Curr Allergy Asthma Rep (2016) 16:70
DOI 10.1007/s11882-016-0650-5

Novel Biologicals for the Treatment of Allergic Diseases and Asthma

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Abstract
Purpose of Review The development of biological therapies has rapidly progressed during the last few years, and major advances were reported for the treatment of allergic diseases, such as atopic dermatitis, allergic rhinitis, urticaria, food allergy, and asthma. Here, we review biologicals targeting the type 2 immune response involving Th2 cells, type 2 innate lymphoid cells, natural killer T cells, mast cells, basophils, and epithelial cells, such as IL-4, IL-5, IL-13, IL-31, tumor necrosis factor alpha (TNF-α), and thymic stromal lymphopoietin (TSLP).
Recent Findings The biologicals that have been currently approved for asthma are omalizumab targeting IgE and reslizumab and mepolizumab targeting interleukin (IL)-5. Many other monoclonal antibodies are currently in various phases of clinical development. The new biological therapies for allergic diseases will eventually be tailored to the endotypes of these diseases and the identification of novel biomarkers.
Summary Further development of novel biologicals for the treatment of allergic diseases and asthma will be possible upon improved understanding of mechanisms of allergic diseases. Accordingly, further refinement of endotypes of allergen-specific and non-specific type 2 immune response and related inflammatory mediators is needed for optimal treatment of allergic diseases.

Keywords Allergy · Asthma · Biological · Biomarker · Endotype · Monoclonal antibodies

Introduction

The pathophysiologies of allergic diseases are complex and influenced by many factors, including genetic susceptibility, route of antigen exposure, allergen dose, time of exposure, and structural characteristics of the antigen [1, 2]. Biologicals (or biologics) are therapeutic agents with large molecular weights synthesized by living organisms, which target a specific determinant, e.g., monoclonal antibodies (mAbs) that bind to cytokines or receptors involved in the inflammatory pathways [3••, 4, 5••]. Since the mechanisms involved in asthma and allergy are complex and can be redundant, the use of a specific biological may be beneficial for only a certain subgroup of patients, i.e., those with well-defined endotypes [6, 7•]. It is now thought that some previous clinical trials may have been unsuccessful, because they were performed without any attempt to classify patients into subgroups according to pathophysiology and in particular, according to endotype [3••, 4, 5••]. A well-defined endotype has a stable

This article is part of the Topical Collection on *Allergies and the Environment*

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Electronic supplementary material The online version of this article (doi:10.1007/s11882-016-0650-5) contains supplementary material, which is available to authorized users.

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Published online: 09 September 2016

pattern of key pathogenic mechanisms, which are linked to a clinical phenotype of disease through biomarkers [6, 8]. Therefore, to benefit from biologicals, detailed knowledge of the various underlying pathophysiology, endotypes, and biomarkers of each allergic disease is needed [9, 10]. For a better understanding of the biologicals to be discussed, we will first briefly introduce the concept of disease phenotypes, endotypes, and biomarkers, followed by mechanisms involved in allergic reactions.

Phenotypes and Endotypes of Chronic Diseases and Biologicals

With a significant shift from chemicals to biologicals, the new era of drug development is now leading to the development of biomarkers and endophenotyping of the diseases for a better patient care, which is called stratified medicine, precision medicine, or personalized medicine [11, 12, 13•]. The identification of "phenotypes" of a complex disease covers the observable clinically relevant properties of the disease, but does not show direct relationship to disease etiology and pathophysiology. In complex diseases, different pathogenetic mechanisms might cause similar disease symptoms: however, they may require different ways of treatments [14]. An "endotype" identifies disease subgroups linked to pathophysiological mechanisms. A classification of complex diseases based on the concept of endotypes provides advantages for epidemiological, genetic, and drug-related studies. Accordingly, clinical trials of targeted therapies in allergic patients need to be classified into endotypes and appropriate treatments administered [10]. Since several clinical trials with anti-cytokine approaches failed to fulfill the primary outcomes in highly heterogeneous diseases, there is a hope that implementing the endotype concept of these diseases will help to tailor the right treatment to the right patient.

Pathophysiology of Allergic Diseases and its Relationship to Biologicals

Allergic diseases including asthma, atopic dermatitis (AD), allergic rhinitis, conjunctivitis, urticaria, and food allergy affect approximately 1 billion patients worldwide and are caused by complex immune responses to environmental antigens, driven by various cellular and molecular mechanisms [1, 15•]. Many of these biological steps and interactions in disease pathogenesis represent molecular targets for the development of novel biologicals. Allergic responses occur with a prerequisite of sensitization to allergens and the development of memory T and B cell responses along with effector functions of IgE. At the initial stage, IL-4 produced by T cells, basophils, and natural killer T (NKT) cells, and IL-33 and thymic stromal lymphopoietin (TSLP) produced by epithelial cells acting via polarizing dendritic cells (DC), can promote Th2-type differentiation, leading to type 2 immune response. Th2 cells are capable of producing Th2 cytokines such as IL-4 and IL-13, which are essential for the induction of immunoglobulin class switching to IgE during the sensitization phase. A hypersensitivity reaction then occurs when the same allergens enter the skin or mucosa and trigger type I Fcε receptors by cross-linking allergen-specific IgE on mast cells leading to the release of the mediators such as histamine, leukotrienes, prostaglandins, tryptase, heparin, serotonin, and proteases [16, 17].

Asthma is characterized by airway hyper-responsiveness, commonly accompanied by chronic airway inflammation followed by tissue repair and regeneration [18]. In general, asthma is categorized as type 2 immune response-associated or non-type 2 immune response-associated, in which type 2 asthma include early-onset allergic asthma, late-onset eosinophilic asthma, and exercise-induced asthma while non-type 2 asthma include obesity-associated asthma, neutrophilic asthma, and paucigranulocytic asthma [19]. In studies of people with asthma, increased numbers of $CD4^+$ T cells, which produce IL-4 and IL-5, are found in bronchoalveolar lavage (BAL) fluid, mucosal biopsies, and peripheral blood to a degree correlating with the severity of airway eosinophilia [20, 21]. As such, eosinophilic inflammation is believed to be a major contributor to the pathophysiologic changes and remodeling seen in asthmatic patients. When activated by allergens, airway epithelial cells produce cytokines, including IL-25, IL-33, and TSLP. These cytokines are considered to be essential early initiators of type 2 innate and adaptive immune responses and are proposed to contribute to the pathogenesis of asthma [22]. The presence of serum IgE is the prototypical hallmark of adaptive immunity, driven by IL-4-induced class switching of the immunoglobulins synthesized by B cells [23•] (Fig. 1).

