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Monoclonal antibodies: the new magic bullets for allergy: IUPHAR Review 17

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Allergic diseases and conditions are widespread and their incidence is on the increase. They are characterized by the activation of mast cells resident in tissues and the consequent infiltration and stimulation of several inflammatory cells, predominantly eosinophils. Cell–cell cross-talk and the release of mediators are responsible for the symptoms and for the modulation of the response. The gold standard of therapeutic intervention is still glucocorticosteroids, although they are not effective in all patients and may cause numerous side effects. Symptomatic medications are also widespread. As research has led to deeper insights into the mechanisms governing the diseases, new avenues have been opened resulting in recent years in the development of monoclonal antibodies (mAbs) such as anti-IgE mAbs (omalizumab) and others still undergoing clinical trials aimed to specifically target molecules involved in the migration and stimulation of inflammatory cells. In this review, we summarize new developments in the field of anti-allergic mAbs with special emphasis on the treatment of asthma, particularly severe forms of this condition, and atopic dermatitis, which are two unmet clinical needs.

Abbreviations

AD, atopic dermatitis; AEU, allergic effector unit; AHR, airway hyper-responsiveness; AI, allergic inflammation; COPD, chronic obstructive pulmonary disease; Eos, eosinophils; GCs, glucocorticosteroids; GM-CSF, granulocyte–macrophage colony-stimulating factor; LTs, leukotrienes; mAbs, monoclonal antibodies; MCs, mast cells; Th2, T-helper type-2 cells; TSLP, thymic stromal lymphopoietin

Tables of Links

TARGETS	
GPCRs[a]	**Catalytic receptors**[b]
CCR3	GM-CSF receptor
CXCR2	IL-1 receptor-like 1 (ST2)
NPSR1	IL-4 α receptor
Enzymes[c]	IL-9 receptor
ADAM33	IL-13 α 1 receptor
Carboxypeptidase A3	IL-17A receptor
	IL-31 β receptor
	TSLP receptor

LIGANDS		
Benralizumab	IL-12	Lebrikizumab
Brodalumab	IL-13	Mepolizumab
Dupilumab	IL-17A	Nitric oxide (NO)
Eotaxin (CCL11)	IL-17F	Omalizumab
GM-CSF	IL-22	Pascolizumab
IL-1β	IL-23	Reslizumab
IL-4	IL-25	Secukinumab
IL-5	IL-31	TSLP
IL-9	IL-33	Ustekinumab

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c]Alexander *et al.*, 2015a,b,c).

Introduction

The story of monoclonal antibodies (mAbs) began with the discovery that serum from patients recovering from infectious diseases contained immunoglobulins capable of curing the diseases of other people. Thus started the research to replace human immunoglobulins that, although successful in their applications, presented several limitations in availability and potency (Yamada, 2011). Many of these limitations are now at least partially resolved by mAbs that were first produced (Kohler and Milstein, 1975) by fusing B-cells from immunized mice with lymphoma cells. However, murine mAbs caused immune reactions. More recently, recombinant technology has produced chimeric, humanized and fully human mAbs (Harding *et al.,* 2010) in which partial or complete replacement with human sequences has resulted in less immunogenicity and this has contributed to the explosion of mAbs now available (Ecker *et al.,* 2015). Currently, mAbs-based formulations are in development and are being produced using different approaches, ranging from transgenic mouse technologies and the use of human hybridoma and transformed cells (Nelson *et al.,* 2010) to phage-display technology (Hammers and Stanley, 2014). Several hundred mAbs (Razinkov *et al.,* 2015) have been produced with the majority being devoted to the treatment of autoimmune diseases and tumours (Oldham and Dillman, 2008).

Regardless of their specific target disease, mAbs have both positive and negative aspects. Compared with conventional drugs, mAbs are highly specific therapies characterized by a long $t_{1/2}$ (up to 4 weeks thus not requiring frequent dosing) and slow distribution into the tissues (Hansel *et al.,* 2010). Disadvantages associated with mAbs are their large size, which might be responsible for an uneven penetration into the tissue, the need for parental administration and the complexity of the structure of the protein, which may result in difficulties in cloning procedures and the need for considerable resources to optimize their production (Razinkov *et al.,* 2015).

The toxicity of mAbs can result from either target or off-target effects. Toxic target-associated effects of mAbs are the result of their 'exaggerated pharmacology' and are specifically associated with the blocking or increased effect of the target molecule on the target cells or tissues, for example, immunosuppression and the risk of infection from diseases with TNF-specific mAbs. In contrast, off-target effects can result from the binding of mAbs to target antigens at sites not relevant for their therapeutic effect (Brennan *et al.,* 2010). Specifically, immunomodulatory mAbs have been reported to produce hypersensitivity, acute anaphylaxis (IgE-mediated), pseudoallergic reactions (IgE-unrelated reactions possibly due to immune cell and complement activation) and cytokine release syndrome.

In this review, we discuss some of the most recent mAbs that have been approved for use and are in clinical trials for the treatment of allergic diseases/allergic inflammation (AI) (Figure 1), in particular asthma and atopic dermatitis (AD), which are currently unmet clinical needs.

