Asthma Treatment

Standard Therapy, Biologics, Bronchial Thermoplasty, and Beyond

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Asthma Definition

- No clear and unified definition exists

- Chronic inflammatory disorder of the airways
- Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells play a role
- In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning

Pathophysiology – brief primer

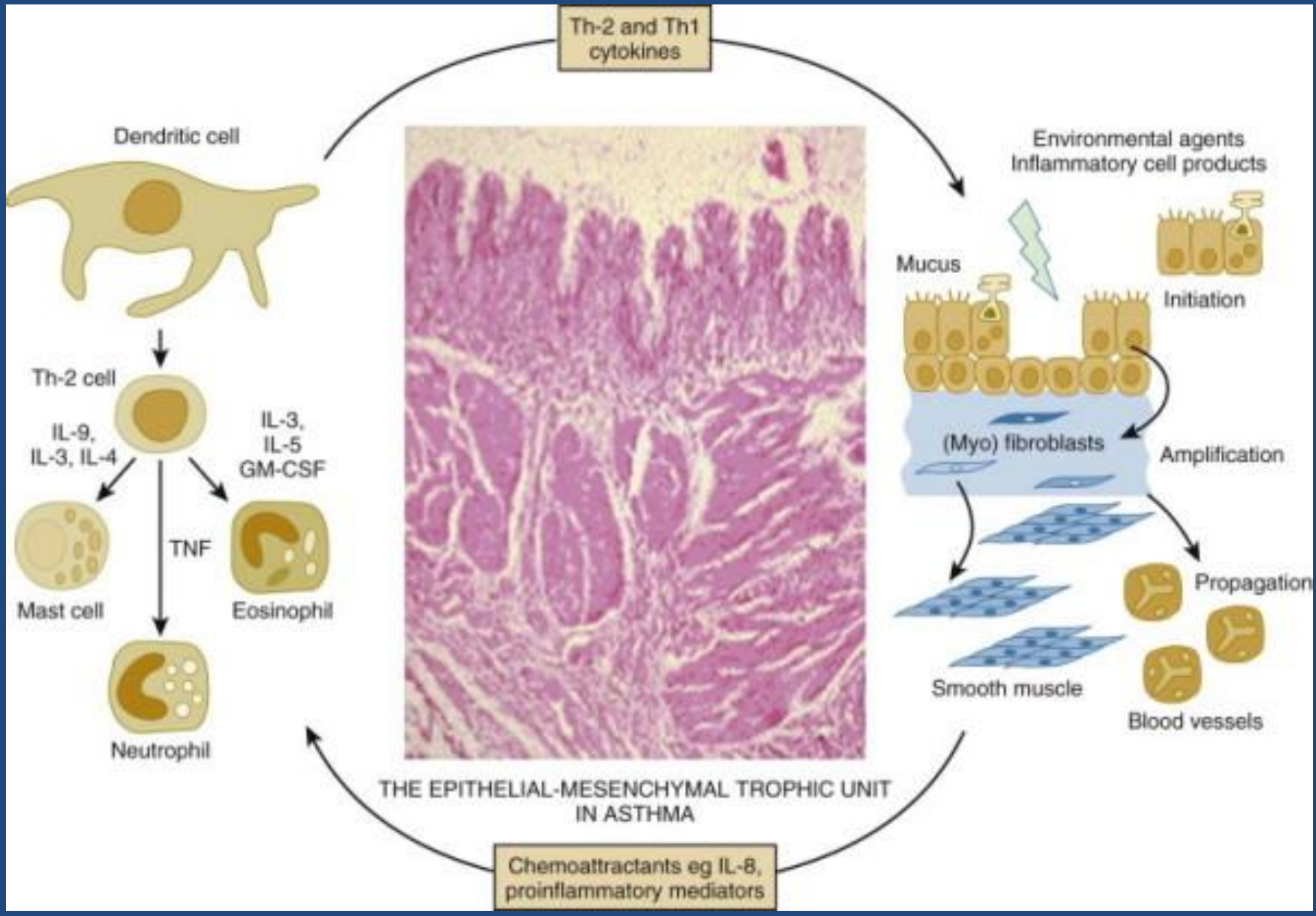
- Asthma is multifactorial in origin
- Inflammation is the cornerstone of pathology
  - Immune system
  - Cytokines
  - Epithelium

Risk factors

- Hygiene hypothesis
- Atopy
- Infections (RSV, rhinovirus)
- Obesity (adipokines, TNF-α, IL-6, leptin)
- Tobacco use
- Genetics
- Environmental exposure

Airway remodeling

- Structural alteration of the airway
- Feature of chronic asthma
- Pathophysiology
  - Deposition of collagen in sub-epithelium
  - Airway smooth muscle (ASM) hyperplasia
  - Proliferation of submucosal glands
- Leads to permanent airflow limitation


Th-2 and Th1 cytokines
Dendritic cell
Th-2 cell
IL-9, IL-3, IL-4
IL-3, IL-5 GM-CSF
TNF
Mast cell
Eosinophil
Neutrophil
Environmental agents
Inflammatory cell products
Mucus
Initiation
(Myo) fibroblasts
Amplification
Propagation
Smooth muscle
Blood vessels
THE EPITHELIAL-MESENCHYMAL TROPHIC UNIT IN ASTHMA
Chemoattractants eg IL-8, proinflammatory mediators

Diagnosis of asthma

- History
  - Personal (wheezing, cough, dyspnea)
  - Family history of asthma
  - Presence of triggers
    - Environmental
    - Work related

Diagnosis of asthma

- Spirometry
  - FEV1 – forced expiratory volume during 1st second
  - Most standardized test of airflow obstruction
    - Objective
    - Non-patient-reported (if good effort)
  - Increase of 12% AND 200cc after bronchodilator
    - Indicates reversible airflow obstruction
    - Suggestive **but not diagnostic** of asthma

Diagnosis of asthma

- Accepted approach when evidence VERY convincing
  - History
  - Response to bronchodilator on PFTs
- Bronchoprovocation challenge can be used when diagnosis unclear

Airway hyperresponsiveness

- AHR to environmental stimuli = hallmark of asthma
- Patients who have normal PFTs but are suspected of asthma will develop bronchoconstriction in response to a stimulus (provocative challenge)

