

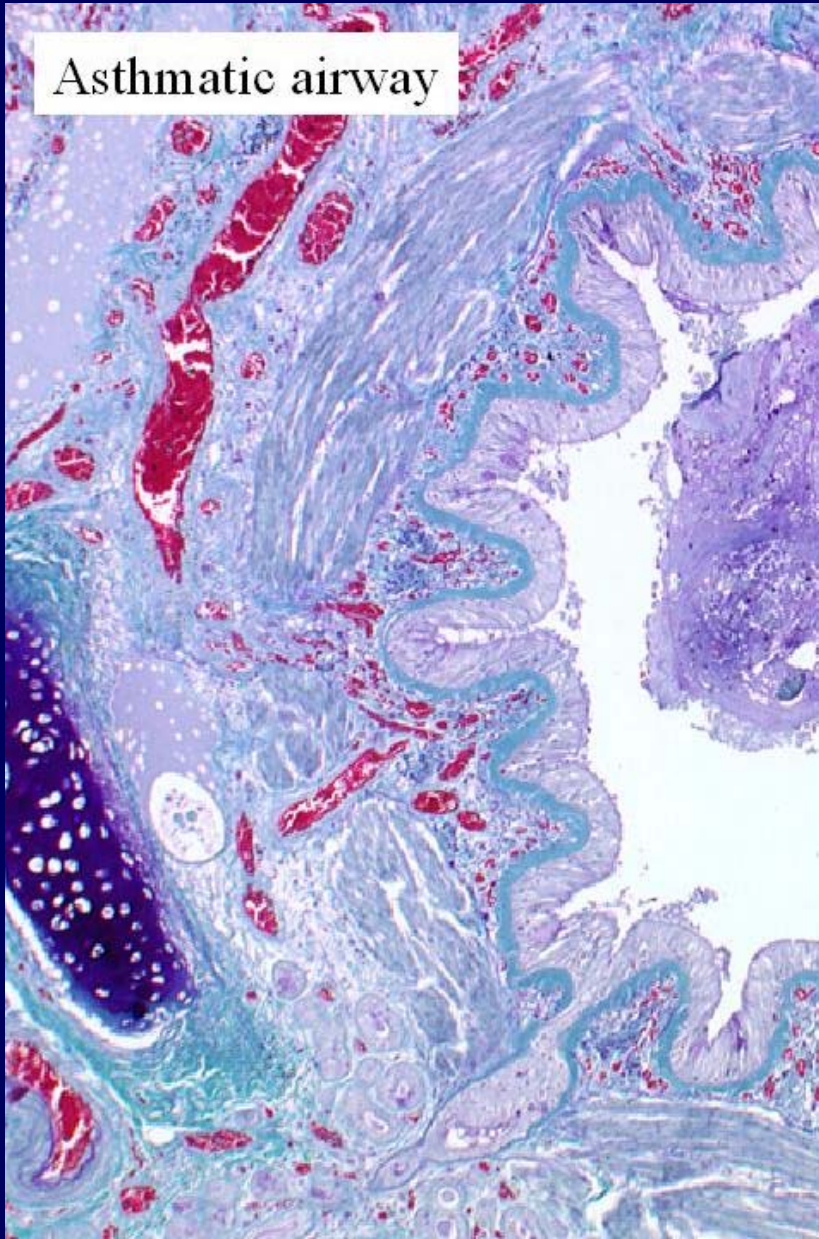
Asthma mechanisms update 2005

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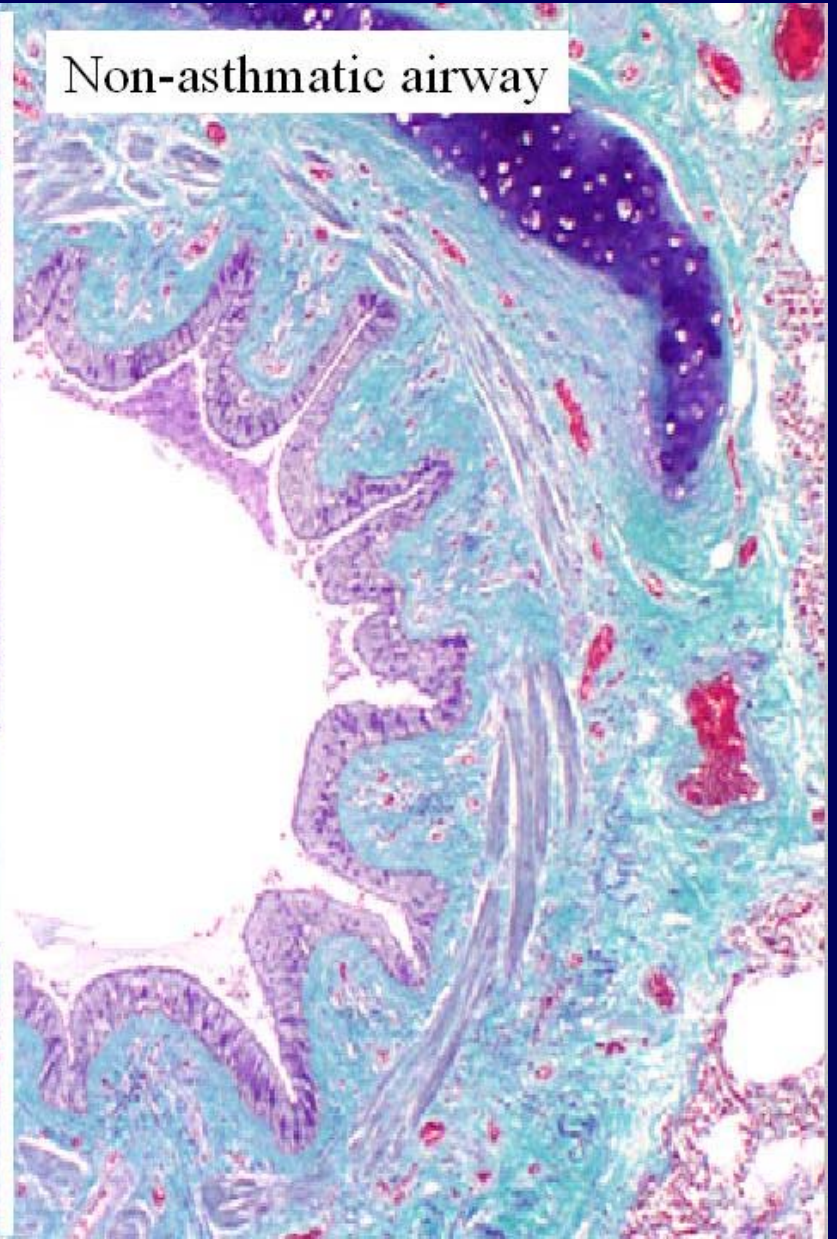
Asthma hypothesis

- **Hypothesis 50 years ago:** abnormal contractility of bronchial smooth muscles
- **Hypothesis 20 years ago:** airway inflammation
- **Hypothesis today:** combination of abnormal smooth muscle behavior and allergic inflammation

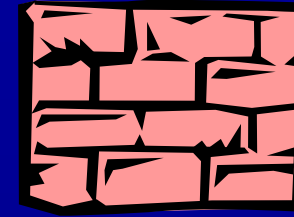
Asthmatic airway



Non-asthmatic airway



One airway - two diseases!



Airway Inflammation

ASMC abnormality

Normal

—

—

Atopy

+

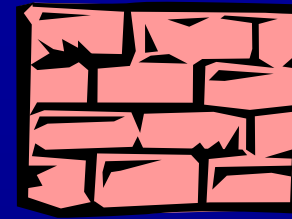
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Asthma

+

+

One airway - two diseases! Switzerland



Airway Inflammation

ASMC abnormality

Normal

-

-

Atopy

35%

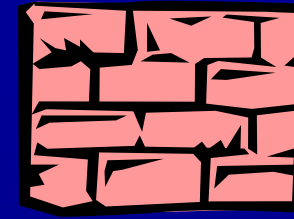
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Asthma

