



# Progress and Challenges in Finding a Cure for Asthma

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## ABSTRACT

Asthma is an obstructive inflammatory disease of the airways. The number of people affected is still rising and is becoming a global health problem. The main features of asthma are chronic Th2-biased inflammation and the production of allergen specific IgE antibodies. The mast cell and eosinophilic infiltration together with the persistent secretion of pro-inflammatory cytokines causes tissue damage resulting in remodeling of the airways. This results in exacerbated bronchial contractility, sub-epithelial fibrosis and goblet cell hyperplasia. Therefore, asthma is a complex disease with two main pathological characteristics. Several treatments are available on the market targeting the inflammatory component of the disease, such as corticosteroids. However, once treatment stops the hyperactivated structural cells keep secreting inflammatory mediators thereby recruiting the immune cells to the lung again. As such, current treatment regimens are suppressing the symptoms but will not result in a cure for asthma. Therefore, targeting both tissue remodeling and inflammation might prove to be a necessity in order to find a curative treatment for asthma. In this article we will discuss current therapies targeting inflammation and as well as some novel therapies focusing on lung remodeling in conjunction with inflammation.

**Key words:** Asthma, cure, novel therapies

## ABSTRAK

Asma adalah penyakit inflamasi yang mengganggu saluran pernapasan. Saat ini jumlah penderita asma makin meningkat dan hal ini telah menjadi isu kesehatan dunia. Gejala utama penyakit asma adalah inflamasi kronis sel Th2 yang *bias* serta produksi IgE yang merupakan antibodi yang menarget allergen secara spesifik. Infiltrasi *mast cell* dan *eosinophil* bersama-sama dengan sekresi sitokin pro-inflamasi menyebabkan kerusakan jaringan yang pada akhirnya menyebabkan *remodelling* saluran pernapasan. Proses tersebut mengganggu kemampuan kontraksi *bronchial*, menyebabkan fibrosis sel sub-epitel dan hiperplasia sel goblet. Oleh karena itu, asma merupakan penyakit kompleks yang memiliki dua karakter patologi utama. Berbagai pengobatan telah tersedia di pasaran, salah satunya adalah kortikosteroid yang menarget komponen inflamasi. Namun ketika proses pengobatan dihentikan, sel struktural yang sudah teraktivasi secara berlebihan akan terus mensekresi sitokin-sitokin yang berperan sebagai mediator inflamasi. Proses ini akan menyebabkan sel-sel imun masuk kembali ke dalam paru-paru. Pengobatan dengan cara tersebut hanya akan mengurangi gejala asma, namun tidak dapat menyembuhkan penyakit tersebut. Pengobatan yang ditujukan pada inflamasi dan *remodelling* jaringan secara bersamaan, diprediksi menjadi pilihan yang tepat untuk terapi asma di masa akan datang. Artikel ini membahas terapi yang telah dilakukan selama ini dan beberapa terapi baru yang menargetkan perubahan struktur paru-paru dan inflamasi secara bersamaan. **Gabriella Gita Febriana, Victor Christoff de Vries. Perkembangan dan Tantangan dalam Pengobatan Asma.**

**Kata kunci:** Asma, kesembuhan, terapi baru

## INTRODUCTION

Hypersensitivity is the collective name for diseases in which an aberrant immune response is mounted against innocuous agent, for instance allergens and haptens. In the 1960's Gell and Coombs designed a classification which divides the type of response in four major groups.<sup>1</sup> However, with the increasing knowledge of the immune system, this classification has been revised many times and currently there are 5 classes of hypersensitivity<sup>2</sup> of which type IV has been

subdivided in 4 distinct phenotypic responses (see table 1).<sup>3</sup> In this review we will talk about chronic asthma, a combined type I and type IVb hypersensitivity.

Asthma is an obstructive inflammatory airway disease characterized by the production of allergen specific IgE and a mainly Th2 driven immune response. Furthermore, accumulation of eosinophils and mast cells contribute to the severity of this disease.<sup>4</sup> As a consequence of the chronic

inflammation, the continuous release of pro-inflammatory mediators as well as the release of mast cell derived proteases by degranulation leads to tissue damage and aberrant "emergency" repair responses which includes goblet cell hyperplasia and increased mucus production, an increase in smooth muscle mass and sub-epithelial fibrosis.<sup>5</sup> These changes are collectively known as tissue remodeling and together with inflammation contribute to the asthma pathogenesis (figure 1).

