MAHIDOL UNIVERSITY
Wisdom of the Land

Airway Pharmacology for Asthma & COPD

Review & Update

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Asthma & COPD

- Asthma & COPD are heterogeneous disease, usually characterized by chronic airway inflammation, over time, cause "airway remodeling" (permanent damage)
- Asthma & COPD are both obstructive lung disease & inflammatory disease
  - Obstructive component: Bronchoconstriction
  - Inflammatory component: Airway edema, goblet cell hyperplasia, mucus secretion, and cytokine release by immune cells
- Medications used to treat asthma act in one of two ways:
  - By relaxing bronchial smooth muscle: Bronchodilator
  - By treating inflammation: Anti-inflammatory agent

Common drugs for asthma & COPD

Bronchodilators

β_2-agonist (BA)

- **SABA: Short-acting BA**
  - **4-6 hr**
  - Salbutamol, Terbutaline
- **LABA: Long-acting BA**
  - **12 hr (twice-daily)**
  - Salmeterol, Formoterol
- **Ultra-LABA: Ultra long-acting BA**
  - **24 hr (once-daily)**
  - Indacaterol, Vilanterol, Olodaterol, Abediterol, Carmoterol

Muscarinic M_3 antagonist (MA)

- **SAMA: Short-acting MA**
  - **4-6 hr**
  - Ipratropium
- **LAMA: Long-acting MA**
  - **12 hr (twice-daily)**
  - Aclidinium
- **Ultra-LAMA: Ultra-long-acting MA**
  - **24 hr (once-daily)**
  - Tiotropium, Glycopyrronium, Umeclidinium

Anti-inflammatory agent

- **Inhaled corticosteroid (ICS)**
  - Budesonide, fluticasone, beclomethasone, mometasone

Biological products

- **Anti-IgE**
  - Omalizumab
- **Anti-IL5** (for eosinophilic asthma)
  - Mepolizumab (anti-IL5), Reslizumab (anti-IL5), Benralizumab (anti-IL5Ra)
- **Anti-IL4:** Dupilumab
- **Anti-TSLP:** Tezepelumab

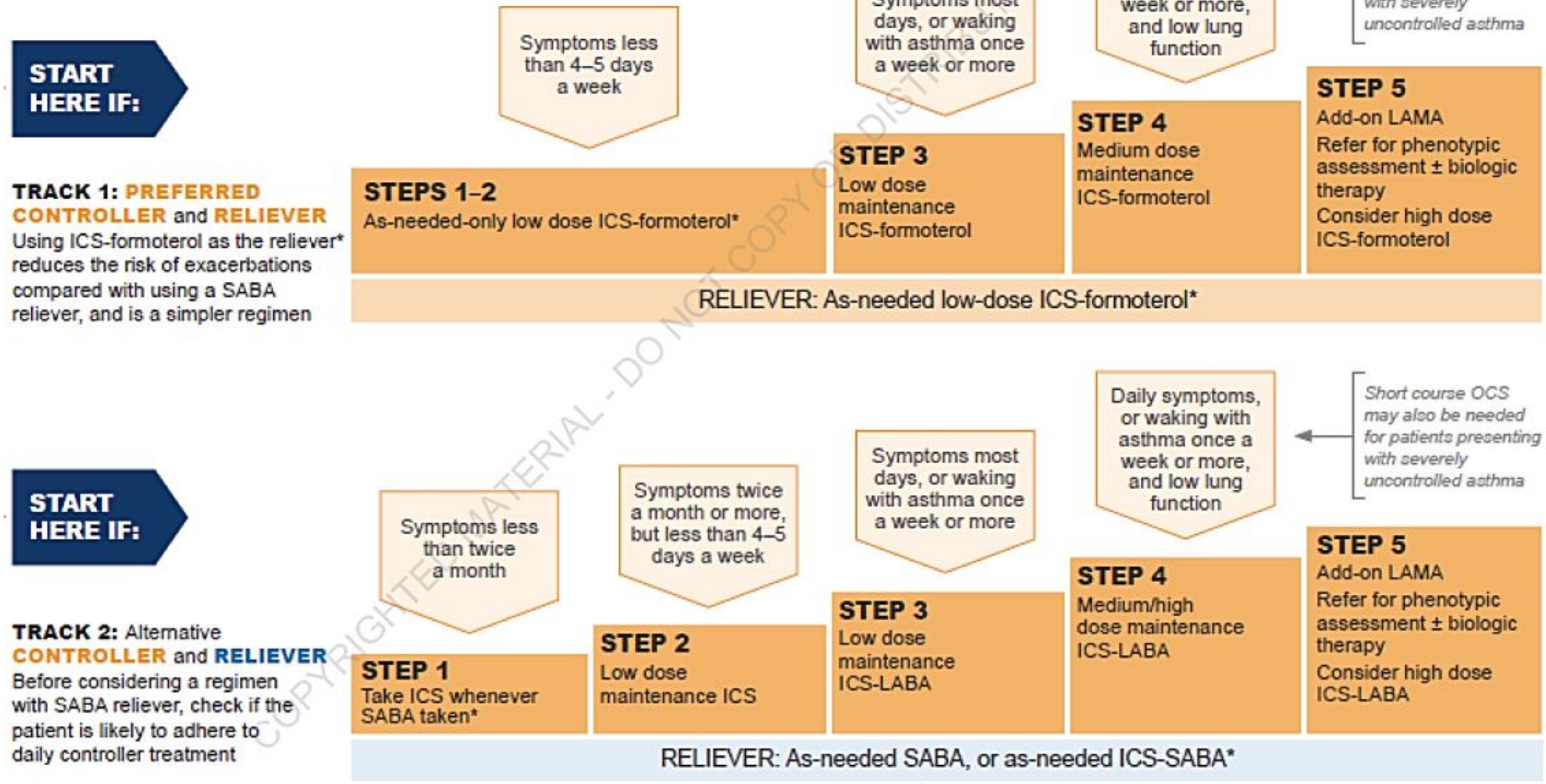
Warisara Parichatikanond

TSLP: Thymic stromal lymphopoietin

GINA guideline for asthma 2023

For adults and adolescents (≥ 12)