In the allergic inflammatory response, several soluble and cellular targets are the feasible targets for mAbs-based drugs at

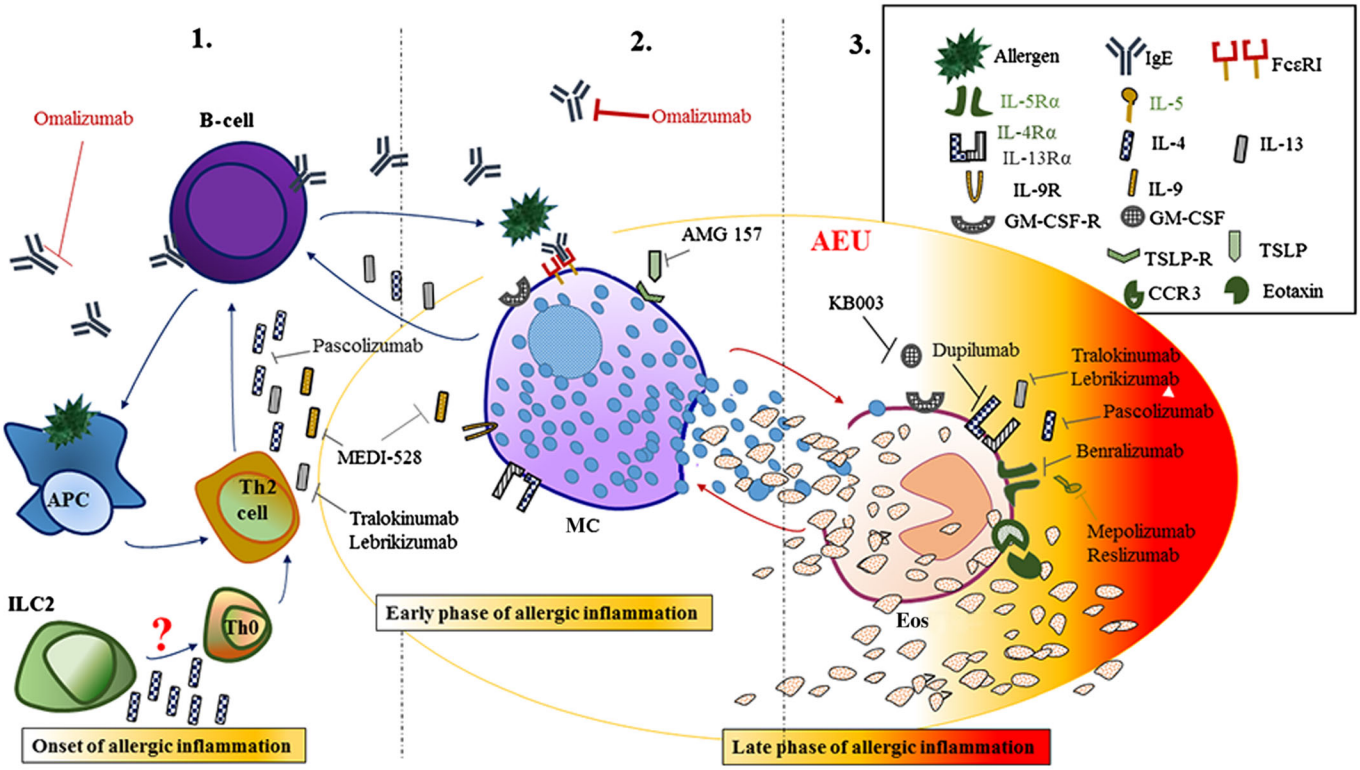

Figure 1

Schematic view of the updated targets for mAb therapy in the initiation and amplification of AI.

its onset (1), and then at the early (2) and the late and chronic stages (3). (Figure 1).

The allergic inflammatory response

Allergic diseases that comprise allergic asthma, rhinitis and conjunctivitis, AD, food and drug allergies are widespread conditions affecting ~15% of the world global population. Their incidence is on the increase and thus has a negative impact on the quality of life, as they sometimes lead to life-threatening conditions such as fatal asthma and anaphylaxis (Pawankar, 2014).