Lymphoid cells that lack rearranged T and B cell antigen receptors and markers for myeloid and lymphoid cell lineages have been recently defined as innate lymphoid cells (ILCs). ILCs control the mucosal environment through close interaction with epithelial cells and other tissue cells, production of cytokines, and induction of chemokines that recruit suitable cell populations to initiate and promote distinct types of immune response development and tissue inflammation [24–26]. ILCs have a similar cytokine pattern to T cells; for example, ILC1 mainly produce IFN-γ. As a part of the development of type 2 immunity in allergic diseases and asthma, ILC2 produce IL-5 and IL-13 [24]. As the third ILC population, ILC3 produce IL-17 and IL-22 [27], the same cytokines produced by Th17 cells, in type 3 immunity [27]. Certain endotypes of allergic diseases can be characterized by cytokines of Th1- or Th17-type, with increased neutrophils, presence of type-I interferons and IL-17-producing T cells, leading to non-type 2

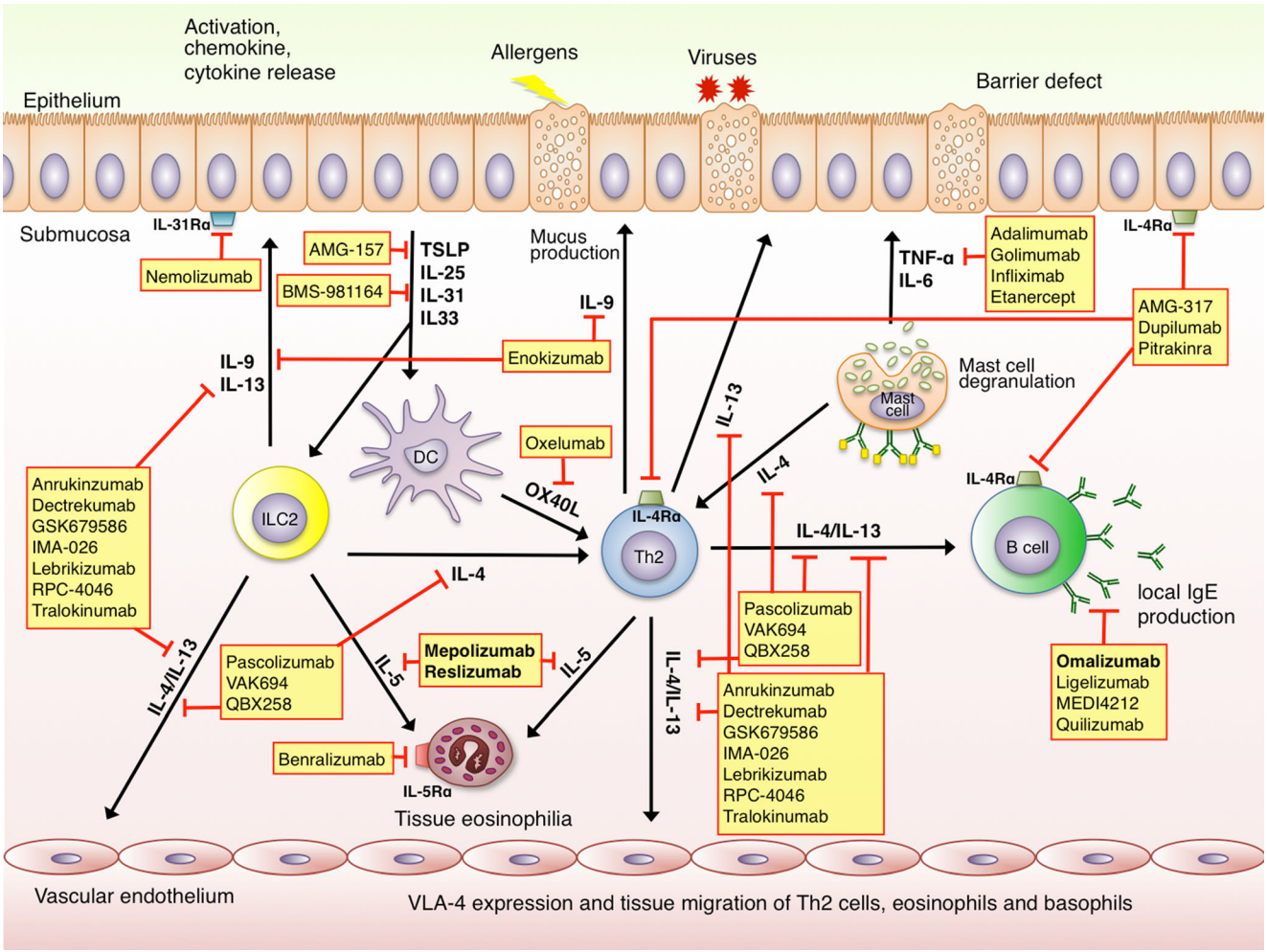


Fig. 1 The components of type 2 inflammation and the biologicals targeting them. In an allergic reaction, allergens and/or pathogens that enter through body surfaces (e.g., the skin or lungs) are phagocytosed by antigen-presenting cells, e.g., dendritic cells (DC), which mature with the help of different cytokines produced by activated epithelial cells, e.g., thymic stromal lymphopoietin (TSLP), IL-25, IL-31, and IL-33, as well as direct contact with microbial products. Type 2 innate lymphoid cells (ILC2) also become activated by IL-25 among other factors, resulting in the production of IL-5 and IL-13, which can act on eosinophils and epithelial cells, respectively. Th2 cells produce type 2 cytokines IL-4, IL-5, IL-9, and IL-13 that exert their effects on many other cell types including B cells, eosinophils, mast cells, epithelial cells, and airway goblet cells to modulate type 2 inflammation. Activated allergen-specific B cells can differentiate with the help of Th2 type cytokines into IgE-producing plasma cells. Allergen-specific IgE molecules produced by B cells and plasma cells are bound to mast cells and basophils. Re-exposure to the specific allergens, which bind to these IgE molecules on mast cells and basophils, leads to the release of various mediators, such as histamine, prostaglandins, and proteases. The names of the biologicals targeting cytokines, cytokine receptors and IgE involved in the inflammation are shown in the *yellow boxes*. Biologicals approved for asthma treatment are in *bold font*. *DC*, dendritic cell; *ILC2*, type 2 innate lymphoid cell