Provocative challenge

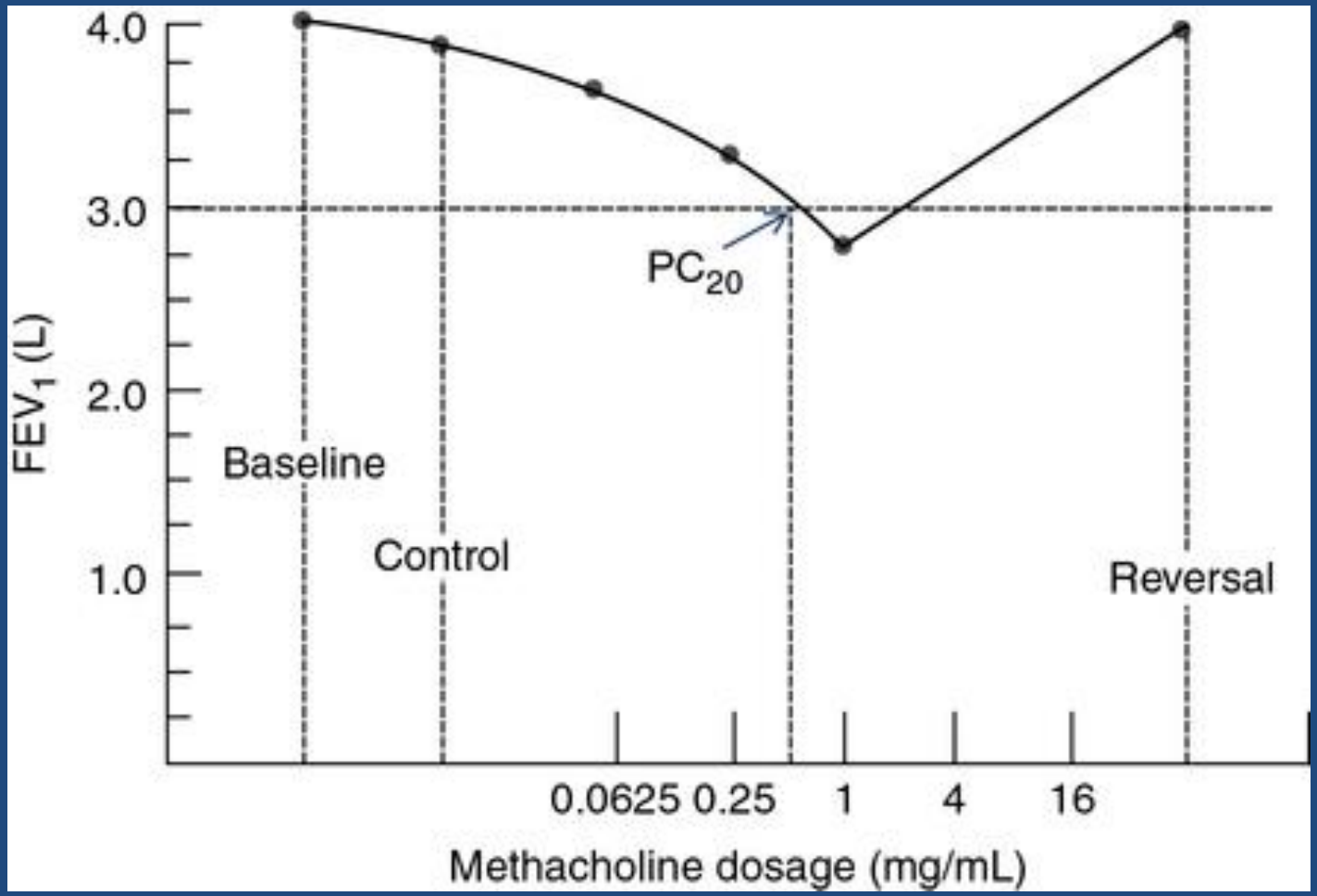
- Direct stimulation of the airways with an agent that is known to provoke bronchoconstriction via direct action on airway smooth muscles
- Agents
  - Methacholine
  - Mannitol
  - Histamine
  - Adenosine

Methacholine

- A longer-acting derivative of acetylcholine
- Standard agent of choice in the US and Europe
  - ATS (American Thoracic Society)
  - ERS (European Respiratory Society)

Methacholine inhalation challenge

- Inhalation solutions from 0.03mg/ml to 16 mg/ml
- Test :
  - Diluent inhalated
  - FEV1 measured x 2 at 30 and 90 seconds
  - Increased concentration is delivered
- **PC20** : concentration at which FEV1 decreases by 20%
- Positive test = PC20 of 8 mg/ml or less
- Negative test = PC20 of 16 mg/ml
  - Convincingly rules out asthma
- PC20 concentration is associated with asthma severity


4.0
3.0
2.0
1.0
FEV1 (L)
PC20
Baseline
Control
Reversal
0.0625 0.25 1 4 16
Methacholine dosage (mg/mL)

Severity of asthma

- Mild intermittent
- Mild Persistent
- Moderate Persistent
- Severe Persistent

Mild intermittent asthma

- Normal spirometry
- Symptoms < 2 / week
- Night symptoms < 2 / month
- Albuterol use < 2 / week
- 0-1 asthma exacerbations / year
  - Requiring prednisone

Persistent asthma

- 2 or more exacerbations / year
  - Requiring prednisone
  - ER visit or hospitalization
  - Missed school / work

Mild persistent asthma

- Normal spirometry
- Symptoms > 2 / week but not every day
- Night symptoms 3 - 4 / month
- Albuterol use > 2 / week but not every day
- >2 asthma exacerbations / year

Moderate persistent asthma

- Mild drop in FEV1 (still more than 60% predicted)
- Symptoms : daily
- Night symptoms > 1 / week but not every night
- Albuterol use : daily
- >2 asthma exacerbations / year

Severe persistent asthma

- FEV1 moderately reduced (<60% predicted)
- Symptoms : many times / day
- Night symptoms : nightly
- Albuterol use : many times / day
- >2 asthma exacerbations / year