Atopy is the genetic predisposition of certain individuals to develop hypersensitivity reactions to innocuous substances and is influenced by environmental factors (Sengler *et al.,* 2002). Several genes have been hypothesized to have a key role such as *DPP10, PCDH1, HLAG, NPSR1, PHF11, PLAUR, ADAM33* (reviewed in Portelli *et al.,* 2015) and, most recently, *S100A4* (Bruhn *et al.,* 2014). Most of these genes have been identified by studying the association between variants such as single nucleotide polymorphisms (SNPs) in the major pathways known to take part in AI and asthma (reviewed in Vercelli, 2008). Nutrition and environmental changes such as outdoor and indoor pollution, climate change and reduced biodiversity are likely to contribute to the rise in the prevalence of allergic diseases (Pawankar, 2014). Allergic diseases are caused by exposures of atopic individuals to allergens (Platts-Mills and Woodfolk, 2011), which trigger sensitization mechanisms with the production of cytokines by mostly T-helper type-2 cells (Th2) (i.e. IL-4, IL-5 and IL-13) thus stimulating the production of specific IgE antibodies from B-cells (Nielsen *et al.,* 2002). IgE binds to the high-affinity receptor FcεRI expressed by resident mast cells (MCs) in tissues giving rise to the early phase of AI that is the result of activation of multiple signalling pathways and consequent degranulation and release of preformed granular mediators such as histamine, neutral proteases, proteoglycans and the synthesis/release of lipid-derived mediators (reviewed in (Moon *et al.,* 2014). These substances together with several cytokines and chemokines produced at later time points by MCs have a role in the generation of the late phase in which other cell types such as eosinophils (Eos), lymphocytes, macrophages and basophils are recruited into the tissue (Shakoory *et al.,* 2004). The dominant cells of late phase responses and chronic allergy are the Eos, whose activation results in the release of highly basic specific proteins from cytosolic granules, reactive oxygen species and cysteinyl leukotrienes (LTs) as well as an array of chemokines and cytokines. These mediators influence MCs to further modulate inflammation and tissue damage (Landolina *et al.,* 2015). Moreover, MCs continue to retain the potential to release mediators, to have a soluble cross-talk and to hold a physical cross-talk mediated by couples of ligands/receptors with Eos. This cross-talk that we have named the allergic effector unit (AEU) enhances the effects of these two cells thus amplifying the late phase and chronic outcomes of AI (Elishmereni *et al.,* 2011). Moreover, other inflammatory cells infiltrated into the tissue and resident MCs can also interact to enhance the inflammatory response (Landolina *et al.,* 2015). Importantly, the AEU and other cellular interactions indicate a non-IgE mediated activation of MCs and its consequences, a process that has to be taken into consideration for an efficient anti-allergic therapy in addition to the targeting of IgE-dependent mechanisms.

The general mechanisms of allergic diseases, in spite of the different tissues and organs in which these events take place, are very similar, with the main symptoms due to MCs and inflammatory cell activation. Nevertheless, some local variations in cell populations and pathways do exist.

Asthma is a highly heterogeneous disease characterized by airway hyper-responsiveness (AHR), smooth muscle contraction and inflammation, which, if persistent, can lead to structural changes, all resulting in narrowing of the airway, obstruction and consequent restricted airflow and shortness of breath (Ishmael, 2011). Asthma affects 300 million people worldwide (Trevor and Deshane, 2014) with severe asthma exacerbations responsible for 250000 deaths annually (Pawankar, 2014). Asthma is characterized by different clinical/inflammatory phenotypes: allergic/eosinophilic asthma, non-allergic/neutrophilic asthma and paucigranulocytic asthma distinguished according to the number of the sputum granulocytes induced (Simpson *et al.,* 2006) with different biomarkers. Distinct phenotypes and new classifications of asthma are still being proposed (Wenzel, 2012).

Allergic asthma is a Th2-driven inflammatory process characterized by the infiltration of Eos into the airways (Lambrecht and Hammad, 2015) and a high production of the potent Eos chemoattractant, eotaxin, which is generated also by MCs and its production stimulated by IL-4 and IL-13 (Hart, 2001). Neutrophilic asthma is correlated with high numbers of both neutrophils and Th17 cytokines such as IL-17A, IL-17F and IL-22, which have been reported to be present in the sputum (Moore *et al.,* 2014) and respiratory tract of these patients respectively (Newcomb and Peebles, 2013). Different biomarkers derived from induced sputum samples have been shown to be useful to distinguish the inflammatory phenotypes of asthma and possibly predict the responsiveness of patients to certain therapies (i.e. glucocorticosteroids (GCs)). The expression of the genes Charcot–Leydon crystal protein, carboxypeptidase A3 and deoxyribonuclease I-like 3 have been reported to be increased in patients with eosinophilic asthma, whereas the expression of IL-1β, alkaline phosphatase, tissue non-specific isozyme and chemokine receptor 2 (CXCR2) are higher in patients with neutrophilic asthma (Baines *et al.,* 2014).

On the other hand, different candidates have been proposed as possible biomarkers for eosinophilic asthma including fractional exhaled air NO, serum periostin (reviewed in Kim *et al.,* 2014) and chloride channel accessory 1 in airway epithelial brushings of asthmatic individuals (Peters *et al.,* 2014).

In addition to asthma, high numbers of Eos together with granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-5 and IL-13 also distinguish other allergic inflammatory conditions of the upper airways such as chronic rhinosinusitis (Kato, 2015) where both IL-5 and IL-13 are directly/indirectly correlated and promote Eos functions. Specifically, IL-5 controls all the checkpoints of Eos life span from their expansion in the bone marrow, their release into the blood, enhanced adhesion to endothelial cells, to final

maturation, survival and activation (Landolina and Levi-Schaffer, 2014). IL-13 activates macrophages, B-cells and epithelial cells, which trigger different events such as the recruitment of Eos and Th2 cells, IgE-dependent reactions and remodelling phenomena (Kato, 2015).

AD, also known as atopic eczema, is one of the most common inflammatory skin diseases characterized by pruritic skin lesions and mainly affecting paediatric patients. Barrier dysfunction partly due to filaggrin mutation/defective function, a decrease in antimicrobial peptides and enhanced IL-22 expression characterize this disease (reviewed in (Miyagaki and Sugaya, 2015)).

