

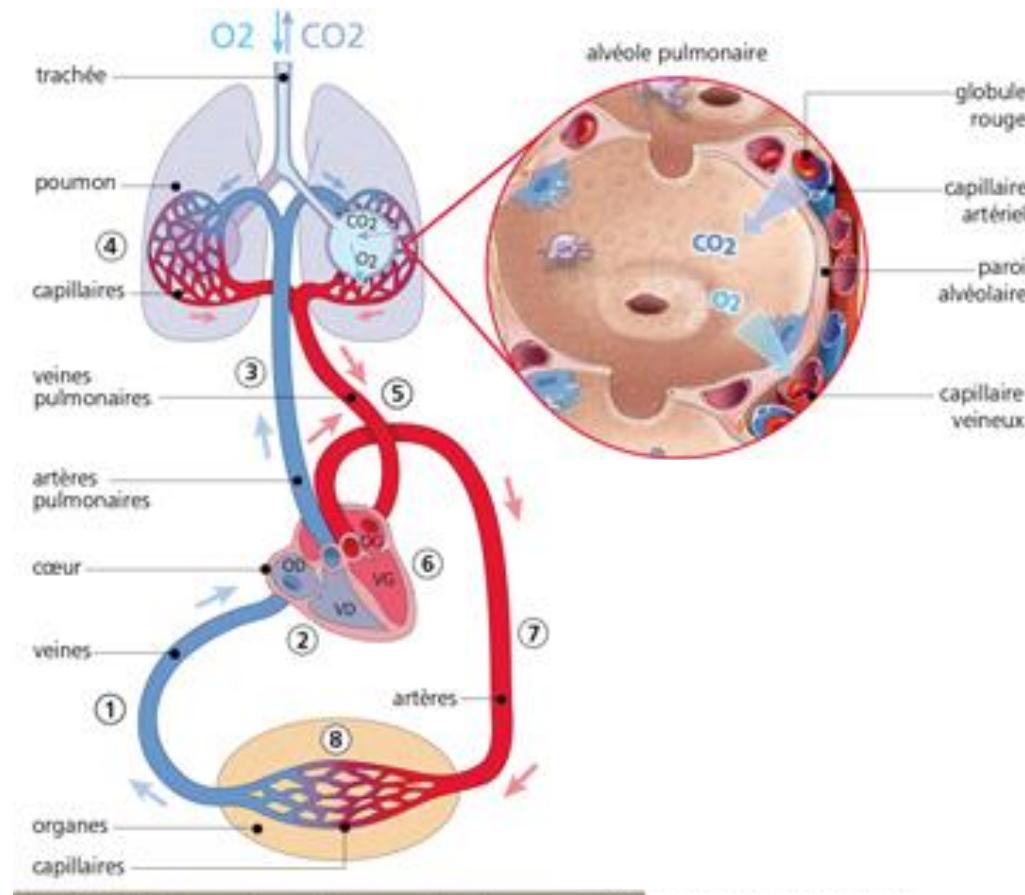


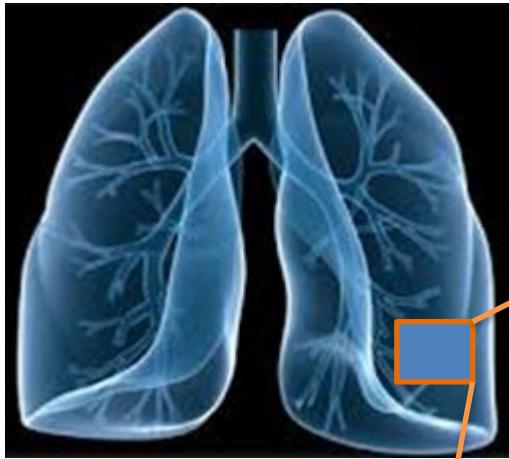
Pathophysiology of chronic lung diseases - Part 1/3

Pr Charles Pilette, MD PhD

Université catholique de Louvain – IREC - PNEU
Cliniques universitaires St-Luc - pneumology

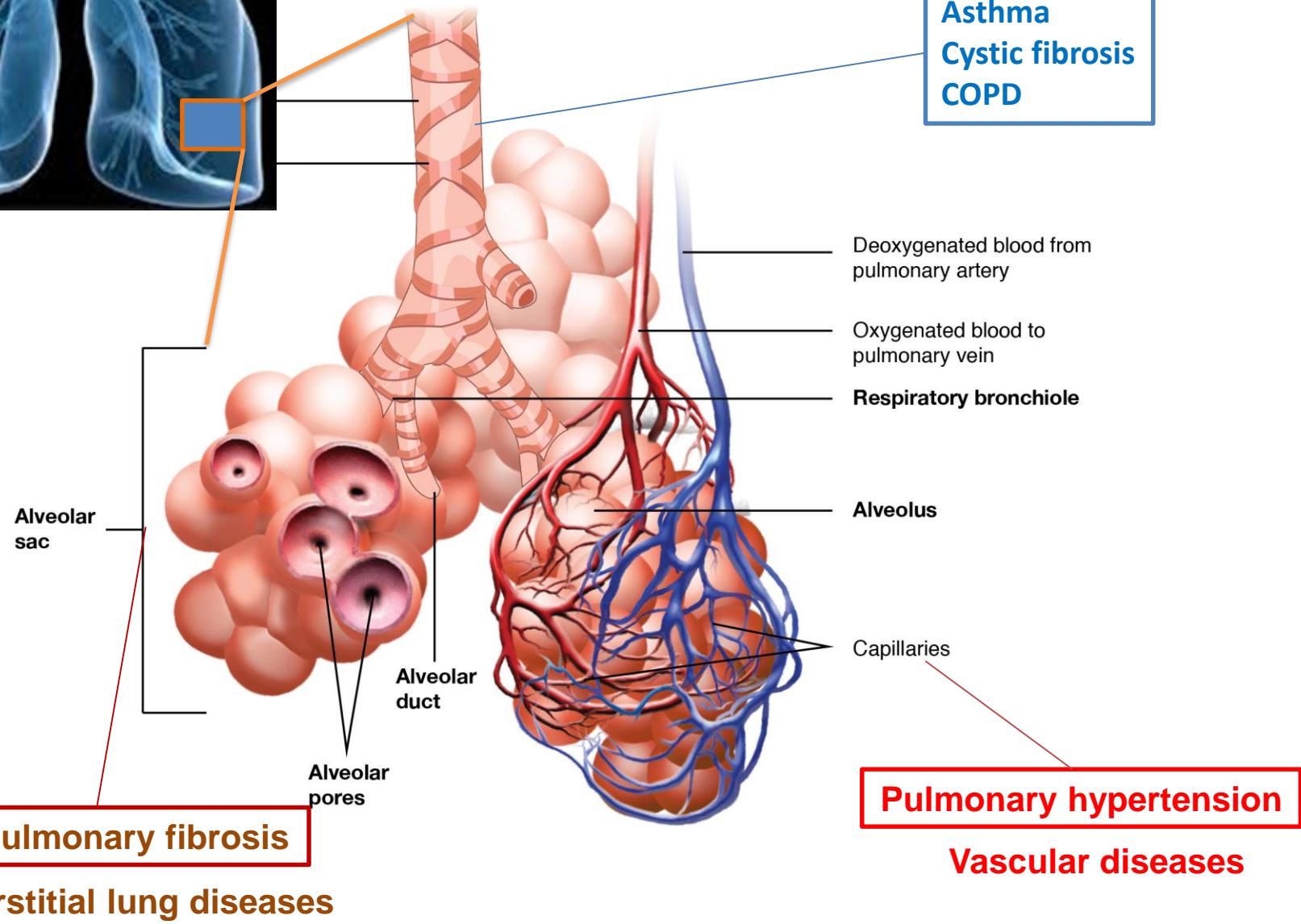
Hematosis, the primary role of the lungs





Airway diseases

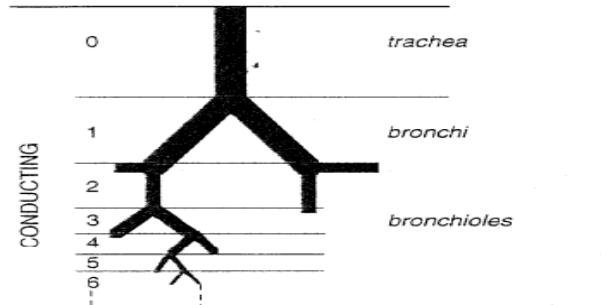
Asthma
Cystic fibrosis
COPD



Anatomy of human, adult airways

Zone conductrice

Distal Conducting airways,
G8-16



« Small airways » (<2mm)

Zone respiratoire

Acinar airways
G16-24

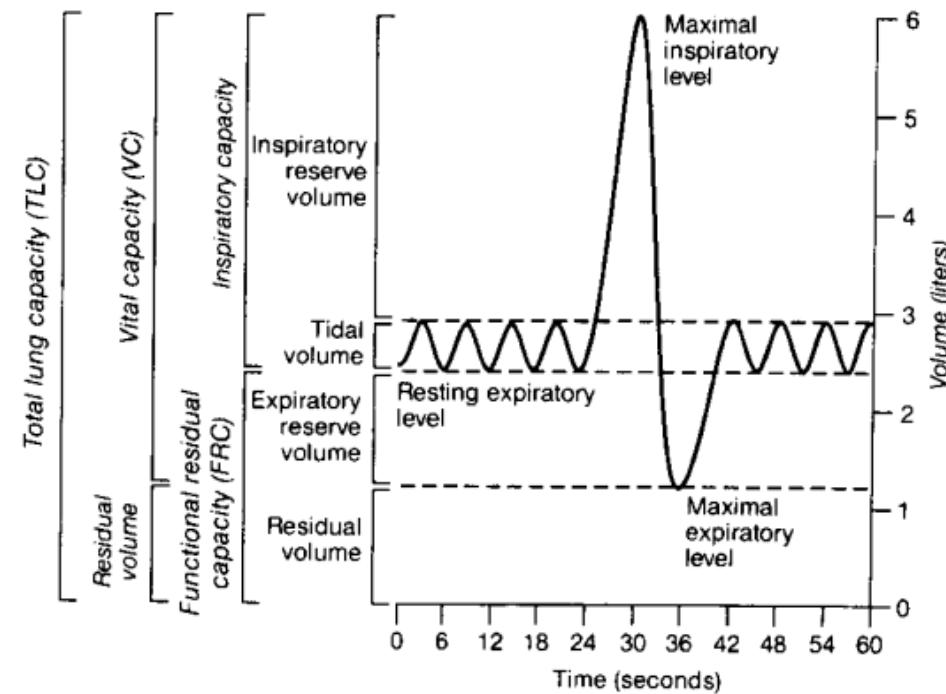


~17x106 airway branches of bronchioles
~500x106 alveoli

Airway	Generation	Number per Generation	Diameter (mm)	Length (mm)	Total Cross Section (cm ²)	Velocity ^a (mm/s)	Residence Time ^b (ms)
Trachea	0	1	18	120	2.5	3900	30
Main bronchus	1	2	12	48	2.3	4300	11
Lobar bronchus	2	4	8.3	19	2.1	4600	4.1
Segmental bronchus	4	16	4.5	13	2.5	3900	3.2
Bronchi with cartilage in wall	8	260	1.9	6.4	6.9	1400	4.4
Terminal bronchus	11	2000	1.1	3.9	20	520	7.4
Bronchioles with muscles in wall	14	16,000	0.74	2.3	69	140	16
Terminal bronchiole	16	66,000	0.60	1.6	180	54	31
Respiratory bronchiole	18	0.26×10^6	0.50	1.2	530	19	60
Alveolar duct	21	2×10^6	0.43	0.7	3200	3.2	210
Alveolar sac	23	8×10^6	0.41	0.5	72,000	0.9	550
Alveoli		300×10^6	0.28	0.2			

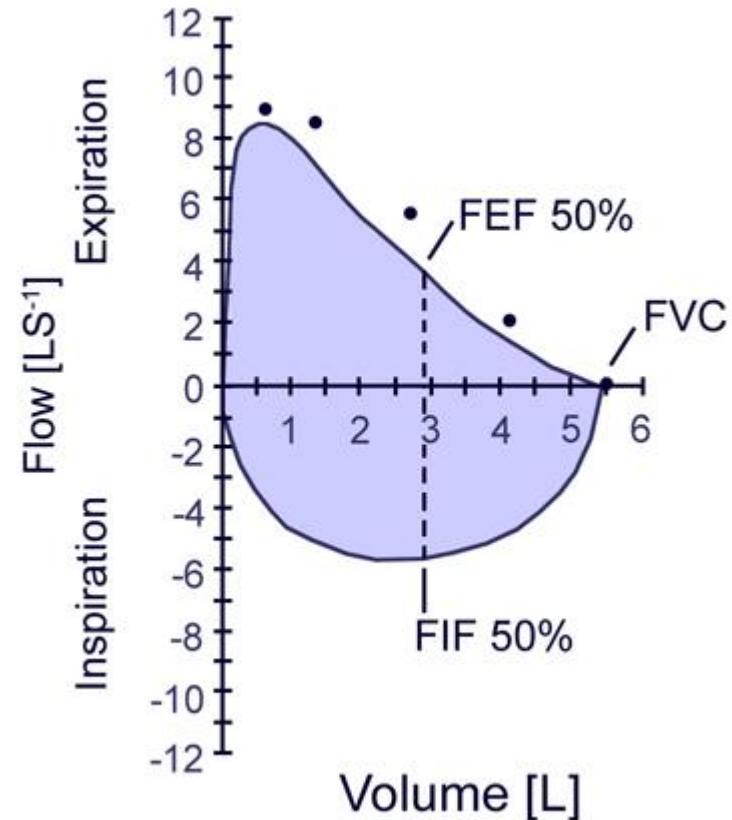
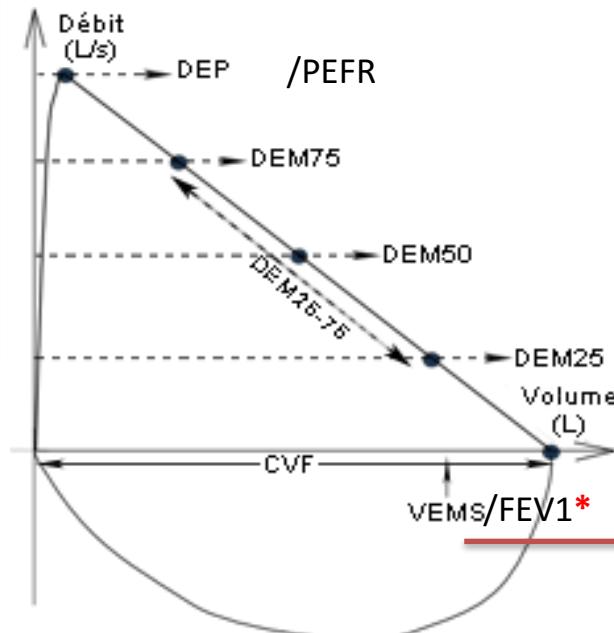
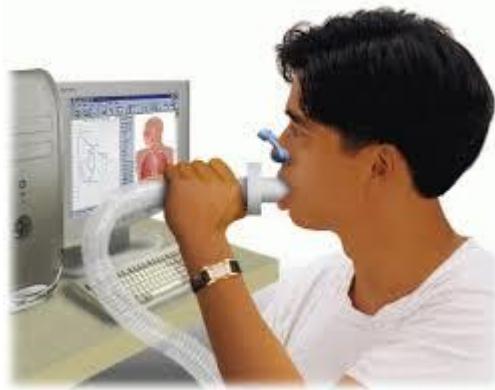
Pulmonary function tests

« Static volumes »



