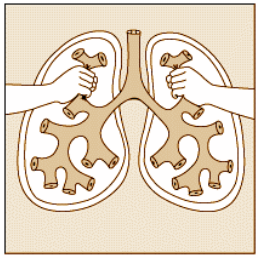
Pharmacology of respiratory system
Therapy of bronchial asthma and COPD

http://portal.jfmed.uniba.sk/index-en.php



Definition of bronchial asthma

Chronic inflammatory disease of airways, with participation of various cells and cell elements, particularly mastocytes, eozinophiles, T-lymfocytes, macrophages, neutrophiles and epithelial cells. This inflammation cause in susceptible individuals recurrent episodes or attacks of wheezing, cough, dyspnea and chest oppressions, mainly during night and in the morning. Concommitantly there is diffuse, but variable obstruction of airways, which is often reversible either spontaneously or after treatment. The inflammation is responsible also for enhancing of bronchial hyperreactivity to various stimuli.

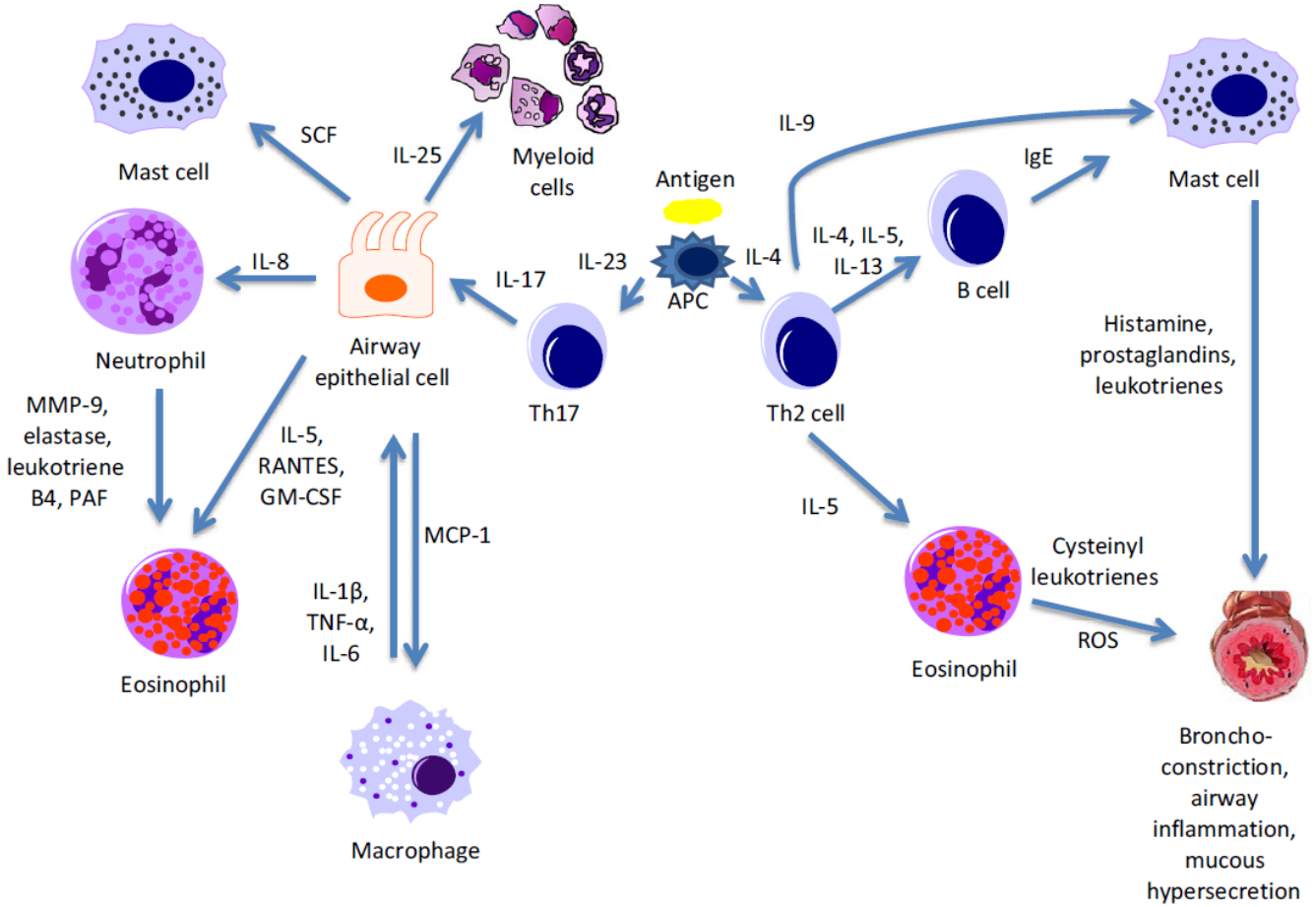
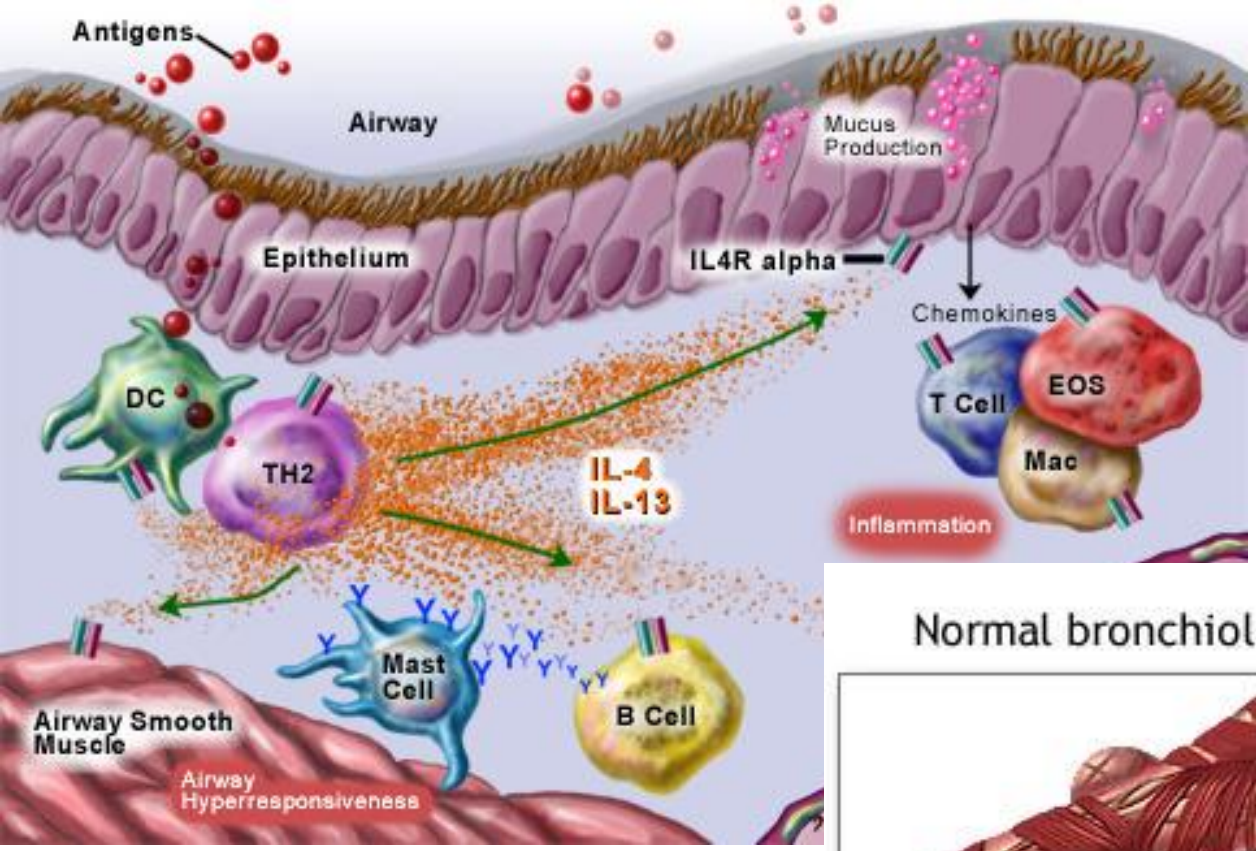
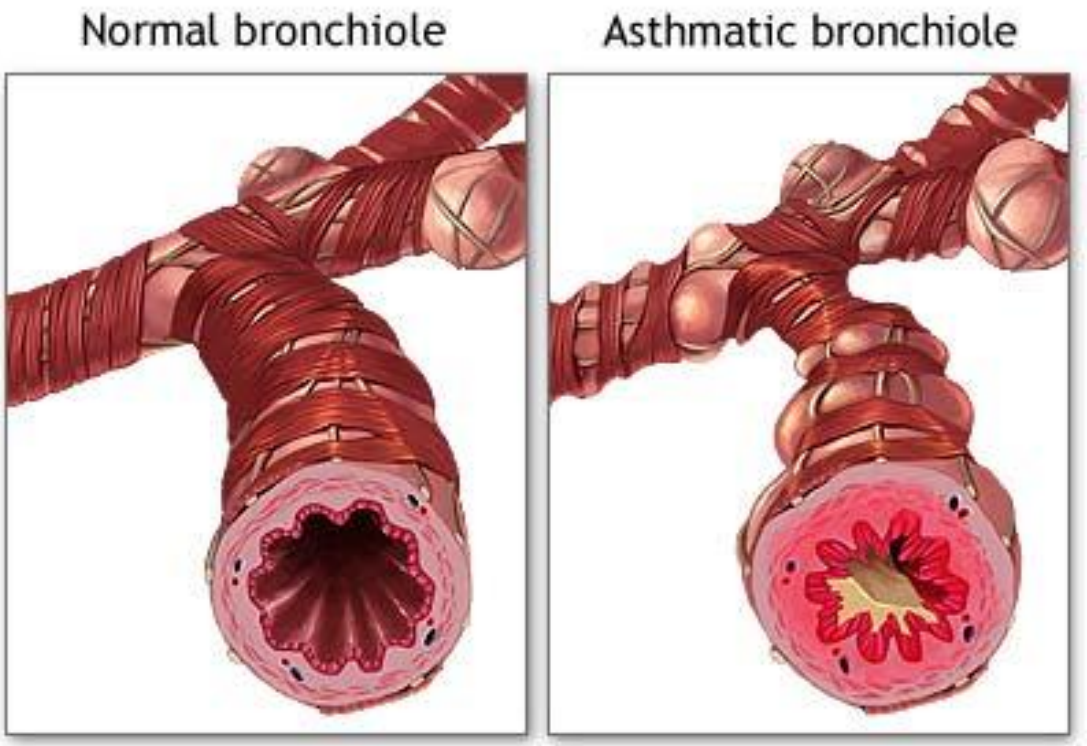


Figure 1 Th2 and Th17 allergen responses in the asthmatic airway. Upon allergen presentation to Th0 cells by antigen-presenting cells (APC), Th cells differentiate into Th2 cells in the presence of IL-4, and Th17 cells in the presence of IL-23. Th2 cells then go on to produce IL-4-, IL-5-, and IL-13-activating B cells to release IgE which attaches to the surface of mast cells. When stimulated by antigen, mast cells release histamine, prostaglandins, and leukotrienes resulting in smooth muscle bronchoconstriction, airway inflammation, and mucous hypersecretion. Eosinophils activated by IL-5 produce cysteinyl leukotrienes and reactive oxygen species (ROS), which act in a similar manner on the airways, and additionally contribute to oxidative stress. Th17 cells producing IL-17 act on airway epithelial cells to stimulate the release of multiple factors. These factors include macrophage chemoattractant protein-1 (MCP-1) which recruits macrophages, IL-5, regulated on activation, normal T cell expressed and secreted (RANTES), and GM-CSF (granulocyte–macrophage colony-stimulating factor) which activate eosinophils, IL-8 which mobilizes neutrophils, stem cell factor (SCF) which works to promote mast cell survival, and IL-25 which induces myeloid cells to release Th2-type cytokines. Neutrophils release matrix metalloproteinase 9 (MMP9), elastase, leukotriene B4, and platelet-activating factor (PAF), which work to enhance the activity of eosinophils. Activated macrophages release IL-1, tumor necrosis factor alpha (TNF-a), and IL-6 which interact with other inflammatory cells and result in a positive feedback loop with airway epithelial cells.

Trevor JL, Deshane JS. Refractory asthma: mechanisms, targets, and therapy. Allergy 2014; 69: 817–827.

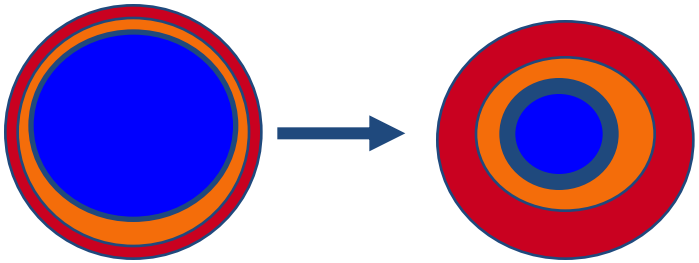
Allergy **69** (2014) 817–827 © 2014 The Authors. *Allergy* Published by John Wiley & Sons Ltd.


Antigens
Airway
Mucus Production
Epithelium
IL4R alpha
Chemokines
DC
TH2
T Cell
EOS
Mac
IL-4
IL-13
Inflammation
Mast Cell
B Cell
Airway Smooth Muscle
Airway Hyperresponsiveness


Normal bronchiole
Asthmatic bronchiole

A.D.A.M.

Pathogenesis of BA



- Eozinophil inflammation
- Bronchoconstriction
- Edema of mucous mebranes (plasma leakage, vasodilation)
- Hypersecretion of mucus
- Activation of senzoric nerve endings (cough, cholinergic reflexes)
- Remodeling of lung parenchyma (fibrosis, smooth muscle hypertrophy, more vessels and cells)

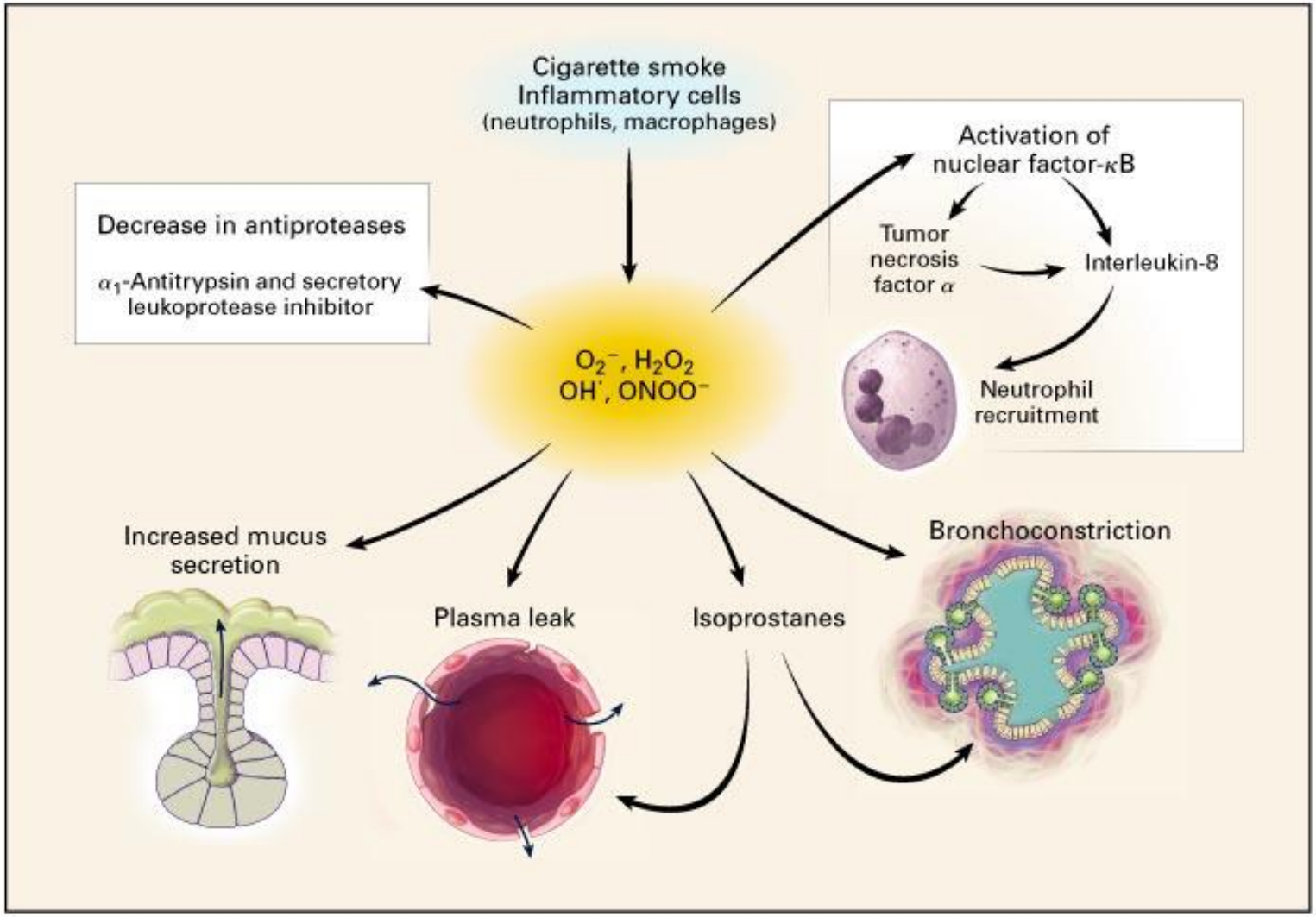
Symptomatology of BA

- Cough
- Dyspnea
- Wheezing
- Mucus
- Morning troubles
- Positive pacient´s history

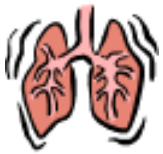
Definition of COPD

COPD is disease characterised by limitation of air flow through airways, which is not completely reversible. The limitation of air flow has usually progressive character and is associated with inflammatory reaction of lungs to various particules or gases.

