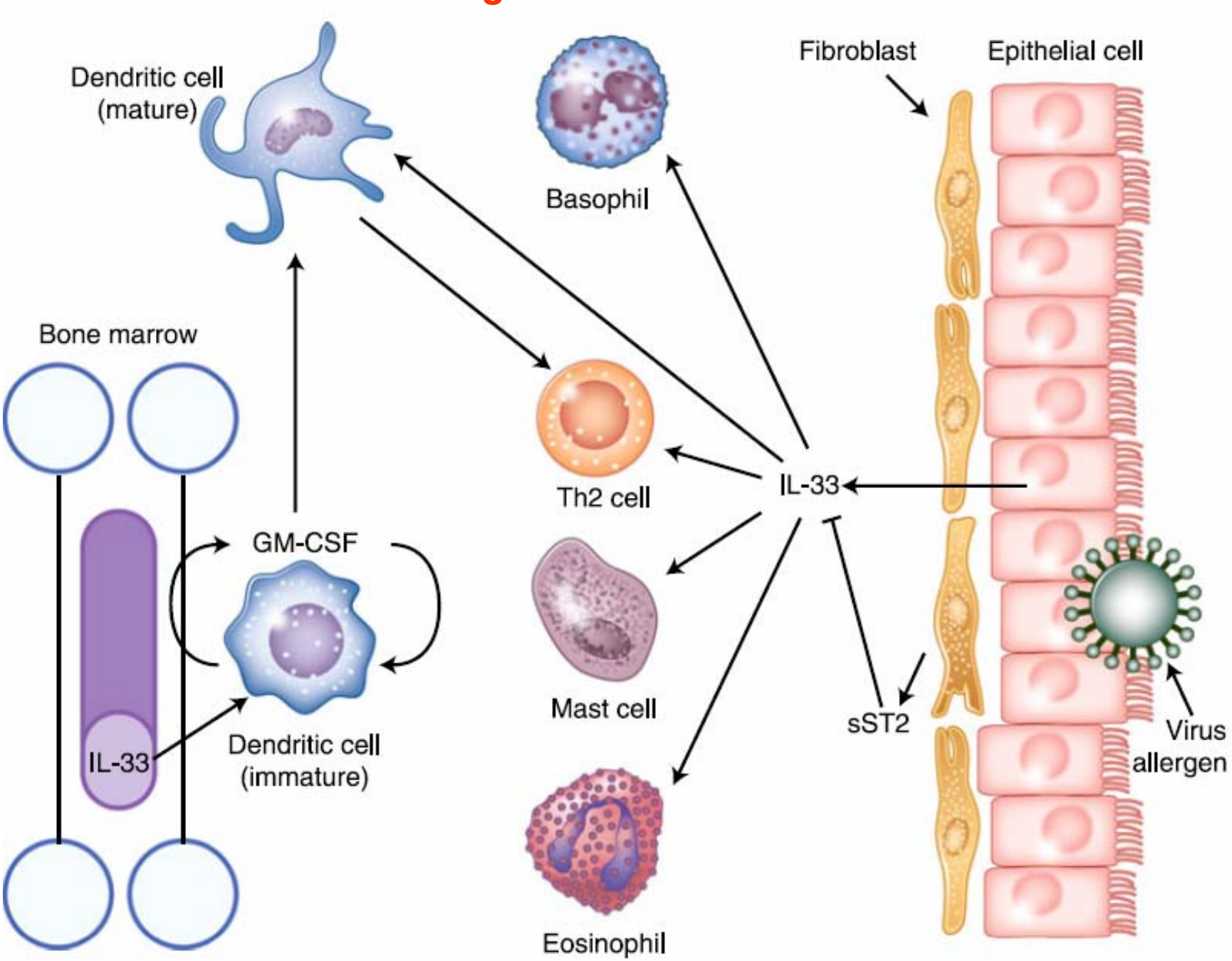
Oral synthesis inhibitors

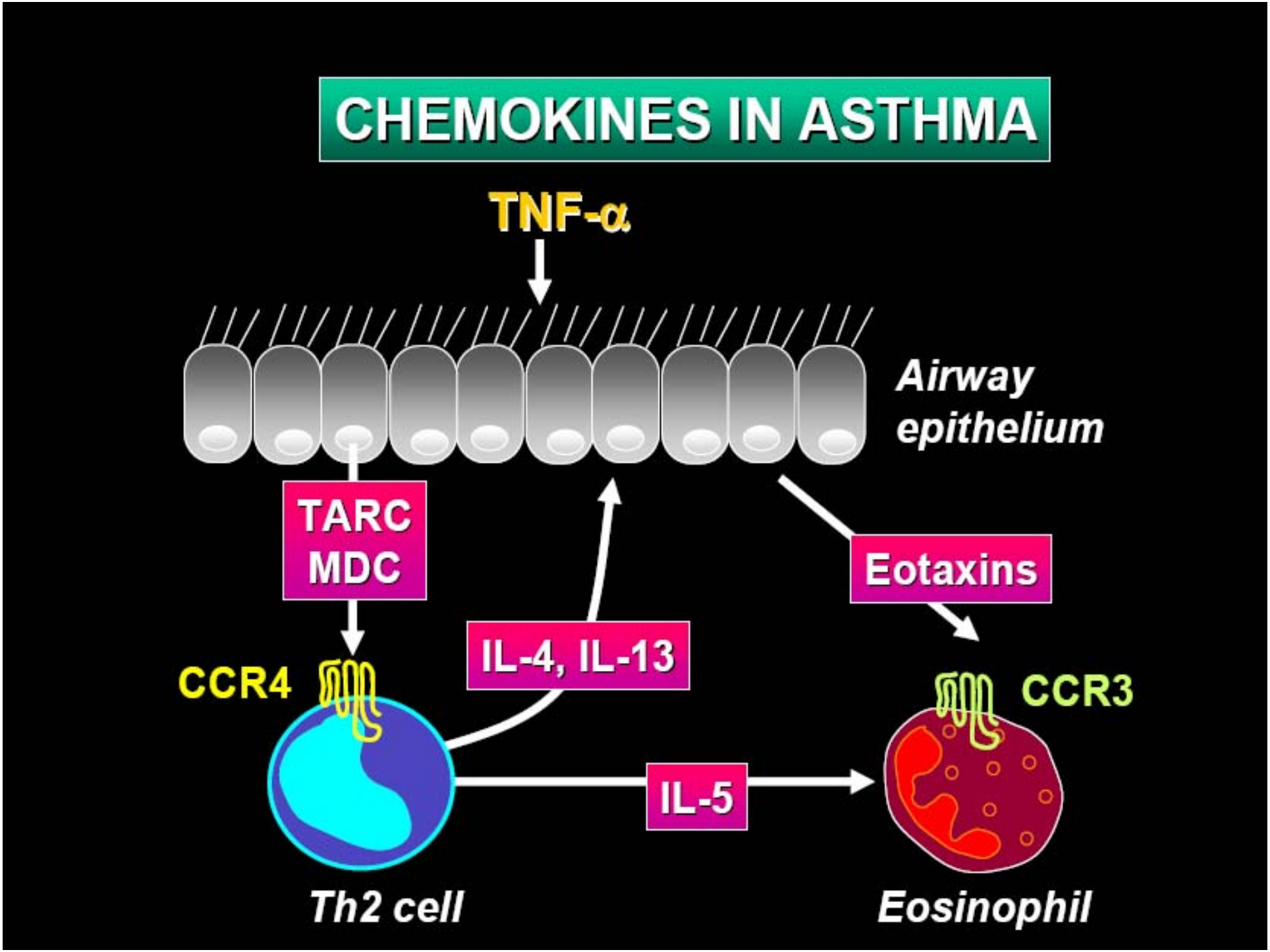
- Two oral agents that inhibit cytokine synthesis are undergoing clinical trials.
- Suplatast tosilate inhibit the production of IL-4 and IL-5.
- Clinical trials with suplatast: improvement in airway inflammation, airway hyperresponsiveness, clinical symptoms, and peak expiratory flow rates.
- Suplatast has also decreases serum IgE levels.
- AVP-13358 has suppressed IgE, CD23, and TH2 cytokine responses ex vivo and in vitro in mouse and human cell assays.