immune response [28]. Figure 2 illustrates the phenotypes and some endotypes of type 2 and non-type 2 immune response that can be targeted by different biologicals [3••, 29•].

Biomarkers of Type 2 Immune Response to Therapeutics

Although previous studies have suggested many biomarkers, there is a broader consensus for the following biomarkers of type 2 immune response in asthma. They include blood eosinophilia, specific IgE, serum periostin level, serum dipeptidyl peptidase 4, in blood; sputum eosinophilia and IL-13 levels in induced sputum; and fraction of exhaled nitric oxide (FENO) in exhaled breath [30]. Blood eosinophilia can predict response to corticosteroids, and treatments using anti-IL-4/IL-13 [31] and anti-IL-5 [13•, 32] while sputum eosinophil levels have been linked to response to inhaled steroids [33] and anti-IL-13 and anti-IL-5 therapy [13•, 32, 34–36]. Serum periostin [37], serum dipeptidyl peptidase 4 levels [38], and sputum IL-13 levels [39] have been shown to predict responses to anti-IL-13 therapy in asthma patients, whereas FENO values have been correlated with eosinophilic airway inflammation in steroid-naive asthmatic patients. The current developmental status of clinical

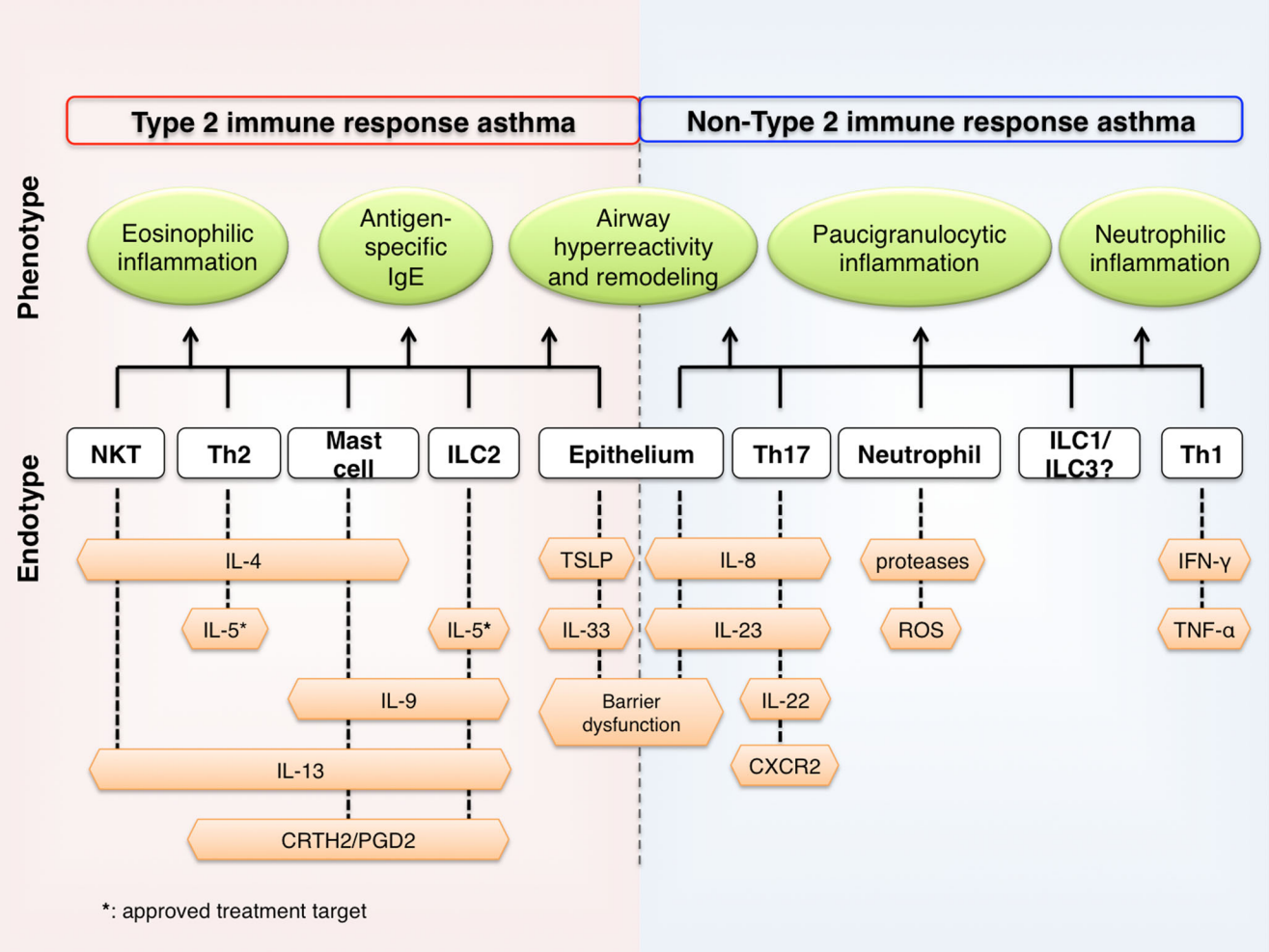


Fig. 2 Phenotypes and endotypes of type 2 and non-type 2 immune response in asthmatic patients. In type 2 immune response-driven asthma, the main phenotypes are eosinophilic inflammation; allergic sensitization with evidence of antigen-specific IgE; and airway hyperreactivity and remodeling. In non-type 2 immune response-driven asthma, the main phenotypes seen are based on the inflammation pattern, e.g., neutrophilic or paucigranulocytic, and also airway hyperreactivity and remodeling. Both the innate and acquired immune responses may contribute to the underlying endotypes for both types of immune responses. IL-5 is an approved treatment target. *ILC*, innate lymphoid cell; *NKT*, natural killer T cell; *PGD2*, prostaglandin D2; *ROS*, reactive oxygen species

trials of these biologicals in different allergic and urticarial diseases is summarized in Supplementary Table 1.