Pathogenesis of COPD



www.medscape.com



Differences between COPD and BA

	ASTHMA	COPD
Prevalence	5-10%	>10%
Inflammation	eozinophiles	neutrophiles
Causal Th	hyposenzibilization	??? stop smoking
Smoking	No?	Yes
Symptomatic Th	**bronchodilators**	**bronchodilators**
Prognosis	stabilization, healing	progression
Disease onset	rapid	progressive
Reversibility of obstruc.	over 15%	No or small
Hyperreactivity	always	sometimes

Prevzaté od Bigby, San Diego 2000

Classification of BA

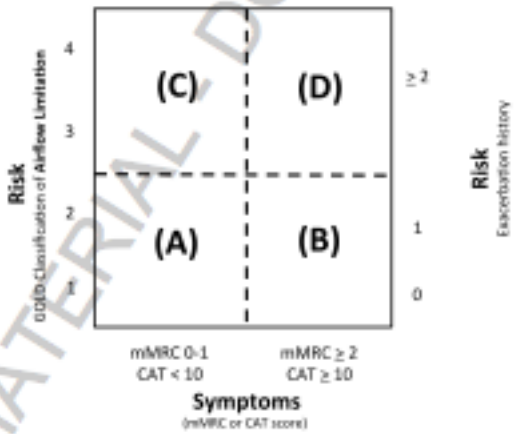
- 1. level - Mild intermitent asthma
- 2. level - Mild persistent asthma
- 3. level - Moderate persistent asthma
- 4. level - Severe persistent asthma

Figure 2. Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV_1

Stage I: Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage II: Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage III: Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage IV: Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Table 4. Combined Assessment of COPD

(When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.)



Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

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Vaše meno: Dnešný dátum:

Ako by ste popísali vašu chronickú obštrukčnú chorobu pľúc (CHOCHP)? Vyplňte test vyhodnotenia CHOCHP (COPD Assessment TestTM) (CAT)

Tento dotazník pomôže vám a profesionálnemu zdravotníkovi posúdiť vplyv CHOCHP(chronická obštrukčná choroba pľúc) na vaše zdravie a každodenný život. Vaše odpovede a hodnotenie testu môžete vy a profesionálny zdravotník použiť na zlepšenie manažmentu choroby CHOCHP a získanie čo možno najväčšieho prínosu z liečby CHOCHP.

Príklad: Som veľmi šťastný/á 0 X 2 3 4 5 Som veľmi smutný/á

			VÝSLEDOK
Nikdy nekašlem	0 1 X 3 4 5	Stále kašlem	2
V hrudníku nemám vôbec hlien	0 1 X 3 4 5	hlien Hrudník mám celkom plný hlienu	2
Vôbec nepociťujem tlak na hrudníku	0 X 2 3 4 5	Pociťujem výrazný tlak na hrudníku	1
Po zdolaní kopca alebo jedného poschodia nie som zadychčaný/á	X 1 2 3 4 5	Po zdolaní kopca alebo jedného poschodia som veľmi zadychčaný/á	0
Moja činnosť v domácnosti nie je vôbec obmedzená	0 X 2 3 4 5	Moja činnosť v domácnosti je veľmi obmedzená	1
Aj napriek stavu pľúc s istotou vychádzam von z domova	0 X 2 3 4 5	V dôsledku stavu pľúc nemám vôbec istotu vyjsť z domova	1
Spím hlbokým spánkom	0 X 2 3 4 5	Nespím hlbokým spánkom v dôsledku stavu mojich pľúc	1
Mám veľa energie	0 X 2 3 4 5	Nemám vôbec žiadnu energiu	1
		Kliknutím zobrazíte celkové skóre	9

COPD Assessment Test a logo CAT je ochranná známka skupiny spoločností GlaxoSmithKline.
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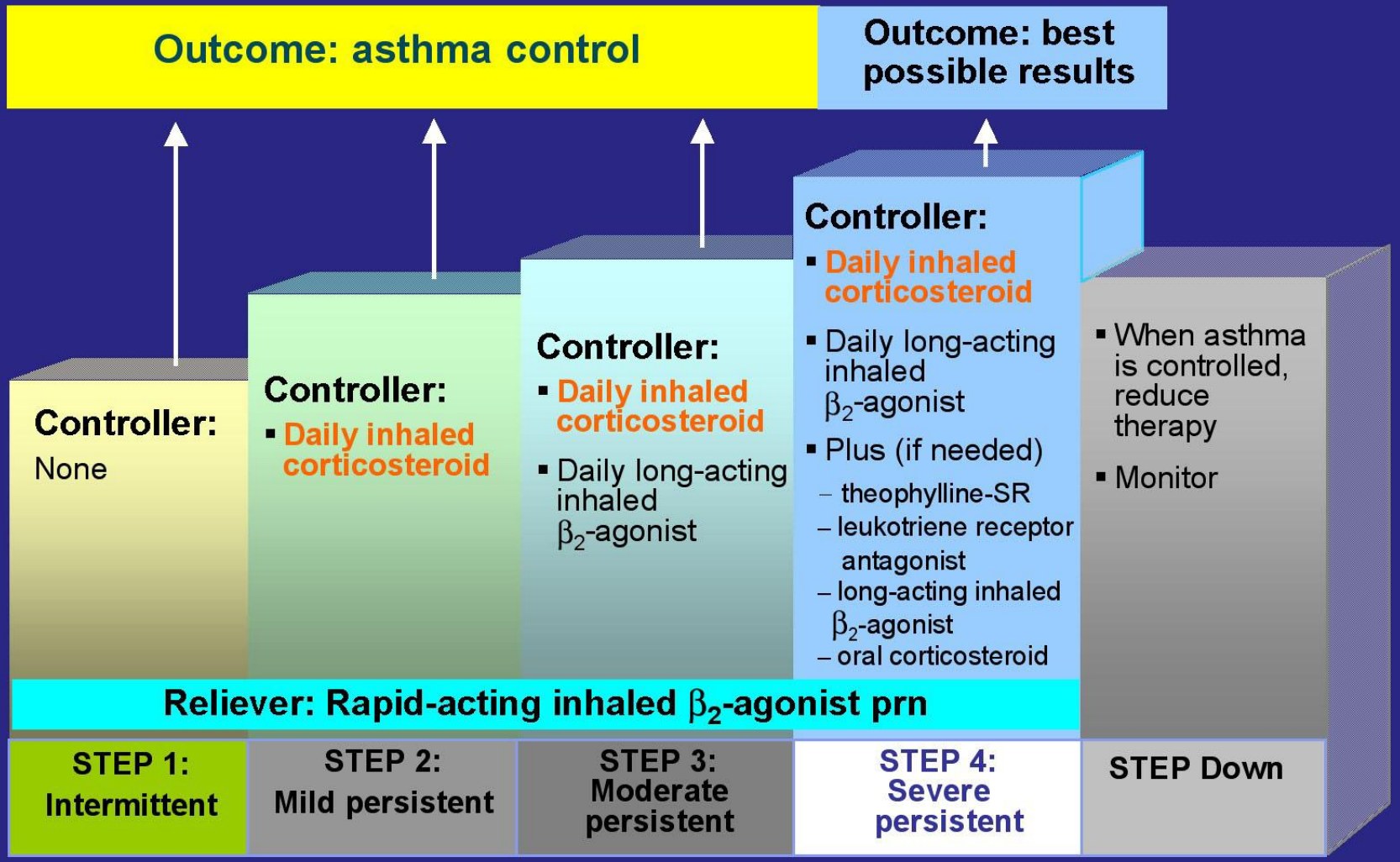
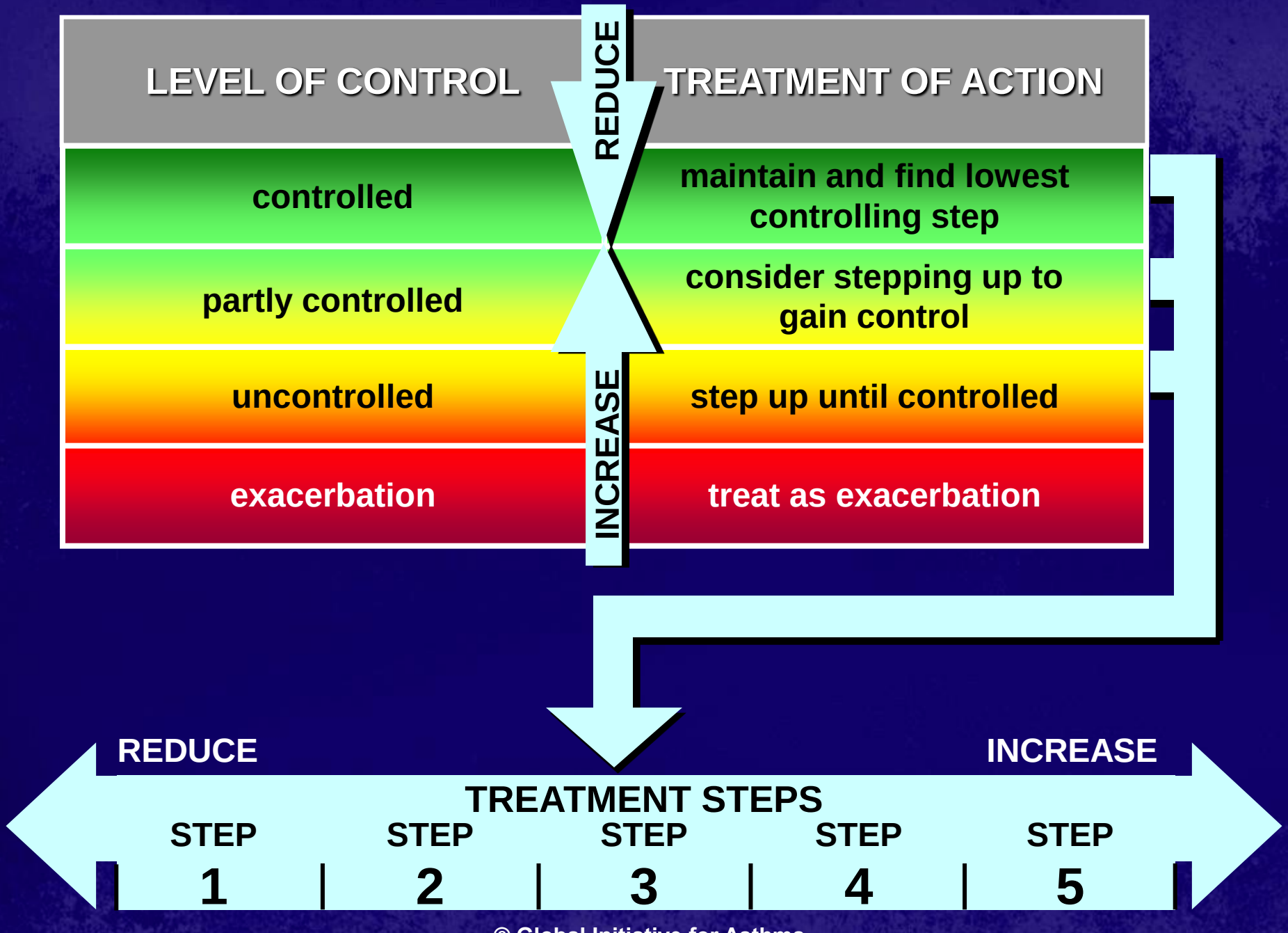
Therapy of BA

- Diagnostics
- Regular examinations and monitoring
- Depistage and control of worsening factors
- Long-term pharmacological treatment
- Management of asthma exacerbations
- Education and leading of asthamtic patients to partnership in treatment

GINA stepwise approach to asthma therapy in adults



Adapted from GINA; www.ginasthma.com, 2002.



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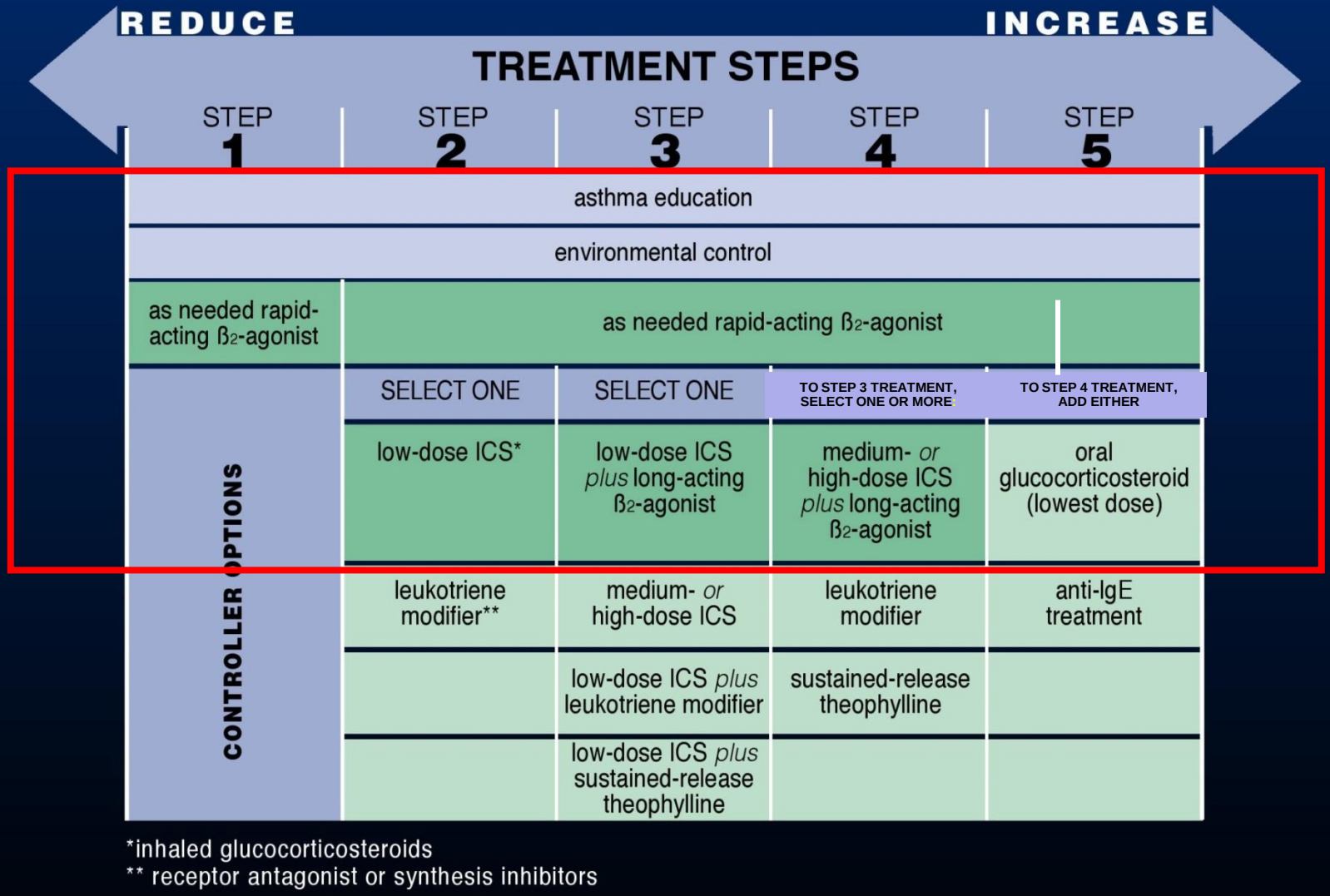

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Shaded green - preferred controller options

Therapy of acute symptoms in AB

„Relievers“ (rescuing drugs)

- **Short-acting β_2-sympatomimetics (β_2-agonists) - SABA**

  Muscarinic antagonists (anticholinergics) - SAMA

- Systemic corticoisteroids in a rescue dose
- Theophylline???

Long-term pharmacological treatment

Controllers (preventive drugs)

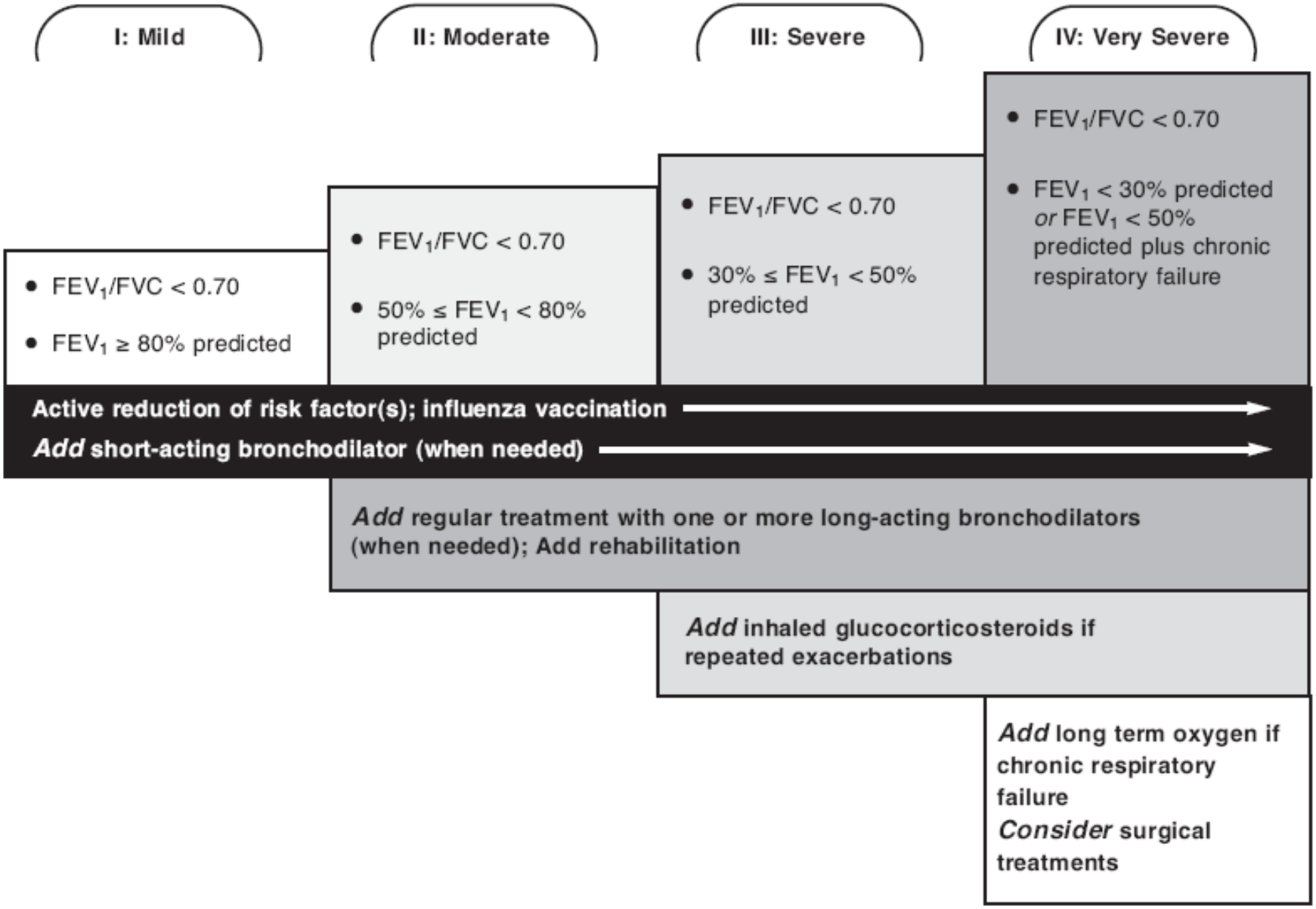
- **Inhalative and systemic corticoids**
- **Cromones**
- **Long-acting β_2-sympatomimetics (β_2-agonists) - LABA**
- **Theophyllines with sustained release**
- **Antileukotriens (LT modifiers)**
- **Omalizumab (antibodies against IgE)**

Management of COPD

- Diagnostics and disease monitoring
- Reduction of risk factors
- Treatment of stabile COPD
- Treatment of exacerbations

Figure 7. Therapy at Each Stage of COPD

Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD.



