Έρευνα γύρω από νεότερα φάρμακα στο Άσθμα

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7η Πνευμονολογική Κλινική Γ.Ν.Ν.Θ.Α «Η ΣΩΤΗΡΙΑ»
Συντονιστής Ομάδας Άσθματος της ΕΠΕ

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Βόλος, Ξενοδοχείο Xenia Volou, 10-12 Απριλίου 2009

Χρειαζόμαστε καινούργια φάρμακα στο άσθμα?

- **Τα φάρμακα που έχουμε έως τώρα στο άσθμα είναι αποτελεσματικά στους περισσότερους (≈ 90%) αλλά ΟΧΙ ΣΕ ΟΛΟΥΣ τους ασθματικούς**

- **Μεγάλες μελέτες έχουν δείξει ότι δεν έχουμε καλό ΕΛΕΓΧΟ του άσθματος στην πλειοψηφία των ασθενών μας**
  - ***The INSPIRE study BMC Pulm Med. 2006***
  - ***Canonica GW et al GAPP survey Allergy 2007;***
  - ***Gaga M, et al, Chest 2005***
  - ***Holgate ST et al. BMC Pulm Med 2006***

- **Σοβαρό άσθμα: σοβαρό πρόβλημα, χωρίς λύση με τα υπάρχοντα φάρμακα**

- **Φαινότυποι άσθματος: διαφορετικά πρότυπα ανταπόκρισης στη θεραπεία**

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα

New glucocorticoids
New bronchodilators

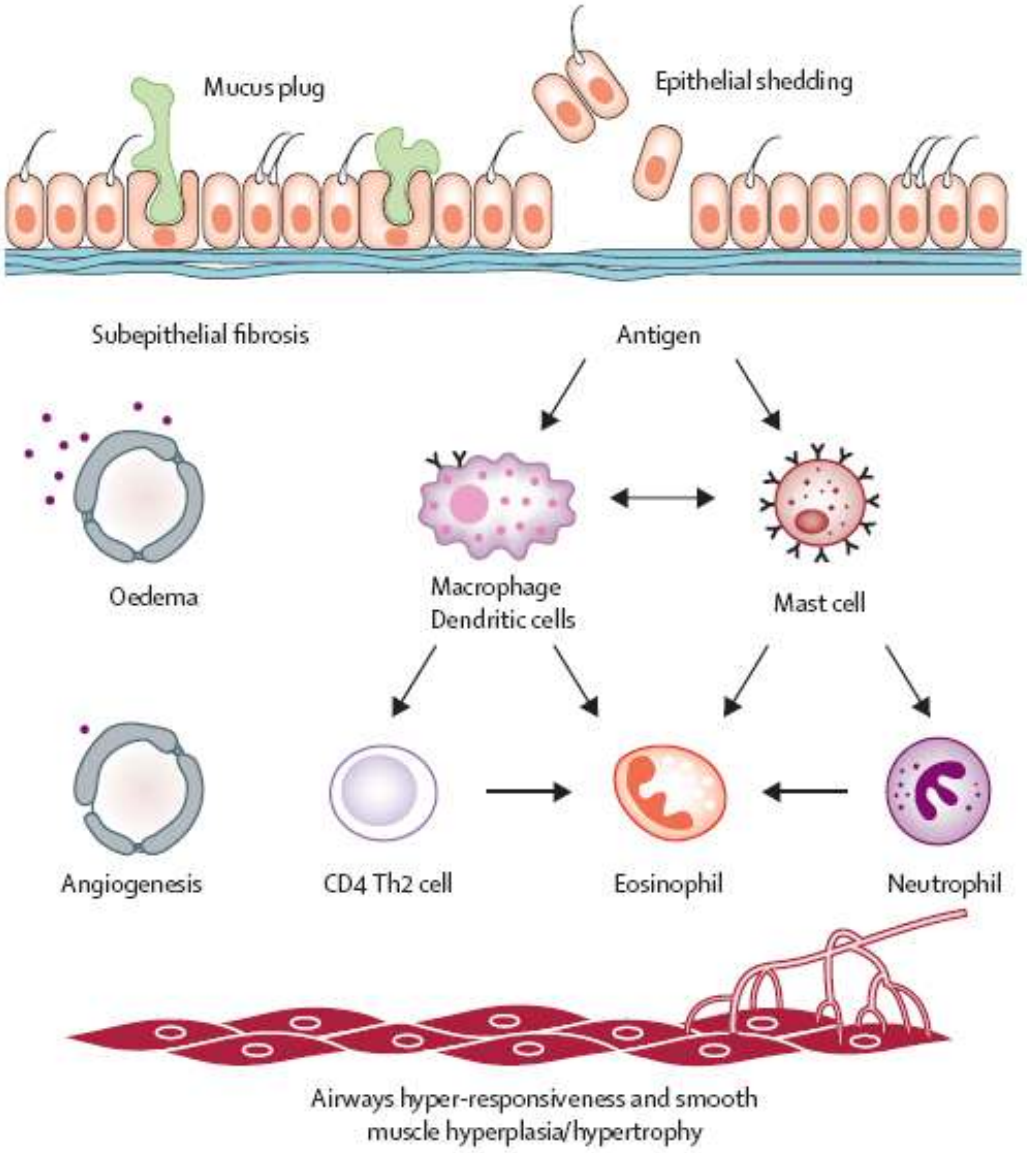
PDE4 inhibitors

Transcription factor and/or kinase inhibitors
- NFκB
- NF-AT
- GATA-3
- STAT1, STAT6
- PPAR
- p38 MAPK
- JNK
- PI3K

Adhesion blockers
- ICAM1
- VLA4

Mediator antagonists
- Antihistamines
- Leucotrienes
- Prostaglandins
- Neurokinins
- Adenosine
- Nitric oxide

Antioxidants



Immunomodulation
- Sublingual immunotherapy
- T-cell peptides
- Immunostimulatory oligonucleotides
- Treg modulators
- Dendritic cell inhibitors
- T-cell costimulatory molecules

Anti-allergy drugs
- Anti-IgE
- Anti-CD23

Cytokine inhibitors
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Chemokine receptor inhibitor
- CCR3, CCR4, CCR8, CRTh2
- CXCR1/2/3

Chemokine receptor agonists
- CCR5

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Βελτίωση υπαρχόντων φαρμάκων

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1

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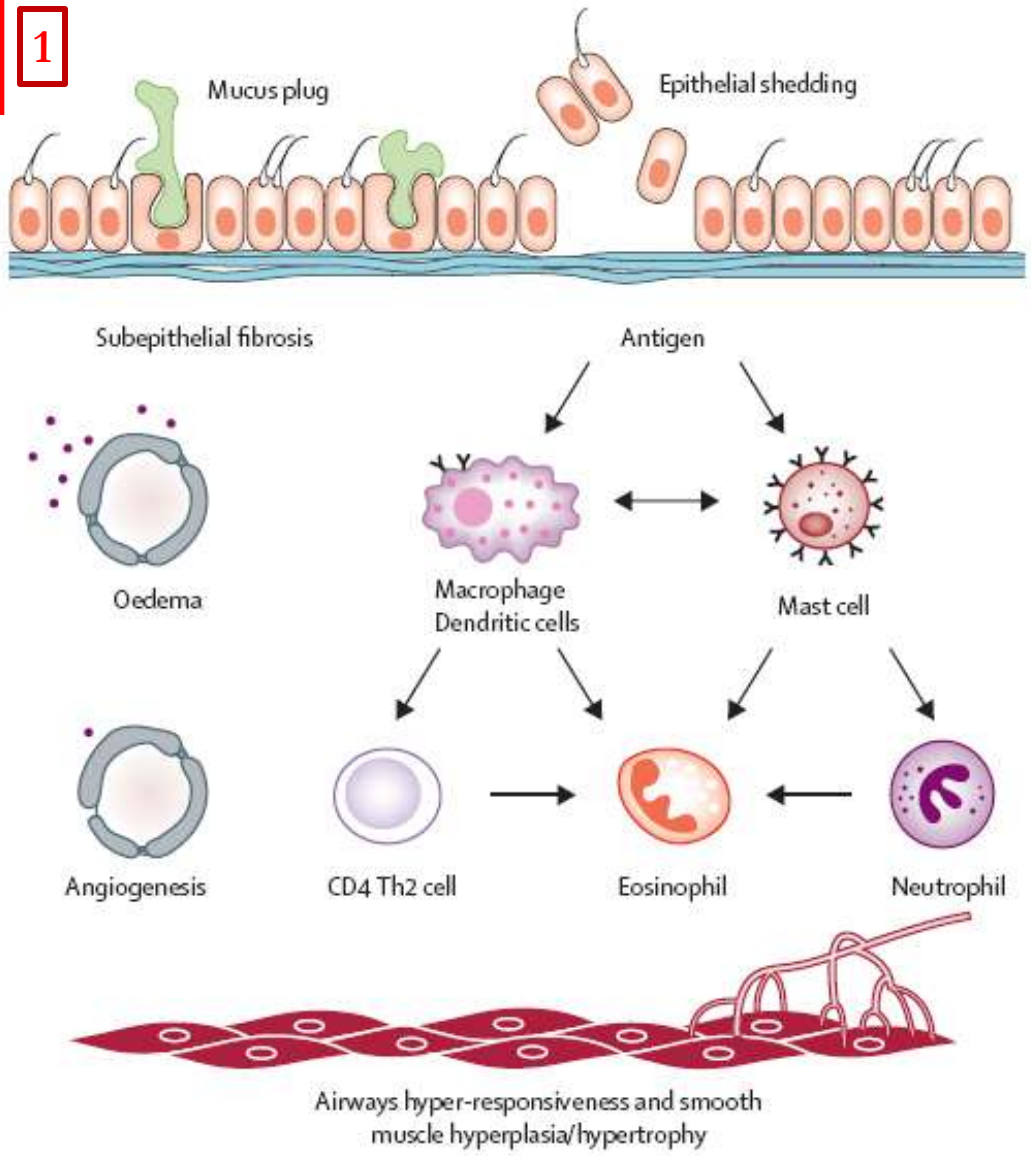