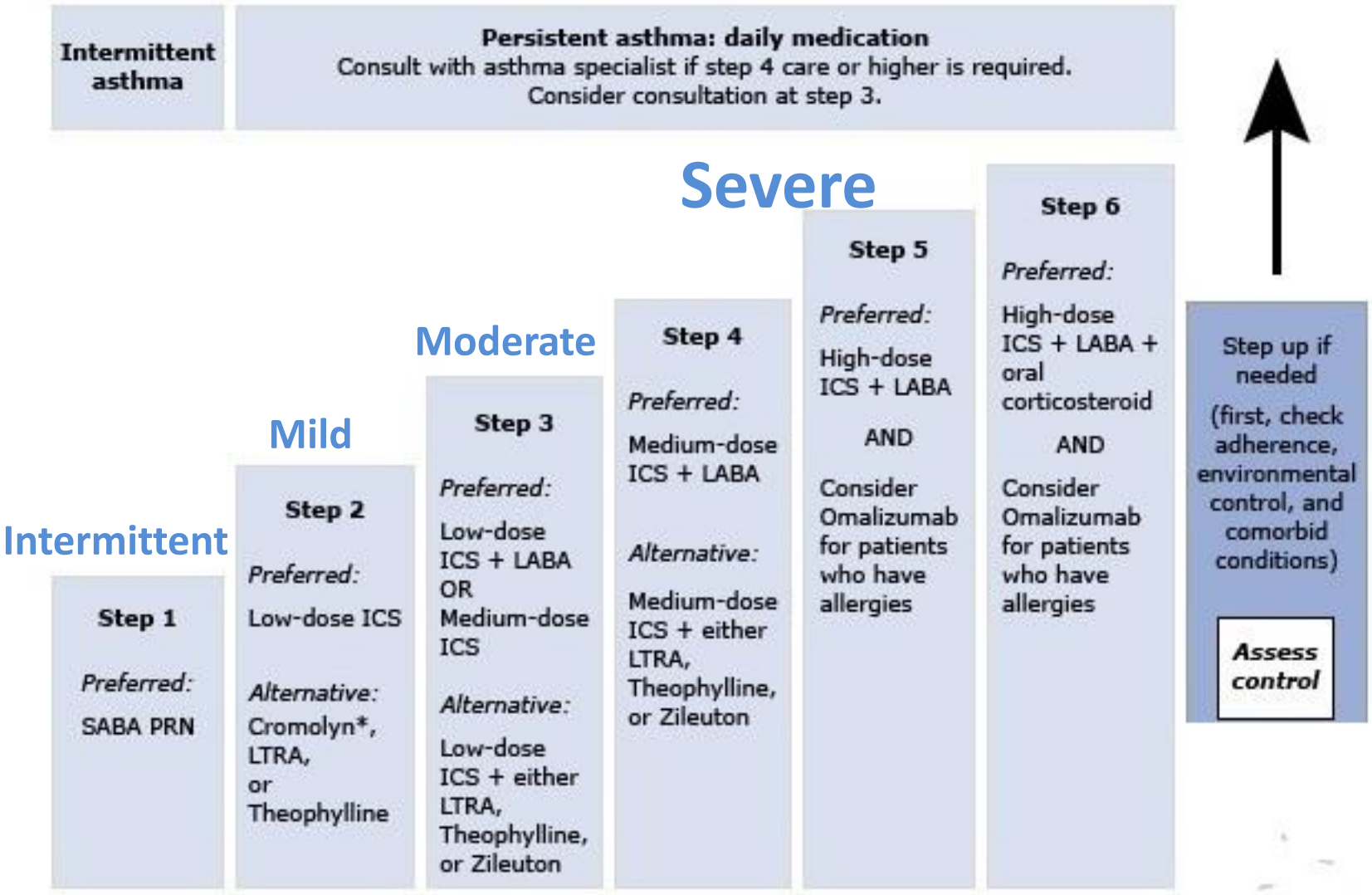
Standard treatment of asthma

- Depends on asthma severity
- Stepwise approach
  - Short acting broncodilator (SABA)
  - Inhaled corticosteroid (ICS)
  - Long acting bronchodilator (LABA)
  - Leukotriene antagonist (LTRA)
- Systemic glucocorticoid during exacerbations
  - Prednisone 40mg x 5 days
  - No need for taper

Standard treatment of asthma

- Most asthmatics can be well controlled on SABA + ICS
- Most asthmatics are unnecessarily on SABA + ICS/LABA

Stepwise approach for managing asthma in youths greater than or equal to 12 years of age and adults