It is evident that single checkpoints in the AI loop, that is, cytokines as well as their receptors, can be targeted to avoid the next step, to impede the involvement of other cells and to thus prevent the development of the chronic stages of AI and additional detrimental events.

Current treatment of allergic diseases: from symptoms to mechanism

Current management of allergic diseases includes GCs, antihistamines, LT antagonists, MC stabilizers, anticholinergics, β-agonists and the potentially disease-modifying allergen-specific immunotherapy. GCs (Trevor and Deshane, 2014) and antihistamines (Cataldi *et al.,* 2014) are gold standard treatments for allergic diseases as a result, respectively, of their anti-inflammatory and symptom relief properties. However, these drugs are not the solution for the treatment of allergic diseases as the antihistamines are mostly symptomatic medications and the GCs often cause several severe side effects and are not efficacious for all patients (Quax *et al.,* 2013). Thus, there is a need to strike out with new pathways and different targets especially for the treatment of asthma and AD by exploring the new possibility of using mAbs.

As discussed above, IgE-mediated stimulation of MCs is a critical event for the initiation of AI followed by downstream events that culminate in the recruitment/activation of Eos to mark the late and chronic stages of allergy. Moreover, there is an abundance of literature supporting the concept of Eos as multifunctional leukocytes playing a pivotal role in infections and in different airway disorders and a specific decrease in their number is one of the final goals of therapy (Landolina and Levi-Schaffer, 2014). The initiation and amplification of AI that selectively target MCs, IgE, pro-inflammatory chemokines and cytokines taking part in intercellular communication networks and Eos have been targeted by mAbs, focusing on the specificity their effects.

Most up-to-date targets in allergy: from the molecule to the disease

Targeting IgE in allergic diseases

IgE has been identified as an effective diagnostic biomarker, capable of potently switching on the machinery of allergic reactions within minutes of allergen exposure, and is a clinically efficient therapeutic target for allergic diseases (Licari *et al.,* 2015). Once released from plasma cells, IgE binds principally to FcεRI on MCs triggering various effector responses including the release of mediators leading to AI reactions.

Omalizumab is a commercially available recombinant humanized anti-IgE mAb ($IgG_1κ$) (Xolair) (Table 1) that specifically binds serum-free IgE at its CH3 domain in the proximity of the binding site for FcεRI (Jensen *et al.,* 2015), thereby blocking its interaction with FcεRI on MCs, basophils, antigen-presenting cells (APCs) and other inflammatory cells. This results in (1) a reduction in free IgE, (2) subsequent down-regulation of FcεRI on the key inflammatory cells and interruption of the allergic cascade, (3) a reduction in the levels of peripheral and bronchial tissue Eos, GM-CSF, IL-2, IL-4 and IL-13 with relative attenuation of the inflammation, (4) decreased allergen presentation to T-cells and the production of Th2 cytokines (Holgate *et al.,* 2009). Much effort has been made also to target B-cell-associated membrane IgE to eradicate *a priori* the IgE-expressing B-cells so that they will not differentiate into IgE-secreting plasma cells, thus reducing the amount of total free IgE (Chen *et al.,* 2010; Chowdhury *et al.,* 2012). However, because these Abs, currently in clinical trials, bind to a specific region proximal to the membrane, do not neutralize soluble, circulating IgE and do not block the interaction between IgE and FcεRI, no real interruption of the allergic cascade will take place, thus showing that membrane IgE is not worth targeting (Nyborg *et al.,* 2015).

Omalizumab is already in use as add-on therapy for moderate-to-severe persistent allergic asthma reducing the incidence of asthma exacerbations with a long-term efficacy and an excellent safety profile. In the study of Lai *et al.* (2015, there were no drug-related adverse events associated with its use except for sporadic and mild local reactions. However, other studies have reported 'an incidence of 0.2% of anaphylaxis in 57,300 patients', type-III hypersensitive reactions (serum-sickness-like) such as fever, arthritis/arthralgia, rash and lymphadenopathy (Galvao and Castells, 2015). This is possibly due to anti-allotypic or anti-idiotypic Abs (IgE or IgG) against this reagent that were either pre-existing, or developed after initial exposures or generated as a response to the aggregated preparations of Xolair (Cox *et al.,* 2007). In addition to allergic asthma, omalizumab is the only licensed therapy for chronic spontaneous urticaria unmanageable with H_1receptor antihistamines (Zuberbier and Maurer, 2015) with a good safety/efficacy profile (Sussman *et al.,* 2014) for administration lasting more than 1 year (Har *et al.,* 2015). Furthermore, omalizumab has been under recent investigations for the treatment of perennial and seasonal allergic rhinitis (Vashisht and Casale, 2013), food allergy (Bauer *et al.,* 2015) (Umetsu *et al.,* 2015), chronic rhinosinusitis (Tsabouri *et al.,* 2014), AD (Yalcin, 2014) and so on.

In the case of asthma, rhinitis and AD, their coexistence in paediatric patients both in the presence and absence of IgE sensitization questions the concept of the real dominance of IgE as a causal mechanism (Pinart *et al.,* 2014).

In his attempt to predict which patient might benefit mostly from omalizumab treatment, Bousquet *et al.* (2007 showed that there is no reliable indication within pretreatment baseline variables in asthmatic patients.

