

Therapeutic monoclonal antibodies in allergy: Targeting IgE, cytokine, and alarmin pathways

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Summary

The etiology of allergy is closely linked to type 2 inflammatory responses ultimately leading to the production of allergen-specific immunoglobulin E (IgE), a key driver of many allergic conditions. At a high level, initial allergen exposure disrupts epithelial integrity, triggering local inflammation via alarmins including IL-25, IL-33, and TSLP, which activate type 2 innate lymphoid cells as well as other immune cells to secrete type 2 cytokines IL-4, IL-5 and IL-13, promoting Th2 cell development and eosinophil recruitment. Th2 cell dependent B cell activation promotes the production of allergen-specific IgE, which stably binds to basophils and mast cells. Rapid degranulation of these cells upon allergen re-exposure leads to allergic symptoms. Recent advances in our understanding of the molecular and cellular mechanisms underlying allergic pathophysiology have significantly shaped the development of therapeutic intervention strategies. In this review, we highlight key therapeutic targets within the allergic cascade with a particular focus on past, current and future treatment approaches using monoclonal antibodies. Specific targeting of alarmins, type 2 cytokines and IgE has shown varying degrees of clinical benefit in different allergic indications including asthma, chronic spontaneous urticaria, atopic dermatitis, chronic rhinosinusitis with nasal polyps, food allergies and eosinophilic esophagitis. While multiple therapeutic antibodies have been approved for clinical use, scientists are still working on ways to improve on current treatment approaches. Here, we provide context to understand therapeutic targeting strategies and their limitations, discussing both knowledge gaps and promising future directions to enhancing clinical efficacy in allergic disease management.

KEYWORDS

allergy, dupilumab, IgE, mepolizumab, omalizumab, reslizumab, tezepelumab, therapeutic antibodies

1 | INTRODUCTION

Since the discovery of immunoglobulin E (IgE) as the antibody isotype responsible for immediate hypersensitivity reactions^{1–3} our

understanding of the network of cells and cytokines that drive allergic pathology has greatly expanded.⁴ These insights have been derived from basic research and confirmed by clinical programs targeting core pathways in the allergic cascade. This review will

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introduce key therapeutic targets in allergic disorders and the insights gained from these interventions, with a focus on monoclonal antibodies.

Defining the etiology of allergy has remained a challenge in part because of the diverse stimuli capable of driving type 2 inflammatory responses. Allergic disorders have overlapping inflammatory patterns with parasitic diseases and have thus been framed as the dysregulation of immune responses evolved to expel parasites or neutralize noxious agents at the host-environment interface like the airway, gut and skin.⁵ Within this framework the evolution of allergic pathology can be broken down into several stages. First, after the loss of epithelial integrity, exposure to allergens initiates adaptive immune responses^{6,7} (Figure 1). Insult to epithelial barrier tissues triggers rapid local inflammatory responses driven by the release of

the alarmins IL-25, IL-33, and TSLP from the epithelium and proximal immune cells. These alarmins work in concert to induce dendritic cells expression of OX40-ligand and type 2 cytokines,^{8,9} activate ILC2s to secrete IL-13 and IL-5, and ultimately promote T helper 2 cells (Th2) development and eosinophil recruitment.¹⁰ Antigen activated mature Th2 cells then serve as a key source of the canonical type 2 cytokines, including IL-4, which is essential for promoting B cell class switching and the production of allergen-specific IgE. In the periphery, allergen-specific IgE is bound by basophils and mast cells where it can trigger rapid inflammatory responses, including anaphylaxis, upon allergen re-exposure. Ultimately the aforementioned cascade of events must be considered in the context of the chronic nature of allergy, which is marked by numerous allergen exposures and prolonged inflammation. Therefore, in many cases, the allergic

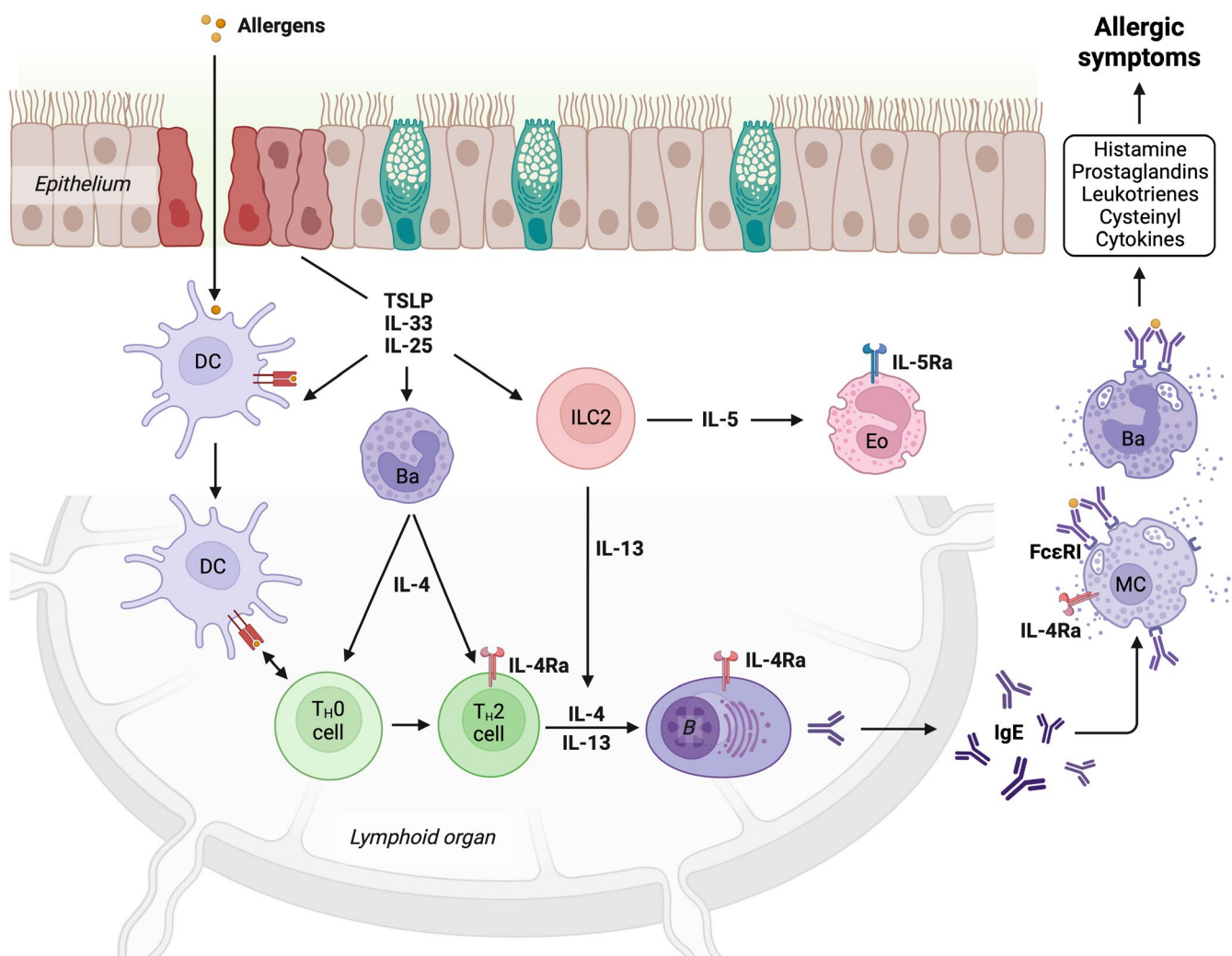


FIGURE 1 The allergic cascade. Allergens enter our body through damaged epithelial barriers, where they are recognized, taken-up, processed, transported to the draining lymph node and displayed by dendritic cells via MHC II to naïve T cells. In the presence of type 2 inflammation, which is induced by epithelium derived alarmins and IL-4, these naïve T cells polarize into T helper 2 cells and instruct B cells to undergo isotype switching to IgE. The IgE is systemically distributed and binds to basophils and mast cells both in local tissue and in the periphery. Allergen re-exposure triggers degranulation of these allergic effector cells and results in the release of multiple soluble mediators inducing allergic symptoms. Ba, basophils; B, B cell; DC, dendritic cells; FcεRI, high-affinity IgE receptor; ILC2, type 2 innate lymphoid cells; IL, interleukin; IgE, Immunoglobulin E; MC, mast cells; Th0 cell, naïve T cell; Th2 cell, t helper 2 cell; TSLP, thymic stromal lymphopoietin.

mediators listed above act to perpetuate and reinforce pathology at multiple levels via multiple cell types as discussed below.

1.1 | Alarmins

Epithelial cells, fibroblasts, and immune cells positioned at barrier surfaces are able to secrete the alarmins TSLP, IL-25, and IL-33 in response to danger signals or cellular damage.¹¹ TSLP release can be triggered by mechanical stress, proteases, and a host of pathogen associated molecular patterns (PAMPs).¹² IL-25 is both constitutively released by keratinocytes and can be induced by pathogen proteases and PAMPs in epithelial tissues.¹³ In contrast the alarmin IL-33 is constitutively expressed in the nucleus of epithelial cells and other cells and is primarily released following cellular damage. IL-33 released from cells can be further processed by host or exogenous proteases into highly active isoforms.^{14,15} Once released these alarmins are not required for the clonal expansion of T cells in response to antigen exposure, but they are critical for subsequent Th2 polarization,¹⁶ and the blockade of all three alarmin pathways greatly attenuates local type 2 inflammation and tissue remodeling in models of parasitic infection and allergy.¹⁷

Similar to the diverse molecular mechanisms that initiate alarmin release, the alarmins themselves exhibit significant structural variability. TSLP is a member of the IL-2 family of cytokines and signals through a heterodimer of TSLPR and IL-7Ra,¹⁸ IL-33 is a member of the IL-1 cytokine family and signals via binding to ST2 (IL-1RL1) and subsequent recruitment of the IL-1 receptor accessory protein (IL-1RAcP),¹⁹ and IL-25 is a member of the IL-17 family and binds with two IL-17RB subunits to form a complex which subsequently engages IL-17RA to drive downstream signaling.²⁰

Despite their molecular diversity, alarmins appear to have evolved partially redundant pathways to induce inflammation at barrier surfaces in response to environmental stimuli, and to trigger similar downstream events, such as the production of IL-13 from ILC2s.¹⁷ This redundancy could be one reason that the most profound effects on type 2 inflammation occur when multiple alarmin pathways are suppressed. However, individual targeting of alarmin pathways has been reported to be sufficient in reducing type 2 inflammation in many models of allergic disease.²¹

1.2 | Type 2 cytokines

The canonical type 2 cytokines IL-4, IL-5 and IL-13 are produced by multiple innate and adaptive immune cells. IL-4 is primarily secreted by basophils and Th2 cells, while IL-13 is predominantly expressed by Th2 cells and ILC2s and can be quickly induced by alarmin mediated activation of ILC2s.^{22–24} IL-4 signals through type I receptor complexes composed of the IL-4 receptor (IL-4Ra) and common gamma chain (γ c) or type II receptor complexes composed of heterodimers of IL-4Ra and IL-13 receptor 1 (IL-13Ra1).²⁵ In contrast IL-13 can signal via type II receptors mentioned above as well as the IL-13Ra2

receptor, which can negatively regulate IL-13 function and has also been implicated in IL-13 mediated upregulation of TGF- β 1 expression in fibrosis.²⁶ Although these cytokines share some common receptor components, their biologic functions are diverse. For example, IL-4 depletion greatly impairs Th2 development and IgE production owing in part to distribution of type I receptors on lymphocytes, while IL-13 depletion does not impact IgE production but does limit tissue fibrosis and goblet cell hyperplasia.²⁵ Importantly class switch recombination to IgE requires IL-4. It has recently been suggested that allergen-specific IgE reservoirs are sustained by memory IgG1 memory B-cells that continually class switch to express IgE.²⁷ IL-5, produced by activated ILC2s, Th2 cells, and other cells, recruits and promotes the survival and proliferation of eosinophils in tissues. IL-5 signals via complexes of IL-5Ra and the common beta chain (β c),²⁸ and targeting soluble cytokine and receptor have both been shown to effectively block IL-5 signaling.²⁹

1.3 | Immunoglobulin E (IgE)

IgE is best known for its key role in immediate hypersensitivity reactions upon allergen exposure and is the primary driver of allergen induced anaphylaxis. However, IgE plays an underappreciated role in facilitating antigen acquisition and presentation (IgE-FAP), amplifying adaptive immune responses, and triggering the release of multiple cytokines including the canonical type 2 cytokines and alarmins described above.