2023



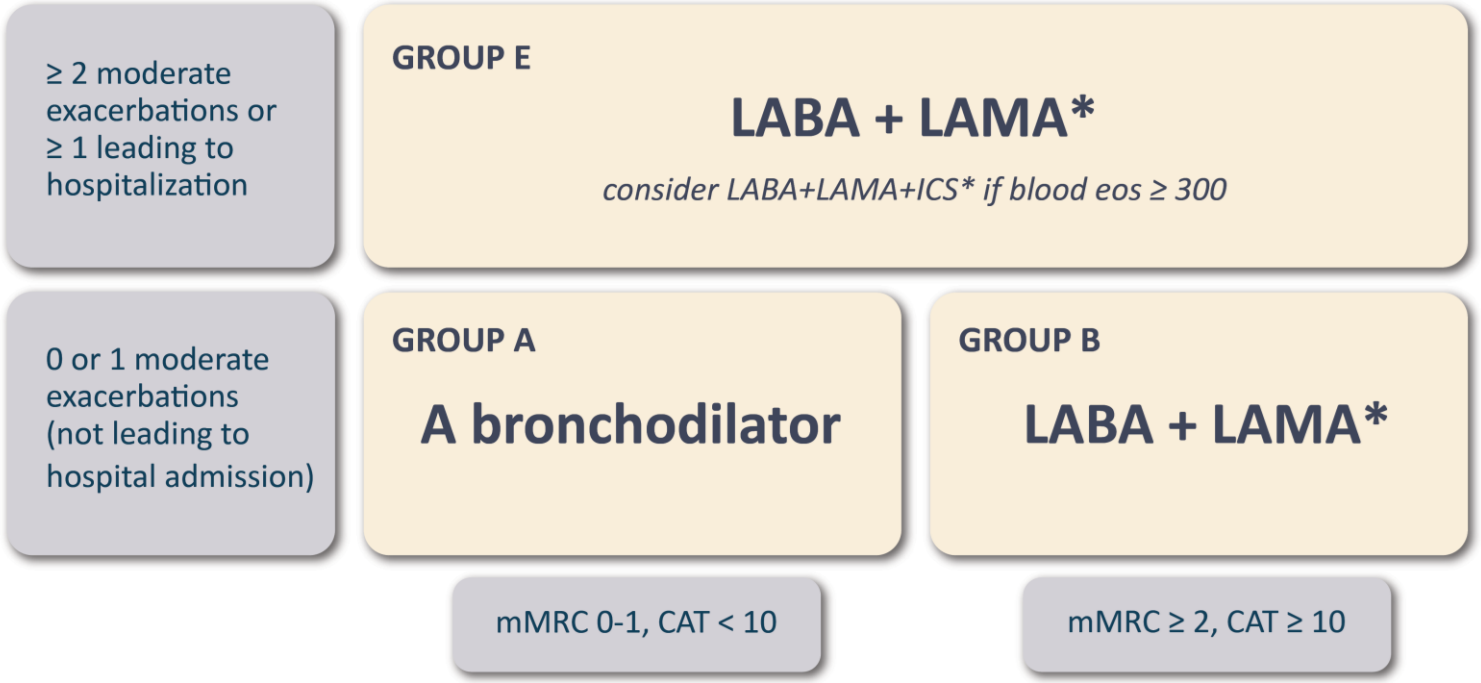
Global INitiative for Asthma (GINA) 2023

GOLD guideline for COPD 2023

2023

Initial Pharmacological Treatment

Figure 4.2



*single inhaler therapy may be more convenient and effective than multiple inhalers
Exacerbations refers to the number of exacerbations per year