Although different schools of thought are present and more questions are being raised, omalizumab has proven to be a major success as a treatment for both asthma and chronic urticaria with a new generation of anti-IgE Abs currently

Table 1

A list of mAbs for asthma and AD discussed in the review are shown with some of their characteristics

Name of the mAb	Trade name/company	Target of the mAb	Status/Effective	Indicaton
Omalizumab	Xolair (Genetech/Novartis)	IgE (Cε3 domain)	Commercially available	severe, persistent allergic asthma* chronic idiopathic urticaria§
QGE031 (ligelizumab)	Tanox/Novartis	IgE (Cε3 domain)	Phase II	allergic asthma (NCT01703312)¶ AD (NCT01552629)¶ chronic spontaneous urticaria (NCT02477332)¶
Dupilumab	Regeneron Pharmaceuticals/Sanofi-Aventis	IL-4 α receptor	Phase III	allergic asthma (NCT02414854)¶ AD (NCT02277769)¶
Pascolizumab	GlaxoSmithLKline	IL-4	Phase II	symptomatic steriod-naive asthma (NCT00024544)¶
Tralokinumab	Cambridge Antibody Technology/ MedImmune	IL-13	Phase III Phase II	Uncontrolled asthma (NCT02161757)¶ AD (NCT02347176)¶
Lebrikizumab	Tanox/Chugai Pharmaceutical	IL-13	Phase III Phase II	Uncontrolled asthma (NCT01987492)¶ AD (NCT02340234)¶
Mepolizumab	Nucala (GlaxoSmithKline)	IL-5	Phase III terminated	Uncontrolled eosinophilic asthma (Mukherjee *et al.*, 2014) (NCT01691521)¶
Reslizumab	Cinquil (Celltech R& D/Teva Pharmaceutical Industries)	IL-5	Phase III terminated	Uncontrolled eosinophilic asthma (NCT01285323)¶
Benralizumab	Kyowa Hakko/AstraZeneca; BioWa; MedImmune	IL-5 α receptor	Phase III	Eosinophilic asthma (NCT02322775)¶
KB003	KaloBios Pharmaceuticals	GM-CSF	Phase II	Moderate-to-severe asthma (NCT01603277)¶
MEDI-528	Genaera Corporation; Ludwig Institute for Cancer Research/MedImmune	IL-9	Phase II	Uncontrolled asthma (Oh *et al.*, 2013).
Brodalumab	Amgen Inc.; AstraZeneca/MedImmune	IL-17A receptor	Phase II	Moderate-to-severe asthma (Busse *et al.*, 2013) (NCT01199289)¶
AIN457 (secukinumab)	Novartis	IL-17A	Phase II	Uncontrolled asthma (NCT01478360)¶
Ustekinumab	Centocor/Janssen-Cilag	p40 submit of both IL-12/IL-23	Phase II	AD (NCT01806662)¶
ILV-094	Pfizer/Wyeth	IL-22	Phase II	AD (NCT01941537)¶
BMS-981164	Bristol-Myers Squibb; ZymoGenetics	IL-31	Phase I	AD (NCT01614756)¶
AMG282	Amgen	IL-33	Phase I	Mild atopic asthma (NCT01928368)¶
AMG157	Amgen/AstraZeneca	TSLP	Phase II Phase I	Uncontrolled asthma (NCT02054130)¶ AD (NCT0075042)¶

*https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/1063/xolair-omalizumab.
§http://www.marketwatch.com/story/novartis-announces-fda-approval-of-xolair-omalizumab-for-chronic-idiopathic-urticaria-ciu-a-form-of-chronic-hives-2014-03-21.
¶https://clinicaltrials.gov/(ClinicalTrials.gov. Identifier).

under development, such as the humanized QGE031 (ligelizumab) (IgG1) in Phase II trials for allergic asthma (https://clinicaltrials.gov NCT01703312), AD (https://clinicaltrials.gov NCT01552629) and chronic spontaneous urticaria (https://clinicaltrials.gov NCT02477332) (Table 1).

Targeting Th2-associated cytokines. IL-4, IL-5, eotaxin, GM-CSF, IL-9, IL-13 and their receptors

IL-4 and IL-13 have been considered for a long time the most important players in airway AI as they are (1) 'promoters' of both Ig class switching to the IgE isotype and differentiation to Ab-producing plasma cells; (2) 'recruiters' of Eos to the airways via their shared IL-4 α receptor, –IL-13α1 receptor, expressed on Eos (Myrtek *et al.,* 2004); and (3) 'stimulators' of other cells such as MCs and structural cells. Additionally, IL-13 stimulates airway fibrosis and mucus hypersecretion in asthma (Hershey, 2003).

Dupilumab, a human anti-IL-4 α receptor mAb (IgG4) was shown to reduce asthma exacerbations, improve lung functions and reduce Th2-associated inflammatory markers in patients with persistent, moderate-to-severe asthma (Wenzel *et al.,* 2013). In AD patients, dupilumab showed rapid improvement of the AD molecular signature (Hamilton *et al.,* 2014) thus encouraging Phase III clinical trials to investigate its efficacy and safety in monotherapy in moderate-to-severe AD patients (http://clinicaltrials.gov NCT02277769). Nevertheless, the Phase III study that is still ongoing shows promising effects of the mAb (Table 1).