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Table 1: The adapted Gell-Coombs classification of hypersensitivity reactions<sup>1</sup>

Hypersensitivity classification	Characteristic	Alternative name	Examples
<b>Type I</b>	IgE and IgG4, mast cells, eosinophils	Allergy	Atopy, Asthma, Rhinitis, anaphylaxis
<b>Type II</b>	IgG or IgM, (complement), membrane attack complex, FcR <sup>+</sup> cells	Cytotoxic antibody dependent hypersensitivity	Goodpasture's syndrome, rheumatic heart disease, membranous nephropathy
<b>Type III</b>	IgG, complement, neutrophils	Immune complex disease	SLE, Extrinsic allergic alveolitis, serum sickness
<b>Type IV (a-d)*</b>	Immune cell mediated <b>IVa</b> : Th1 cells, macrophage activation <b>IVb</b> : Th2 cells, Eosinophils <b>IVc</b> : Perforin/Gramzyme B (CTL), T-cells <b>IVd</b> : CXCL8, GM-CSF, T-cells, Neutrophils	Delayed type hypersensitivity	Contact dermatitis (IVa and IVc), Chronic asthma/Rhinitis (IVb), chronic transplant rejection (IVc), AGEF and behçet's disease (IVd)
<b>Type V**</b>	IgG or IgM, complement	Receptor mediated auto-immune disease	Graves' disease, Myasthenia Gravis

\* = The sub-classification could not be made by the original Gell-Coombs classification due to the lack of knowledge about the various subsets of T-cells.<sup>2</sup>

\*\* = Type V is an additional type that has been introduced to distinguish a sub-class of Type II hypersensitivity. In type V hypersensitivity antibody binding to the target cells impacts receptor signaling instead of opsonizing the cells by binding to non-receptor cell surface molecules.<sup>3</sup>

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**ON THE ORIGINS OF ASTHMA: THE DEVELOPING LUNG**

Asthma is a complex disease and the origins are multi-factorial. There is a plethora of evidence suggesting that some asthmatic patients were already primed during development.<sup>6</sup> This priming can be due to external factors influencing *in utero* lung development by epigenetic changes, such as parental smoking, air pollution and infectious diseases<sup>6-8</sup> but can also have a genetic basis. Genome-wide association studies have identified over 100 genes predisposing the fetus to development of asthma later in life.<sup>9</sup>

Lung development is a complex process starting in the fourth week of gestation and continues years after birth. The appearance of the lung buds marks the earliest stage of lung development after which branching of the airways and blood vessels develop simultaneously. Due to the complex nature of the lung, multiple morphogenic pathways are active, with the main signaling molecules being FGF (fibroblast growth factor), BMP-4 (bone morphogenic protein-4), SHH (sonic

hedgehog) and TGFβ.<sup>10</sup> The FGF9 and the FGF10/SHH/Ptch pathway are involved in branching morphogenesis and the development of bronchial and vascular smooth muscle cells<sup>11-12</sup> and several genes of both the HH and FGF pathway have been linked to the development of asthma.<sup>13-15</sup> The FGF pathway is tightly regulated by TGFβ, which is known to play an important role in tissue remodeling in the adult asthmatic lung.<sup>16</sup> The developmental pathways stay active during the full progression of the lung development, including the canalicular stage, development of the lung parenchyma which branches out of the terminal bronchioli and form the dense vascular network of the lung, the saccular phase, formation of alveolar sacs which also branch out from the terminal bronchioli, and lastly the alveolar phase, formed from the new sacculi, where gas exchange takes place. The involvement of the different developmental pathways has been described in detail.<sup>17</sup> The final stage of lung development is alveolar multiplication, which begins at term and continues for 2 to 3 years post-natal.