6%

6%

One airway - two diseases! Australia/England



Airway Inflammation

ASMC abnormality

Normal

—

-

Atopy

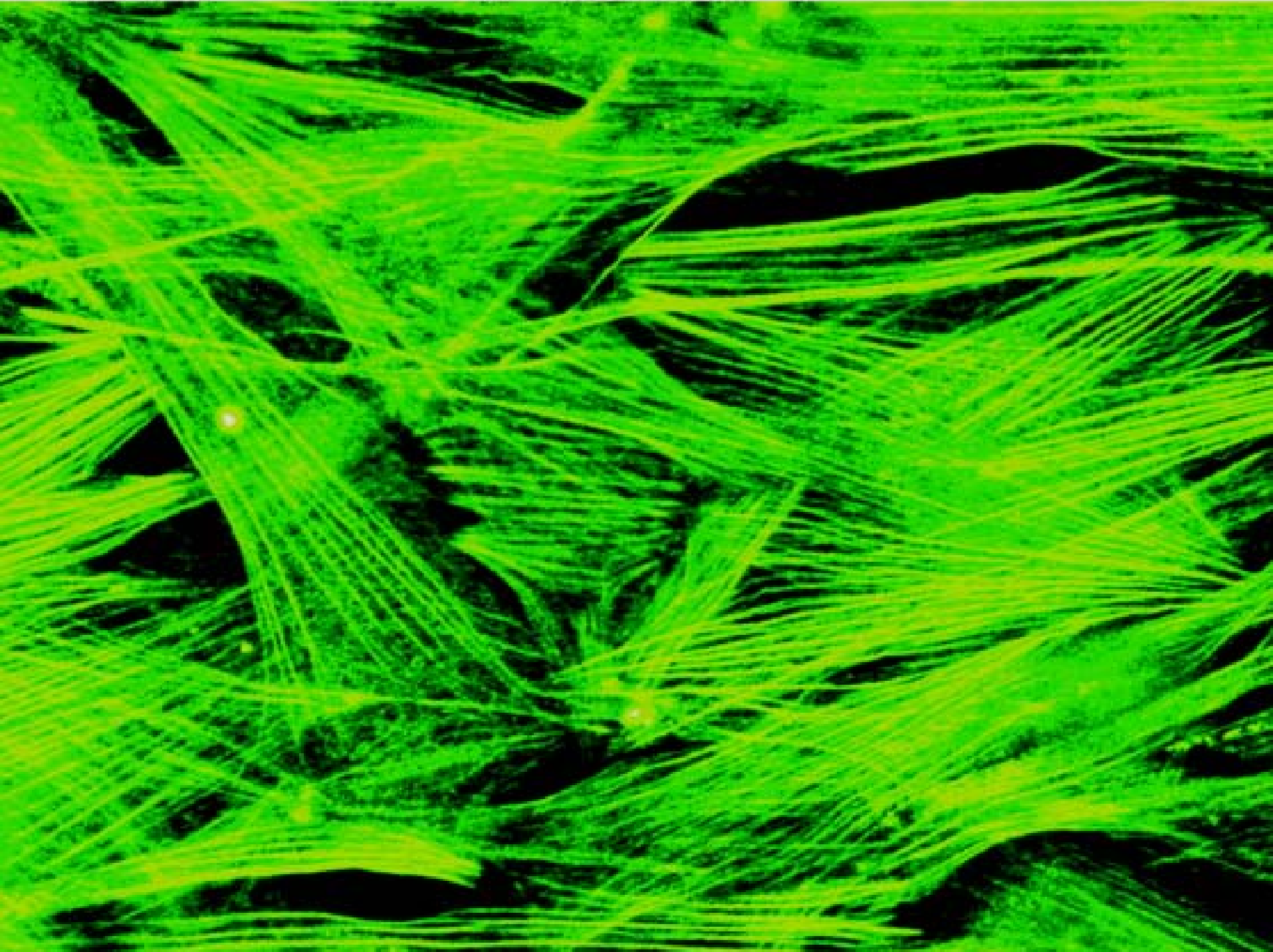
35%

-

Asthma

11%

11%



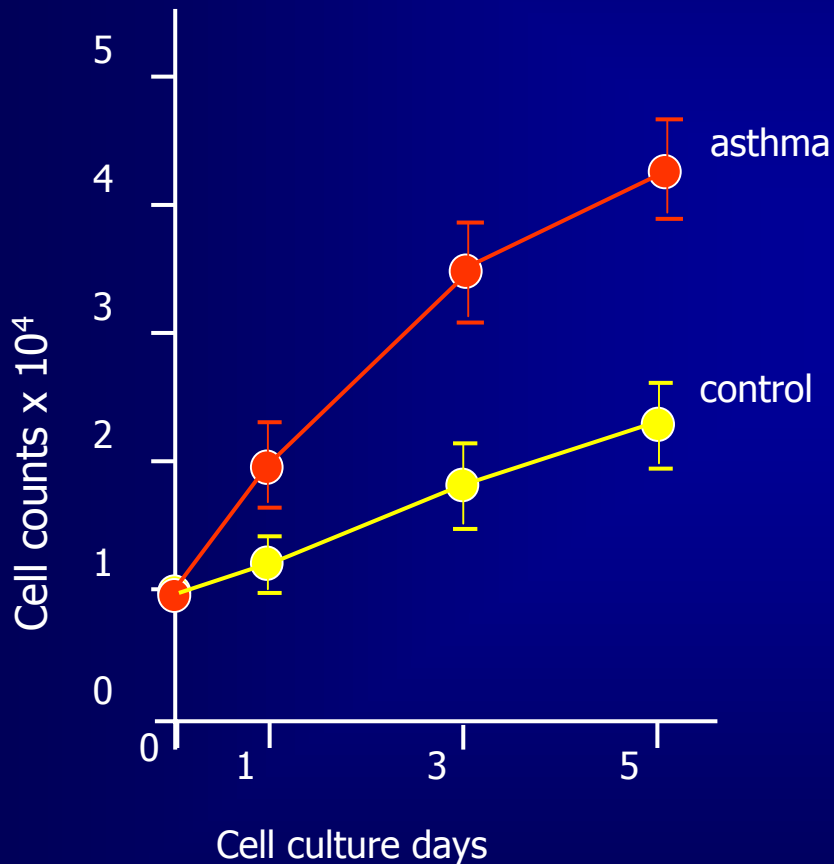
Clinical features of smooth muscle cell function in asthma

- Dyspnea
- Cough?
- Bronchial hyperreactivity
 - exercise, methacholine, histamine, NaCl, mannitol
- Airway obstruction
 - reversible/irreversible
- Experiments with deep breath

Smooth muscles are not only bronchoconstrictors!

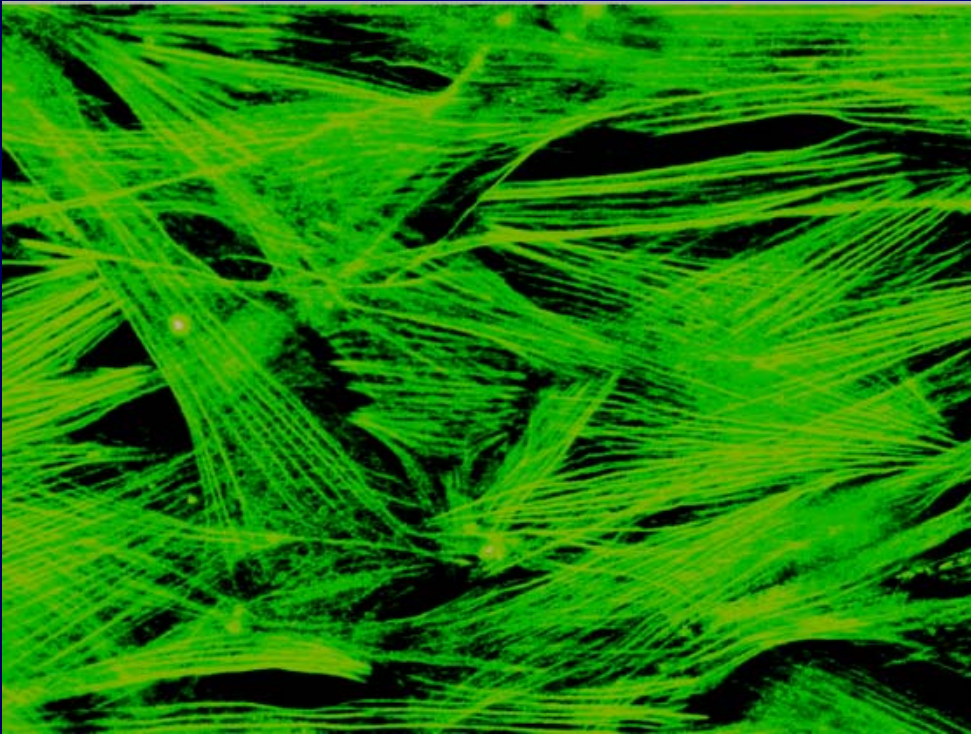
- Proliferation
- Interleukin-release
- Production of extracellular matrix
- response to inflammatory stimuli

ASMC proliferation and asthma



ASMC proliferation is markedly increased in asthma, but normal in COPD/emphysema

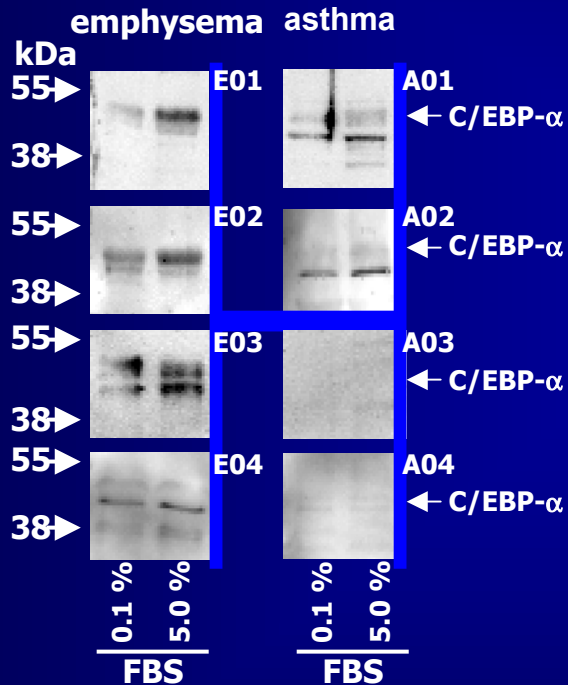
Regulation of smooth muscle cell proliferation