Biologicals Targeting Cytokines

Targeted biological therapies for the treatment of allergic diseases, including monoclonal antibodies and fusion proteins against cytokines and/or their receptors and non-cytokine targets like ligands and IgE are summarized in Table 1. The development of monoclonal antibodies has been highly progressive, with the transition from mouse mAbs first available in 1986 [40] to chimeric mAbs available in 1994 [41]. This was followed by humanized mAbs available in 1997, and finally, a fully human mAb was available in 2002, thanks to advances in genetic engineering and molecular biology [42]. Figure 3 illustrates the structural transition from mouse mAbs to human mAbs, with the intermediate developments of chimeric mAbs (made from mouse antibody variable regions containing antigen-binding sites combined with human antibody constant regions), and humanized mAbs (with only the hypervariable regions of mAbs from mouse origin) created in between. Today, most therapeutic mAbs available are humanized and human mAbs.

There are constant attempts at using new biological molecules to modulate the effects of cytokines involved in the inflammatory processes underlying asthma and allergy (Fig. 1), with outcomes ranging from successful to being discontinued even though they may be approved for other indications. This further not only suggests the complexity of allergic diseases and the challenges of cytokine inhibitors to treat them but also provides some insights into the predominant or minor role of individual cytokines in the pathogenesis of these diseases.

Table 1 Biologicals used for allergic diseases and urticaria. The biologicals are arranged according to their target antigen of cytokine related or non-cytokine, followed by drug name

Target antigen	Drug name (alternative or brand name)	Molecule
Cytokine		
IL-1β	Canakinumab (Ilaris)	Human mAb
	Rilonacept (Arcalyst)	Dimeric fusion protein/recombinant fusion proteins
IL-1R1	Anakinra (Kineret; Antril)	Recombinant human IL-1Ra
IL-4	Altrakincept (Nuvance)	Recombinant IL-4Ra
	Pascolizumab (SB 240683)	Humanized mAb
	VAK694	Human mAb
IL-4/IL-13	QBX258 (VAK-694/dectrekumab; VAK-694/QAX-576)	mAbs targeting IL-4 (VAK694) and IL-13 (QAX576)
IL-4Rα	AMG-317	Human mAb
	Dupilumab (SAR2311893; REGN668)	Human mAb
	Pitrakinra (Aerovant; AER-001; BAY-16-9996)	Human recombinant protein of IL-4 mutein
IL-5	Mepolizumab (SB 240563; Bosatria; Nucala)	Humanized mAb
	Reslizumab (SCH55700; CDP 835; CEP-38072; CINQAIR; CTx 55700; DCP 835; SCH 5570; SCH 55700; TRFK-5)	Humanized mAb
IL-5Rα	Benralizumab (MEDI-563; BIW-8405; BIW-8405-IL-5R; KHK 4563)	Humanized mAb
IL-9	Enokizumab (MEDI-528; 7F3com-2H2)	Humanized mAb
IL-12p40 and IL-23p40	Ustekinumab (Stelara; CNTO-1275)	Human mAb
IL-13	Anrukinzumab (IMA-638; PF-05230917)	Humanized mAb
	Dectrekumab (QAX576)	Human mAb
	GSK679586	Humanized mAb
	IMA-026	Humanized mAb
	Lebrikizumab (MILR1444A; PRO-301444; RG-3637; RO-5490255; TNX-650)	Humanized mAb
	RPC-4046 (ABT-308)	Humanized mAb
	Tralokinumab (CAT-354)	Human mAb
IL-17A	Secukinumab (Cosentyx; AIN-457; KB-03303A; NVP-AIN 457)	Human mAb
IL-17RA	Brodalumab (AMG-827; KHK-4827)	Human mAb
IL-22	Fezakinumab (ILV-094; PF-5212367)	Human mAb
IL-31	BMS-981164	Humanized mAb
IL-31R	Nemolizumab (CIM331)	Humanized mAb
GM-CSF	Lenzilumab (KB003)	Human mAb
TNF	Adalimumab (Humira; ABT-D2E7; D2E7; LU 200134; Raheara)	Human mAb
	Golimumab (Simponi; CNTO-148)	Human mAb
	Infliximab (Remicade; cA2; CenTNF; Remicade; TA-650)	Chimeric mAb
TNF + LT-β	Etanercept (Enbrel; p75TNFR-Ig; rhu TNFR-Fc; TNFR-Fc-p75; TNR-001)	TNFR-IgG1-Fc fusion protein
TSLP	AMG-157 (MEDI-9929)	Human mAb
Non-cytokine		
IgE	Ligelizumab (QGE031)	Humanized mAb
	MEDI4212	Human mAb
	Omalizumab (Xolair, Xolairoid)	Humanized mAb
IgE, M1' segment	Quilizumab (MEMP1972A, RG7449)	Humanized mAb
CCR4	Mogamulizumab (KW0761; AMG-761; KM8761; Poteligeo)	Defucosylated, humanized mAb
CD2	Alefacept (Amevive; ASP 0485; BG 9273; BG 9712)	Recombinant LFA-3/IgG1 human fusion protein
CD11a	Efalizumab (Raptiva, Xanelim)	Humanized mAb
CD20	Rituximab (Rituximab, Rituxan)	Chimeric mAb
CD25	Daclizumab (Zenapax)	Humanized mAb
CD252 (OX40L)	Oxelumab (huMAb OX40L; RG 4930; RO4989991)	Human mAb