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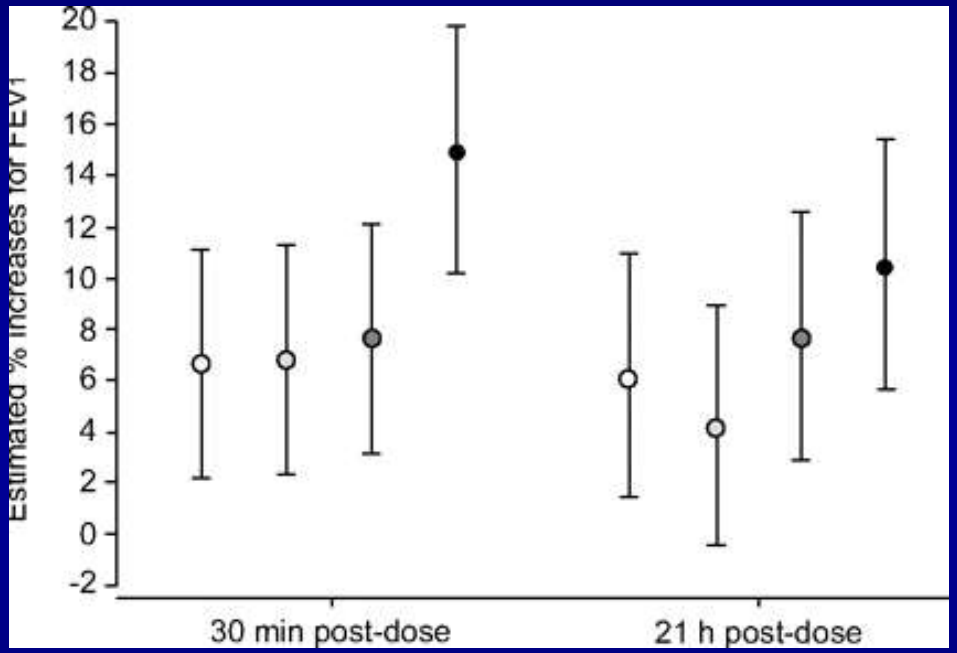
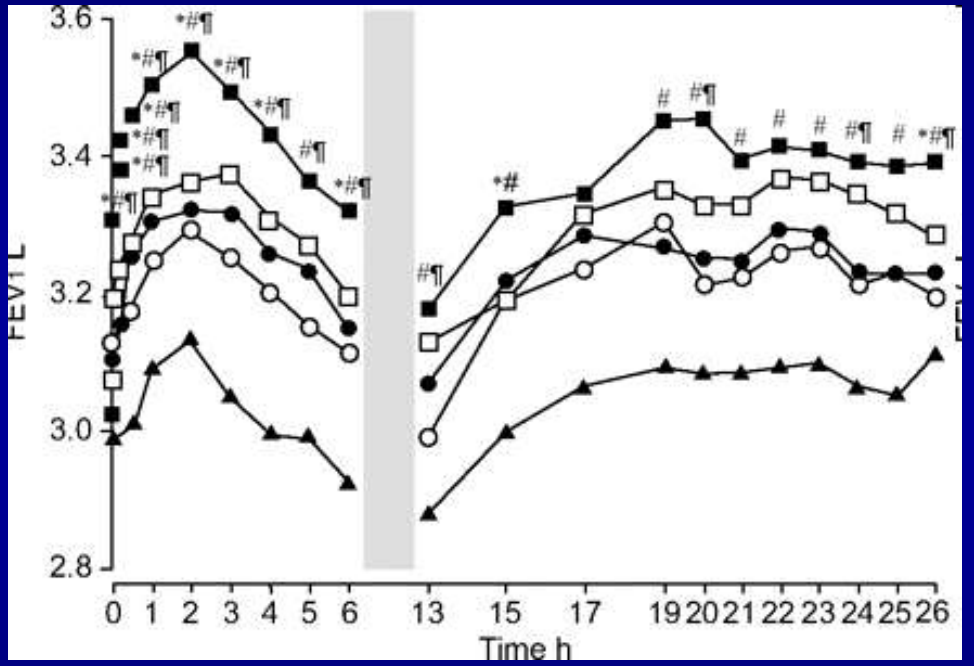
Βελτίωση υπαρχόντων φαρμάκων
Νέα βρογχοδιασταλτικά

- **Ultra-long acting β_2-agonists (24ωρης δράσης β_2-διεγέρτες)**
  - Indacaterol (Novartis)
  - Carmoterol (Chiesi)
  - GSK159797
- **Βρογχοδιασταλτικά με δράση > 24 ωρών, γρήγορη έναρξη δράσης, κατάλληλα για χορήγηση άπαξ ημερησίως**
- **Φαίνεται να μπορούν να αυξήσουν και την διάρκεια δράσης των ICS. Ένας νέος συνδυασμός *ultra LABA+ICS once daily* θα βελτίωνε σίγουρα την συμμόρφωση**

Indacaterol in asthma





Single 200 and 400 µg doses of indacaterol provided *effective and sustained 24-h bronchodilator control* with a *rapid onset of action (<5 min*) and a *good tolerability and safety profile* in asthmatic patients

Beeh KM et al. *ERJ* 2007

Indacaterol in asthma

- **LaForce C et all, Allergy Jan 2008**

  436 patients with persistent asthma were randomized to 7 days treatment with once-daily indacaterol 50, 100, 200, or 400 microg Serial 24-h spirometry was performed on days 1 and 7

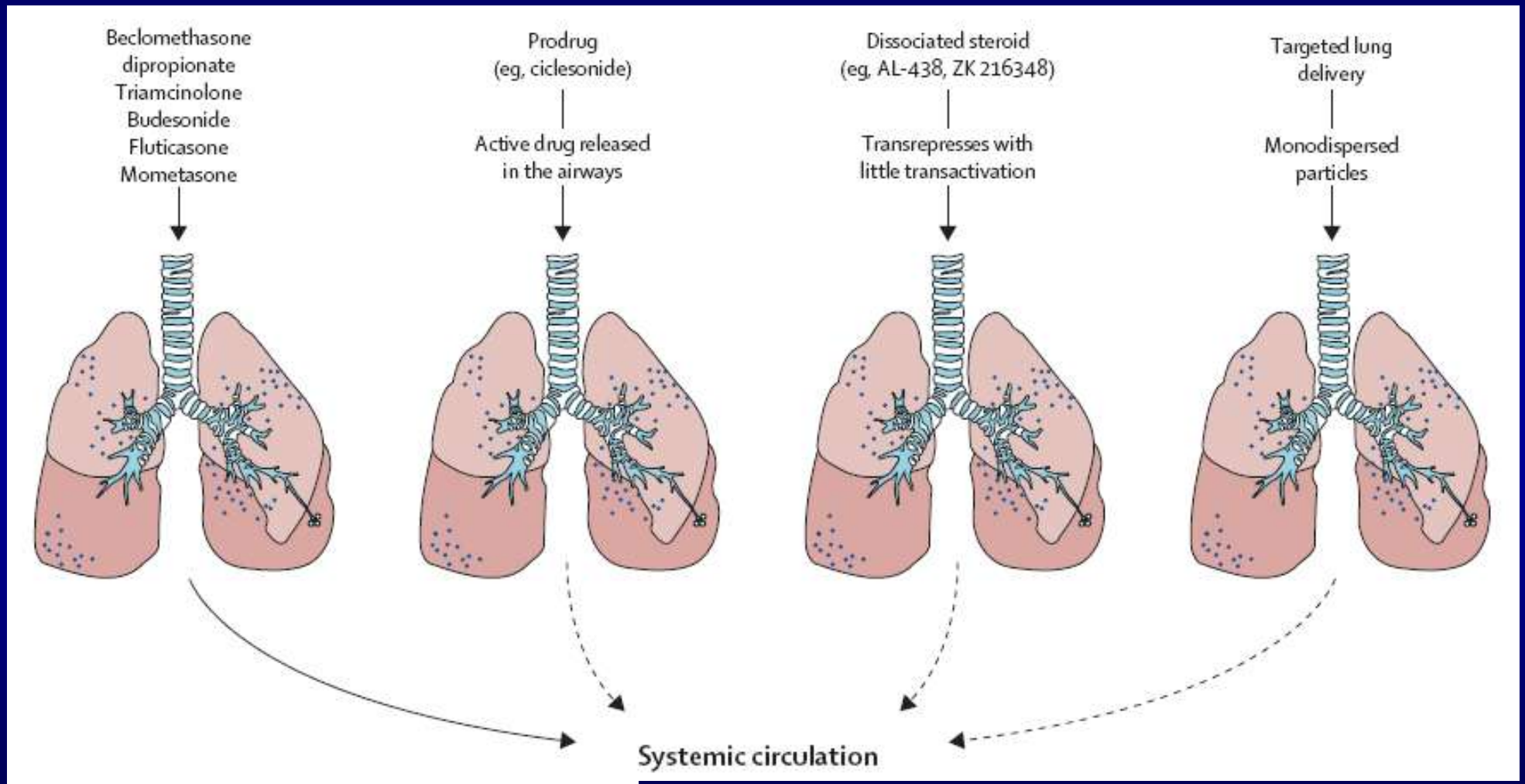
  All doses of indacaterol increased the mean time-standardized AUC of FEV_1 from 22 to 24 h postdose (P <or= 0.001 vs placebo) on days 1 and 7. *Indacaterol 200 microg appears the optimum dose*, offering the best efficacy/safety balance.