- SMC proliferation is regulated by:
- activation of the glucocorticoid receptor
 - CAAT-enhancing binding protein (C/EBP- α)
 - C/EBP- α forms a complex with the glucocorticoid receptor

C/EBP- α and asthmatic smooth muscle cells

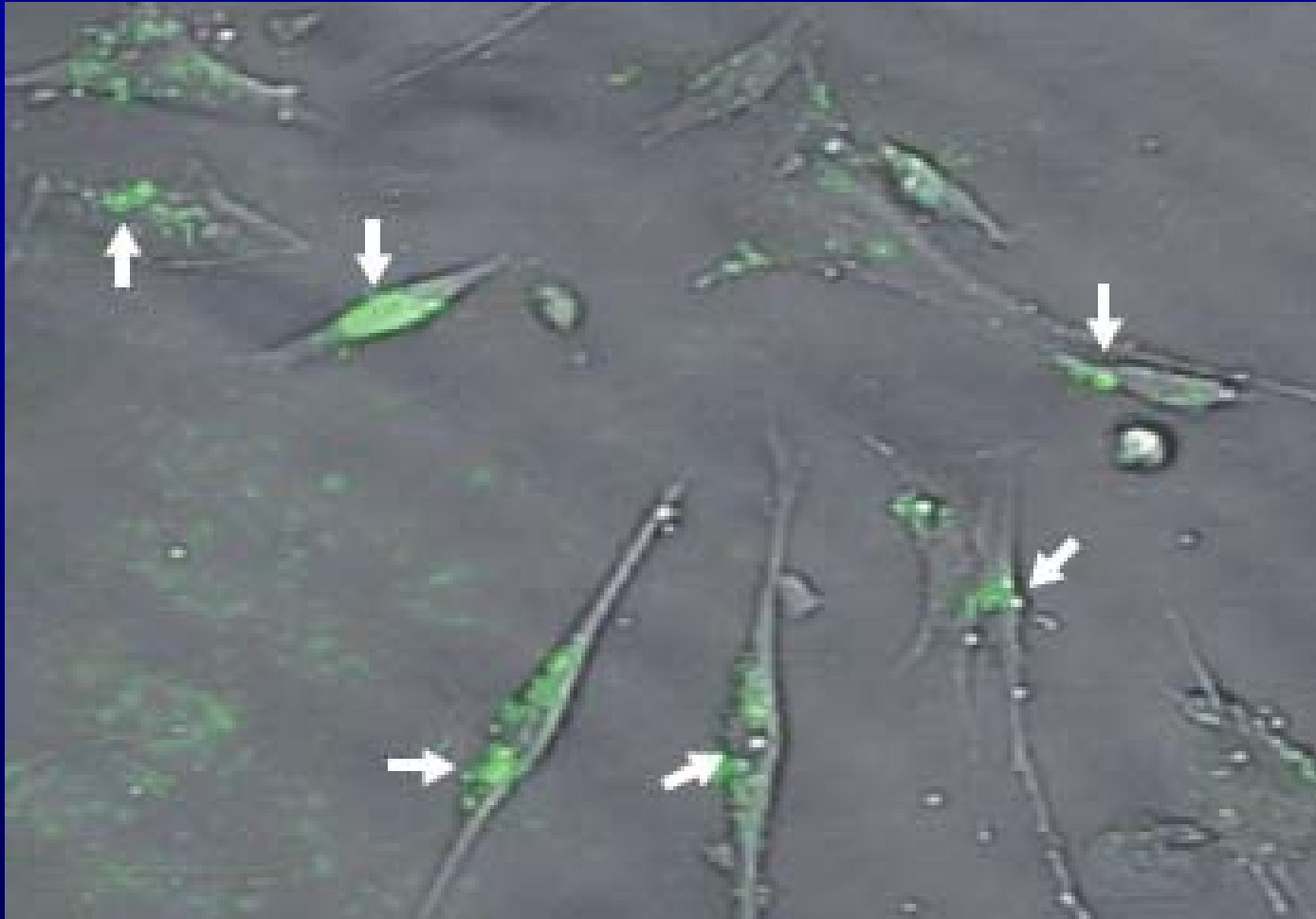
C/EBP- α protein



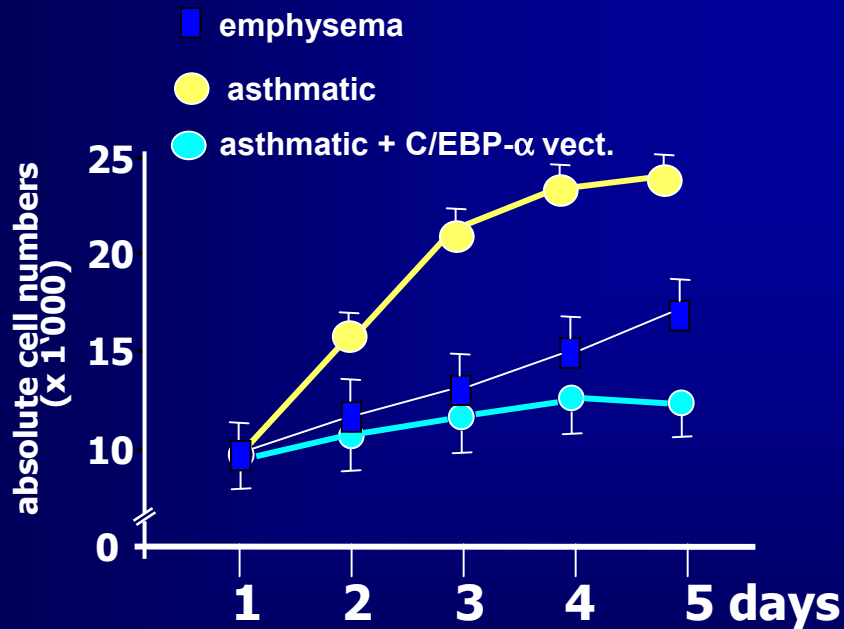
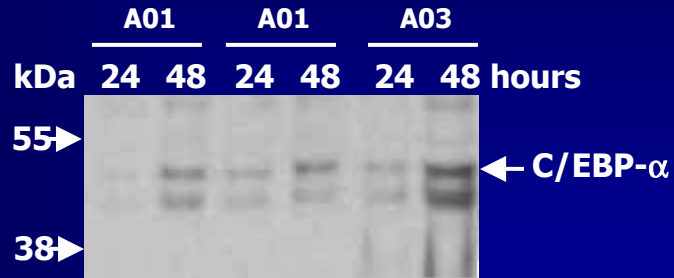
The transcription factor C/EBP- α is missing in ASMC of asthmatics, but normal in emphysema and controls