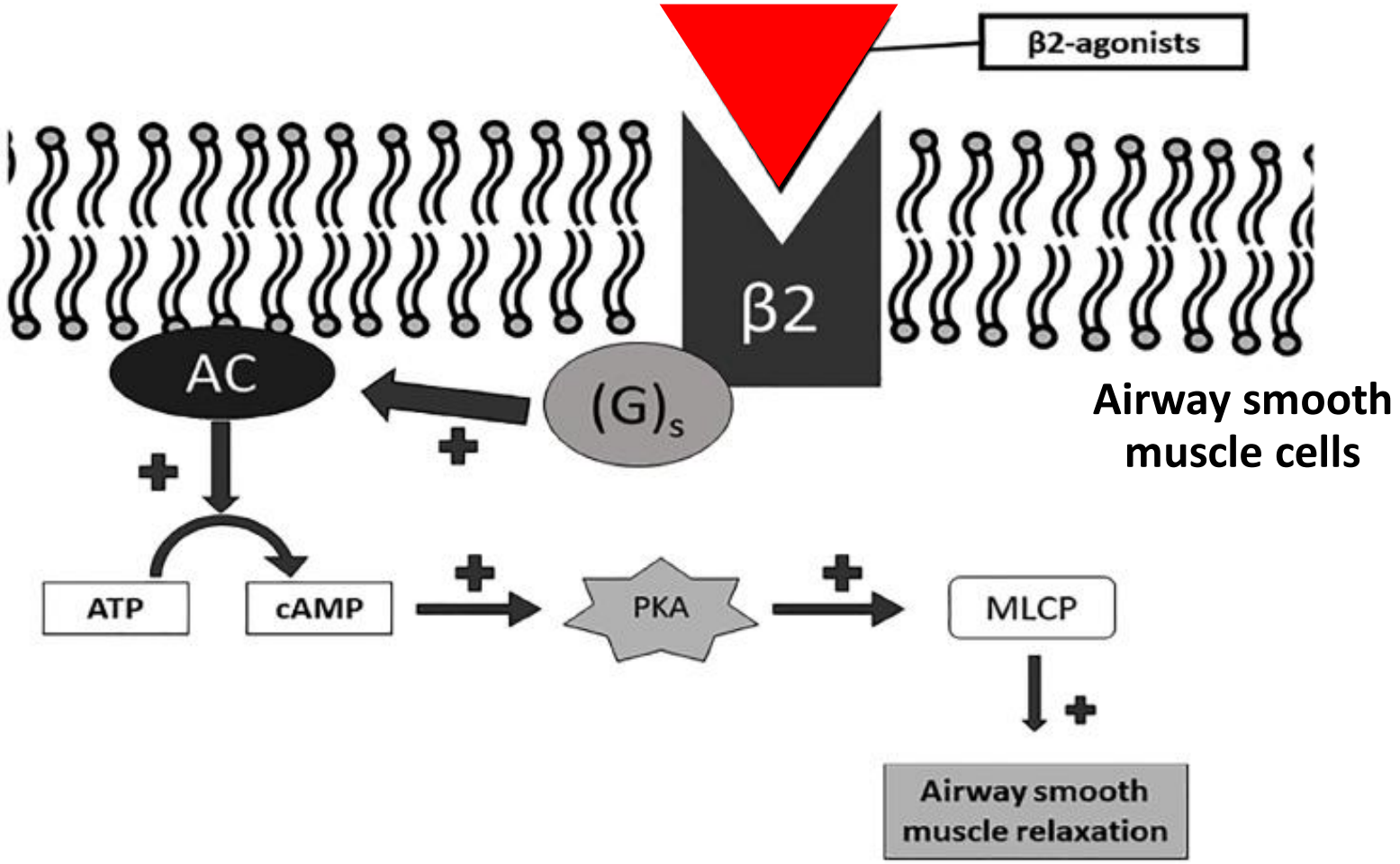
Inhaled Bronchodilators

- **Inhaled long-acting bronchodilators** are most often given on a regular basis to prevent or reduce symptoms in asthma & COPD
- **Aim:**
  - ☑ Reduce symptoms (bronchial obstruction & airflow limitation)
  - ☑ Reduce frequency & severity of exacerbations
  - ☑ Improve exercise tolerance
  - ☑ Improve health status

- Main: β_2-agonist & Muscarinic M_3 antagonist
- To date, there is no clinical trial evidence that any medications modify long-term rate of decline in lung function

β_2-agonist

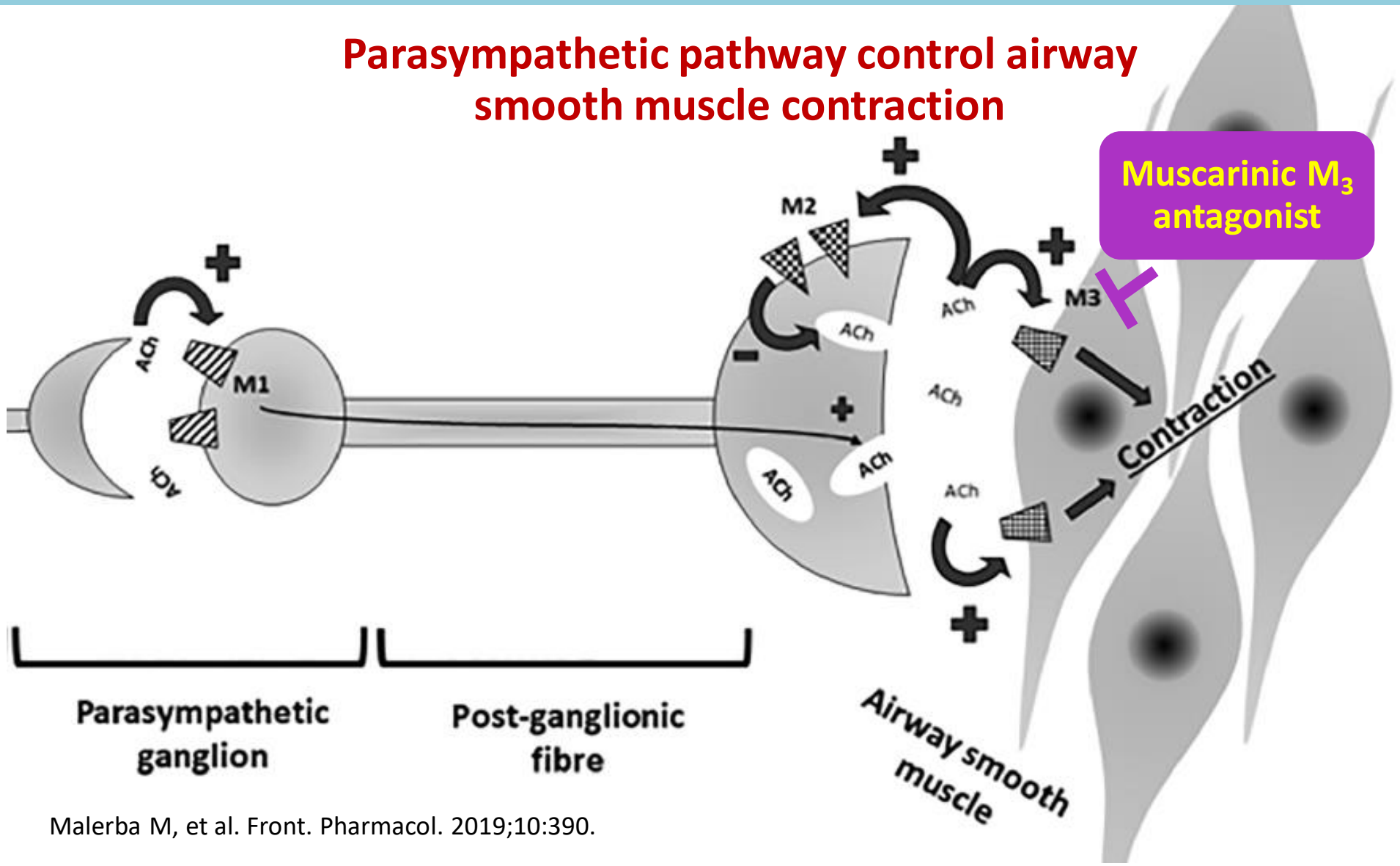
Signaling pathway of β_2-receptor activation



Malerba M, et al. Front. Pharmacol. 2019;10:390.

Muscarinic M_3 antagonist

Parasympathetic pathway control airway smooth muscle contraction



Malerba M, et al. Front. Pharmacol. 2019;10:390.