The biology of IgE is best understood in the context of its high-affinity receptor Fc ϵ RI, expressed as a stable tetramer ($\alpha\beta\gamma\delta$) on mast cells and basophils,³⁰ and as a trimer ($\alpha\gamma\gamma$) on dendritic cell (DC) subsets and monocytes, where it is steadily endocytosed and recycled.³¹ The Fc ϵ RI alpha chain (Fc ϵ RI α) binds IgE in a similar orientation as other Fc receptors, however the kinetics of IgE and Fc ϵ RI interactions are unique. Fc ϵ RI is the highest affinity immunoglobulin receptor,^{32–34} and the dissociation of IgE from this receptor is at least 10-fold slower than IgG1 from Fc γ RI³⁵ and multiple orders of magnitude slower than other immunoglobulin Fc interactions. This allows IgE:Fc ϵ RI complexes to imbue mast cells in tissue with memory for antigens targeted by IgE. In human transfusion studies in patients with hypogammaglobulinemia, the half-life of exogenously provided IgE is only ~2 days in the absence of endogenous IgE, yet patient reactivity to allergens recognized by exogenous IgE persists for 50 days.³⁶ Likewise, in IgE deficient mice, injected IgE is undetectable after 6 days in the blood, yet systemic allergen reactivity is detectable for well over a month.³⁷

The remarkable stability of IgE:Fc ϵ RI complexes is compounded by the extreme sensitivity of basophils and mast cells expressing Fc ϵ RI. Paradoxically, partial loss of surface IgE in these cells can even increase effector cell sensitivity to stimulation via the remaining IgE receptor complexes,^{38,39} and low levels of allergen-reactive IgE are sufficient to drive cellular activation.^{40,41} Recent studies also suggest that allergen-reactive IgE is produced at high concentrations locally,^{38,39,42–44} exposing long-lived tissue resident mast cells to an

abundance of allergen-specific IgE. This combination of high affinity binding, high cellular sensitivity, and local production of IgE in tissues works in concert to make rapid and complete inhibition of IgE challenging. Even in the presence of highly potent IgE inhibitors, which effectively eliminate free IgE from the serum, reactivity to allergens in skin prick testing persists for months.⁴⁵ The durable sensitization of FcεRI bearing mast cell and basophils, and their subsequent activation, sustains an allergy permissive milieu with the release of cytokines and mediators that recruit, remodel, and sustain adaptive responses to allergens.

Beyond the sensitization of mast cells and basophils, trimeric FcεRI on plasmacytoid DCs (pDCs), has been shown to enhance antigen presentation and pDC activation.^{46,47} Likewise, removal of IgE from pDC populations has been shown to enhance the generation of regulatory T cells in human peripheral blood mononuclear cell (PBMC) cultures.⁴⁸ Prior studies have demonstrated that antigen induced activation and subsequent IL-4 release from mast cells can promote regulatory T cell (Treg) dysfunction, and IgE knockdown or inhibition can rescue Treg activity.^{49,50} These studies suggest IgE signaling in pDCs can directly skew T cell responses. Therefore, engagement and activation of IgE receptor complexes on DC subsets may potentiate IgE focused antigen-specific responses, while blockade of this pathway may facilitate reestablishment of antigen tolerance. This agonistic effect of IgE on T-cell responses does not appear to be simply mediated by recruitment of antigen to DCs via IgE, as soluble monomeric IgE-antigen fusions that do not crosslink receptors induce systemic tolerance.⁵¹ Instead, these studies demonstrate that IgE not only potently traffics antigen to pDC subsets via high affinity binding to FcεRI, but that IgE crosslinking and signaling can work in concert to enhance, suppress, or skew T-cell responses via FcεRI on DCs and mast cells. This multifaceted nature of FcεRI allows the receptor to perpetuate the production of more antigen reactive T cells, and mediate terminal effector functions that drive anaphylaxis and allergy.

While the aforementioned studies highlight the emerging role of FcεRI in potentiating and regulating adaptive responses, the role of the low-affinity IgE receptor CD23 in antigen presentation and amplification of adaptive immune responses has also been extensively studied. Starting at sites of antigen exposure in the lung and gut, CD23 is expressed at the epithelium and facilitates bidirectional transcytosis of IgE and IgE:antigen complexes.⁵²⁻⁵⁵ In the tissue these immune complexes readily bind CD23 positive B cells and serve as extremely potent antigen sources. This effect, termed IgE-FAP, has been shown to amplify antibody responses by greater than 100-fold and dramatically enhance antigen specific T cell proliferation.^{56,57} IgE-FAP is driven by IgE transport on CD23⁺ B cells to follicles in spleen, where IgE:antigen complexes can be captured by CD11c⁺ dendritic cells^{58,59} and internalized, degraded, and presented to T cells.⁶⁰ This diverse set of potential outcomes for IgE:antigen complexes is enabled by two distinct CD23 isoforms (CD23a and b) that act in concert with IgE and immune cells to surveil the lumen of the airway and gut and collect antigens for efficient antigen presentation. This underappreciated role of

IgE serves to initiate and potentiate allergic disease in tissues and demonstrates that an effective IgE blockade should be able to inhibit IgE interaction with multiple receptor types across multiple tissues and physiologic spaces.

1.4 | Other important regulatory receptors on allergic effector cells

Several other receptors including stem cell factor receptor (KIT) and sialic-acid-binding immunoglobulin-like lectins (Siglecs) are expressed on allergic effector cells. KIT is the principal receptor for stem cell factor (SCF) and plays central roles in multiple biologic processes including hematopoiesis as well as melanocyte, germ and gut cell development.⁶¹ It is a type III receptor tyrosine kinase which consists of five extracellular Ig-like domains and is activated via by soluble or cell bound dimeric SCF isoforms that promote receptor dimerization.⁶² Blockade of SCF binding to KIT or targeting of the fourth and fifth Ig-like dimerization domains of KIT, prevent KIT dimerization and suppress KIT signaling. KIT is expressed at very high levels on the surface of mast cells, is required for mast cell development and survival, and synergizes with other mast cell activating receptors to enhance mast cell responses.⁶³

Siglecs are a diverse family of sialic-acid-binding lectins that are broadly expressed across many hematopoietic lineages and other cells. Siglecs primarily serve to modulate signaling via intracellular immunoreceptor tyrosine-based inhibitory (ITIM) motifs following ligation, crosslinking, or receptor co-localization,⁶⁴ yet the biology of Siglec receptors and their glycan ligands is complex and capable of inducing a wide range of downstream events depending on the cellular context and distribution of their glycan ligands.⁶⁵ Of the Siglec family, Siglec-8 and Siglec-6 have emerged as therapeutic targets in allergy as each are expressed mast cells and basophils among other cells.⁶⁶ Ligation of Siglec-8 or 6 is primarily thought to stimulate ITIM mediated recruitment of phosphatases and subsequent suppression of multiple allergic pathways including IgE mediated FcεRI signalling,⁶⁵ however antibody ligation of Siglec-8 has also been shown to induce apoptosis in eosinophils and promotes antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/ADCP) of Siglec positive cells.⁶⁷

2 | THERAPEUTIC ANTIBODIES IN ALLERGY

Over the last two decades, the therapeutic use of monoclonal antibodies has gained significant momentum across various diseases, including allergic disorders. This advancement is largely due to the continuously increasing understanding of molecular and cellular mechanisms involved the allergic cascade, which has enabled the identification of specific targets for therapeutic intervention. While several monoclonal antibodies have been developed, only a few have been approved for clinical use in allergy management to date (Figure 2).