C/EBP- α is normally expressed in lymphocytes of asthmatics

Successful CEBP alpha transfection in asthmatic ASMC

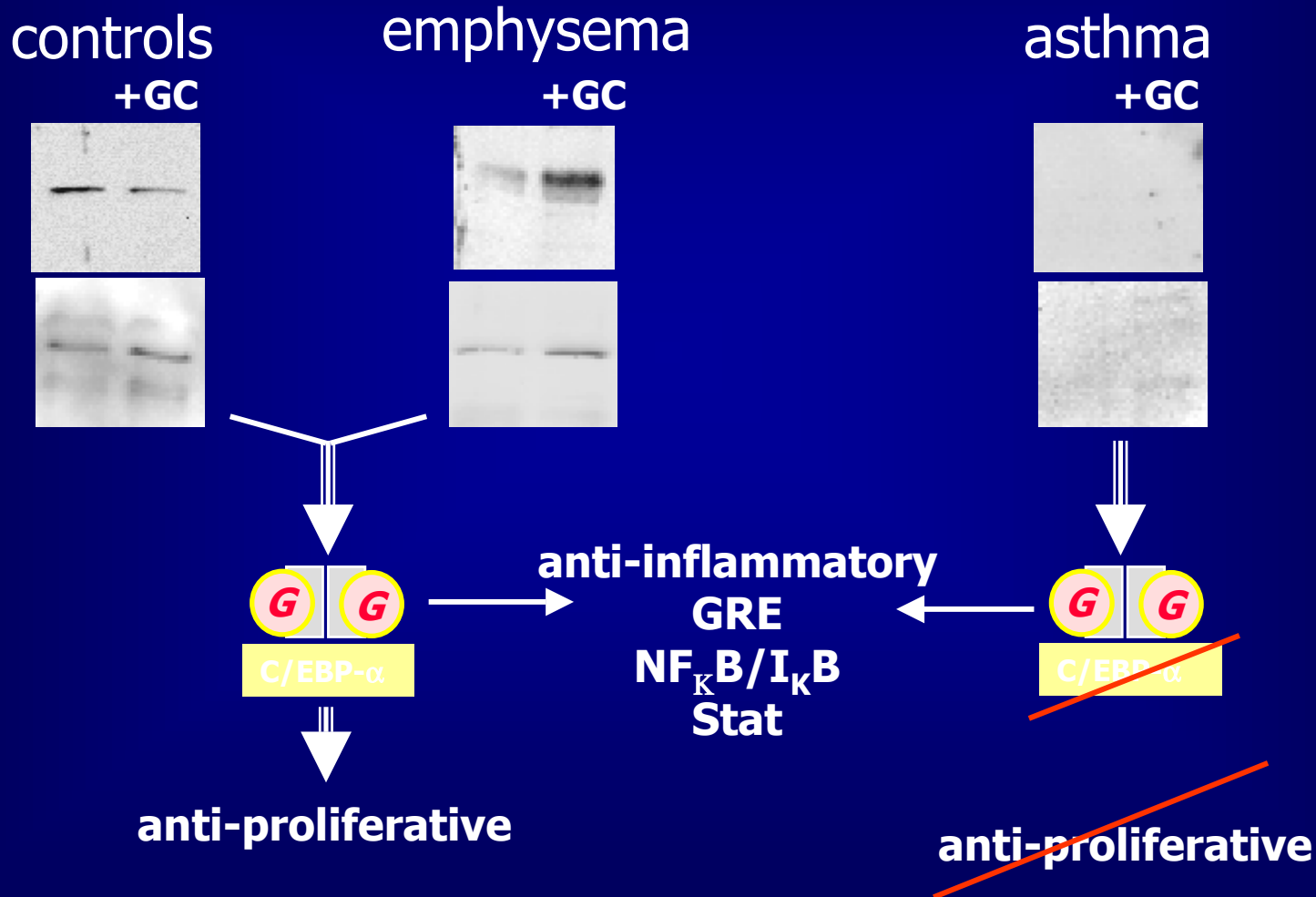


C/EBP- α and asthma

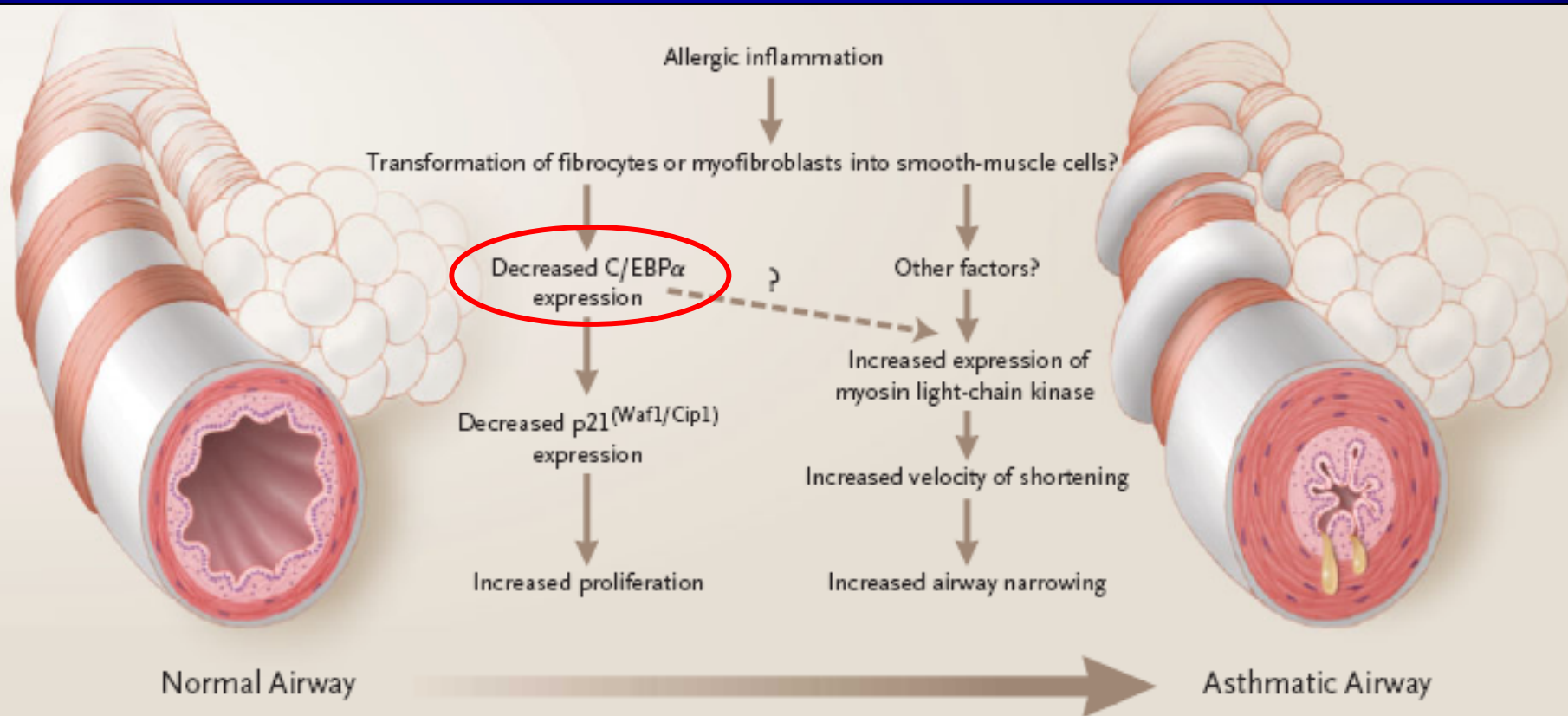


Asthmatic ASMC proliferation can be normalized by transfection with C/EBP- α

Consequences of a lack of C/EBP- α expression in bronchial smooth muscle cells