GM-CSF granulocyte-macrophage colony-stimulating factor, *LFA-3* lymphocyte function-associated antigen 3, *LT* lymphotoxin, *mAb* monoclonal antibody, *TNF* tumor necrosis factor, *TSLP* thymic stromal lymphopoietin

Biologicals Targeting Cytokines of Type 2 Inflammation

IL-4

IL-4 plays a key role in inducing IgE isotype switching, T cell polarization into Th2 cells, and the subsequent generation of IL-4, IL-5, and IL-13 by Th2 cells. It is also involved in promoting the migration of Th2 cells and eosinophils into inflamed tissues and in the development of myeloid DCs. It signals by binding to its receptor, which is a heterodimer of IL-4Rα (CD124) and IL-13Rα1. IL-4Rα is expressed on many cell types including CD4+ and CD8+ T cells, B cells, macrophages, lung epithelial cells, airway goblet cells, and smooth muscle cells. Biologicals

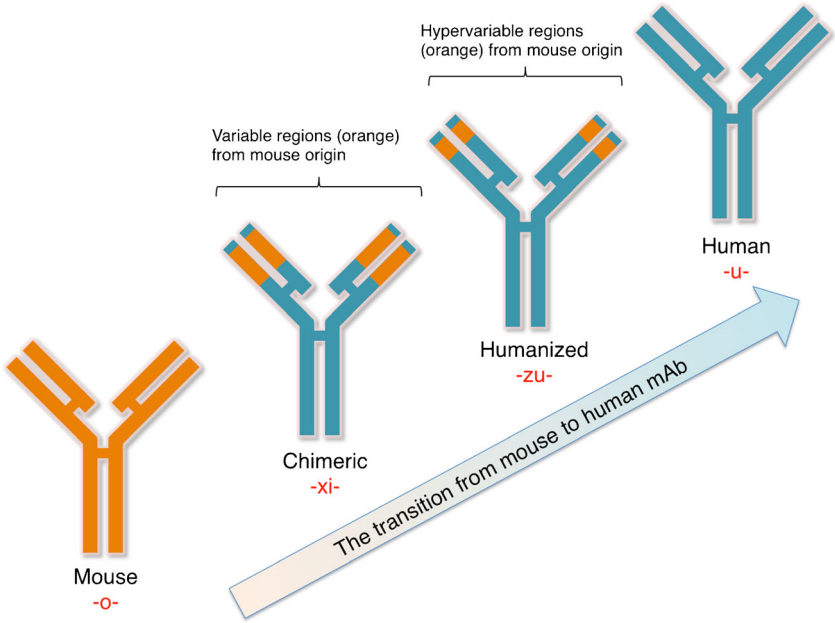


Fig. 3 The transition from mouse, to chimeric, to humanized, and to human monoclonal antibodies (mAbs). A chimeric mAb contains mouse antibody variable regions combined with human antibody constant regions, while in a humanized mAb, only the hypervariable regions of mAb are from mouse origin. The part of nomenclature just before the suffix *-mab* (monoclonal antibody) shows the source inflix: *-o-* is used for mouse, *-xi-* for chimeric, *-zu-* for humanized and *-u-* for human

targeting IL-4 include anti-IL-4 neutralizing mAbs: pascolizumab and VAK694; and IL-4 receptor antagonists: AMG-317, dupilumab, and pitrakinra. Altrakincept, a recombinant IL-4Rα that captures soluble IL-4 and prevents their binding to IL-4 receptors, has been discontinued by its manufacturer since the phase 3 clinical trial failed to confirm its earlier promising results. Since there is a high redundancy of IL-4 and IL-13 signaling, blocking of both IL-4 and IL-13 has been suggested to be necessary for the efficacy of this therapy.

Treatment with dupilumab that binds to the alpha subunit of the interleukin-4 receptor (IL-4Rα) effectively blocks downstream signaling via the receptors for IL-4 and IL-13 and improved the lung function and reduced the frequency of exacerbations in people with moderate to severe asthma with high levels of eosinophils in the blood [43]. Though these beneficial effects are promising, studies with longer follow-up periods will be necessary to determine the long-term efficacy of dupilumab. Dupilumab is also well known to be effective against AD, where treatment in adults with moderate to severe AD resulted in marked improvement of eczema and pruritus as well as reduction of the thymus and activation-regulated chemokine (TARC) levels, confirming the central role of the Th2 axis in patients with AD [44•]. Moreover, patients receiving dupilumab had less frequent skin infections compared to patients receiving placebo. Dupilumab was designated as a "breakthrough therapy" for AD in November 2014 by the US Food and Drug Administration (FDA). Breakthrough therapy designation aims to help a quick delivery of promising new drugs to the market. Recently, the use of dupilumab with topical corticosteroids (TCS) has been reported to significantly improve overall disease severity at 16 and 52 weeks compared to treatment with TCS alone in a phase 3 trial in patients with inadequately controlled moderate-to-severe AD [45].

IL-5

IL-5 is a key cytokine for eosinophil differentiation and survival, thus playing an important role in eosinophilia. The IL-5 receptor has α- and β-subunits, with IL-5Rα the target binding site of IL-5 and IL-5Rβ responsible for signaling. IL-5Rα is expressed on eosinophils, basophils, and B cells. Biologicals targeting IL-5 and its receptor include anti-IL-5 mAbs: mepolizumab and reslizumab; and anti-IL-5Rα mAb: benralizumab.

Eosinophilia in lung tissue is driven by IL-5, which supports the recruitment of eosinophils to the lung tissues via production of eotaxins. Although in early studies, reducing the number of eosinophils using mepolizumab did not lead to the improvement of asthma symptoms, it did affect eosinophil counts in the sputum and blood [46]. Many recent phase 3 trials reported efficacy in eosinophilic asthma [13•, 35, 36] and it has recently received market authorization. Mepolizumab had no efficacy in patients with AD but it caused a significant decrease in peripheral blood eosinophils [47, 48]. This may be due to the relatively short duration of mepolizumab treatment used in the study [5••]. Reslizumab has also been found to be effective in asthma patients: it resulted in greater reductions in sputum eosinophils, improvements in airway function, and a trend towards greater asthma control compared to placebo [49]. The US FDA has recently approved reslizumab for the use as additional maintenance treatment in adult severe asthmatic patients with an eosinophilic phenotype.