MEDI 528 ANTICUERPO MONOCLONAL DE APLICACION SUBCUTANEA PARA ASMA NO CONTROLADA

Posible new Targets IL-33 and TSLP

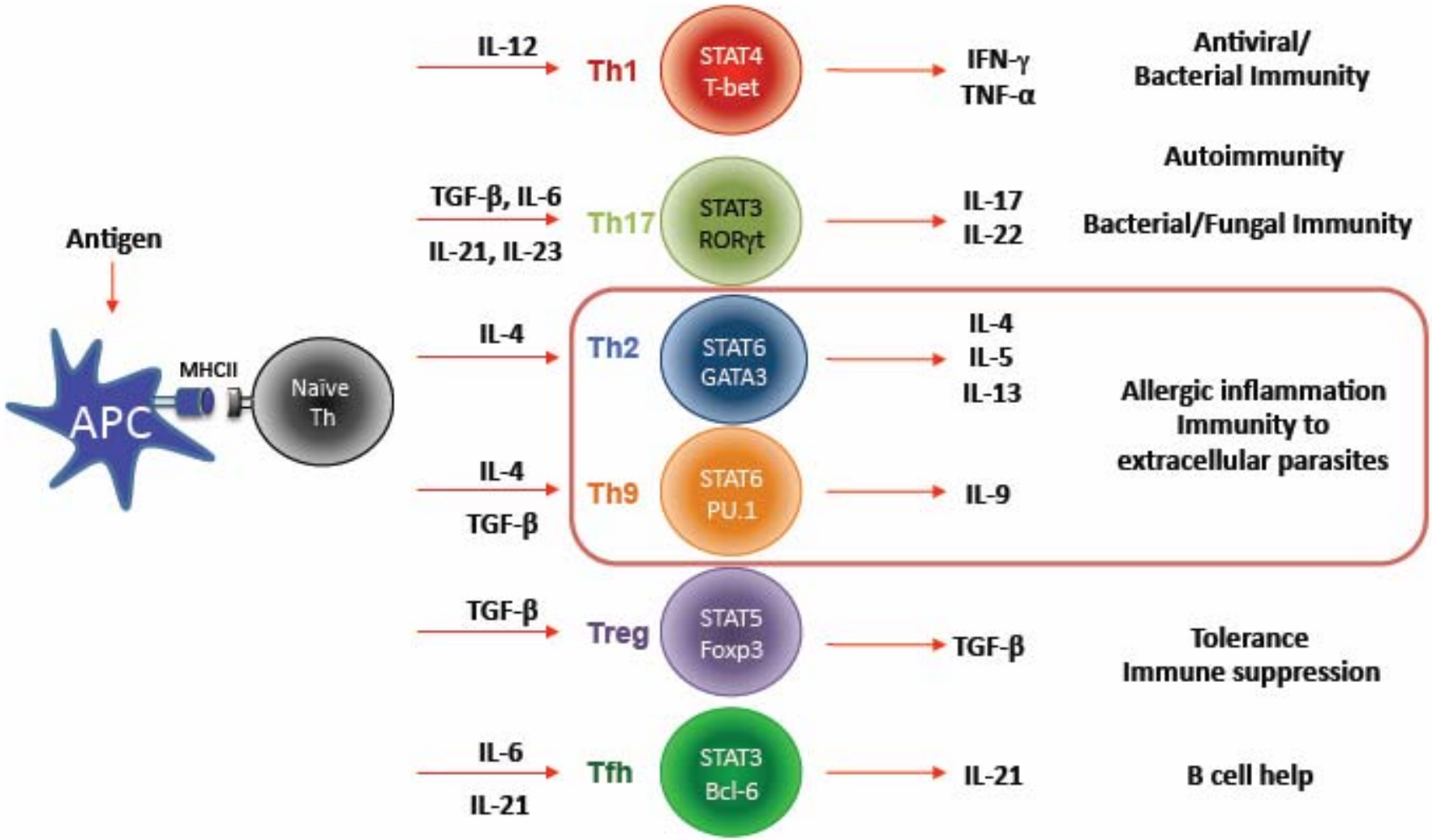



CHEMOKINES IN ASTHMA
TNF-α
Airway epithelium
TARC
MDC
Eotaxins
IL-4, IL-13
CCR4
CCR3
IL-5
Th2 cell
Eosinophil

TARGETING TH2 PATHWAYS IN ASTHMATIC PATIENTS

- Allergen challenge,=> TH2 cells are recruited into the airways in asthmatic patients predominantly through interaction of epithelial cell–derived Ccl17 and Ccl22 with the CCR4 receptor.
- Supernatant from allergen-challenged asthmatic bronchial explants is highly chemoattractant to TH2 cells
- Can be completely blocked by an mAb against CCR4.
- Defucosylated human IgG mAb (Potelligent technology50) against CCR4 (mogamulizumab, AMG 761) to eliminate cells bearing this receptor through enhanced antibody-dependent cell cytotoxicity,
- A single injection resulted in a profound and sustained reduction in circulating TH2 cell counts, with lower non–cell-depleting doses reducing TH2 cytokine generation

FUNDACION CIDEA


Antigen
APC
MHCII
Naïve Th
IL-12
Th1
STAT4 T-bet
IFN-γ TNF-α
Antiviral/ Bacterial Immunity
TGF-β, IL-6
IL-21, IL-23
Th17
STAT3 RORγt
IL-17 IL-22
Autoimmunity
Bacterial/Fungal Immunity
IL-4
Th2
STAT6 GATA3
IL-4 IL-5 IL-13
IL-4
TGF-β
Th9
STAT6 PU.1
IL-9
Allergic inflammation Immunity to extracellular parasites
TGF-β
Treg
STAT5 Foxp3
TGF-β
Tolerance Immune suppression
IL-6
IL-21
Tfh
STAT3 Bcl-6
IL-21
B cell help