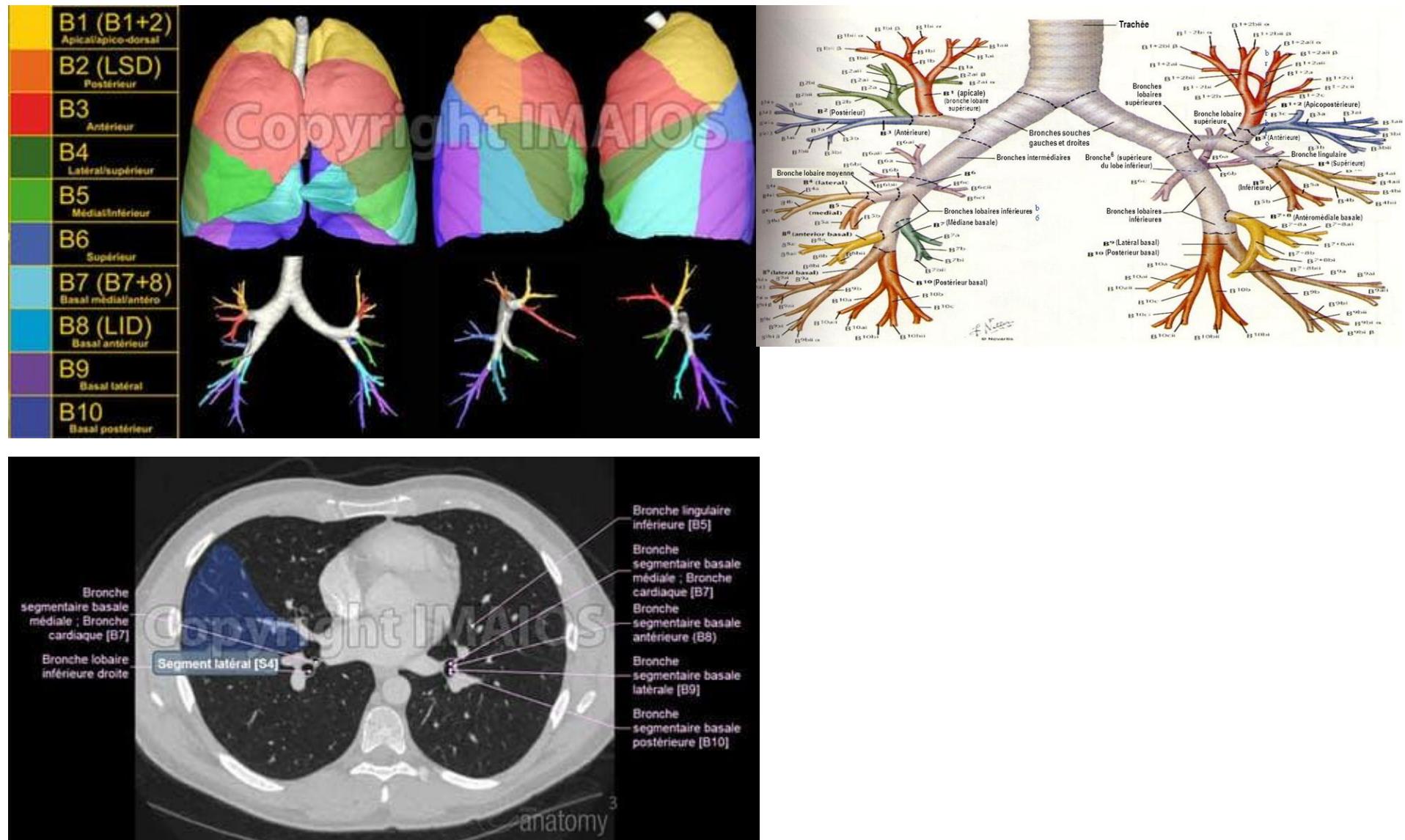
Whole-body or restrained plethysmography

« Forced volumes »



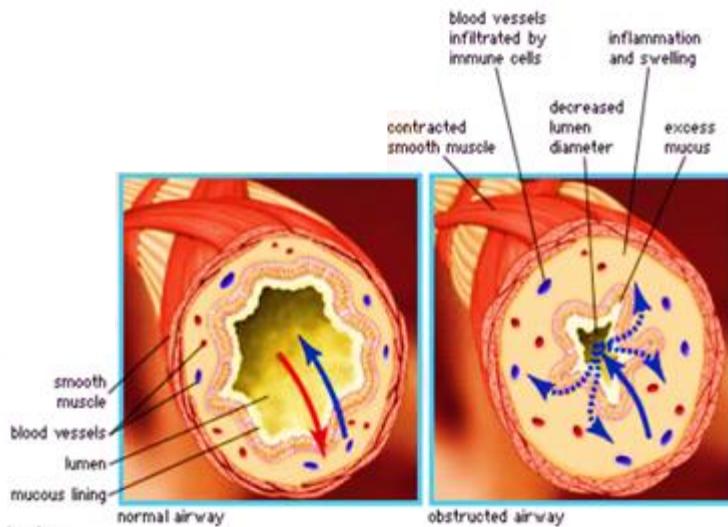
* Forced expiratory volume in 1 sec. (FEV1; L, % pred)

Lung imaging (segmentation)

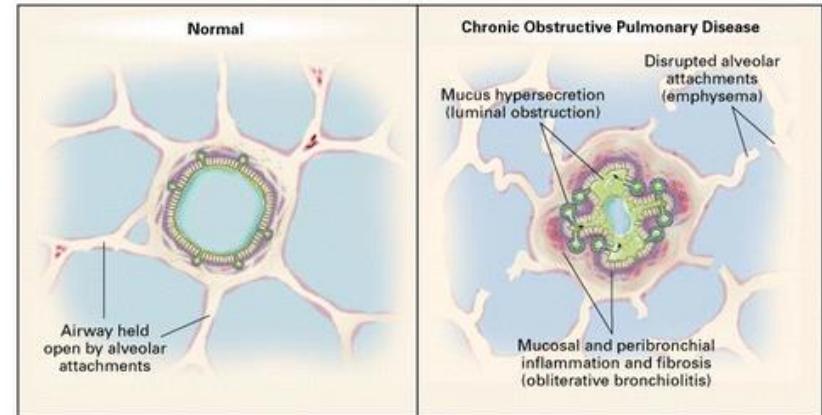


Chronic obstructive airway diseases

Bronchoconstriction (asthma)



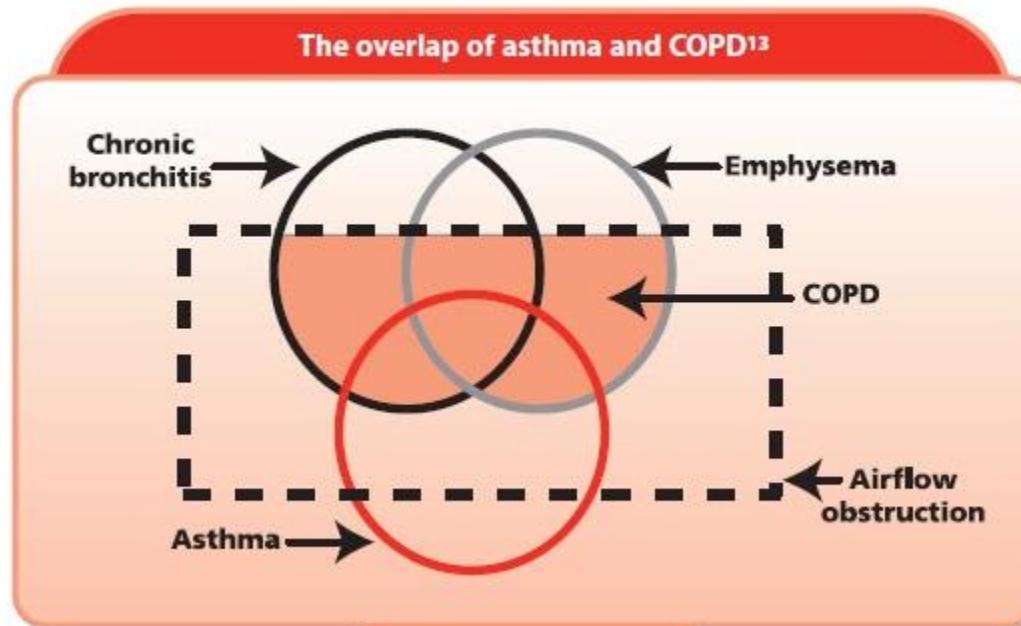
(Fixed) bronchial remodelling (COPD)



Reversed by β_2 -agonists
(and/or by steroids)

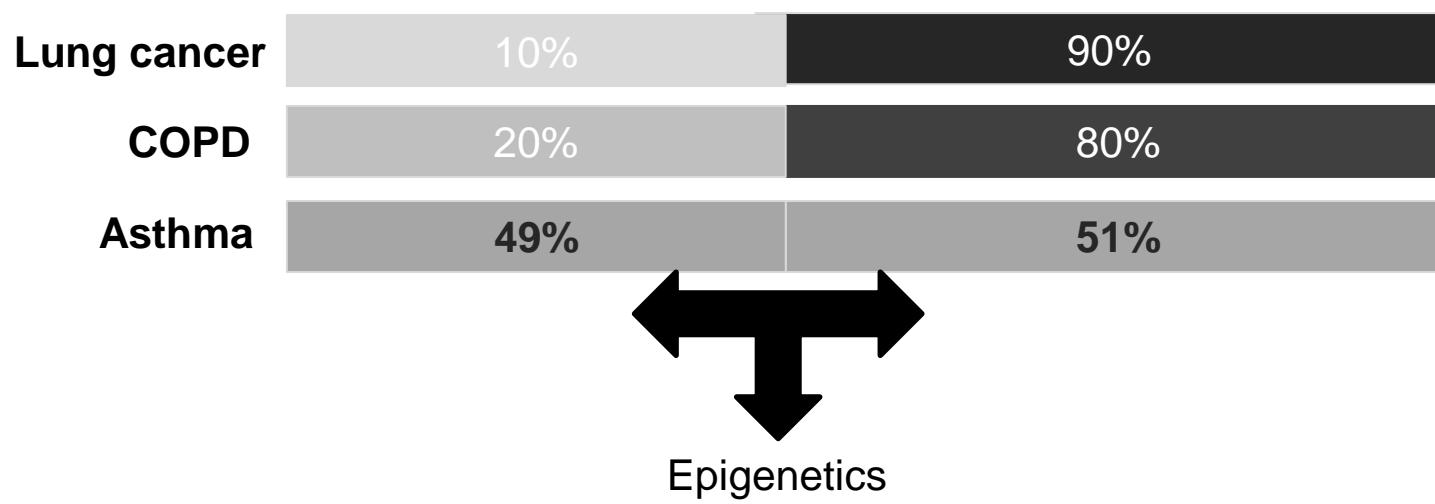
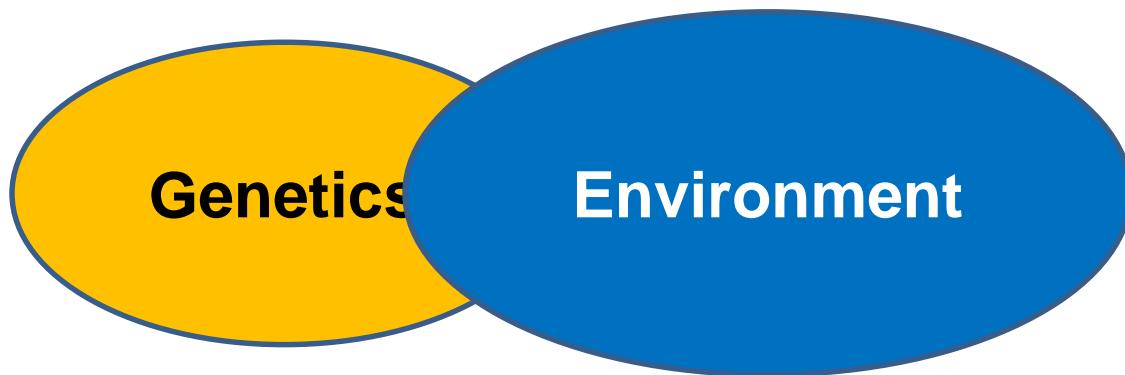
Not/poorly reversible

Chronic obstructive airway diseases

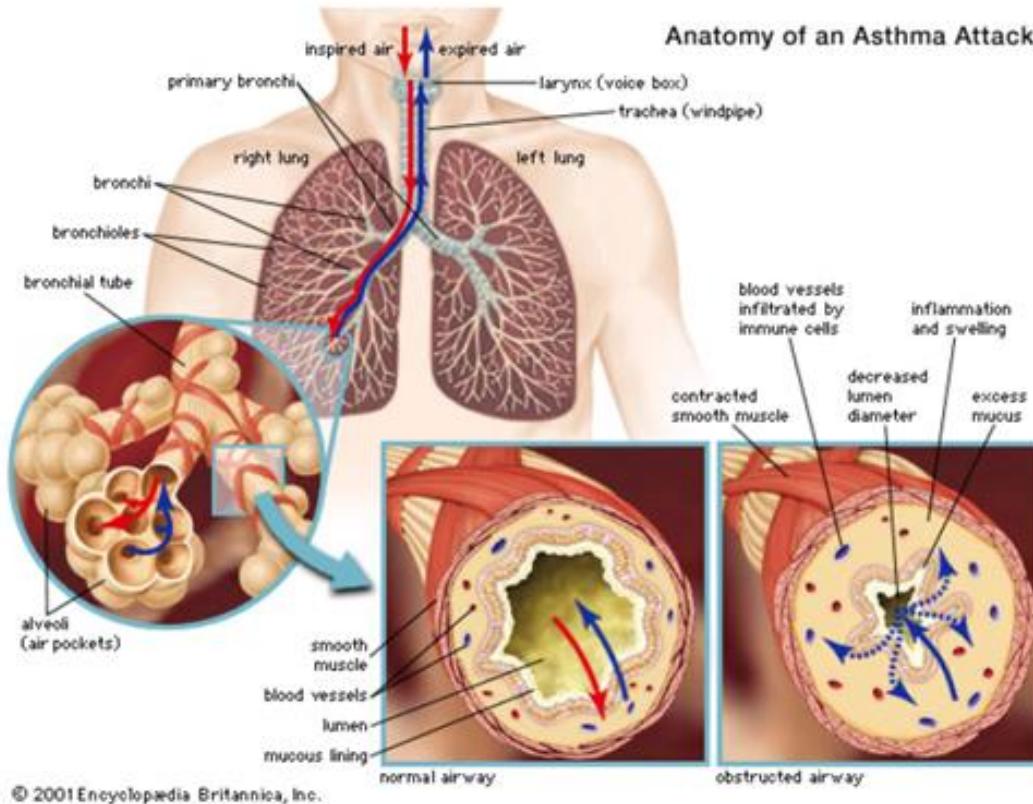


Chronic obstructive airway diseases

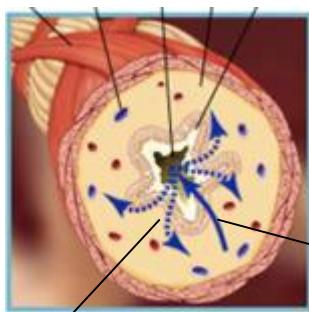
	Prevalence	Primary defect	Driving cofactors (development, severity)
Asthma	++ (5-10%)	Multigenic, allergy	Smoke, allergens, genetics, multiple factors...
COPD	+	Smoking (25%)	Genetics (α 1-AP, SNPs), Chronic infection
Cystic fibrosis (CF)	rare	Monogenic: CFTR (75% delF508)	Genetic (<i>modifying genes</i>) Chronic infection - <i>P aeruginosa</i>
Primary ciliary dysK (PCD)	rare	Cilium genes	Chronic infection
Non-CF bronchiectasis	+	Multigenic?	Chronic infection
CTD-related	rare	autoimmunity	?



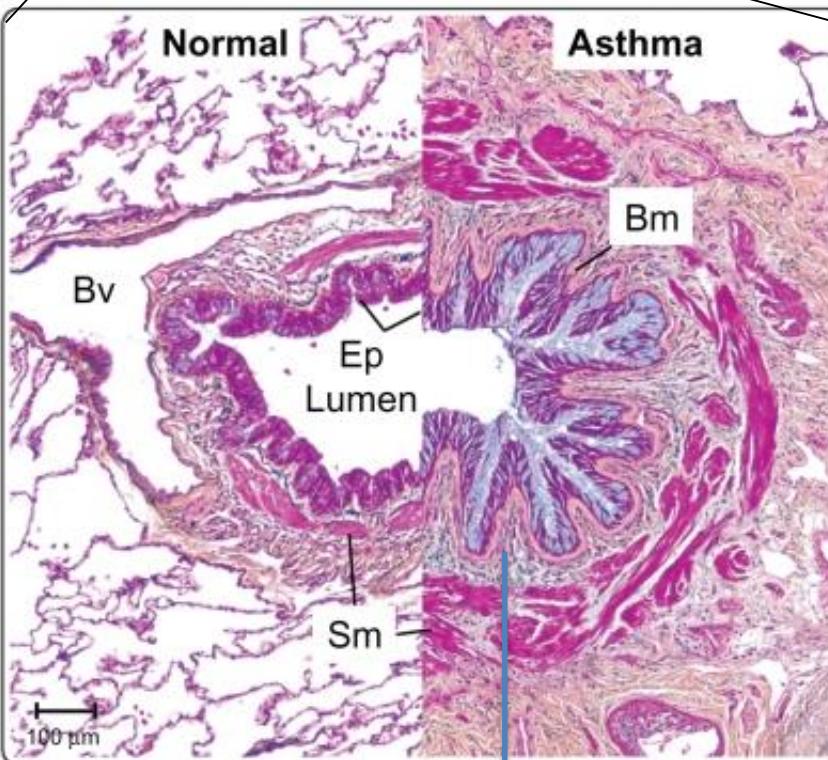
Asthma pathophysiology



- **Bronchospasm (smooth muscle contraction)** → acute symptoms
- Mucus plugs
- Airway inflammation/edema