Pathogenesis of asthma

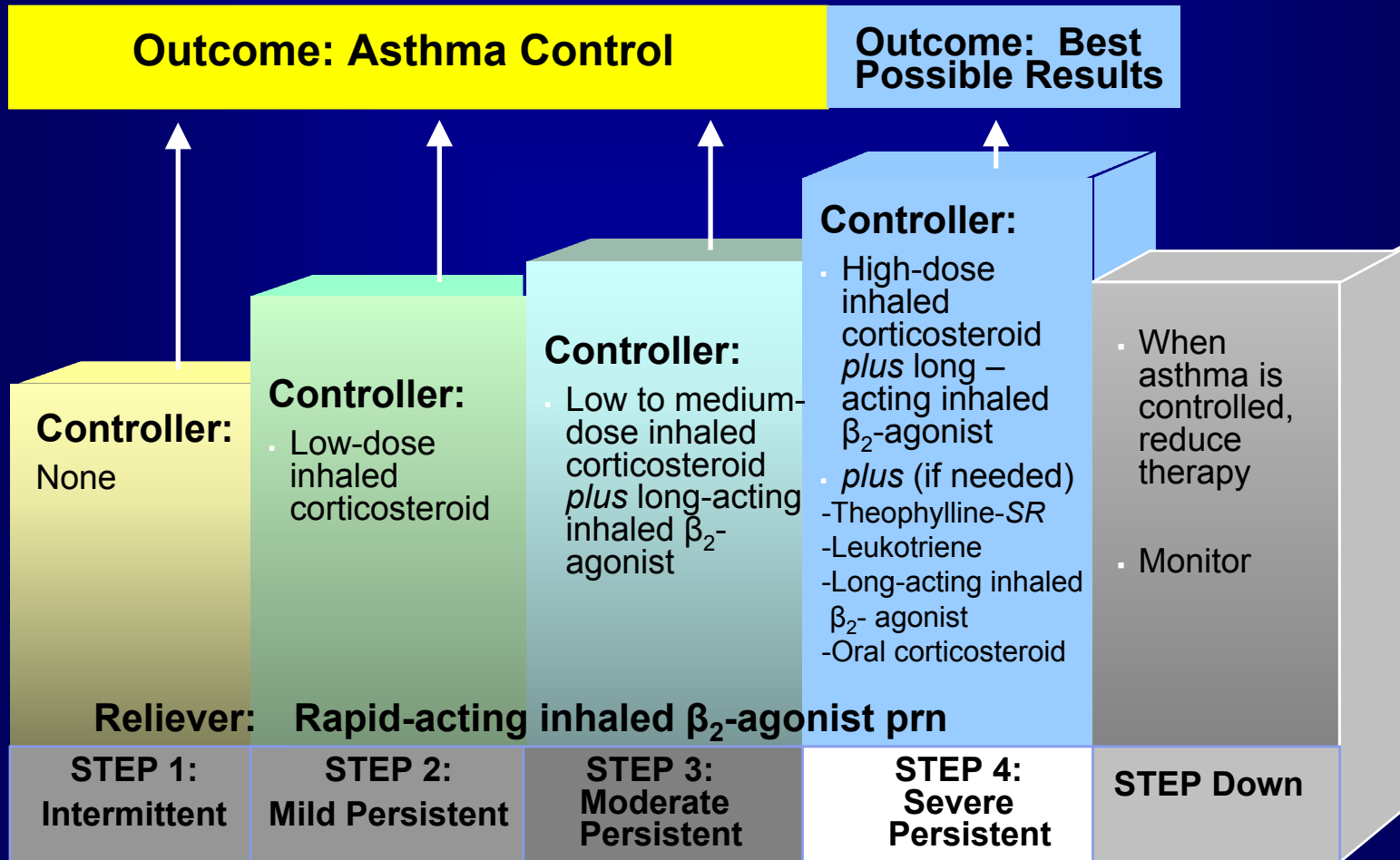






Long-term Asthma Management

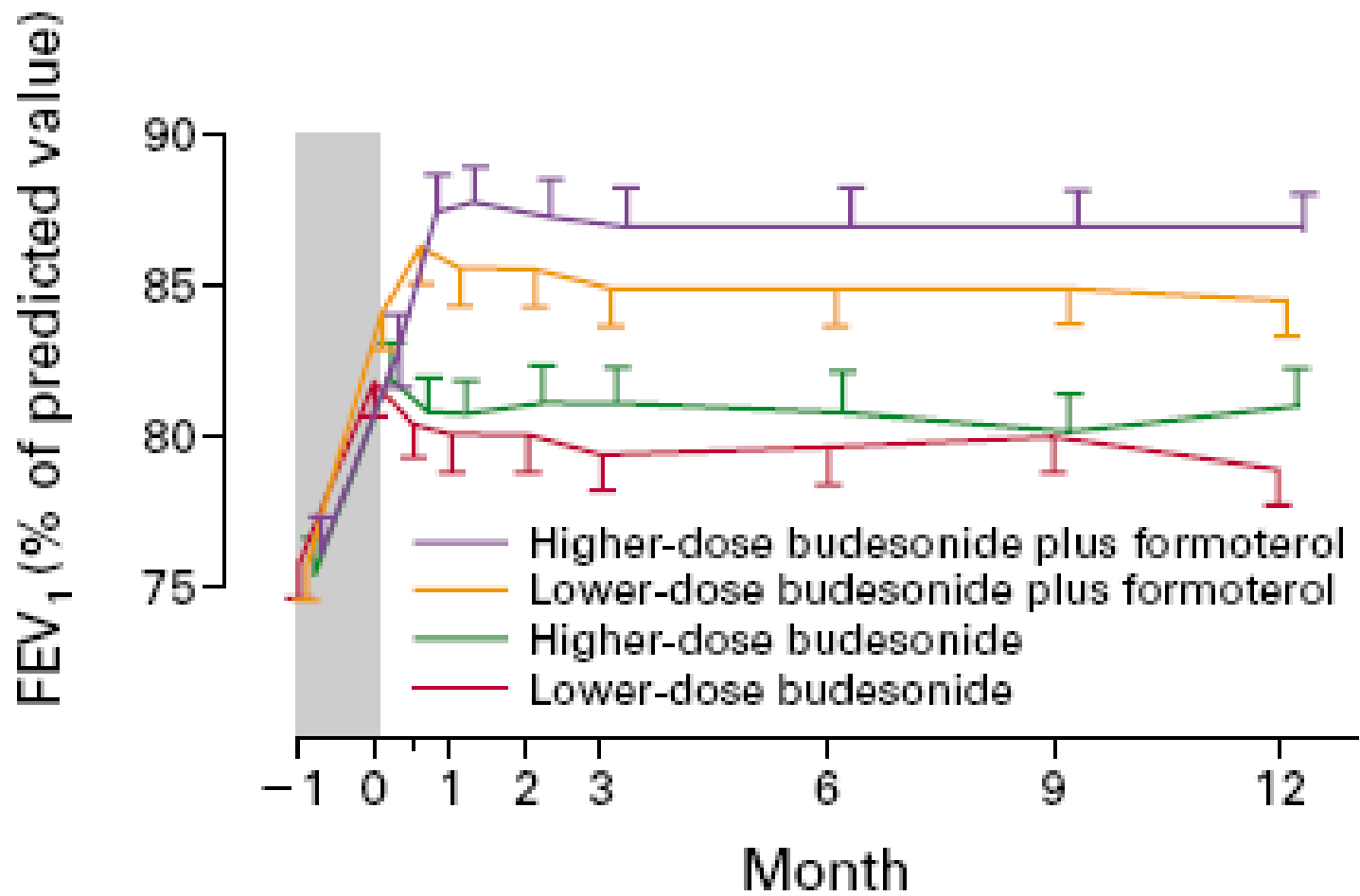
Stepwise Approach to Asthma Therapy Adults/Children Older Than 5 yrs

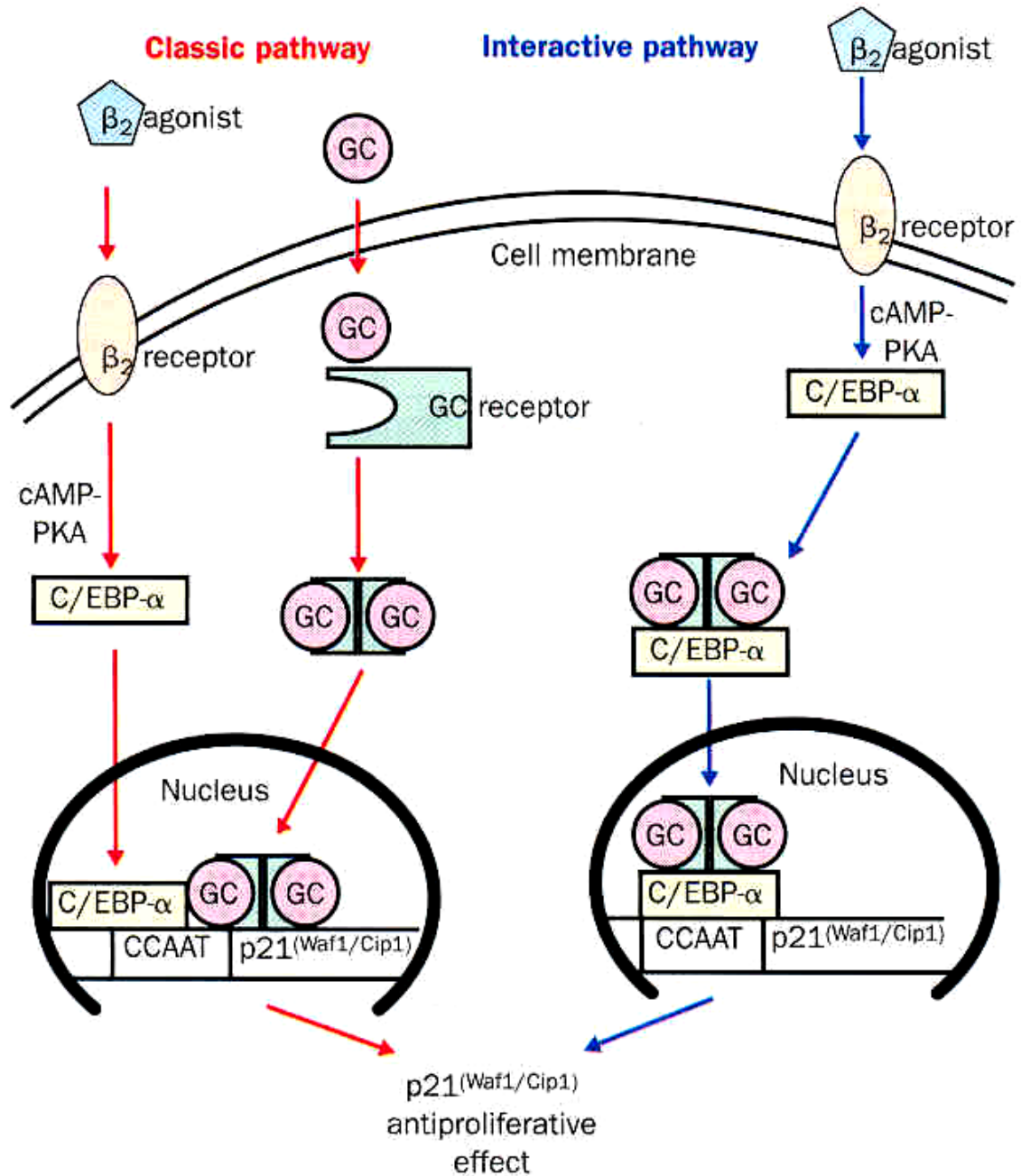


Alternative controller and reliever medications may be considered (see text).