- NHLBI 2007

Standard treatment of asthma

- Once patient is treated, their asthma severity commonly decreases

Novel therapies

- Bronchial thermoplasty
- Biologics
- Future

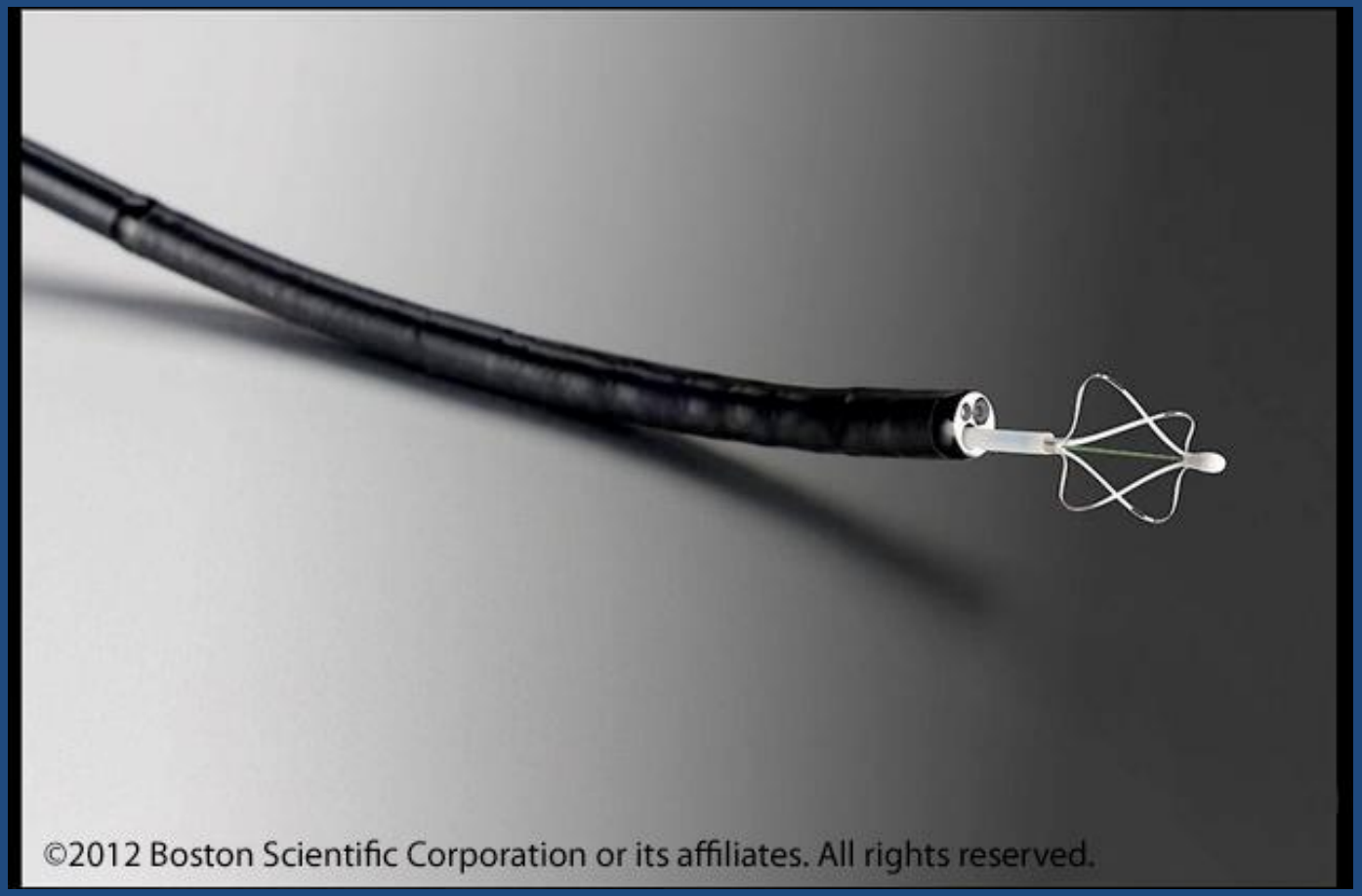
Bronchial thermoplasty

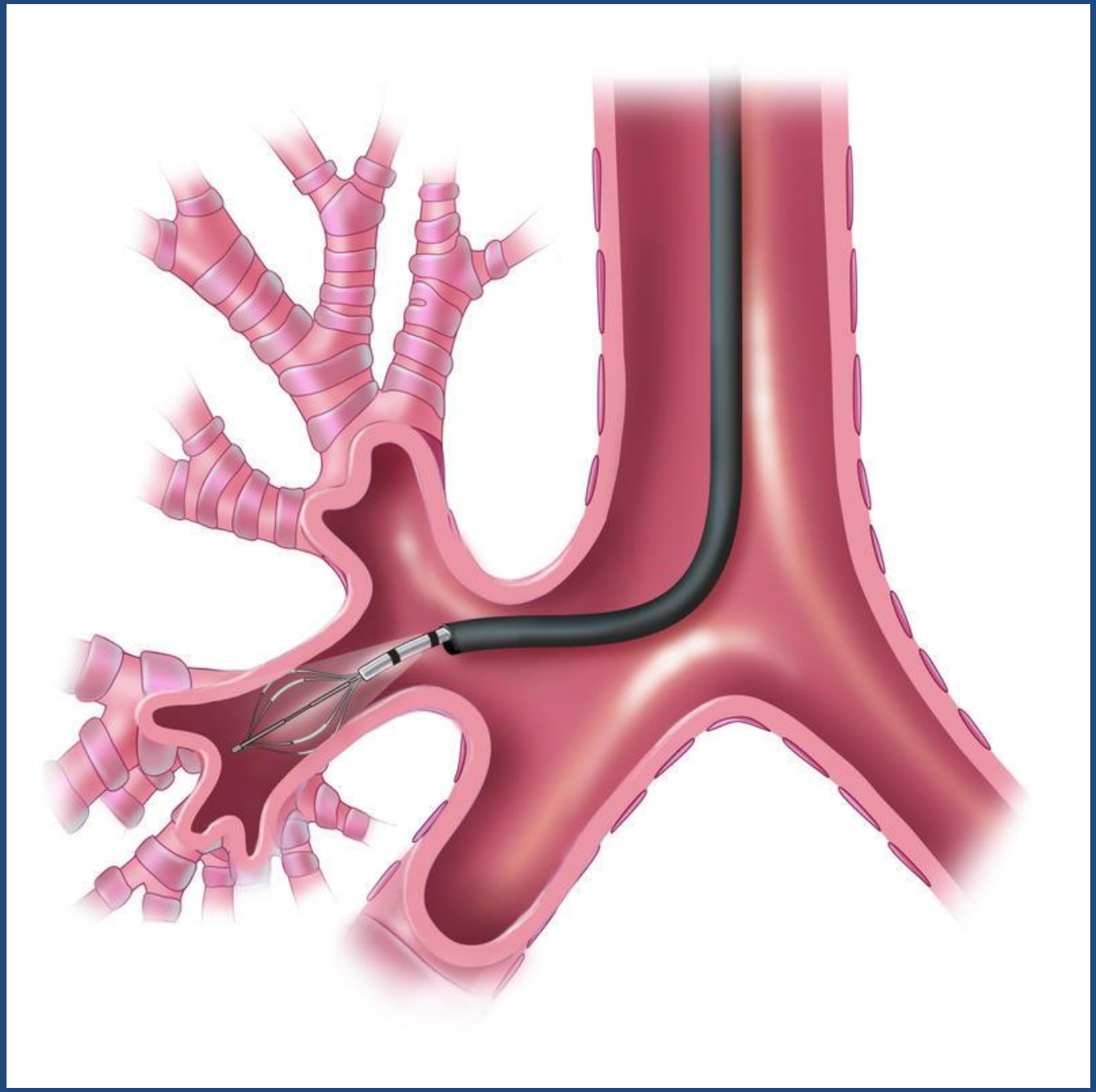
- Asthma is a disease of inflammation first and foremost
- Asthma exacerbation causes contraction of airway smooth muscles (ASM)
  - Airways narrow → Increased airflow obstruction