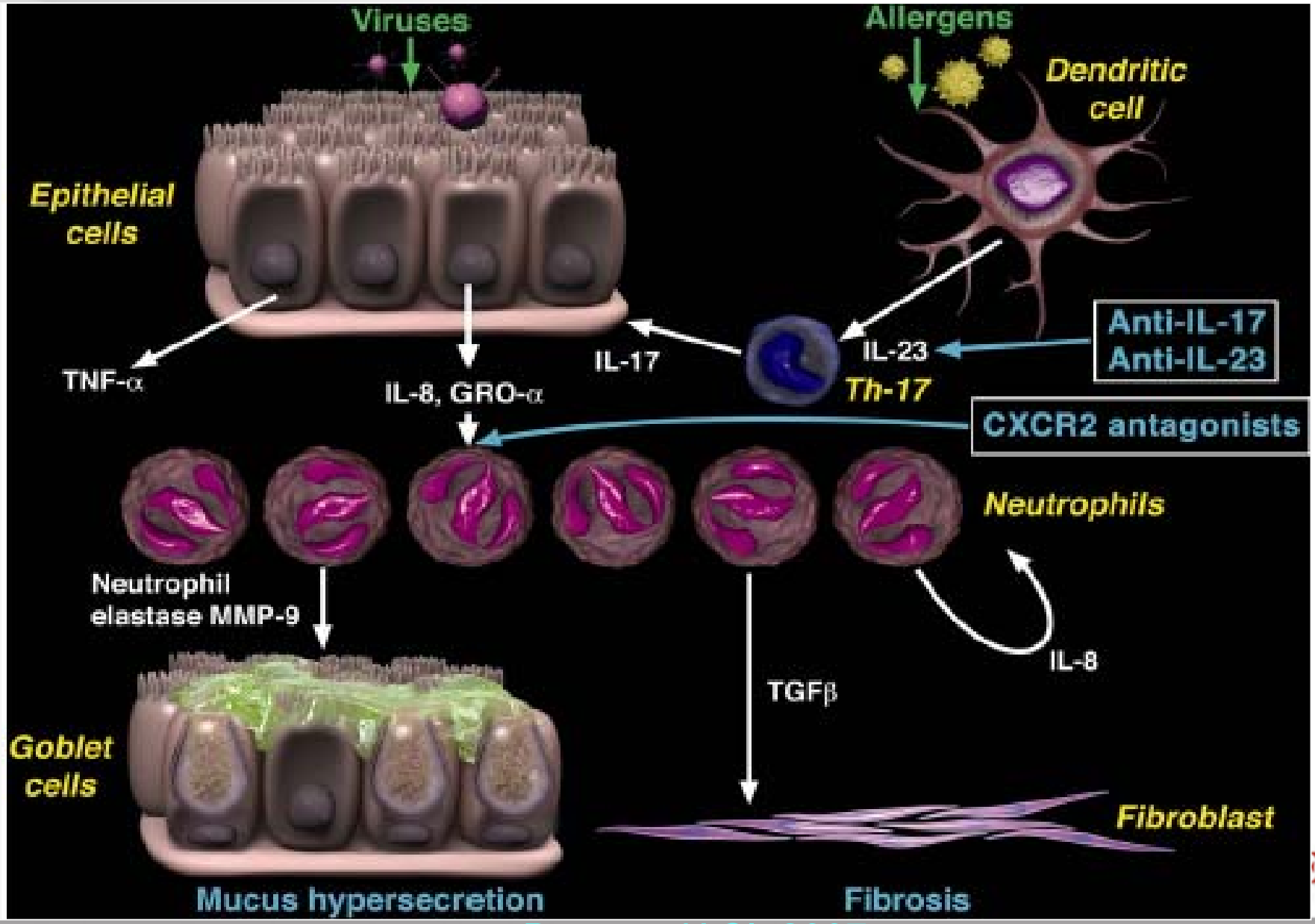
What do we know?

- Asthma is a heterogeneous disease that is driven by numerous T-cell subsets, including TH2, TH17, and TH9 cells.
- Interactions between genetic susceptibility and the environment determine the pathophysiology of disease.
- Blocking the action of the TH2 cytokines IL-5 and IL-13 is only effective in a small subgroup of patients.

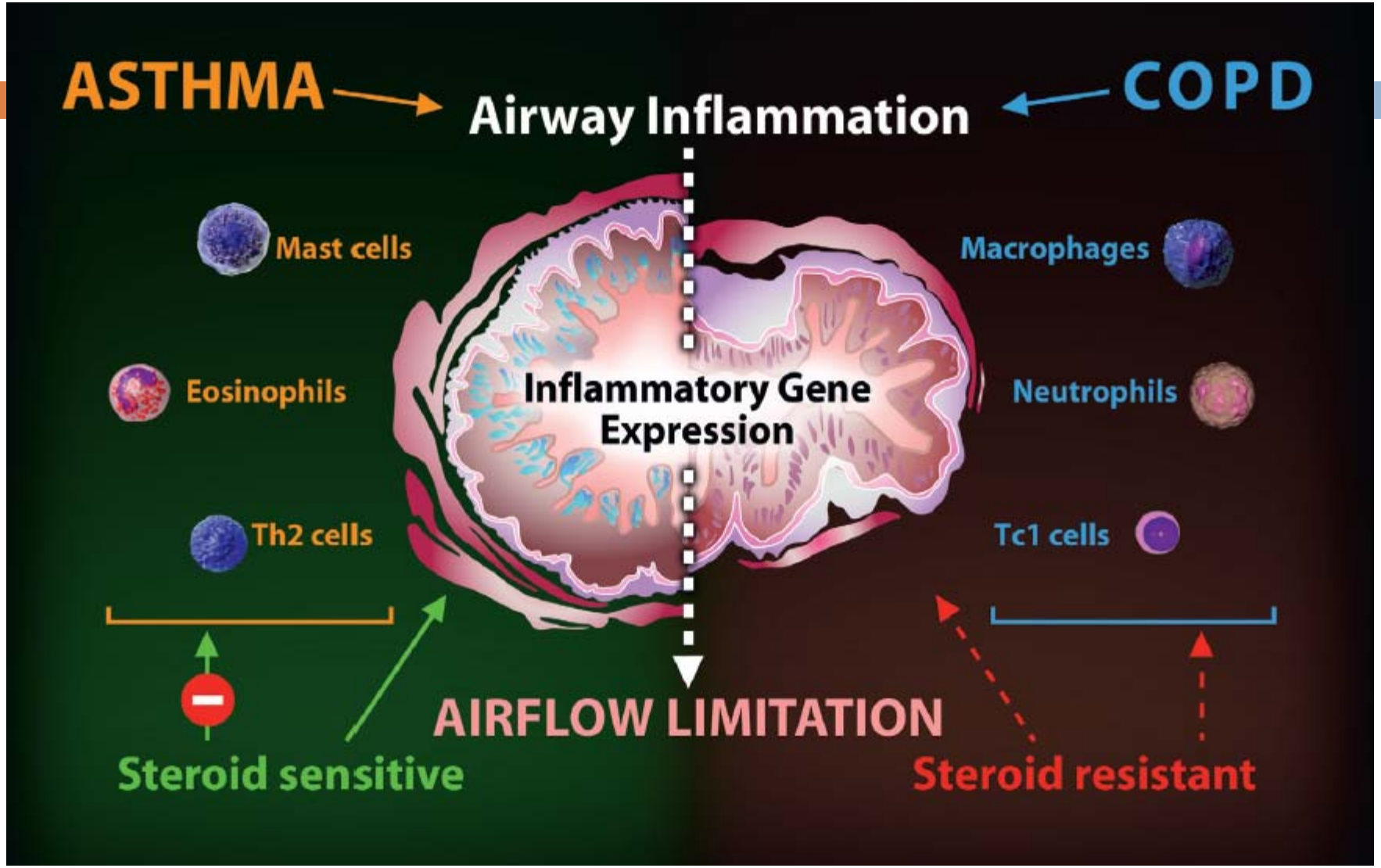
What is still unknown?