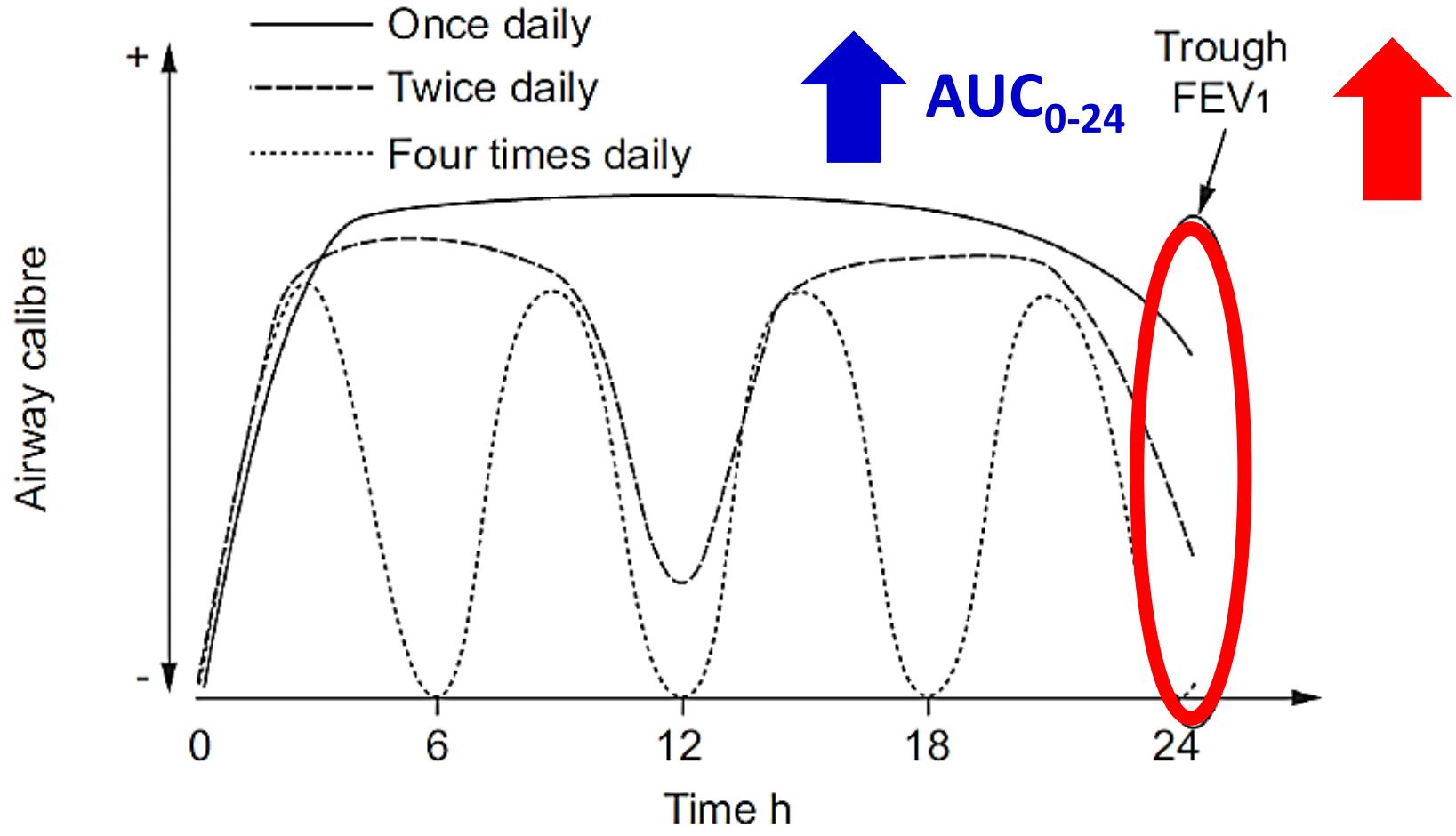
Long-acting bronchodilators

- **Long-acting bronchodilators** improve clinical outcomes including lung function, symptoms, quality of life and exacerbations
- Combination **LABA/ICS** and **LABA/LAMA** as **once a day formulation** are the norm for maintenance of **asthma** & **COPD**, respectively
- **"New generation long-acting bronchodilators":**

  Once-daily -> "ULTRA"

  - ☑ **Longer duration of action (>24 h)**
  - ☑ **Fast onset of action**
  - ☑ **Favorable safety profile**
  - ☑ **Efficient & convenient device**

Effects of long-acting vs. short-acting bronchodilators on 24-h airway tone



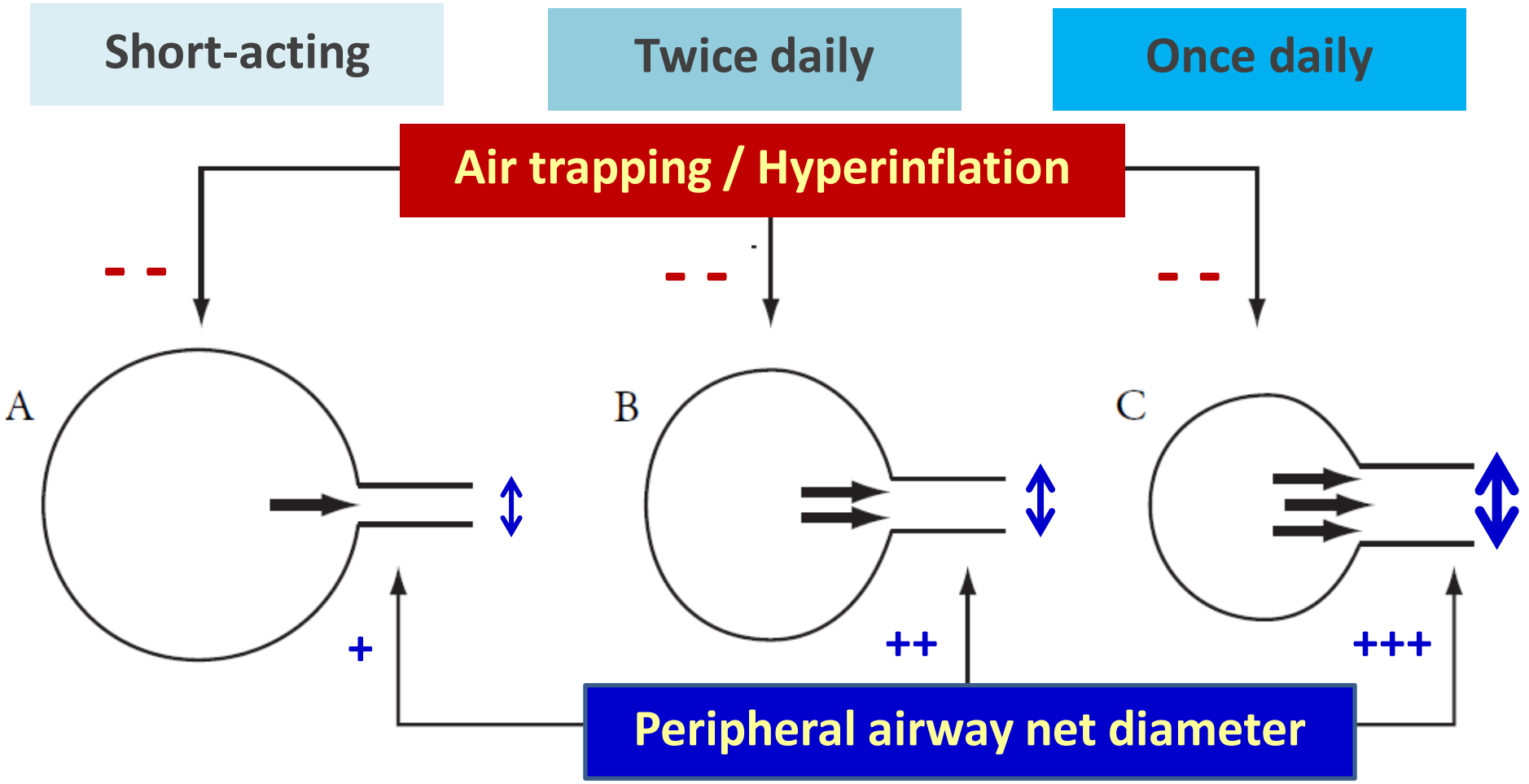
With extended duration, the net area under time/airflow curve (AUC) increases, persistent bronchorelaxant effects (less variable) and increased trough FEV1