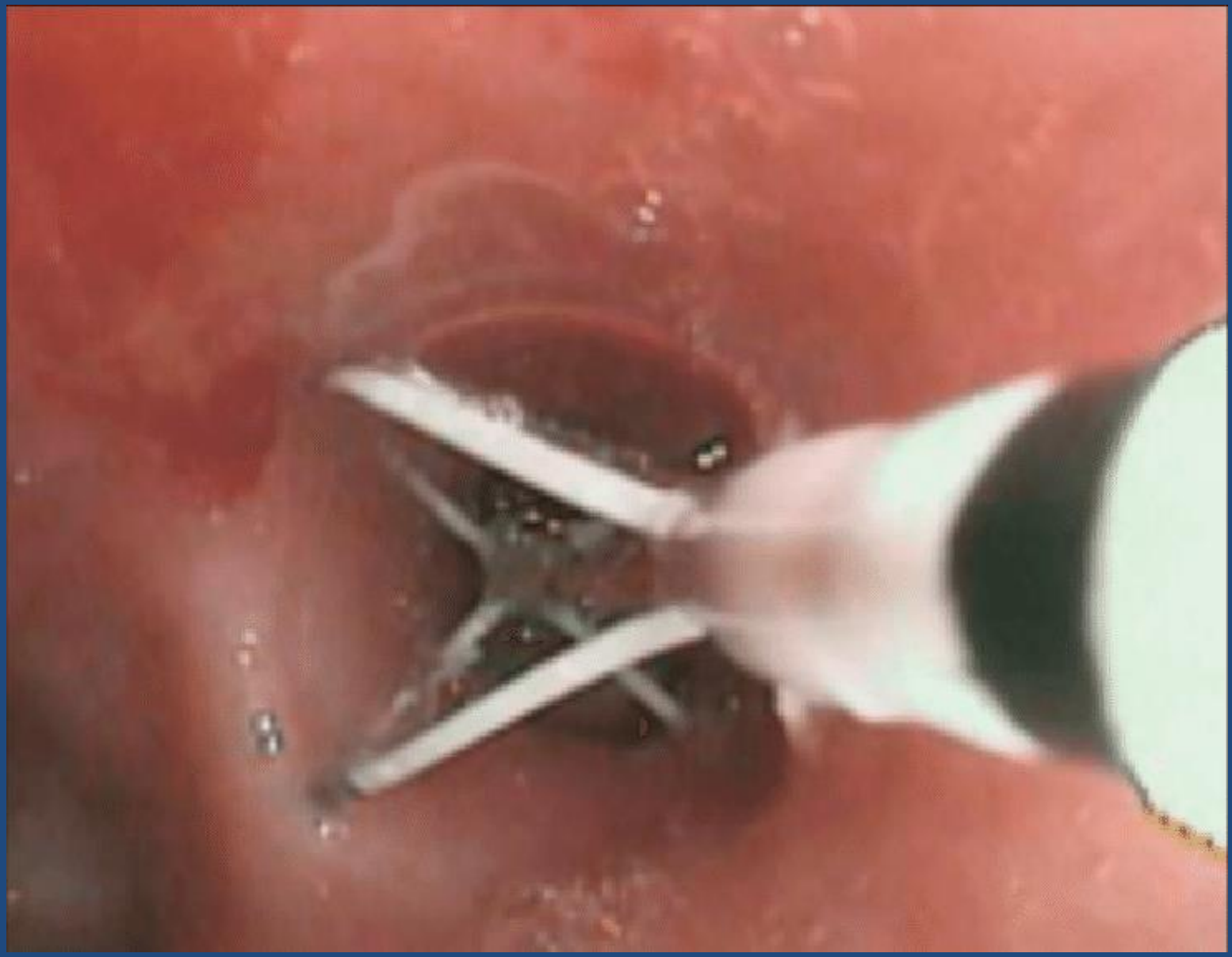
Bronchial thermoplasty

- BT aims at disrupting ASM
  - Radiofrequency energy is delivered into the wall of the airway, heating it up
  - Cartilage has minimal water content – little effect
  - Airway smooth muscle proteins coagulate
    - Disruption of sarcomeres
    - Impeded ability to contract
    - Thinning of muscle over time

Bronchial Thermoplasty

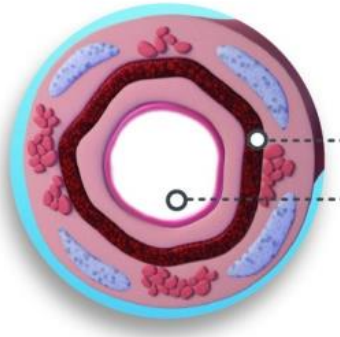






Airways Before and After Bronchial Thermoplasty Treatment

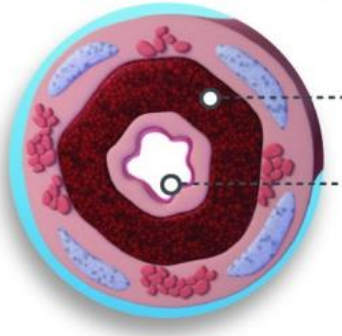
Airway of Person without Asthma



Normal band of airway muscle

Open airway where air travels

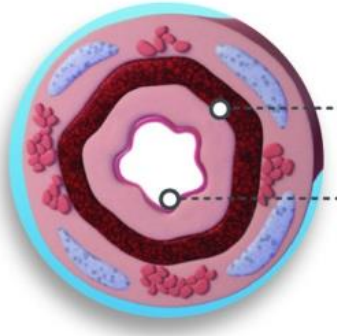
Airway of Person with Severe Asthma



More airway muscle causes airway to narrow

This is where the device applies heat to the airway wall during BT treatment

Airway of Person with Severe Asthma after Treatment



Reduced airway muscle after BT treatment

After BT, the inside airway wall and other tissue heals, but airway muscle is reduced

Bronchial thermoplasty

- Procedure
- 3 bronchoscopies
  - At least 6 weeks apart (allows healing)
    - #1 RLL
    - #2 LLL
    - #3 RUL and LUL