IL-9

IL-9 plays a role in the development and attraction of mast cells and the differentiation and activation of Th2 cells. It also

contributes to the phenotype of airway hyper-responsiveness by acting on lung epithelial and smooth muscle cells [50]. IL-9 acts by binding to IL-9R consisting of α-chain (IL-9Rα) and the common γ-chain. Enokizumab (or MEDI-528) is an anti-IL-9 mAb, which showed an acceptable safety profile and potential clinical activity in two phase 2 trials [51] but another trial later found that the addition of MEDI-528 to existing asthma controller medications did not improve asthma control questionnaire-6 scores, asthma exacerbation rates, or forced expiratory volume in 1 s (FEV_1) values [52].

IL-13

Similar to IL-4 and using the same signaling pathways, IL-13 activates B cells to produce IgE, and induces goblet cell hyperplasia, mucous production, epithelial activation, chemokine secretion, airway hyper-responsiveness, and remodeling. The high-affinity receptor of IL-13 is a heterodimer of IL-4Rα/IL-13Rα1. IL-13Rα1 is present on eosinophils, B cells, monocytes, macrophages, smooth muscle cells, lung epithelial cells, airway goblet cells, and endothelial cells. Biologicals that target IL-13 are anti-IL-13 mAbs: anrukinzumab, dectrekumab, GSK679586, IMA-026, lebrikizumab, RPC-4046, and tralokinumab.

In a phase 2 trial, blocking IL-13 with lebrikizumab improved lung function parameters, particularly periostin, which correlates with IL-13 levels and thus might serve as a biomarker in clinical practice to determine a patient's asthma endotype [37, 53]. However, neither exacerbation rates nor asthma symptoms were reduced in that study [37]. Another IL-13 antibody (anrukinzumab) had no effect on allergen-induced airway hyper-responsiveness or sputum eosinophil counts [54]. In a phase 2b study, tralokinumab had an acceptable safety and tolerability profile but did not significantly reduce asthma exacerbation in patients with severe uncontrolled asthma [38]. It did, however, improve FEV_1, suggesting a possible treatment effect in a defined population of patients with severe uncontrolled asthma [38]. Further studies are required to determine whether anti-IL-13 monoclonal antibodies will be clinically beneficial.

TSLP

In association with increased Th2 responses and epithelial cell proliferation, TSLP plays a pivotal role in the pathogenesis of asthma [55, 56]. It is an epithelial-derived cytokine that exerts its effect through its receptor, TSLP-R, which is a heterodimeric receptor that consists of the IL-7 receptor alpha chain (IL-7Rα) and the TSLP receptor alpha chain 1 (TSLPRα). In hematopoietic cells, TSLP-R is mainly expressed in DCs, monocytes, B cells, T cells, NK cells, invariant natural killer T (iNKT) cells, eosinophils, basophils, and mast cells [57]. In a double-blind, placebo-controlled study, treatment with the anti-TSLP monoclonal antibody AMG-157 reduced allergen-induced bronchoconstriction and airway inflammation before and after allergen challenge [58]. Thus, TSLP could be effective against allergen-induced airway responses and persistent airway inflammation in patients with allergic asthma. Further clinical studies are needed to evaluate the potential benefit of AMG-157.

Biologicals Targeting Cytokines of Non-type 2 Inflammation

IL-12 and IL-23

IL-12 and IL-23 are involved in T cell polarization and effector functions and may affect B cell responses. IL-12 and IL-23 cytokines have a common subunit, the p40 subunit, with the other subunit, a p35 and a p19, respectively. IL-12 binds to the IL-12R (comprised of IL-12Rβ1 and IL-12Rβ2), whereas the receptor for IL-23 is IL-23R/IL-12Rb1 [7•]. These receptors for IL-12 and IL-23 are present on activated T cells, NK cells, DCs, and macrophages. The mAb targeting the p40 subunit is called ustekinumab.

Ustekinumab has been licensed for psoriasis, but studies are ongoing for AD. Clinical improvement of AD was observed after treatment with ustekinumab, and, in some cases of severe refractory AD, a complete resolution of the lesions and pruritus was also observed after ustekinumab treatment was initiated [59–61]. Nevertheless, further studies are needed to confirm the usefulness of ustekinumab in AD.

IL-17

IL-17 (or IL-17A) can induce the production of cytokines (e.g., IL-6, tumor necrosis factor alpha [TNF-α]), chemokines, inflammatory effectors, and antimicrobial proteins. IL-17-induced glucocorticoid insensitivity in airway epithelial cells appears to be related to reduction of histone deacetylase 2 activity [62]. Thus, IL-17 could be involved in neutrophilic asthma as well as corticosteroid insensitivity. IL-17A and IL-17F can exist as homodimers or as IL-17A-IL-17F heterodimers. Their receptor is a multimer composed of IL-17RA and IL-17RC [63]. IL-17RA is found on several cells including epithelial cells, keratinocytes, endothelial cells, B cells, T cells, and fibroblasts [63]. Biologicals targeting IL-17 include an anti-IL-17A mAb: secukinumab and an anti-IL-17 receptor mAb: brodalumab. Secukinumab has been licensed for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis. Although the inhibition of IL-17 receptor A had no effect on subjects with asthma as a whole, a subgroup analysis showed an effect with uncertain significance [64]. Inhibition of IL-17A alone by secukinumab is not sufficient to inhibit ozone-induced airway neutrophilia in humans [65]. Further studies are needed to determine whether secukinumab might benefit patients with certain endotypes of asthma.

IL-1

Biologicals against several other cytokines that play important roles in causing or worsening allergic responses have also been developed, for example, against IL-1β. For IL-1β, there is an anti-IL-1β mAb (canakinumab), an IL-1 trap (rilonacept), and a recombinant IL-1 receptor antagonist (anakinra). Autoinflammatory diseases such as the cryopyrin-associated periodic syndromes (CAPS) can be associated with urticaria. CAPS is a spectrum of autoinflammatory syndromes including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease [66]. CAPS are generally caused by autosomal-dominant mutations of the NLR family pyrin domain containing 3 (NLRP3). Anakinra, a recombinant human interleukin-1 receptor antagonist (IL-1Ra), yielded promising results against various autoinflammatory diseases including associated urticaria [67].