Wedzicha JA, et al. Eur Respir J 2012; 40: 1545–54

Model of lung deflation with increased airway calibre

Asthma & COPD: Inflammation & airflow limitation

➡ ↓FEV1 + Air trapping ➡ Hyperinflation



Beeh KM, Beier J. Adv Ther 2010;27:150-9

National Asthma Council AUSTRALIA

Monotherapy
β_2-agonist

SABA RELIEVERS

Ventolin Inhaler † ^
salbutamol 100mcg

Asmol Inhaler † ^
salbutamol 100mcg

Bricanyl Turbuhaler [a c]
terbutaline 500mcg

Airomir Autohaler ‡ #
salbutamol 100mcg

LABA MEDICATIONS

Oxis Turbuhaler ‡
formoterol
6mcg • 12mcg

Serevent Accuhaler ‡
salmeterol
50mcg

Onbrez Breezhaler #
indacaterol
150mcg • 300mcg

National Asthma Council Australia, 2022

National Asthma Council AUSTRALIA

Monotherapy
Muscarinic M_3 antagonist

SAMA MEDICATION

Atrovent Metered Aerosol † ^
ipratropium 21mcg

Yupelri Nebulizer
Revefenacin 175mcg

LAMA MEDICATIONS

Spiriva Respimat # ‡/ª
tiotropium 2.5mcg

Spiriva Handihaler #
tiotropium 18mcg

Braltus Zonda #
tiotropium 13mcg

Bretaris Genuair #
aclidinium 322mcg

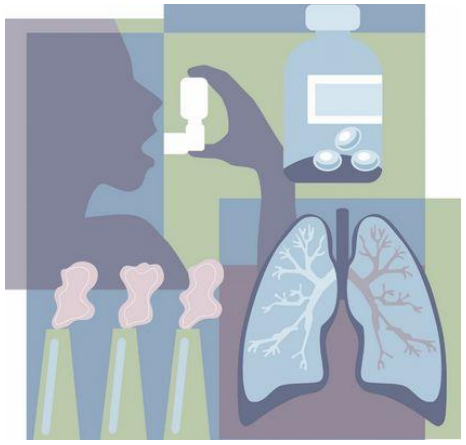
Seebri Breezhaler #
glycopyrronium 50mcg

Incruse Ellipta #
umeclidinium 62.5mcg

National Asthma Council Australia, 2022

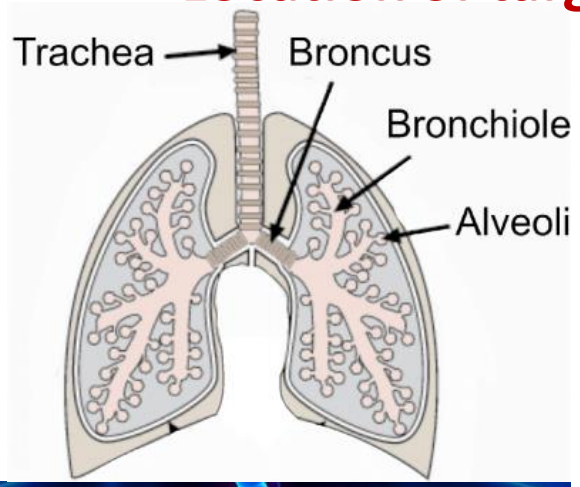
Combination: Dual / Triple therapy
LABA / LAMA & LABA / ICS & LABA / LAMA / ICS