Asthma-therapy if inhaled steroids are not sufficient

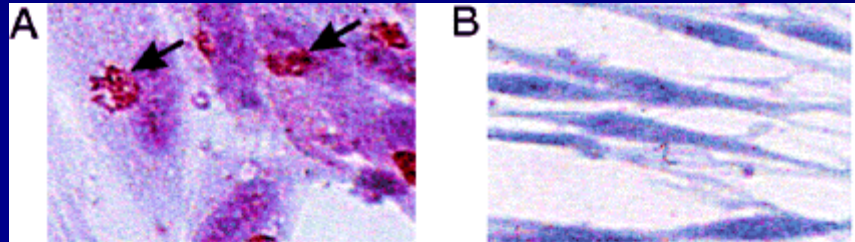
- Increased Dose?
- Long-acting beta-agonists?
- Leukotriene-antagonists?
- Anti-IgE?



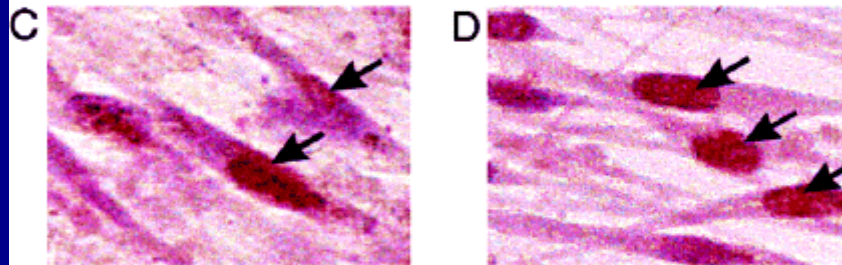


Interaction of the adrenergic system with glucocorticoids

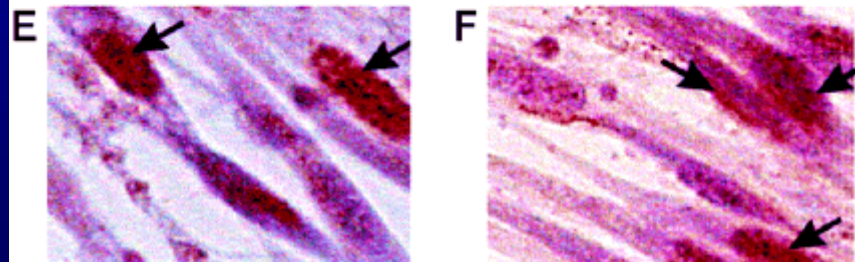
Growing cells



Steroids



Betaagonists



Western blots

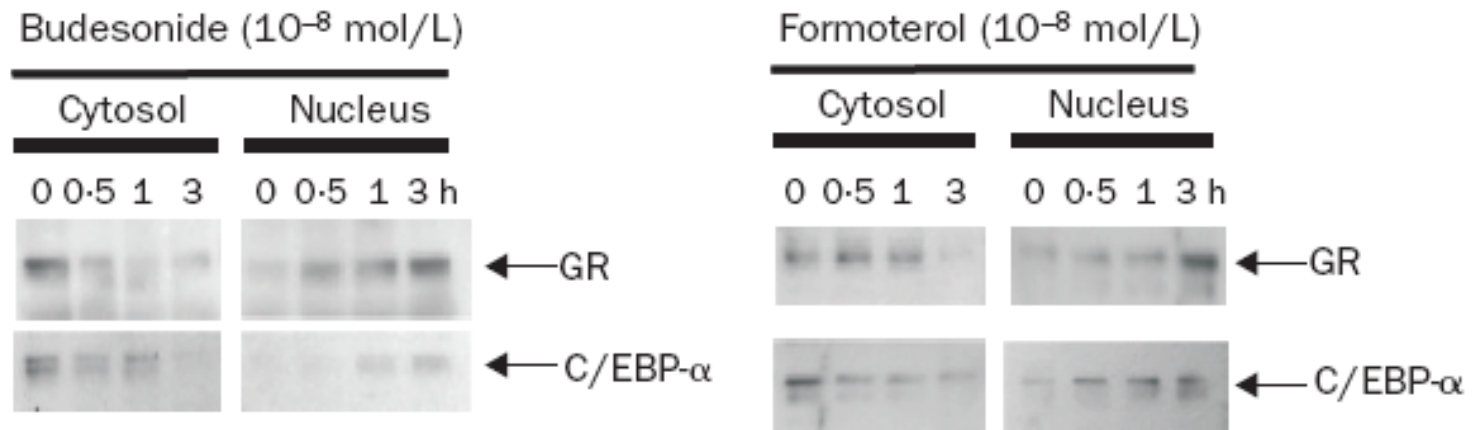
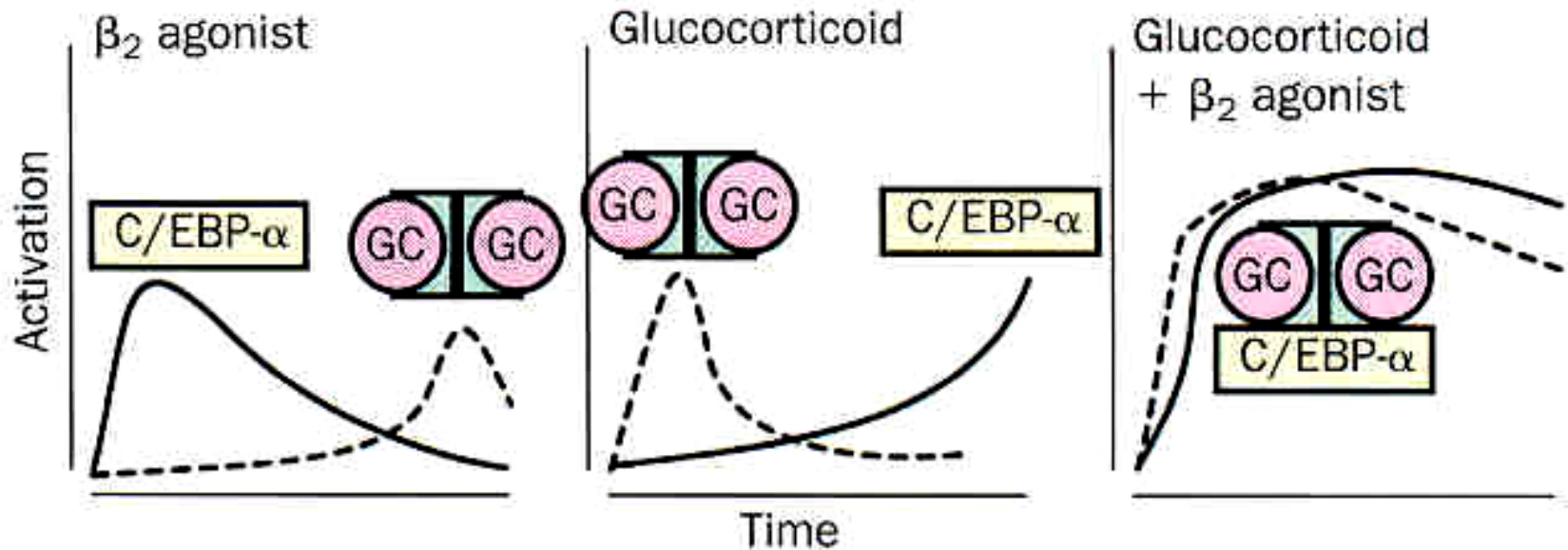


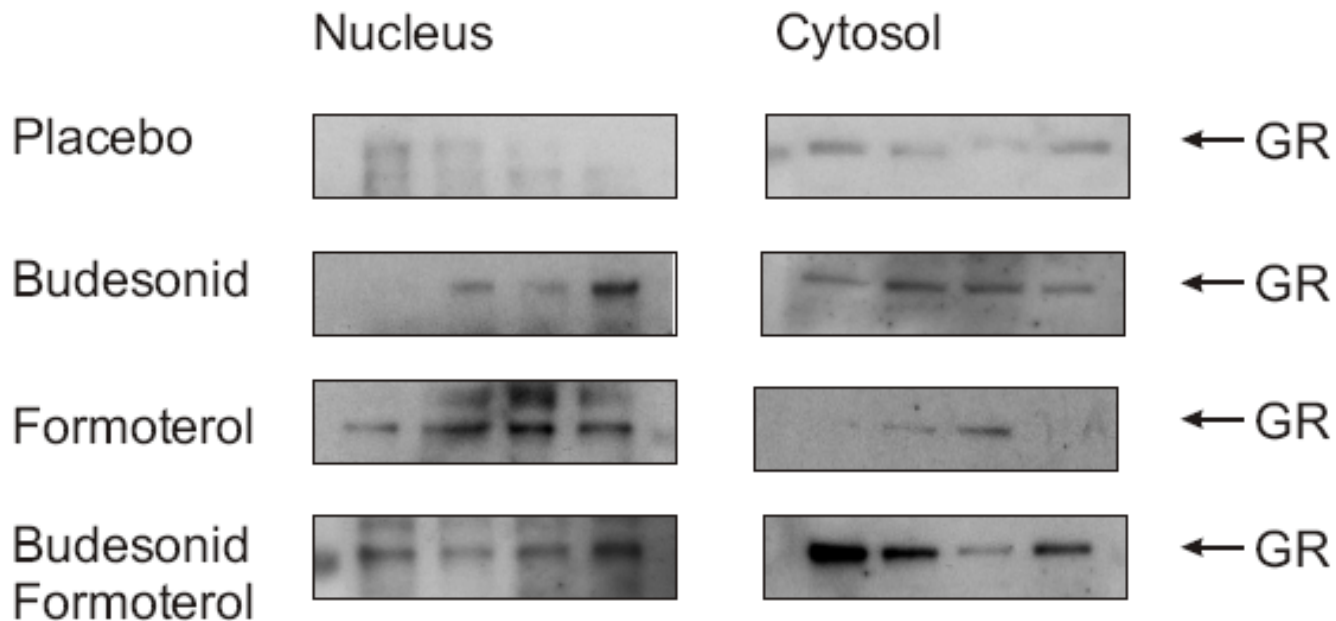
Figure 1: **Activation and translocation of the glucocorticoid receptor (GR) in human bronchial airway smooth muscle cells (BSMC)**