Bronchial thermoplasty

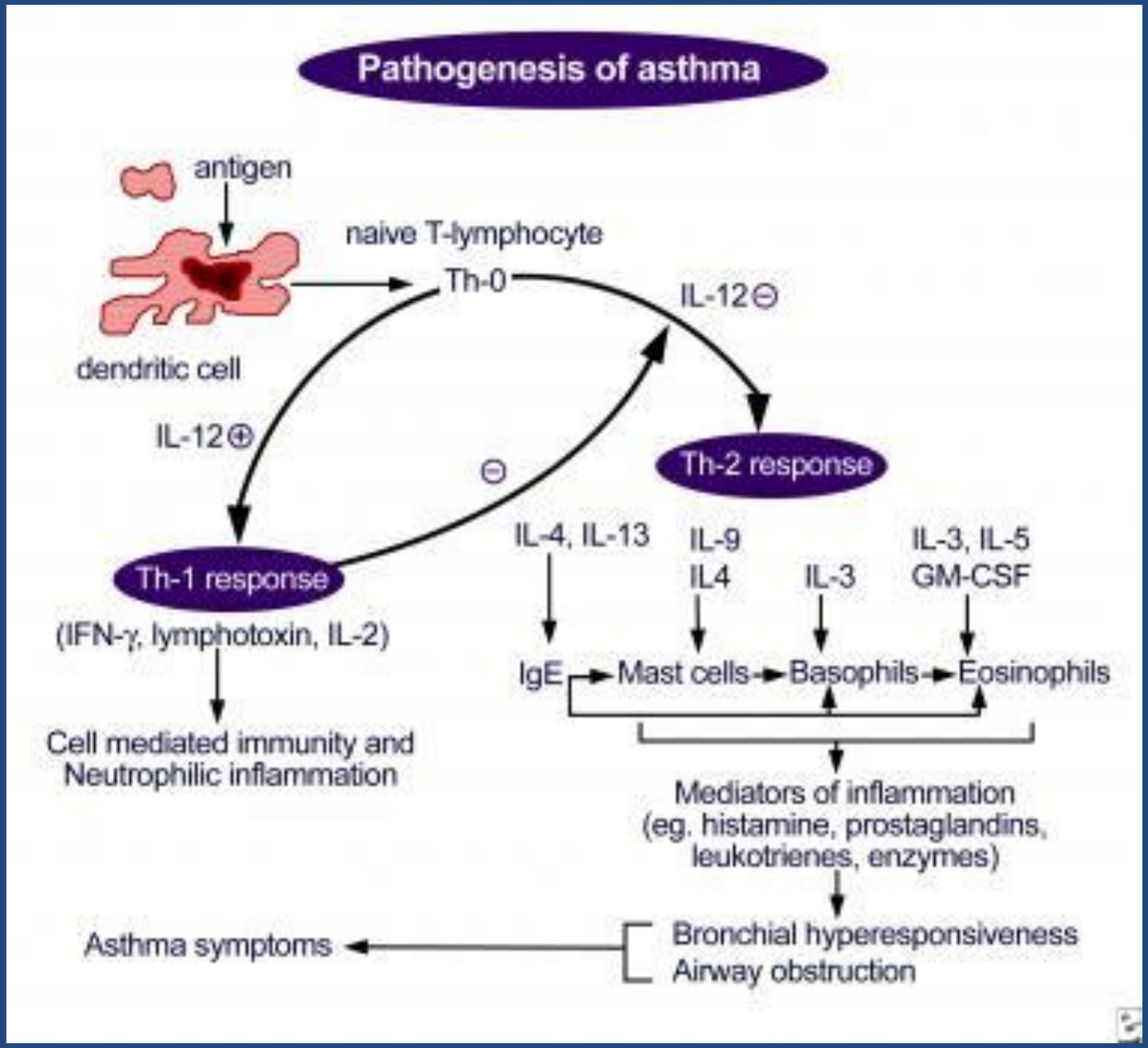
- Follow up studies now of 7 years
- Decreased number of asthma exacerbations
- Decreased number of severe asthma exacerbations
- Less missed days at work / school

Bronchial thermoplasty

- What BT is not
- It is not a cure for asthma
- Patients still need :
  - Asthma action plan (home Rx for prednisone)
  - SABA
  - Maintenance inhaler

Biologics

- Monoclonal antibodies designed to interrupt inflammatory cascade in asthma
- Binding
  - Inflammatory cytokine (IgE, Interleukins)
  - Receptor