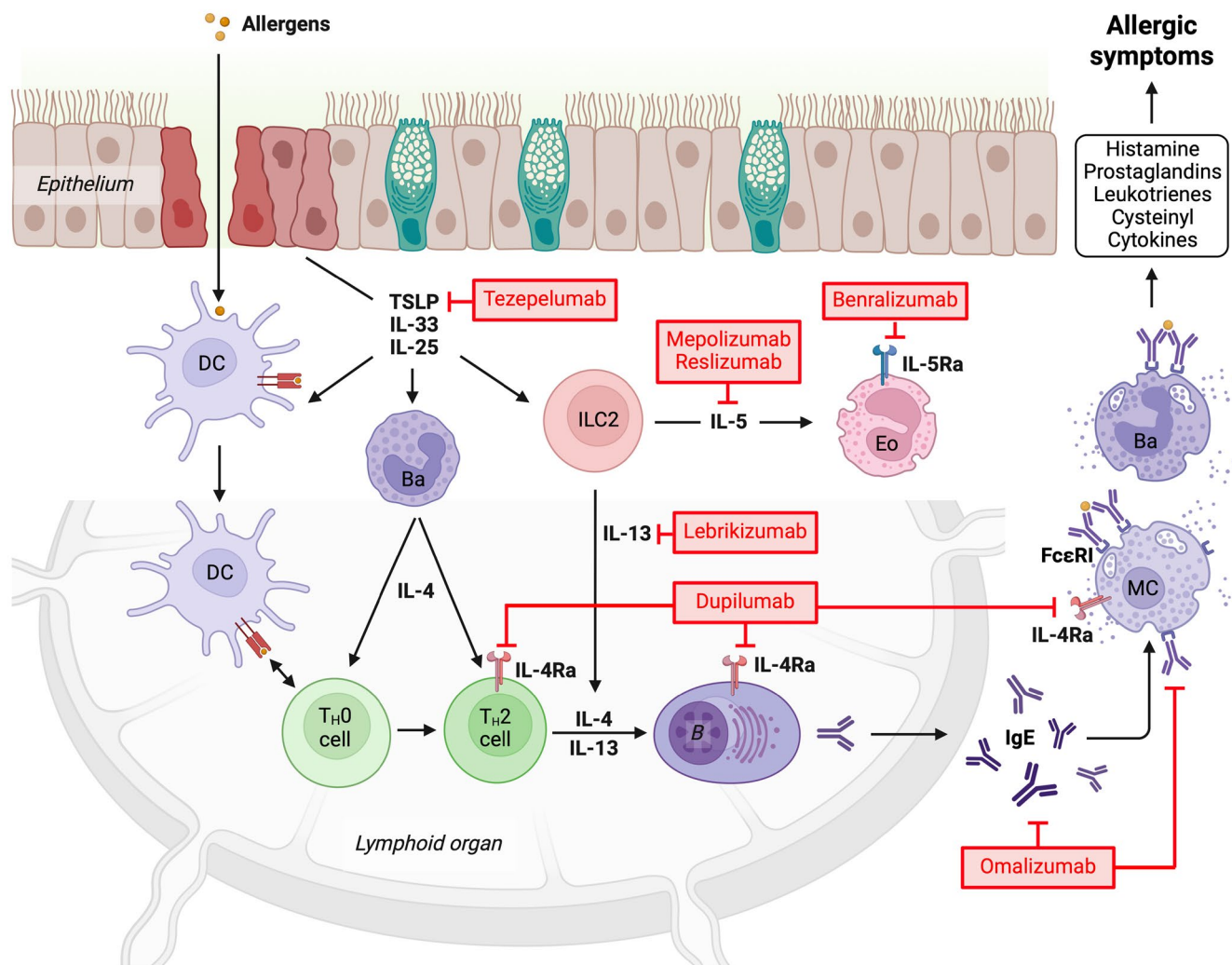


FIGURE 2 Approved therapeutic monoclonal antibodies in allergy. The six monoclonal antibodies (in red) omalizumab (anti-IgE), dupilumab (anti-IL-4Ra), benralizumab (anti-IL5Ra), mepolizumab (anti-IL-5), reslizumab (anti-IL-5), lebrikizumab (anti-IL13) and tezepelumab (anti-TSLP) interfere at different levels in the allergic cascade. Many of them target multiple cells or mechanisms, which might be beneficial for their therapeutic efficacy.

2.1 | Classical anti-IgE antibodies

2.1.1 | Omalizumab

The original conceptual framework for developing anti-IgEs as a treatment for allergies was based on defining three desired functional characteristics: (i) high-affinity IgE binding able to compete with FcεRI interactions; (ii) lack of binding to IgE:FcεRI complexes on mast cells or basophils to prevent receptor crosslinking and activation and (iii) lack of binding to IgE:CD23 complexes.⁶⁸ Omalizumab was the first anti-IgE antibody approved for clinical use, although parallel clinical studies were contemporaneously carried out with another anti-IgE (CGP51901/CGP56901/TNX-901/talizumab) that did not advance into phase III clinical trials at that time.⁶⁸ Omalizumab was developed from a murine anti-human IgE monoclonal antibody (MAE11) and was selected based on its binding to free IgE and lack of binding to IgE:FcεRI complexes on mast cells.⁶⁹ Humanization of

MAE11 was carried out by grafting MAE11 CDRs onto consensus human framework sequences with 5 human-murine framework mutations required to recapitulate MAE11 affinity.⁶⁹ The resulting humanized antibody (rhuMAb-E25) was advanced into clinical trials for the treatment of allergic rhinitis and asthma^{70–73} and approved for therapeutic use in 2003 for moderate to severe asthma under the tradename Xolair. Xolair has since been approved for the treatment of chronic spontaneous urticaria (CSU) in 2014, allergic asthma in children in 2016, chronic rhinosinusitis with nasal polyps (CRSwNP) in adults in 2020, and food allergies in children and adults in 2024.

Omalizumab treatment in patients results in the reduction of free IgE levels and blocks IgE binding to mast cells and basophils, as expected from its competitive binding with FcεRI. Omalizumab forms immune complexes with IgE, with some preference to assemble into 3:3 hexamers rather than larger immune aggregates.⁶⁸ These complexes are not cleared from serum and their formation results in unexpected increases in the total IgE in serum, which accumulates at

up to six to ten times basal IgE levels. The accumulation of “neutralized” IgE in immune complexes that is still able to bind allergen may contribute to the protective therapeutic benefit of omalizumab.⁶⁸ Omalizumab treatment also results in the downregulation of FcεRI levels on circulating basophils and dendritic cells,^{74–76} reducing their ability to be sensitized by IgE and activated by allergens. The downregulation of FcεRI in basophils likely occurs through two contributing mechanisms: (i) the intrinsic, more rapid degradative turnover of FcεRI in cells in the absence of IgE binding and (ii) the turnover and production of new basophils, also occurring in the absence of free IgE and therefore lacking stabilized FcεRI levels. While omalizumab treatment results in relatively rapid decline in free IgE levels, clinical benefit emerges over much longer periods, indicating that the absolute reduction in free IgE is a rather poor indicator of therapeutic efficacy.

Omalizumab engages an IgE epitope in the constant epsilon (Cε) 3 domains, adjacent to the binding site for FcεRIα,^{77,78} with only 2 IgE amino acids in common between the omalizumab and FcεRI interaction sites. However, omalizumab binding to IgE sterically blocks FcεRI binding. In addition, one of the omalizumab epitopes is also buried by Cε2 domains in their folded-back, bent conformation. Binding of omalizumab interferes with this bent IgE conformation, which could also contribute to inhibiting FcεRI binding.⁷⁸ Omalizumab also inhibits the binding of CD23, through significant overlap of their respective binding sites on IgE and through substantial steric clashes of the two IgE ligands.⁷⁷ Although omalizumab was originally selected for therapeutic development because it competes with FcεRI but does not engage IgE:FcεRI complexes on effector cells, recent studies have demonstrated that omalizumab can form transient complexes and actively dissociate IgE from the receptor.^{79–81} Initially, this observation was only described for high omalizumab concentrations, which raised the question of how physiologically relevant the additional mode-of-action might be in vivo.⁷⁹ However, additional experimentation has revealed that the mechanism was not only concentration but also time dependent.⁸⁰ In other words, over prolonged exposure periods removal of IgE from FcεRI could even be observed at physiological omalizumab concentrations.

2.1.2 | Ligelizumab

Ligelizumab is a more recent anti-IgE therapeutic candidate developed by Novartis that has its roots in earlier clinical studies. Ligelizumab is a high-affinity variant ($K_D \sim 17$ pM) based on the CGP51901/CGP56901/TNX-901/talizumab series of anti-IgE antibodies developed in the 1990s. CGP51901 was a murine/human chimeric IgG1 antibody that underwent phase I and phase II clinical trials for allergic rhinitis and allergic asthma.^{68,82–84} CPG56901 (TNX-901/talizumab) was a humanized variant of CGP51901⁸⁵ that underwent additional Phase II clinical trials for the treatment of peanut allergy,^{86,87} providing the first promising indication that anti-IgE therapeutics could be effective in treating food allergies. These studies showed that peanut allergic patients treated with TNX-901

exhibited an increase resistance to peanut exposure from roughly half a peanut to nine peanuts—a level of resistance that could protect against most accidental exposures. Although TNX-901/talizumab was not developed further, ligelizumab builds on these prior promising studies, with the expectation that its high affinity for IgE would lead to increased clinical benefit over both TNX-901 and omalizumab. This expectation follows naturally from the concept that the sequestration of free IgE by anti-IgEs would represent a key correlate of therapeutic efficacy. Surprisingly, this expectation for ligelizumab has not been borne out by multiple phase III clinical studies (in CSU and asthma),^{88,89} raising important mechanistic questions about the pharmacologic basis of anti-IgE therapy.

Initially, ligelizumab showed significant promise in early phase II clinical trials for allergic asthma and CSU, consistent with its potential to outperform omalizumab due to its higher IgE binding affinity.^{45,90} Compared to omalizumab, it led to greater suppression of free IgE as well as longer lasting suppression of IgE levels in patients. Surprisingly, these results and promising clinical observations have been followed by disappointing phase II and III clinical trials of ligelizumab in allergic asthma,⁸⁹ CSU,⁸⁸ chronic inducible urticaria (CIndU; NCT05024058) and food allergy (NCT04984876), although a long-term extension study is ongoing (NCT05678959) and a food allergy trial with higher dosing is planned for late 2024. While ligelizumab is more effective than omalizumab at blocking IgE-binding to its high-affinity receptor and more effectively suppresses free IgE in allergic patients, it is striking that this increased potency has not translated into improved therapeutic efficacy. These findings clearly challenge the original conceptual framework for anti-IgE therapeutic development.

Key mechanistic differences between ligelizumab and omalizumab have emerged through structural and functional studies of these antibodies, which have contributed to understanding the clinical observations.^{77,78,80,89} Ligelizumab and omalizumab engage IgE through overlapping, but distinct, epitopes on IgE. While the omalizumab epitope lies within a single Cε3 domain,^{77,78} the ligelizumab epitope is shifted such that ligelizumab binds IgE across two Cε3 domains.⁸⁰ This difference in positioning on IgE of ligelizumab relative to omalizumab results in key differential structural and functional attributes. While ligelizumab binding more substantially interferes with FcεRI binding through steric blocking, IgE-bound omalizumab is offset to one side of the receptor complex in a position that has a substantially smaller volume of overlap with FcεRI binding. One functional consequence of this positioning difference is that ligelizumab exhibits no observable activity in transiently engaging IgE:FcεRI complexes and activating their dissociation.⁸⁰ A second functional outcome of the ligelizumab binding epitope and Fab binding pose, is that ligelizumab is a significantly weaker inhibitor of IgE:CD23 interactions as compared to omalizumab.^{80,89} The clinical studies of ligelizumab clearly indicate that increasing anti-IgE potency in blocking IgE:FcεRI binding does not provide a simple correlate for therapeutic efficacy. These additional functional differences between ligelizumab and omalizumab, due to the way in which they each engage IgE, could potentially account for the disappointing clinical

impact of ligelizumab. On the other hand, while studies support a role for IgE:CD23 complexes in allergic asthma^{55,91–94} and food allergies,^{52,95–99} it is unclear whether this would be true for CSU and could explain ligelizumab's generally disappointing clinical outcomes. Further studies are needed to address these questions.