IL-31

IL-31 is considered to be responsible for the development of pruritus in AD [68]. The mAbs targeting IL-31 and its receptor are BMS-981164 and nemolizumab (CIM331), respectively. Very recently, a clinical trial of nemolizumab has confirmed the safety and efficacy of its use in treatment [69] and a single subcutaneous administration of anti-IL-31RA decreased pruritus, sleep disturbance, and topical use of hydrocortisone. Therefore, inhibition of IL-31 by means of anti-IL-31RA treatment may become a novel therapeutic option for AD [69].

TNF

TNF inhibitors which are indicated in other immunological disorders and trialed in allergic conditions, include anti-TNF mAbs: adalimumab, golimumab, infliximab; and TNFR-IgG1-Fc fusion protein: etanercept. TNF-α has been observed in bronchial biopsies and has been demonstrated to play a role in asthma pathogenesis [9, 70, 71]. However, a recent study showed no clinical efficacy of etanercept in subjects with moderate-to-severe persistent asthma over 12 weeks [72]. In a small study of patients with corticosteroid-refractory severe asthma, however, etanercept did lead to decreased bronchial hyper-responsiveness [73]. Infliximab, another TNF-α inhibitor, was associated with lower rates of exacerbations among symptomatic moderate asthma patients. As in the case of etanercept, however, the available data are limited, and the efficacy of therapy directed against TNF-α must be evaluated in larger studies.

Although TNF inhibitors are widely available for the treatment of psoriasis, pilot studies of the TNF inhibitors etanercept and infliximab in AD have shown that they are ineffective for AD [74, 75]. In addition, these treatments increased the risk of viral and bacterial infections in the patients. These results suggest a limited pathological role of TNF-α as a single predominant agent in AD compared to its role in psoriasis.

A retrospective study on the efficacy and safety of inhibitors of TNF-α, adalimumab, and etanercept, in 20 adult patients with chronic urticaria showed that 12 (60 %) patients obtained complete or almost complete resolution of urticaria after onset of therapy with either adalimumab or etanercept [76]. Therefore, adalimumab and etanercept may be effective treatment options in patients with chronic urticaria. However, these biological agents need to be examined in double-blind, placebo-controlled studies.

Biologicals Targeting Non-cytokines

Targeting IgE

The most popular and successful biological target for non-cytokines has been IgE. B cells can be targeted by anti-IgE or anti-CD20 mAbs. The biologicals targeting IgE include anti-IgE mAbs: omalizumab, ligelizumab, and MEDI4212; and mAbs targeting the extracellular segment (M1') of membrane IgE [77]: quilizumab. Omalizumab, which binds to the site that IgE molecules use to attach to FcεRI and cannot crosslink cell surface-expressed IgE, effectively reduced IgE and FceR1 expression on mast cells, basophils, and DCs [78].

Another biological that targets CD20, rituximab, lacks effectiveness as CD20 is only highly expressed on B cells, but not plasmablasts and plasma cells which produce IgE, and therefore are resistant to anti-CD20 treatment [79]. Omalizumab has been approved for asthma and chronic spontaneous urticaria treatments [80–82]. It is the first biological for children ages six and above with uncontrolled allergic asthma, recently approved by FDA. The efficacy of omalizumab in severe allergic asthma and the results of studies on the IL-4/IL-13 pathway modifiers in this endotype point to a central role of IgE and Th2 cytokines [28]. In addition, omalizumab has been used to treat intrinsic-type (non-allergic) asthma associated with nasal polyps, leading to attenuation of the frequency of asthma exacerbations [83].

The efficacy of omalizumab in patients with AD remains controversial. Anti-IgE therapy with omalizumab in severe refractory AD decreases the levels of cytokines that are involved in Th2 polarization, including TSLP, TARC, and OX40L, but the treated patients' clinical outcomes according to the scoring atopic dermatitis (SCORAD) system were comparable to those in the control group [84]. Conversely, data from another clinical study indicated that a particular subgroup of patients with AD could be improved by anti-IgE treatment. These patients are possibly characterized by the absence of *filaggrin* mutations [85]. Intriguingly, most AD patients resistant to omalizumab treatment had very high IgE

levels before omalizumab treatment, which might explain the treatment failure [86]. Thus, more studies are needed to validate the efficacy of omalizumab in AD [87].

Although omalizumab is not approved for use in allergic rhinitis, it has been studied extensively, and a meta-analysis of trials has shown consistent reductions in nasal symptom severity [6, 88]. Omalizumab not only improves rhinitis symptoms but also restores the effectiveness of antihistamine medications and improves quality of life [89, 90]. One study revealed that patients with low free IgE following omalizumab treatment during the pollen season had significantly less severe symptoms compared with the placebo group [6, 89, 90]. Supporting its efficacy in rhinitis, it was shown that compared with placebo-treated patients, asthma patients who also had allergic rhinitis tolerated omalizumab treatment and demonstrated significant reductions of rhinitis symptoms [91]. Another study has shown the efficacy of omalizumab for reducing nasal and ocular symptoms in Japanese cedar pollen allergic rhinitis [92]. The authors demonstrated a direct correlation between low free IgE and reduced severity of symptoms [92]. The same group later studied omalizumab re-treatment and found that serum free IgE levels decreased to below the target level in all patients [93]. In addition, there was no serious adverse event, and no anti-omalizumab antibodies were detected [93]. Thus, omalizumab can be effective in asthma patients who also have allergic rhinitis.