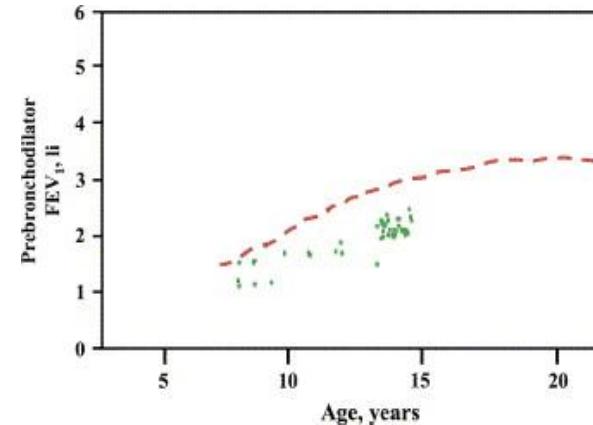
Airway pathology in asthma



*Airway fibrosis

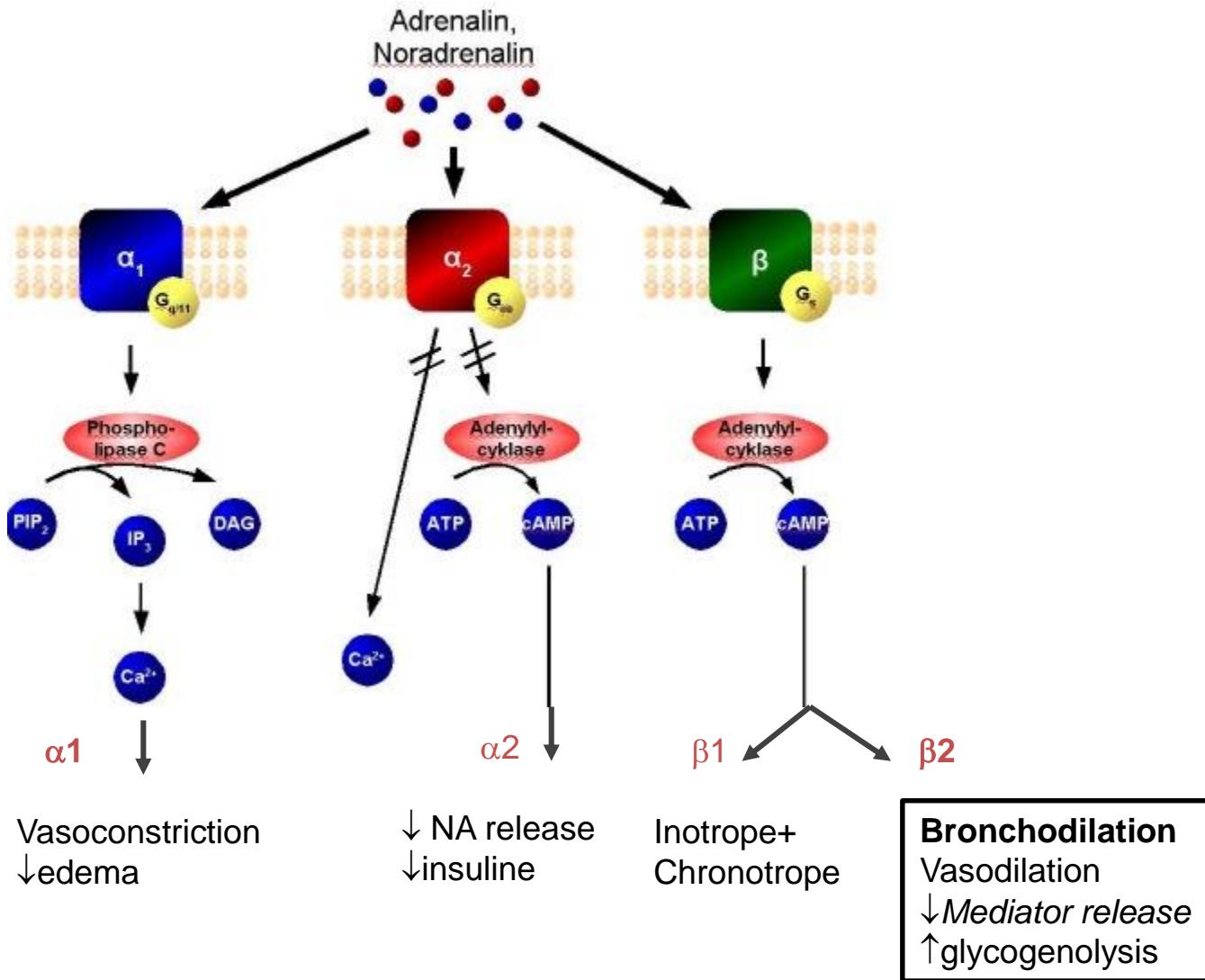
- Edema, granulocyte infiltration (eos)
- Epithelial changes:
 - Shedding
 - Goblet cell hyperplasia +/- plugs
 - Basal membrane thickening
+/- peribronchial fibrosis*
- Smooth muscle hypertrophy

Decline in airway function

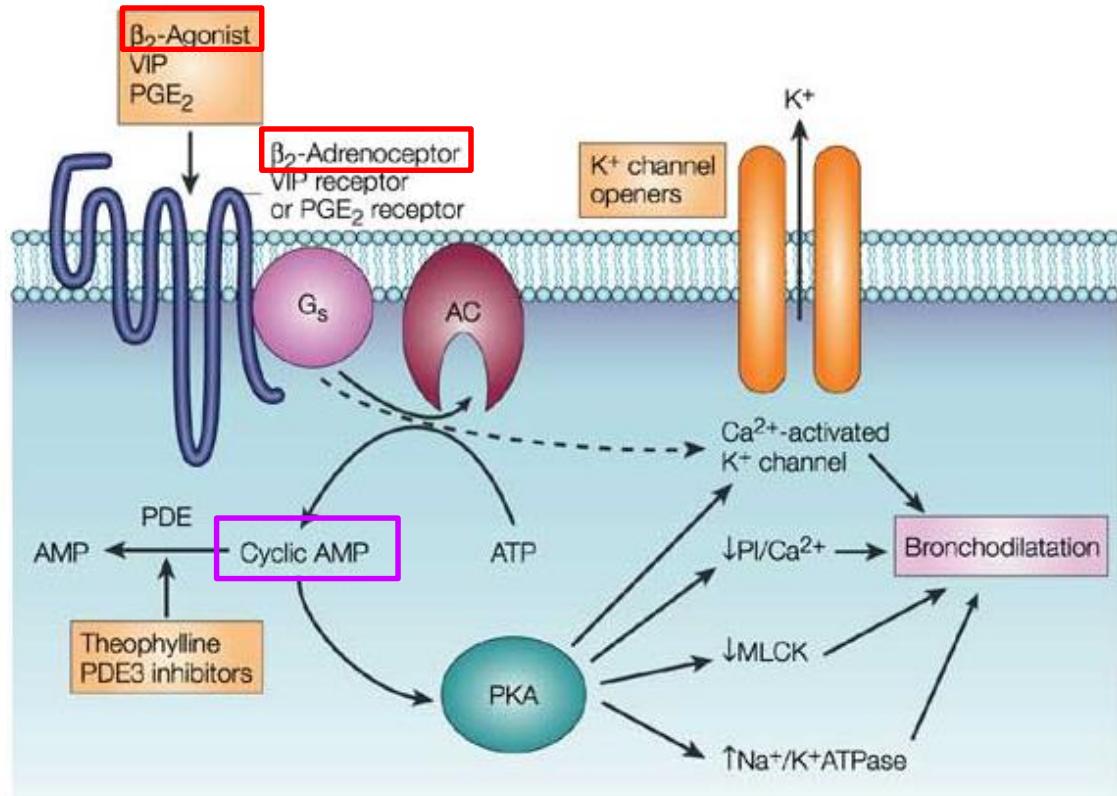
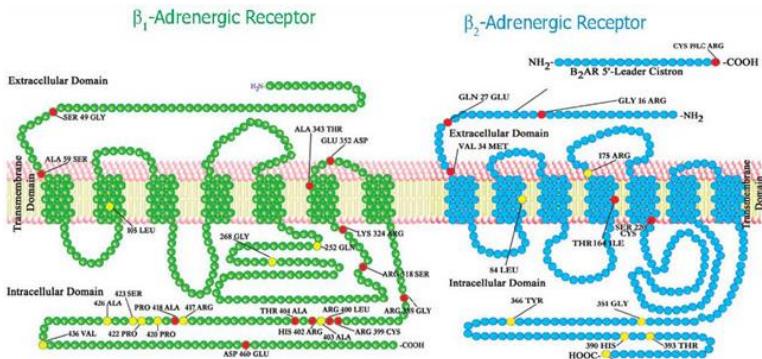


Treatment of asthma

- **Short-acting bronchodilators: β_2 -agonists (SABA): salbutamol (VENTOLIN[®]) (or anticholinergics: ipratropium)**
 - ➔ Symptom relief
 - ➔ Before exposure to a trigger (e.g. exercise, allergen)



Bronchodilation through β_2 AR



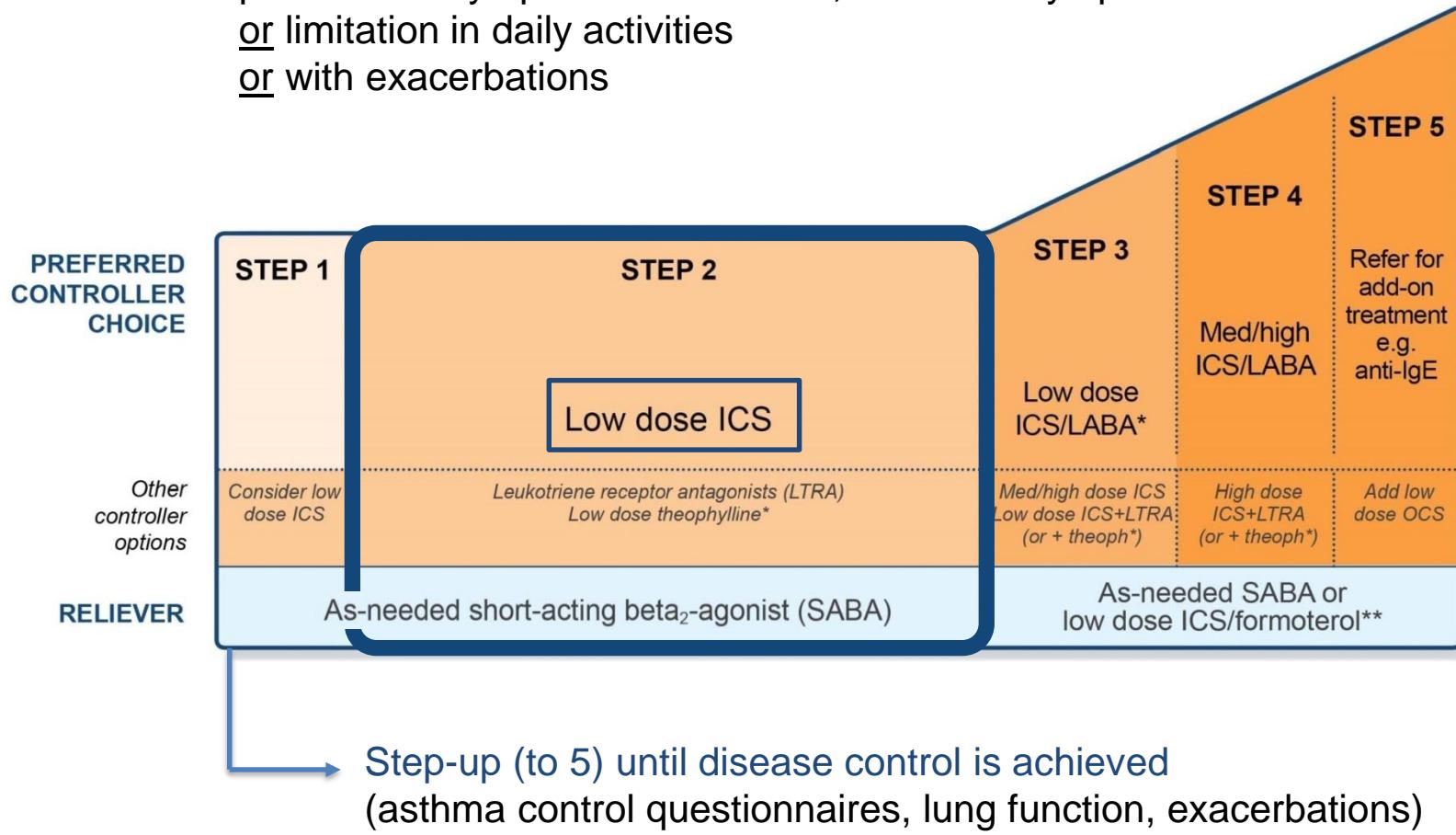
Bronchial smooth muscular cell

Treatment of asthma

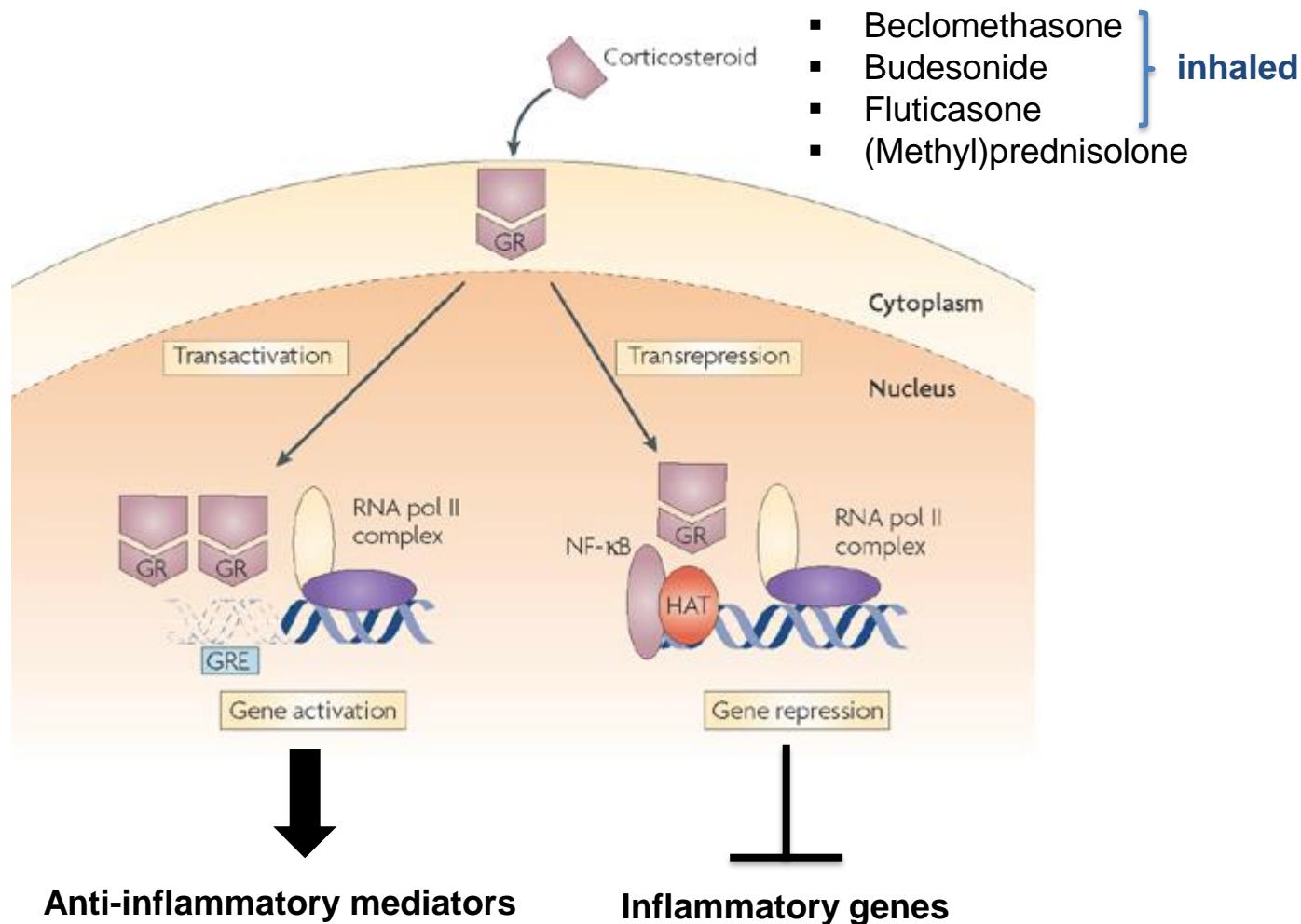
- Short-acting bronchodilators: β_2 -agonists (SABA): salbutamol (VENTOLIN[®])
(or anticholinergics: ipratropium)
 - ➔ Symptom relief
 - ➔ Before exposure to a trigger (e.g. exercise, allergen)
- Anti-inflammatories, as maintenance/preventive treatment
 - ➔ **Inhaled corticosteroids (ICS) = cornerstone therapy**
 - +/- Add-on drug(s):
 - ➔ Long-acting β_2 -agonists (LABA): formotérol, salmétérol, vilantérol
 - ➔ Leukotriene receptor antagonists (LTRA): montelukast, zafirlukast
 - ➔ Theophylline (slow-release, low dose)
- Allergen-specific immunotherapy
 - ➔ Selected cases with allergic rhinitis to a dominant allergen (pollen, dust mite)
- Environmental measures and control of comorbidities
 - ➔ Allergen avoidance (HDM) & environmental control
 - ➔ Treatment of aggravating factors (overweight, smoking, rhinitis, GE reflux...)