- **Kanniess F et all, J Asthma Dec 2008**

  115 patients with chronic persistent asthma were randomized in a double-blind, incomplete-block cross-over design to sequences of four 7-day treatment periods (separated by 7-day washouts) with indacaterol 100, 200, 300, 400, or 600 mcg or placebo, once daily. After the fourth washout, patients received 1 day of open-label formoterol 12 mg twice daily

  For standardized FEV_1 AUC at 22 to 24 hours, *indacaterol doses >or=200 mcg were superior to placebo ($p < 0.05$) and similar or greater than formoterol 12 mcg twice daily* .

Βελτίωση υπαρχόντων φαρμάκων
Νέα εισπνεόμενα κορτικοειδή



Approaches to reduce the side-effects of inhaled corticosteroids

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανταγωνιστές φωσφοδιεστερασών

New glucocorticoids
New bronchodilators

PDE4 inhibitors 2

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- NFκB
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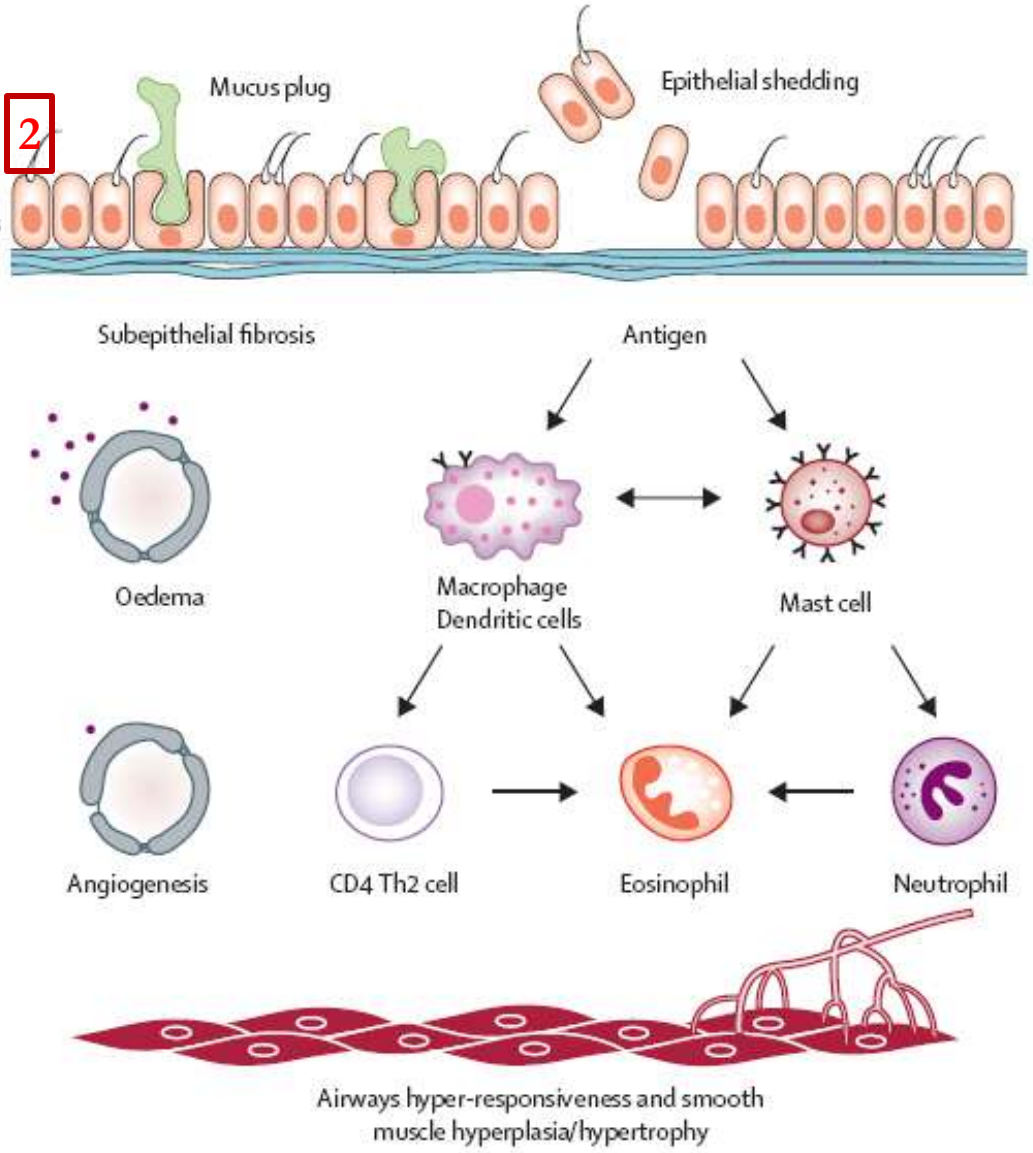

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Αγωνιστές φωσφοδιεστερασών

- **Αναστολείς PDE4**

  PDE4 inhibitors such as ***roflumilast and cilomilast*** prevent eosinophilic inflammation, are able to suppress neutrophilic inflammation and exert distinct anti-inflammatory effects compared with those seen with corticosteroids, suggesting that PDE4 inhibitors could be useful in the treatment of severe asthma.

  – Cilomilast

    In a parallel-group trial, cilomilast caused small improvements in FEV1 at 6 weeks, although this was lost by 12 months. *Fan Chung K Eur J Pharmacol. 2006*

  – Roflumilast

    499 patients (FEV1= 50-85% pred.) received roflumilast 500 microg once daily or BDP 200 microg twice daily (400 microg/day) for 12 weeks There were no significant differences between roflumilast and BDP with regard to improvement in FEV1 and FVC. Roflumilast and BDP showed small improvements in median asthma symptom scores and reduced rescue medication use . *Bousquet J, et all Allergy 2006*

  – ***The problem of nausea and vomiting*** that occurs at the top of the dose–effect curve has not been overcome despite improved isoform selectivity

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανταγωνιστές κινασών

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New bronchodilators

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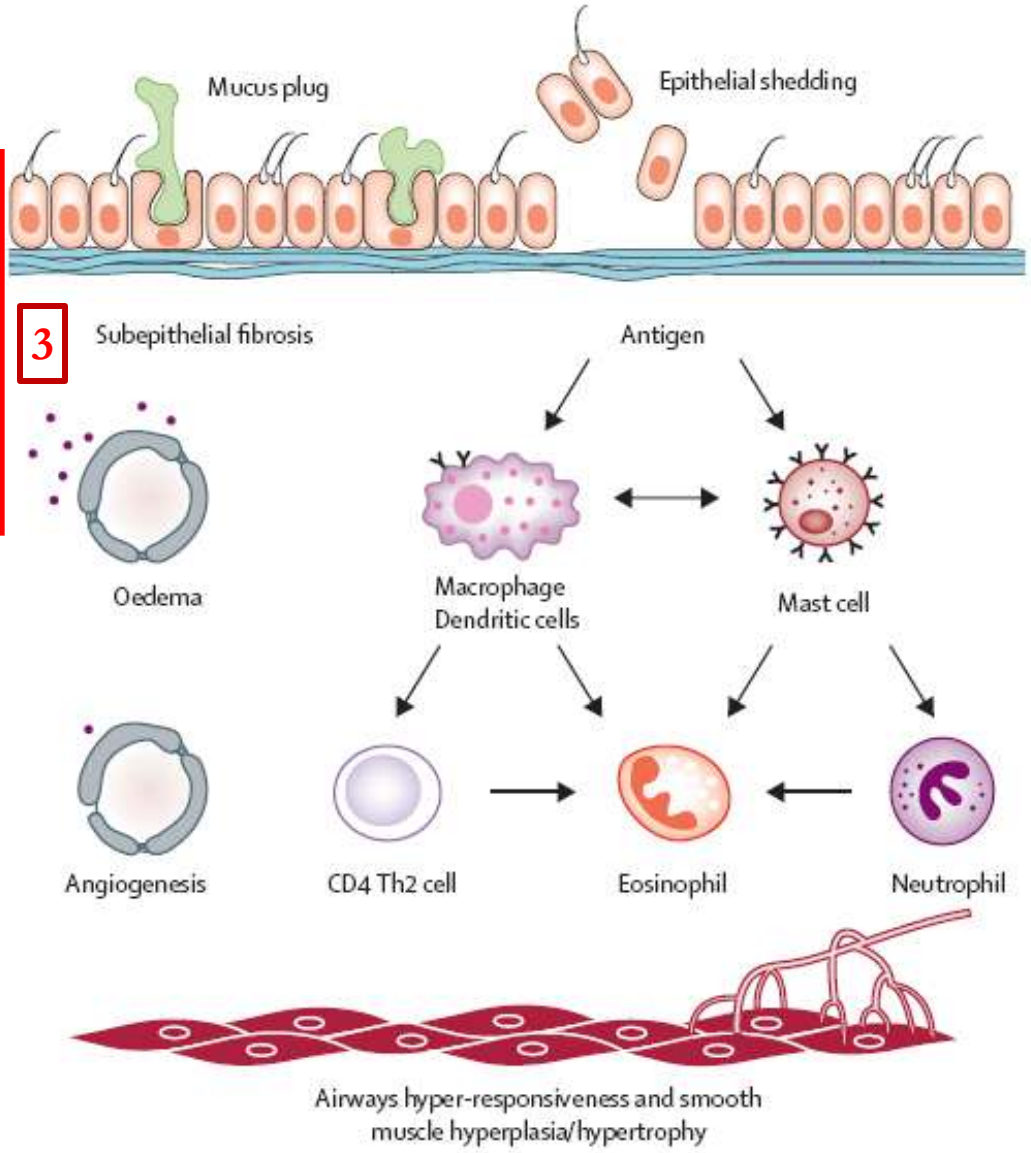

