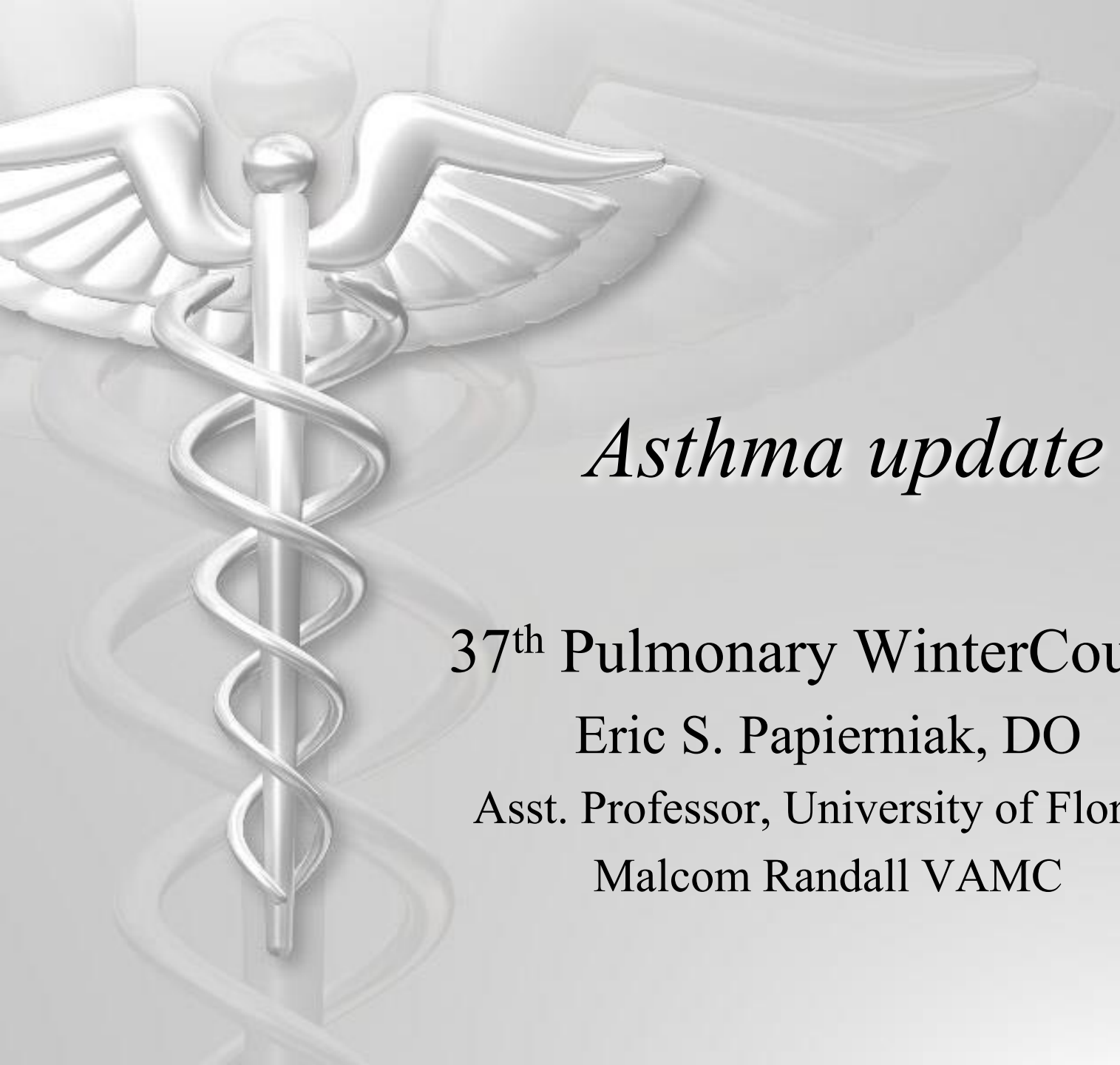


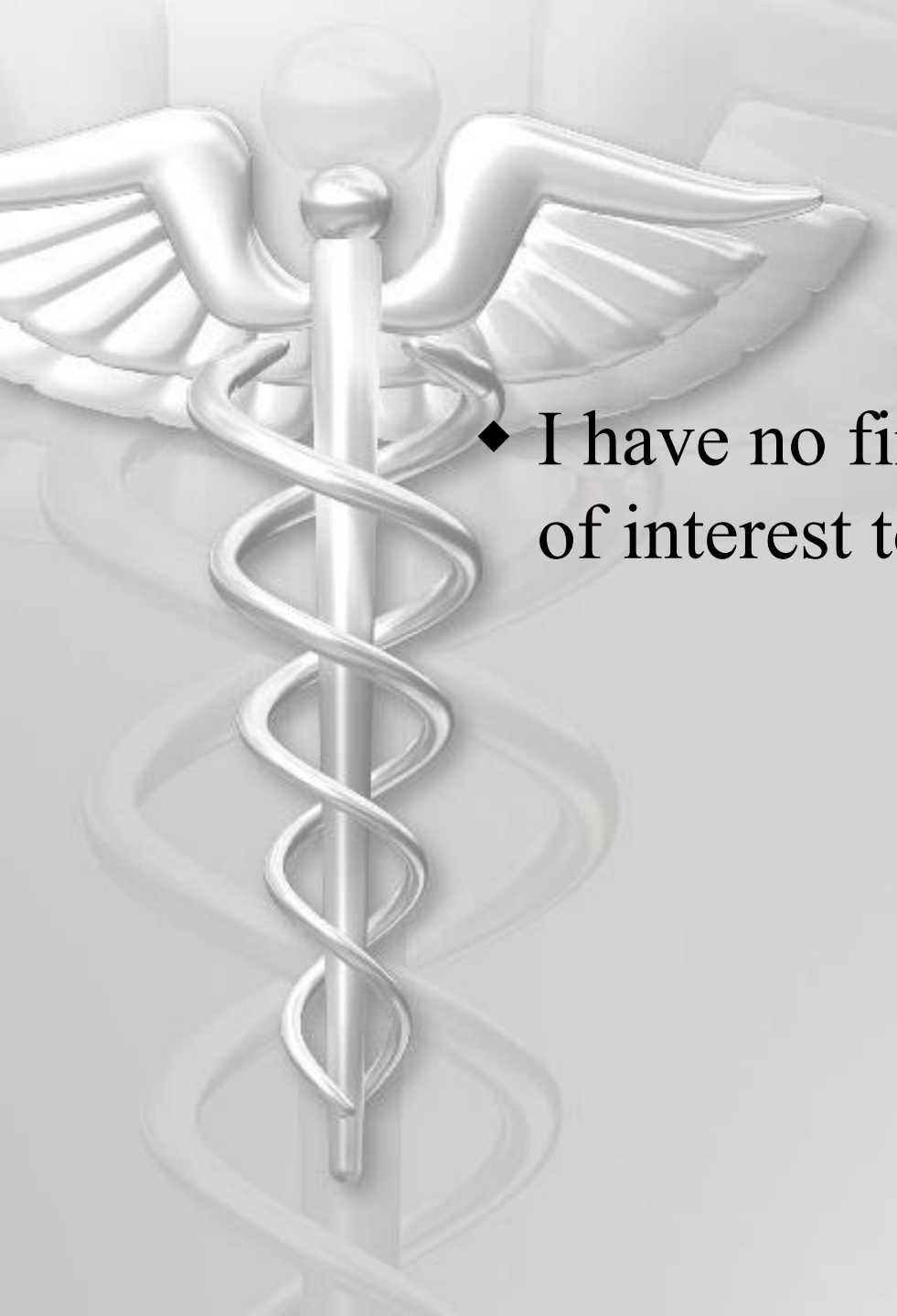
Asthma update 2016

37th Pulmonary WinterCourse

Eric S. Papierniak, DO

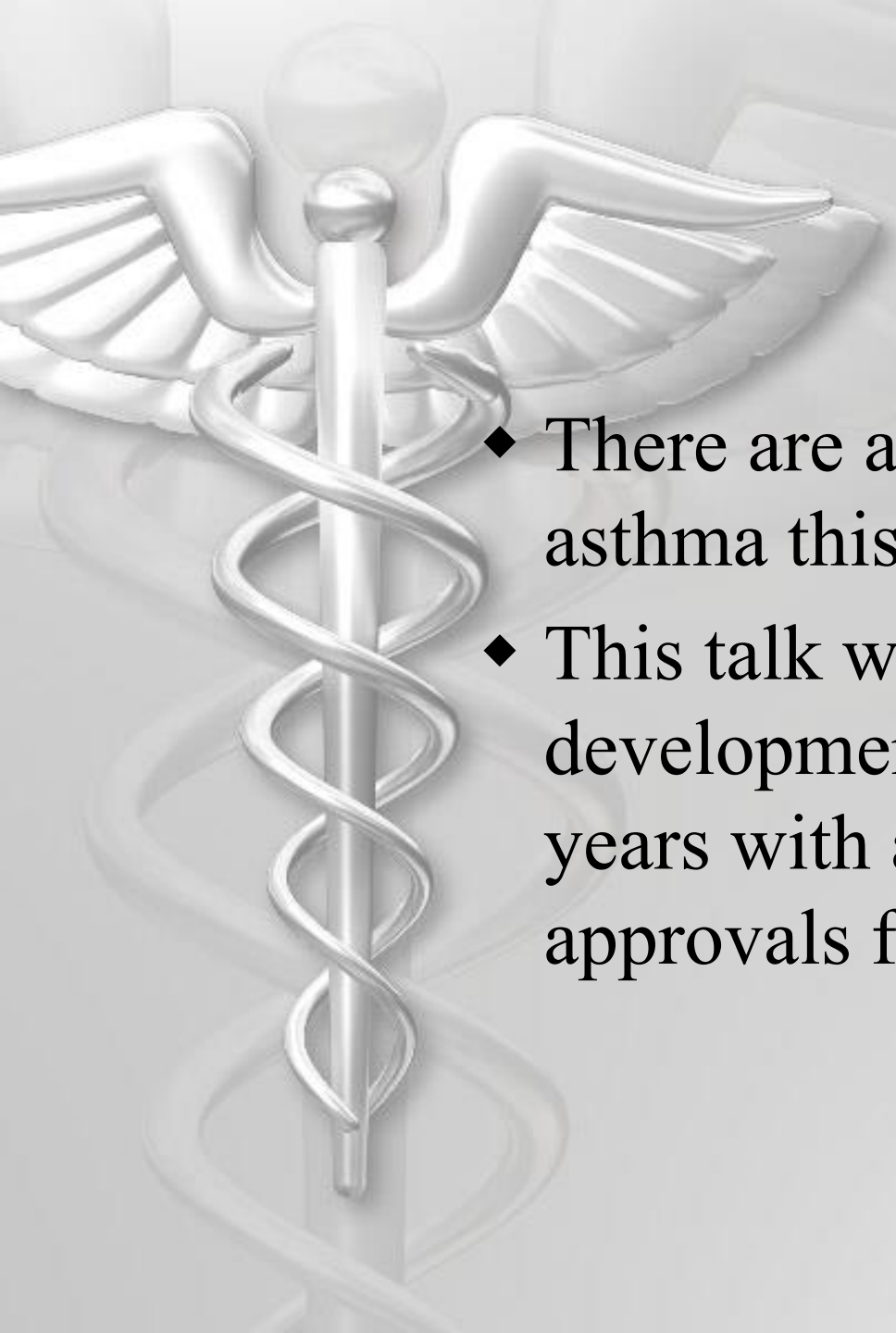
Asst. Professor, University of Florida

Malcom Randall VAMC



Disclosures

- I have no financial or other conflicts of interest to report

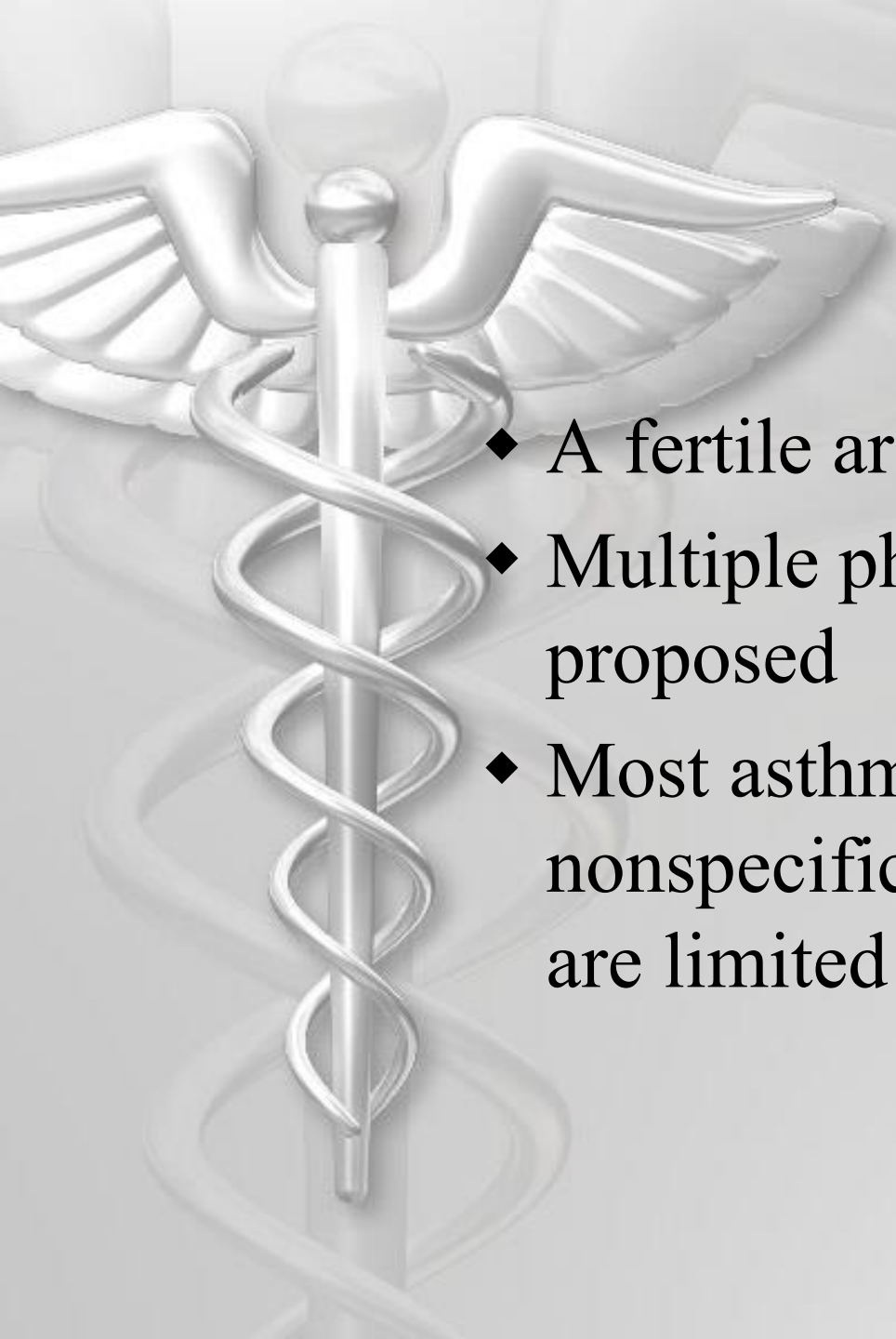


Overview

- There are actually new treatments in asthma this year!
- This talk will cover the new developments over the past few years with a focus on the latest FDA approvals for asthma

Overview

- Mepolizumab (Nucala)
- Reslizumab
- Tiotropium (Spiriva)
- Bronchial thermoplasty
- Azithromycin (Zithromax)



Phenotyping

- A fertile area of research
- Multiple phenotypes have been proposed
- Most asthma therapies are nonspecific so clinical applications are limited at the present time

Phenotyping

- The only significant exception is the broad division of patients based on the presence or absence of significant eosinophilia
- The currently available novel/targeted therapies are essentially all directed at the eosinophilic phenotype