Pathogenesis of asthma
antigen
naive T-lymphocyte
Th-0
IL-12⊖
dendritic cell
IL-12⊕
⊖
Th-2 response
IL-4, IL-13
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(IFN-γ, lymphotoxin, IL-2)
IgE
Mast cells
Basophils
Eosinophils
Cell mediated immunity and
Neutrophilic inflammation
Mediators of inflammation
(eg. histamine, prostaglandins,
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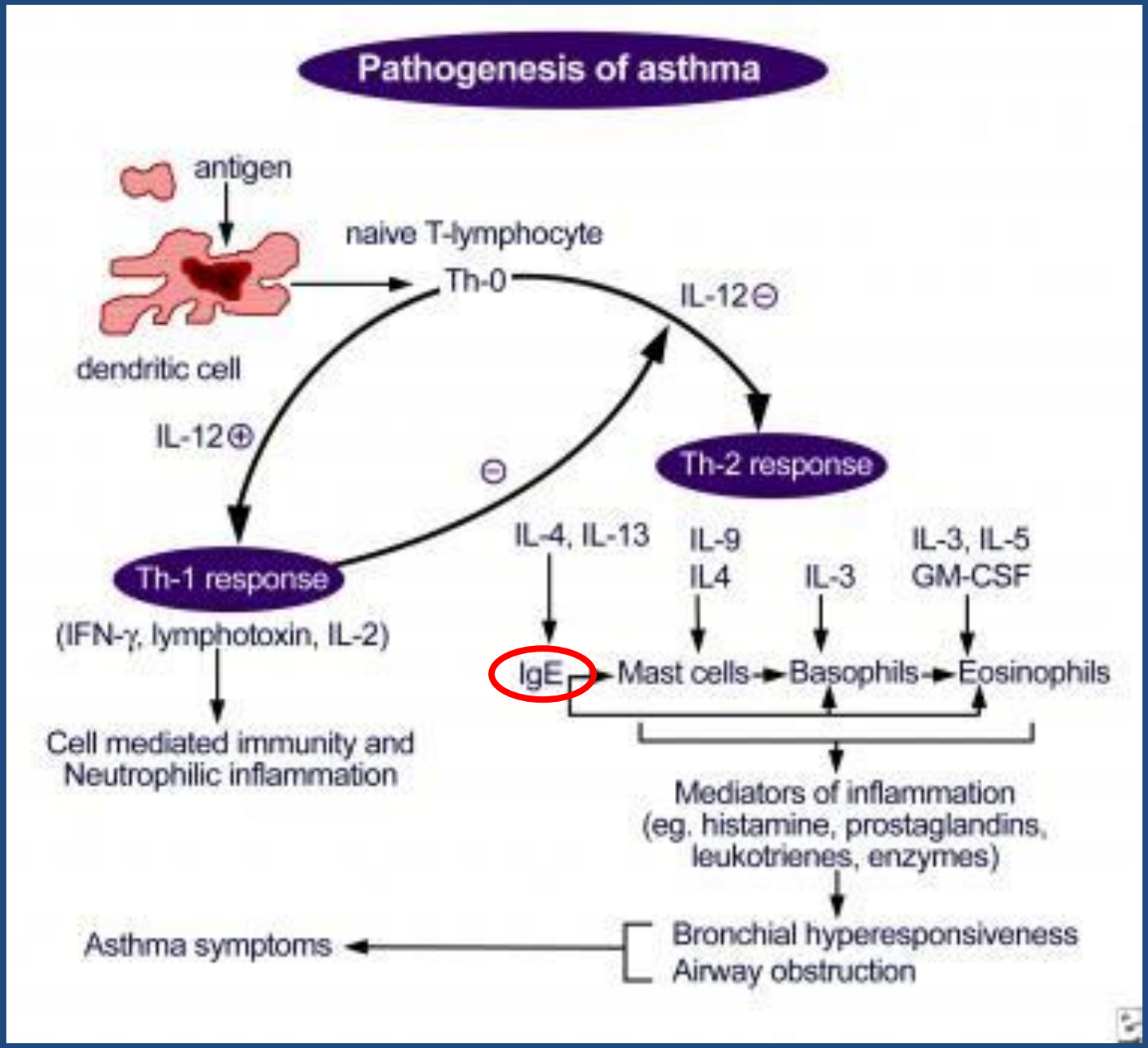
Asthma symptoms
Bronchial hyperesponsiveness
Airway obstruction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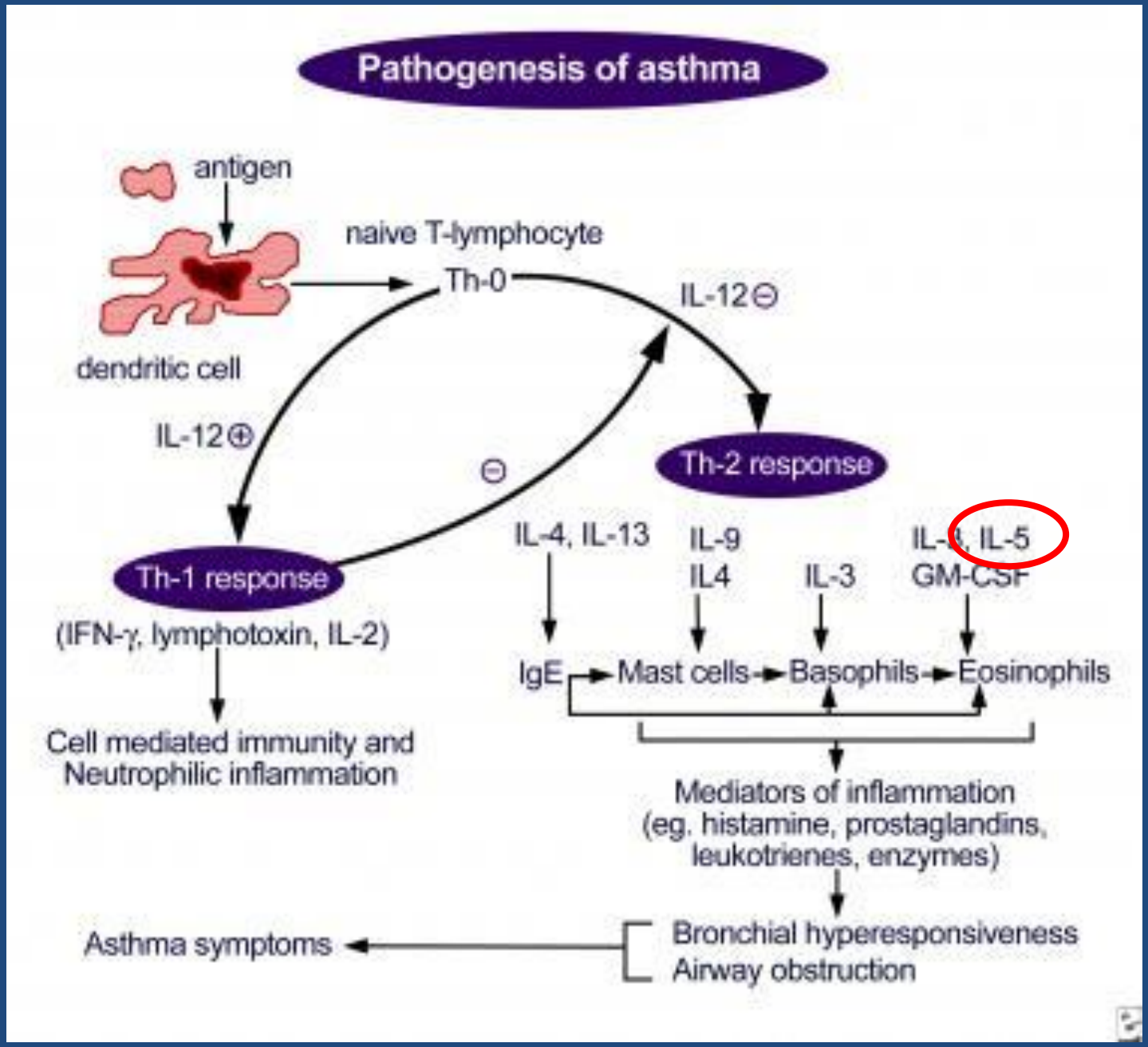
Biologics

- Anti IgE
  - Omalizumab
  - Ligelizumab (under research)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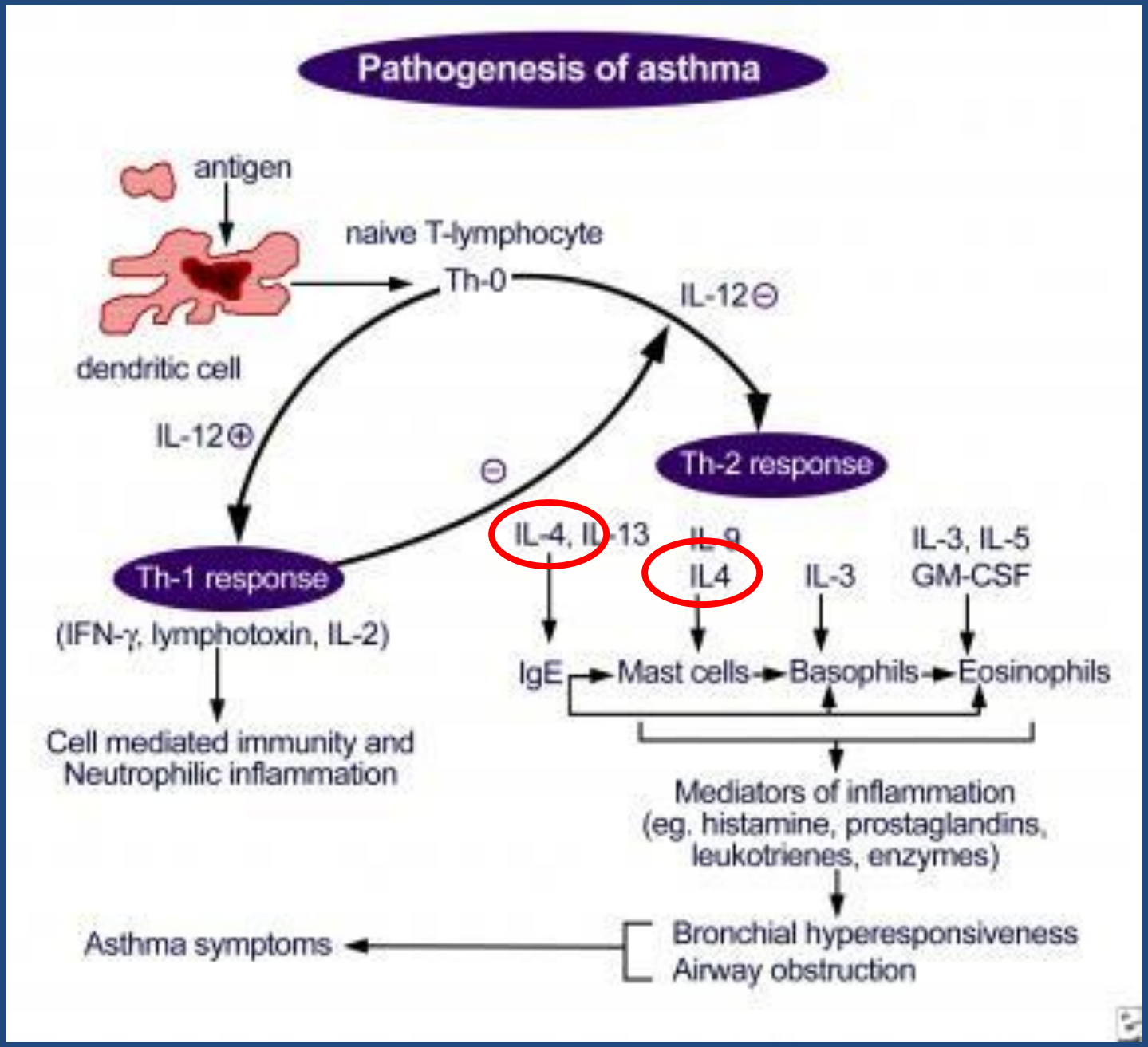
Biologics