Manage Stable COPD: All COPD Patients

- Avoidance of risk factors
  - smoking cessation
  - reduction of indoor pollution
  - reduction of occupational exposure
- Influenza vaccination

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Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

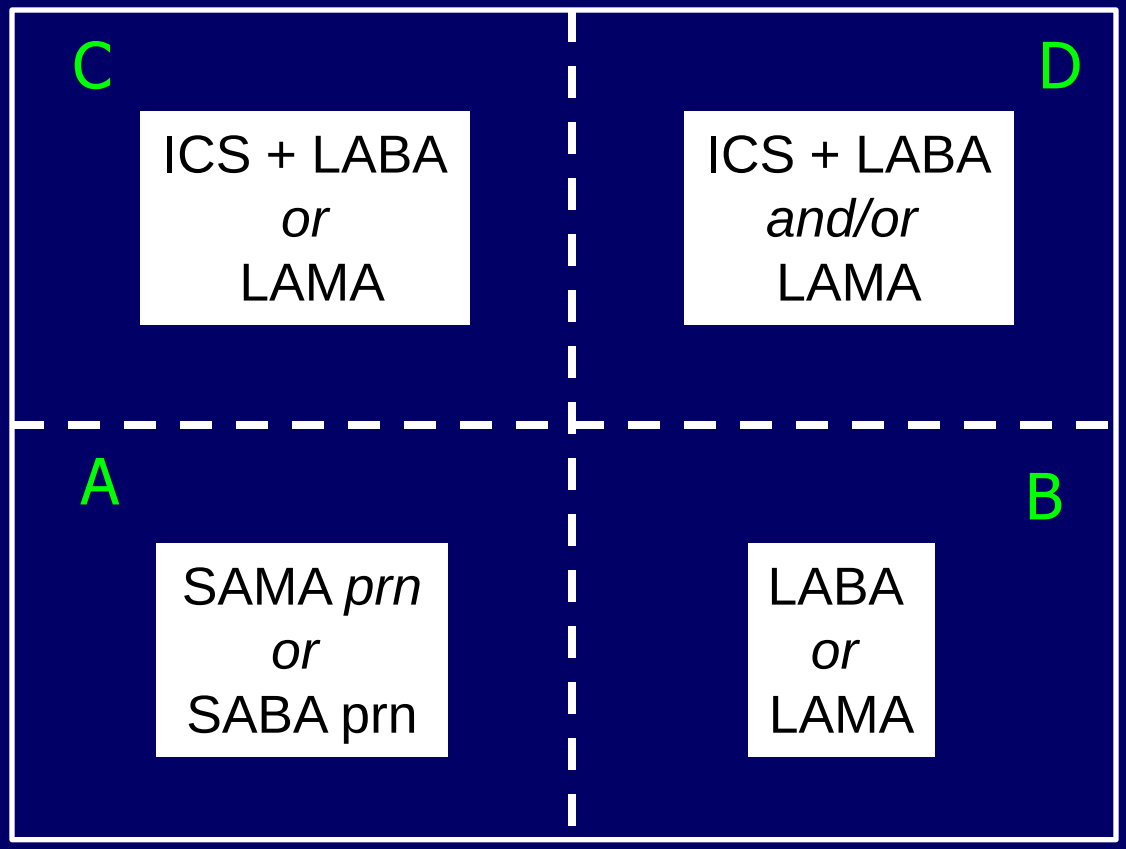
Patient	Recommended First choice	Alternative choice		Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA		Theophylline
B	LAMA *or* LABA	LAMA and LABA		SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.		SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.		Carbocysteine *SABA and/or* SAMA Theophylline

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE

http://www.catestonline.org/english/index_Slovakia.htm



GOLD 4

GOLD 3

GOLD 2

GOLD 1

2 or more
or
≥ 1 leading to hospital admission

1 (not leading to hospital admission)

0

Exacerbations per year

CAT < 10
mMRC 0-1

CAT ≥ 10
mMRC ≥ 2

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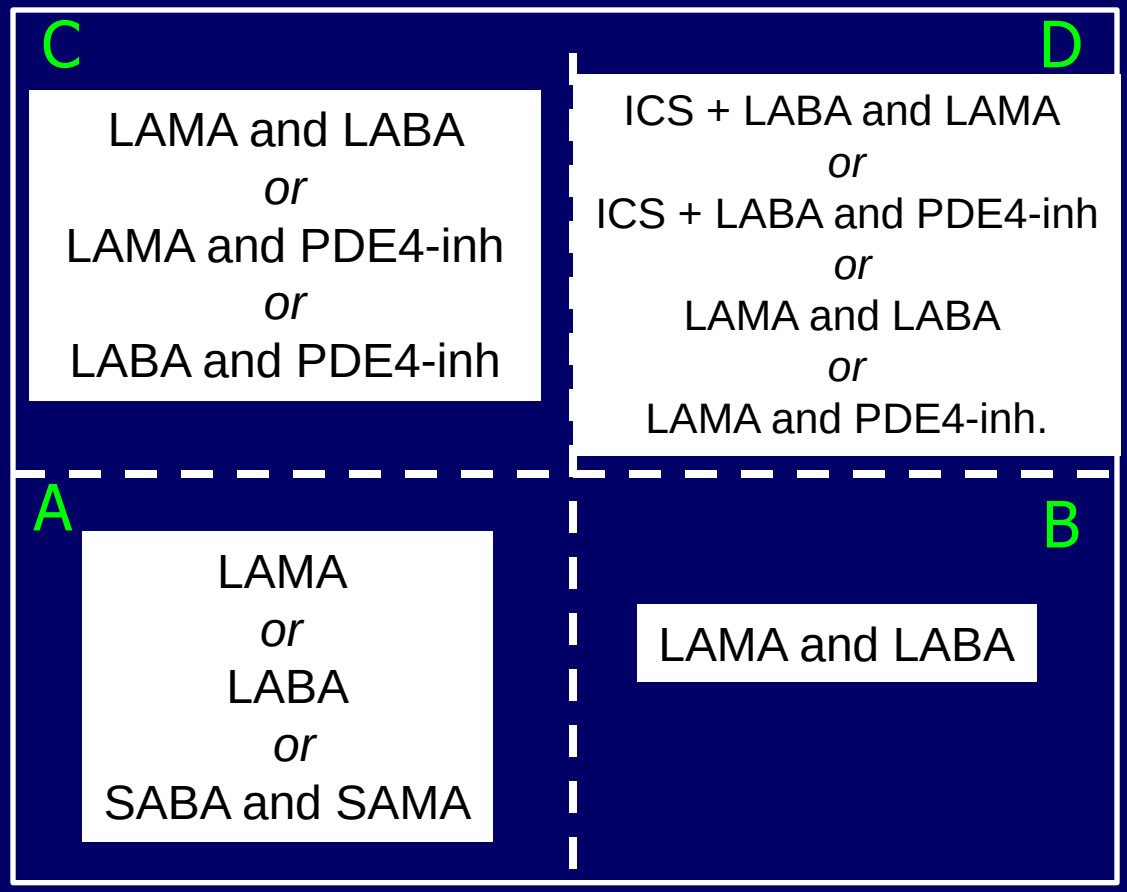
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

ALTERNATIVE CHOICE



GOLD 4

GOLD 3

GOLD 2

GOLD 1

2 or more
or
≥ 1 leading to hospital admission

1 (not leading to hospital admission)

0

Exacerbations per year

CAT < 10
mMRC 0-1

CAT ≥ 10
mMRC ≥ 2

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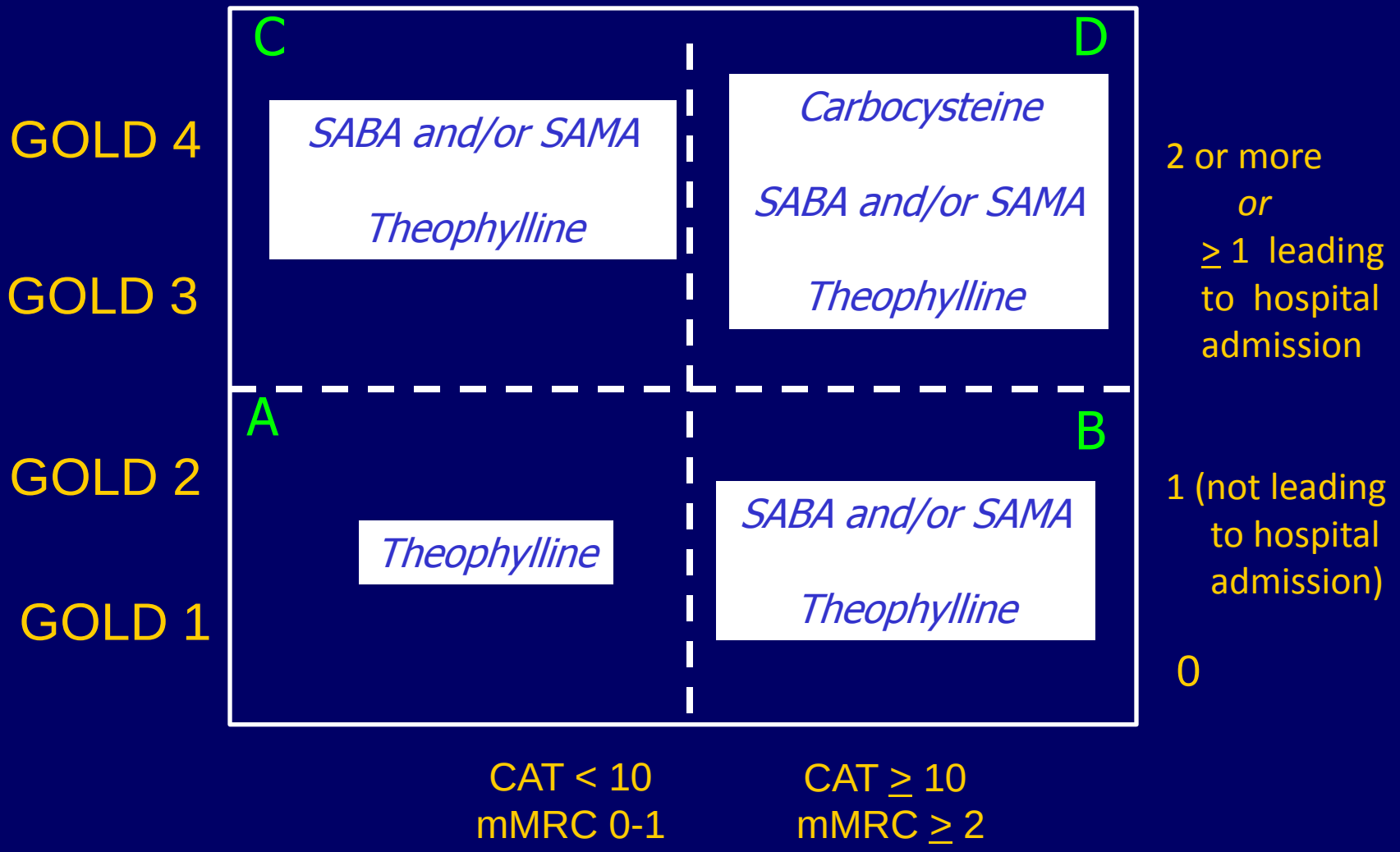
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

OTHER POSSIBLE TREATMENTS



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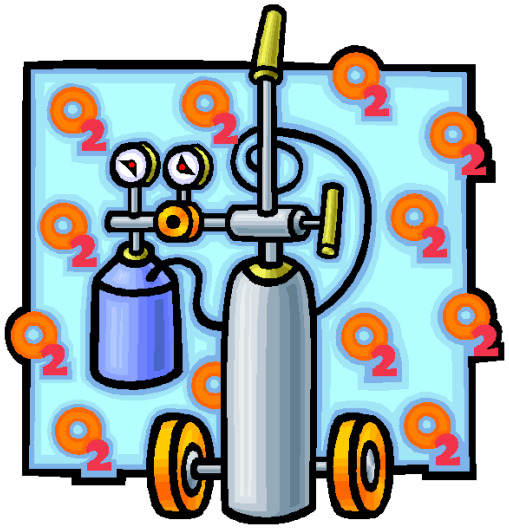
Treatment of stable COPD

Pharmacological:

- Bronchodilators
- Glucorticoids
- Other forms



Non-pharmacological:

- Smoking cessation
- Rehabilitation
- Oxygen therapy
- Mechanical assistance of ventilation
- Surgical treatment

Bronchodilators

- parasympatholytics
- β2- sympathomimetics
- metylxanthines
- combinations

Figure 9. Bronchodilators in Stable COPD

- Bronchodilator medications are central to symptom management in COPD.
- Inhaled therapy is preferred.
- The choice between β_2-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- Long-acting inhaled bronchodilators are more effective and convenient.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Other forms of pharmacotherapy

- Vaccination (influenza, pneumococcus)
- Substitutive therapy α1-antitrypsin
- Antimicrobial therapy (exacerbations)
- Mucolytics
- Antioxidants
- Imunoregulators
- Antitussives

Drugs used in the therapy of BA and COPD

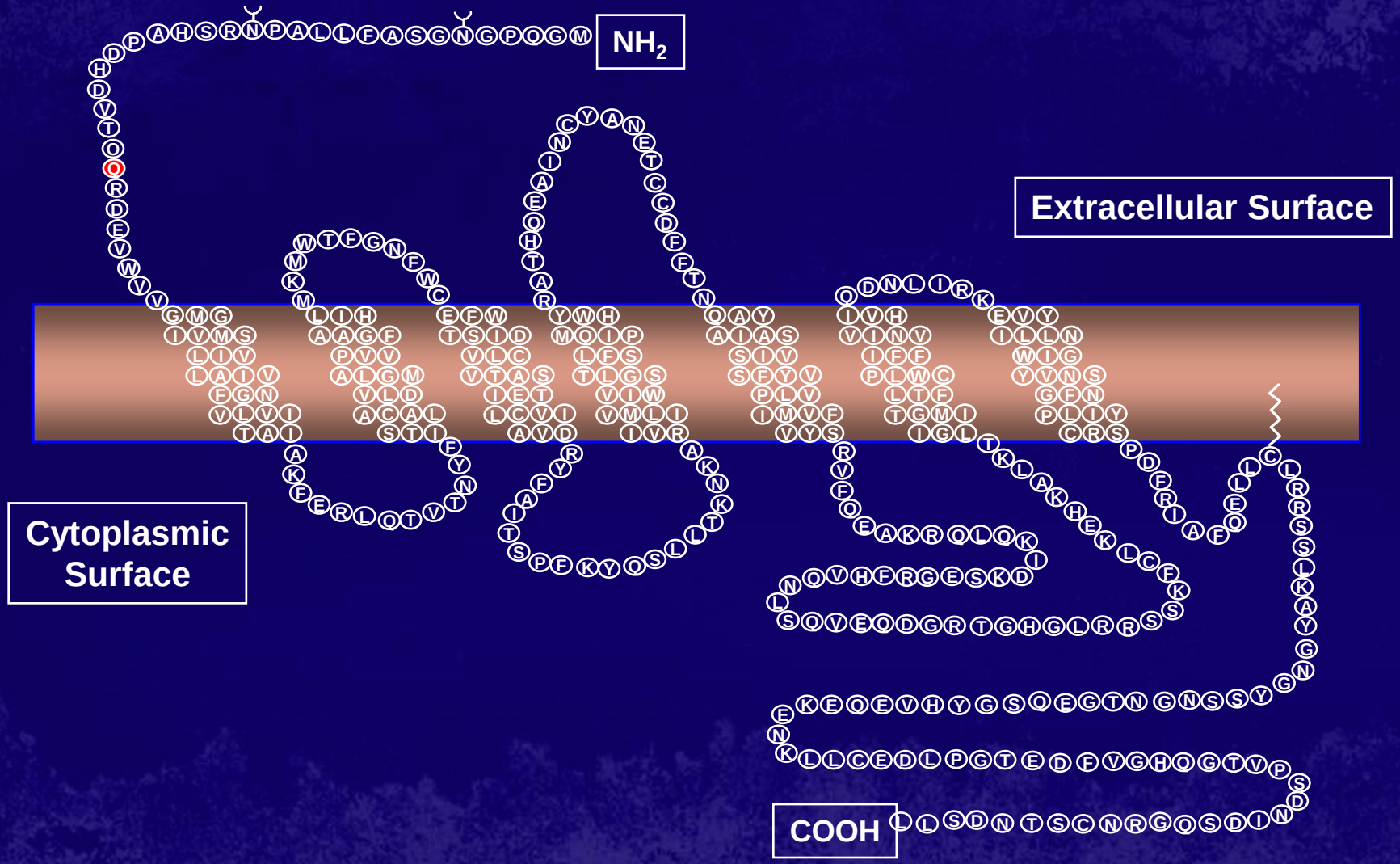
β_2-agonists - history

- 1960 – non-selective – epinephrine parenterally, inhalative isoprenaline
- 1970-1989 – selective on β_2 receptors – short-acting (salbutamol, fenoterol, terbutalin)
- Selective on β_2 receptors – with longer activity, peroral use (salbutamol as Volmax tbl., clenbuterol and procaterol in form of tbl. and syrup)
- Since 1982 – selective on β_2 receptors - long-active inhalative (long-active: salmeterol Serevent, formoterol Foradil)