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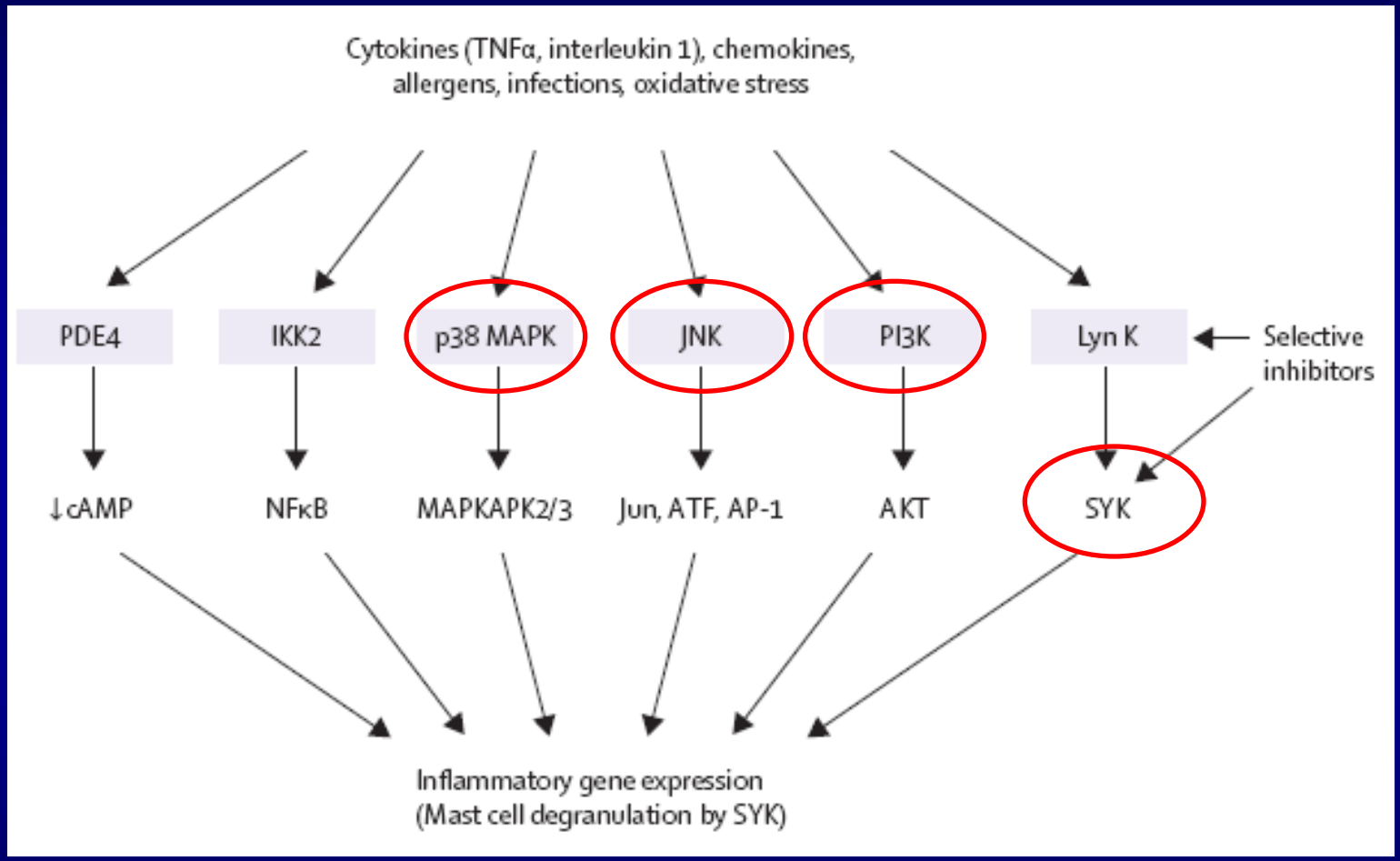

Kinases have a critical role in the ***expression and activation of inflammatory mediators*** in the airway, in both resident and infiltrating cell function **and airway remodelling**. Changes in kinase activation status have been reported in all asthmatic patients, but **particularly in those with severe asthma** where an association with reduced glucocorticoid responsiveness has been proposed.

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Ανταγωνιστές κινασών

- **Αναστολείς p38 MAPK**
  SB2439063 (GlaxoSmithKline, UK) and 101757 (ISIS Pharmaceuticals, USA)

They reduce the release of inflammatory mediators and some characteristics of allergic inflammation in animal models ***Adcock IM et all, Eur J Pharmacol. 2006***
Safety issues remain a concern for long-term use

- **Αναστολείς JNK**
  SP600125 (Celgene, USA)

Reduces accumulation of eosinophils and lymphocytes in BAL, serum IgE production and smooth muscle proliferation after repeated allergen exposure in animal models of asthma. ***Nath P et all, Eur J Pharmacol. 2006***

- **Αναστολείς Spleen tyrosine kinase (SYK)**
  BAY 61-3606 (Bayer, Japan), R343 (Rigel-Pfizer, USA)

Had inhibitory effects on human basophils, eosinophils, and monocytes and attenuated ovalbumin-induced airway inflammation in rats. ***Yamamoto N et all, J Pharmacol Exp Ther 2003***

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New bronchodilators

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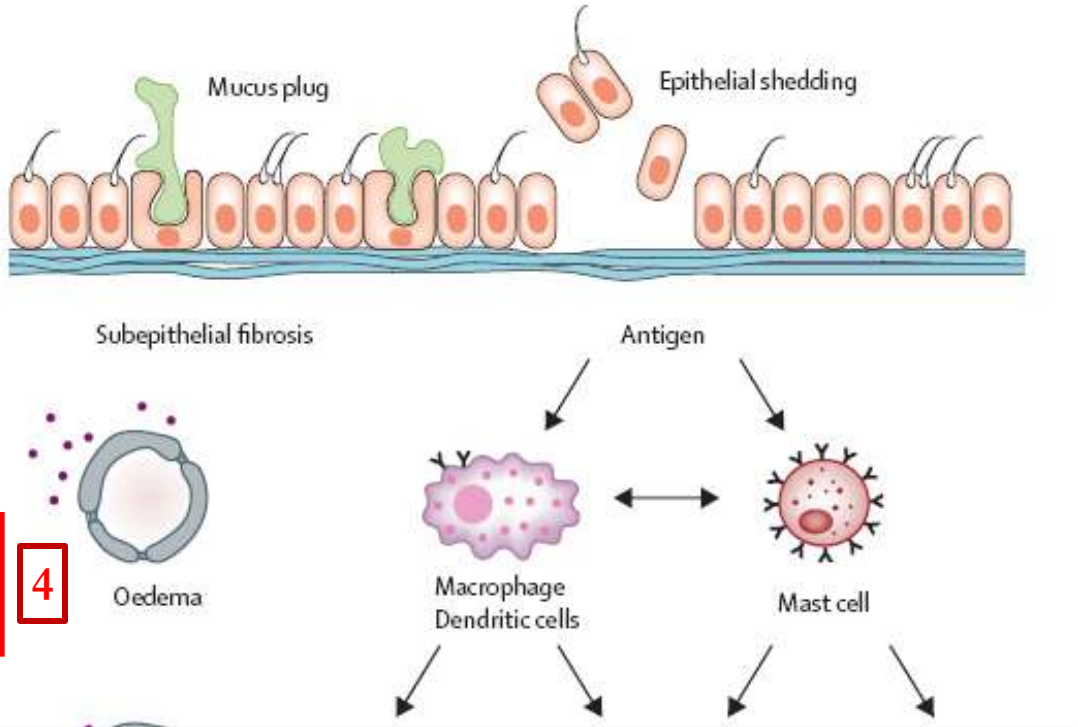