2.1.3 | HAE1

HAE1 (PRO98498) was developed by Genentech as an affinity-matured, potential second generation anti-IgE therapeutic. HAE1 was engineered using a phage display approach yielding a variant with 9 amino acid differences that has an ~25-fold higher binding affinity compared to omalizumab (Fab K_D ~0.6 nM vs. ~15 nM), as a result primarily of a slowed dissociation rate.^{100,101} HAE1 showed more potent inhibition of IgE binding to FcεRI and inhibition of huFcεRI-RBL cell activation than omalizumab *in vitro*.¹⁰⁰ Preclinical efficacy was further assessed by observing the suppression of free IgE in cynomolgus monkeys, and free IgE was used as a biomarker for pharmacodynamic behavior of HAE1 and its potential for therapeutic efficacy. HAE1 showed a greater ability to suppress free IgE levels, as compared to omalizumab, and resulted in the accumulation of higher levels of IgE:drug complexes.¹⁰¹ Modeling of the ability of HAE1 to suppress free IgE was used to guide the clinical development program, based on the expectation that the higher HAE1 affinity would allow for lower drug:IgE dosing ratios to achieve the desired level of free IgE suppression. However, we now have, in hindsight, substantial evidence from ligelizumab clinical trials that indicate that free IgE suppression is not the sole contributor to anti-IgE clinical efficacy. Phase I and Phase II clinical studies with HAE1 incorporated designs based on this foundation, but development of HAE1 was halted after two people developed hypersensitivity reactions during the Phase II studies.

At the time that the HAE1 development program was underway, the idea that omalizumab, or its derivatives, could potentially interact with and dissociate IgE:FcεRI complexes was antithetical to the founding concepts of the original anti-IgE drug development programs. Thus, it was not until over a decade later in studies that were specifically designed to re-engineer omalizumab disruptive activities that the impact of the HAE1 program on IgE:FcεRI complex dissociation was assessed.¹⁰² In these studies, omalizumab disruptive activity was re-engineered using a yeast-display approach, revealing a direct link between omalizumab binding affinity and disruptive potency (see below). At this time, it was discovered that HAE1 antibody could more potently dissociate IgE:FcεRI complexes and more rapidly desensitize human basophils than omalizumab. These observations indicate that HAE1 not only achieved increased potency in blocking IgE:FcεRI interactions, similar to ligelizumab, but it had the potential to more rapidly desensitize allergic effector cells and maintain potent CD23 blockade. It remains to be established whether these improved functional attributes, and in particular the more rapid desensitization of allergic effector cells, could have yielded a more effective and safe anti-IgE therapeutic.

2.2 | Alternative approaches to targeting the IgE pathway

While targeting free serum IgE in allergic diseases has become a clinically validated strategy, it requires frequent dosing every 2–4 weeks depending on body weight and IgE levels of the patient. Furthermore, dosing limitations restrict the use of omalizumab in adults (>12 years) to patients with IgE levels <700 kU/L. These obvious constraints of the classical anti-IgE approach to blocking free serum IgE prompted researchers to investigate other possibilities, including direct targeting of the cellular source of IgE production, namely IgE-expressing B cells.¹⁰³ Isotype switching to IgE in B cells leads to a transient expression of membrane IgE (mIgE).^{104,105} Several strategies to target such IgE producing B cells by engaging mIgE or other specific IgE⁺ B-cell markers with monoclonal antibodies have been developed in various research programs. Even though none of these approaches have been approved for clinical use yet, we will highlight several interesting strategies here.

2.2.1 | Quilizumab (h47H4)

Compared to soluble IgE, mIgE contains an additional 52 amino acid long domain, known as M1' (or M1 prime, me.1, or CemX), located between the constant heavy chain 4 (CH4) domain and the C-terminal membrane-anchor peptide of the epsilon chain on human B cells.¹⁰⁶ The monoclonal mouse anti-human IgE antibody 47H4, which recognizes the M1' domain of mIgE, has been developed at Genentech. In an experimental allergy mouse model using transgenic mice carrying the human M1' domain in the mouse IgE locus, 47H4 demonstrated a reduction in serum IgE levels and number of IgE-producing plasma cells *in vivo*.^{107,108} The authors concluded that 47H4 most likely induces apoptosis in mIgE⁺ B cells. Following these studies, an afucosylated humanized version of the antibody, known as quilizumab, was generated.¹⁰⁹ The removal of fucose from the IgG antibody increases binding affinity to FcγRIIIa, enhancing ADCC by NK cells and increasing quilizumab's efficacy to drive mIgE⁺ B cells into programmed cell death. A phase I clinical trial for allergic rhinitis (NCT01160861) and a phase II clinical trial for allergen-induced asthma (NCT01196039) revealed encouraging results, with quilizumab treatment reducing total and allergen-specific IgE levels by 35% and 40%, respectively.¹¹⁰ The treatment also improved clinical signs of allergen-induced asthma. Surprisingly, quilizumab treatment only partially reduced serum IgE levels and did not significantly improve clinical outcomes in subsequent phase II clinical trials with allergic asthma patients (NCT01582503)¹¹¹ or CSU patients (NCT01987947).¹¹¹ The unexpected results of these trials may be attributed to the infrequent and transient presence of short-lived mIgE⁺ B cells, along with increasing evidence that the memory of the IgE compartment originates in a CD23-positive IgG memory B cell pool (i.e., MBC2), which undergoes sequential and potentially repetitive isotype switching to IgE.^{112,113} To our knowledge the quilizumab program is no longer being actively pursued.

2.2.2 | XmaB7195

The anti-IgE antibody XmaB7195 is a humanized, affinity-enhanced variant of MaE11,¹¹⁴ the murine parental antibody of omalizumab, with an altered Fc-region to improve binding to the inhibitory receptor FcγRIIb implemented with the goal of accelerating clearance of anti-IgE:IgE immune complexes from the circulation. Initially developed at Xencor, XmaB7195 aims to neutralize free serum IgE and reduce IgE production by promoting the aggregation of FcγRIIb and mIgE on the B cell surface.^{115,116} In a severe combined immunodeficiency (SCID) mouse model engrafted with human PBMCs, XmaB7195 decreased free IgE levels and prevented the formation of IgE-secreting plasma cells. The effectiveness of this dual-targeting strategy was also assessed in a phase Ia clinical trial with 72 healthy volunteers and individuals with high IgE levels (NCT02148744). Several subjects with high IgE levels (300–3000 kU/L) reached undetectable free IgE levels ($<9.59 \text{ ng/mL} = <4 \text{ kU/L}$) following single dose intravenous XmaB7195 infusion. Additionally, soluble free and total IgE, basophil surface IgE and FcεRI levels showed pronounced reductions. As for the most important adverse events, transient dose-dependent thrombocytopenia and one drug-related severe bronchospasm with trial discontinuation was reported. A subsequent phase Ib clinical trial (NCT02881853) for subcutaneous administration was conducted and completed in 2017. However, no results have been communicated to date. In February 2020 Aimmune Therapeutics acquired an exclusive license from Xencor to develop and commercialize the antibody (renamed to AIMab7195). While they planned to develop AIMab7195 as an adjunct treatment to oral immunotherapy, to explore treatment outcomes in patients with food allergies, Aimmune Therapeutics was subsequently acquired by Nestlé in October 2020.

2.2.3 | UB-221 (8D6)

In 2012, a new monoclonal anti-IgE antibody named 8D6 was developed at United BioPharma, which was reported to bind the Cε3 domain of IgE with fourfold higher affinity than omalizumab (apparent $K_D \sim 59 \text{ pM}$ versus $K_D \sim 230 \text{ pM}$, as measured with intact IgG antibodies). 8D6 has a unique binding feature in that it blocks the interaction between IgE and FcεRI but does not interfere with IgE binding to CD23.¹¹⁷ Similar to ligelizumab, 8D6 can recognize CD23-IgE complexes on the cell surface.^{80,117} However, 8D6:IgE unlike ligelizumab:IgE complexes can still interact with CD23. In a recent follow-up study a humanized version of 8D6, termed UB-221, has been characterized and tested in a phase I clinical trial in patients with CSU.¹¹⁸ UB-221 exhibited the same binding characteristics as its murine predecessor. With higher affinity for free IgE compared to omalizumab, UB-221 showed equal effectiveness to ligelizumab in neutralizing IgE levels *ex vivo* in sera from patients with atopic dermatitis—some of which contained total IgE levels $>10,000 \text{ kU/L}$ ($24 \mu\text{g/mL}$). *In vitro*, UB-221 suppressed IgE-mediated degranulation of rat basophilic leukemia cells expressing human FcεRIα

(i.e., RBL SX-38) with sevenfold higher efficacy than omalizumab. Additionally, UB-221 was shown to markedly reduce the synthesis of IgE in PBMC cultures from healthy donors stimulated with IL-4 and anti-CD40 antibody at both the protein and mRNA level. In direct comparison, this inhibition was superior to that achieved with omalizumab or ligelizumab. The exact mechanism of how UB-221 achieves inhibition of IgE production in B cells, however, remains elusive. The authors speculate that the effect might result from modulating the CD23 pathway possibly by directly cross-linking the receptor and thereby reducing IgE production. As CD23 lacks intracellular signaling domains more research is needed to confirm this hypothesis. In nonhuman primates and human IgE (IGHE) knock-in mice, single application of UB-221 rapidly reduced serum IgE levels to $>90\%$. In the mice, IgE suppression lasted for ~ 14 days before IgE levels gradually rebounded back to baseline, whereas IgE levels in cynomolgus monkeys were maximally reduced for less than 1 day and reached baseline in <10 days. In the phase I, open-label, dose-escalation trial single intravenous infusion in CSU, UB-221 was found to be safe and well-tolerated. With an estimated serum half-life of 16–22 days at doses between 0.6 and 10 mg/kg , UB-221 led to a significant reduction in serum free IgE levels and a rapid, dose-dependent decrease in the weekly UAS7 scores, which measure disease symptoms. In summary, the current data warrants evaluation of UB-221 in further clinical trials.

2.2.4 | IgE_{TRAP}-Fc protein (YH35324)

IgE_{TRAP} is a fusion protein consisting of two extracellular domains of FcεRIα linked to a hybrid IgD/IgG4 Fc domain.¹¹⁹ While the extracellular FcεRIα domains were incorporated with the aim to bind and neutralize IgE, the engineered Fc-domain has been chosen to potentially reduce the likelihood of IgG1 Fc-mediated side effects such as ADCC, complement-dependent cytotoxicity (CDC), and IgG-mediated anaphylaxis. IgE_{TRAP} retains the neonatal Fc-receptor (FcRn) binding site, which is crucial for *in vivo* half-life extension. However, as its eight N-linked glycosylation sites might enhance clearance, IgE_{TRAP} was sialylated by co-transfecting a α -2,6-sialyltransferase in CHO DG44 cells, which led to capping of the glycans with sialic acids. Compared to omalizumab IgE_{TRAP} showed superiority in certain functional features. IgE_{TRAP} showed a 69-fold higher binding affinity for human IgE compared to omalizumab in surface plasmon resonance measurements, which was mainly driven by a slower dissociation rate. Using the human mast cell line LAD2, IgE_{TRAP} was more effective than omalizumab in inhibiting IgE-mediated degranulation. In cynomolgus monkeys, IgE_{TRAP} reduced free serum IgE levels more effectively and for a longer duration than omalizumab. A single dose of IgE_{TRAP} decreased IgE levels below the detection limit and maintained IgE suppression for 10 days, while omalizumab failed to fully reduce free IgE levels and its suppressive effect lasted only 3 days. In a mouse model of IgE-mediated passive systemic anaphylaxis, IgE_{TRAP} fully suppressed the allergic reaction as measured by drop in body core temperature.