Table 1 Asthma phenotypes in relation to characteristics

	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Genetics	Response to therapy
Early-onset allergic	Early onset; mild to severe	Allergic symptoms and other diseases	Specific IgE; T_H2 cytokines; thick SBM	17q12; T_H2-related genes	Corticosteroid-responsive; T_H2-targeted
Late-onset eosinophilic	Adult onset; often severe	Sinusitis; less allergic	Corticosteroid-refractory eosinophilia; IL-5		Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory
Exercise-induced		Mild; intermittent with exercise	Mast-cell activation; T_H2 cytokines; cysteinyl leukotrienes		Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9
Obesity-related	Adult onset	Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear	Lack of T_H2 biomarkers; oxidative stress		Responsive to weight loss, antioxidants and possibly to hormonal therapy
Neutrophilic		Low FEV1; more air trapping	Sputum neutrophilia; T_H17 pathways; IL-8		Possibly responsive to macrolide antibiotics

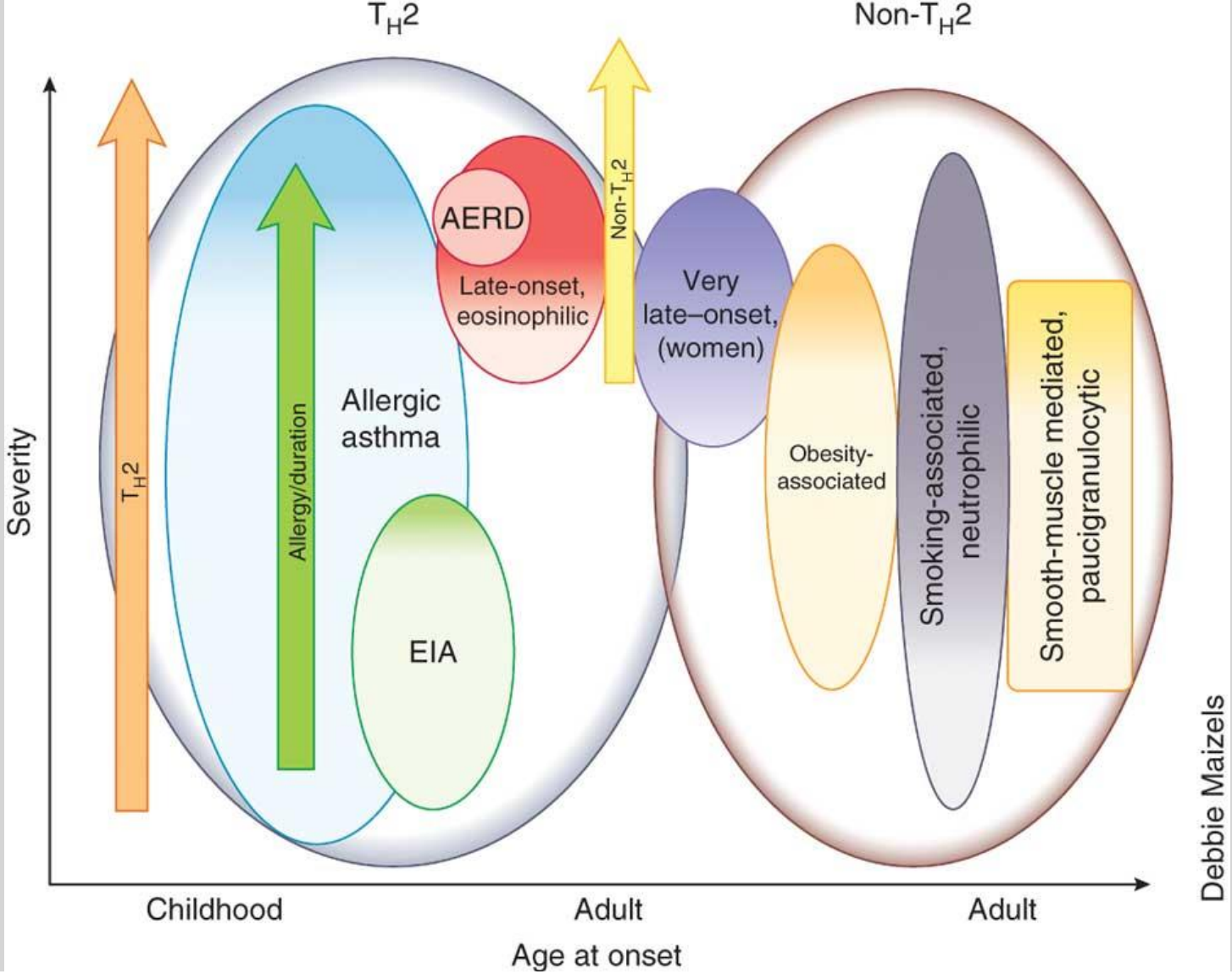
Wenzel, S. Nat Med 2012 May 4;18(5): 716-25. Used with permission.