- Role of T-cell plasticity in determining individual asthma phenotypes
- Whether systemic or pulmonary immune profiles best determine therapeutic responses
- How best to characterize T-cell profiles and their mediators in patients
- The molecular mechanisms underlying T-cell plasticity in asthma and whether they can be manipulated to modulate T-cell fate and function

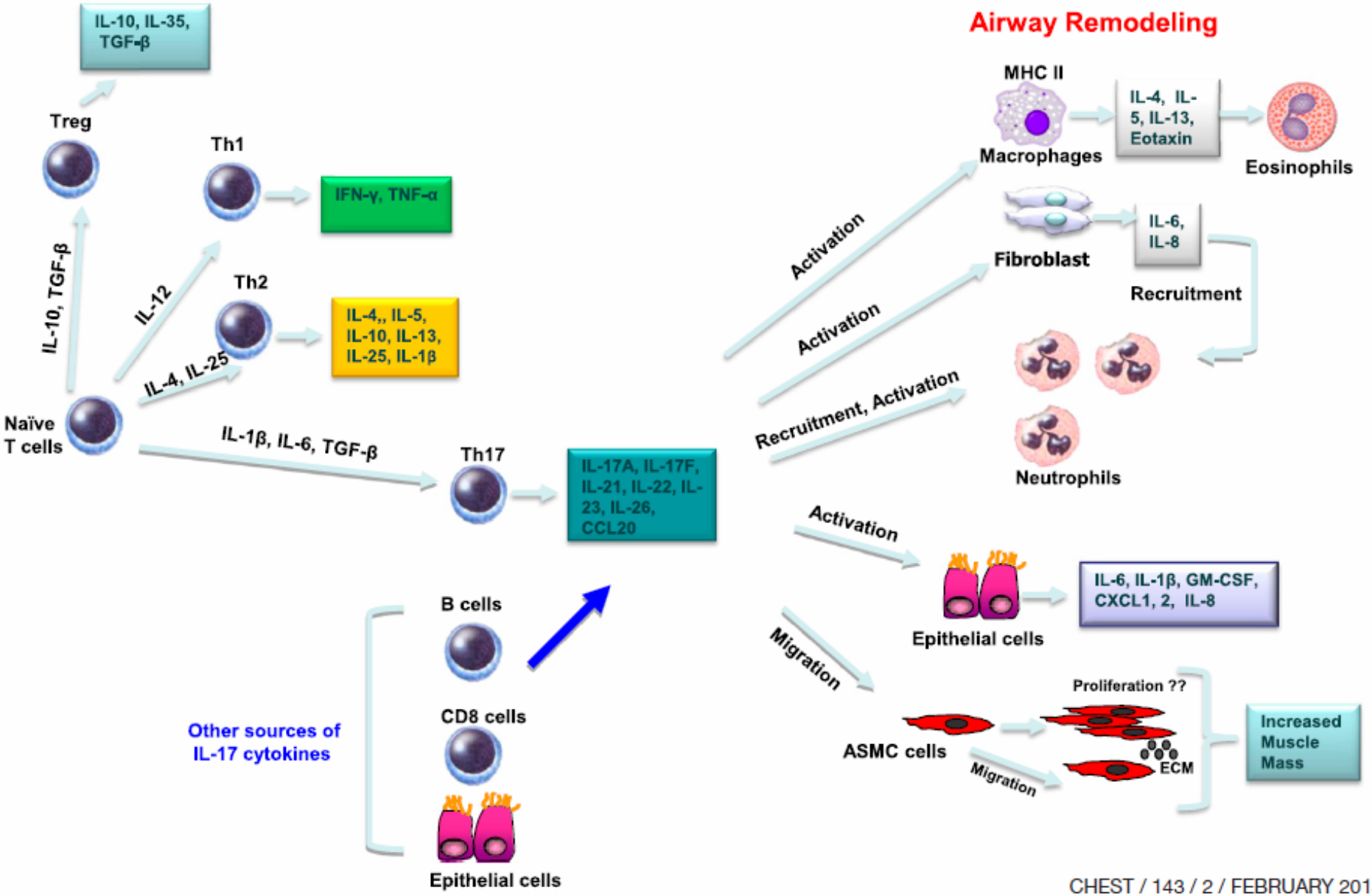
Neutrophilic inflammation in asthma



Barnes, JACI, 2007


ASTHMA
Airway Inflammation
COPD
Mast cells
Eosinophils
Th2 cells
Inflammatory Gene Expression
Macrophages
Neutrophils
Tc1 cells
AIRFLOW LIMITATION
Steroid sensitive
Steroid resistant