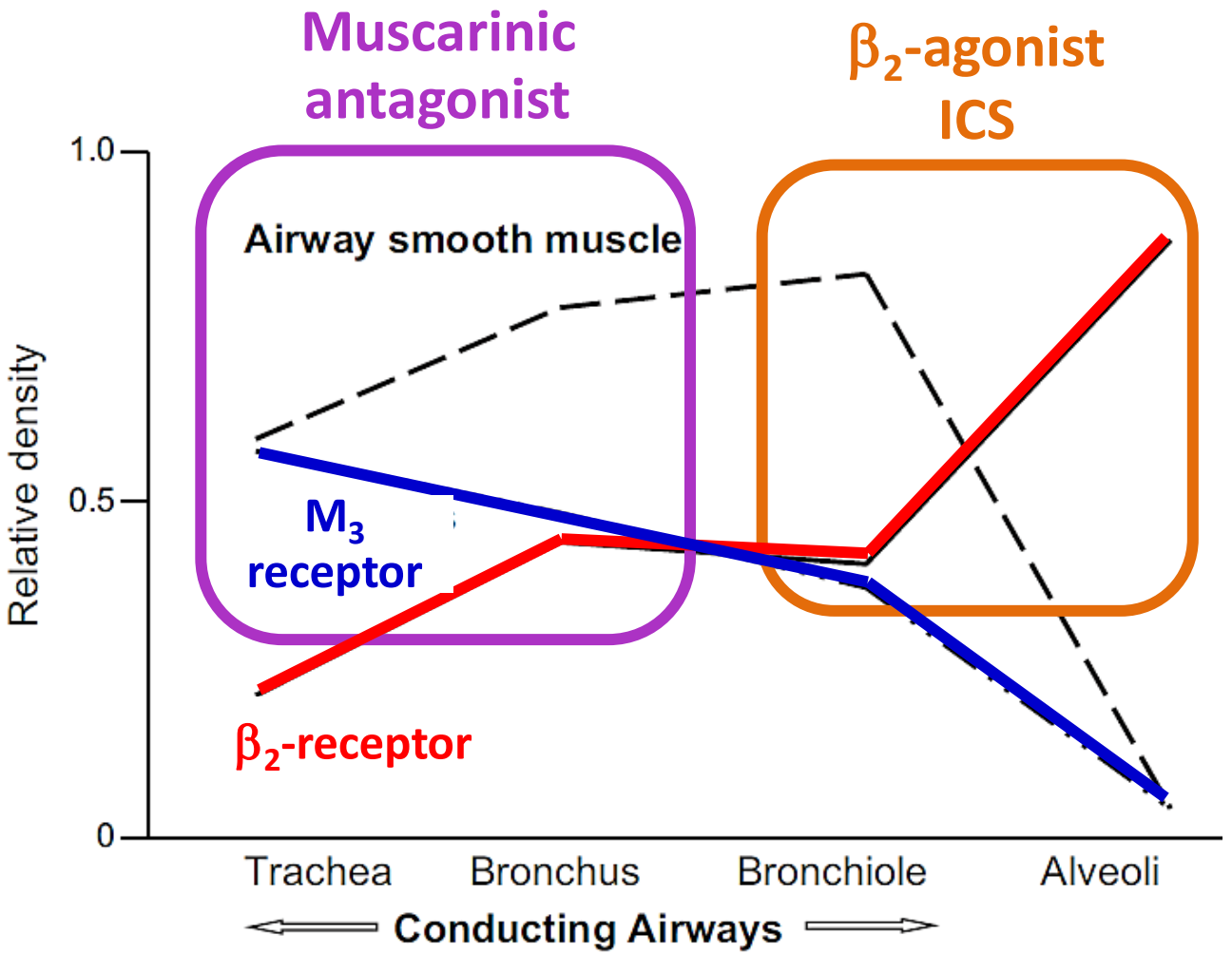
- **Combining bronchodilators with <u>different</u> mechanisms & durations of action is more effective than either component alone**
  - ☑ **Increase degree of bronchodilation**
  - ☑ **Lower risk of side-effects (compared to increase dose of a single bronchodilator)**
  - ☑ **Improve outcome: Symptoms, lung function (FEV1), exacerbation, quality of life**
  - ☑ **Better adherence (Single inhaler)**
  - ☑ **? Mortality rate**



Improved lung function with combination treatment

Location of targets for bronchodilators in human airways





Haughney J, et al. Respiratory Medicine 2010; 125-31

National Asthma Council AUSTRALIA

Combination: Dual therapy

LABA / LAMA

LAMA/LABA COMBINATIONS

Spiolto Respimat [c]
tiotropium/olodaterol
2.5/2.5

Brimica Genuair [c]
aclidinium/formoterol
340/12

Ultibro Breezhaler [c]
indacaterol/glycopyrronium
110/50

Anoro Ellipta [c]
umeclidinium/vilanterol
62.5/25

all units in mcg

LABA / ICS

ICS/LABA COMBINATIONS

Seretide MDI [a]
fluticasone propionate/salmeterol
50/25 • 125/25 • 250/25 [c]

Fluticasone + Salmeterol Cipla Inhaler [a]
fluticasone propionate/salmeterol
125/25 • 250/25 [c]

Seretide Accuhaler [a]
fluticasone propionate/salmeterol
100/50 • 250/50 • 500/50 [c]

Flutiform Inhaler [a]
fluticasone propionate/formoterol
50/5 • 125/5 • 250/10

Symbicort Turbuhaler [a]
budesonide/formoterol
100/6 • 200/6 • 400/12 [c]

DuoResp Spiromax [a]
budesonide/formoterol
200/6 • 400/12 [c]

Symbicort Rapihaler [a]
budesonide/formoterol
50/3 • 100/3 • 200/6 [c]

Breo Ellipta [a]
fluticasone furoate/vilanterol
100/25 [c] • 200/25

Fostair Inhaler [a]
beclometasone/formoterol
100/6

Atectura Breezhaler [a]
Indacaterol/mometasone
125/62.5 • 125/127.5 • 125/260

Combination: Triple therapy

LABA / LAMA / ICS

ICS/LAMA/LABA

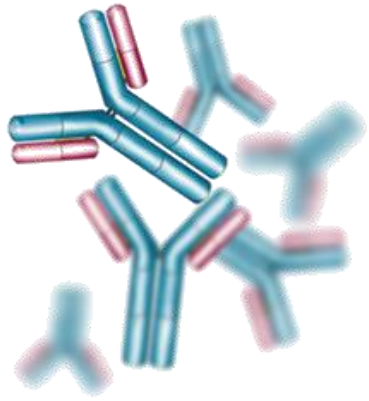
Trelegy Ellipta [a c]
fluticasone furoate/
umeclidinium/vilanterol
100/62.5/25mcg

Enerzair Breezhaler [a]
Indacaterol/glycopyrronium/
mometasone
114/46/136mcg • 114/46/68mcg