Th-1 vs Th-2

- A Th-2 (or Th-2 high) phenotype characterizes what is likely a slight majority of asthmatics
- This group is characterized by eosinophilia and is the best understood group in terms of pathogenesis

Th-1 vs Th-2

- The Th-1 (or Th-2 low) phenotype is quite poorly understood by comparison
- Characterized by a neutrophilic response and relative steroid insensitivity
- Typically older and obese



TH2 asthma consists of both early- and later-onset disease over a range of severities. It is likely that the majority of early-onset allergic asthma is mild but that an increasing complexity of immune processes leads to greater severity. Later-onset eosinophilic asthma without traditional allergic elements is more likely to be severe, whereas EIA is a milder form of TH2 asthma. Non-TH2 asthma includes very late–onset, obesity-associated asthma as well as smoking-related and neutrophilic asthma, and asthma in which affected individuals show little inflammation. The intensity of the colors represents the range of severity; the relative sizes of the subcircles suggest relative proportions of affected individuals.

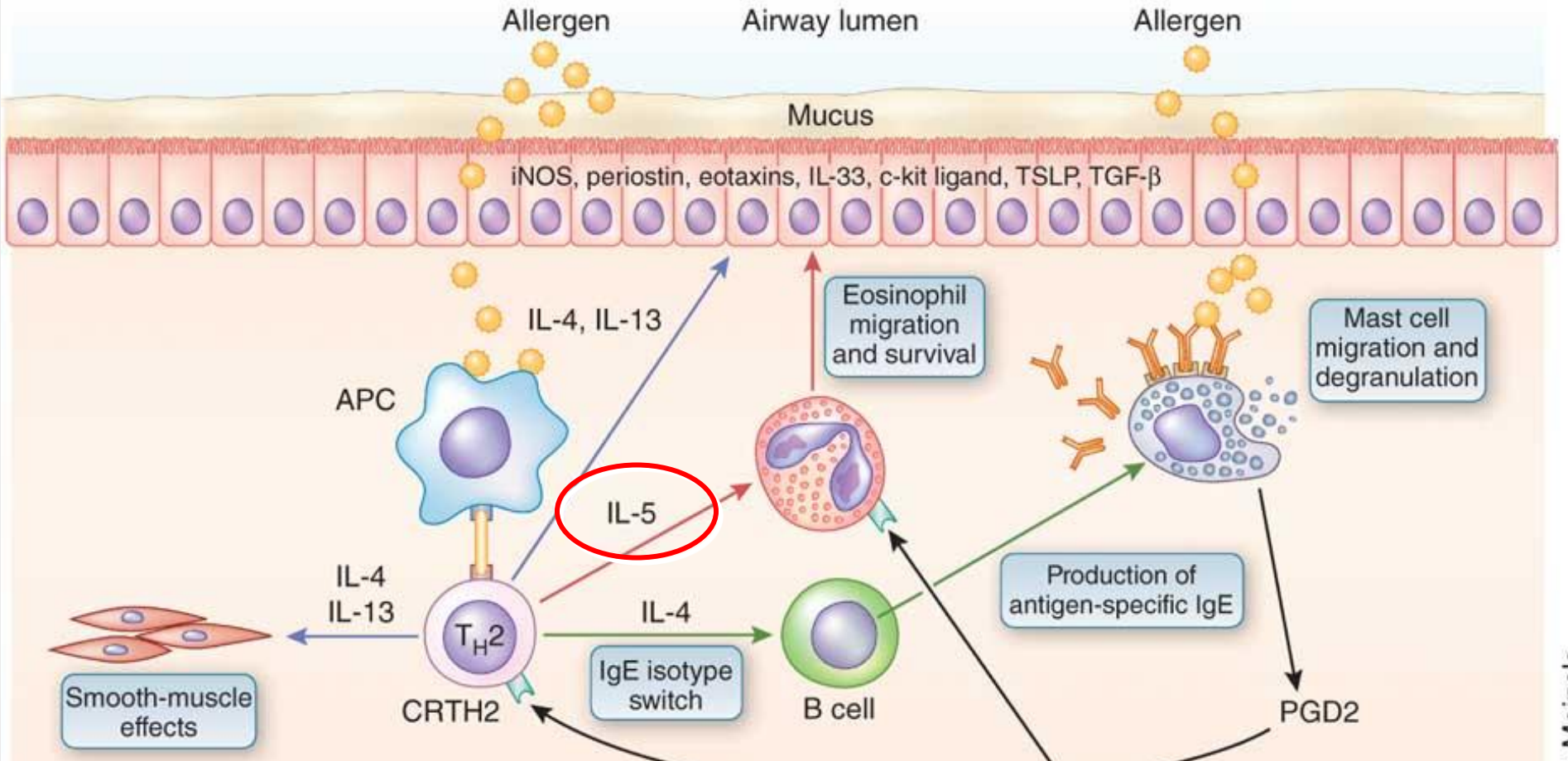
Wenzel, S. Nat Med 2012 May 4;18(5): 716-25. Used with permission.

New/emerging treatments

- 2 new approvals by the FDA in 2015 (mepolizumab, tiotropium)
- 1 expected in early 2016 (reslizumab)

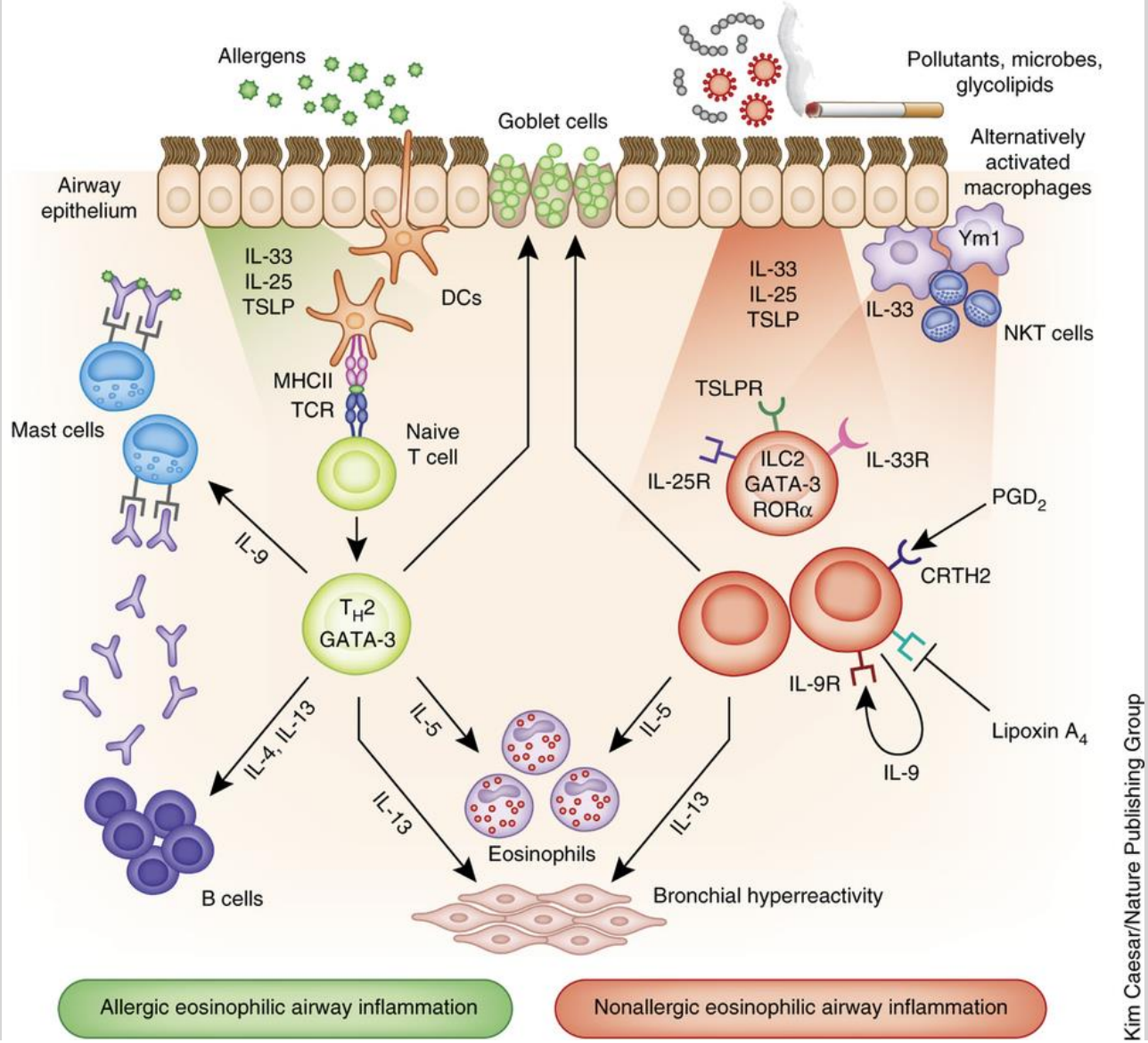
Mepolizumab (Nucala)

- Humanized monoclonal antibody against interleukin-5 (IL-5)
- IL-5 is felt to be the most specific cytokine in eosinophil regulatory pathways