Recently, a first in human study examining IgE_{Trap} in a randomized, double-blind phase I clinical trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics was conducted in individuals with atopy.¹²⁰ In a first assessment, healthy or atopic adults with mild allergic conditions and IgE levels between 30 and 700 kU/L were treated with different doses IgE_{Trap}, omalizumab, or a placebo. In the second part of the study subjects with IgE levels >700 kU/L received either IgE_{Trap} or omalizumab. The study results indicate that treatment-emergent adverse events occurred in 38.5% of participants in the first part and 62.5% in second part of the study. These events were primarily mild or moderate, with no serious adverse events, treatment discontinuations due to adverse effects, or anaphylaxis reported. IgE_{Trap} showed a dose-proportional increase in peak concentration and total exposure over the dosage range. The drug also significantly reduced free serum IgE levels, with a greater and longer-lasting effect compared to omalizumab. In conclusion, these data suggest that IgE_{Trap} is mostly safe and warrant further investigation as to whether IgE_{Trap} might be suitable to treat subjects with atopic conditions.

2.2.5 | Lumiliximab (IDEC-152)

In the 1990's Fujiwara et al. observed that CD23 deficient mice have increased and sustained antigen-specific IgE levels compared to wild-type mice, while T and B cell development seemed normal.¹²¹ Their findings provided strong evidence that CD23 is involved in negative regulation of IgE synthesis. On the other hand, monoclonal antibodies against human CD23 have been reported to inhibit the production of IgE in IL-4 stimulated human PBMC cultures by several groups^{122–124} further substantiating the regulatory role of CD23 in this context. While anti-CD23 antibodies can potentially affect multiple aspects of the allergic cascade, different in vitro studies have suggested that crosslinking of membrane CD23 with an IgG receptor could be a key mode-of-action to downregulate IgE synthesis.^{125–127} In vivo, anti-CD23 antibodies inhibited antigen-specific IgE responses¹²⁸ and blocked lung eosinophil infiltration in murine asthma models.⁹¹ A chimeric macaque/human anti-CD23 monoclonal antibody consisting of cynomolgus macaque variable regions and human IgG1 constant regions, known as Lumiliximab (IDEC-152), has been developed at IDEC Pharmaceuticals¹²⁵ and tested in a phase I, singledose, dose-escalating clinical trial with allergic asthma patients.¹²⁹ The antibody showed a favorable safety profile and dose-dependently decreased mean IgE levels. However, no clinical disease amelioration as measured by change in FEV1, was observed upon single dose application. Interestingly, the study found a reduction in total CD19⁺ B cell counts, since CD23 is not exclusively expressed on IgE-producing B cells. While the assessment of its use in allergic disorders was ceased after this phase I trial, lumiliximab was further tested in chronic lymphocytic leukemia (CLL), to deplete CD23⁺ B cells. However, this program has also been halted as the study failed to meet primary endpoints in a phase II/III clinical trial.¹³⁰

2.3 | Anti-cytokine receptor antibodies

2.3.1 | Dupilumab (Dupixent)

Dupilumab is a humanized monoclonal IgG4 antibody against the alpha subunit of the interleukin-4 receptor (IL-4R α), which is the common chain of the IL-4 and IL-13 receptor. The antibody has been co-developed at Regeneron Pharmaceuticals and Sanofi. To date, it has been approved for the treatment of several allergic and inflammatory conditions, including moderate-to-severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, prurigo nodularis and most recently for chronic obstructive pulmonary disease (COPD) with raised blood eosinophils. While the positive results of two phase III clinical trials with dupilumab in CSU have recently been published,¹³¹ it has already been approved as add-on therapy to standard-of-care H1 antihistamines for CSU in Japan. Dupilumab works by inhibiting the biological activity of both IL-4 and IL-13, which are key drivers of the Th2 response. By doing so, dupilumab targets multiple molecular and cellular mechanisms in the allergic cascade, which has been demonstrated in human in vitro culture systems and humanized mouse asthma models.¹³² Interestingly, dupilumab has been shown to prevent isotype class switching to IgE in B cells in vitro and to suppress IgE levels in vivo.^{132,133} In that sense, it blocks IgE pathophysiology upstream of monoclonal antibodies directly targeting IgE. However, IgE suppression is less effective, incomplete and requires long treatment periods (1 year for approximately 70% reduction).¹³² While direct comparison with omalizumab in a prospective clinical trial is lacking, no clinically significant differences in efficacy outcomes were reported in indirect retrospective evaluations.¹³⁴

2.3.2 | Benralizumab (Faserna)

Benralizumab is a humanized, afucosylated, monoclonal IgG1 antibody that targets the IL-5 receptor alpha chain (IL-5R α) on the surface of eosinophils and basophils.¹³⁵ Developed by AstraZeneca's biologics research and development branch, MedImmune, it has been approved as add-on maintenance treatment of severe eosinophilic asthma. Besides blocking the biological activity of IL-5, benralizumab has been shown to drive eosinophils into apoptosis via ADCC.²⁹ IL-5 is a crucial cytokine for the growth, differentiation, recruitment, and survival of eosinophils, which play a significant role in the pathophysiology of eosinophilic asthma and other allergic conditions. Benralizumab mediated elimination of these cells, reduces inflammation and helps to control asthma symptoms and exacerbations. Clinical studies have shown that benralizumab is highly effective in reducing eosinophil counts, improving lung function, and decreasing the frequency of asthma exacerbations in patients with severe eosinophilic asthma.^{136,137} Its ability to target and deplete eosinophils makes it a powerful therapeutic option for patients with difficult-to-control asthma characterized by elevated eosinophil levels.

2.4 | Approved anti-Th2 cytokine antibodies

2.4.1 | Mepolizumab (Nucala) and Reslizumab (Cinqair)

Mepolizumab is a fully humanized monoclonal IgG1 antibody from GSK targeting IL-5. The antibody binds IL-5 with high affinity and inhibits its interaction with the IL-5 receptor, which is predominantly expressed on eosinophils. This approach has been shown to result in a reduction of eosinophil counts in blood and tissues.¹³⁸ A single intravenous injection led to a remarkable reduction of blood eosinophils, which persisted for 30 days.¹³⁹ While initial studies in asthma did not show the expected clinical effectiveness,¹⁴⁰ Mepolizumab has in the meantime been approved for the treatment of severe eosinophilic asthma,¹⁴¹ eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome (HES) and as an add-on therapy to intranasal corticosteroids in CRSwNP. Clinical trials have demonstrated its efficacy in decreasing the frequency of asthma exacerbations,¹⁴² improving lung function,¹⁴³ and managing symptoms in other eosinophilic conditions.¹⁴⁴

Reslizumab is a fully humanized monoclonal IgG4 antibody also targeting IL-5 initially developed at Cephalon, which was acquired by Teva Pharmaceuticals in 2011. It is approved as add-on maintenance treatment of severe eosinophilic asthma.¹⁴⁵ While a direct comparative in vitro study has demonstrated that reslizumab features an 11–26 fold higher affinity and neutralization potency for IL-5 than mepolizumab,¹⁴⁶ indirect comparisons of clinical outcomes did not show major differences between the two antibodies.

2.4.2 | Tezepelumab (Tezspire)

Tezepelumab is a fully human monoclonal IgG2 antibody that inhibits the epithelial-cell-derived alarmin TSLP. The antibody which has been co-developed by Amgen and AstraZeneca binds TSLP with high affinity (~60 pM),¹⁸ preventing its interaction with the TSLP receptor complex. This blockade interrupts the signaling cascade that leads to the production and release of pro-inflammatory cytokines and chemokines, reducing inflammation and hyperresponsiveness in the airways. Tezepelumab is approved as an add-on maintenance treatment for patients with severe asthma, particularly those who are inadequately controlled with standard therapies such as inhaled corticosteroids and long-acting beta-agonists.¹⁴⁷ Interestingly, tezepelumab is effective irrespective of baseline eosinophil counts.¹⁴⁸ The findings that tezepelumab reduced blood eosinophil count as well as levels of fractional exhaled nitric oxide (FeNO) and IgE, indicate that the antibody is able to suppress multiple inflammatory pathways. The effect of tezepelumab on these biomarker levels may be related to decreased interleukin-5 and interleukin-13 levels.¹⁴⁹ Reduction in total IgE levels may be linked to suppression of IL-4 and IL-13 concentrations, leading to less efficient B cell isotype class switching to IgE. Clinical trials have demonstrated that tezepelumab significantly reduces the rate of asthma exacerbations, improves lung function,

and enhances asthma control compared to placebo.¹⁵⁰ Further, a phase IIb clinical trial has recently demonstrated promising results for the treatment of CSU.¹⁵¹ These data support the concept that TSLP inhibition may have broader physiological effects than targeting individual type 2 cytokines.

2.4.3 | Lebrikizumab (Ebglyss)

Lebrikizumab is a humanized IgG4 anti-IL-13 monoclonal antibody developed by Almirall and Eli Lilly. The antibody binds IL-13 with an affinity <10 pM.¹⁵² Lebrikizumab-bound IL-13 is still able to bind its cell surface receptors, but the antibody sterically prevents the heterodimerization of IL-4R α /IL-13R α 1 (Type 2 receptor) and thus its downstream signaling. However, it does not affect the binding of IL-13 to the IL-13R α 2 decoy receptor.¹⁵³ Lebrikizumab has been assessed for the treatment of both atopic dermatitis and asthma. Initial phase III clinical trial data in moderate-to-severe asthma did not demonstrate consistent efficacy.¹⁵⁴ However, reanalysis in a well-defined type 2 asthma population with elevated blood eosinophils, elevated FeNO,¹⁵⁵ reported a successful outcome with reduced asthma exacerbations. In two identically designed phase III clinical trials for atopic dermatitis, Lebrikizumab therapy demonstrated significantly improved skin clearance, itch, and interference of itch with sleep.¹⁵⁶ Currently, its use is restricted to the treatment of atopic dermatitis.¹⁵⁷

2.4.4 | Antibodies in clinical trials for the treatment of allergy

Apart from the clinically approved monoclonal antibodies to treat different allergic conditions, additional drug candidates are currently undergoing clinical evaluation in a variety of allergic indications (Table 1). While some of them are directed against pre-validated targets such as IL-4R α , IL-5, IL-13 or TSLP, others explore new therapeutic routes for example, by (i) neutralizing the alarmin IL-33, an important driver of type 2 immunity, (ii) blocking inflammatory cytokine signaling involved in allergic itch (e.g., IL-31R), or (iii) preventing interaction between T cells (e.g., OX40) and TSLP-activated DCs (e.g., OX40L) to inhibit Th2 cell mediated immune responses. While this topic has been covered extensively in other reviews,^{170,171} the table provides an overview of current efforts and strategies to develop more effective monoclonal antibody-based drugs for the treatment of allergies.