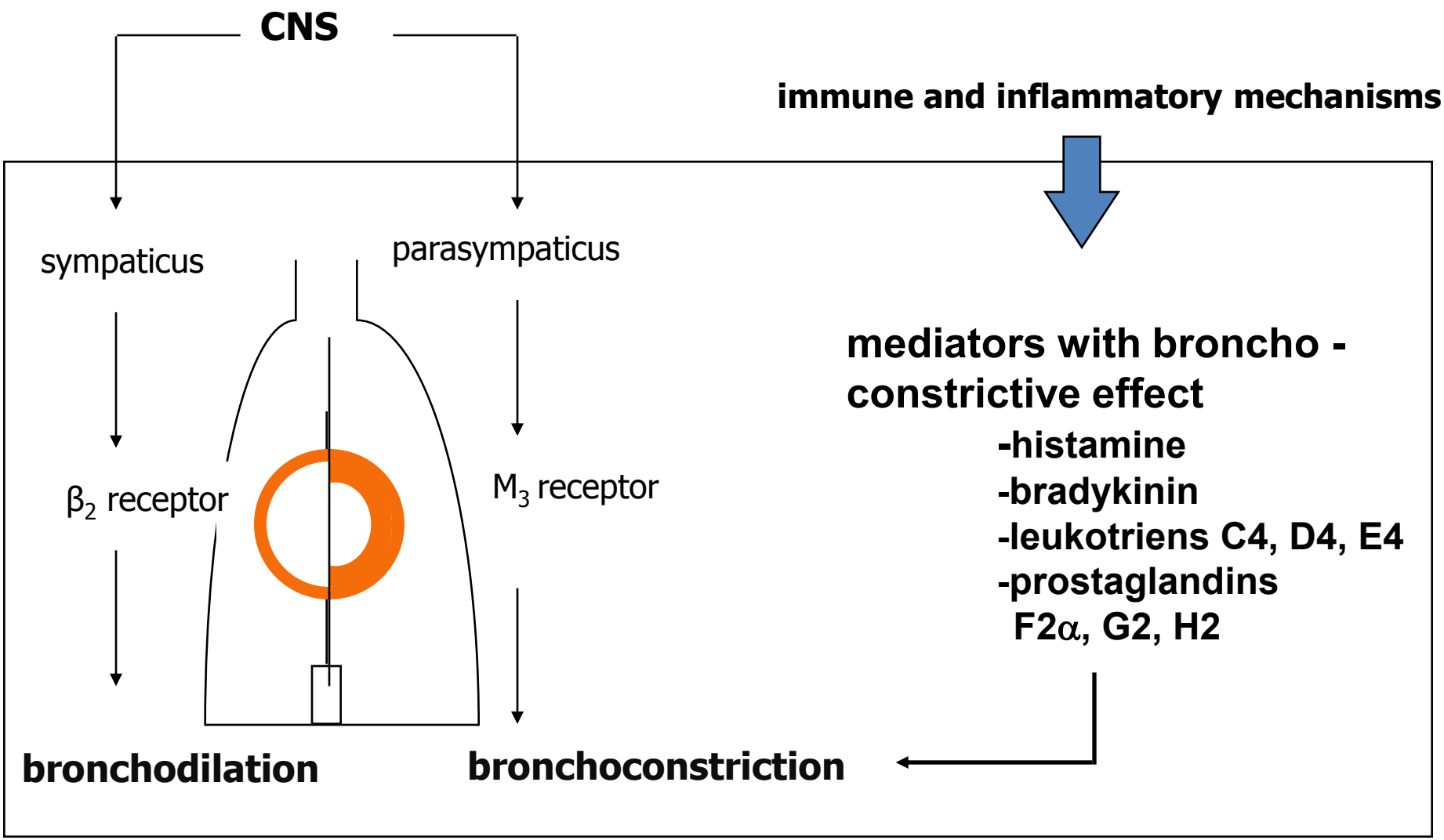
Distribution of β_1 a β_2 receptors and their effects

organ	β_1	β_2
heart	+ inotropic + chronotropic	-
vessels	-	vasodilation
bronchi	-	bronchodilation
uterus	-	tocolysis
skeletal muscles	-	tremor
fat tissue	lipolysis (β_3)	
carbohydrates metabolism		glykogenolysis

β_2 - receptor



Neurohumoral regulation of smooth muscle tone in respiratory system



Effects of ß$_2$-agonists on tracheobronchial tree

- **bronchodilation via bronchial smooth muscle relaxation**
- **inhibition of mediators releasing from mastocytes, eosinophiles and basophiles**
- **increasing of mucociliar transport via increase of cilia motion frequency**
- **smaller permeability of capillaries, relieving of mucous membrane edema caused by inflammatory mediators**
- **stimulation of epithelial cells to enhanced secretion of Cl^- and H_2O to bronchi**

Adverse effects of ß$_2$-agonists

- **tremor of sceletal muscles**
- **tachycardia, various kinds of dysrythmias**
- **metabolic changes:**
  - **increase: insuline level, lactate, pyruvate and ketones**
  - **decrease: serum levels of K^+, Ca^{++}, Mg^{++}**

- **anxiety, insomnia, confusness**
- **headache**
- **paradoxical bronchospasm**
- **allergic reactions**

Problems by regular use of β_2-agonists

- paradoxical bronchospasm
- tolerance
  - loss of bronchodilatative effect
  - loss of security from bronchoprovocative stimuli
- increase of bronchial hyperreactivity
- increase of morbidity
- increase of mortality

Contraindications of β_2-agonists

- hyperthyreosis
- IHD, dysrhythmias
- hypokaliemia
- hypersensitivity to preparation
- sympathomimetics overdosing

Role of ß$_2$-agonists in the therapy of obstructive airways diseases = the base of symptomatic treatment

Bronchial asthma

- drug of choice in acute exacerbation of asthma - as „reliever"
- preventive drug in asthma induced by effort
- in monotherapy indicated only in intermittent asthma
  - i.e. dyspnea attacks les than 1x per week
  - Night dyspnea less than 2x per month
  - PEF, FEV1 better than 80% and their variability is under 20%
- - all other levels of asthma – basic symptomatic drug - „rescue treatment"

COPD

- basic symptomatic drug - if the disorder is min. partially reversible

Other

- in patients with airways diseases with presence of obstruction – as basic symptomatic drug (bronchiectasis, obliterating bronchiolitis etc.)

β_2-agonists

A. SABA

- **Salbutamol** — **VENTOLIN, VENTILASTIN**
- **Fenoterol** — **BEROTEC (with ipratropium – BERODUAL)**
- **Terbutalin** — **Bricanyl**
- **Albuterol** — **Proventil**
- **Levalbuterol** — **Xopenex**

B. LABA - peroral

- **Salbutamol** — **SALBUTAMOL, VENTOLIN tbl**
- **Clenbuterol** — **SPIROPENT sir.**
- **Procaterol** — **Lontermin**

C. LABA - inhalatory

- **Salmeterol** — **SEREVENT (with fluticasone SERETIDE)**
- **Formoterol** — **FORADIL , OXIS, FORMANO, FORMOVENT (with budesonide SYMBICORT, with fluticasone FLUTIFORM, with beclomethasone FOSTER)**
- **Indacaterol** — **ONBREZ, HIROBRIZ, ULTIBRO, ULUNAR (with glycopyrronium)**
- **Vilanterol** — **RELVAR ELLIPTA (with fluticasone furoate)**
- **Olodanterol** — **STRIVERDI**

History of parasympatholytics (anticholinergics, muscarinic antagonists)

Datura stramonium – inhalation of stalk smoke – beneficial in asthmatics

- 1833 isolation of atropin (in that time daturin)

Atropa belladonnae

- 1900 sir Cohen – therapy of asthma by supraren extract (sympatomimetics + corticosteroids)

Effects of parasympatholytics

Quarternary nitrogen derivatives

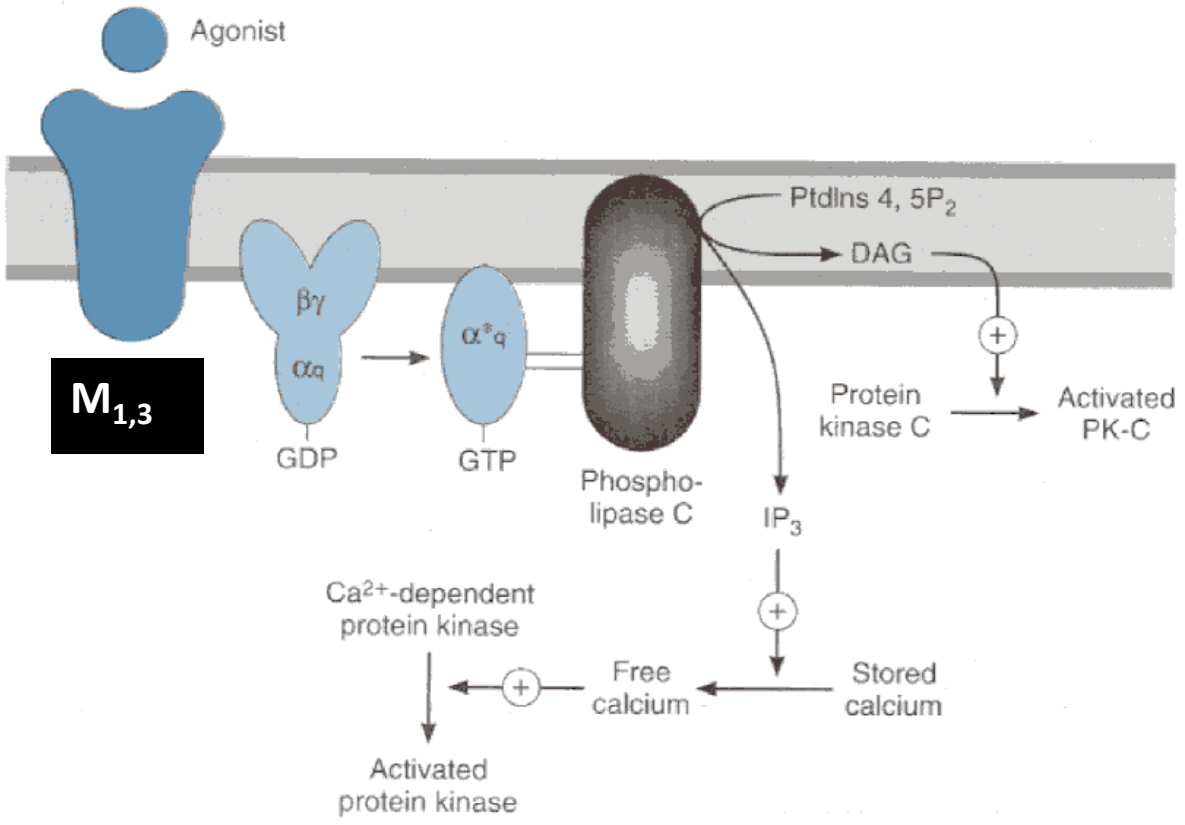
- **Bronchodilation**
- **Inhibition of bronchoconstriction**
- **Inhibition of airways mucus secretion**
- **Enhanced selectivity to smooth muscle**
- **No absorbtion in intestine**
- **No crossing through blood-brain barrier**

Mechanism of action

Influencing of M receptors

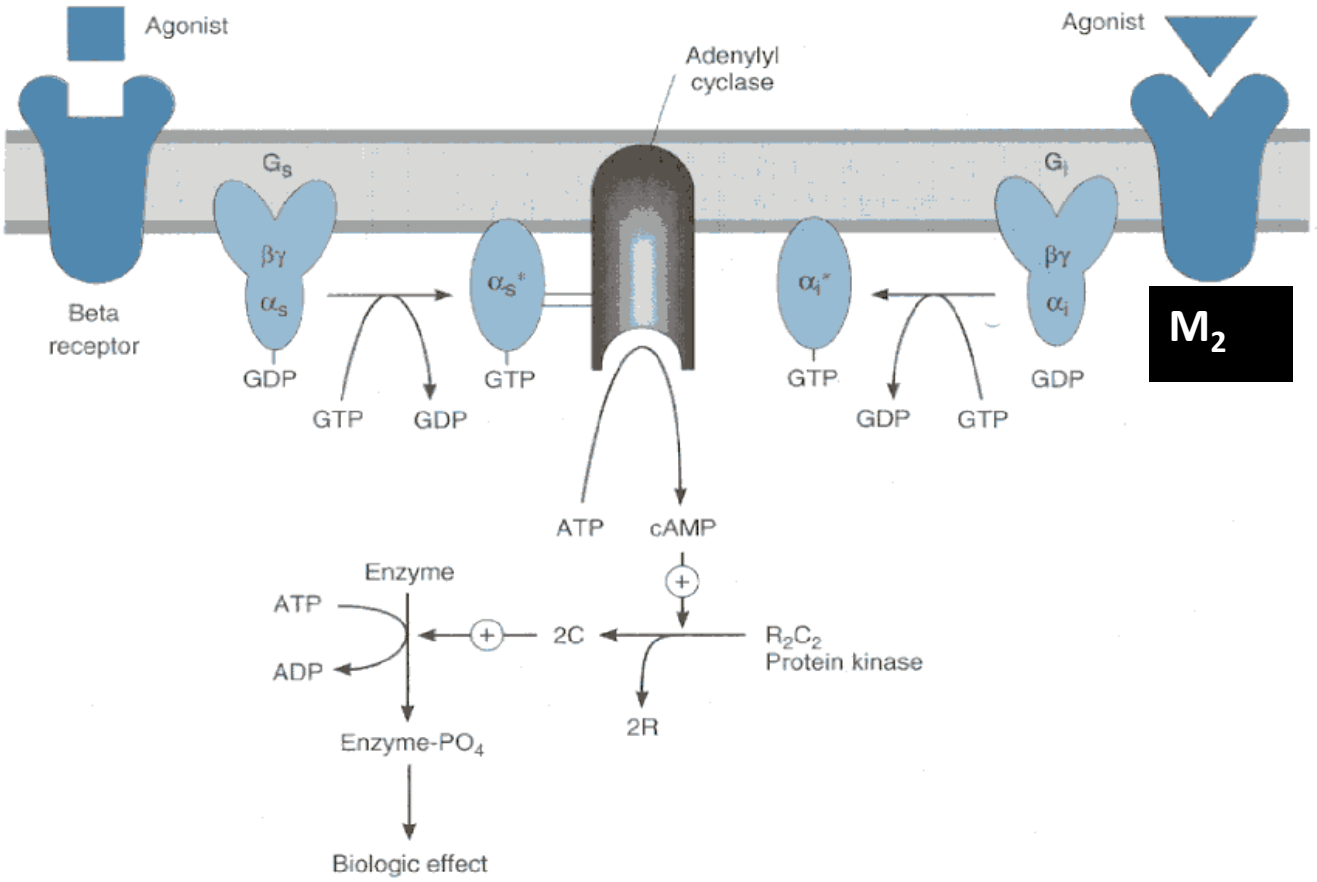
- M_1 – parasympathetic ganglions – mediation of transmission, submucosal glands, alveolar epithelium
- M_2 – presynaptic membrane of nerve endings – inhibition of ACH release
- M_3 – smooth muscle, submucously, endothelium of vessels, bronchial epithelium

M_1 and M_3 receptor

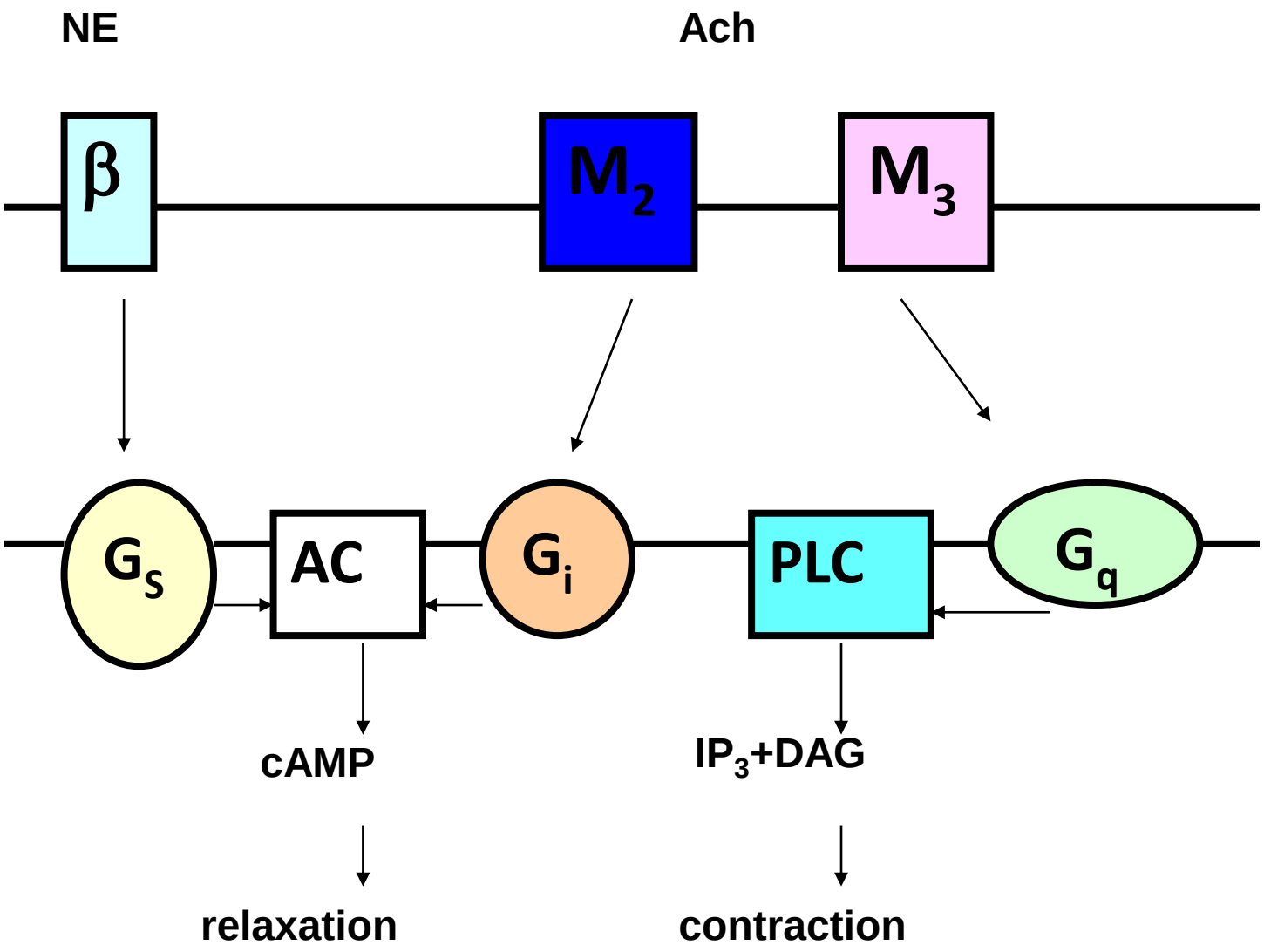


Like α_1 receptor, via $G_{q/p}$ protein

M_2 receptor



Like α_2 receptor, via G_i protein


NE
Ach
β
M2
M3
GS
AC
Gi
PLC
Gq
cAMP
IP3+DAG
relaxation
contraction

Parasympatholytics

- Ipratropium bromid ATROVENT
- Oxitropium bromid Oxivent
- Tiotropium bromid SPIRIVA
- Aklidínium bromid BRETARIS GENUAIR
- Glykopyrónium bromid SEEBRI BREEZHALER