Th17 production, regulation, and role in asthma and COPD



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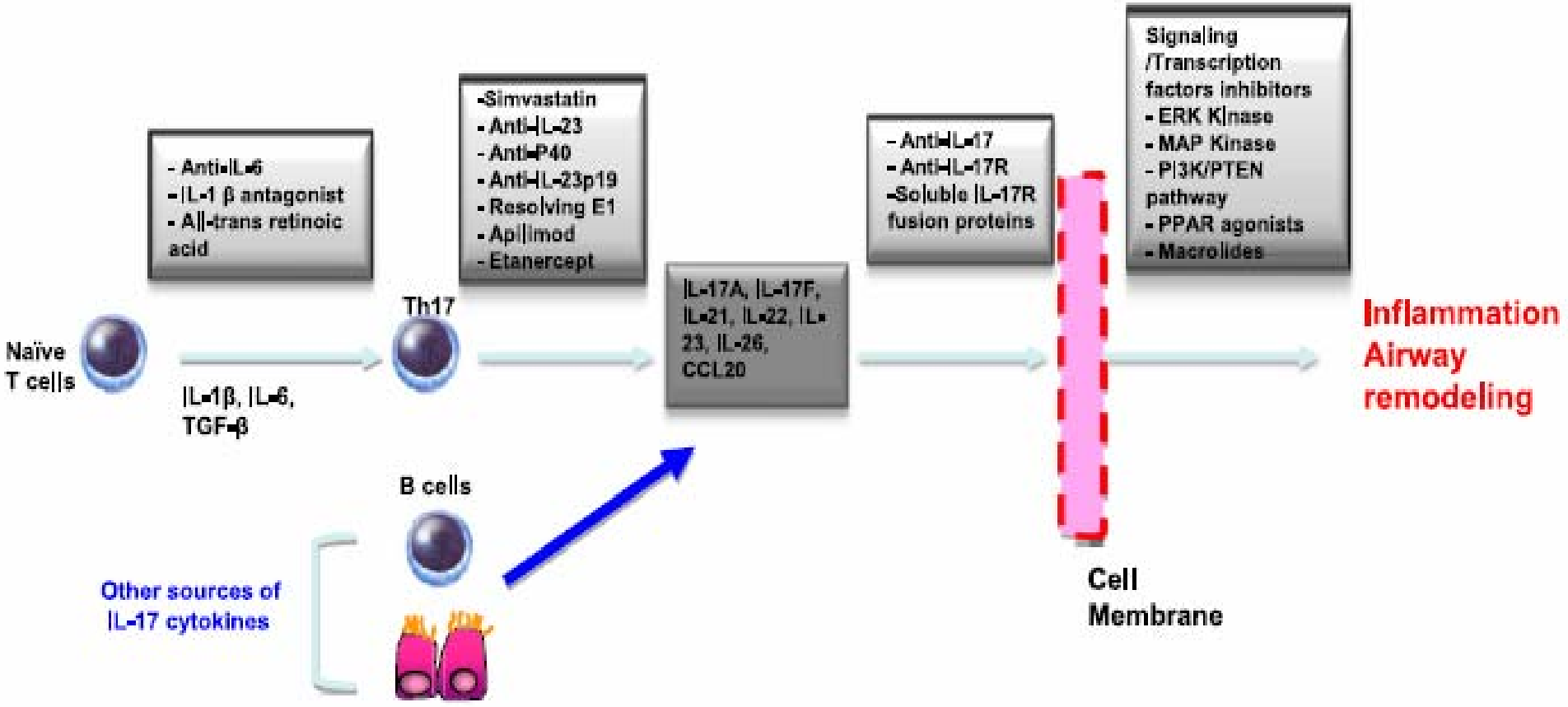
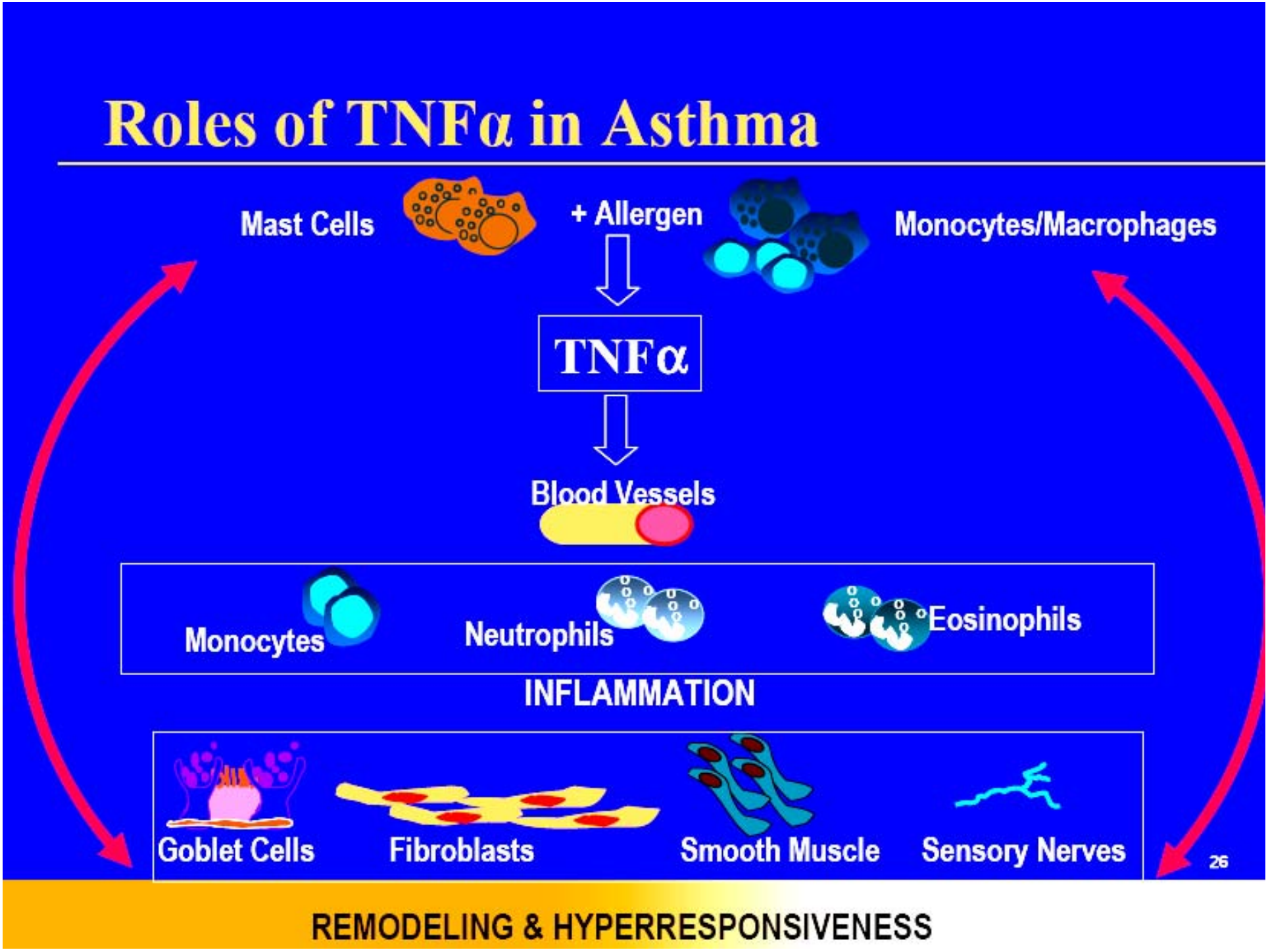
Targeting Th17/IL-17