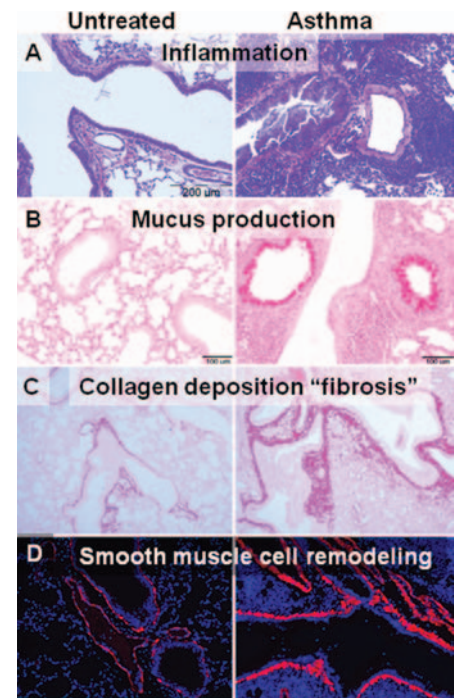


Figure 1: Main pathologies of the asthmatic lung. In a mouse model of asthma the changes in the lung as well as the Th2 mediated inflammation are well recapitulated compared to the human situation. Left panels are untreated mice and the right panels are of mice treated for 8 weeks with ovalbumin (100µg intranasal). The A/J mouse has a physiological relevant induction of allergic airway inflammation as repeated application of the allergen through the nose induces the asthma phenotype without prior sensitization (intraperitoneal allergen+adjuvant). **A.** H&E staining showing an increase in inflammation. **B.** PAS-staining showing goblet cell hyperplasia and increased mucus secretion. **C.** Picro-Sirius Red staining for collagen showing increased collagen deposition in the sub-epithelial layers as readout for fibrosis. **D.** Immunofluorescent staining for alpha-smooth muscle cell actin showing increased smooth muscle cell mass.

**Inflammation and remodeling, two sides of the same coin**

Asthma pathology consists of two parts, chronic inflammation and tissue remodeling. These events are intertwined and it is not clear which initiates asthma, but it is likely that both options are valid depending on the individual. The first barrier allergens encounter is the bronchial epithelial layer, which will get activated to signal to the immune system. Hyper-responsiveness of the epithelium, as is the case in asthma, can induce a pro-inflammatory phenotype in dendritic cells.<sup>18</sup> In an atopy susceptible individual or a Th2 driven environment, for instance due to previous viral infections, these



dendritic cells will induce Th2 differentiation and subsequent IgE production,<sup>19</sup> hallmarks of asthma. From mouse studies it became clear that toll-like receptor 4 (TLR4, LPS receptor), on presumably epithelial cells is absolutely required for the allergic response to house dust mite.<sup>20</sup> The LPS/Allergen activation of the epithelium induced the secretion of allergy associated inflammatory mediators such as GM-CSF, IL25, IL33 and TSLP. These mediators can drive the allergic Th2 phenotype observed in asthma. Furthermore, the epithelium in the asthmatic lung produces chemotactic factors for Th2 cells (CCL17, TARC) and CD8<sup>+</sup> T-cells and neutrophils (IL-8, CXCL8). IL-8, in turn, contributes to the mucus hypersecretion by stabilization of Mucin 5A (*muc5A* RNA).<sup>21</sup> As such the epithelium plays an important role in the initiation of allergic airway inflammation and the onset of asthma.

Once the chronic stage of inflammation is established, many structural changes will contribute to the persistence of the complex pathology of asthma. The mutual impact of immune cells and structural cells induces a perpetuation of the chronic state (figure 2). The most pronounced change in the epithelium of asthmatic patients is the increase in goblet cells (goblet cell hyperplasia) at the expense of ciliated cells. This is induced by the hallmark cytokines of asthma, IL4 and IL13 which impact the expression of FoxA2 and SPDEF, transcription factors involved in goblet cell development.<sup>22-23</sup> However, many other inflammatory mediators have been implicated in the development of goblet cell hyperplasia such as IL9, IL33 and IL18.<sup>24</sup> A second major change is the thickening of the airway smooth muscle cells (ASM). In asthma, the remodeled ASM undergo a phenotypic