Parasympatolytics in combination

- Ipratropium bromid + fenoterol - BERODUAL
- Ipratropium bromid + salbutamol - Combivent
- Glycopyrronium + indakaterol

Tiotropium bromid

- Slower onset than ipratropium, longer time of persistance at M receptors
  - M_1 – 14,6 h
  - M_2 – 3,6 h
  - M_3 – 34,7 h (ipratropium 16 min)

Pharmacodynamic type of selectivity

History of xanthines

Caffeine	1820	coffee bean
Theobromine	1842	cocoa berry
Caffeine	1885	Fisher and Ach
Theophylline	1888	tea leaves
Theophylline	1937	clinical use

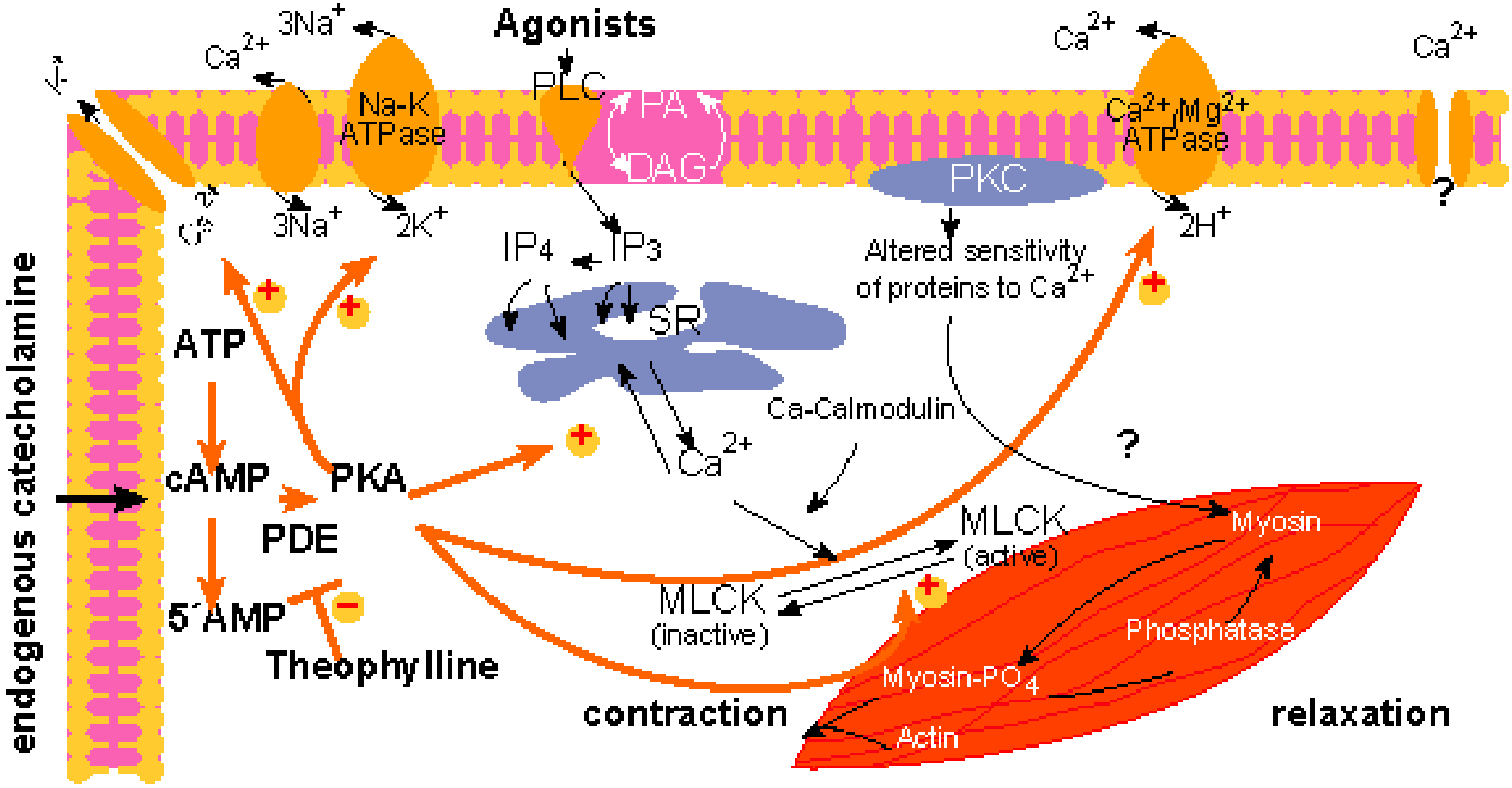
- **Seventies years Aerolate – SR formulation**
- **10years ago – third place for xanthines in the treatment of obstructive diseases**
- **Use on the first place in COPD in Italy, on the second place in Austria and Germany**

Mechanism of action

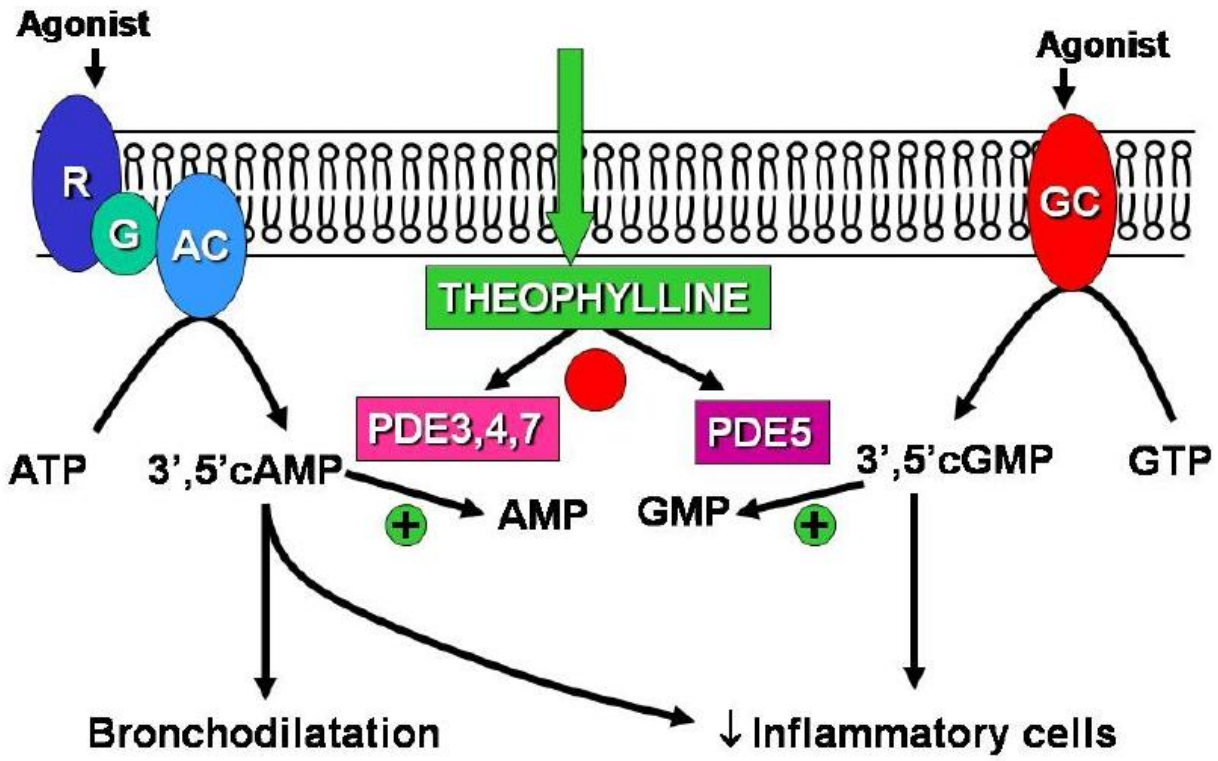
- **Inhibitory**
  - ↓ activity of **PDE**
  - ↓ activity of **adenosine receptors** (A_1, A_{2A}, A_{2B}, P_{2Y})
  - ↓ intracellular release of **Ca^{2+}**
  - ↓ release of various **mediators**
  - ↓ production and effects of **prostaglandins**
  - ↓ release of **acetylcholine**
  - ↓ activity of **NF-κB** (its nuclear translocation)
- **Stimulatory**
  - ↑ activity of **histone-deacetylase**
  - ↑ release of **IL-10**
  - ↑ release of **epinephrine**
  - ↑ production of **musuc**
  - ↑ **mucociliar** transport
  - ↑ secretion of **surfactant**
  - Membrane stabilisation – opening of **maxi-K^+ channels**
  - ↑ **apoptosis**
  - ↑ scavanging of **ROS**

Nosáľová 2000, Barnes 2005, Spicuzza et al. 2006, Tilley 2011

Regulation of Airway Smooth Muscle Contraction and Relaxation



Theophylline – non-selective PDE inhibitor



Key: R = receptor, Gs = stimulatory G-protein, AC = adenylyl cyclase, GC = guanylyl cyclase, PDE = phosphodiesterase, cAMP = cyclic adenosine monophosphate, ATP = adenosine triphosphate, cGMP = cyclic guanosine monophosphate, GTP = guanosine triphosphate.

Barnes PJ. *Pharmaceuticals* 2010, *3* (3), 725-747

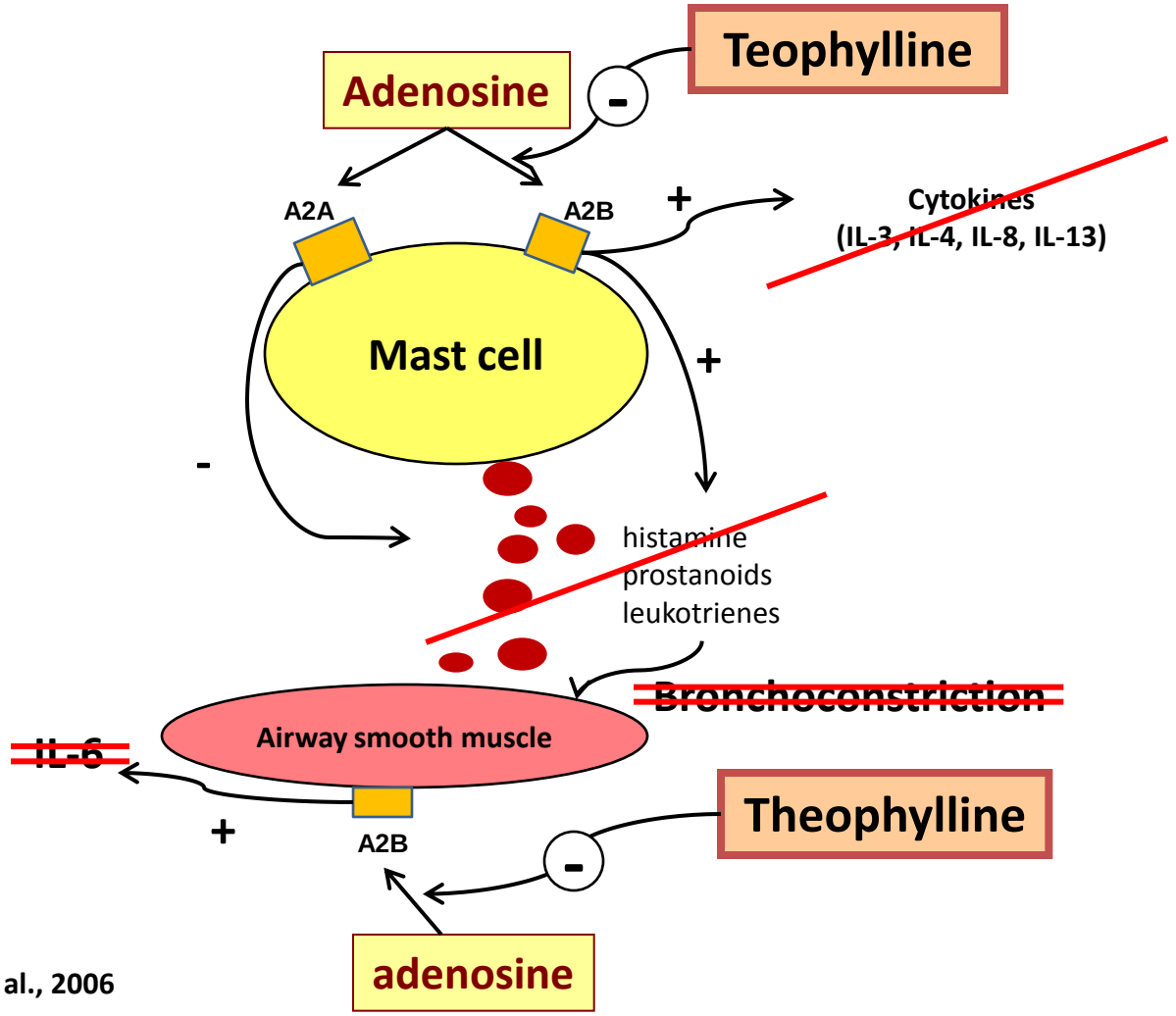
PDE isoenzymes

⇒ **direct cell localisation**

⇒ **modulate:**

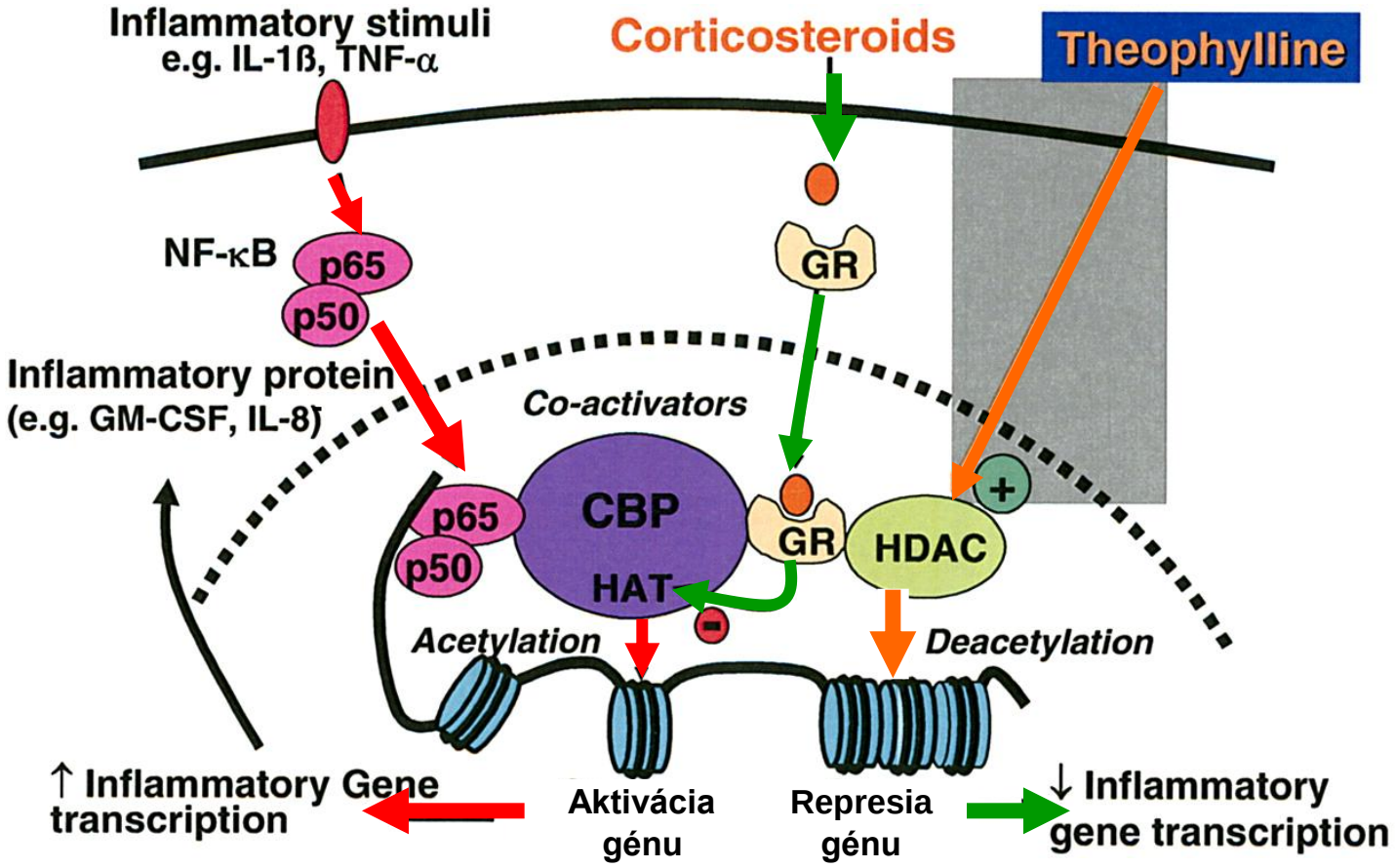
- eozinophiles – PDE 4
- neutrophiles – PDE 4
- macrophages – PDE 3 a 4
- T-lymphocytes – PDE 3,4 a 5
- airways smooth muscle – PDE 3 a 4