Pascolizumab, a humanized anti-IL-4 mAb (IgG1) showed good potential in preclinical studies (Hart *et al.,* 2002) with ongoing Phase II trials to test its clinical efficacy in asthma (http://clinicaltrials.gov NCT00024544) (Table 1).

Tralokinumab, a human IL-13-neutralizing mAb (IgG4) inhibited AHR and bronchoalveolar lavage eosinophilia in antigen-challenged animal models (May *et al.,* 2012), and its efficacy/safety profile is now being evaluated in a Phase III study in uncontrolled asthma (http://clinicaltrials.gov NCT02161757) and in a Phase IIb trial in AD (http://clinicaltrials.gov NCT02347176) (Table 1).

Another humanized anti-IL-13 mAb (IgG4), lebrikizumab, improved lung functions and provided benefit in the treatment of severe uncontrolled asthma (Scheerens *et al.,* 2014). Its efficacy is currently under evaluation in patients with severe GCs-dependent asthma (http://clinicaltrials.gov NCT01987492), and Phase II studies are underway to assess its safety/adequacy profile in persistent, moderate-to-severe AD (http://clinicaltrials.gov NCT02340234) (Table 1). Apparently the IL-13–IL-4 axis has a huge potential for the treatment of asthma with clinically encouraging results for both anti-IL-4 α receptor, and anti-IL-13 mAbs in asthmatic patients with measurable type-2 signatures, stressing the importance of the differentiation of asthma phenotype before treatment choice. Regarding this, serum periostin, fractional exhaled air NO and blood Eos have been shown to represent promising predictive and pharmacodynamic biomarkers for patients undergoing therapies with anti-IL-13, anti-IL-5 and anti-IgE, possibly correlating with a clinical benefit from these treatments (Arron *et al.,* 2013). In addition to type-2 high asthma, specific inhibition of this pathway has shown positive outcomes in AD patients (Fajt and Wenzel, 2015).

IL-5 masterminds most of the Eos functions from expansion to maturation, survival and activation. To selectively block IL-5 activities (and not other Th2 cytokines), anti-IL-5 neutralizing mAbs (mepolizumab and reslizumab) and Abs that block IL-5 α receptor, (benralizumab) have been developed (reviewed in Landolina and Levi-Schaffer (2014)) and investigated in clinical trials in mild atopic, moderate persistent and eosinophilic asthma (Table 1). Mepolizumab is a humanized mAb (IgG_1) currently in Phase III trial for severe uncontrolled refractory asthma (study terminated http://clinicaltrials.gov NCT01691521), which, through its high affinity binding to free IL-5, prevents the activation of the IL-5 α receptor, (Mukherjee *et al.,* 2014).

Mepolizumab effectively depletes Eos numbers in the airways, bone marrow and blood and reduces asthma exacerbation frequencies but, puzzlingly, has no effects on the signs of clinical asthma (Pavord *et al.,* 2012). Reslizumab is another humanized mAb ($IgG_{4/k}$) against IL-5 that has recently completed a Phase III trial (http://clinicaltrials.gov NCT01285323), showing a reduction in sputum Eos and significant improvement in lung function (Castro *et al.,* 2011). Benralizumab (MEDI-563) is a humanized, afucosylated mAb ($IgG_1κ$) targeting the IL-5 α receptor, that is expressed by both mature Eos and their progenitors (Rothenberg and Hogan, 2006). In patients affected by uncontrolled Eos asthma, benralizumab reduced exacerbations and Eos blood count (Castro *et al.,* 2014) and improved lung functions (Mukherjee *et al.,* 2014). Benralizumab is currently in a Phase III clinical trial (http://clinicaltrials.gov NCT02138916) to assess whether it also reduces chronic obstructive pulmonary disease (COPD) exacerbation rate in patients with moderate to very severe COPD. In general, the approach targeting IL-5 or its receptor has been successful in reducing asthma exacerbations as well as its symptoms and effects on airway function. However, whether the first strategy (target IL-5) is preferable to the second strategy (target IL-5 receptor) for treating asthma and possibly other Eos disorders still needs to be determined.

The 'Th2-like chemokine' eotaxins (eotaxin 1, eotaxin 2 and eotaxin 3) but especially their high-affinity receptor C-C chemokine receptor type 3 (CCR3) have been recently targeted by mAbs to impede Eos migration and activation and, therefore, indicated for asthma treatment. In view of the poor performance of these candidates in monotherapy, their combination with IL-5-targeted treatment has been suggested as a better option for inhibiting AI (Landolina and Levi-Schaffer, 2014). Additionally, the growth factor GM-CSF has a critical role in Eos differentiation and survival (Landolina and Levi-Schaffer, 2014). Animal studies (murine model of allergic asthma) showed that specifically targeting it using anti-mouse GM-CSF polyclonal Ab inhibited airway inflammation, mucus generation and bronchial hyperresponsiveness (Yamashita *et al.,* 2002) thus suggesting it might be an appealing target in asthma. KB003 (KaloBios) is a humanized mAb (IgG1) that directly binds to GM-CSF thus blocking its binding to the GM-CSF receptor and is now in Phase II trial for moderate-to-severe asthma (http://clinicaltrials.gov NCT01603277) (Table 1).