Trimbow Inhaler [c]
Beclometasone/Formoterol/
Glycopyrronium
100/6/10mcg

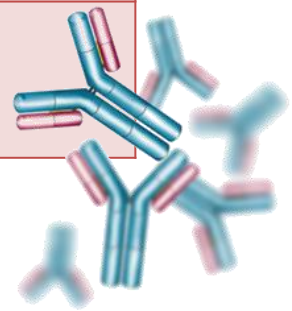
National Asthma Council Australia, 2022

Current biological products for uncontrolled severe asthma

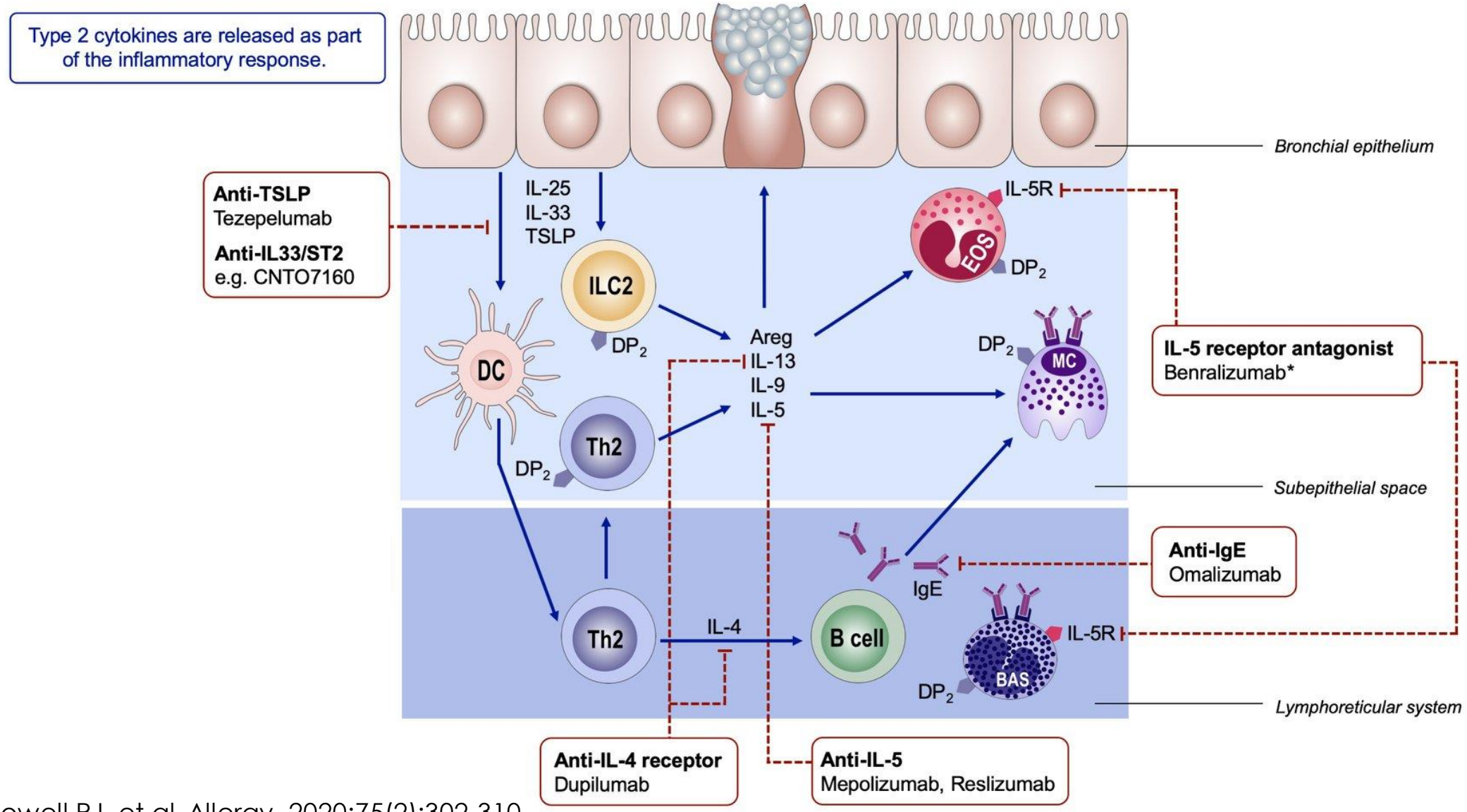


Biological products for severe asthma

Class	Name	Regimen	Age (Years)	Asthma indication
Anti-IgE	Omalizumab	SC, q 2-4 wk	≥6	Severe allergic asthma
Anti-IL5	Mepolizumab Reslizumab	SC, q 4 wk IV, q 4 wk	≥6 ≥18	Severe eosinophilic/ Type 2 asthma
Anti-IL5R	Benralizumab	SC, q 8 wk	≥12	
Anti-IL4Rα	Dupilumab	SC, q 2 wk	≥6	Severe eosinophilic/ Type 2 asthma, or maintenance OCS
Anti-TSLP **(*GINA 2022)**	Tezepelumab	SC, q 4 wk	≥12	Severe asthma