Combination strategies incorporating biological immune response modifiers are expected to substantially expand the treatment scope of allergen-specific immunotherapy [94]. Supporting this concept, a combination therapy consisting of allergen-specific immunotherapy and omalizumab has been proposed as a therapeutic option [95]. Combination therapy induced long-lasting inhibitory antibody function for up to 42 weeks, a longer duration than that achieved by either treatment alone [95]. In a more recent study, however, treatment with omalizumab in combination with allergen-specific immunotherapy in patients with allergic rhinitis reduced symptoms during the treatment course, but this effect did not last after the treatment stopped [96]. Thus, the combination of omalizumab and allergen-specific immunotherapy was beneficial against allergic rhinitis symptoms, but had no prolonged effect after patients were shifted to allergen-specific immunotherapy only [94].

Recently, omalizumab has been shown to be efficacious against urticaria, and the latest EAACI/GALEN/EDF/WAO guidelines suggest an algorithm for omalizumab treatment [97, 98]. Nearly half of all chronic urticaria patients have autoantibodies against the high-affinity IgE receptor FcεRI, suggesting an underlying autoimmune etiology [5••]. Randomized clinical trials have demonstrated the efficacy of omalizumab for the treatment of chronic urticaria [99, 100]. The results of these trials have shown that omalizumab was well tolerated and that it reduced the signs and symptoms of chronic urticaria. Thus, omalizumab is an effective treatment option for patients with chronic urticaria with IgE autoantibodies who are refractory to conventional treatment as well as for patients with antihistamine-resistant chronic urticaria [99]. After the discontinuation of omalizumab, however, symptoms gradually recurred over about 10 weeks [100]. Another study revealed an attenuation of skin symptoms in connection with omalizumab treatment as well as improvement in quality of life [101].

Omalizumab has also been explored as an adjunctive therapy for food allergy, with multiple studies showing safe and rapid desensitization rates to cow's milk, peanut, or multiple foods simultaneously [102–104]. However, the first randomized, double-blind, placebo-controlled trial of

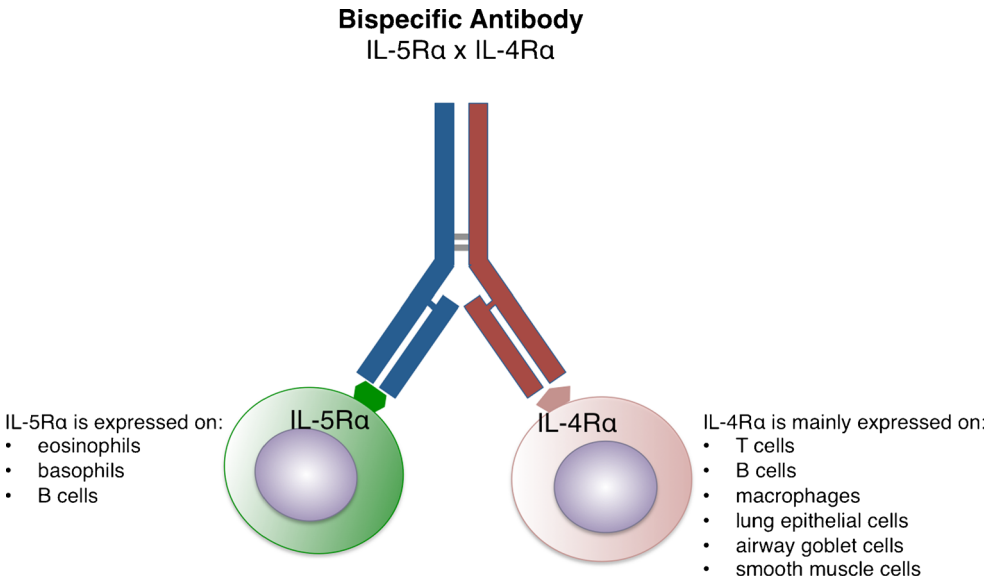


Fig. 4 An example of a bispecific antibody that targets more than one cell or receptor. A bispecific antibody that targets IL-5Rα and IL-4Rα simultaneously. IL-5Rα can be expressed on eosinophils, basophils, and B cells while IL-4Rα is mainly expressed on T cells, B cells, macrophages, lung epithelial cells, airway goblet cells, and smooth muscle cells

omalizumab in combination with oral immunotherapy for food allergy found significant improvements in safety but not in outcomes or efficacy [105•]. Therefore, further studies are needed to confirm the results of combination oral immunotherapy incorporating omalizumab.

The Future of Biologicals

The future of research and development in biologicals is promising with the application of new knowledge and development in bioengineering and immunology, so that the designs of these therapeutics can be optimized and improved for clinical efficacy and cost-effective production. Besides mAbs, other approaches that target RNAs and specific molecules are also advancing in research in this area [106, 107•]. The combined use of biologicals are being considered as viable therapeutic strategies, for example, treatment by combining mAbs to IgE and mAbs to B cell CD20 [108].

Creating bispecific antibodies that target more than one cell or receptor is an innovative approach for the future; for example, a bispecific antibody can be developed that has affinity for both IL-5 receptor and IL-4 receptor (Fig. 4). In addition, the combination of biological therapeutics with allergen-specific immunotherapy may also enhance the efficiency of immunomodulation of allergic diseases [1]. However, most importantly, treatments for allergic diseases have to be tailored to disease endotypes, being identified by respective endotype-specific biomarkers. Thus, it is crucial to identify and confirm disease endotype-specific biomarkers that identify responsive patients to certain biologicals to enable successful treatment. One reasonable suggestion is to co-develop a specific biomarker and endotyping program within the frame of a biological that is under development.

Acknowledgments The authors' lab has been supported by the Swiss National Science Foundation grant 320030–140772. H.T.T. is a recipient of EAACI Exchange Research Fellowship 2016 and receives a short-term grant (304/PPSP/61313076) from Universiti Sains Malaysia.

Compliance with Ethical Standards

Conflict of Interest Drs. Tan and Sugita declare no conflicts of interest relevant to this manuscript. Dr. Akdis is a consultant for Actellion, Aventis, Stallergenes, Allergopharma, and Circacia; is employed by the Swiss Institute of Allergy and Asthma Research, University of Zurich; and has received grants from Novartis, PREDICTA: European Commission's Seventh Framework Programme no. 260895, the Swiss National Science Foundation, MeDALL: European Commission's Seventh Framework Programme no. 261357, and the Christine Kühne-Center for Allergy Research and Education.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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