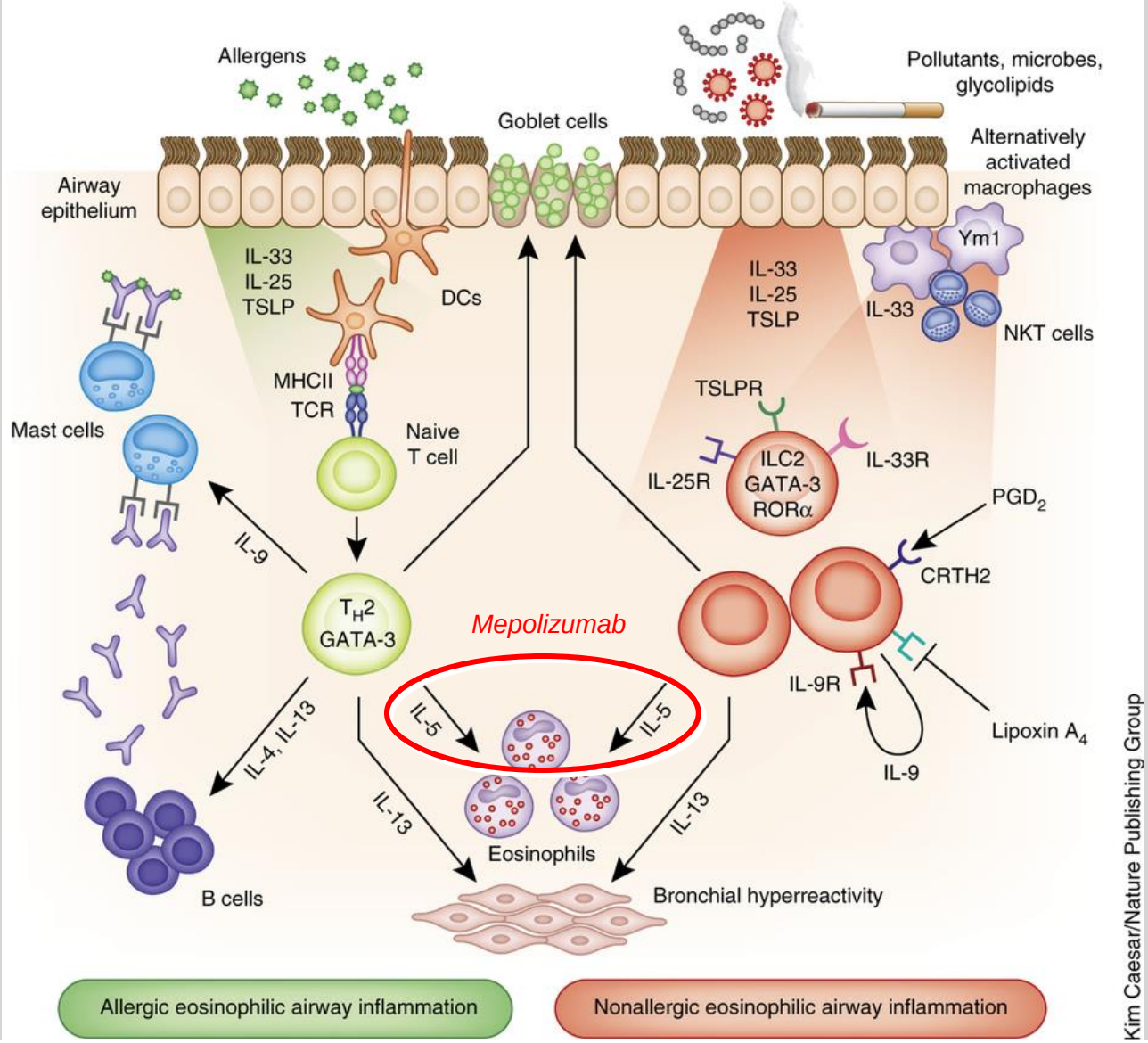
The pathway begins with the development of T_H2 cells and their production of the cytokines IL-4, IL-5 and IL-13. These cytokines stimulate allergic and eosinophilic inflammation as well as epithelial and smooth-muscle changes that contribute to asthma pathobiology. APC, antigen-presenting cell; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; iNOS, induced nitric oxide synthase; PGD2, prostaglandin D2; TSLP, thymic stromal lymphoprotein.

Wenzel, S. Nat Med 2012 May 4;18(5): 716-25. Used with permission.



In atopic asthma (left), eosinophilic airway inflammation and BHR are driven by adaptive T_H2 cells that are stimulated by DCs to produce IL-5, IL-13 and IL-4, the latter driving IgE synthesis. In nonatopic or intrinsic asthma (right), which is not dependent on adaptive immunity, ILC2 cells produce IL-5 and IL-13 and thus cause eosinophilia and BHR. As there is no specific allergen involved and as ILC2 cells produce little IL-4, there is no associated IgE response from B cells. Modified from ref. 185. MHCII, MHC class II; TSLPR, receptor for TSLP; NKT cells, natural killer T cells.

Lambrecht, et al. Nat Immunol 2015 Jan;16(1):45-56. Used with permission.



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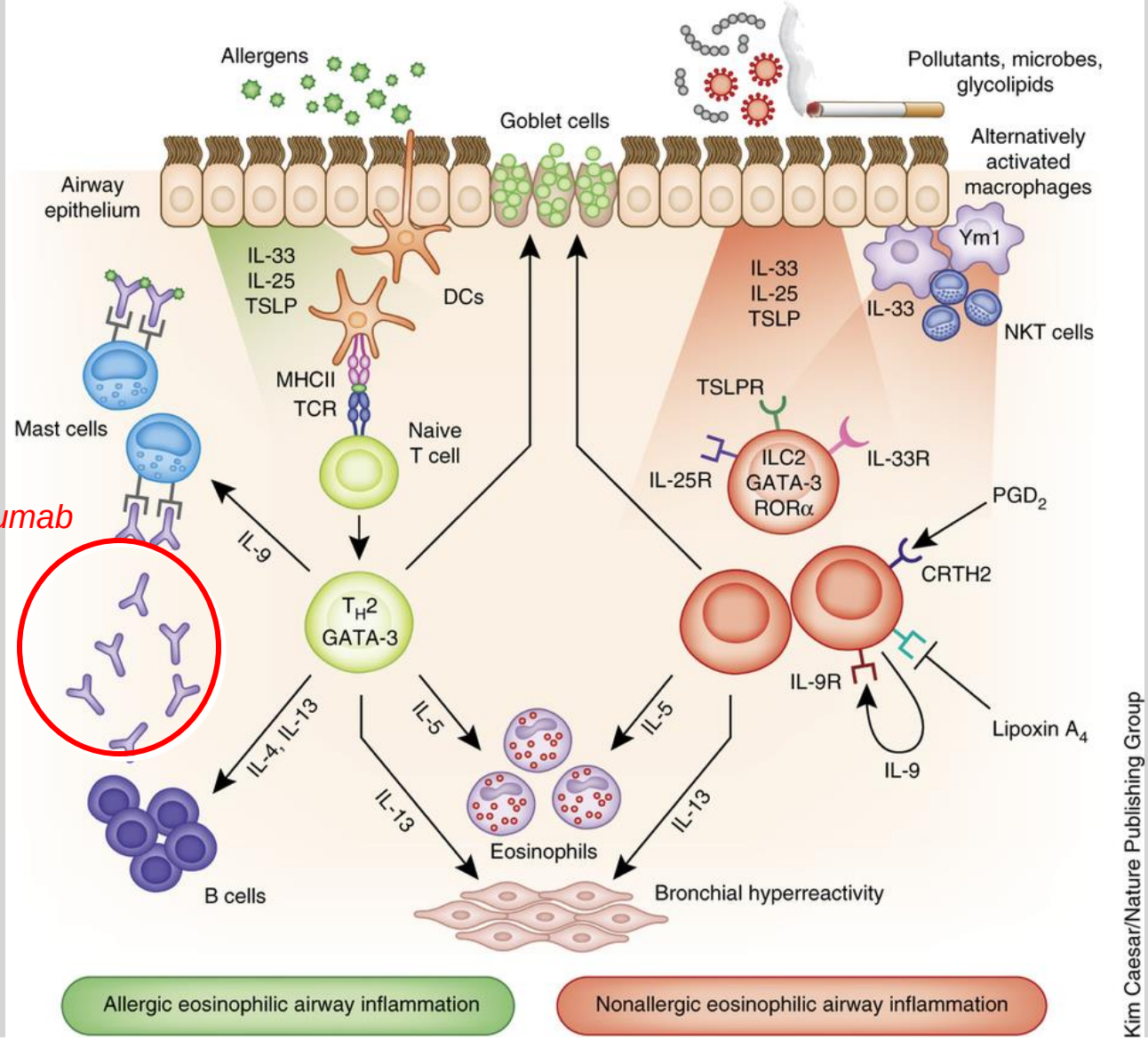
Omalizumab (Xolair)

- Applies to a more discrete patient population
- Anti-IgE mAb
- Criteria:
  - Skin or serum allergen testing positive for a year-round allergen such as dust mites, molds, animal dander, *et cetera*
  - An elevation in total serum IgE



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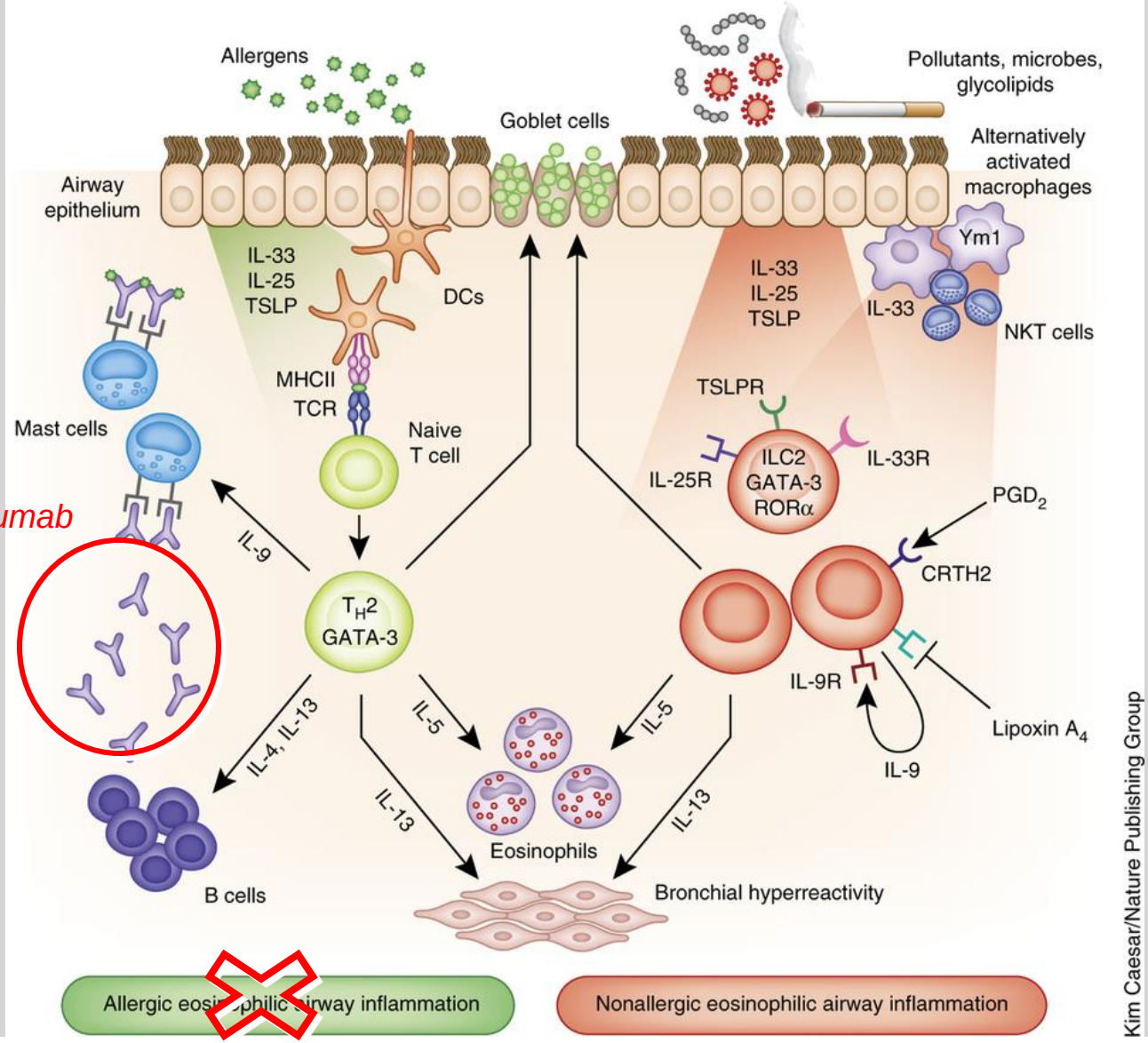