Antiproliferative balance of the adrenergic and steroid signalling pathways

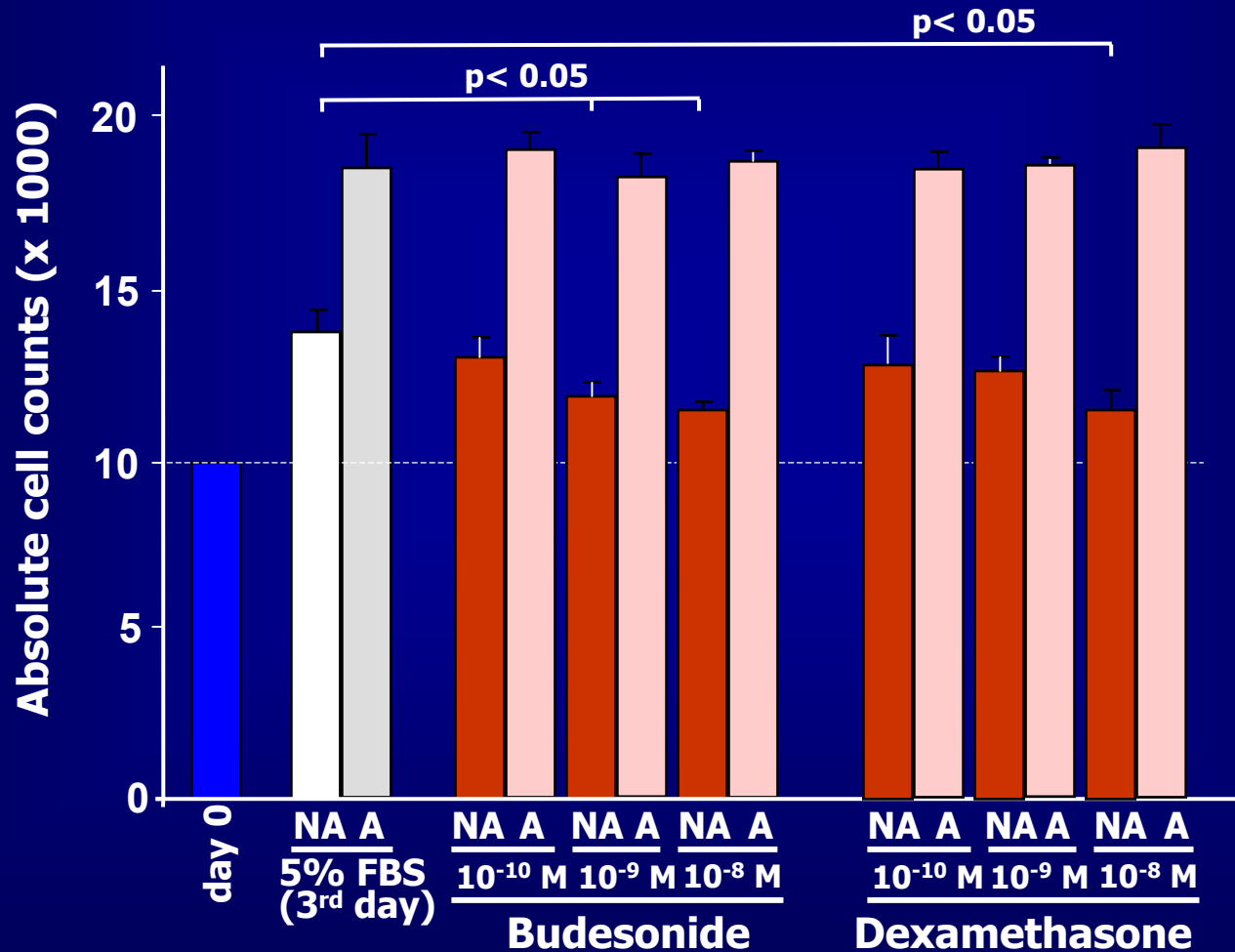


Glucocorticoid receptor activation after inhalation of betaagonists and/or steroids