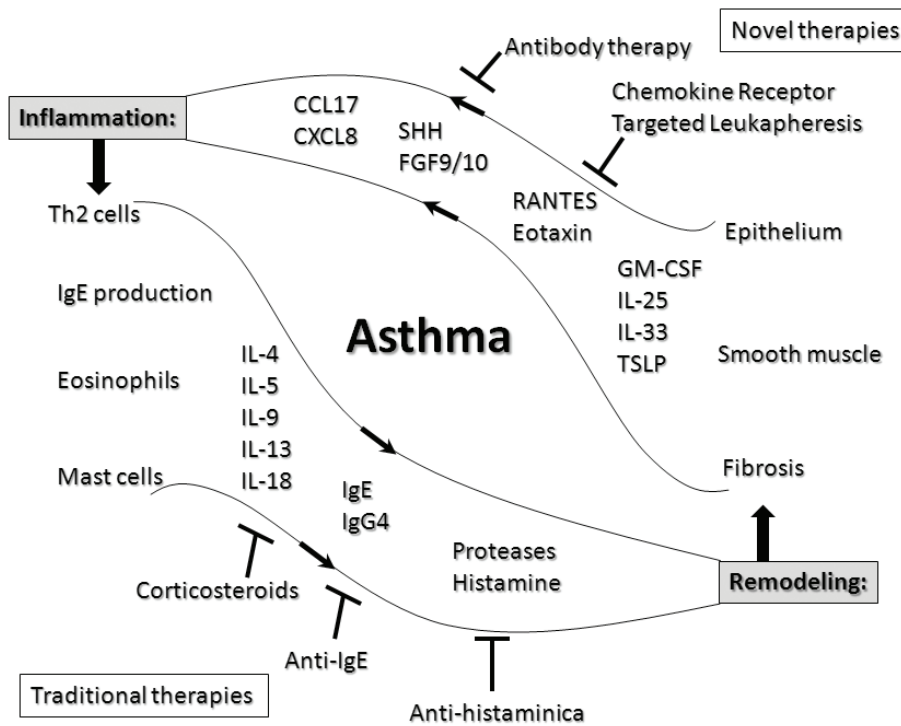
change from contractile to secretory which is influenced by the inflammation induced changes in the extracellular matrix composition. Furthermore, remodeled ASM express the FcεRI and will get activated by crosslinking of the receptor by IgE.<sup>25</sup> Molecules produced by the ASM can trigger a heightened Th2 response and include eotaxin (eosinophil recruitment), RANTES (T-cell, eosinophil and neutrophil recruitment) and GM-CSF.<sup>26-28</sup> Another characteristic of asthma is the presence of mast cells in the remodeled ASM.<sup>29</sup> The activation of the mast cells and consequential degranulation induces strong bronchial contraction.<sup>30</sup> Lastly, the expression of CD40 and OX40L on the remodeled ASM contributes to T-cell activation, longevity and increase cytokine production and impairs Treg generation and functionality.<sup>31</sup> The amount of current understanding of the interplay of structural cells and immune cells is substantial and has been recently reviewed in detail.<sup>24</sup> However, this understanding has not yet resulted in effective therapies, even though emerging strategies might promise a first step in finding a cure for asthma.

**Current Treatments for Asthma**

Current therapies to treat the pathogenesis of asthma, as any other type of allergy, are geared towards either inhibiting IgE or the effector pathways, i.e. mainly T-cells and related inflammatory products. However, as we will discuss now, these therapies seem to only suppress and temporarily alleviate the symptoms but do not result in a permanent solution for the patients.

**Corticosteroids/ $\beta_2$ -agonist: the "gold standard" in asthma management.**

General immunosuppressants, such as corticosteroids (e.g. fluticasone and budesonide), are widely used for the long-term treatment of asthma. This treatment also seems to have effect on permeability of the vasculature, diminishing extravasation of immune cells and shows a modest inhibitory effect on mucus production.<sup>32</sup> However, treatments using corticosteroids are often palliative, rather than curative. Douoll, *et al.* showed no significant effect of corticosteroids therapy on the pathological manifestation of asthma in a small cohort of children, introducing some controversy on the use of corticosteroids as asthma therapy.<sup>33</sup> However, the combination with inhaled  $\beta_2$ -agonist