Omalizumab

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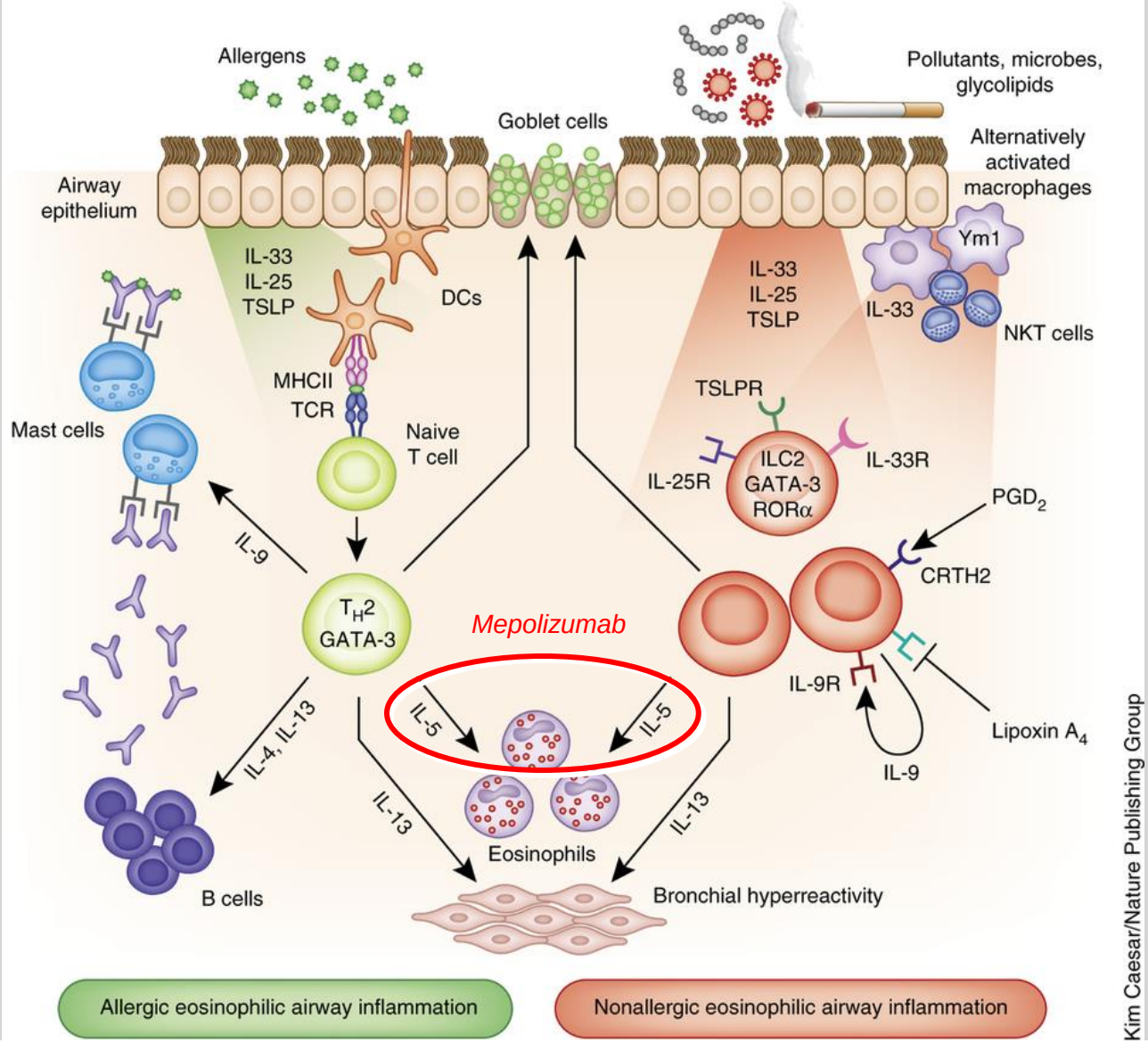

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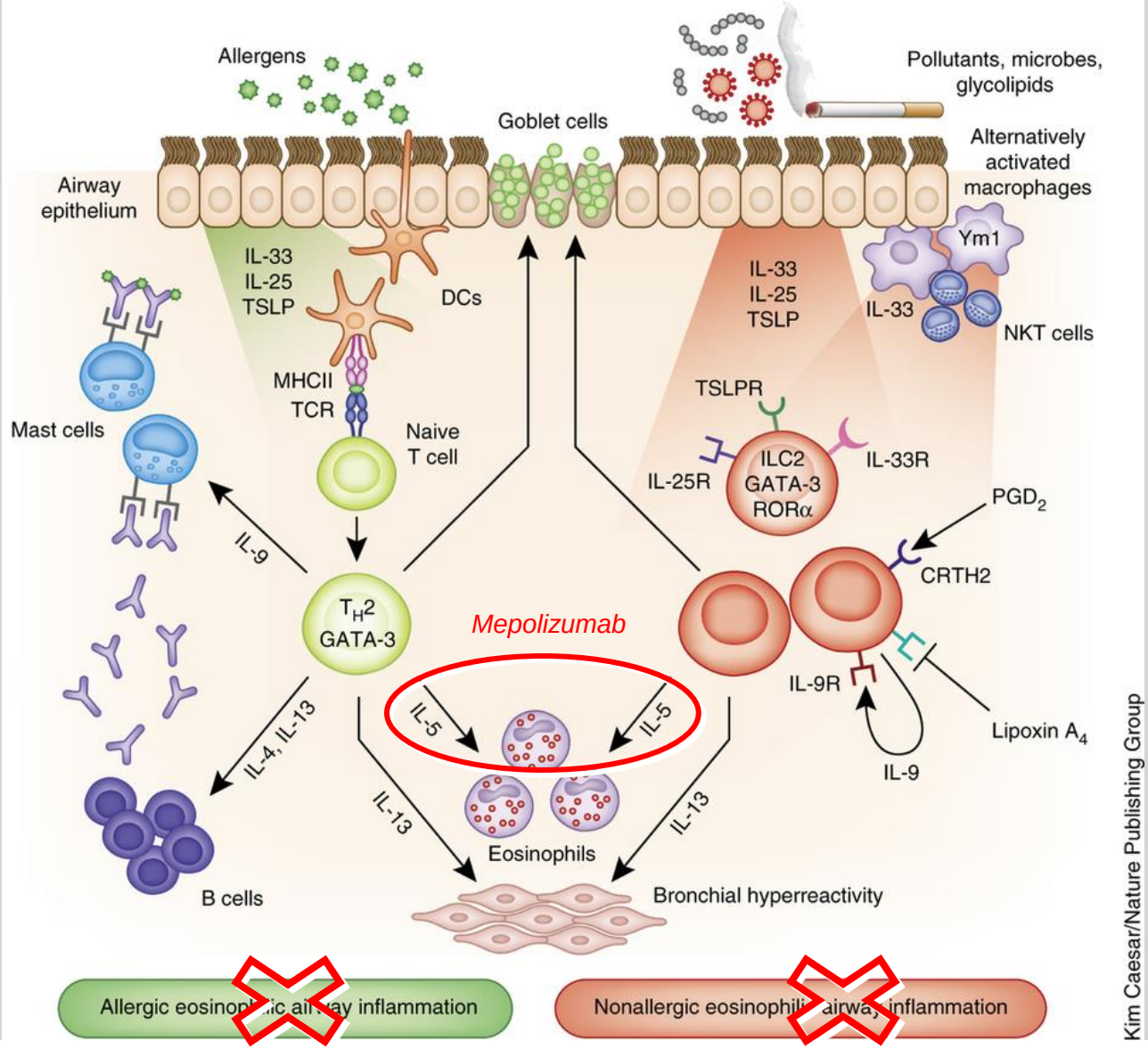

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Lambrecht, et al. Nat Immunol 2015 Jan;16(1):45-56. Used with permission.