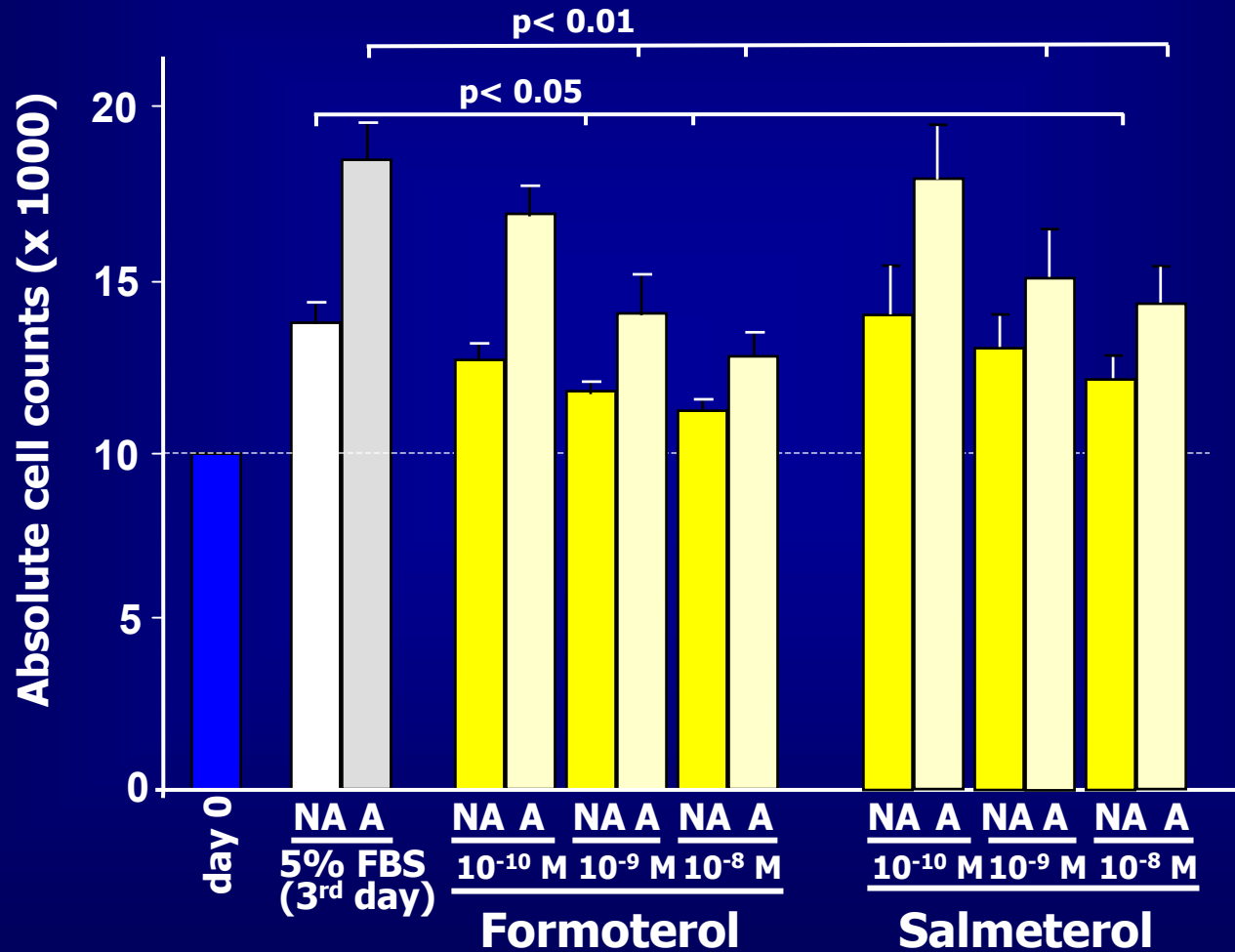
Western blot



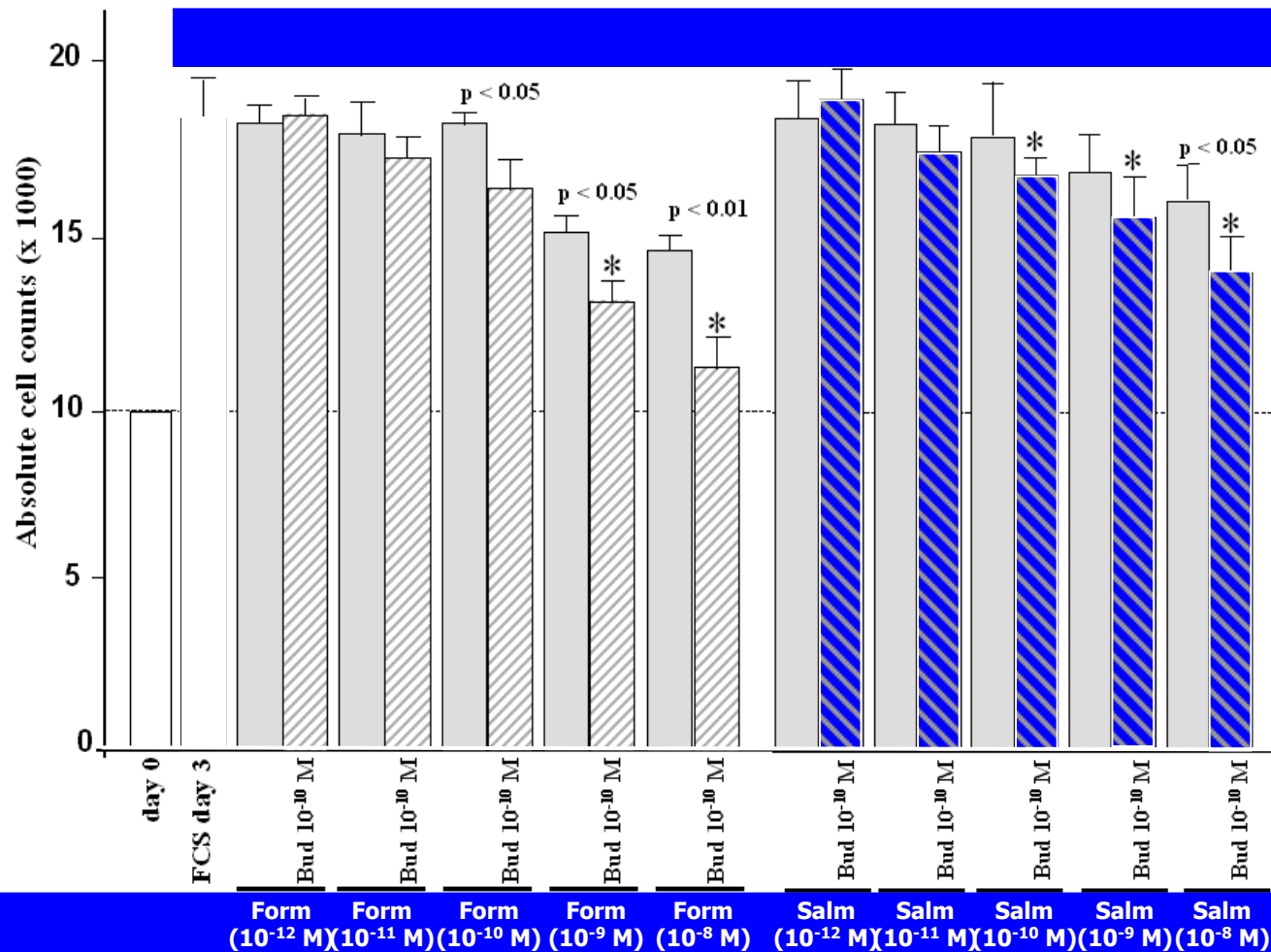
Anti-proliferative effect of glucocorticoids



Anti-proliferative effect of β_2 -agonists



Glucocorticoids support the action of b2-agonists in airway smooth muscle cells of asthma patients



β 2-agonists upregulate the negative cell cycle regulators p21(Waf1/Cip1) and p27(Kip) in airway smooth muscle cells

Formoterol (10^{-8} M)

control

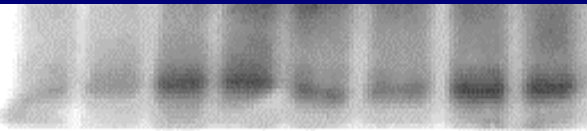
asthma

0 6 12 24 0 6 12 24 hrs

p21▶



p27▶



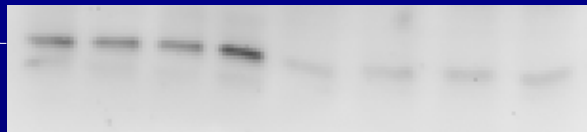
Salmeterol (10^{-8} M)

control

asthma

0 6 12 24 0 6 12 24 hrs

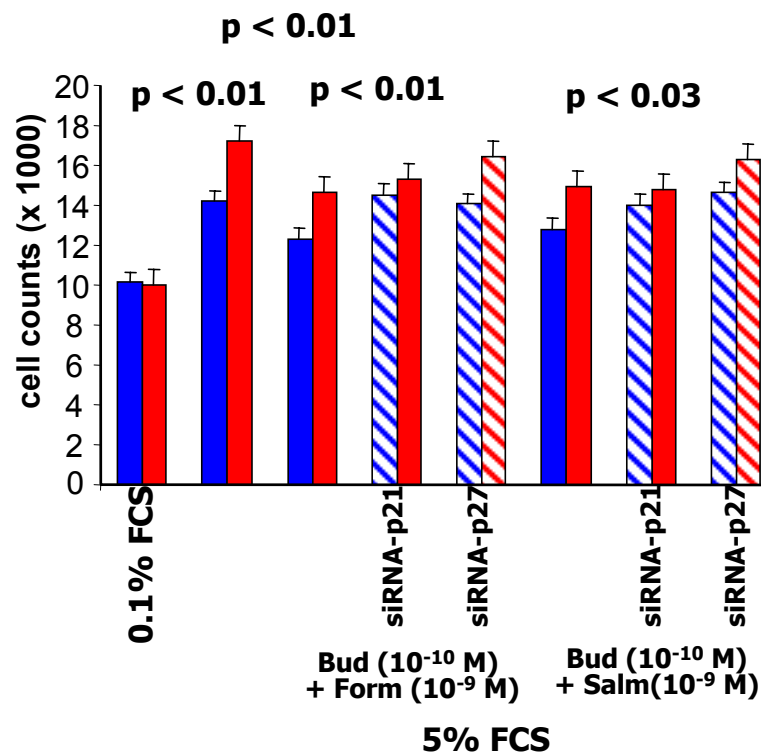
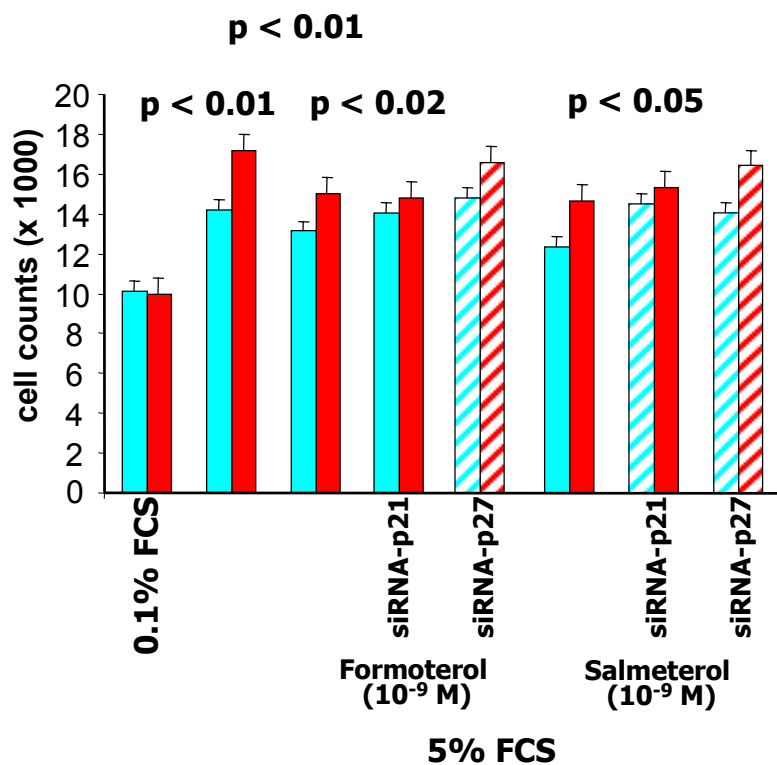
p21▶



p27▶



The anti-proliferative protein in asthma and their stimulation by budesonide and b2-agonists



■ non-asthmatic
■ asthmatic

Summary

- Increased proliferation in asthmatic bronchial smooth muscle cells
- Lack of CEBPalpha in asthmatics
- Normalisation by transfection with CEBPalpha
- No antiproliferative action of steroids in asthma
- Activation of the GR also by betaagonists
- Antiproliferative action of betaagonists via p27 in asthmatics