**Figure 2: Schematic representation of the mutual interactions between inflammation and tissue remodeling.** At the onset of asthma the inflammatory component is most likely prominent, however the initial hyper-responsiveness of the epithelium when encountering the allergen might be the initial trigger to skew the immune response to the aberrant Th2 phenotype. However, once the chronic stage of asthma is reached remodeling and inflammation are equally important in maintaining this persistent inflammatory environment. Some of the main players as well as a selection of current and recently developed treatments are depicted. Due to the close relation between inflammation and remodeling in asthma we are of the opinion that targeting only inflammation will not lead to a cure of asthma since stopping the treatment will restart the cycle by the pro-inflammatory mediators produced by the hyper-activated and remodeled structural cells of the lung. Hence, novel therapies are under development targeting this component of the pathology of asthma, and combinatory therapies might be required to simultaneously treat both pathological hallmarks of asthma.



(e.g. salmeterol and formoterol) seems to be more effective. Recently it was shown that SIT (single inhaler therapy containing budesonide/formoterol) reduced the number of exacerbations and hospitalizations in a large cohort of over 9000 patients with moderate to severe asthma.<sup>34</sup> However, the effects of this treatment only last for a few days, so even though the SIT approach provides a complete asthma management approach, it does not provide a cure.<sup>35</sup>

**Targeting IgE**

IgE is one of the hallmarks of asthma and is the main cause for degranulation of lung infiltrating mast cells. This leads to the release of many mediators among which a wide variety of proteases inducing severe tissue damage. Therefore, IgE showed good potential to be a target for asthma therapeutics. Omalizumab is a humanized recombinant monoclonal IgE neutralizing antibody. The antibody binds to free serum IgE and also reduces the expression of the F<sub>ε</sub>R1, the high affinity receptor for IgE and is used for moderate to severe corticosteroid resistant asthma. A recent study showed reduced exacerbations and circulating eosinophils and periostin, a systemic biomarker for eosinophilic airway inflammation after treatment with omalizumab in a cohort of 850 patients with uncontrolled severe chronic asthma.<sup>36</sup> Furthermore, the use of omalizumab reduced the requirements of corticosteroids.<sup>37</sup> However, in patients requiring very high doses of corticosteroids (fluticasone >1000µg/day) no significant improvements were observed, however also here the patients could reduce the amount of corticosteroids to control the exacerbations.<sup>38</sup> It should be noted that treatment for over a year with omalizumab did reduce the frequency of exacerbation and improved the quality of life in a similar cohort of patients.<sup>39</sup> As such omalizumab could be good add-on therapy for people with uncontrolled moderate to severe asthma who poorly respond to high doses of corticosteroids or β<sub>2</sub>-agonists.

**Specific Allergen Immunotherapy (SIT) and Peptide Immune Therapy (PIT)**

Some of the ‘newer’ approaches for asthma treatments are based on desensitization and induction of tolerance towards the allergen. However, this idea was already introduced in 1911 by Noon *et al.* to treat pollen allergy, “hay fever”.<sup>40-41</sup> Specific Allergen Immunotherapy

(SIT), also known as allergen-specific immune therapy (AIT/ASIT), and the more recently developed Peptide Immune Therapy (PIT) influence both cellular and humoral immune responses.<sup>42</sup> Administration can be sublingual (SLIT) or subcutaneous (SIT) with SLIT having a superior safety profile. Effects can last for years after treatment due to the generation of memory suppressor cells. Other effects on the immune response are a deviation from Th2 to a more Th1 response, reduced production of allergen specific IgE, generation of antigen specific IL10/TGFβ producing regulatory T-cells, IL10<sup>+</sup> B-cells and tolerogenic dendritic cells.<sup>42</sup> Although the efficacy in allergic rhinoconjunctivitis and allergic rhinitis has been shown to ameliorate the clinical symptoms,<sup>43</sup> the effects for the treatment of asthma are marginal.<sup>44</sup> On the other hand, this suggests that optimization and improvement of the current treatment regimens could result in more pronounced clinical effects, even with the notion that SIT treatment in asthma has a significant placebo effect.<sup>45</sup> It should be noted that this therapy can have severe side-effect, such as anaphylaxis and generation of auto-immunity and should therefore only be used in cases of severe or corticosteroid resistant asthma.<sup>46</sup> Another drawback of the therapy is the extensive treatment period up to 5 years to show efficacy in some patients. Therefore, further studies and potential new approaches should be explored in order to improve the efficacy of SIT for asthma.