Teophylline – antagonist of adenosine receptors



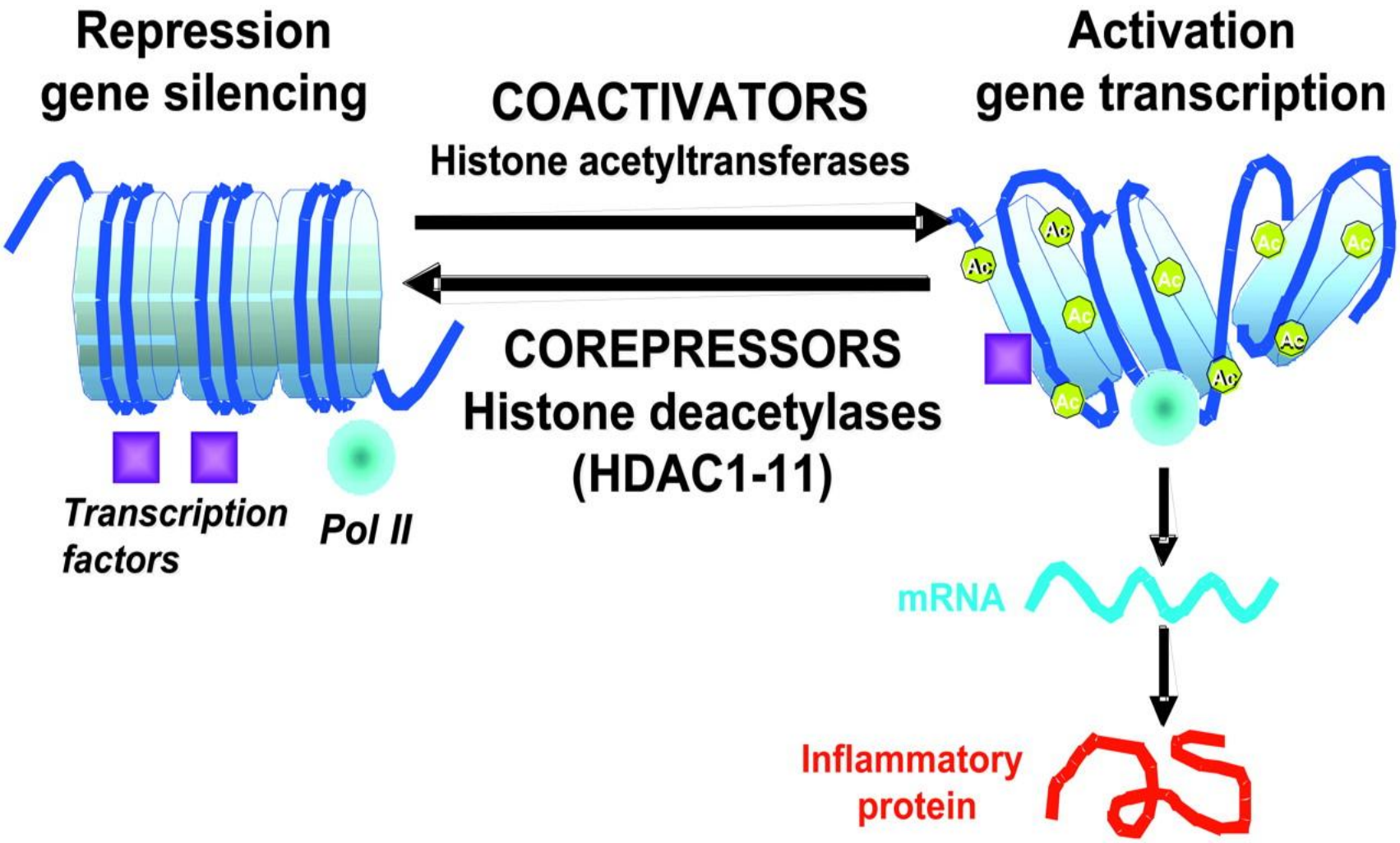
Holgate, 2005, Spicuzza et al., 2006

Mechanism of action – influencing HDAC



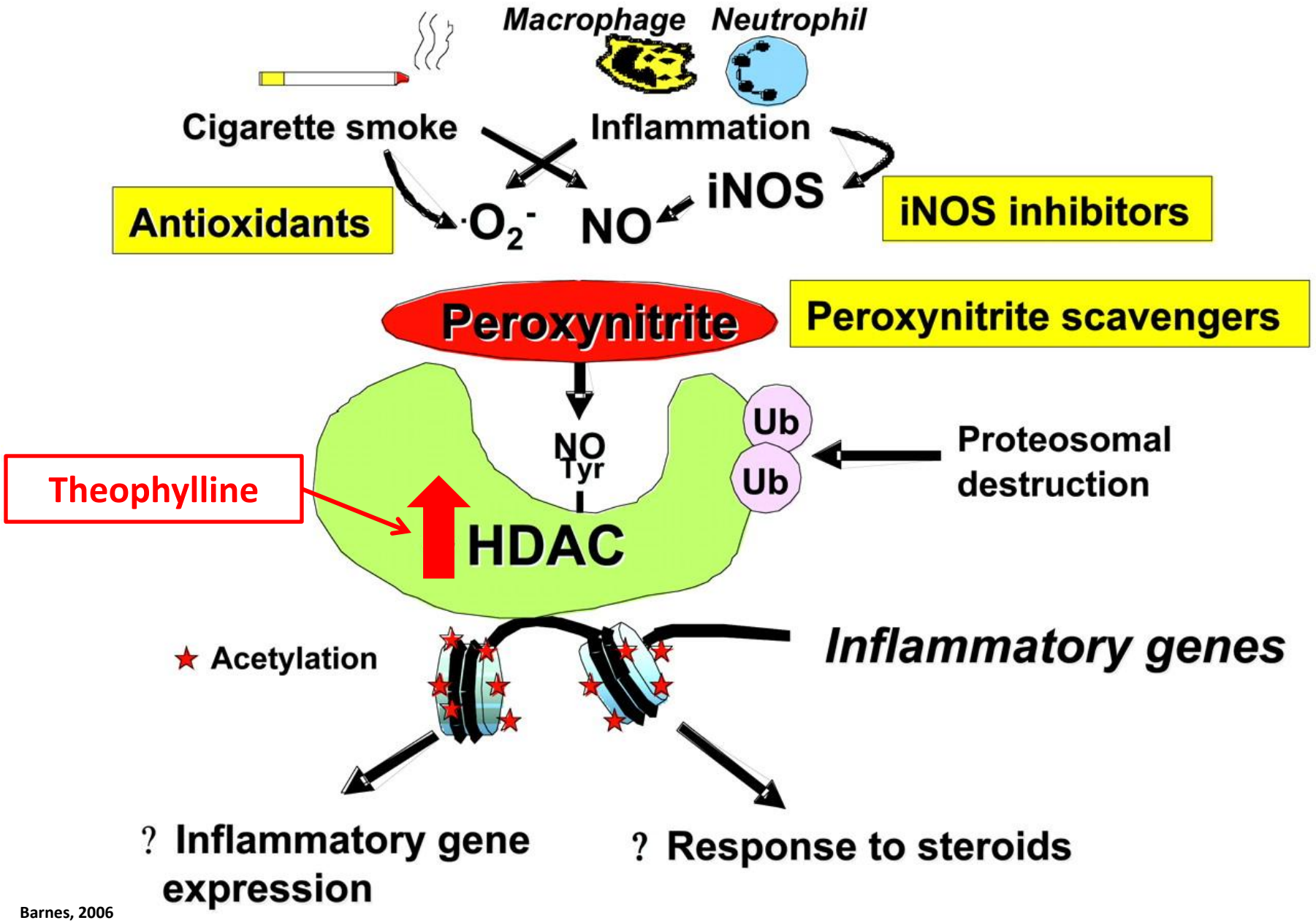
Barnes PJ, 2005

Chromatin remodeling and gene expression



Barnes, 2006

Reasons for decreased activity of HDAC in COPD



Barnes, 2006

Xanthines effects

Pulmonary:

- ✓ **bronchodilation**
- ✓ **increase mucocilliary transport**
- ✓ **decrease bronchial reactivity**
- ✓ **inhibition of mediator releasing**
- ✓ **suppression of inflammation**
- ✓ **decrease pulmonary hypertension**
- ✓ **suppression of pulmonary vessels permeability**

Xanthines effects

Extrapulmonary:

- ✓ **increase of diaphragm contractility**
- ✓ **heart and vessels (↓ PVR and BP, dilation of coronary arteries, inotropy)**
- ✓ **CNS stimulation**
- ✓ **enhances diuresis**
- ✓ **increase gastric secretion**
- ✓ **suppression of uterus contractions**
- ✓ **stimulation of respiratory centre**

Xanthines nowadays

- Preference of SR forms (slow, sustained release)
- Use as bronchodilators after β_2-agonists and anticholinergics
- Use particularly in COPD, less in asthma
- Monitoring of activity by determination of serum or saliva concentration of theophylline and its relation to effect
- New classes of PDE and their inhibitors

Indications of xanthines in COPD

Peroral SR forms

- ✓ moderate and severe obstruction (especially 3rd and 4th stage)
- ✓ prevention of night obstructions and O_2 desaturation
- ✓ disease of small bronchioles
- ✓ no response to previous antiphlogistic and bronchodilatatory therapy

Indications of xanthines in COPD

Peroral forms with short effect

- ✓ **only in cases with better individual toleration**

Intravenous form

- ✓ **acute exacerbations of COPD, event. with decompensation of cor pulmonale, where did not help usual therapy (essential monitoring)**

Metylxanthines – interactions in COPD

Increased metabolism of theophylline	Decreased metabolism of theophylline
Tobacco smoking Anticonvulsives Rifampicin Alcohol	Elderly Arterial hypoxemia(PaO2 6 kPa, 45 mm Hg) Respiratory acidosis Heart failure Liver cirrhosis Erythromycine Chinolons Cimetidine Viral infections

Monitoring of theophylline concentrations in serum

- **Recommended level is various in different authors**
- **Barnes 1999: 8 – 15 mg/l**
  - **5-10 mg/l – anti-inflammatory**
  - **10-15 mg/l - bronchodilating**

Adverse effects of xanthines

Most often in dose more than 20 mg/l

- **from 5 mg/l – headache, nausea, GIT discomfort, restlessness, hyperacidity, increased diuresis**
- **from 15 mg/l – arrhythmias, vomiting**
- **from 20 mg/l – hypo- or hypertension, hyperglycaemia, possible brain damage**

Contraindications of xanthines

- acute peptic ulceration
- epilepsy
- gastroesophageal reflux
- allergy

Metylxanthines

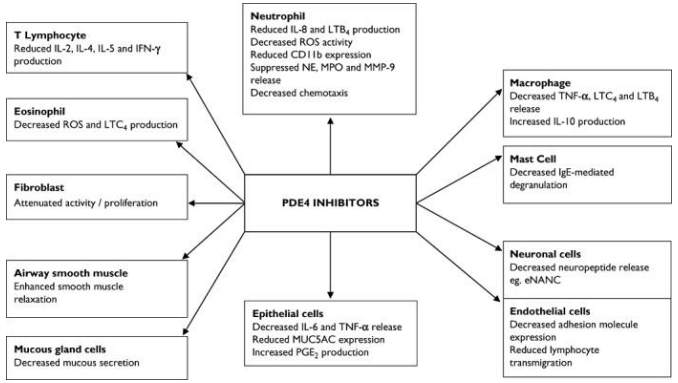
- **Theophyllin 12 h – AFONILLUM SR, EUPHYLLIN CRN (RESPICUR), Euphylong, Spophyllin retard, Teotard, Theo-Dur, Theodyl, THEOPLUS, Theophyllard**
- **Theophyllin 24 hours – Uni-Dur SR, Unilair**
- **Aminophyllin short – SYNTOPHYLLIN, Aminophyllin**
- **Aminophyllin 12 h – Aminophyllinum retard Lek**
- **Etofyllin – short – Oxyphyllin**
- **Etofyllin + theophyllin - Oxantil**

Perspectives of PDE inhibitors

- **11 classes of PDE**
- **In COPD the best are inhibitors of PDE 4, event. combination of 3 and 4**
- **Inhalatory , perorally**
- **Milrinon (3), enoximon (3), rolipram (4), zardaverin (3,4), benafentrin (3,4), zaprinast (5), motapizon (3), Ariflo (SB 20499, 4), denbufyllin (4)**

Selective PDE4 inhibitors

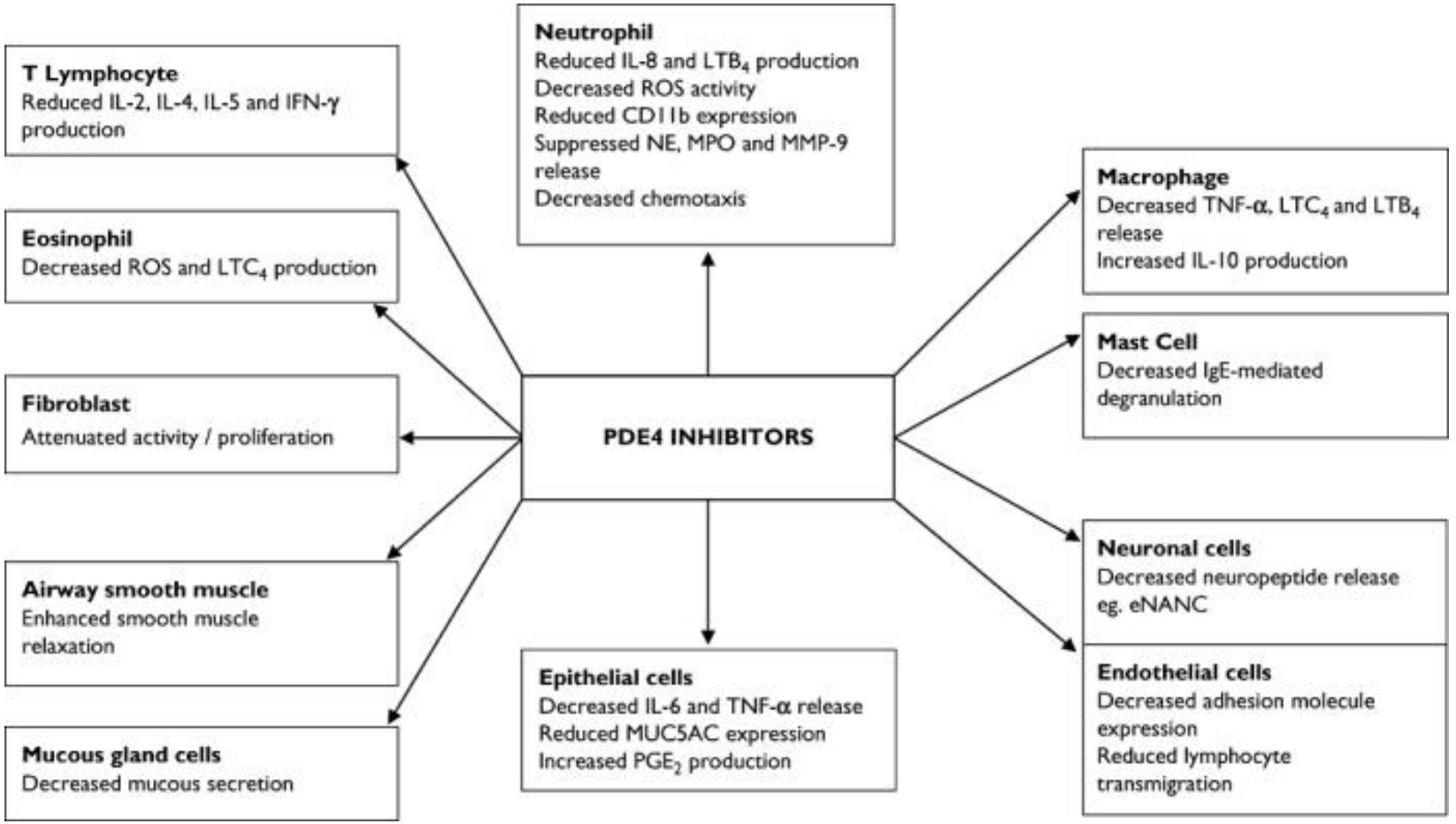
- increase **cAMP**
- ↓ activation of T-cells
- ↓ WBC functions
- ↓ activation of macrophagues
- relax ASM (dual inhibition of PDE3/4)
- ↓ cytokine release (TNF-α)



  - **rolipram, citalopram** – 1st generation → AE (nausea, vomiting)
  - **cilomilast, roflumilast, piclamilast** – 2nd generation→ same antiinflammatory and immunomodulatory effects, less bronchodilation, less adverse effects

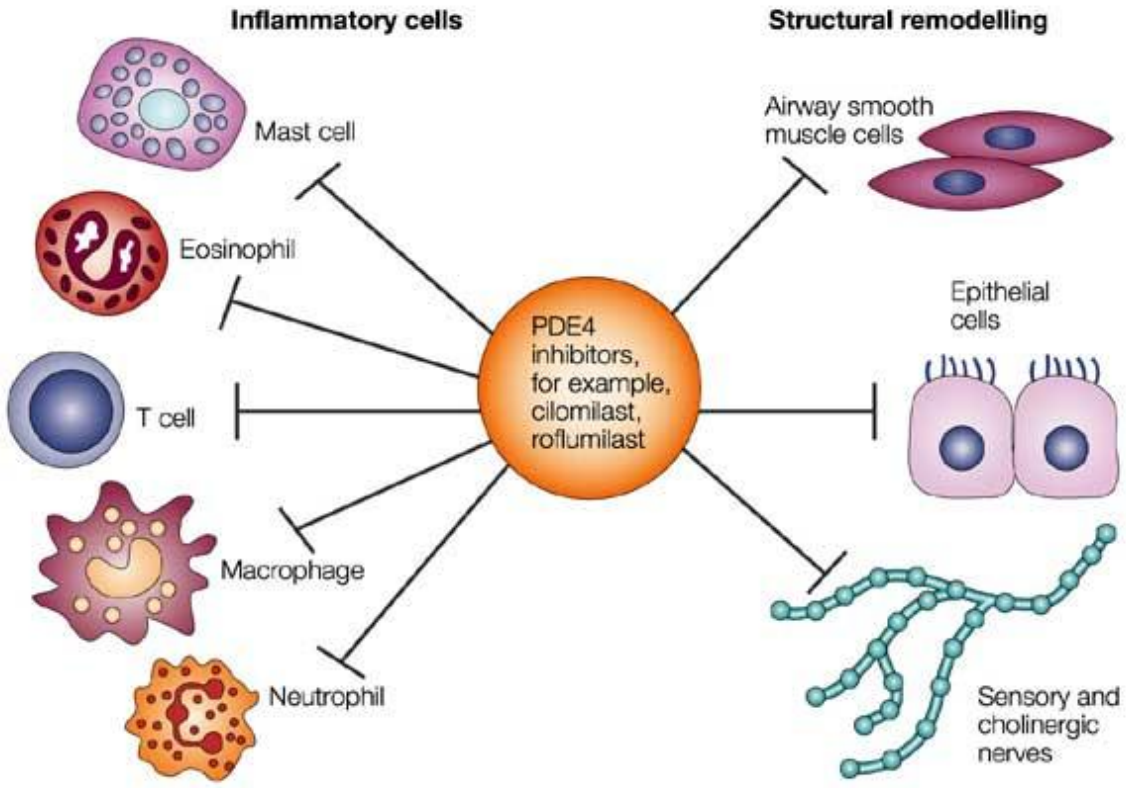
Giembycz et al. 2005, Sanz et al. 2005, Lipworth 2005, Antoniu 2006, Karish a Gagnon 2006, Spina 2008, Barnes 2009, Vestbo et al. 2009, Wang et al. 2010