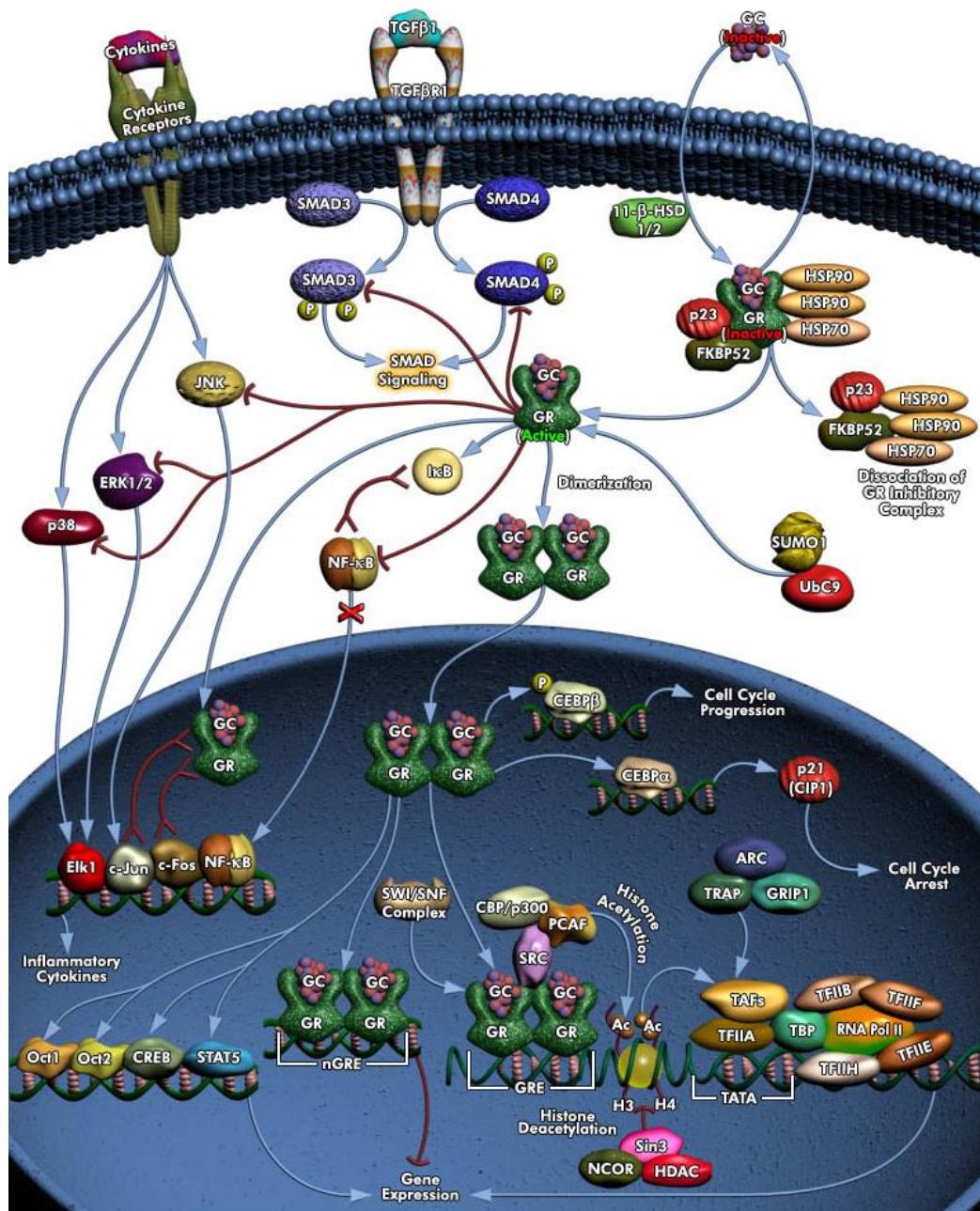
GINA guidelines for asthma therapy

→ patient with symptoms $\geq 2x/\text{month}$, nocturnal symptoms
or limitation in daily activities
or with exacerbations

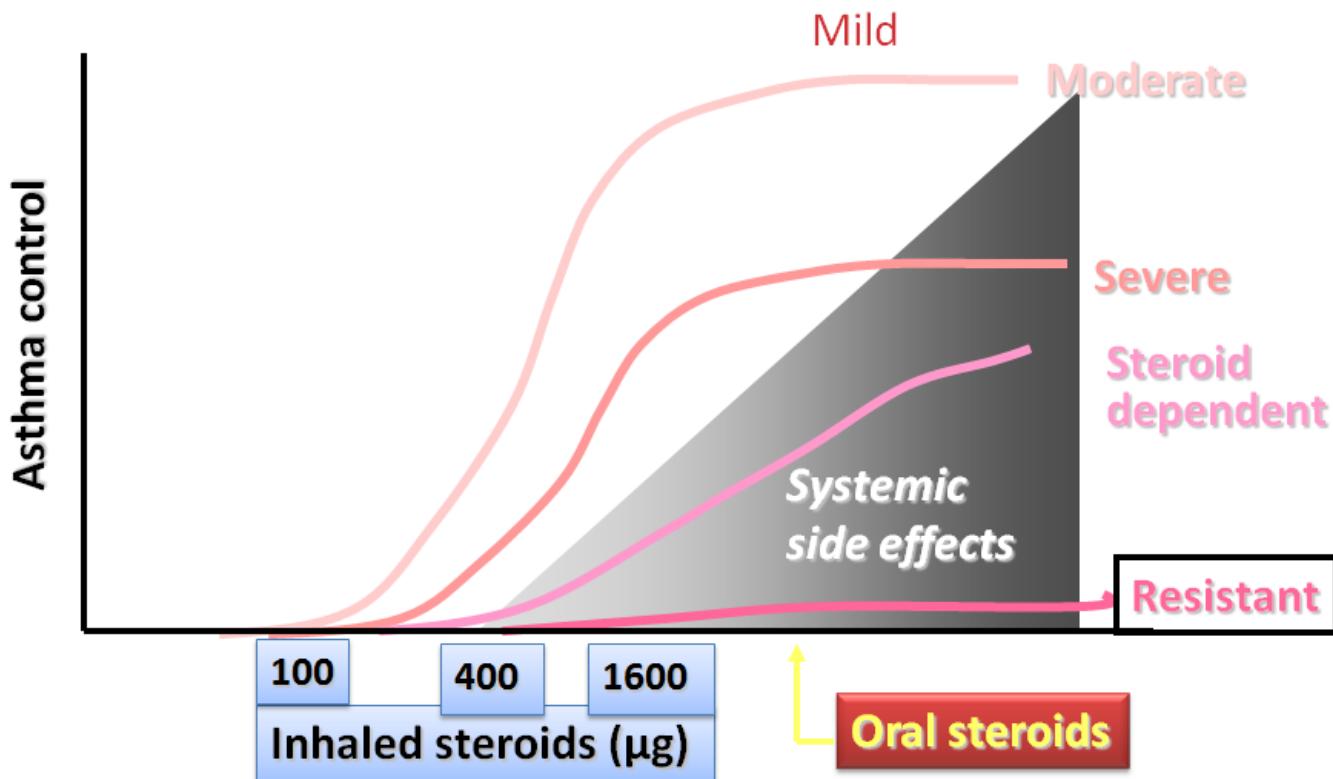


Anti-inflammatory activity through GR





Spectrum of steroid responsiveness



DPI

pMDI



Problematic/uncontrolled asthma

Difficult asthma

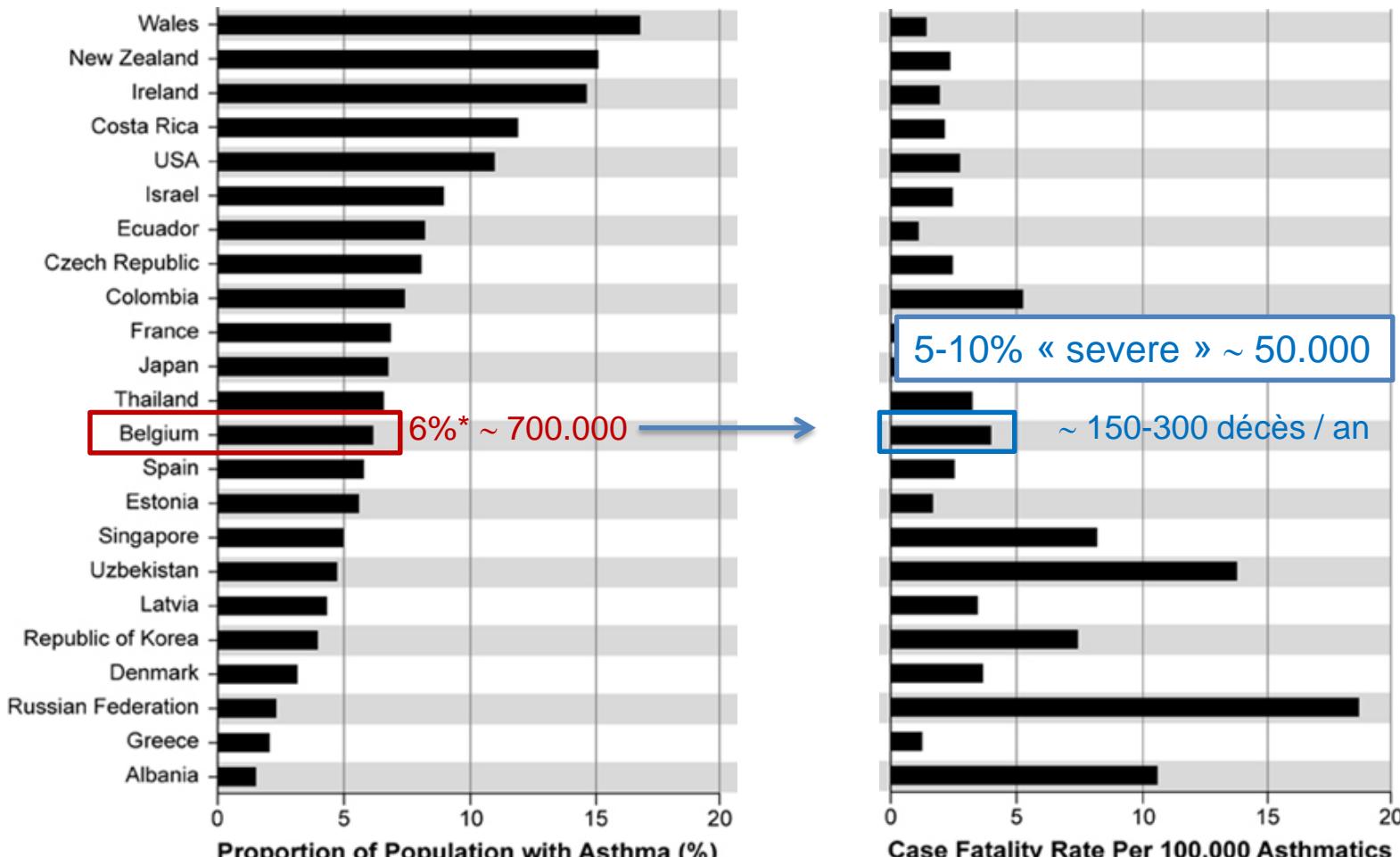
- Wrong diagnosis
- **Poor adherence**
- **Poor inhalation technique**
- Co-morbid rhinitis, GER, obesity
- Vocal cord dysfunction
- Drugs (β -blockers, NSAID)
- Smoking
- Environment (allergens...)
- Psychosocial factors

Severe asthma

- Persistent symptoms
 - Severe exacerbations
 - Persistent airway obstruction
- Despite a GINA 4-5 treatment and/or maintenance oral CS $\geq 50\%$ of the previous yr

→ **Medical need for new therapies**

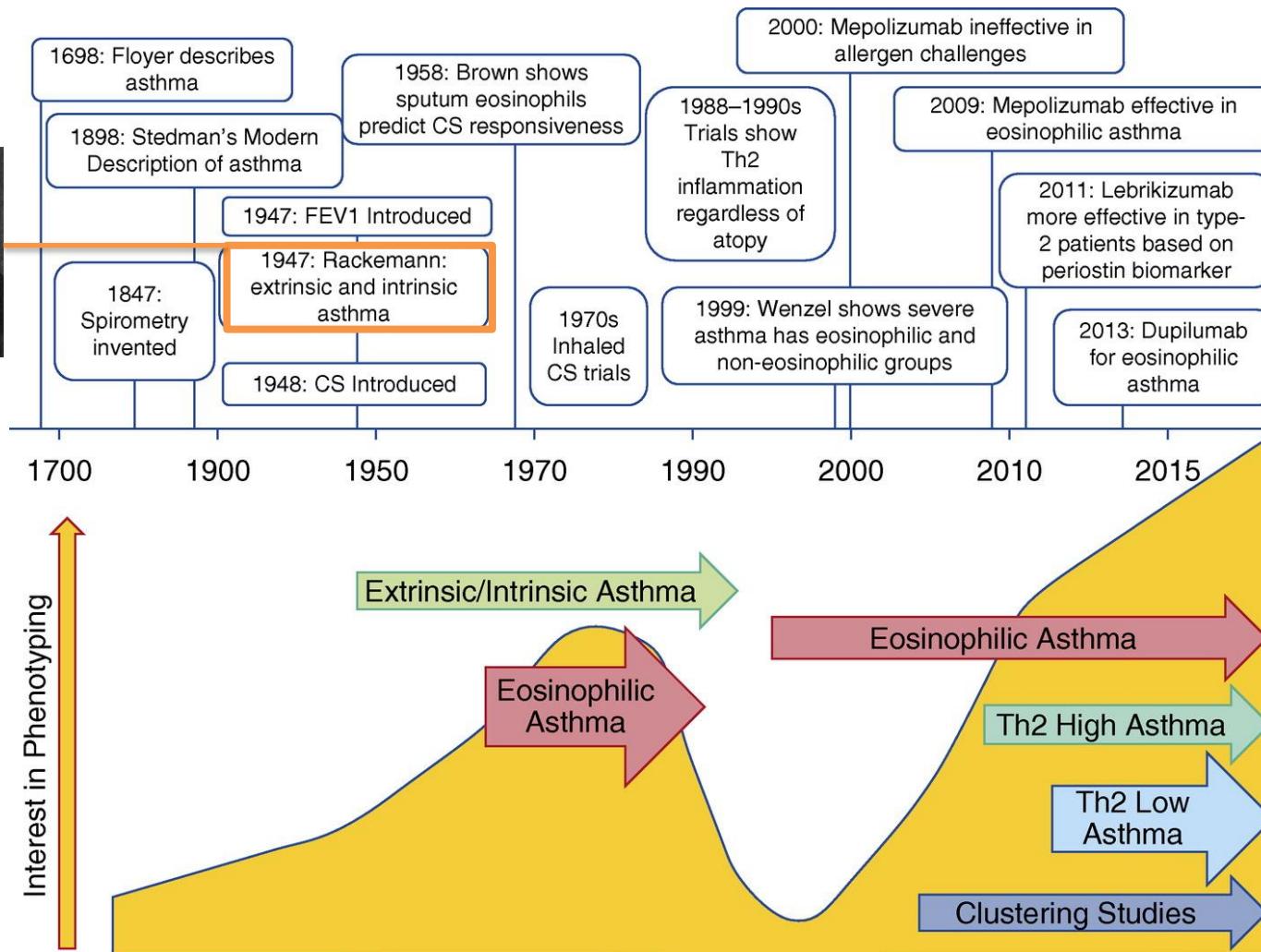
Asthma prevalence



*50% of those reporting symptoms (12%)

Population belge: 11.2M (2013)

Asthme phenotypes



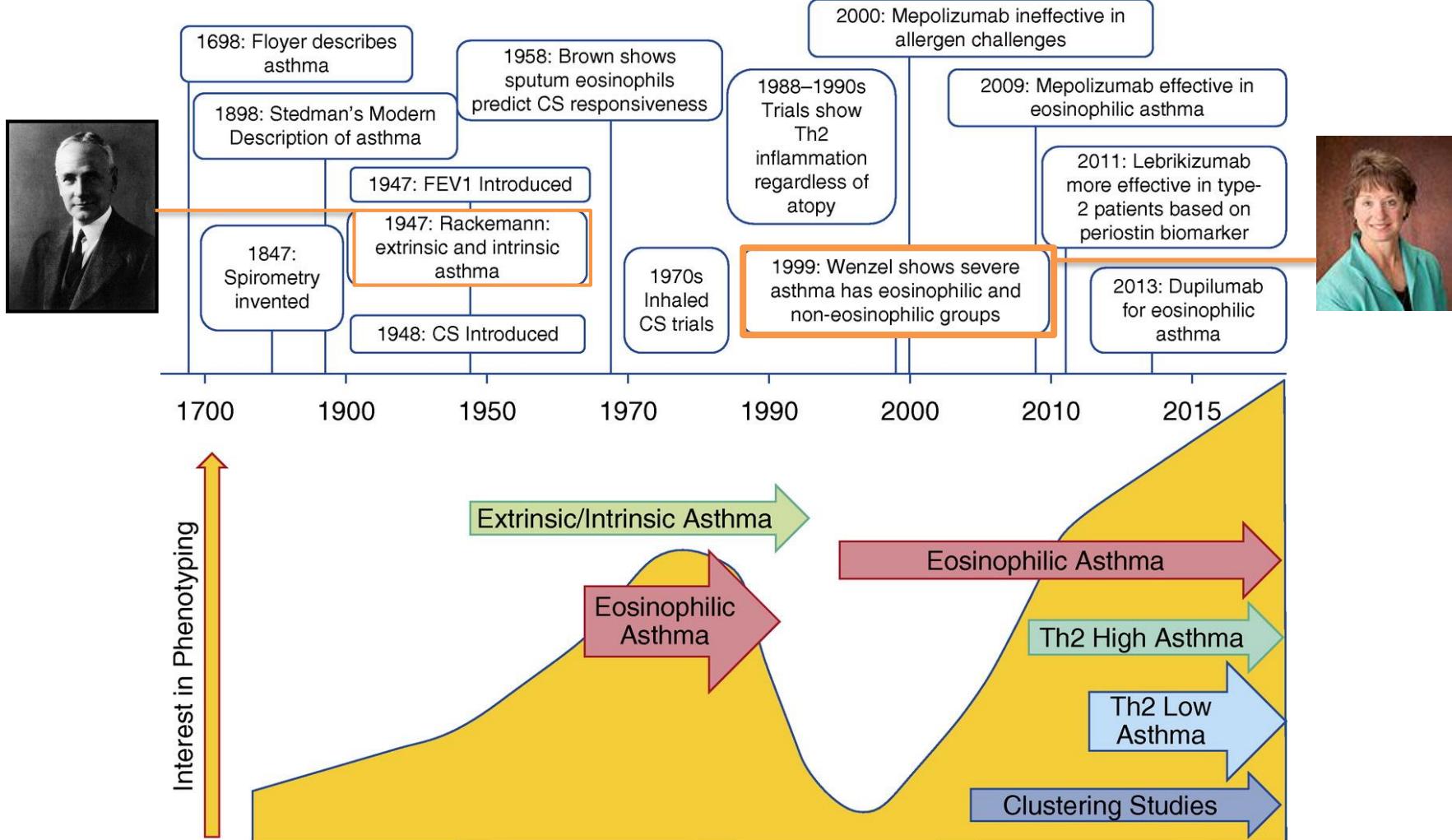


Rackeman
(1947)