**NEAR FUTURE DEVELOPMENTS FOR NOVEL THERAPIES**

**Immune-modulation by targeted leukapheresis (TLA)**

Although immune therapy shows great promise other immune modulatory therapies are under development. Clinical trials for a novel immune modulatory treatment will commence in Indonesia in 2014. Chemokine-receptor targeted leukapheresis (TLA) was developed for inflammatory bowel disease, e.g. Crohn’s disease and ulcerative colitis.<sup>47</sup> However, it could easily be adapted for allergies (personal correspondence Prof. Dr. Hans Glise one of the developers of this therapy currently working at the Indonesian Institute for LifeSciences, i3L in Jakarta). Unlike IBD in which the disease causing immune cells are recruited to the site of inflammation by ligation of CCR9 (gut-homing receptor), in allergy a wide variety of

chemokines are involved. There are however some difference in recruitment of Th1 versus Th2 cells that could be explored. Th1 cells are recruited by binding of the respective ligands to CCR1/CXCR3/CCR5, whereas Th2 cells reach the lung by ligation of the CCR3/CCR4/CCR8. This difference could be utilized to filter out the allergy associated Th2 cells which are en route to the lung. Interestingly, the use of CCR3 (eotaxin receptor) would also target eosinophils which are prominent present in the lungs of asthmatics. Unless the use of multiple chemo-attractants in one or serially placed TLA devices with different chemo-attractants is feasible, CCR3 might be the best choice to test out this novel therapy for persistent airway inflammation, although it would only target a specific population of immune cells. One option would be to combine this therapy with SIT to potentially reduce the duration of the SIT treatment by simultaneously inducing suppressive allergen specific memory response and removal of newly generated pro-inflammatory cells, such as Th2-cells and eosinophils. TLA however is rather invasive due to the extracorporeal circulation during the leukapheresis but could provide benefits for severe and corticosteroid resistant asthma patients.

**Antibody based immune therapy targeting tissue remodeling**

All the therapies we discussed modulate the aberrant immune response during allergy in various ways in order to either reduce the number of cell or to dampen the effector function of the immune response. We already emphasized that asthma is a complex disease with two main pathologies, inflammation and tissue remodeling. Even though this is well described, very little progress has been made in developing therapies that target tissue remodeling. Many consider tissue remodeling as the point of no return, and consider it similar to scarification and as such, irreversible. As mentioned before genome-wide studies showed reactivation of susceptibility loci in lung developmental pathway, such as the Wnt/FGF/SHH pathway, during chronic asthma.<sup>13-15</sup> Therefore targeting these pathways might prove beneficial.

One of those promising pathways is the hedgehog (HH) pathway. This pathway is involved in generation of epithelial cells,



in which the HH protein is expressed. Responding cells include epithelial cells, smooth muscle cells and fibroblast, all three are hyper-activated and functionally changed in asthma. Additionally it has recently been shown that HH pathway is involved in the generation of Th2 cells.<sup>48</sup> In vitro studies with human cells showed that HH augments the activation and proliferation of CD4 T-cells.<sup>49-</sup>  
<sup>50</sup> Studies performed in Singapore inhibiting the HH-pathway, targeting tissue remodeling,

showed great promise for this approach (VdV, manuscript submitted) and when combined with the conventional therapies, targeting inflammation, could provide a more permanent solution for people suffering from asthma.

### Conclusions

The number of people with airway allergies is increasing every year and millions of people are affected worldwide. Current therapies

geared towards management of the disease by targeting inflammatory responses are palliative rather than curative. Novel strategies such as SIT, TLA and antibody mediated neutralization of effector molecules show great promise. However, we believe that in order to cure asthma combinatory therapies targeting both pathologies of asthma, inflammation and remodeling, will have to be developed in order to find a permanent solution to this increasing health problem.

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