IL-9 is a pleiotropic cytokine supporting the growth/activity of MCs, increasing IgE production by B-cells/up-regulating FcεRI and thus is associated with atopic diseases (Oh *et al.,* 2011). The expression of IL-9 and its receptor is increased in the airways of asthmatic patients (Shimbara *et al.,* 2000) and correlates with

bronchoconstriction, mucus secretion and mucosal oedema and the tendency to develop AHR (Farahani *et al.,* 2014). In murine models of acute and chronic AI, the reduced production of IL-9 corresponded to diminished tissue MC numbers and expression of proteases, making this cytokine an intriguing target (Sehra *et al.,* 2015). However, MEDI-528, a humanized mAb (IgG_1) binding to IL-9, showed no beneficial effects in asthma exacerbations or health-related quality of life in patients with uncontrolled asthma (Oh *et al.,* 2013) (Table 1). This is an example of how promising observations in animal models do not always translate into therapeutic successes in patients.

Targeting Th17, Th22 and associated cytokines

Recently, the recognition that Th2 is involved in AI has extended to Th1 and to a new population of Th17/Th22 producing IL-17/IL-22. However, the relative role of these T-helper cells is still being investigated especially with regard to AD.

IL-17A together with IL-17F are 'guardians' of host defence and mucosal barriers against pathogen invasion and 'recruiters of the pro-inflammatory battalion' (cytokines, antimicrobial peptides and chemokines), which recruit 'major force' innate immune cells (neutrophils and macrophages) to the site of infection leading to the elimination of the pathogen (Reynolds *et al.,* 2010). IL-17A has a major role in the pathogenesis of severe asthma (structural modification of epithelial cells and smooth muscle contraction) and is associated with the appearance of its symptoms (high levels in induced sputum and bronchial biopsies from patients suffering from severe asthma) (Chesne *et al.,* 2014).

MAbs against IL-17A as well as its receptor are currently under development (Table 1). The effectiveness of selective neutralization of IL-17A through the human mAb AIN457 (secukinumab) (IgG1k) is currently being evaluated in patients with uncontrolled asthma in Phase II trials (http://clinicaltrials.gov NCT01478360). Blocking of the IL-17A receptor and its signalling using the human mAb (IgG*2*) brodalumab has been used to treat the development and persistence of moderate-to-severe asthma; however, no beneficial effect has been found (www.clinicaltrials.gov NCT01199289) (Busse *et al.,* 2013).

Moreover, IL-17A is implicated in AD as its deficiency in two murine models of AD reduced the spontaneous development of AD-like conditions (Nakajima *et al.,* 2014), and an increase in its levels in acute AD lesions compared with non-lesional skin was reported in patients (Gittler *et al.,* 2012).

Ustekinumab, a fully human mAb (IgG1k) targeting the p40 subunit of both IL-12 and IL-23 (this cytokine is specifically valuable for the maintenance of Th17 cells) was used in an off-label manner to treat AD patients not responding to other systemic treatments (www.clinicaltrials.gov NCT01806662) (Table 1). It was postulated that the neutralization of IL-12/IL-23 by ustekinumab might preclude the up-regulation of Th17 cells in AD. Although a positive response accompanied by a safe profile were reported, additional studies are needed to establish the real validity of ustekinumab as a treatment for AD (Agusti-Mejias *et al.,* 2013).

IL-22 is a T-cell-derived cytokine playing a critical role in skin homeostasis, coordinating keratinocyte proliferation/differentiation and the production of antimicrobial peptides (Fujita, 2013). Strong activation of IL-22 is associated with the pathogenesis of psoriasis and AD in which MCs have been recently found to produce this cytokine (Mashiko *et al.,* 2015). Phase II clinical trials are currently evaluating the clinical efficacy and mechanism of action of the human anti-IL-22 mAb (IgGIA) ILV-094 in patients with AD (www.clinicaltrials.gov NCT01941537). Because this cytokine functionally inhibits the production of barrier proteins and antimicrobial peptides, its neutralization is expected to reverse the disease.

IL-31 is a helical cytokine, a member of the gp130/IL-6 cytokine family, and is preferentially expressed by activated Th2 CD4+ T-cells. IL-31 has numerous effects on the immune system, which are mediated through the heterodimeric receptor complex IL-31 β receptor, (oncostatin M-specific receptor, β subunit; OSMR β) and have recently received much attention. In particular, IL-31 has a role in the pathogenesis of AD with higher levels of the cytokine present in AD patients biopsy specimens compared with healthy individuals (reviewed in Zhang *et al.,* 2008). The most attractive feature of IL-31 is probably its ability to induce itching/scratching behaviour in an animal model of AD (Arai *et al.,* 2013). In AD patients, IL-31 determined late onset itch responses rather than immediate ones raising the question of whether its pruritic effects are direct or indirect (Hawro *et al.,* 2014). Phase I studies using the human IL-31 mAb BMS-981164 (IgG) have recently been completed in AD patients, but no results have been reported as yet (www.clinicaltrials.gov NCT01614756) (Table 1).