PDE4 inhibitors and inflammation



Currie et al. 2008, Boswell-Smith et al. 2006

PDE4 inhibitors and inflammation



Barnes, *Nature Reviews Drug Discovery 2004* , 3, 831-844
Hatzelmann et al. 2010

New recently aproved PDE4 inhibitor

- **roflumilast** (DAXAS) **–** July 2010 – approved by **EMA for use in EU**
- Once daily, p.o. tablets, 500 µg
- ***Indication:*** **maintenance treatment of severe COPD (FEV1 post-brochodilator less then 50% predicted) associated with chronic bronchitis in patients with a history of frequent exacerbations as add on to bronchodilator treatment**
- AE – diarrhoea (5,9 %), weight loss (3,4 %), nausea (2,9 %), abdominal pain (1,9 %) and headache (1,7 %).

http://www.ema.europa.eu/docs/sk_SK/document_library/EPAR_-_Summary_for_the_public/human/001179/WC500095211.pdf

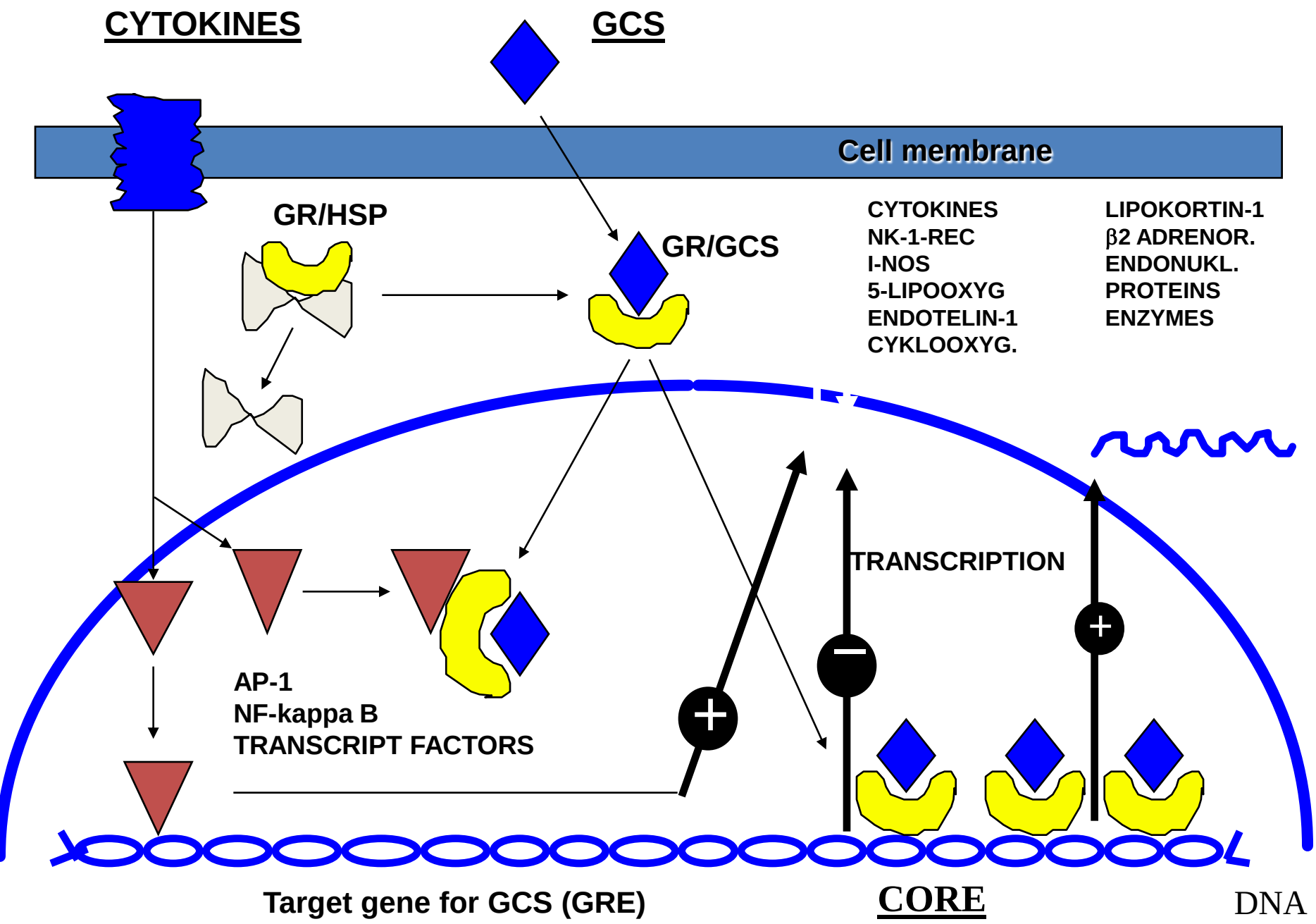
Corticosteroids

- **Systemic – since 1949 – preventive and rapid-acting antiasthmatics**
- **Inhalative – last 20 years – preventive antiasthmatics (controlors)**

- **1970 TAA - Triamcinolon Acetate**
- **1972 BDP - Beclometazon dipropionate**
- **1978 FLU - Flunizolid**
- **1980 BUD - Budesonid**
- **1993 FP - Fluticazon propionate**
- **1996 MOM - Mometazon Furoate**

Corticosteroids

- not as direct muscle relaxants (however, indirect bronchodilators)
- strong suppression of inflammatory response e.g. by inhibition of arachidonic acid release from cell membranes, decreased production of PG and LT (inflammation mediators)
- stopping the migration and decrease of bronchial hyperreactivity, edema suppression
- prevention of chronic irreversible changes (hypertrophy and hyperplasia of airways smooth muscle, subendothelial fibrosis and thickening of mucous basal membranes)
- increase sensitivity and expression of β-adrenergic receptors of smooth muscles to β_2 -agonists


CYTOKINES
GCS
Cell membrane
GR/HSP
GR/GCS
CYTOKINES
NK-1-REC
I-NOS
5-LIPOOXYG
ENDOTELIN-1
CYKLOOXYG.
LIPOKORTIN-1
β2 ADRENOR.
ENDONUKL.
PROTEINS
ENZYMES
TRANSCRIPTION
AP-1
NF-kappa B
TRANSCRIPT FACTORS
Target gene for GCS (GRE)
CORE
DNA

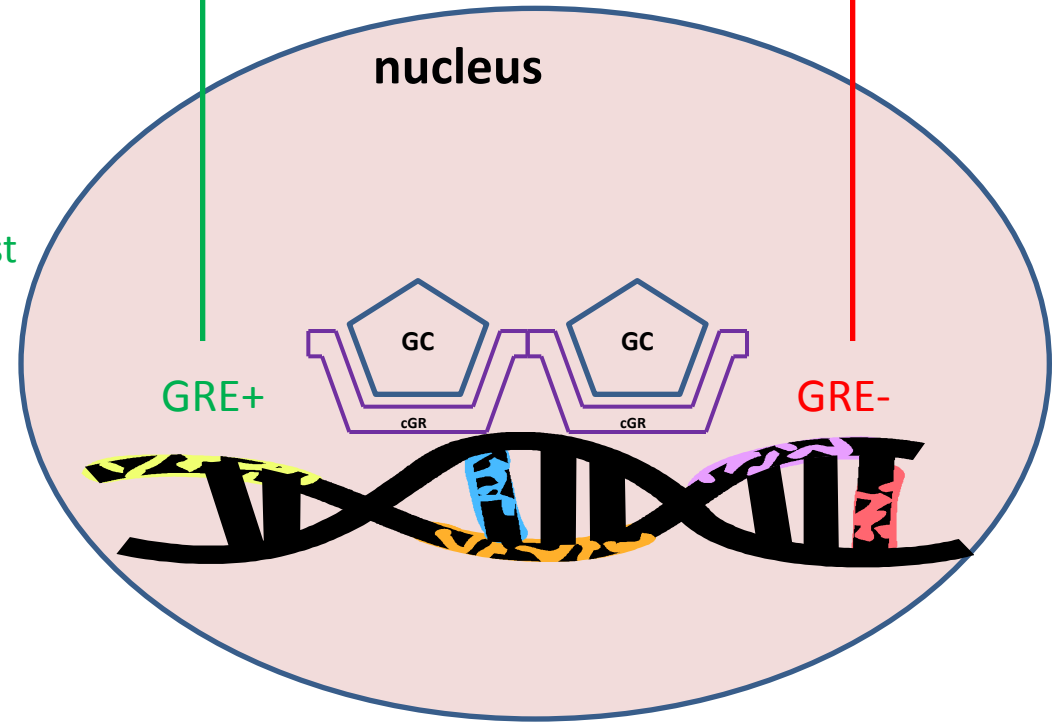
Trans-activation

↑ transcription of genes coding antiinflammatory proteins

↑ lipocortin-1

↑ interleukin-10

↑ interleukin-1-receptor antagonist



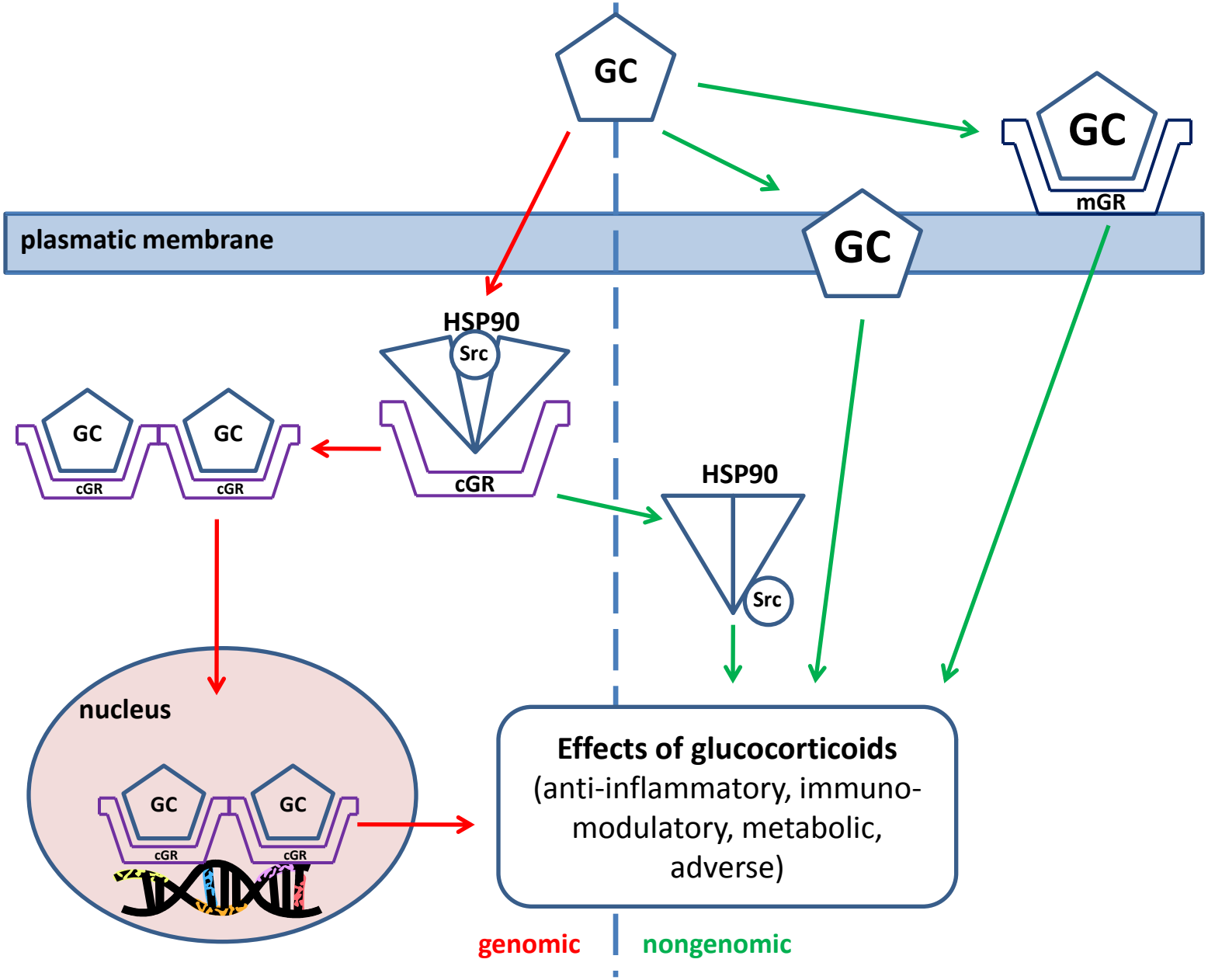
Trans-repression

↓ AP-1

↓ NF-κB

↓ IRF3

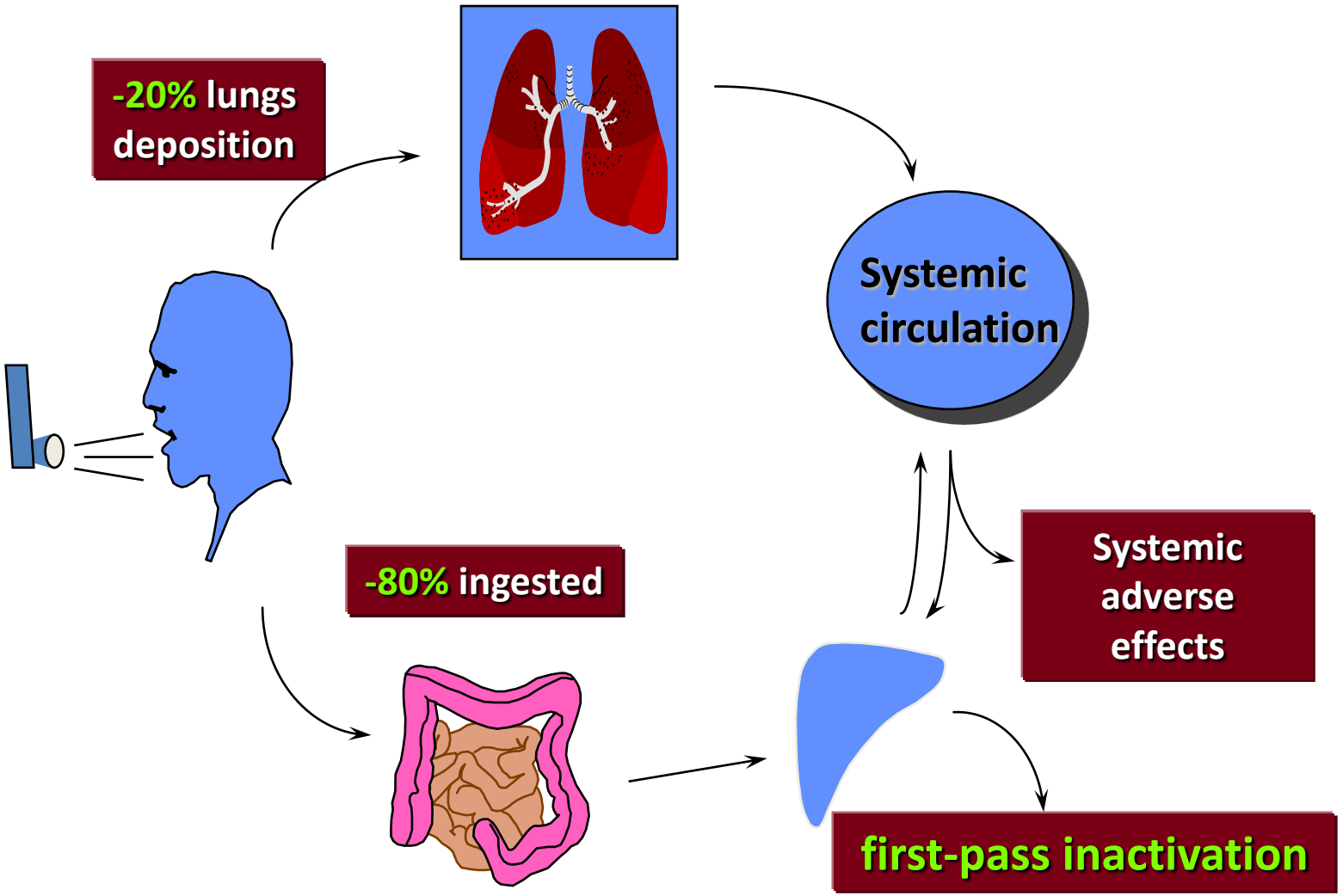
↓ expression of inflammatory genes (cytokines, enzymes, receptors, adhesion molecules)


GC
GC
mGR
plasmatic membrane
GC
HSP90
Src
GC
GC
cGR
cGR
cGR
HSP90
Src
nucleus
GC
GC
cGR
cGR
Effects of glucocorticoids
(anti-inflammatory, immuno-
modulatory, metabolic,
adverse)
genomic
nongenomic