MENSA trial

- 576 patients with history of frequent exacerbations (2+) randomized to mepolizumab or placebo
- Statistically significant:
  - Reduction in significant exacerbations (ED/hospitalization)
  - Increase in FEV1 (~100mL)
  - SGRQ and ACQ scores

Ortega, et al., N Engl J Med 2014 Sep 25;371(13):1198-207

SIRIUS trial

- 135 adults with severe eosinophilic asthma on oral glucocorticoids
- Compared to placebo:
  - Reduction in steroid dose (50%)
  - Reduced exacerbation rate (32%)
  - ACQ score improvement was both statistically and clinically significant

Bel, et al., N Engl J Med 2014 Sep 25;371(13):1189-97

Patient selection

- FDA indication: Patients with severe asthma aged 12 years and older and with an eosinophilic phenotype
- Dose: 100mg every 4 weeks by subcutaneous injection
- No adjustment for age, weight, or renal/hepatic disease

Omalizumab Doses (mgs) Administered SQ Injection Every 4 Weeks (≥12 Years of Age)

Baseline IgE IU/mL	Body Weight (kg)				
	30-60	>60-70	>70-80	>80-90	>90-150
30-100	150	150	150	150	300
>100-200	300	300	300	300	
>200-300	300	Administered Every 2 Weeks			

Omalizumab Doses (mgs) Administered SQ Injection Every 2 Weeks (≥12 Years of Age)

Baseline IgE IU/mL	Body Weight (kg)				
	30-60	>60-70	>70-80	>80-90	>90-150
>100-200	Administered Every 4 Weeks				225
>200-300		225	225	225	300
>300-400	225	225	300	300	
>400-500	300	300	375	375	
>500-600	300	375			
>600-700	375	Do Not Dose			

Eosinophilia

- The phase 2 mepolizumab trial (DREAM) used sputum eosinophilia as a criteria but as this test is not widely available it was dropped

Pavord et al., Lancet 2012 Aug 18;380(9842):651-9

Eosinophilia

- Defined in the MENSA/SIRIUS trials as either:
- Peripheral eosinophil count of 150/microliter or more during optimization phase
- 300/microliter or more in the prior 12 months

Reslizumab

- Another anti-IL-5 monoclonal antibody
- Similar indication for eosinophilic asthma
- Used a higher eosinophil cut off (400) based on a greater predictive value for sputum eosinophilia

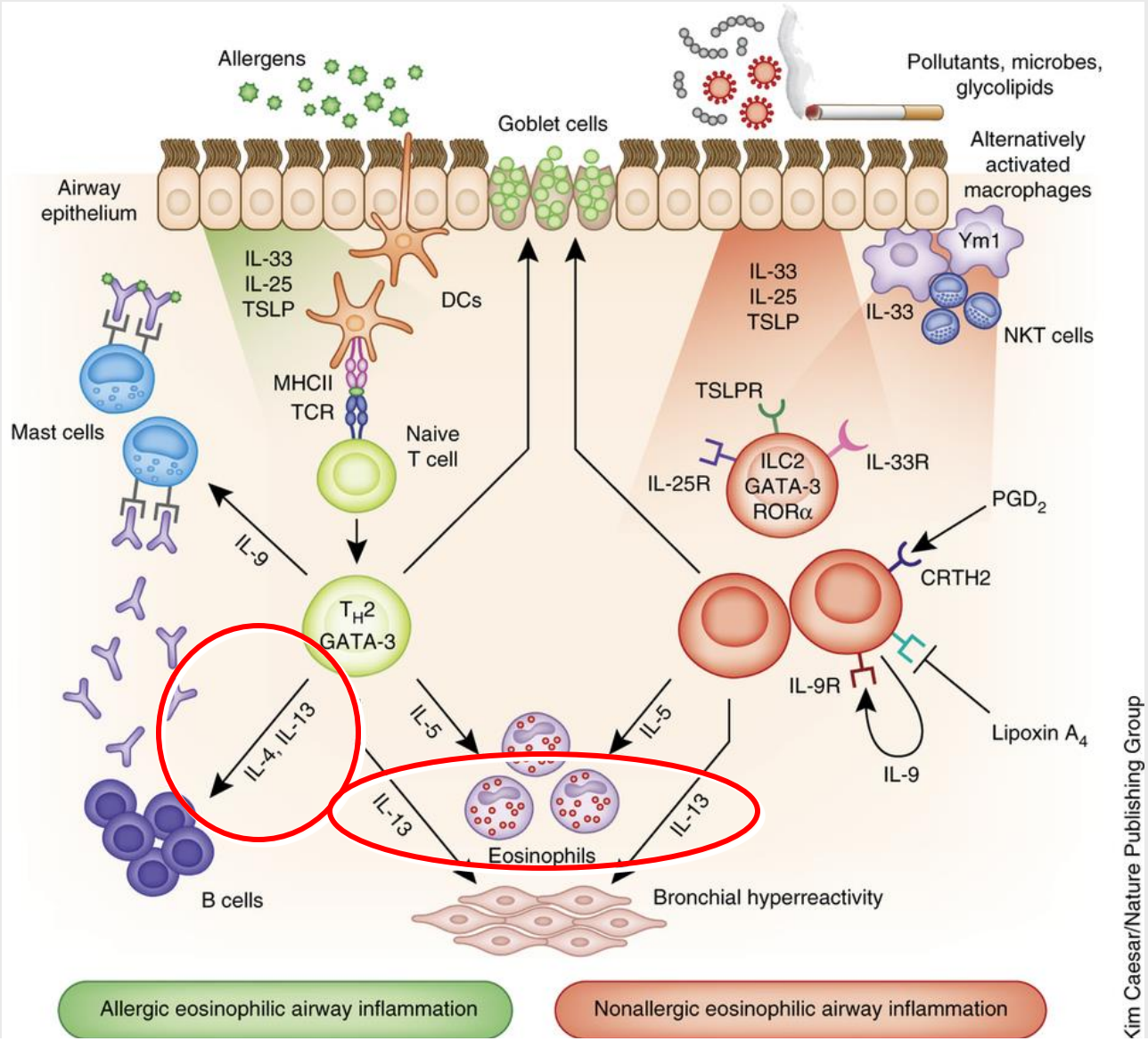
Castro, et al., Lancet Respir Med 2105 Feb. (3):355-66

Reslizumab

- One major difference with mepolizumab: requires IV infusion instead of sc injection
- Recommended for approval for age 18 and above by FDA advisory committee in Dec 2015
- Expected final decision in March

Other noteworthy mAb

- Benralizumab: Also targets IL-5
- Dupilumab: Directed against the IL-4/IL-13 “complex”
  - Designated as a breakthrough drug by the FDA
  - Effective for eczema/atopic dermatitis as well
- Both entering phase III trials



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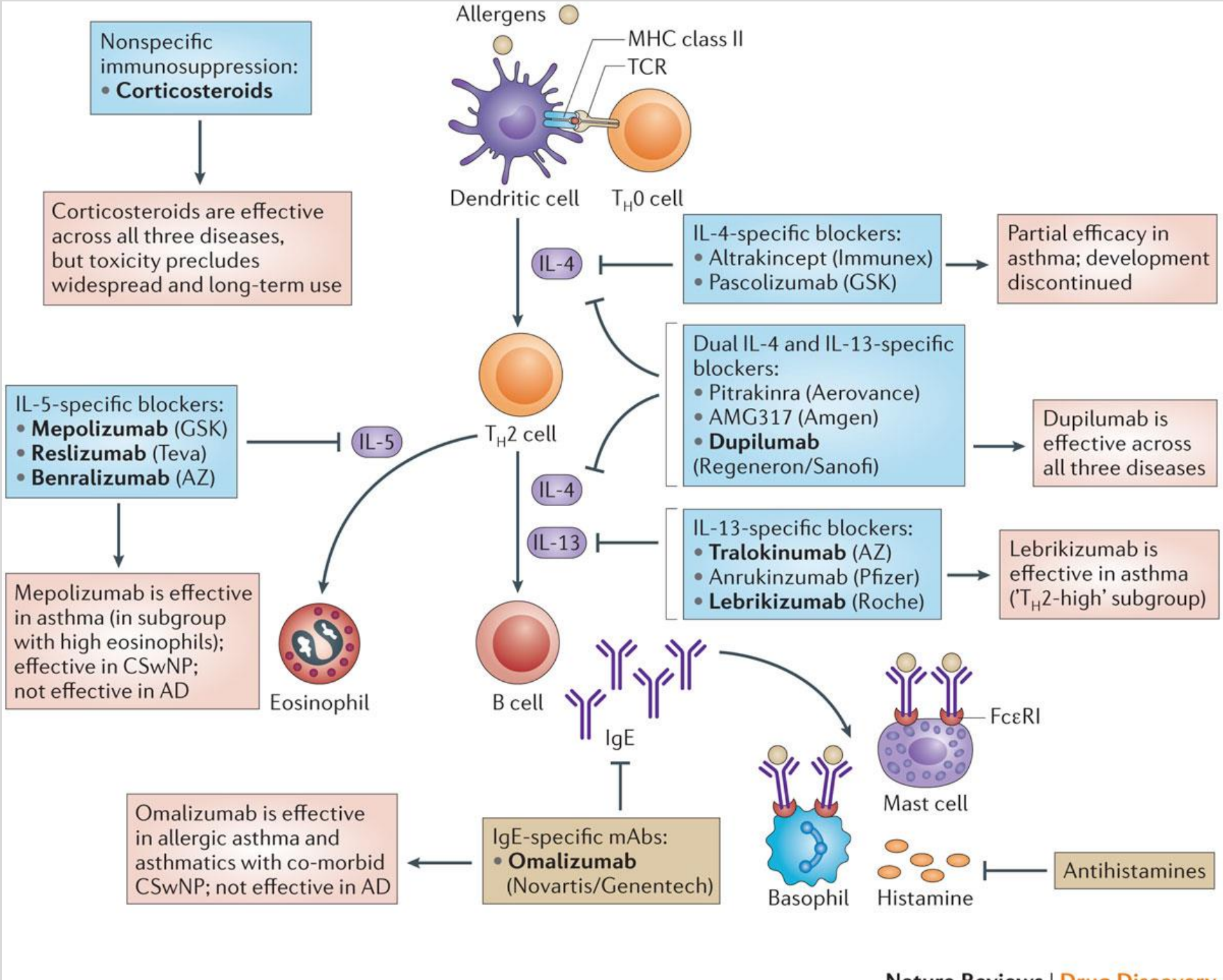
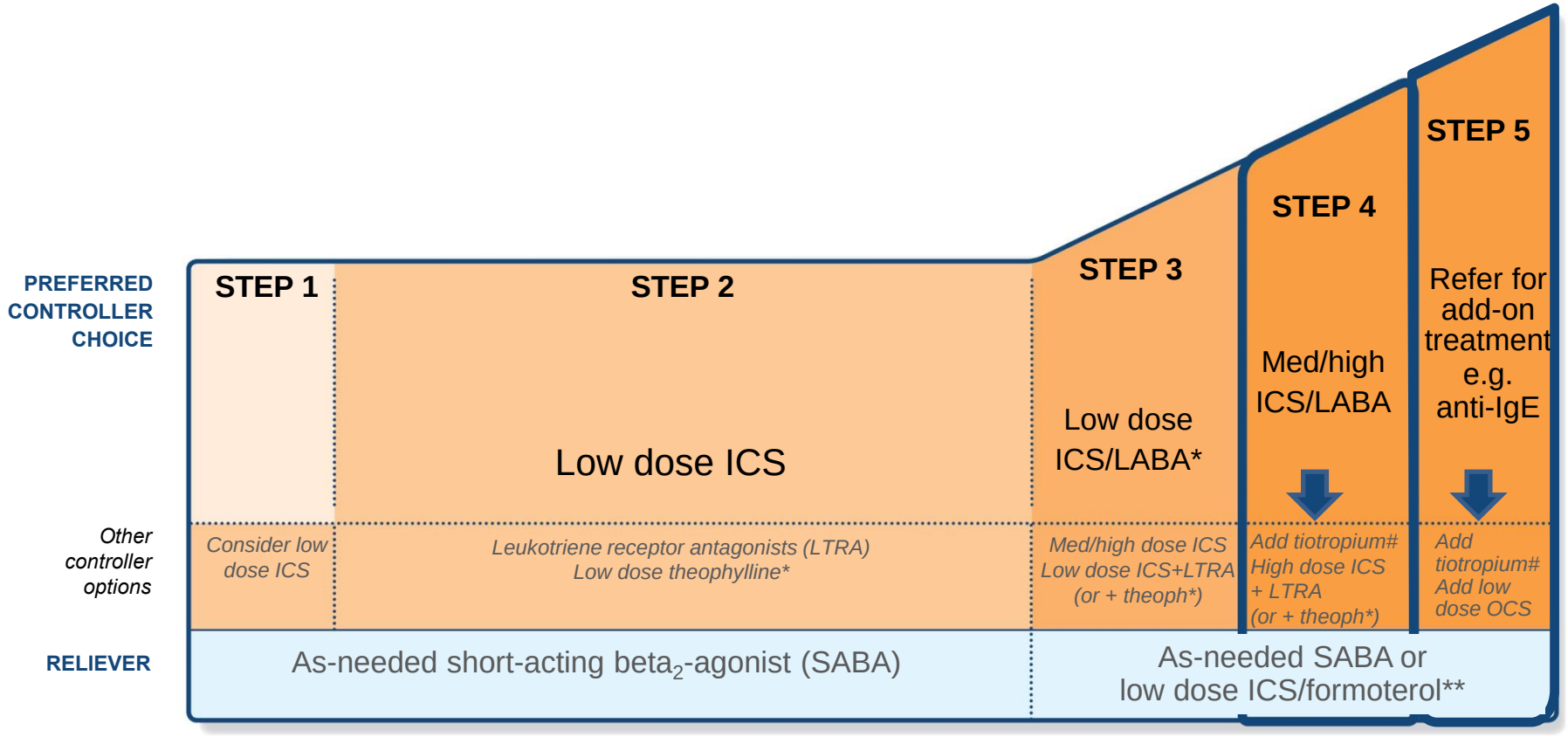