Much interest has been generated by the very late antigen-4 (VLA4), which is involved in the recruitment of eosinophils and T cells. However, ***the clinical outcome of trials of these agents in patients with asthma have been disappointing*** and indeed the development of some classes of these drugs was placed on hold by the FDA because of reports of progressive multifocal leucoencephalopathy in patients taking natalizumab

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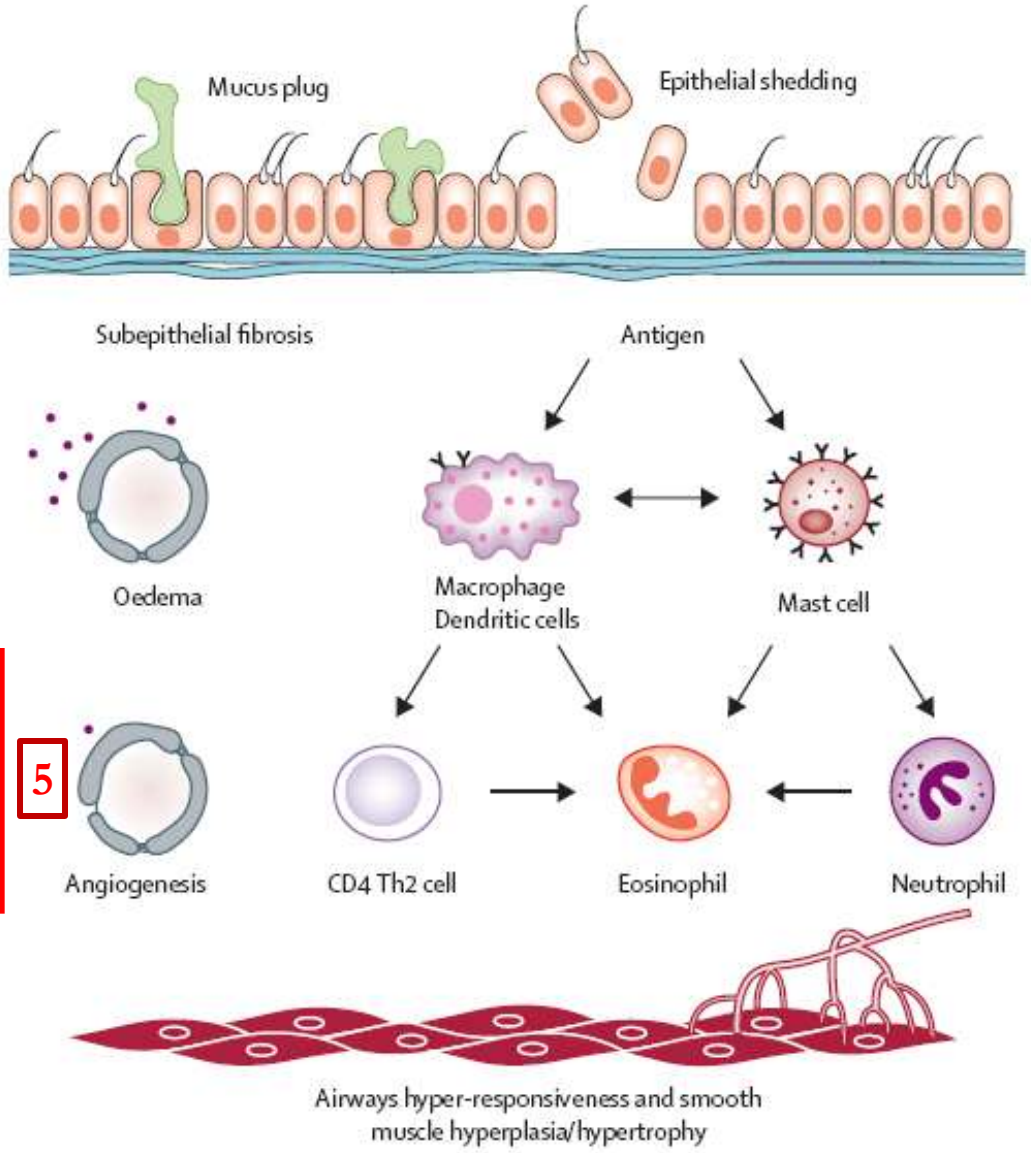

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Ανταγωνιστές μεσολαβητών

- **Ανταγωνιστές υποδοχέων PGD2**
  Prostaglandin PGD2, produced by mast cells, acts mainly through the protein-coupled receptor DP2 (also known as CRTh2, chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes) to mediate Th2 recruitment and activation

- eosinophilia and mucus cell hyperplasia

ODC9101 (Oxagen, UK)
in phase IIa clinical trials for asthma

- LY2331111 (Eli Lilly, USA)
παλιές μελέτες (Barnes 1996) δεν έχουν δείξει αποτελεσματικότητα στο άσθμα

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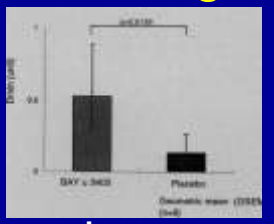
  χρησιμοποιείται στην Ιαπωνία για τη θεραπεία της αλλεργικής ρινίτιδας

  Aizawa H et all, Chest 1996 Ramatroban reduces BHR in asthmatics.



  – TM30089 (7TM Pharma, Denmark)

  Uller L et all, Respir Res. 2007 TM30089, displayed high selectivity for and antagonistic potency on mouse CRTh2 and inhibits asthma pathology in vivo by reducing peribronchial eosinophilia and mucus cell hyperplasia

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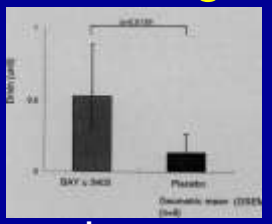

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- **Ανταγωνιστές υποδοχέων LTB4 (BLT1 antagonist)**

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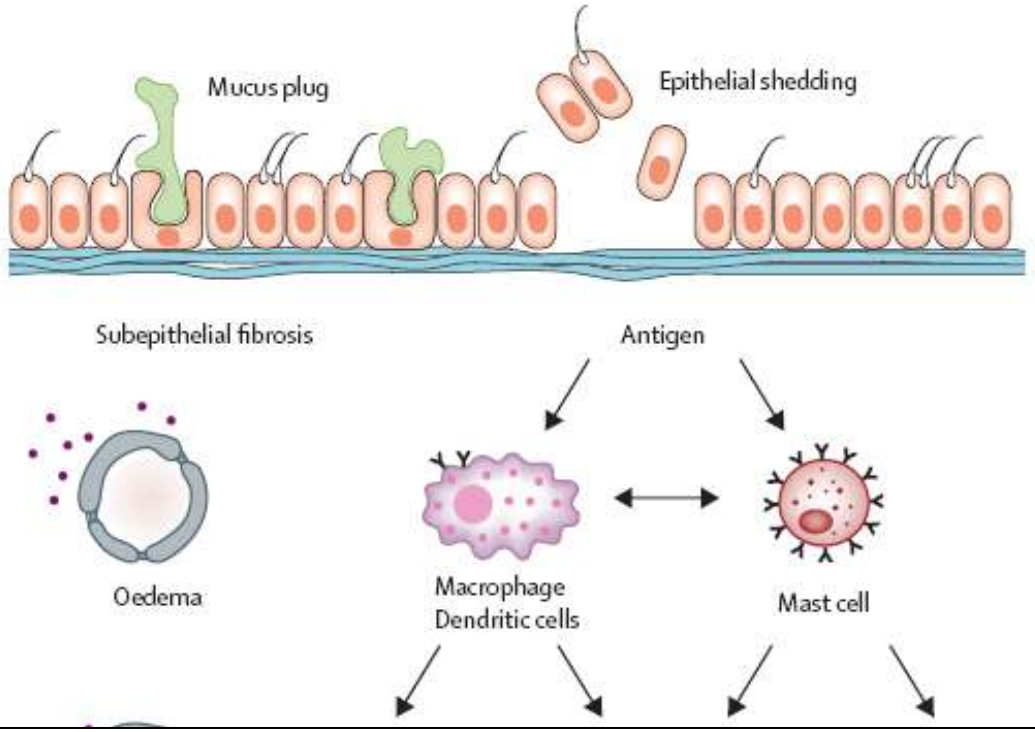

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Current anti-oxidants *do not seem to affect the redox balance in the airways* of human beings. Therefore, ***smarter and more potent drugs are required*** to target the correct cellular compartment.