	Extrinsic asthma	Intrinsic asthma
Demography	F=H	F>H
Onset	Early	Late (> 30 yrs)
Familial history	+	(-)
Triggering factors	Allergens	Non specific
Upper airway	Rhinitis	Sinusitis/polyps
Immunopathology	<ul style="list-style-type: none">▪ Eos, MC, Th2▪ Total IgE ↑▪ Specific IgE +	<ul style="list-style-type: none">▪ Idem!▪ Total IgE ↑ (30%)▪ Specific IgE -

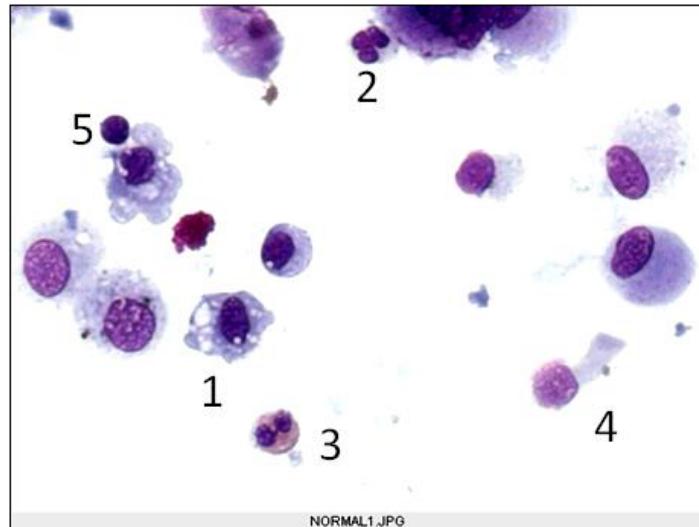


Asthme phenotypes





Eosinophilic asthma



1. Macrophage
2. Neutrophil
3. Eosinophil
4. Epithelial cell
5. Lymphocyte

- Tissue (22/mm²)
- Sputum (2-3%)
- **Blood (300-500/ μ L)**
- **Exhaled nitric oxide (35 ppb)**
- Periostin (25-50 ng/mL)
→ CV (intra-subject) 20-25%
- Regulation by steroids

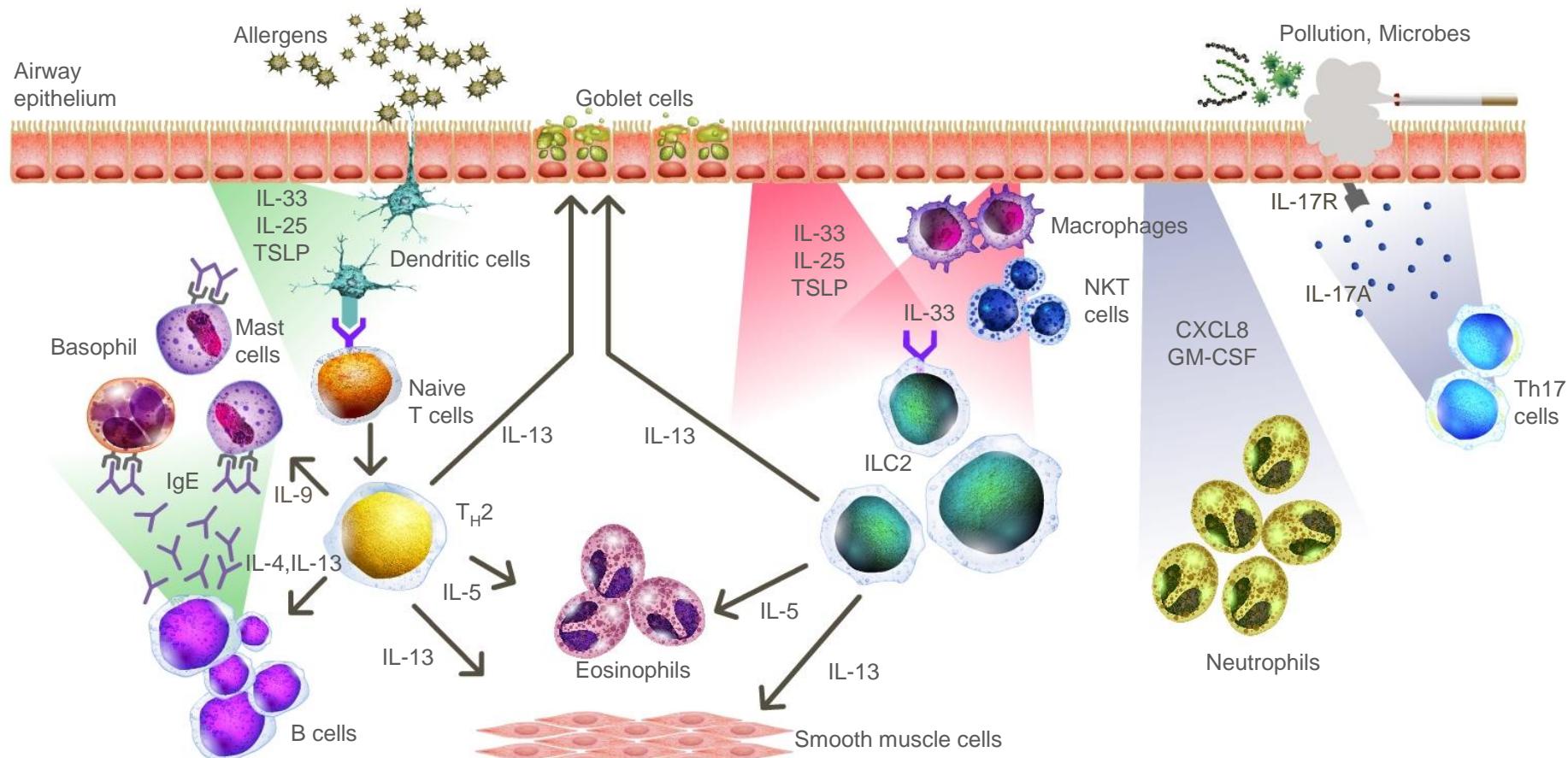
Asthma endotypes

- **Phenotype:** characteristics of an organism integrating genes-env interactions
- **Endotype:** subtype of a pathology that is associated with distinct functional or pathological characteristics

Eos asthma

	Allergic	Eosinophilic	Exercise-induced	Other (non T2)
Frequency	++ (75%)	+ (10%)	Frequent in athletes	+ (10-20%?)
Onset	Early (< 30y)	Late (> 30y)	variable	
Pathology	Epithelial aggression (Ag, virus) – IgE allergy	? non-allergenic ILC2 (except ABPA?)	? High flow of dry and cold air	<ul style="list-style-type: none">▪ Neurendocrine▪ Neutrophilic
Co-morbidities	<ul style="list-style-type: none">▪ Rhinitis (50-90%)▪ Dermatitis (40%)	<ul style="list-style-type: none">▪ Sinusitis +/- polyps▪ ASA syndrome▪ 2ary: ABPA, EGPA	None (viruses)	<ul style="list-style-type: none">▪ Obesity, Mnp▪ Smoking
Eosinophils IgE (kU/mL)	500-1000 >>100	>1000 (ou 500 sous CSO) Variable (>1000 ABPA)	<500	<500 variable

Asthma: pathophysiology of endo(pheno)types



Atopic eosinophilic asthma

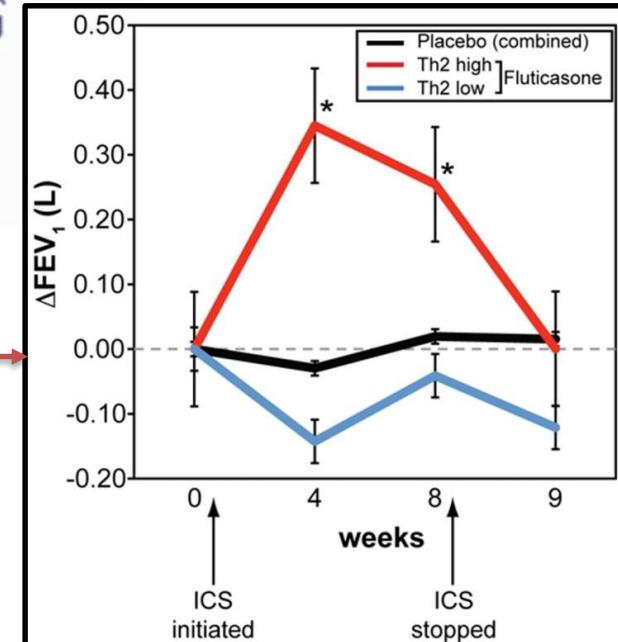
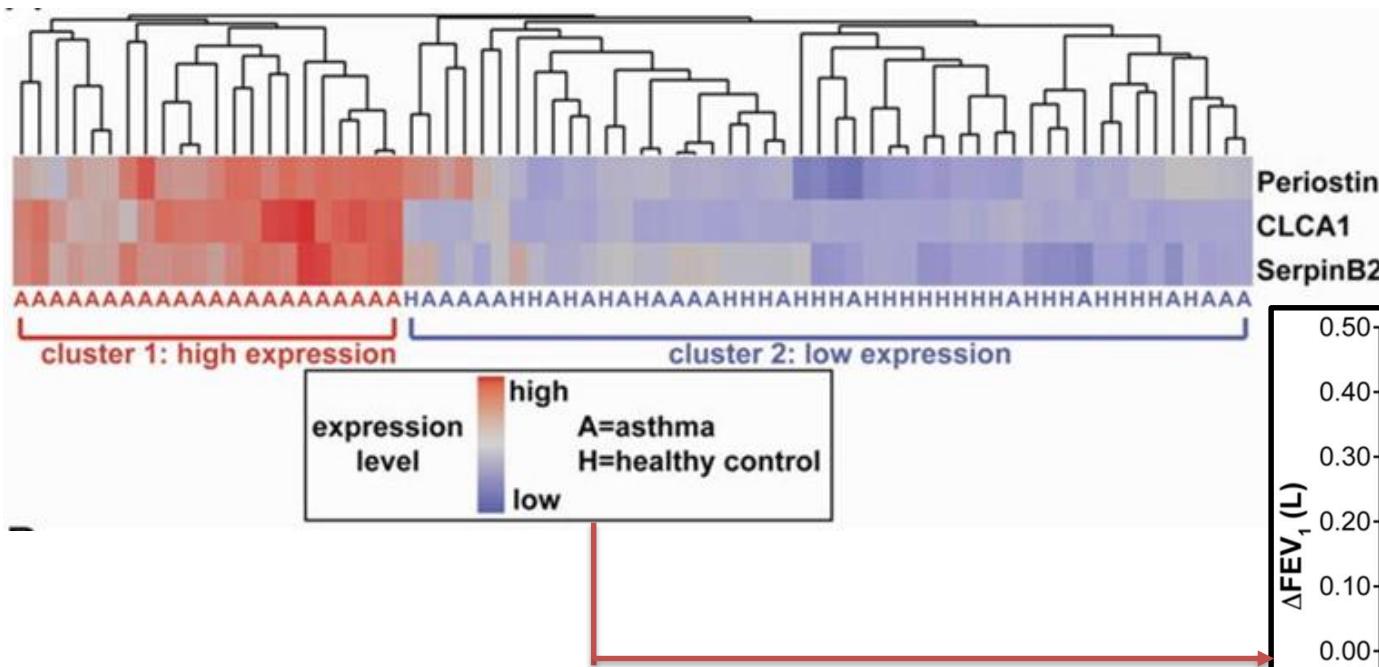
Non-atopic eosinophilic asthma

Neutrophilic asthma

Ig = immunoglobulin; IL = interleukin; NKT cells = natural killer T cells;
TSLP = thymic stromal lymphopoitietin; TSLPR = thymic stromal lymphopoitietin receptor

Biomarkers for steroid responsiveness

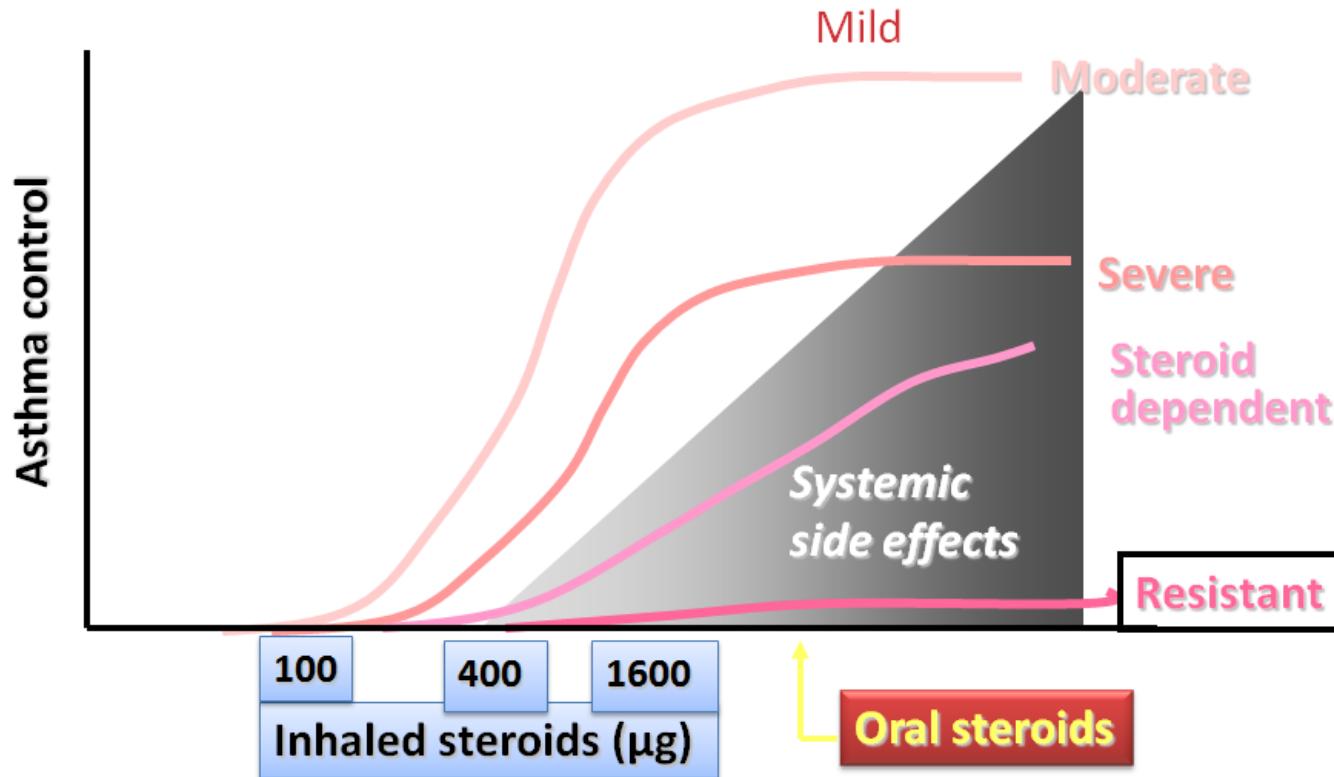
- Exhaled NO
- Sputum eosinophils (> 3%)
- Type 2 epithelial signature (\leftarrow IL-13)
- ~50% of patients with ICS naive, mild-moderate asthma



Woodruff PG et al. PNAS 2007

Bhakta NR & Woodruff PG. Immunol Rev 2011

From bench...	...to bedside
Allergens (1873)	→ Allergen immunotherapy (1911)
Inflammation - eosino (1950's)	→ Inhaled corticosteroids (1972)