2.5 | Other therapeutic antibodies under development

2.5.1 | Barzolvolimab (CDX-0159)

Barzolvolimab, also known as CDX-0159, is a humanized monoclonal IgG1 antibody designed to target KIT with high picomolar affinity and

TABLE 1 Anti-cytokine and cytokine receptor antibodies in Phase 2 and 3 clinical trials for the treatment of allergic conditions.

Target/antibody	Clinical stage	Company	References
IL-4Rα			
MG-K10	Phase 2 in asthma and AD	Shanghai Mabgeek Biotech	NCT05382910, NCT05466877
CM310	Phase 2/3 in asthma, AD and CRSwNP	Keymed Biosciences	NCT05186909, NCT05715320, NCT05436275 ¹⁵⁸
AK120	Phase 2 in asthma	Akeso	NCT05155020 ¹⁵⁹
Rademikibart	Phase 2 in asthma	Simcere Pharmaceutical	NCT06488755 ¹⁶⁰
IL-5			
Depemokimab	Phase 3 completed in asthma	GSK	NCT04718389 ¹⁶¹
Varokibart	Phase 2 in asthma	Teva Pharmaceutical Industries	NCT04847674
SHR-1703	Phase 2 in asthma	Jiangsu Hengrui Pharma	NCT05522439
IL-13			
Tralokinumab	Phase 3 in AD	Leo Pharma	NCT03526861 ¹⁶²
Cendakimab	Phase 3 completed in AD	Celgene/Abbvie	NCT04800315 ¹⁶³
IL-31R			
Nemolizumab	Phase 3 completed in AD	Galderma	jRCT2031230174 ¹⁶⁴
IL-33			
Etokimab	Phase 2 completed in severe eosinophilic asthma and peanut allergy	Anaptys Bio	NCT02920021 ¹⁶⁵
Itepekimab	Phase 2 completed in asthma	Regeneron/ Sanofi	NCT03387852 ¹⁶⁶
Tozorakimab	Phase 2 in asthma	AstraZeneca	NCT04570657 ¹⁶⁷
TSLP			
AIO-001	Phase 2 ready in asthma	GSK/ Aiolos Bio	NCT06170827
BSI-045B	Phase 2 in AD	Biosion	NCT05114889
TQC2731	Phase 2 in CRSwNP	Chia Tai Tianqing Pharmaceutical Group	NCT06036927, NCT05472324
UPB-101	Phase 2 in asthma, CRSwNP	Upstream Bio	NCT06196879, NCT06164704
CSJ117	Phase 2 in asthma	Novartis	NCT04410523 ¹⁶⁸
SHR-1905	Phase 2 in asthma and CRSwNP	GSK	NCT05593250, NCT05891483
CM326	Phase 2 in asthma, AD and CRSwNP	Keymed Biosciences	NCT05774340, NCT05671445, NCT05324137
OX-40			
Rocatinlimab	Phase 2/3 in asthma and AD	Amgen	NCT06376045, NCT05633355
BAT6026	Phase 2 in AD	Bio-Thera Solutions	NCT06094179
OX-40L			
Amltelimab	Phase 2/3 in asthma and AD	Sanofi	NCT06033833, NCT06130566 ¹⁶⁹

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps.

inhibit its function. While Celldex has developed its predecessor CDX-0158 (KTN0158) for the treatment of KIT-positive neoplasms such as advanced refractory gastrointestinal stromal tumors (GIST),^{172,173} they subsequently started to implement CDX-0159 to target mast cells in allergic diseases. Compared to CDX-0158, CDX-0159 carries modifications in its Fc portion to abolish Fc γ R and C1q receptor binding to prevent unwanted Fc γ R-dependent mast cell activation potentially leading to infusion reactions. Further mutations (i.e., YTE) were introduced to increase the binding affinity for FcRn, reducing the

rate of in vivo clearance and extending the antibody's serum half-life. CDX-0159 has been reported to inhibit SCF-dependent KIT activation *in vitro*.¹⁷⁴ In a phase Ia clinical trial it demonstrated a systemic and prolonged mast cell ablation upon in healthy volunteers. Further CDX-0159 treatment reduced skin mast cells and substantially ameliorated disease activity in a phase Ib with chronic inducible urticaria and systemic dermatographism patients.¹⁷⁵ While a phase II clinical trial in CSU is currently still ongoing (NCT05368285), top line results on angioedema relief have been communicated.¹⁷⁶

2.5.2 | Lirentelimab (AK002) and other anti-Siglec antibodies

A humanized non-fucosylated monoclonal IgG1 antibody, AK002, targeting Siglec-8 has been developed by Allakos and analyzed for treatment of diseases associated with mast cell and eosinophil-driven inflammation. The ITIM-containing inhibitory Siglec-8 is selectively expressed on mast cells, eosinophils and basophils. Different studies have shown that AK002 depletes eosinophils by ADCC and prevents mast cell activation through inhibitory signaling via Siglec-8.¹⁷⁷⁻¹⁸⁰ Initially, AK002 showed safety, tolerability and bioavailability in a phase I clinical trial with healthy volunteers (NCT04324268). However, despite successful depletion of eosinophils (95–96%), Lirentelimab failed to meet primary endpoints in two phase II clinical trials with CSU (NCT05528861) and Atopic Dermatitis (NCT05155085) patients. While this Siglec-8 program with AK002 has been stopped, Allakos has developed the agonistic humanized IgG1 monoclonal antibody AK006 against Siglec-6. AK006 has been reported to induce strong inhibitory signaling in human mast cells¹⁸¹ and to trigger ADCP leading to a reduction in mast cell numbers *in vivo*.⁶⁷ A phase I clinical trial in healthy volunteers and subjects with CSU has been initiated (NCT06072157).

2.5.3 | Anti-Orai1 (DS-2741a)

ORAI1 is a transmembrane pore-forming subunit forming the hexameric structure of the calcium release-activated calcium (CRAC) channel. It regulates cellular uptake of calcium, which is critical for several biological processes in various cell types including activation of T cells and mast cells. While mutations in the Orai1 gene can cause severe combined immunodeficiency (SCID), characterized by impaired T cell function and a compromised immune

system,¹⁸² Orai1 knockout mice exhibit reduced T cell cytokine production and mast cell activation.¹⁸³ Thus, targeted approaches to specifically inhibit ORAI1 have been assessed. Daiichi Sankyo has developed DS-2741a, a humanized anti-ORAI1 IgG1 antibody, which attenuated bone marrow derived mast cell (BMMC) degranulation *in vitro* and the passive cutaneous anaphylaxis reaction *in vivo* in human Orai1 transgenic mice.¹⁸⁴ Further, DS-2741a induced suppression of cytokines release triggered by store-operated Ca^{2+} entry in a variety of T helper subsets. *In vivo*, DS-2741a treatment resulted in an amelioration of dermatitis in a mouse model of mite antigen-induced atopic dermatitis.¹⁸⁴ Since Orai1 is widely expressed, it remains to be investigated whether such an approach could be associated with overt unwanted side effects. Further studies are needed to assess the therapeutic potential of targeting ORAI1 in allergic diseases.

3 | COMPARATIVE ANALYSIS OF THERAPEUTIC ANTIBODIES

The availability of many different biologicals for the treatment of allergic conditions (Table 2) enables the possibility of tailoring the therapy for a patient's disease phenotype/endotype in a personalized manner. At the same time, it requires a detailed diagnostic work-up and informed therapeutic decision-making based on well-established biomarkers. As reviewed in detail elsewhere,¹⁹⁵ additional factors such as patient co-morbidities, practical aspects surrounding drug delivery (e.g., frequency of injection, location of administration, ability to receive delivery and properly store medication) and personal situation of the patient (e.g., age, work hours, caretaker demands and travel frequency) can influence the choice of the most suitable treatment. There are clear guidelines from EAACI^{196,197} and GINA¹⁹⁸ for the use of biologicals in asthma.

TABLE 2 Overview of clinically approved monoclonal antibodies across different allergic indications.

mAb	Target	Asthma	CSU	AD	CRSwNP	Food allergy	EoE
Omalizumab	IgE	Approved	Approved	Limited efficacy ¹⁸⁵	Approved	Approved	Limited efficacy ¹⁸⁶
Dupilumab	IL-4R α	Approved	Approved (add-on)*	Approved	Approved	-	Approved
Benralizumab	IL-5R	Approved (add-on, severe eosinophilic)	Limited efficacy ¹⁸⁷	Limited efficacy ¹⁸⁸	Limited efficacy ¹⁸⁹	-	Limited efficacy ¹⁹⁰
Mepolizumab	IL-5	Approved (add-on, severe eosinophilic)	-	-	Approved (add-on)	-	Limited efficacy ¹⁹¹
Reslizumab	IL-5	Approved (add-on, severe eosinophilic)	-	-	-	-	Limited efficacy ¹⁹²
Tezepelumab	TSLP	Approved (add-on)	Promising phase 2b ¹⁵¹	Limited efficacy ¹⁹³	-	-	ODD
Lebrikizumab	IL-13	Limited efficacy ¹⁹⁴	-	Approved	-	-	-

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; ODD, orphan drug designation.

*In Japan.

Moreover, EAACI provided guidelines on the use of biologicals in CSRwNP¹⁹⁹ and urticaria.²⁰⁰

Patients with IgE-driven disease pathology benefit from omalizumab treatment across different allergic conditions, as indicated by its broad success and approval across indications (Table 2). The assessment of allergen-specific and total IgE levels can be an important indicator in this context. However, there are exceptions in which high or extreme levels of IgE were associated with worse treatment responses such as in AD.²⁰¹ Furthermore, omalizumab has shown limited efficacy in AD, which might be due to the observation that these patients often exhibit non-IgE mediated aspects of chronic skin inflammation.

IL-4R α targeting therapy with dupilumab can act at multiple points along the allergic cascade and has also shown clinical efficacy across multiple indications.²⁰² It is recommended in conditions with prominent type 2 inflammation characterized by elevated blood eosinophils and/or increased fractional exhaled nitric oxide (FeNO). IL-4 and IL-13 share many biological actions, which can likely be attributed to the overlapping use of the IL-4R α subunit and downstream activation leading to activation of signal transducer and activator of transcription (STAT) pathways. This molecular pharmacology is one reason why approaches targeting IL-4R α chain, such as dupilumab, have proven more successful than isolated approaches that inhibit only IL-13 or IL-4.²⁰³

As the development, recruitment and survival of eosinophils is highly dependent on IL-5, blocking its biological activity with benralizumab, mepolizumab or reslizumab has proven to bring clinical benefit in patients with inflammatory eosinophil in the lung.²⁰⁴ However, these anti-IL5/5R α biologicals target a narrower patient population as they were only approved as add-on maintenance therapy in severe eosinophilic asthma.