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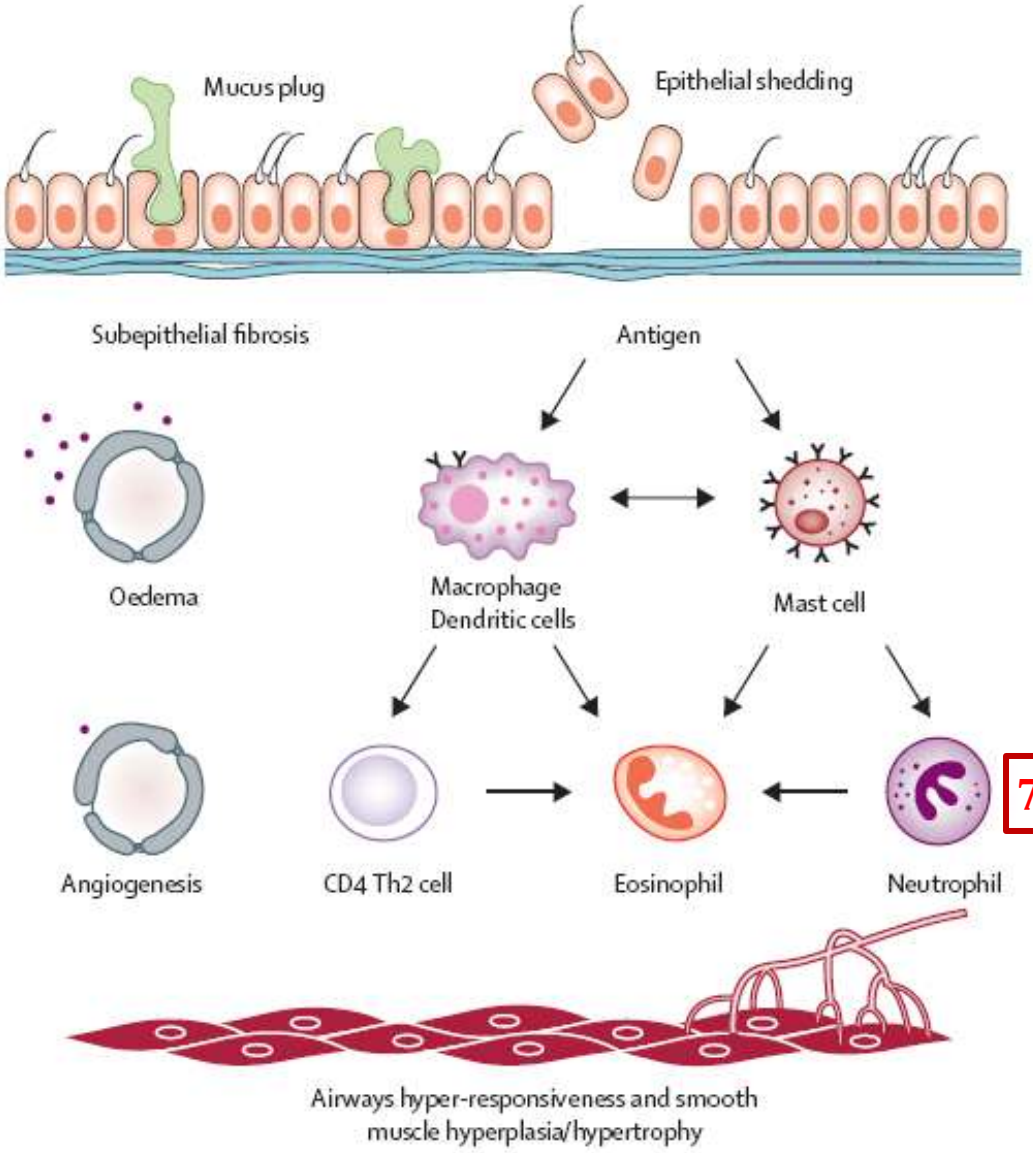

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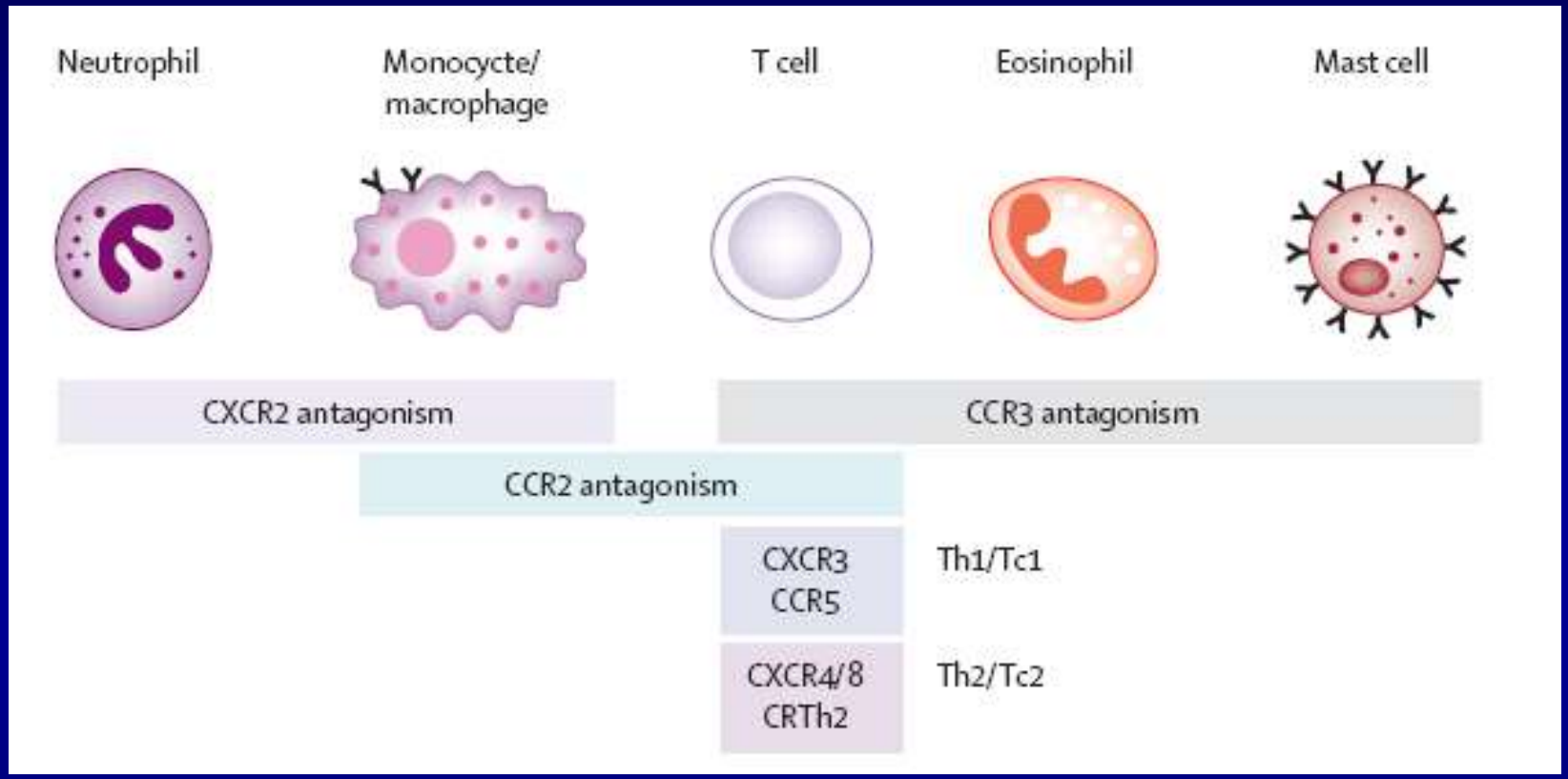
Ανταγωνιστές χημειοκινών



Prevention of inflammatory cell migration into the airways might be achieved by modulation of chemokine receptors. CCR3 antagonists would be predicted to prevent recruitment and activation of T cells, eosinophils, and mast cells in the airways, whereas CXCR2 antagonism would target monocytes/macrophage and neutrophil infiltration. Antagonism of the CCR2 receptor or biological agents against its ligands would prevent mast cell, monocytes/macrophage, and T-cell effects in asthma. Selective targeting of Th1/Tc1 or Th2/Tc2 cells could be achieved with CXCR3 and CCR4/8 or CRTh2 (chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes) antagonism, respectively, or by activation of CCR5 in the case of Th1/Tc1 cells.

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανταγωνιστές χημειοκινών

- **Ανταγωνιστές CCR3**

  The major focus of interest in asthma has been CCR3 and its ligands (CCL11, CCL24, and CCL26), which are increased in asthma

  Ben S et all, Allergy. 2008. Treatment with anti-CCR3 or dexamethasone significantly *inhibited allergen-induced eosinophilia* and CD34(+) progenitor cell infiltration in the lung, which was accompanied by *lower levels of airway hyper-responsiveness* and mucus production in asthmatic mice.

  Gauvreau GM et all, Am J Respir Crit Care Med. 2008 TPI ASM8 *inhibited sputum eosinophil influx* by 46% (P = 0.02) and blunted the increase in total cells (63%) after allergen challenge. TPI ASM8 significantly *reduced the early asthmatic response* (P = 0.04) with a trend for the late asthmatic response (P = 0.08)

  – Met-RANTES

  in phase IIa clinical trials for asthma

  The expression of CXCR1/2 ligands is increased in BAL fluid from asthmatic patients during severe exacerbations. CXCR1/2 antagonists could therefore be particularly effective in the treatment of severe exacerbations or in patients with severe asthma with evidence of neutrophilia.

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- **Ανταγωνιστές CXCR1/2**

  the expression of CXCR1/2 and its ligands is increased in biopsy samples obtained from asthmatic patients during severe exacerbations CXCR1/2 antagonists could therefore be particularly effective in the treatment of severe exacerbations or in patients with severe asthma with evidence of neutrophilia.