DPI

pMDI





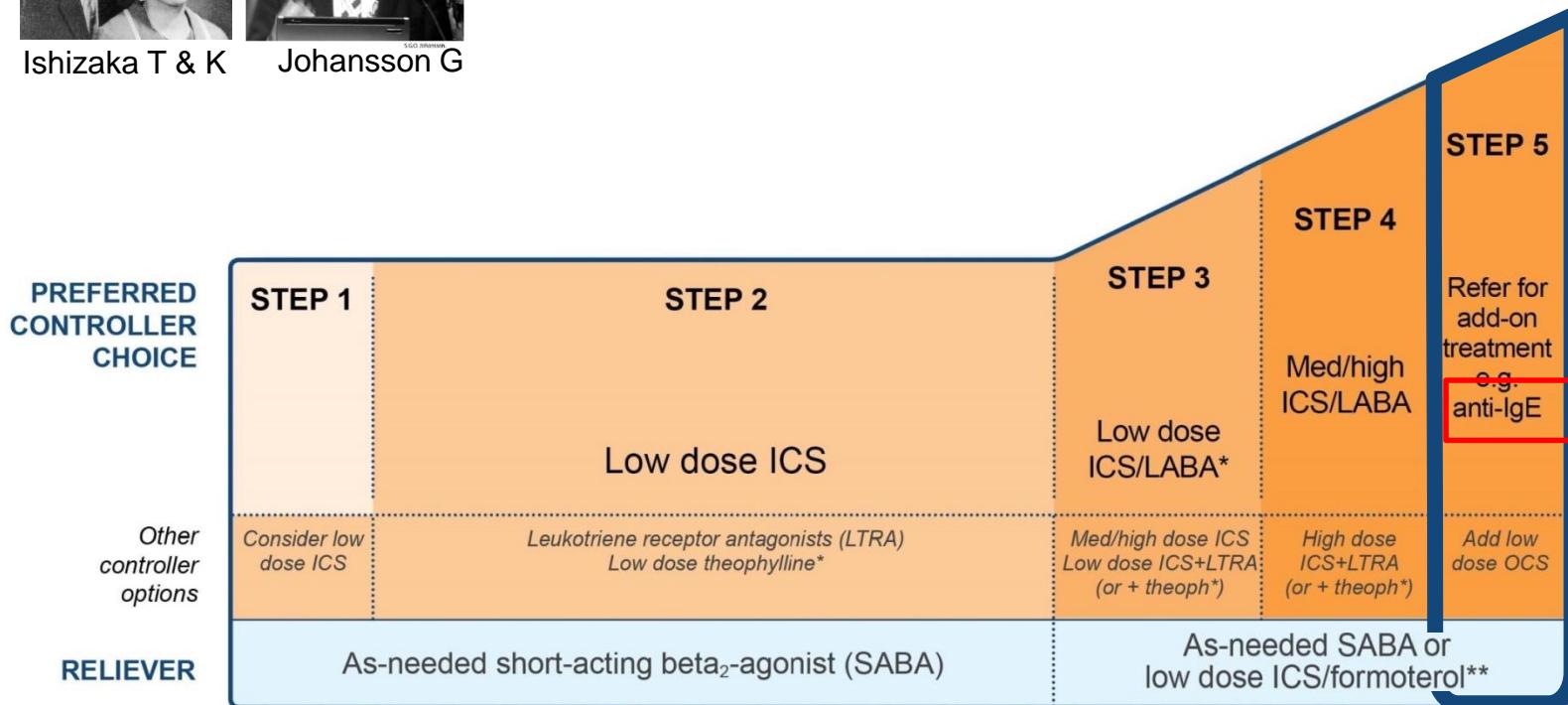
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Allergens (1873)	Allergen immunotherapy (1911)
Inflammation - eosino (1950's)	Inhaled corticosteroids (1972)
IgE, mediator of allergy (1966)	Anti-IgE (2003)



Ishizaka T & K



Johansson G



Step 5 GINA 2014 (*since 2005)

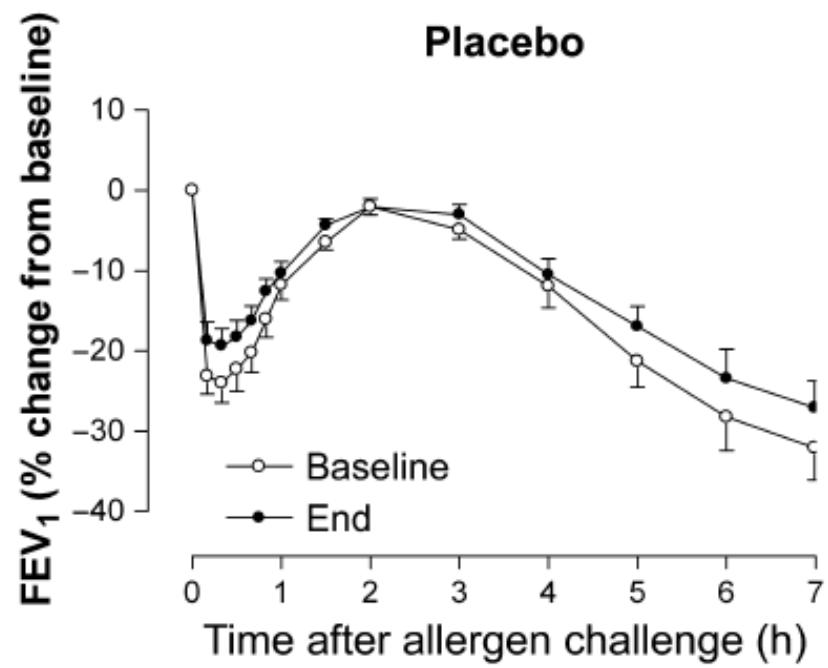
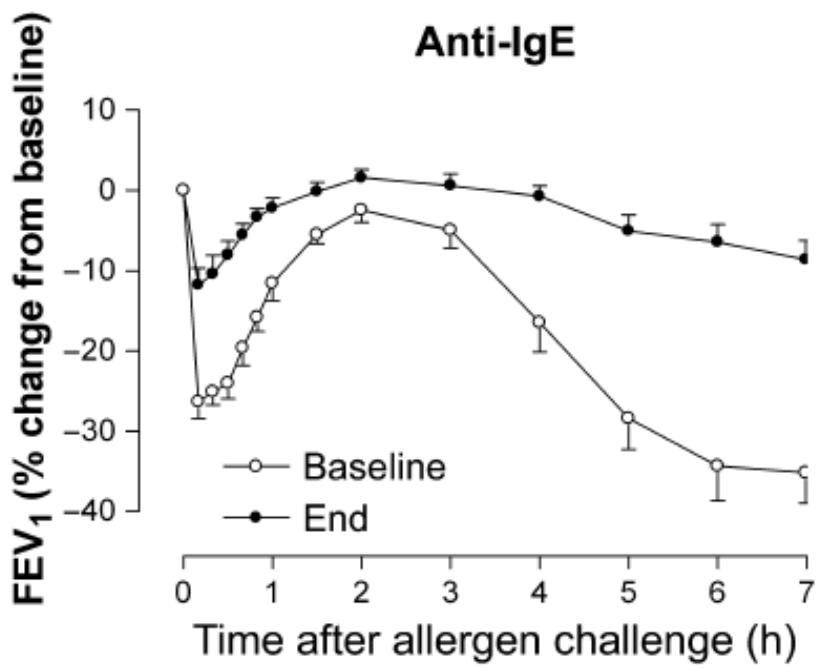
Severe asthma: therapeutic recommandations (GINA 2015, Chung et al. ERJ 2014)

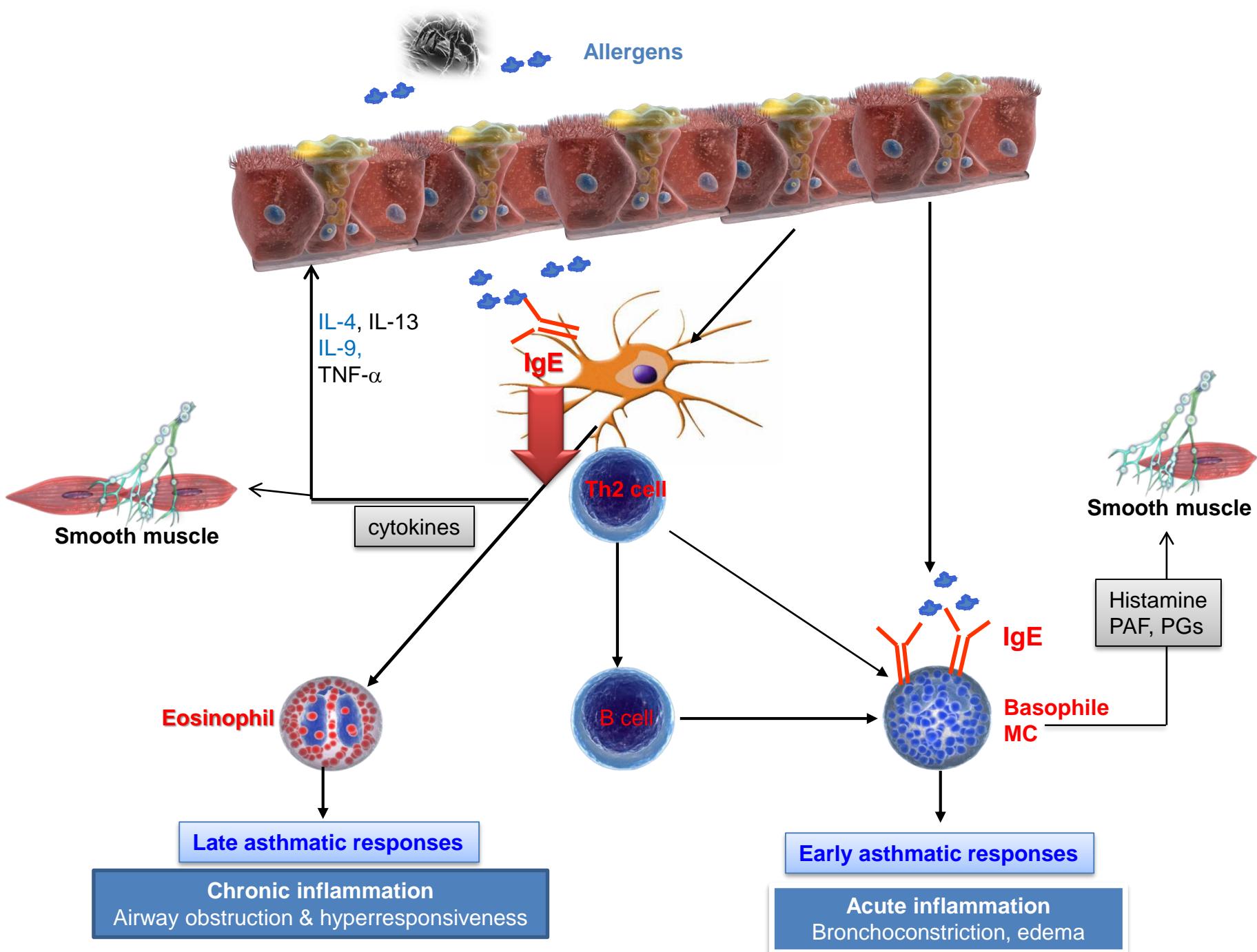
- Refer for specialized investigation
- → Screening and aggressive treatment of aggravating factors
- → Targeted therapy
 - Allergic asthma → anti-IgE: omalizumab (XOLAIR)



Taux d'IgE (UI/mL)	Poids corporel (kg)								
	20-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
>30-100	150	150	150	150	150	150	150	300	300
>100-200	150	150	300	300	300	300	300	450	600
>200-300	150	300	300	300	450	450	450	600	750
>300-400	300	300	450	450	450	600	600		
>400-500	300	450	450	600	600	750	750		
>500-600	300	450	600	600	750				
>600-700	450	450	600	750					

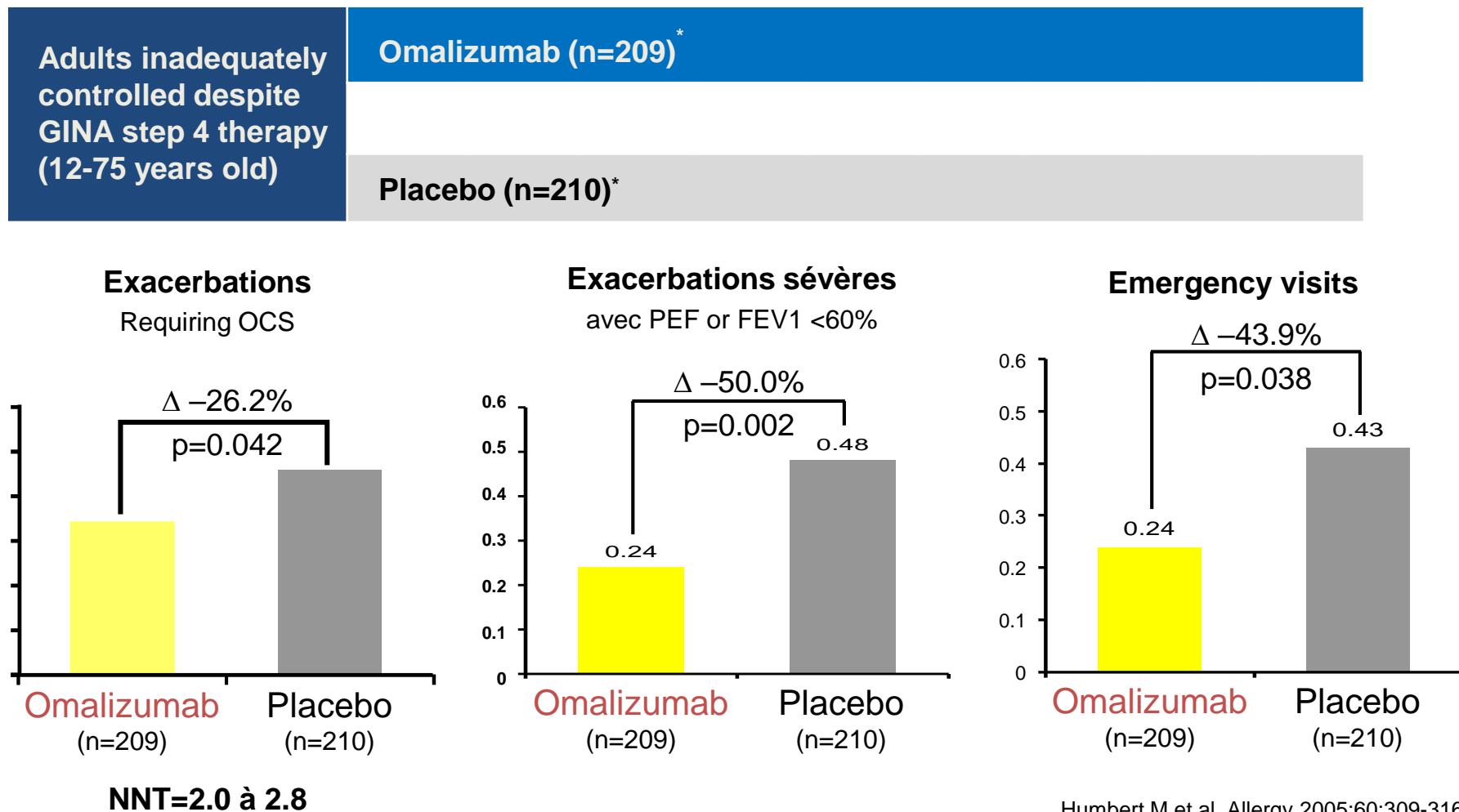
0.016 mg/kg/unité intern. IgE



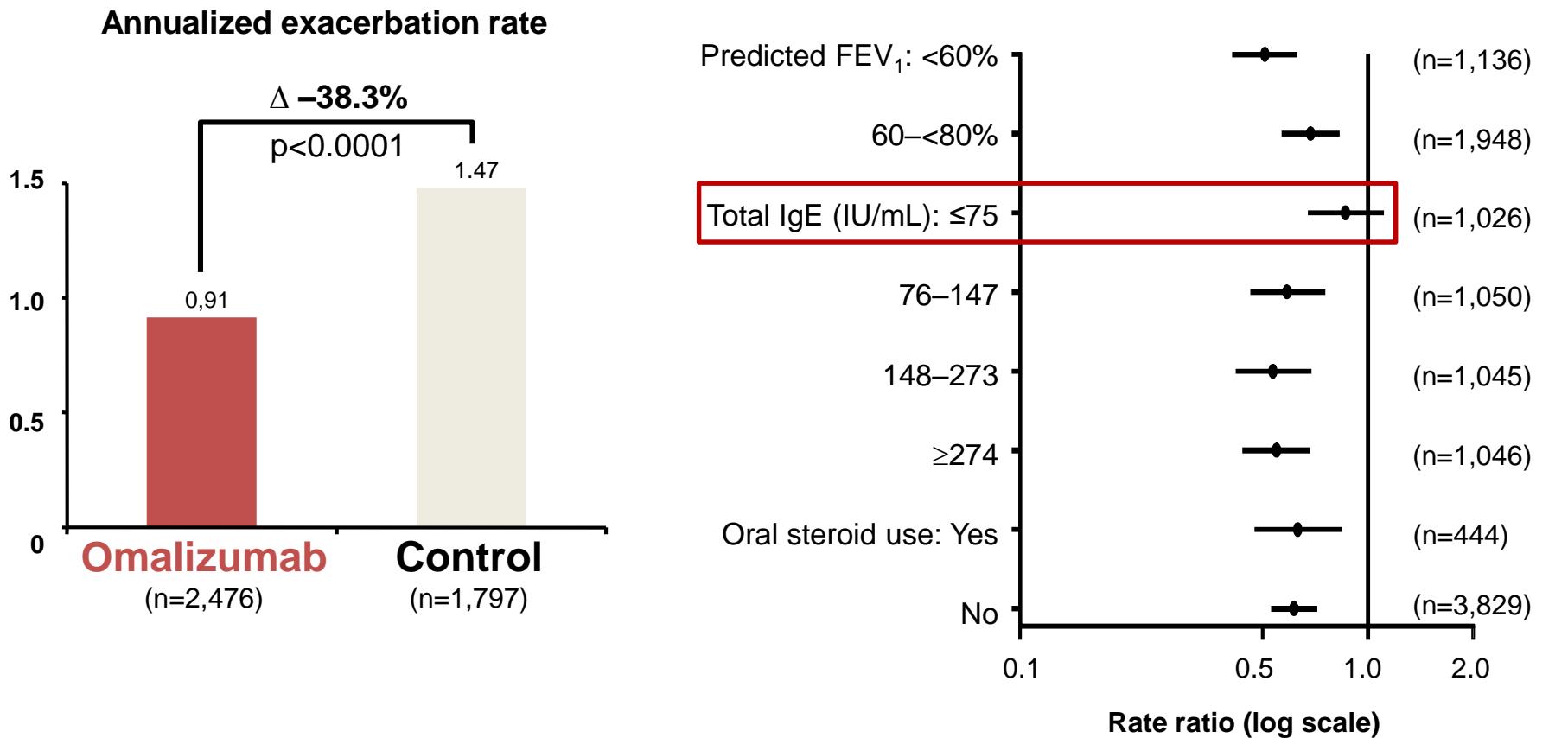


Etude INNOVATE

- Efficacy of add-on omalizumab on **exacerbations** in patients with uncontrolled severe asthma, despite GINA step 4 therapy
- Secondary outcomes: SAE, GETE, AQLQ, FEV1, Symptoms score, safety