Consistent with basic disease models, therapeutic blockade of alarmin pathways has shown promise in settings where eosinophil recruitment and tissue remodeling are key drivers of pathology. TSLP targeted therapies modulate lung function, inflammation, and reduce exacerbation rates in allergic asthma.¹¹ In contrast the same intervention has been less successful in atopic dermatitis (AD), where IL-13 induced tissue remodeling and IL-5 driven eosinophil recruitment are less central to disease pathophysiology.^{12,151}

Currently, there is only limited information available from head-to-head trials of approved biologicals in a specific allergic indication. A prospective direct comparison between dupilumab, mepolizumab, and reslizumab, however, has been performed in severe eosinophilic asthma.²⁰⁵ The study, which included 141 patients, reported comparable clinical outcomes regarding time-to-first exacerbation, exacerbation rate, forced expiratory volume in 1s, and asthma control test score within a 12-month treatment period. An indirect comparison based on meta-analysis of 14 randomized clinical trials (RCTs) in uncontrolled persistent asthma reported greater reductions in annualized severe exacerbation rates for dupilumab as compared to benralizumab, mepolizumab, reslizumab, and omalizumab treatment.²⁰⁶ Additionally, a greater improvement in FEV1 was described for dupilumab at week 12,

24, or 52 than for the other biologics. In another indirect comparison between tezepelumab, mepolizumab, benralizumab, and dupilumab in eosinophilic asthma including 9201 patients from 10 RCTs, it has been reported that tezepelumab and dupilumab were associated with greater improvements in exacerbation rates and lung function than benralizumab or mepolizumab.²⁰⁷ Results from such indirect comparisons should, however, be interpreted with caution until there is reliable data available from direct head-to-head clinical trials.

4 | FUTURE DIRECTIONS AND INNOVATIONS

The continued authorization of omalizumab for treating additional allergic indications, more than 20 years after its initial approval for asthma,⁷² underscores the pivotal role of IgE biology in a wide range of allergic diseases. With food allergy as the most recent example,²⁰⁸ many clinical investigations have demonstrated that targeting and neutralizing IgE remains one of the most important cornerstones of allergic disease management. Current clinical limitations for anti-IgE approaches such as dosing restrictions and frequency of injections, however, call for further improvements in this approach. Given the broad treatment success of omalizumab, we will particularly focus on future directions of anti-IgE treatment strategies in the next sections.

4.1 | Molecular engineering of next-generation IgE inhibitors

Over time it has become evident that developing a next generation anti-IgE treatment that achieves clinical improvement over omalizumab anti-IgE treatment is more difficult than initially anticipated. This has especially been exemplified by the termination of the HAE-1 development program, and disappointing clinical results obtained with both ligelizumab and Xmab7195. For ligelizumab, two phase III clinical trials in asthma and CSU^{88,89} with side-by-side comparison to omalizumab did not yield anticipated improvements in clinical outcome. These studies provide accumulating evidence that solely increasing the affinity of an anti-IgE antibody is insufficient to overcome current therapeutic limitations. Instead, the data rather suggest that other binding characteristics such as IgE epitope specificity and the ability to actively dissociate IgE from Fc ϵ RI might represent important contributors to clinical efficacy.

4.1.1 | Improving existing anti-IgE approaches

With the development of an efficiency screen based on yeast display to simultaneously increase affinity and disruptive potency, we recently laid the experimental and conceptual foundation for the selection and engineering of potent omalizumab variants.¹⁰² In this work,

we characterized a range of anti-IgE antibodies with distinct epitopes, affinities, and disruptive potencies. Clone C02 resulted from such a screen and showed high affinity as well as improved disruptive potency. It completely desensitized basophils from allergic donors within hours at therapeutically relevant doses *ex vivo*. Insertion of flexible Glycine linkers at each Fab elbow (VH/VL) in C02 (C02-H2L2) further increased its disruptive potency. Importantly, we observed that the dwell time of disruptive anti-IgE antibodies on intact IgE:FcεRI complexes prior to disruption is a critical parameter that correlates with their ability to safely remove IgE from human allergic effector cells. Another group has engineered an omalizumab variant, termed FabXol3, by structure guided insertion of three point mutations, two in the VL domain framework region and one in the C_κ domain.^{78,209} FabXol3 featured slightly higher affinity than the unmutated omalizumab Fab and was more efficient in accelerating the dissociation of IgE-Fc from FcεRI. Overall, these findings illustrate the potential of kinetically active disruptive anti-IgE antibodies to enhance therapeutic efficacy of omalizumab. Furthermore, they provide a structural and conceptual framework for engineering optimized next-generation anti-IgE antibodies featuring both highly efficient neutralization and disruptive potency.

Another study described the development of an omalizumab biobetter, AB1904Am15, through the optimization of stability, immunogenicity, affinity and bioavailability.²¹⁰ First the authors replaced two aspartic acid isomerization hotspots in the complementary determining regions (CDRs) and mutated multiple murine framework residues to the homologous human germline antibody sequence. Using yeast display technology in conjunction with a designed mutation library of each CDR in the variable domains they further screened for increased affinity. Additionally, the previously described YTE mutation²¹¹ was inserted into the Fc region of the antibody to prolong its serum half-life. The resulting anti-IgE antibody AB1904Am15 showed favorable biophysical properties with improved molecular stability. The twofold improved affinity resulted in enhanced *in vitro* inhibition of IgE binding to FcεRI and enhanced suppression of IgE induced histamine release in human FcεRI-expressing rat basophilic leukemia cells compared to omalizumab. Further, AB1904Am15 showed a more than twofold longer serum half-life in human FcRn transgenic mice. Finally, the optimized antibody outperformed the original omalizumab antibody in terms of free IgE suppression efficacy in a cynomolgus monkey asthma model *in vivo*. This study further demonstrated the possibilities of improving anti-IgE biologicals. Overcoming current limitations associated with molecular stability and dosing restrictions may hold great promise to optimize clinical efficacy.

4.1.2 | Exploring novel mechanisms and alternative scaffolds

The first systematic description of active IgE dissociation from FcεRI using a disruptive IgE inhibitor has been published in 2012.⁷⁹ In this study, we characterized the binding kinetics of an alternative scaffold molecule, the designed ankyrin protein (DARPin) E2_79, featuring

this accelerated dissociation mechanism. As E2_79 engages a subset of ligand attachment points on IgE, which become exposed during partial IgE:FcεRI complex dissociation, it accelerates the intrinsic dissociation rate and fully removes IgE from the receptor. This work laid the conceptual foundation to develop more potent inhibitors through targeted screening approaches and molecular engineering. In subsequent studies, we generated bispecific DARPins, such as bi53_79, by genetic fusion⁷⁹ and a bispecific antibody-like hybrid molecule between two DARPins and an IgG Fc-domain, KIH_E07_79, using the knobs-in-hole techniques.⁸¹ The latter example represents an interesting molecule as it integrates important functional features from the initially described disruptive DARPin with classical characteristics of IgG antibodies, including a potentially prolonged serum half-life. These studies highlighted the remarkable potency of KIH_E07_79 to neutralize free IgE, rapidly dissociate preformed IgE:FcεRI complexes, terminate IgE-mediated signaling in preactivated human blood basophils *in vitro*, and shut down pre-initiated allergic reactions and anaphylaxis in mice transgenic for human FcεRIα *in vivo*.

A disruptive nanobody, called sdab 026 was reported several years later in 2018.²¹² The authors described an allosteric mechanism for sdab 026, in which both blocking of the IgE:FcεRI interaction as well as disruption of IgE:FcεRI are based on trapping the IgE-Fc Cε3-4 domains in a closed conformation incompatible with FcεRI binding.²¹³ While not yet officially peer-reviewed, various bispecific IgG4 Fc-fusion proteins have been published (patent WO2024003376A1) with sdab 026 (i.e., A1) and an additional less potent or nondisruptive anti-IgE nanobody (i.e., A2-G1), in an analogous approach as previously described for the DARPin Fc-fusions. Several of the bispecific nanobody Fc-fusion molecules, such as NIgG4B1A1(G4S), were shown to efficiently inhibit allergen-mediated reactions in passive cutaneous or systemic anaphylaxis models in mice transgenic for human FcεRIα *in vivo*.

Compared to classical antibodies, the described alternative scaffolds or fusion molecules feature smaller binding sites, which may be advantageous when targeting of specific epitopes important in disruption of high-affinity protein:protein interactions is essential. As such they represent promising approaches for the generation of next-generation anti-IgE biologicals. However, clearly more work needs to be done in order to assess their developability, manufacturability and *in vivo* efficacy as well as safety.

4.1.3 | Unifying different modes-of-action in one molecule

There is a growing body of evidence suggesting that the therapeutic efficacy of anti-IgE biologicals could be significantly increased, if the treatment simultaneously interfered at multiple levels in the allergy cascade.²¹⁴ This could potentially be achieved by developing next-generation anti-IgE molecules exerting multiple modes-of-action (Figure 3). Theoretically, such a novel drug candidate should ideally combine the following molecular characteristics: (i) bind free serum IgE with high affinity to neutralize its biological activity, (ii) efficiently

and rapidly disrupt IgE from its high-affinity receptor FcεRI on the surface of allergic effector cells in the blood (i.e., basophils, dendritic cells) and in tissues (i.e., mast-cells), (iii) inhibit IgE:CD23 interactions to prevent IgE facilitated antigen presentation on dendritic cells or B cells, (iv) suppress IgE production in B cells or eliminate IgE switched B cells.

While a lot of effort has focused on maximizing free IgE neutralization in previous anti-IgE development programs, more recent approaches are starting to optimize additional modes-of-action (Table 3). At this stage, however, more research is needed to evaluate how these functional characteristics will translate into improved therapeutic potential and clinical benefit *in vivo* in humans.