Roles of TNFα in Asthma

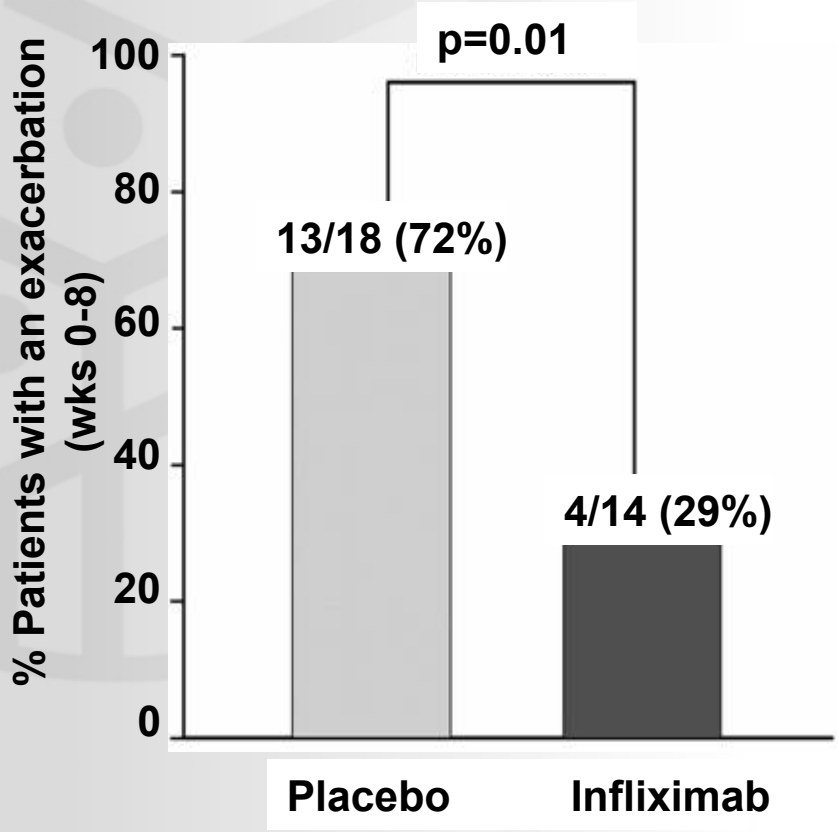


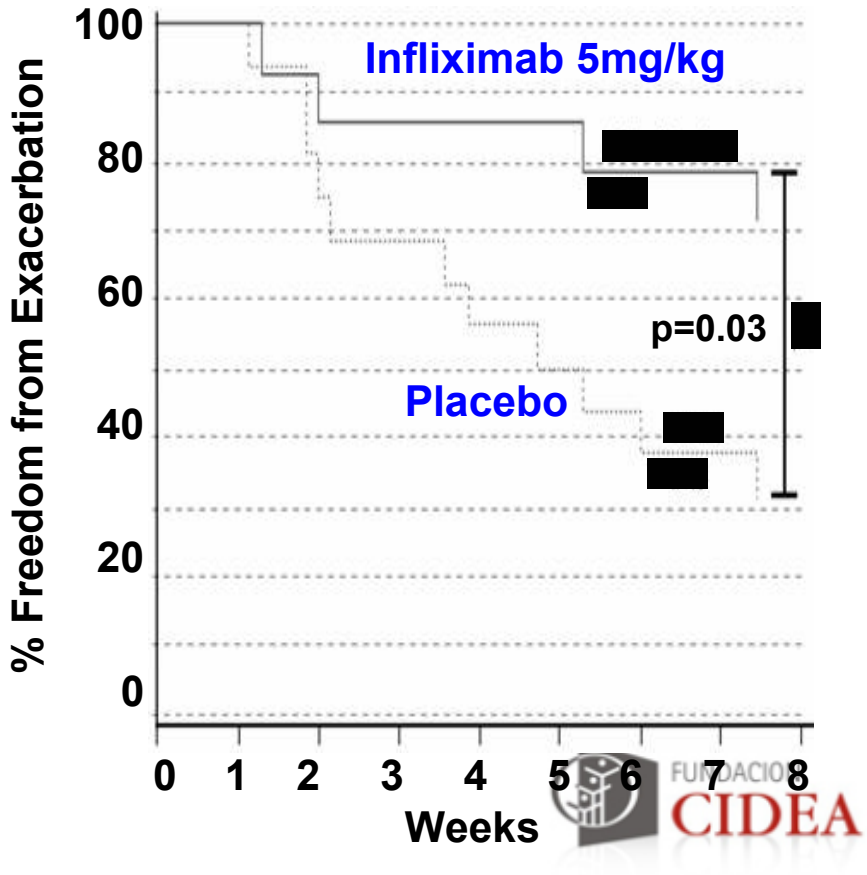
TNF-α driven airway dysfunction?

- Increases airway responsiveness when inhaled
- Associated with neutrophilic airway inflammation
- Induces corticosteroid resistance
- Stimulates fibroblast growth and maturation
- Present in increased amounts in the airway in severe asthma
- Many conditions associated with refractory asthma cause TNF-α upregulation

FUNDACION CIDEA

Anti-TNFα Reduced Exacerbations



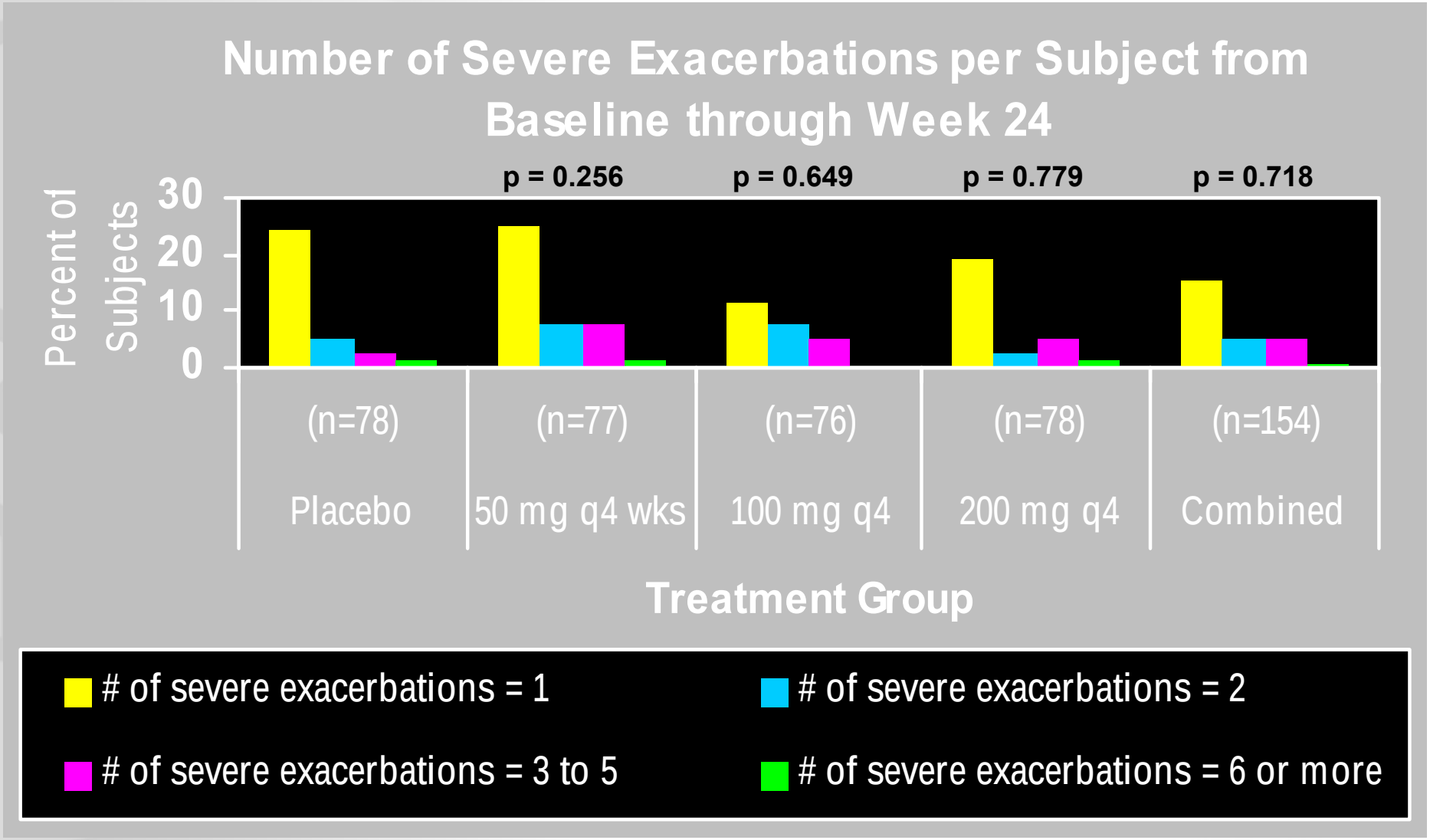


Erin *et al* AJRCCM 2006

Anti-TNFα Therapy for Asthma

	N	Severity	Design	Outcome	Result
Howarth *et al* Thorax 2005	15	GINA V	Open label uncontrolled	1º ACQ 2º FEV_1, AHR	***Improvement ACQ, FEV_1, AHR***
Berry *et al* NEJM 2006	10	7 GINA V 3 GINA IV	Randomised placebo-controlled cross-over	1º AHR & AQLQ 2º FEV_1, eNO, sputum cell counts	***Improvement AQLQ, FEV_1, AHR*** ***↓ sputum histamine***
Morjaria *et al* AJRCCM 2006 (abstract)	39	21 GINA V 18 GINA IV	Randomised placebo-controlled parallel group	1º AQLQ 2º ACQ, FEV_1, PEF, AHR, exacerbations	No benefit compared with placebo
Erin *et al* AJRCCM 2006	38	ICS only	Randomised placebo-controlled parallel group	1º morning PEF 2º FEV_1, exacerbations, Sputum markers	No change in morning PEF ***↓ PEF variability*** ***↓ Exacerbations***
Rouhani *et al* Resp Med 2005	21	β-agonist only	Segmental allergen challenge	Markers of inflammation AHR	Increased TNFR2 in BAL No change in AHR

Golimumab trial : Co-Primary Endpoint: Number of Severe Exacerbations



Note: Imputation using the worst case among similar subjects was applied for subjects who discontinued study participation early.

Resumen .

- Biológicos :aun por confirmarse su rol e indicación
- Exclusivamente para asma severa o no respondedores
- Endotipo específico : tratamientos de nicho
- Desarrollo de marcadores endotípicos imprescindible
- Marcadores géneticos de respuesta o riesgo de eventos adversos estaran disponibles en los próximos años
- Costos directos +Costos infraestructura diagnóstica ??