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανταγωνιστές κυτταροκινών

New glucocorticoids
New bronchodilators

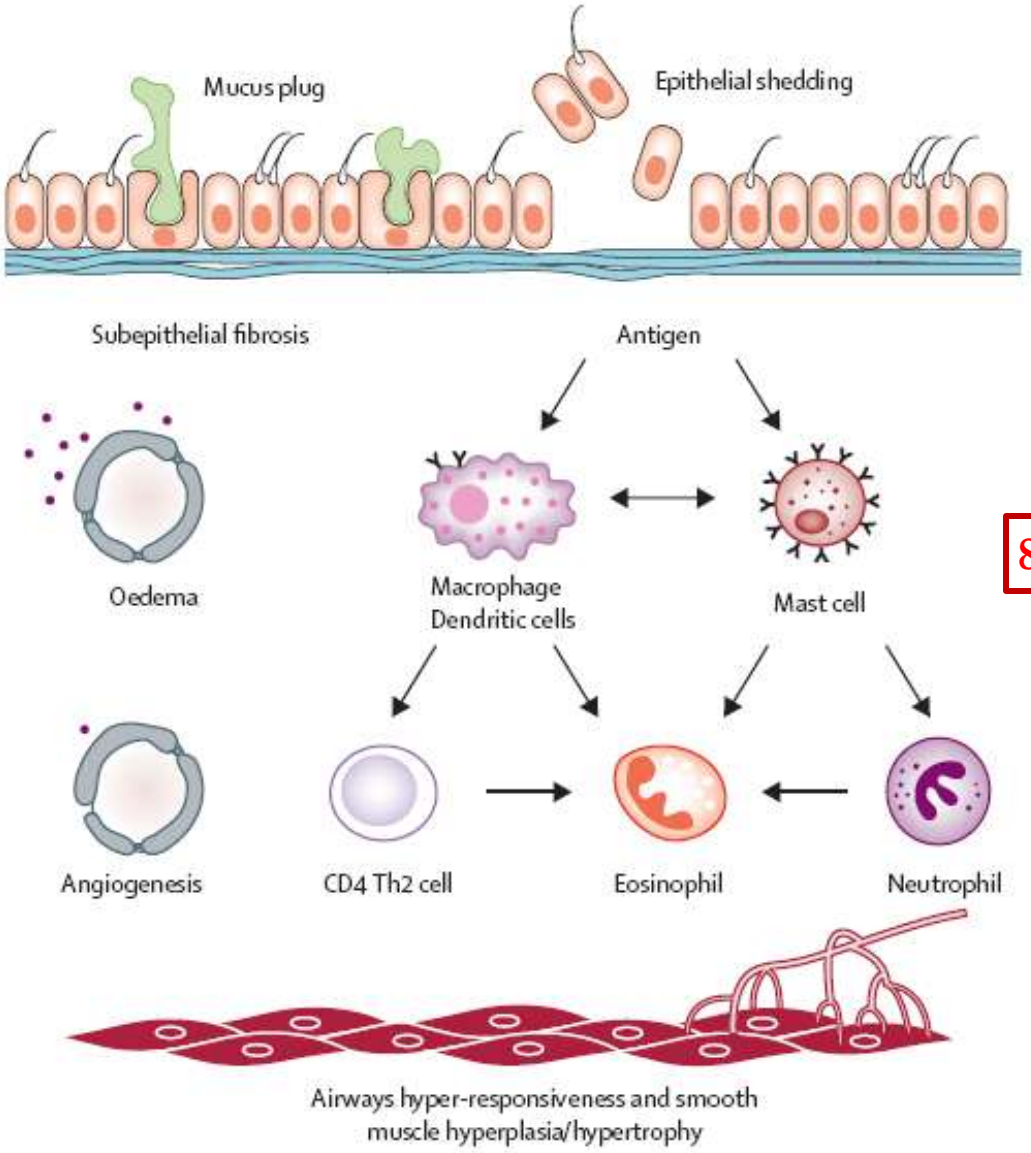
PDE4 inhibitors

Transcription factor and/or kinase inhibitors
- NFκB
- NF-AT
- GATA-3
- STAT1, STAT6
- PPAR
- p38 MAPK
- JNK
- PI3K

Adhesion blockers
- ICAM1
- VLA4

Mediator antagonists
- Antihistamines
- Leucotrienes
- Prostaglandins
- Neurokinins
- Adenosine
- Nitric oxide

Antioxidants



Immunomodulation
- Sublingual immunotherapy
- T-cell peptides
- Immunostimulatory oligonucleotides
- Treg modulators
- Dendritic cell inhibitors
- T-cell costimulatory molecules

Anti-allergy drugs
- Anti-IgE
- Anti-CD23

Cytokine inhibitors
- Interleukins 4, 5, 6, 9, 13, 19, 22, 25
- Thymic stromal lymphopoietin
- TNFα

8

Cytokine agonists
- Interleukins 10, 12, 21, 27
- Interferon (α, β, γ, λ)

Chemokine receptor inhibitor
- CCR3, CCR4, CCR8, CRTh2
- CXCR1/2/3

Chemokine receptor agonists
- CCR5

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανταγωνιστές κυτταροκινών

- **Ανταγωνιστές IL4 και IL13**

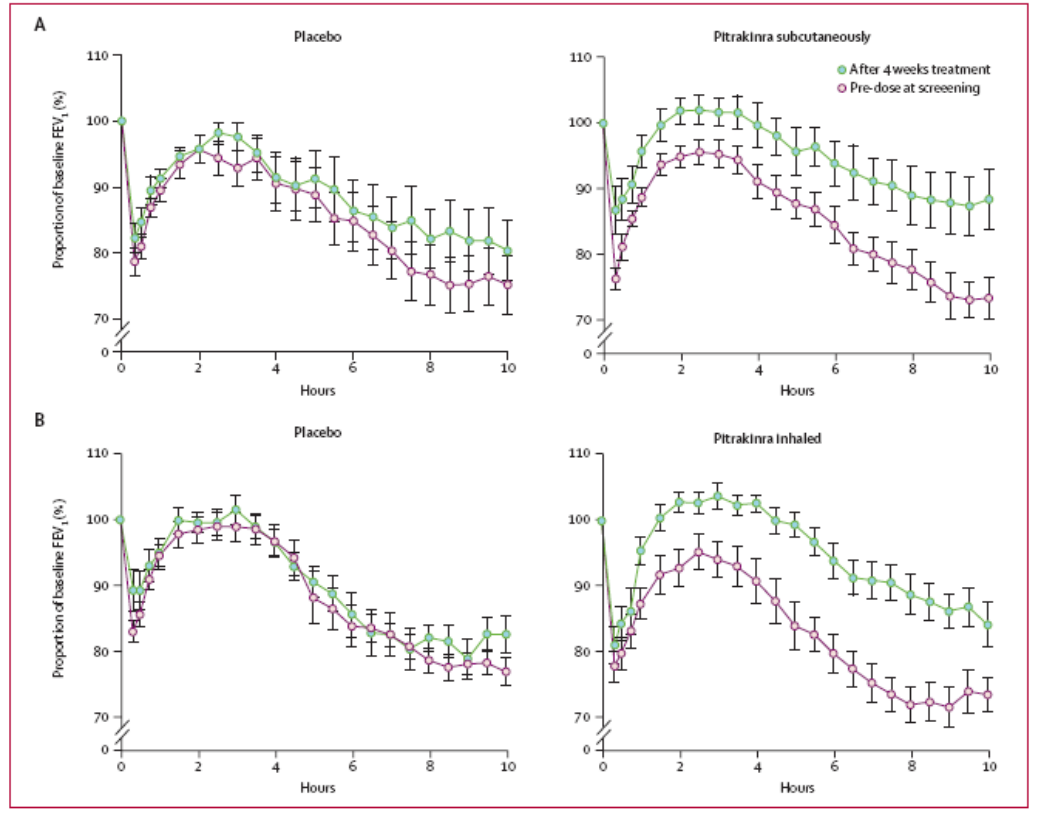
Both interleukin 4 and interleukin 13 are important in B-cell IgE isotype switching, and interleukin 4 is also important in maintaining the Th2 phenotype.

Wenzel S. Lancet 2007. **Pitrakinra**

–ανασυνδυασμένη μορφή της ανθρώπινης IL4 που φέρει 2 μεταλλάξεις στις θέσεις 121 και 124

–δρα μέσω σύνδεσης και αναστολής του υποδοχέα IL4Rα, του κοινού υποδοχέα για την δράση των IL-4 και IL-13

–Ενθαρρυντικά αποτελέσματα από την δράση του Pitrakinra στην καθυστερημένη ασθματική αντίδραση



Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Αγωνιστές κυτταροκινών

- **Αγωνιστές IL10 και IL12**

IL10 and IL12 are intrinsically anti-inflammatory and are therefore potential therapeutic agents. The expression of interleukins 10 and 12 is reduced in patients with severe asthma

Bryan SA. et all Lancet 2000 repeated injections of **interleukin 12** have *no effect* on airway hyper-responsiveness despite marked effects on blood eosinophilia.

Administration of **interleukin 10** has proved effective in animal models of asthma but no studies have been reported in asthmatic patients despite interleukin 10 being approved for psoriasis.

– *unacceptable side-effects* and an alternative strategy to enhance endogenous expression of interleukin 10 through immunomodulatory pathways is preferable.