‘Pooled programme’ of omalizumab trials in severe asthma (93% of patients)



1. Humbert M, et al. Allergy 2005; 2. Ayres JG, et al. Allergy 2004; 3. Vignola AM, et al. Allergy 2004
4. Busse W, et al. J Allergy Clin Immunol 2001; 5. Solèr M, et al. Eur Respir J 2001
6. Holgate ST, et al. Clin Exp Allergy 2004

Critères du traitement anti-IgE (en Belgique)

- **Patient âgé > 12 ans (6 ans*)**
- **Asthme allergique sévère**
 - IgE spécifique ou prick-test cutané + à un allergène pérenne
- **Non contrôlé** malgré CSI haute dose (>1.000 µg/j BDP) + LABA
 - Symptômes diurnes et/ou nocturnes
 - VEMS <80% prédit
 - **≥2 exacerbations sévères** (requérant CSO ou hospitalisation)
- IgE totales 76-700 U/ml (**30-1.300***)
 - Premier remboursement pour 4 mois, à prolonger si réponse excellente/très bonne

*Indications européennes (EMA, update 08/07/2011)

⇒ Réduction du taux d'exacerbation -26 à -50% (Innovate)

⇒ Taux de répondeurs ~ 60% (Innovate, pooled analysis)

Facteurs prédictifs -: IgE ≤ 75 UI/ml

Facteurs prédictifs +: FeNO et Eos ↑

Off label use: ABPA, asthme non allergique, immunothérapie, dermatite atopique

Etude pragmatique de l'omalizumab en Belgique

Respiratory Medicine (2009) 103, 1633–1642

available at www.sciencedirect.com

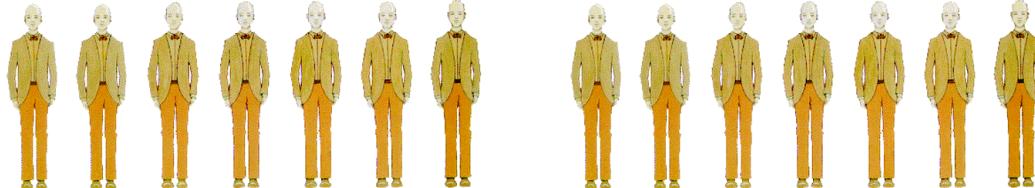


ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

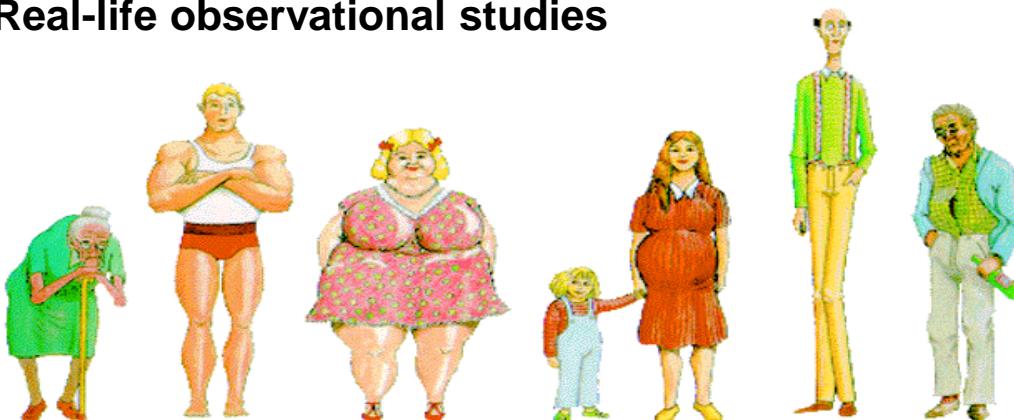


■ Traditional clinical studies (RCT)



⇒ *Efficacy*

■ Real-life observational studies

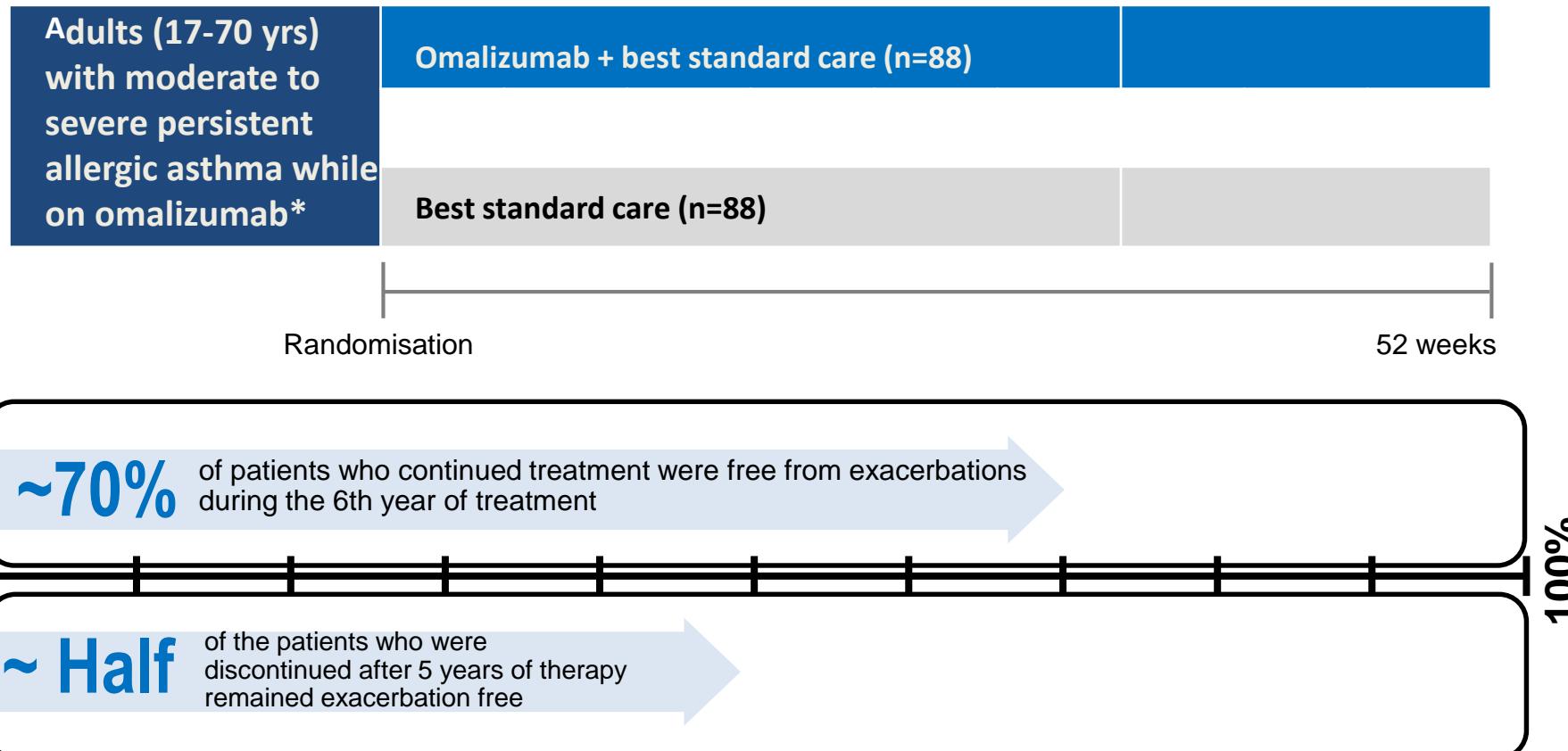


⇒ *Effectiveness*

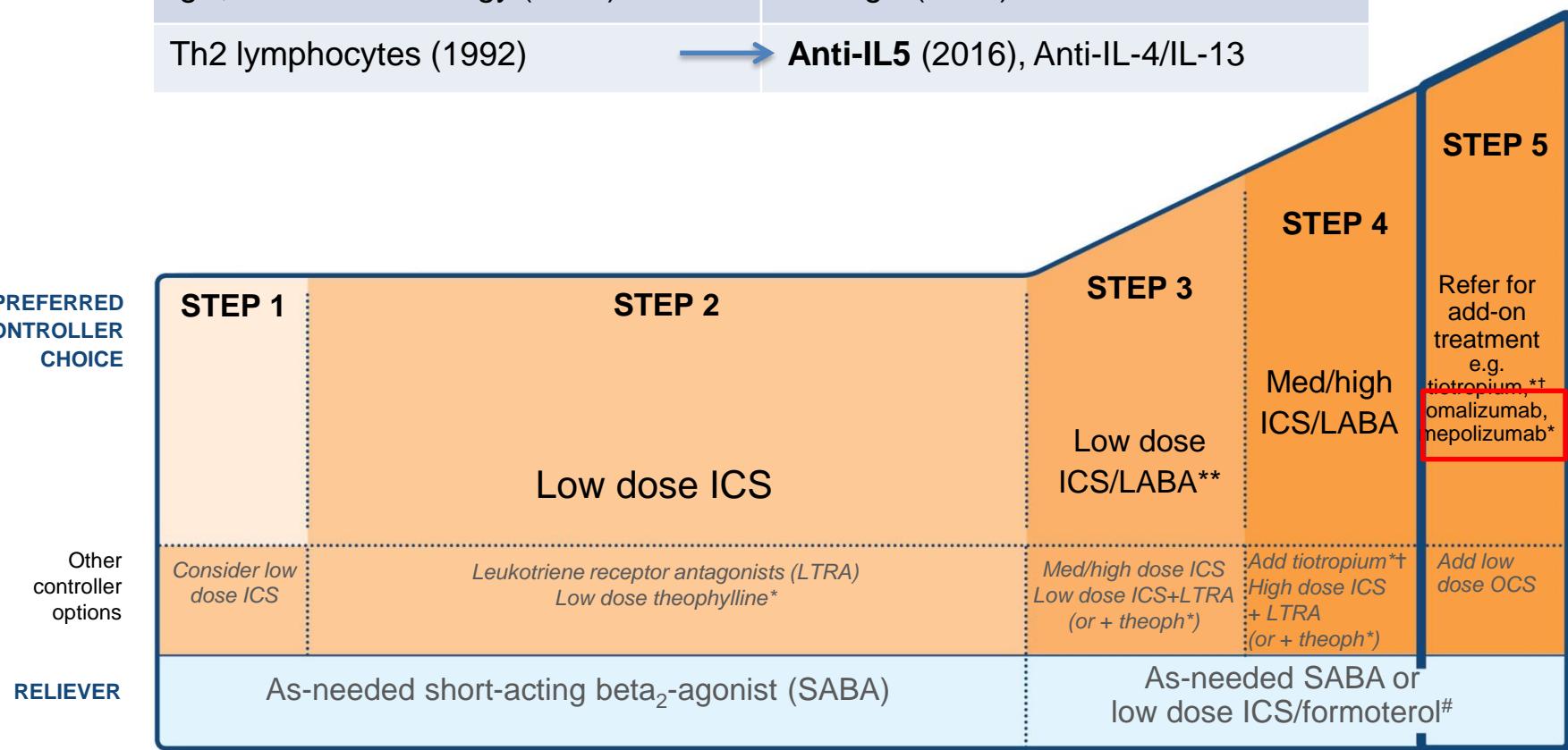
- ↓ Exacerbations (-65%, par rapport aux 12 mois précédents)
- Taux de réponse 72-80%

Etude XPORT

- Efficacité persistante de l'omalizumab après traitement prolongé (≥ 5 ans), avec ou sans poursuite de l'omalizumab pendant l'année de suivi
- Primary outcome: any clinically-significant exacerbation



From bench...	...to bedside
Allergens (1873)	Allergen immunotherapy (1911)
Inflammation - eosino (1950's)	Inhaled corticosteroids (1972)
IgE, mediator of allergy (1966)	Anti-IgE (2003)
Th2 lymphocytes (1992)	→ Anti-IL5 (2016), Anti-IL-4/IL-13



Step 5 GINA 2016

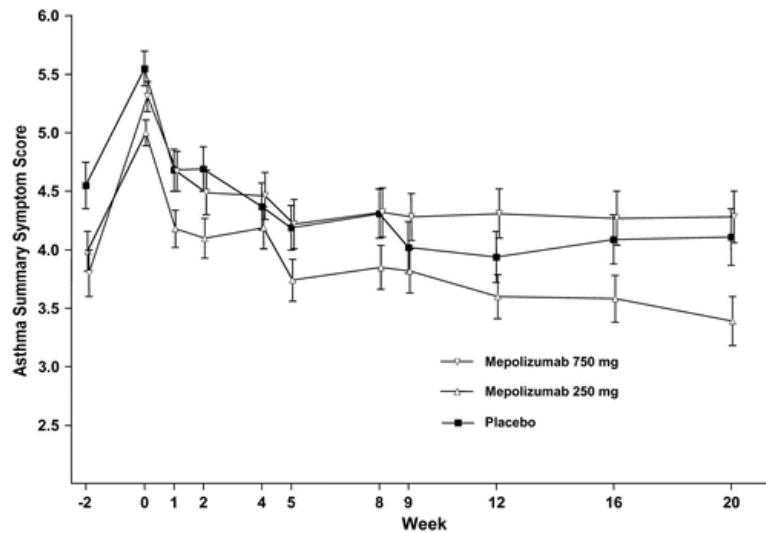
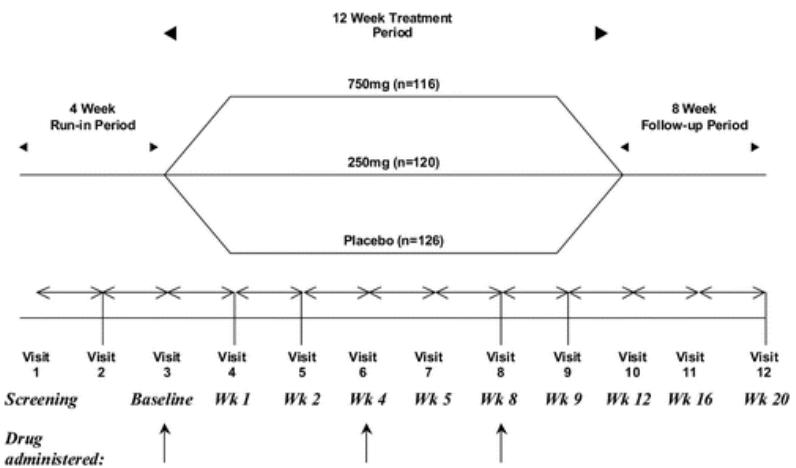
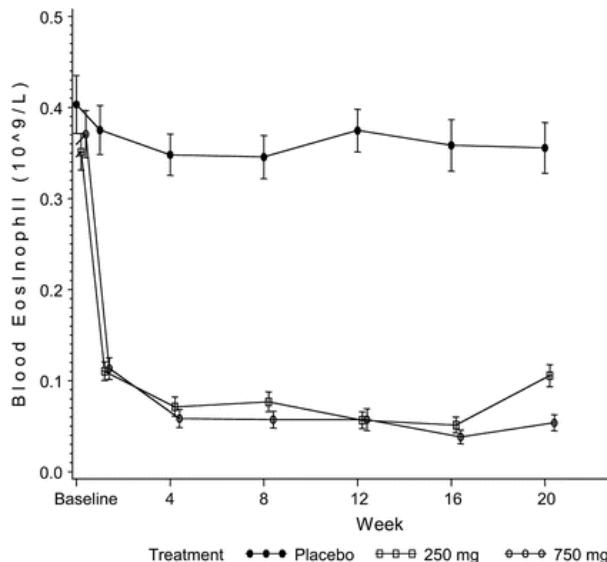
Severe asthma: therapeutic recommandations

(GINA 2015, Chung et al. ERJ 2014)

- Refer for specialized investigation
- → Screening and aggressive treatment of aggravating factors
- → Targeted therapy:
 - **Allergic asthma**
 - anti-IgE: omalizumab (XOLAIR)
 - **Eosinophilic non-allergic asthma**
 - Anti-IL5: mepolizumab (NUCALA)