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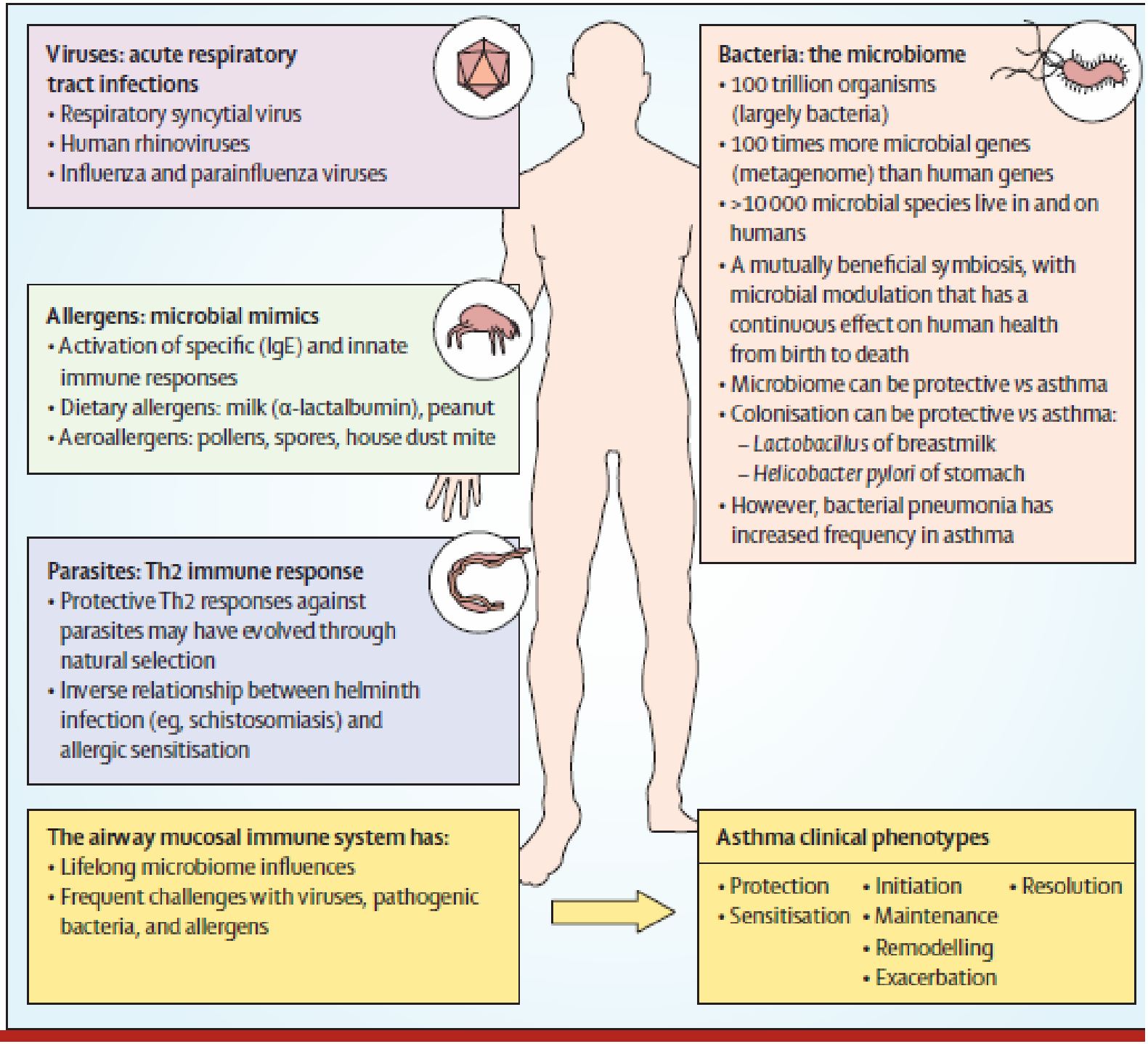
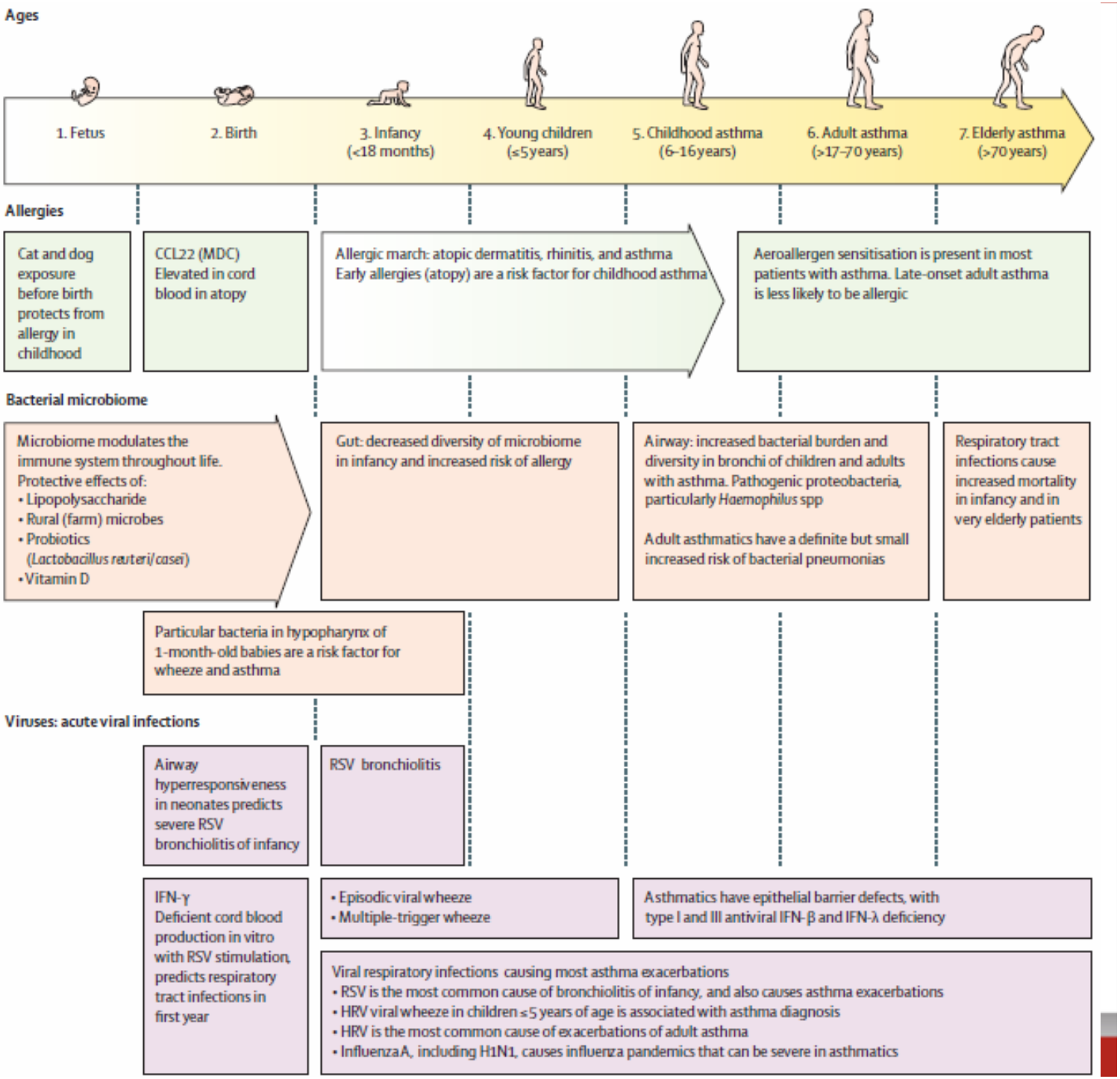
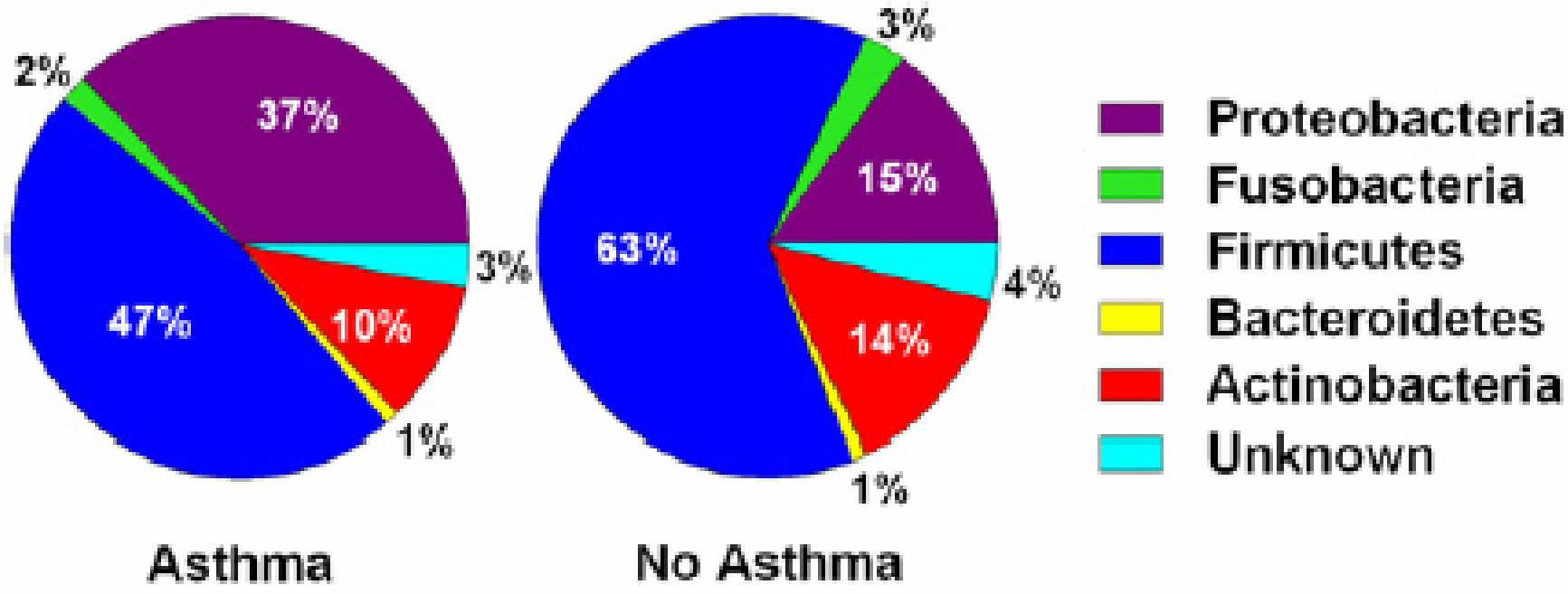
Lancet 2013; 381: 861–73