Nonspecific immunosuppression:
• Corticosteroids
Corticosteroids are effective across all three diseases, but toxicity precludes widespread and long-term use
Allergens
MHC class II
TCR
Dendritic cell
T_H0 cell
IL-4
IL-4-specific blockers:
• Altrakincept (Immunex)
• Pascolizumab (GSK)
Partial efficacy in asthma; development discontinued
Dual IL-4 and IL-13-specific blockers:
• Pitrakinra (Aerovance)
• AMG317 (Amgen)
• Dupilumab (Regeneron/Sanofi)
Dupilumab is effective across all three diseases
IL-5-specific blockers:
• Mepolizumab (GSK)
• Reslizumab (Teva)
• Benralizumab (AZ)
IL-5
T_H2 cell
IL-4
IL-13
IL-13-specific blockers:
• Tralokinumab (AZ)
• Anrukinzumab (Pfizer)
• Lebrikizumab (Roche)
Lebrikizumab is effective in asthma ('T_H2-high' subgroup)
Mepolizumab is effective in asthma (in subgroup with high eosinophils); effective in CSwNP; not effective in AD
Eosinophil
B cell
IgE
FcεRI
Mast cell
Basophil
Histamine
Antihistamines
Omalizumab is effective in allergic asthma and asthmatics with co-morbid CSwNP; not effective in AD
IgE-specific mAbs:
• Omalizumab (Novartis/Genentech)

Tiotropium (Spiriva)

- Long-acting muscarinic antagonist (LAMA)
- In use for over decade as one of the mainstays of COPD therapy
- Asthma recently approved as a second indication by the FDA
- Included in the most recent (2015) GINA guidelines as a possible add-on at step 4

GINA 2015 – changes to Steps 4 and 5



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.

Tiotropium (Spiriva)

- TALC trial was a noninferiority study with 3 crossover arms (210 patients on low-dose beclomethasone at baseline)
  - Double dose of ICS
  - Add LABA to low-dose ICS
  - Add tiotropium to low-dose ICS

Peters, et al. N Engl J Med 2010; 363:1715-1726

TALC trial

- Tiotropium was at least non-inferior to adding a LABA to low-dose ICS in all outcomes
- Tiotropium was superior to doubling the dose of ICS in almost all of the outcomes (so is LABA)
- So: Tiotropium = LABA

Peters, et al. N Engl J Med 2010; 363:1715-1726

PrimoTinA asthma 1&2

- Addition of tiotropium to ICS+LABA increased time to first exacerbation (primary e.p.) and also pre-bronchodilator FEV1 compared to placebo

Kerstjens, et. al. N Engl J Med 2012; 367:1198-1207

BELT trial

- Previously suggested that LABAs were less effective and possibly deleterious in African Americans
- Pragmatic trial of 1070 AA adults randomized to the addition of LABA or tiotropium to their existing dose of ICS

Wechsler, et al., JAMA 2015; 314(16):1720-1730

BELT trial

- No difference in time to first exacerbation, FEV1, or ACQ score between groups
- Not a prespecified outcome but hospitalizations were more frequent in the tiotropium group (p=0.02)

Wechsler, et al., JAMA 2015; 314(16):1720-1730

Bronchial thermoplasty

- Bronchoscopic procedure in which bronchial smooth muscle mass is reduced by (essentially) RF ablation
- Series of 3 procedures
- Not covered by most insurances
- Carries an increased risk of asthma exacerbation immediately after the procedure

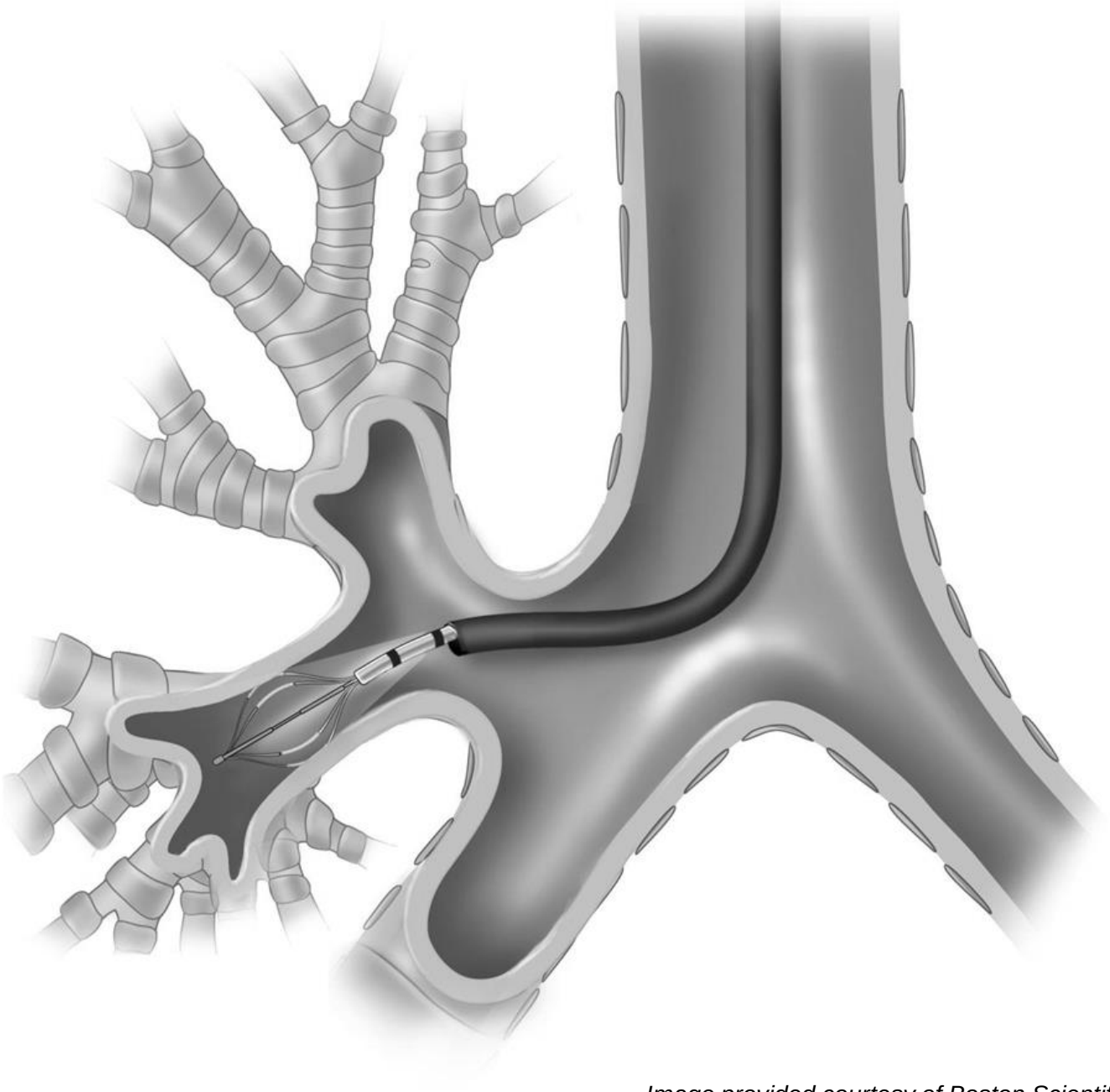
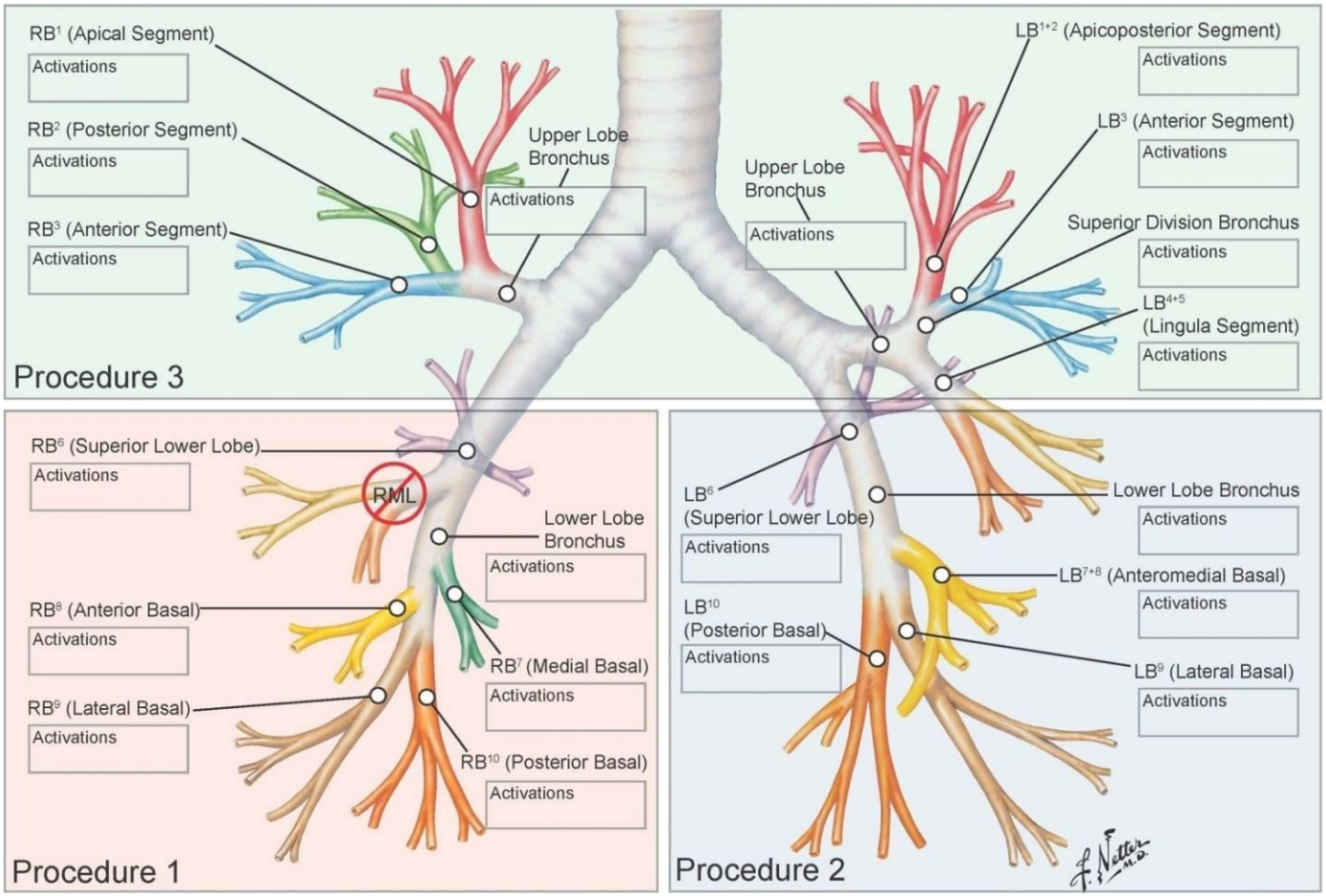