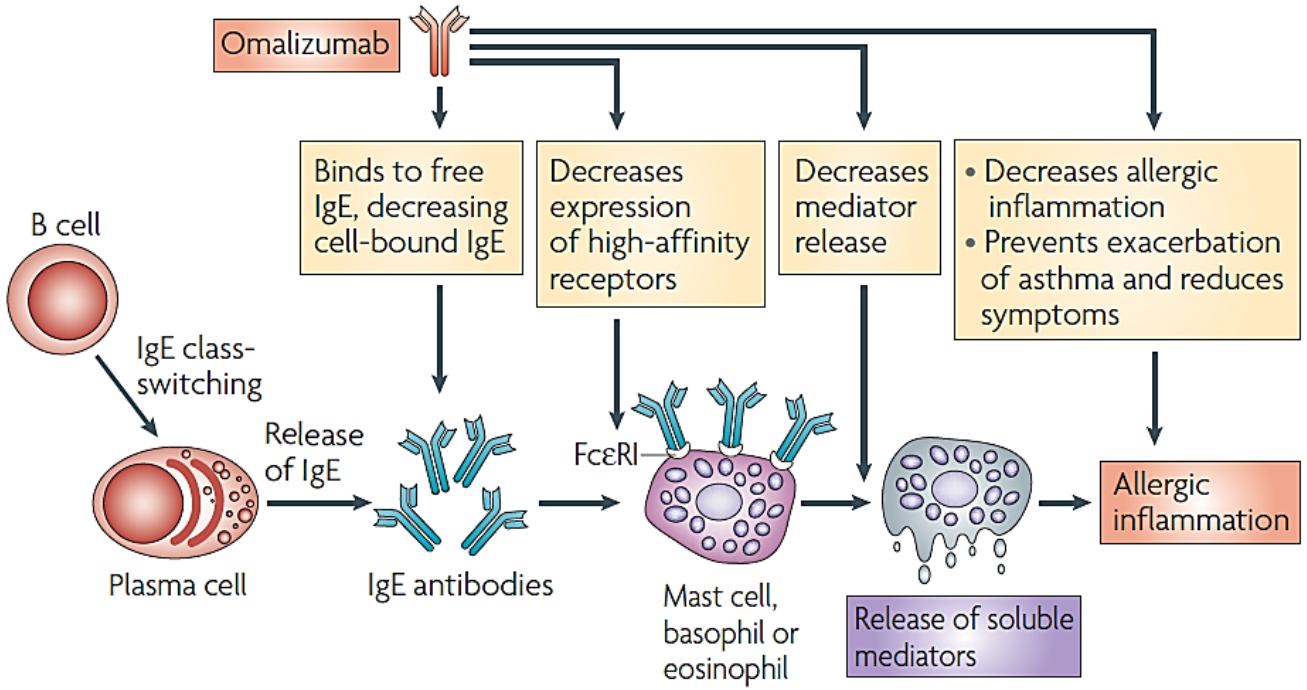
Biological products for severe asthma



McDowell PJ, et al. Allergy. 2020;75(2):302-310.

Anti-IgE
Omalizumab

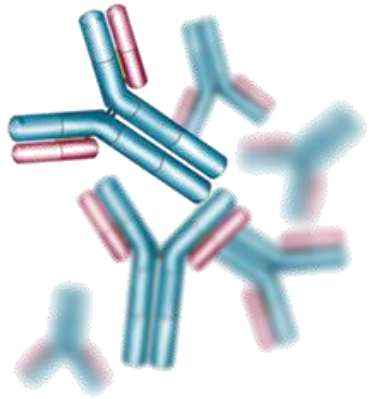
- **Mechanism:** Humanized mAb binds directly to free IgE
- **Indication:** Xolair® (2003): For the treatment of moderate to severe allergic asthma incomplete controlled with ICS (≥ 6 years)
- **Biomarkers:** Serum IgE level: 30-700 IU/mL (≥ 12 years), 30-1300 IU/mL (6-11 years)
- **Route:** SC, q4 wk
- **Outcome:** ↓ Exacerbation, ↑ FEV1, ↑ Quality of life



Nat Rev Immunol 2008; 8:218-30

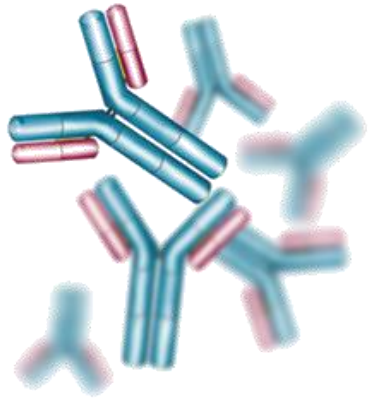
Anti-IL-5
Mepolizumab, Reslizumab, Benralizumab

- **Mechanism:**
  - **Humanized mAb against IL-5: Mepolizumab** (Nucala®, 2015), **Reslizumab** (Cinqair®, 2016)
  - **Humanized mAb targeting IL-5Rα : Benralizumab** (Fasenra®, 2017)
- **Indication: Severe eosinophilic asthma unresponsive to GINA step 4 or 5 therapy**
- **Biomarkers: Blood eosinophils ≥ 300 cells/μl (No strict cutoff)**
- **Route: Mepolizumab (SC, q 4 wk), reslizumab (IV infusion, q 4 wk), benralizumab (SC, q 4-8 wk)**
- **Outcome:**
  - **↓ Exacerbations**
  - **↓ Eosinophil (sputum, blood)**
  - **↑ FEV1**
  - **↑ Quality of life**
  - **ADR: Headache, URI, nasopharyngitis, injection-site reaction**



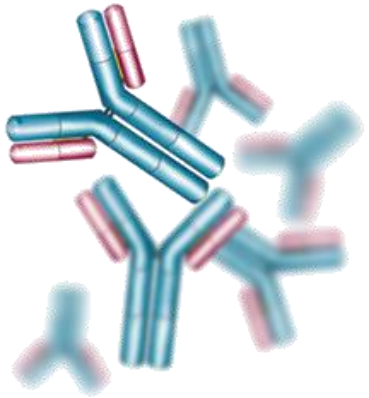
Anti-IL-4
Dupilumab

- **Mechanism:** Fully human mAb against IL-4Rα
- **Indication:** Dupixent® (2018): For add-on maintenance therapy in patients with severe asthma with an eosinophilic phenotype or with corticosteroid-dependent asthma (≥6 years)
- **Route:** SC q2wk
- **Outcomes:**
  - ↓ Exacerbations
  - ↓ Total & allergen-specific IgE
  - ↓ FeNO (a marker of lung inflammation)
  - ↓ Eosinophil (sputum, blood)



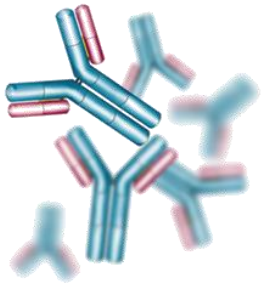
Anti-TSLP
Tezepelumab

- **Mechanism:** Fully human IgG2λ mAb against TSLP
- **Indication:**
  - (Tezspire™, Dec, 2021): For add-on maintenance treatment in patients with severe asthma (≥12 years)
  - with no phenotype (e.g. eosinophilic or allergic) or biomarker limitations.
- **Route:** 210 mg, SC q4wk
- **Outcomes:**
  - ↓ Exacerbations
  - ↑ FEV1
  - ↑ Quality of life
  - ↓ Airway inflammatory cells (eosinophils, neutrophils, T-cells, mast cells
  - ADR: Pharyngitis (bacterial and viral), arthralgia, back pain



Summary

- LABAs & LAMAs improve lung function, dyspnea, health status and reduce exacerbation rate (are preferred over short-acting agents)
- Combination treatment with a LABA/LAMA reduces symptoms and exacerbation rate compared to monotherapy
- Patients may be started on single long-acting therapy or dual long-acting therapy depend on each individual
- Biological therapies against IgE, IL-5, IL-4 and TSLP seem safe and promising in short- and medium-term treatment of adult patients with uncontrolled asthma
- The cost-effectiveness and adverse events associated with the use of each monoclonal antibody should be considered (clinical trials)



"I stopped to smell the flowers. Where's my inhaler?"