Targeting the three epithelial-derived type-2 inflammation-associated cytokines: IL-25, TSLP and IL-33

The three cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) are known to be generated mainly by epithelial cells and to be important promoters of Th2 immune responses.

IL-25 is a cytokine belonging to the family of IL-17 (IL-17E) whose increased expression has been found in the asthmatic bronchial mucosa and dermis of sensitized atopic subjects after allergen stimulation (Corrigan *et al.,* 2011). Together with IL-33, IL-25 has been shown to play a key role in the induction of Th2 cytokine-mediated allergic airway eosinophilia in an experimental mouse model of allergic airway inflammation (Morita *et al.,* 2015). IL-25 is a potential therapeutic target for treatment in allergic asthma (Knolle *et al.,* 2015) and in chronic rhinosinusitis (Shin *et al.,* 2015), but no clinical studies have been reported yet.

IL-33 is a nuclear-associated cytokine belonging to the IL-1 family having multiple roles from tissue homeostasis, to pathological fibrotic reactions and the setting of inflammation (reviewed in Molofsky *et al.,* 2015). Once released, it immediately provokes immune responses mediated by its receptor ST2. Stimulation of the receptor by this cytokine in the extracellular environment has been described as a 'molecular clock' mechanism, capable of self-regulating thus limiting receptor-mediated immunological responses to airway stimuli (Cohen *et al.,* 2015).

AMG 282 is a human mAb that prevents the binding of IL-33 to the ST2 receptor. It is currently being investigated in Phase I as a treatment for mild atopic asthma (http://www.clinicaltrials.gov NCT01928368) (Table 1).

TSLP is mainly an epithelial cell-derived cytokine having a role in initiating AI through the activation of MCs and is strongly associated with asthma and AD, in which levels of TSLP in skin are associated with symptoms and severity of the disease (Leyva-Castillo *et al.,* 2013). TSLP-targeted therapy has been evaluated in allergen-induced airway responses and persistent airway inflammation in patients with allergic asthma using human anti-TSLP mAb (IgG2λ) AMG 157 that binds TSLP and prevents its binding to the receptor (Gauvreau *et al.,* 2014). Treatment with AMG 157 reduced allergen-induced bronchoconstriction, blood/sputum Eos numbers and indexes of airway inflammation before and after allergen challenge (www.clinicaltrials.gov NCT01405963).

AMG 157 is currently under Phase II trials for inadequately controlled, severe asthma (www.clinicaltrials.gov NCT02054130) and in a Phase I study for subjects with moderate-to-severe AD (www.clinicaltrials.gov NCT00757042) (Table 1).

IL-25, IL-33 and TSLP in airway tissue or plasma of asthmatic individuals are currently under investigation as biomarkers to predict the response of these patients to inhaled GCs (http://www.clinicaltrials.gov NCT01973751). Their detection as well as their potential target might be important to choose the optimal treatment for asthmatic patients or to find another option to overcome the lack of improvements with conventional therapy.

Conclusions

The field of mAbs is constantly developing as new evidence emerges on how this strategy is a powerful tool to target different inflammatory processes connected with asthma and AD. Decades of preclinical research have supported the role of IgE and type-2 inflammation including the Th2 cell types and cytokines in the pathogenesis of asthma. Anti-IgE therapy specifically is an excellent example as a treatment for this disease. Although mAbs targeting Th2 cytokines and others targeting Eos have not yet achieved a comparable success, they do show a consistent efficacy and hold good promise. Much progress has also been made in both the understanding and treatment of AD with anti-IL-22 in trials and in near future directions targeting IL-31 as a strategy to inhibit the itching characteristic of this disease. Other targets are still under evaluation.

Because mAbs are characterized by high production costs, it is extremely important to have the proper characterization of the 'right patient' with specific diagnostic markers. This is also the case of the specific phenotype of asthmatic patients carrying the Th2 signature who can greatly benefit from treatment with mAbs targeting Th2 cytokines and Eos. The efficacy of mAbs has been shown, at least for the anticancer drugs, to be substantially enhanced using combination therapy, and this might be advisable also with regard to using mAbs to treat allergic diseases. In particular, combinations of mAbs with 'the classical weapons to fight allergy' – anti-inflammatory or antihistamine drugs or bronchodilators in the case of asthma – might meet the challenge and be valuable to improve the health of the patient. Importantly, possible pharmacodynamic synergistic or additional effects of mAbs with these drugs can emerge. Another point for consideration as regards the mAbs themselves: efforts should be made to create drugs characterized by a higher $t1/2$ that could increase the patient's compliance. Last but not least, the use of mAbs that target inhibitory signals rather than blocking the activating ones might be an additional strategy to the ones already explored to down-regulate the allergic response.

As we continue to elucidate allergy and further characterize signalling pathways and multiple phenotypes of the disease, it becomes more and more evident that the universal key for favourable outcome of therapy is the selection of the appropriate drug for a particular patient. Although disappointing results are frequent and significant failures are commonly reported in the translation between experimental observations in animal models to studies in patients, mAbs present a promising beacon to pursue in the treatment of allergic diseases.

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Conflict of interest

The authors declare no conflicts of interest.

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