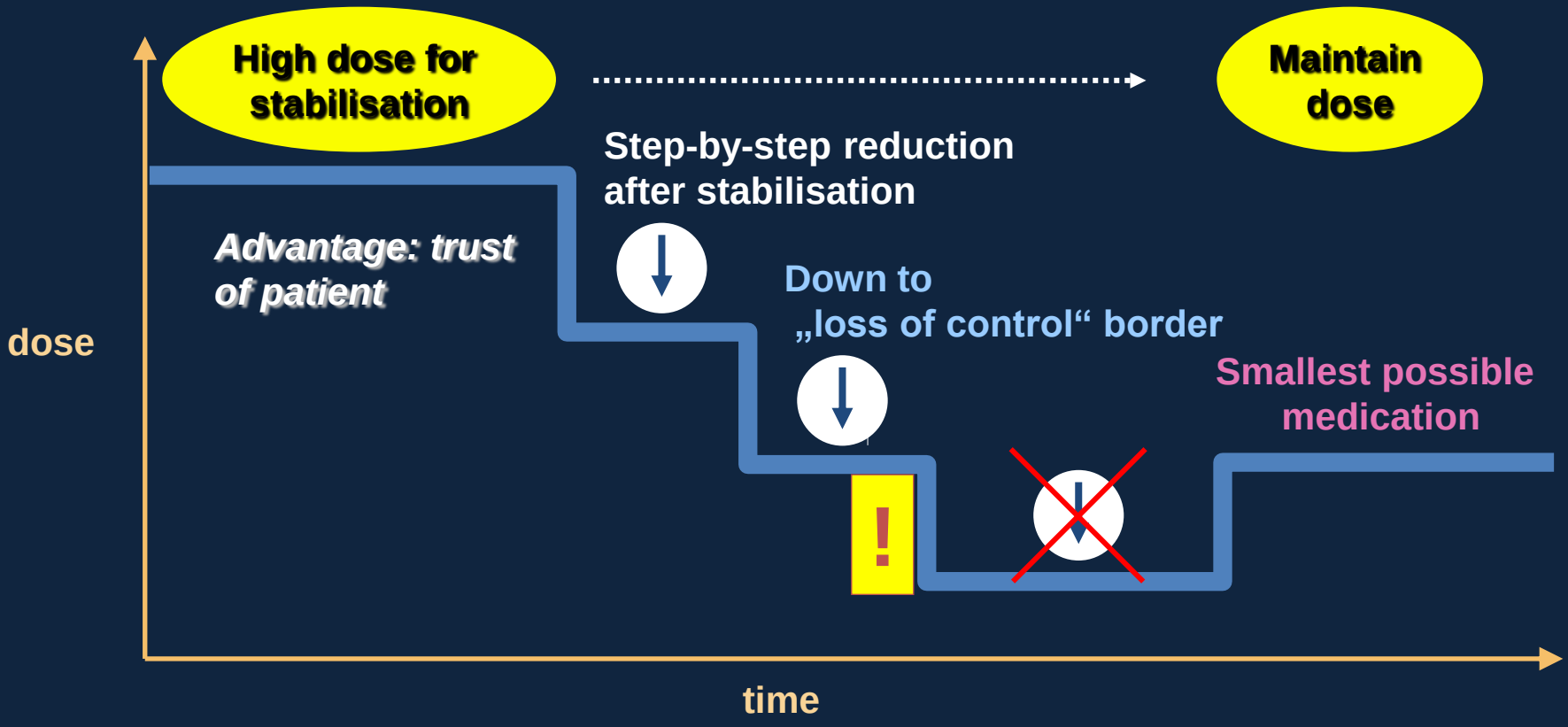
Inhalatory corticosteroids

- **Local effect**
- **Corticoids soluble in fat: beclometazon, budezonid, fluticazon (longest deposition time in lungs, best affinity to corticoid receptor).**
- **In dose up to 800 μm -1 mg/day low incidence of systemic adverse effects.**
- **Decreasing of doses after stabilization of clinical status.**
- **Adverse effects: oropharyngeal candidosis, dysphonia, cough (prevention – washing out of mouth, use of spacers)**

Fate of inhaled CS



Strategy of treatment with ICS

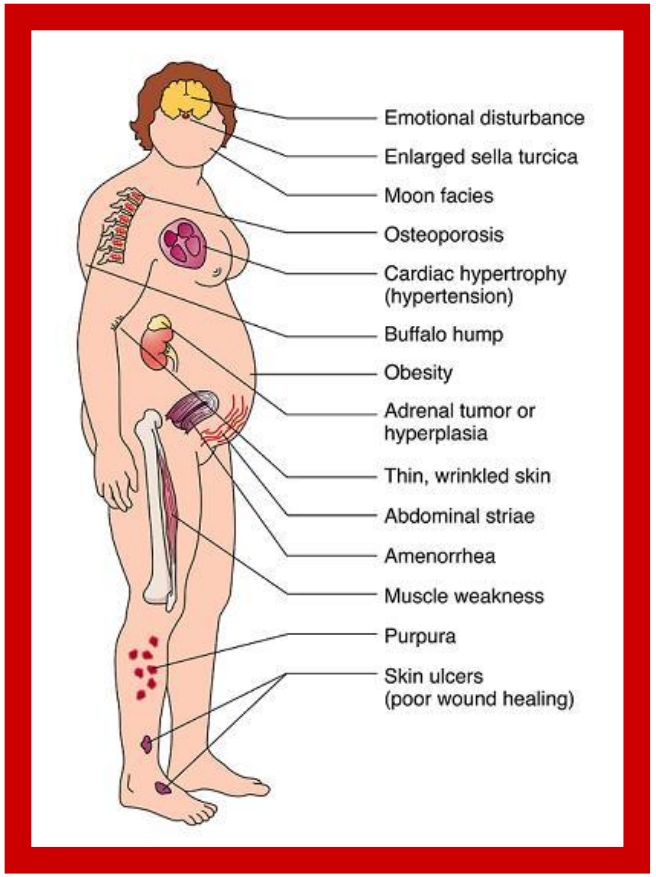


Systemic corticosteroids

- **short-term booster cycle (3-10 days) – „maximal therapy" for treating of severe persistent asthma (treatment failure). Usually as an introduction of long-term therapy of patients with destabilized asthma or in case of sudden worsening of clinical state.**
- **long-term peroral corticosteroid therapy (daily or alternative – i.e. one dose every other day) in patients with severe persistent asthma**
- **peroral administration is preferred to parenteral .**
- **during attack should be administered within 45 minutes.**
- **Hydrocortison, prednison, metylprednison, triamcinolon**

Adverse effects of CS

- mineralocorticoid (hypertension)
- glucocorticoid (steroid induced diabetes)
- antiinflammatory and antianabolic effects (slow wound healing, risk of dissemination of infection, herpetic infections, osteoporosis, slower growth of children, mucous membranes atrophy)
- supression of hypophysis-supraren axis (suppression of endogenous production of CS)
- trombosis
- ulcus disease of stomach and duodenum
- cataracta, glaucoma, ICH



Rang and Dale, 2013

Corticosteroids in COPD

- **Inhalatory**
- **Only in symptomatic patients with positive response or in patients with FEV1 < 50% (3rd and 4th stage)**
- **In exacerbation with ATB**
- **No influence on FEV_1**
- **Long-term peroral treatment is not recommended**

Estimate Comparative Daily Dosages for Inhaled Glucocorticosteroids by Age

Drug	Low Daily Dose (μg)		Medium Daily Dose (μg)		High Daily Dose (μg)	
	> 5 y Age	< 5 y	> 5 y Age	< 5 y	> 5 y Age	< 5 y
Beclomethasone	200-500	100-200	>500-1000	>200-400	>1000	>400
Budesonide	200-600	100-200	600-1000	>200-400	>1000	>400
Budesonide-Neb Inhalation Suspension		250-500		500-1000		>1000
Ciclesonide	80 – 160	80-160	>160-320	>160-320	>320-1280	>320
Flunisolide	500-1000	500-750	>1000-2000	>750-1250	>2000	>1250
Fluticasone	100-250	100-200	>250-500	>200-500	>500	>500
Mometasone furoate	200-400	100-200	> 400-800	>200-400	>800-1200	>400
Triamcinolone acetonide	400-1000	400-800	>1000-2000	>800-1200	>2000	>1200

© Global Initiative for Asthma

Inhalatory corticosteroids

- **Beclometasone** — **BECLOMET, ECOBEC**
- **Budesonide** — **PULMICORT, GIONA, BUDELIN, MIFLONID**
- **Fluticasone** — **FLIXOTIDE**
- **Mometasone** — **ASMANEX**
- **Ciclesonide** — **ALVESCO**

+ combined with β_2 agonists (e.g. SYMBICORT, FLUTIFORM, FOSTER, SERETIDE)

Antibiotics

- **Only in signs of bacterial infection**
- **Perorally**
- **Most often pathogens:**
  - ***Str. pneumoniae, H. influenzae, B. catarrhalis***
- **Aminopenicillins, amoxicillin + clavulanate, ampicillin + sulbactam, cotrimoxazol, TTC, macrolides, cephalosporines of 1st and 2nd generation, new fluorochinolones**

Mucolytics

- **Mucociliar cleanup, decrease viscosity of mucus**
- **Most effective inhalatory, together with sufficient hydratation**
- **Ambroxol (Ambrobene, Ambrosan, Bronchopront, Mucosolvan, Solvolan), bromhexin, mesnum, acetylcystein (Solmucol), carbocystein, erdostein, prenoxdiazine (Libexin)**

Cromoglycates

- Antiinflammatory effects – inhibition of inflammatory cells activity
- For continual antiinflammatory treatment of milder BA forms induced by cold air, allergens, physical and mental activity and air pollution.
- For preventive use and not for acute relieve from symptoms
- Ameliorate lung functions, decrease frequency and severity of attacks decrease airway hyperreactivity

Advantages

- **Safety tested during 50 years of use**
- **Contentment of physicians**
- **Application in children**

Cromoglycates

Disadvantages

- Weaker antiinflammatory effect
- No prevention of remodeling
- Full action after 4-6 weeks (except nedocromil)
- Dosage 4 x daily
- No decrease of mortality
- AE – irritation

Cromoglycates

- **Formulations:**

Natrium cromoglycate: NALCROM, Cromolyn, DCNG Stada, Chomobene, Ditec (contains 1 mg of cromoglycate and 0,05 mg of fenoterol), Intal.

Dosage up to 4x2 inhalations

Natrium nedocromil: Tilade, TILADE MINT.

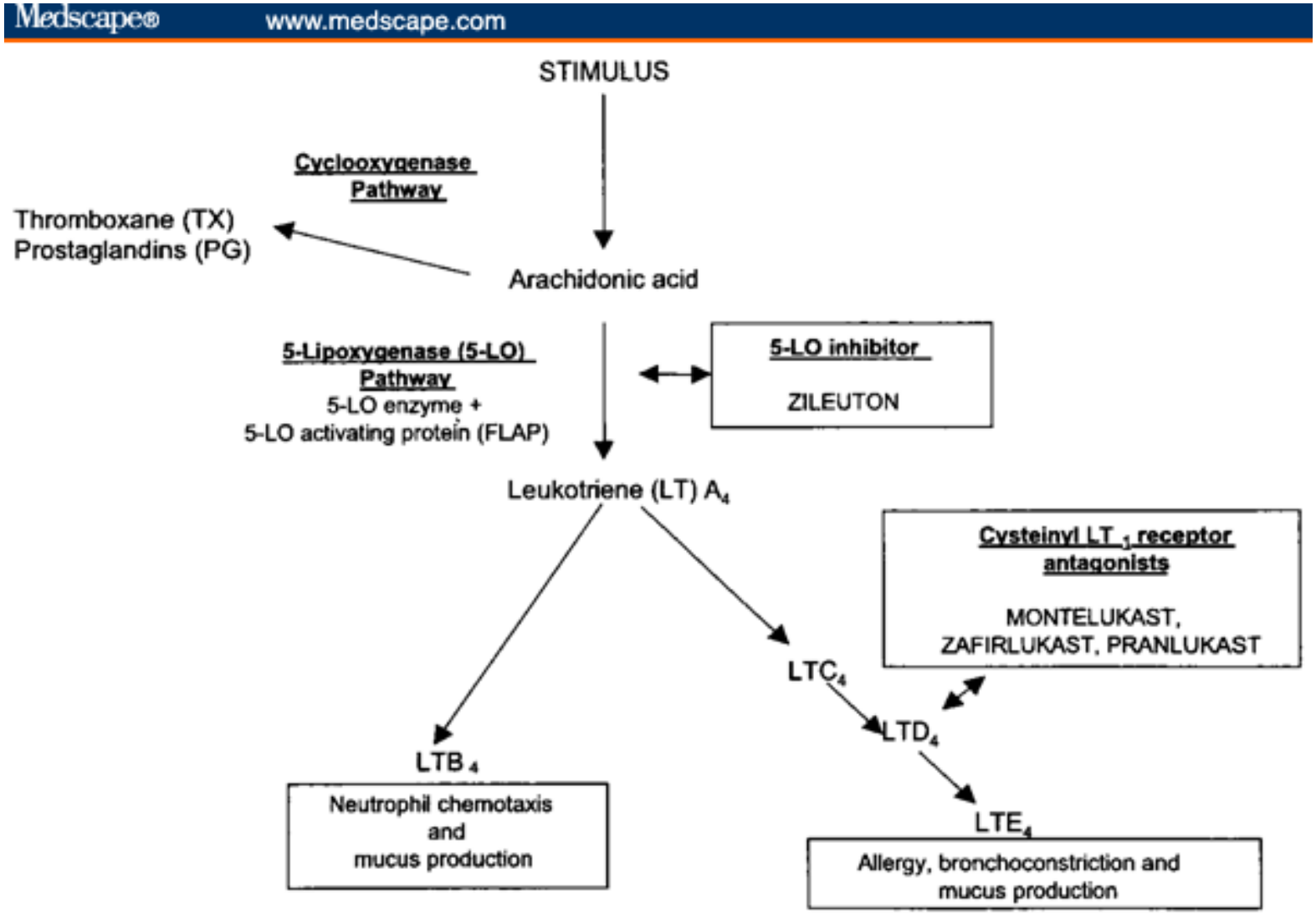
Dosage 2x2 inhalations

Ketotifen

- membrane stabilizer, counts to cromones
- acts antiallergic (inhibition of allergen induced early phase of asthmatic reaction, higher doses inhibit also late phase)
- no reports about antiinflammatory effects
- good practice in children
- full effect after 2 months treatment
- Adverse effect - sedation

ZADITEN, DENEREL

Antileukotriens



Antileukotriens

Advantages

- Tablet form
- Acts in corticoresistent asthma (1-2%)
- Application in children?

Disadvantages

- Weaker antiinflammatory effect
- No prevention of remodeling
- No decrease of mortality
- Adverse effects, rush
- Extreme price

Antileukotrienes

- **Antagonists of LT receptors:**

Zafirlucast – ACCOLATE

2x daily from 12 years

Montelucast – SINGULAIR, ACTAMONE, MONTEXAL, MONTELUKAST, SPIROMON, ASTAMASAN

1 x daily from 6 years

- **5-LO inhibition**

Zileuton – Zyflo

Omalizumab

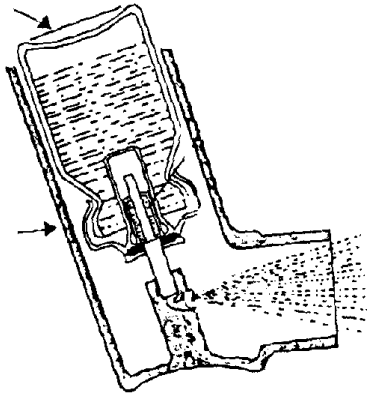
- Antiallergic in allergic asthmatics
- Recombinant human monoclonal antibody IgG **against** human **IgE** – inhibits bound of IgE to receptor on mast cells and basophils
- >12 years
- Expensive (10.000 USD per year)
- **XOLAIR**

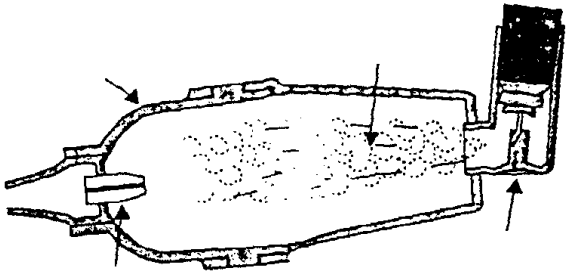
Advantages of inhalational administration

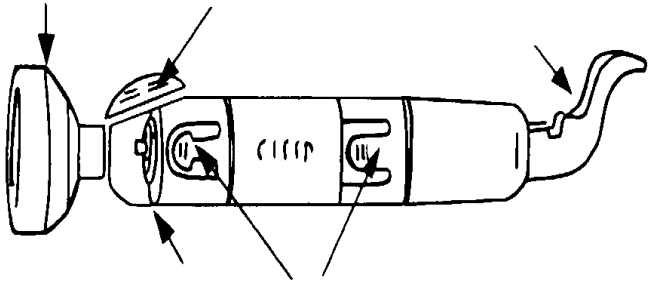
- ✓ Direct drug effect
- ✓ Low total dose
- ✓ Minimalisation of adverse effects

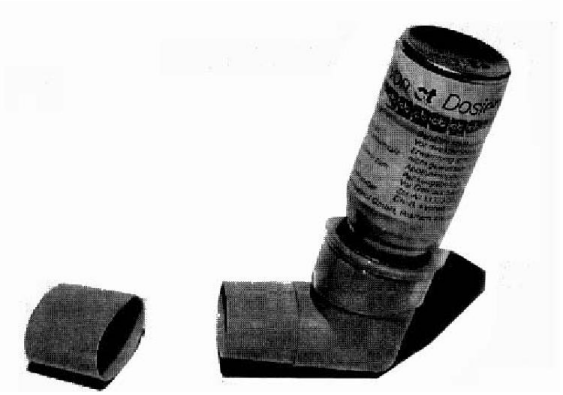
Inhalers

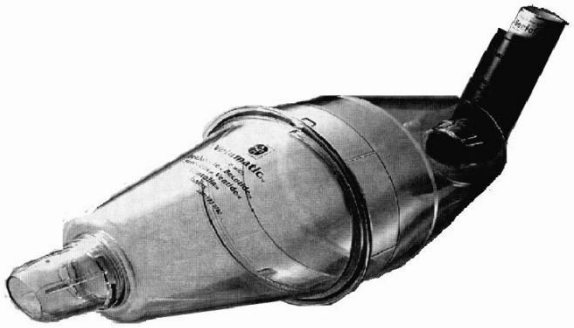
- MDI Metered dose inhaler
- MDI + spacer
- DPMDI + Dry powder metered dose inhaler (DPI)
- Nebulisator
- Discus









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