Image provided courtesy of Boston Scientific corporation

BT Completed in 3 Outpatient Procedures



BT is performed by a BT-certified pulmonologist in 3 outpatient visits, typically scheduled 3 weeks apart.

Image provided courtesy of Boston Scientific corporation

Bronchial thermoplasty

- The role of BT in asthma therapy is controversial
- Hotly debated in the literature as well as international conferences

AIR2 trial

- 288 patients randomized to thermoplasty or a sham procedure (control group)
- Main endpoint: AQLQ scores
  - Statistically significant increase compared to sham procedure
  - Not clinically significant (0.19)

Castro, et al., Am J Respir Crit Care Med 2010 Jan 15;181(2):116-24

AIR2 trial

- Both patient groups had a much larger improvement from baseline AQLQ (1.16 in control group)
- No difference in prespecified secondary endpoints (PEF, FEV1, rescue inhaler use)

Castro, et al., Am J Respir Crit Care Med 2010 Jan 15;181(2):116-24

AIR2 trial

- Significantly fewer ED visits and severe exacerbations were seen but were not part of the study design
- This is one of the major sources of contention based on patient selection criteria, along with a lack of follow up of the control group

Castro, et al., Am J Respir Crit Care Med 2010 Jan 15;181(2):116-24

AIR2 trial

- The size of the increase in AQLQ scores from baseline were also more than 5x higher than the difference between groups
- This leads many to question whether simply educating and improving compliance is more effective than the procedure

Castro, et al., Am J Respir Crit Care Med 2010 Jan 15;181(2):116-24

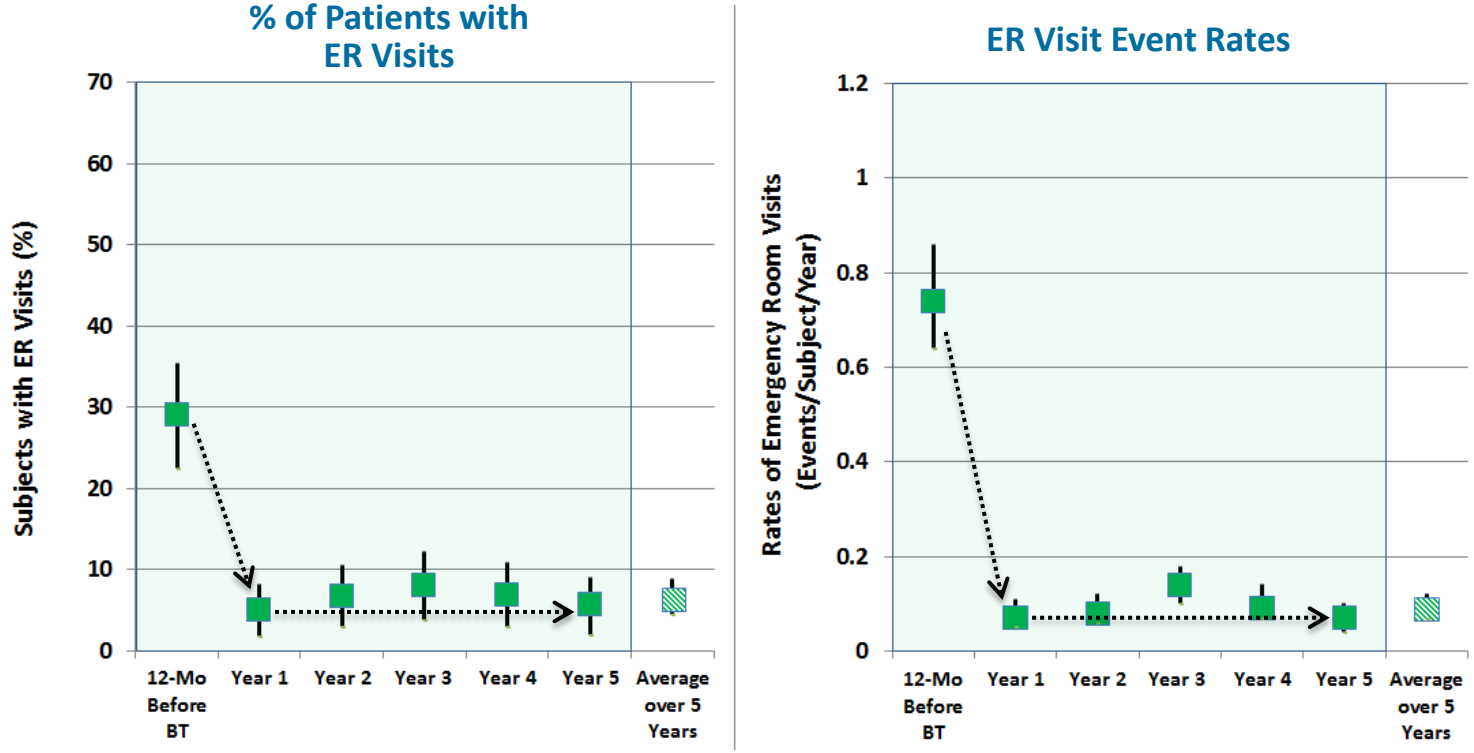
AIR2: 5 year follow up data

- 82% of the original treated patients (no control patients) completed 5 years of follow up
- Designed as a non-inferiority trial comparing each subsequent year of follow up to the first year after treatment

Wechsler, et al., J Allergy Clin Immunol 2013 Dec;132(6): 1295-302

Reduction in ER Visits Maintained out to 5 years[1]

- The reduction in ER visits for respiratory symptoms at Year 1 was maintained out to at least 5 years.



Compared with 1 year prior to BT treatment (baseline):

- **78%** average decrease in percentage of patients having ER visits
- **88%** average decrease in ER visit event rates

1. Wechsler ME, et al. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302 Slide courtesy of Boston Scientific corporation.

AIR2: 5 year follow up data

- Demonstrates persistence of benefit for 5 years post procedure
- Importantly, there was no decline in FEV1 or radiographic evidence of structural changes of the lung on HRCT

Wechsler, et al., J Allergy Clin Immunol 2013 Dec;132(6): 1295-302

Bronchial thermoplasty

- FDA labeling is for “severe persistent asthma inadequately controlled on ICS + LABA”
- Many interventionalists use the AIR2 study inclusion criteria

Simplified AIR2 criteria

- High dose ICS + LABA
- Oral steroids OK if stable dose
- MTX and others excluded
- Less than 3 hospitalizations or 4 pulses of oral steroids in last year
- Stable meds for 4+ weeks
- Nonsmoker (less than 10 pack-year)

Castro, et al. Amer J Respir Crit Care Med 2010 Jan 15;181(2):116-24

Azithromycin

- Aka statins for pulmonologists
- Little quality data concerning use for the treatment of asthma
- One recent RCT of note

AZISAST trial

- Randomized 109 patients on high-dose ICS/LABA (step 4 or 5 per GINA guidelines) to maintenance therapy with azithromycin or placebo
- Dose: 250mg PO 3x/week

Brusselle, et al., Thorax 2013; 88:322-329

AZISAST trial

- Overall, there was no benefit seen with azithromycin therapy with regards to any of the outcomes tested
- However, subgroup analysis showed that patients with non-eosinophilic asthma had fewer exacerbations

Brusselle, et al., Thorax 2013; 88:322-329

AZISAST trial

- Non-eosinophilic asthma was defined as a peripheral eosinophil count less than 200 cells/microliter
- More data is needed but this result suggests azithromycin may be an effective option for the neutrophilic/Th-1 phenotype (COPD is also neutrophilic)

Brusselle, et al., Thorax 2013; 88:322-329

Thank you

- Questions?