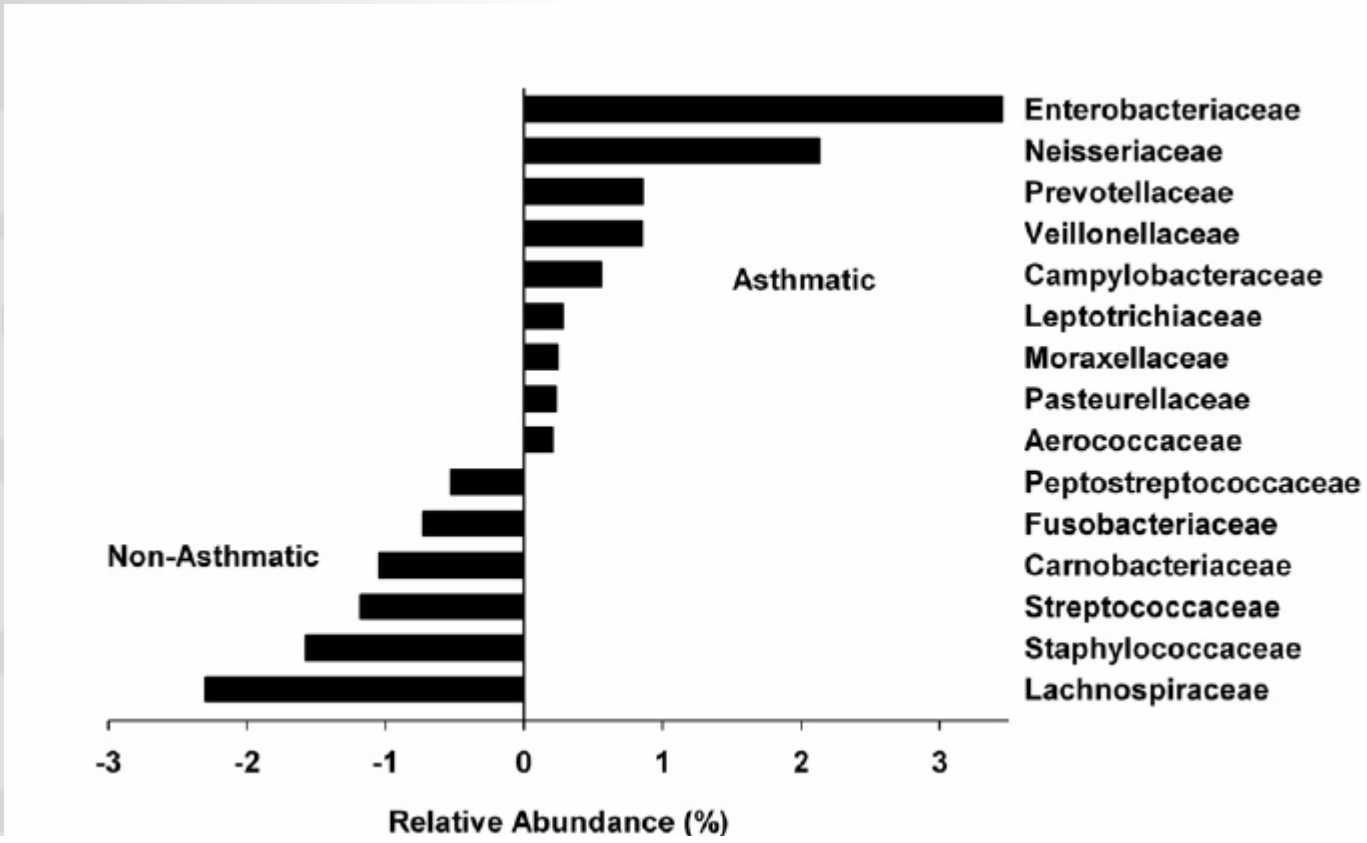
Microbial eff ects during the Seven Ages of Asthma



Median percentage values of bacterial phyla in samples from asthmatic and non asthmatic subjects



Pradeep Reddy Marri, JACI 2013 IN PRESS



Clinical implications: Young adults with mild asthma show changes in the composition of induced sputum microbiota compared with nonasthmatic subjects, and these changes might have implications for asthma pathogenesis and management

MUCHAS GRACIAS

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