- Anti IL-5
  - IL-5 recruits eosinophils to airways
- Drugs binding IL-5
  - Mepolizumab (Nucala)
  - Reslizumab (Cinqair)
- Drug blocking IL-5 receptor
  - Benralizumab (Fasenra)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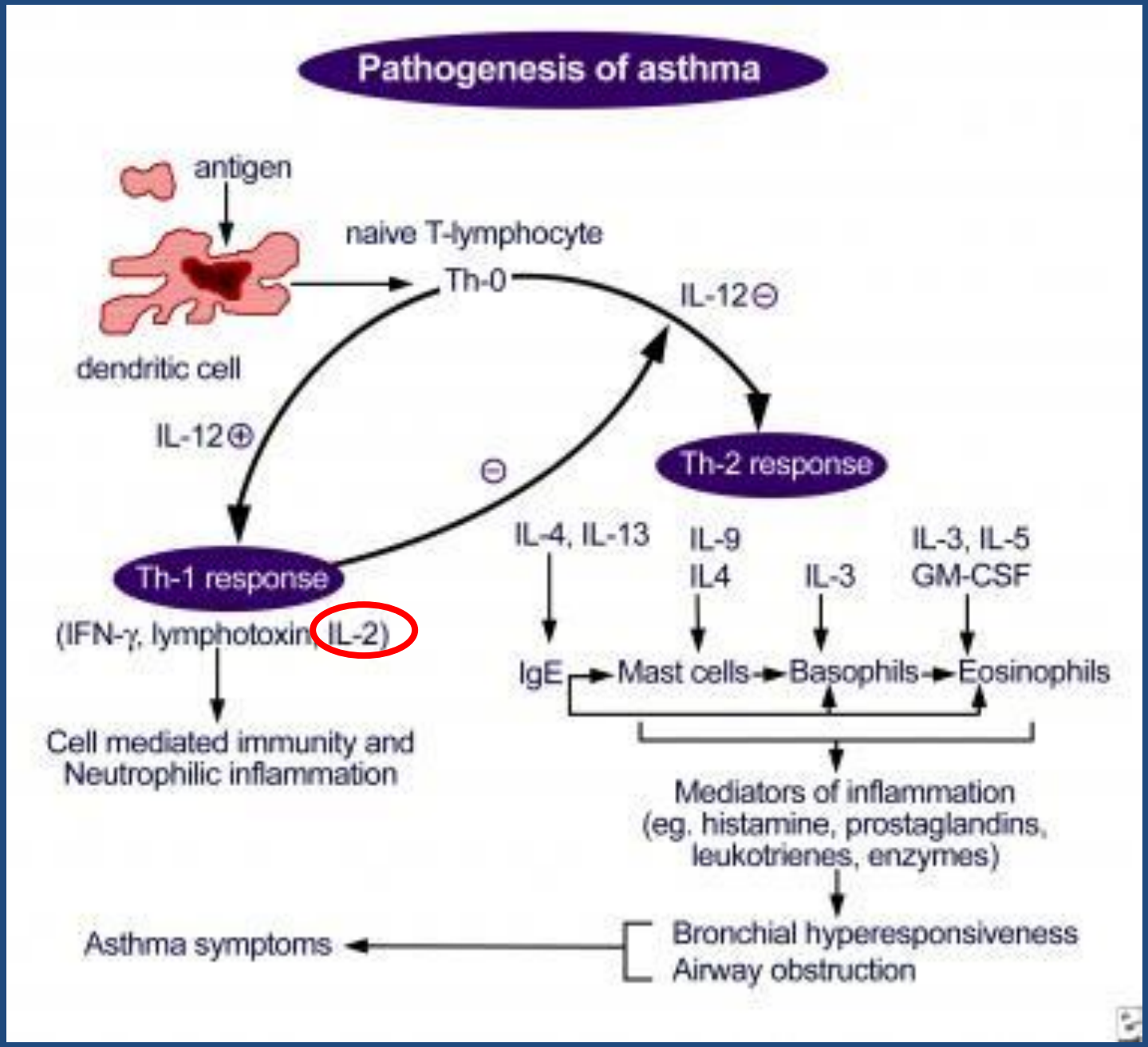
Biologics

- Anti-IL4 receptor Antibody
  - Dupilumab (Dupixent)

Future

- Additional agents in development for multiple cascade targets
- Research is difficult
  - Injectables → systemic side effects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Future

- Anti-IL2 antibody – Daclizumab
  - Not on the market
    - Autoimmune hepatitis
    - Autoimmune colitis

Future

- AZD5423
  - SGRM - selective glucocorticoid receptor modulator
    - Binds receptor in a novel way
    - Proposed to reduce inflammatory response without other effects
  - Inhaled
    - When inhaled, less systemic effects found compared with inhaled steroids
  - Undergoing Phase II trial

Basic Clin Pharm Toxicol; 2017 Oct;121(4):279-289

Thank you

- Questions?