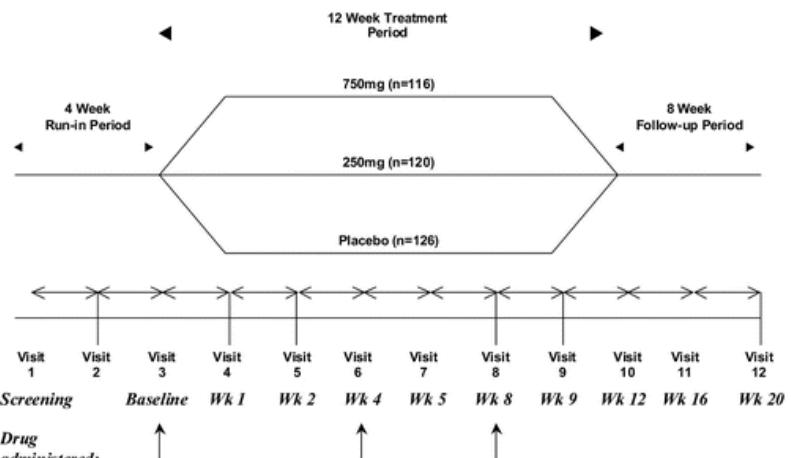
Mepolizumab

- n=362 patients
- Uncontrolled asthma by ICS
(BDP $710 \pm 400 \mu\text{g}$)
- FEV1 $68 \pm 9\%$
- Specific IgE 80-85%
- Eosinophils: $350 \pm 280/\mu\text{L}$



Mepolizumab

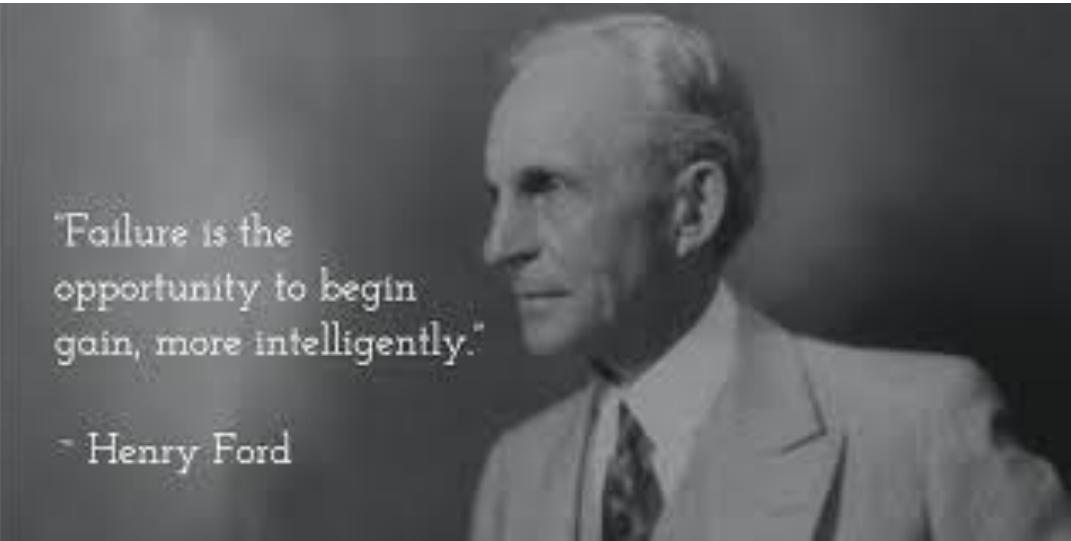
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- Specific IgE 80-85%
- Eosinophils: $350 \pm 280/\mu\text{L}$



Conclusions: Mepolizumab treatment does not appear to add significant clinical benefit in patients with asthma with persistent symptoms despite inhaled corticosteroid therapy.

Further studies are needed to investigate the effect of mepolizumab on exacerbation rates, using protocols specifically tailored to patients with asthma with persistent airway eosinophilia.

Read More: <http://www.atsjournals.org/doi/full/10.1164/rccm.200701-085OC#.V9kGL01V2fA>

A black and white portrait of Henry Ford, an elderly man with white hair, wearing a light-colored suit and tie, looking slightly to his left.

"Failure is the
opportunity to begin
again, more intelligently."

- Henry Ford

Mepolizumab: EMSA trial

- 61 patients
- Severe refractory asthma
- Exacerbations, ≥ 2 in previous yr (5)
- Prednisolone, regular ~55% (10mg)
- IgE sensitisation 68%
- Sputum eosinophils >3%
(Blood eos $350 \pm 300/\mu\text{L}$)

NB: Nasal polyps 33%

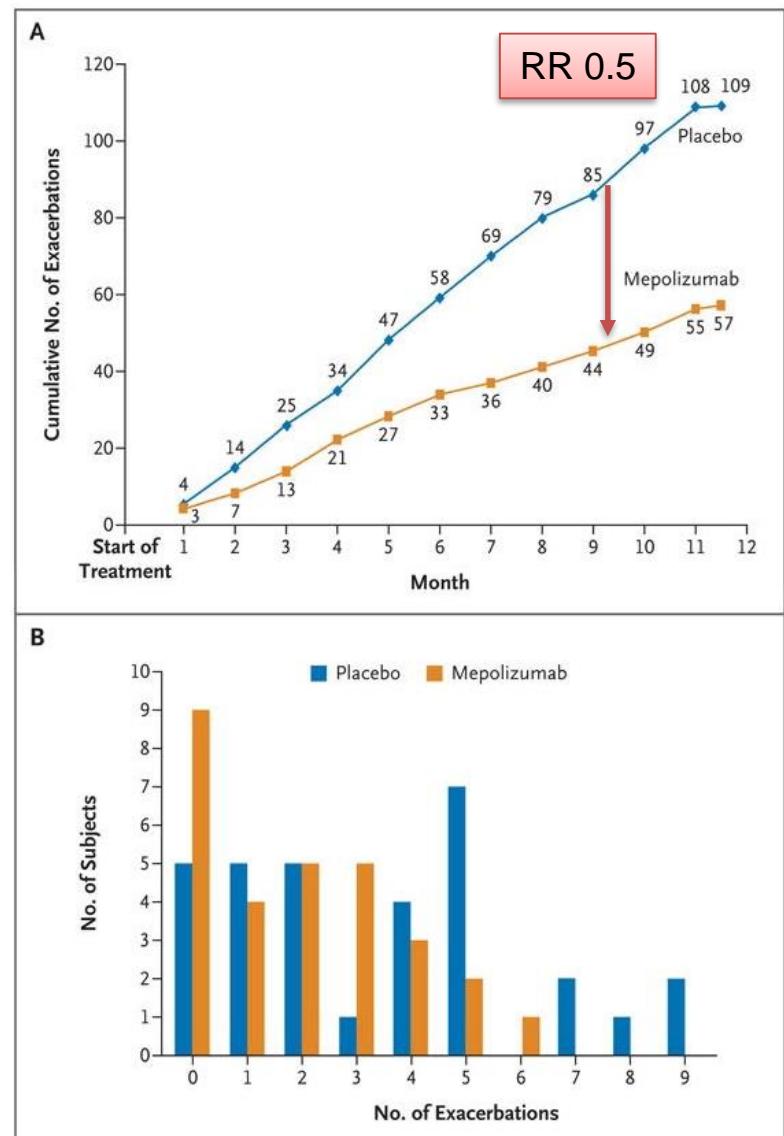
NB: age onset 2-57 (mean 26y)

→ Mepo 75 mg/month 52w

→ Reduction of exacerbations:

→ And improvement of AQLQ

→ No effect on ACQ and FEV1



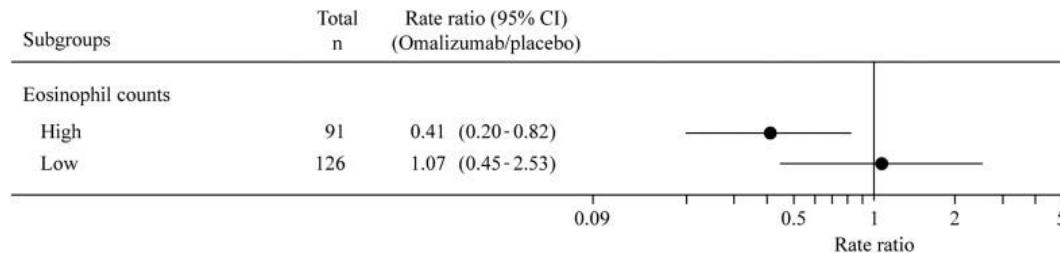
Critères du traitement **anti-IL5 /mepo** (en Belgique)

- Patient âgé ≥ 18 ans
- **Asthme sévère réfractaire à éosinophiles**
 - Eosinophilie sanguine $> 300/\mu\text{L}$ lors instauration et durant les 12 derniers mois
- **Non contrôlé** malgré CSI haute dose ($>1.000 \mu\text{g/j BDP}$) + 1/+^s autre médicament (LABA, antiLT)
 - ~~Symptômes diurnes et/ou nocturnes~~
 - VEMS $<80\%$ prédit
 - **≥ 2 exacerbations sévères** dans l'année (requérant CSO ≥ 3 j ou dose X2 pour patients cortico-dépendants), et/ou visite urgences et/ou hospitalisation) **et/ou traité en continu par un corticoïde systémique**
- **Ou patient déjà traité avec efficacité dans le cadre des études cliniques du mepolizumab**

→ Premier remboursement pour 6 mois, à prolonger si efficace (\downarrow exacerbations)

Autre indication: syndrome hyperéosinophilique (HES)

Biomarkers of response to biotherapies



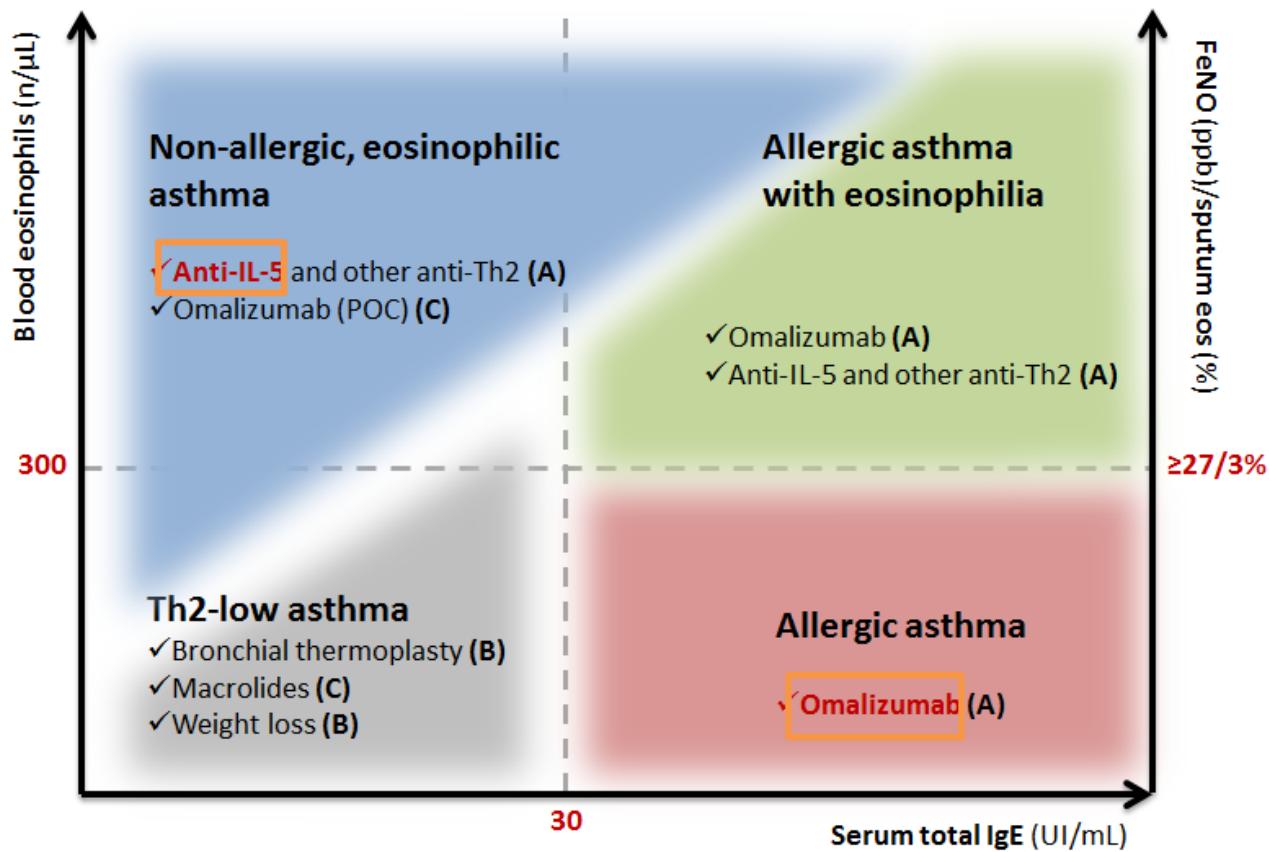
Busse et al. JACI 2013

	Blood eos* (250 – 500/ μ L)	Exhaled NO (19.5 – 40 ppb)	Periostin (25-50 ng/mL)	Serum IgE
Anti-IgE	+ (250)	+		(+) \geq 76 kU/L
Anti-IL5	<u>++</u> (300)	+		0
Anti-IL13	+	+	++	
Anti-IL4R α	-	-	+#	

*Or sputum eos \geq 3%

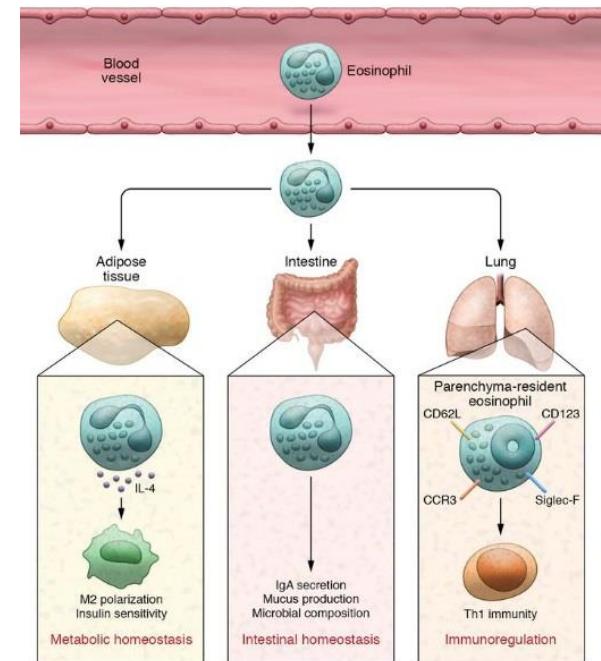
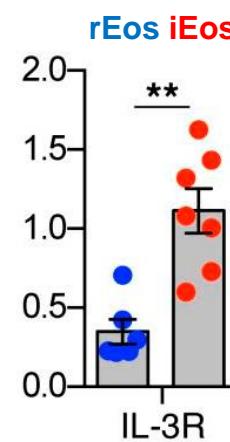
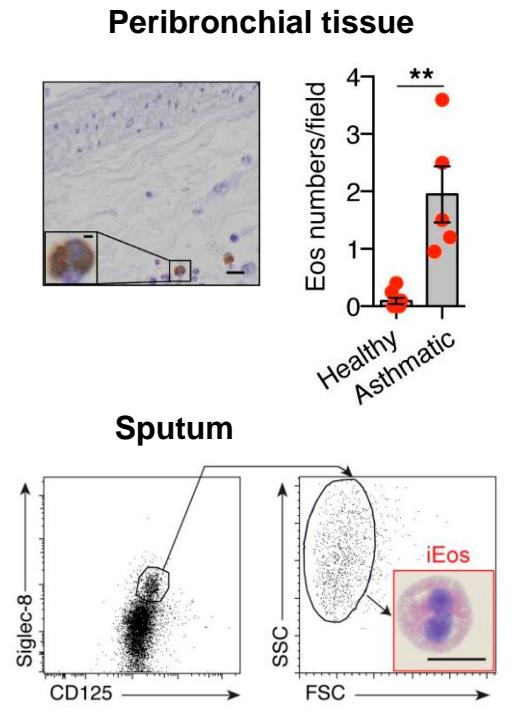
Wenzel S et al. Lancet 2016
#Wenzel S et al. ERS London 2016

Anti-IgE et anti-IL5 biotherapies in severe asthma



From bench...	...to bedside
Allergens (1873)	Allergen immunotherapy (1911)
Inflammation - eosino (1950's)	Inhaled corticosteroids (1972)
IgE, mediator of allergy (1966)	Anti-IgE (2003)
Th2 lymphocytes (1992)	Anti-IL5 (2016), anti-IL-4/IL-13

Resident eosinophils:
a regulatory population?



Future pipelines in severe asthma

From bench...	...to bedside
Allergens (1873)	Allergen immunotherapy (1911)
Inflammation - eosino (1950's)	Inhaled corticosteroids (1972)
IgE, mediator of allergy (1966)	Anti-IgE (2003)
Th2 cells (1992)	Anti-IL5 (2016), anti-IL-4/IL-13
Dendritic cells (1998)	
Epithelio-dendritic axis (2009)	Anti-TSLP, IL-33/ST2...

Neutrophilic inflammation



- **Macrolides (e.g., azithromycine)**
- **Antagonists of CXCR2, TNF, IL-1, IL-17, IL-23**
- **PDE4 inhibitors**
- **Bronchial thermoplasty**