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανοσοτροποποιητικά

New glucocorticoids
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- NFκB
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- STAT1, STAT6
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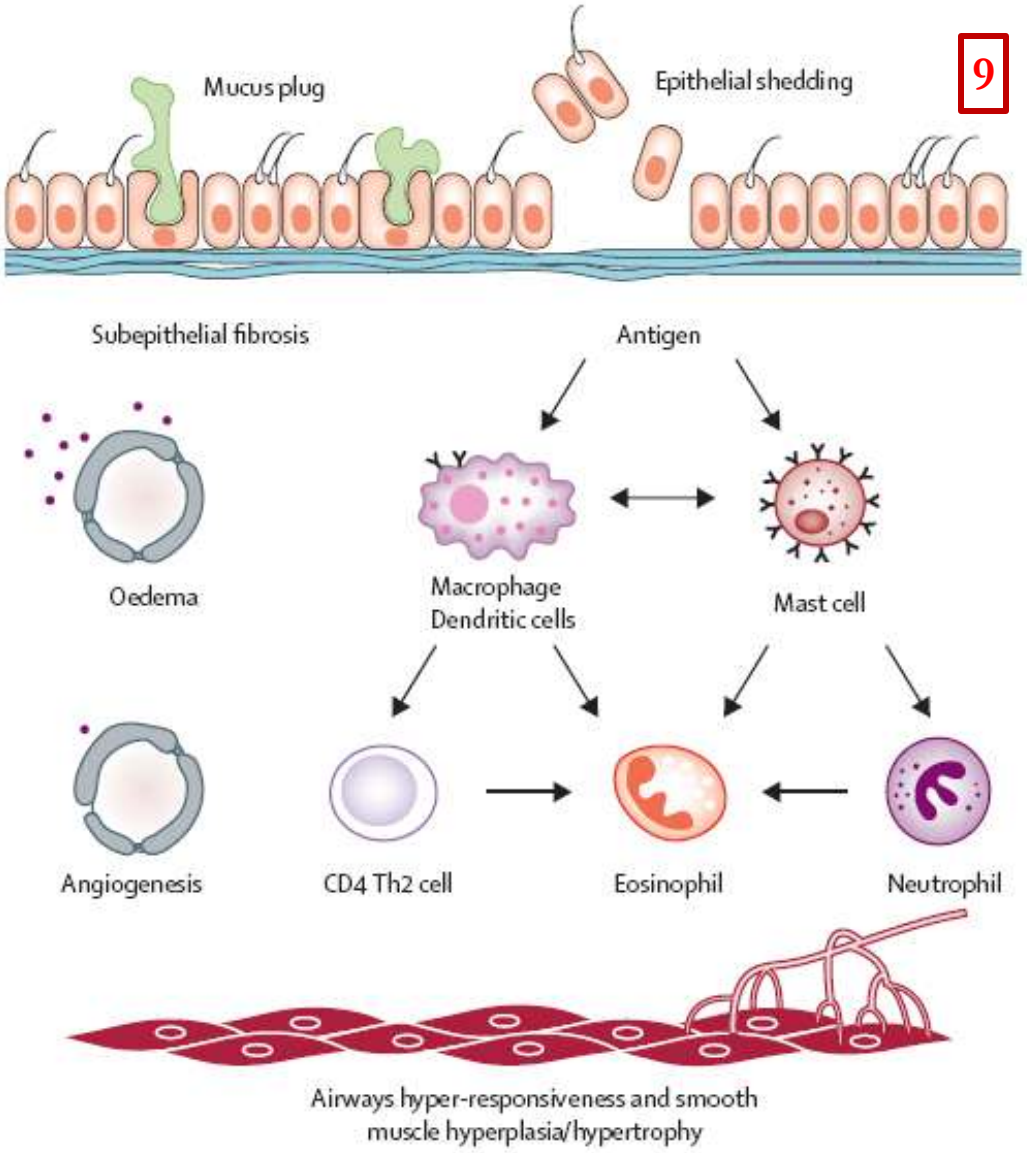

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Chemokine receptor inhibitor
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- CXCR1/2/3

Chemokine receptor agonists
- CCR5

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα
Ανοσοτροποποιητικά

- **Αναστολείς των δενδριτικών κυττάρων**

  FTY720(fingolimod, Novartis), BW245C (Wellcome Research Laboratories)

They suppress dendritic cell function, leading to decreased airway inflammation and bronchial hyper-reactivity in a mouse model (***Hammad H et all, J Exp Med 2007)*** but also strongly attenuates established lung inflammation (**I*dzko et all, J Clin Invest 2006)***

- **Enhancing Treg expression, altering T-cell class switching away from the Th2 response.**

  Specific subcutaneous immunotherapy
  immunostimulatory oligodeoxynucleotides, including CpG oligodeoxy nucleotides

Έρευνα γύρω από νεότερα φάρμακα στο άσθμα

	Function	Drug and stage of development
β_2 adrenergic receptor	Ultra-long bronchodilation	Indacaterol (phase II), carmoterol (phase II), GSK159797 (phase II)
Glucocorticoid receptor	Anti-inflammatory	GSK685689 (phase II), GSK870086 (phase II), AL-438 (phase I), ZK 216348 (phase I)
PGD2/CRTh2 inhibitors	Th2 cell recruitment and activation	TM30089, ODC9101 (phase II), AZD1981 (phase II), ramatroban (phase II)
BLT1 antagonist	Mononuclear/granulocyte recruitment	CP-105696 (phase I), LY293111 (phase II, no effect against allergen challenge)
CCL11	Blocks eosinophil recruitment/activation	CAT-213 (preclinical)
CCR3	Blocks eosinophil recruitment/activation	Met-RANTES (phase II, moderate/severe asthma)
CXCR4	Blocks Th2 activation	AMD070, AMD3100, SP01A (all preclinical for asthma, all phase II HIV, AMD3100 phase III for multiple myeloma)
CXCR1/2	Blocks neutrophil recruitment/activation	Repertaxin (preclinical, phase II for graft *vs* host disease)
Interleukin 5	Blocks eosinophil recruitment/activation	MEDI-563 (phase I, severe asthma), mepolizumab (phase II)
Interleukin 12	..	Interleukin 12 (phase II, no effect on lung function, adverse side-effects, not developed further)
Interleukin 10	Endogenous anti-inflammatory agent	Interleukin 10 (preclinical for asthma, approved for psoriasis/Crohn's disease, recruited in 1999 for asthma)
Interferon γ	..	Interferon γ (phase II, no effect on lung function in severe asthma, not developed further)
Interleukin 13	Key driver of asthmatic inflammation	Pitrakinra (interleukin-4/13 mutein), CAT-354, IMA-638 (both in phase II)
VLA4 antagonist	Adhesion molecule blocker	GW-559090, IVL745, CDP323 (CDP323 phase II, not developed)
PDE4	Anti-inflammatory	GSK256066 (phase II)
p38 MAPK	Anti-inflammatory	GSK681323, GSK856553, VX-745, BIRB-796, Ro-320-1195, Scio-469 (all in phase II), SB2439063, RWJ-67657
JNK	Anti-inflammatory	SP600125, CC-401, CNI-1493 (dual JNK/p38 MAPK) (all in preclinical for asthma; CC-401 and CNI-1493 in phase II in rheumatoid arthritis and Crohn's disease)
SYK	Mast cell degranulation, T-cell and B-cell function	Antisense (preclinical), BAY61-3606 (preclinical), R343 (phase I)
IKK2	Anti-inflammatory	AS206868, SC-514, BMS345541, TPCA-1 (all preclinical, MLN0415 [phase I])
CD23	Reduces IgE	Lumiliximab (phase I)
Sphingosine-1 phosphate receptor	Prevents dendritic cell activity	FTY720 (preclinical for asthma, Phase II for multiple sclerosis and transplant rejection)
DP1	Prevents dendritic cell activity	BW245C (preclinical)
VDR	Increased interleukin-10 expression in Treg cells	Vitamin D3 (phase II, steroid sparing)

THE LANCET

New targets for drug development in asthma

Ian M Adcock, Gaetano Caramori, K Fan Chung

Asthma is a chronic inflammatory disease that affects about 300 million people worldwide, a total that is expected to rise to about 400 million over the next 15–20 years. Most asthmatic individuals respond well to the currently available treatments of inhaled corticosteroids and β-adrenergic agonists; however, 5–10% have severe disease that responds poorly. Improved knowledge of asthma mechanisms has led to the recognition of different asthma phenotypes that might reflect distinct types of inflammation, explaining the effectiveness of anti-leucotrienes and the anti-IgE monoclonal antibody omalizumab in some patients. However, more knowledge of the inflammatory mechanisms within the airways is required. Improvements in available therapies—such as the development of fast-onset, once-a-day combination drugs with better safety profiles—will occur. Other drugs, such as inhaled p38 MAPK inhibitors and anti-oxidants, that target specific pathways or mediators could prove useful as monotherapies, but could also, in combination with corticosteroids, reduce the corticosteroid insensitivity often seen in severe asthma. Biological agents directed against the interleukin-13 pathway and new immunoregulatory agents that modulate functions of T-regulatory and T-helper-17 cells are likely to be successful. Patient-specific treatments will depend on the development of discriminatory handprints of distinct asthma subtypes and are probably over the horizon. Although a cure is unlikely to be developed in the near future, a greater understanding of disease mechanisms could bring such a situation nearer to reality.

Lancet 2008; 372: 1073–87

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