4.2 | Combination and repurposing of existing strategies

4.2.1 | Omalizumab and allergen-specific immunotherapy

Allergen-specific immunotherapy (AIT) is a clinical procedure aimed at re-establishing immunological tolerance against culprit allergens. The treatment involves administration of incrementally increasing doses of allergen extract, which can be delivered via different routes (i.e., subcutaneous, sublingual, oral or

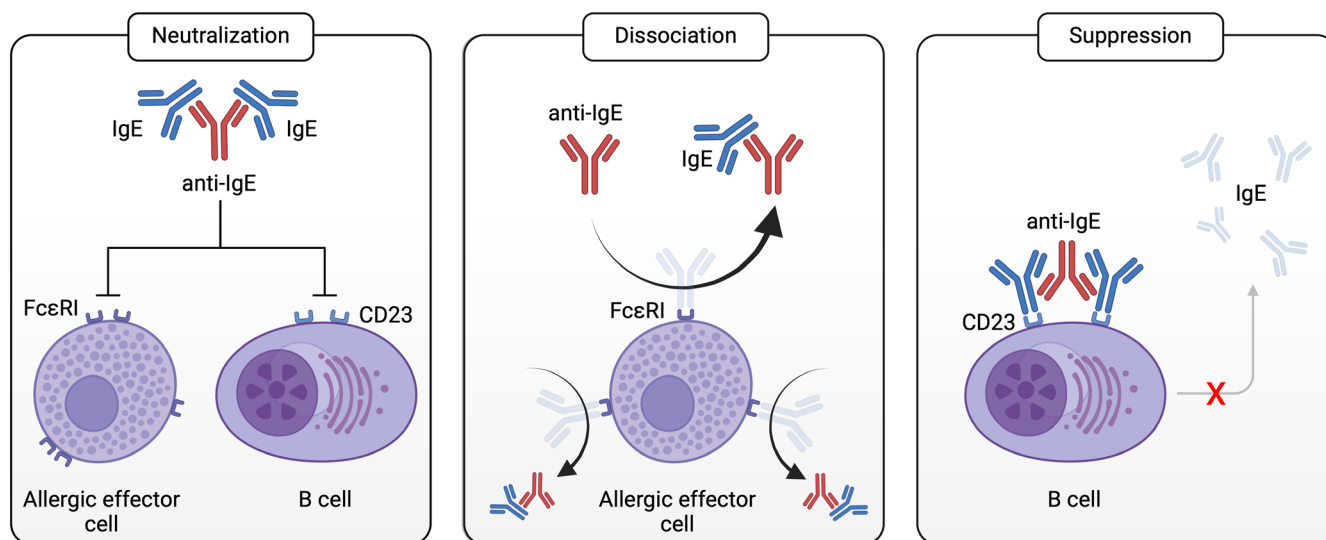


FIGURE 3 Monoclonal anti-IgE antibodies with multiple modes-of-action. Binding of IgE and blocking its interaction with both the high-affinity receptor FcεRIα and the low-affinity receptor CD23 is the most classical characteristic of a therapeutic anti-IgE antibody (left panel). More recently, anti-IgE antibodies have been described, which can actively remove (dissociate) pre-complexed IgE from its high-affinity receptor FcεRIα on allergic effector cells including basophils, mast cells and dendritic cells (middle panel). Some anti-IgE antibodies suppress IgE production in B-cells, most likely through a mechanism involving the binding of IgE:CD23 complexes on the cell surface (right panel). Next-generation anti-IgE antibodies should ideally feature a combination of all these modes-of-action to exhibit maximal therapeutic efficacy.

TABLE 3 Modes-of action comparison for different anti-IgE biologicals.

Anti-IgE biological	Blocking of IgE:FcεRIα	Blocking of IgE:CD23	Disruption of IgE:FcεRIα	Suppression of IgE production
Omalizumab	++	++	+	–
Ligelizumab	+++	+	–	++
HAE1	+++	++*	++	n.a.
Quilizumab	–	–	–	+++
Xmab7195	+++	++	+	++
UB221	+++	–	n.a.	+++
IgE _{Trap} -Fc	+++	–	+	n.a.
C02-H2L2	+++	++*	++	n.a.
AB1904Am15	++	++*	n.a.	n.a.
KIH_E07_79	++	++	+++	++
NIgG4B1A1(G4S)	++	n.a.	+++	n.a.

Note: * inferred from shared epitope with omalizumab.

Abbreviations: efficacy scale: – = absent; + = moderate; ++ = strong; +++ = very strong; n.a., not available.

intralymphatic). Starting out with minute concentrations of allergen, decreases the risk of a systemic reaction. Once a certain maintenance dose is achieved repetitive administration is required to achieve clinical benefit. The overarching goal of the treatment is to shift the allergy prone Th2-dominated immune response towards protective Th1 immunity including the induction of regulatory T cells and allergen-specific IgG antibodies. As suggested in the guidelines, the treatment duration typically spans 3–5 years.²¹⁵ This long-term therapy, results in sustained unresponsiveness and prolonged amelioration of allergic symptoms in a fraction of patients.^{216,217} To increase the safety of AIT and to investigate whether there might be synergistic effects between anti-IgE therapy and AIT, Kuehr et al.²¹⁸ conducted the first clinical trial in which omalizumab was combined with AIT. This randomized, double-blind, placebo-controlled, multi-site study 221 patients suffering from birch and grass pollen-induced seasonal allergic rhinitis. Their results demonstrated that omalizumab conferred a protective effect with different types of allergens and significantly increased the clinical benefit when compared to AIT alone. Many follow-up studies used omalizumab as pretreatment and/or adjunct therapy for AIT mainly in aero, hymenoptera and food allergy,²¹⁹ with the rationale of reducing IgE levels before introducing the allergen to reduce the risk of adverse reactions. Increased safety of AIT upon omalizumab combination has been reported for several of these investigations,^{220–222} however, omalizumab is not yet officially approved for such combination therapy. The OUTMATCH study, a large multicenter clinical trial in food allergy, is currently assessing the benefits of omalizumab adjunct therapy in AIT in a systematic manner.²²³

The efficacy of combined anti-IL-4 therapy with a suboptimal dose of grass pollen subcutaneous immunotherapy to induce sustained tolerance to allergen in seasonal allergic rhinitis patients was assessed in a randomized, double-blind clinical trial. Using allergen-induced skin late-phase response as surrogate marker of therapeutic response, no additional benefit over SCIT alone could be found.²²⁴ Compared to combination therapy using anti-IgE and AIT, current data indicate that IL-4 targeting in conjunction with AIT appears less promising.

4.2.2 | BCMAxCD3 bispecific antibody

B cell maturation antigen (BCMA) is a tumor necrosis factor (TNF) family receptor specifically expressed on plasma B cells (PCs) playing a major role in their survival. The bispecific anti-BCMA/anti-CD3 antibody linvoseltamab (BCMAxCD3) developed at Regeneron to treat multiple myeloma simultaneously engages PCs and T cells inducing T cell mediated killing of the PCs.²²⁵ Recently a novel concept using this antibody to broadly target and remove long-lived PCs in an isotype independent manner combined with blockade of the IL4R α to durably reverse IgE-mediated allergy has been suggested.²²⁶ In a long-term house dust mite sensitization model (>15 weeks) in mice expressing human BCMA and human CD3, application of linvoseltamab efficiently

depleted bone marrow plasma cells (BMPCs). Importantly, all immunoglobulin isotypes (i.e., IgA, IgM, IgE and IgG1) were significantly reduced 1 week following the treatment. Antibody levels recovered to pre-treatment baseline values within 3–5 weeks under continuation of HDM-sensitization. To specifically prevent this rebound effect for IgE, BCMAxCD3 treatment was combined with anti-IL4R α antibody injections. Indeed, sustained suppression of IgE levels was observed, while the other antibody levels reached baseline levels within 9 weeks post BCMAxCD3 application. Systemic challenge of mice undergoing a 14-week HDM sensitization and combined treatment of BCMAxCD3 with anti-IL4R α antibodies did not show any signs of anaphylaxis. Further, the combination of BCMAxCD3 and anti-IL4R α antibody treatment on resting IgE levels in cynomolgus monkeys was tested. In line with results in the mice, an initial drop in IgE and IgA levels with the BCMAxCD3 single treatment was observed. The levels normalized to baseline between 50 and 100 days post injection. Prolonged suppression of IgE was only achieved in the combination treatment. The bispecific BCMAxCD3 antibody was assessed for its ability to eliminate PCs from human PBMCs and BM samples. The antibody specifically ablated PCs but not other B cell subsets in these samples, which is in line with specific BCMA expression on PCs. When culturing BM samples from allergic and nonallergic donors in vitro IgE only accumulated in the culture supernatants of allergic donors. The production of IgE in these samples was fully suppressed upon bispecific BCMAxCD3 antibody treatment. Additionally, initial human data from clinical trials in multiple myeloma patients who received weekly administration of bispecific BCMAxCD3 antibody indicated that IgE levels are completely reduced as early as 4 weeks posttreatment. These data suggest that transient PC ablation using a BCMAxCD3 bispecific antibody combined with persistent inhibition of IgE class switching using an anti-IL4R α antibody might be a promising strategy to achieve IgE depletion. However, there are many questions remaining about the potential risks associated with transient depletion of all immunoglobulins.

4.2.3 | Combination of approved biologicals

When a single biologic is ineffective or insufficient for the management of a given allergic condition within 4 months of treatment, guidelines generally recommended switching to an alternative option¹⁹⁷ instead of adding another therapy. However, interfering with multiple pathophysiological pathways could be beneficial in some patients with mixed allergic phenotypes and/or endotypes. While systematic studies about efficacy and safety of combination therapies are still missing, there are currently around 38 case reports and case series^{227–234} providing insight into the use of dual biologics in co-occurring asthma and atopic dermatitis. These mostly include combinations of (i) omalizumab with add-on dupilumab/mepolizumab or (ii) benralizumab with add-on dupilumab. Improved efficacy of dual biologic therapy has been reported in 21 cases and no major adverse events or safety signals were observed so far.²³⁵ However, further systematic trials and cost-effectiveness evaluations²³⁶ are

required to make a conclusive statement about the usefulness of these approaches.

5 | CONCLUSIONS

The increasingly detailed understanding of the molecular and cellular mechanisms underlying allergic disorders has significantly shaped and advanced the development of therapeutic intervention strategies. Monoclonal antibodies are particularly interesting in this context due to their favorable properties, including long serum half-life, high specificity, customizable affinity and efficacy as well as generally favorable safety profile.²³⁷ Compared to more traditional treatment approaches, such as the use of corticosteroids, monoclonal antibodies can target key components involved in the allergic cascade with higher precision, resulting in fewer side effects and potentially more favorable clinical outcomes. Moreover, molecular engineering has enabled the structural fine-tuning of monoclonal antibodies for specific therapeutic actions and at the same time helped to minimize immunogenicity.^{238,239} Additionally, the production and manufacturing of monoclonal antibodies have significantly evolved over the years.²⁴⁰ Today, there are established, standardized procedures and protocols that ensure consistency and quality in antibody production. The increasing expertise and advancements in biotechnology have streamlined manufacturing pipelines, allowing for the efficient production of monoclonal antibodies used to treat a wide range of diseases.²⁴¹ This standardization and accumulated know-how have enabled the reliable and scalable production of these therapeutic agents, ensuring their availability and effectiveness in clinical settings.

Different monoclonal antibody-based therapies have demonstrated efficacy across a spectrum of allergic conditions, including asthma, atopic dermatitis, chronic spontaneous urticaria, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis and food allergies, underscoring the central role of IgE, type 2 cytokine pathways and alarmins in allergy pathophysiology. Having the choice between multiple approved treatment options enables tailoring therapeutic strategies to individual disease endotypes in a personalized medicine approach. Whether combination therapies will be approved and implemented on a routinely basis in this context is rather unlikely due to associated costs and uncertainties about potential risks of such co-treatments. However, there might be an opportunity for newly developed multispecific drugs that simultaneously target different pathways in the allergic cascade. In addition, the combination of anti-IgE therapy with AIT presents a promising therapeutic avenue. Clinical studies have shown that adjunct use of omalizumab can enhance the safety and efficacy of AIT by reducing the risk of adverse reactions during allergen exposure. This combination strategy holds potential for achieving more durable tolerance to allergens and improving clinical outcomes.

Targeting type 2 cytokine pathways, specifically functions of IL-4, IL-5, and IL-13, holds considerable promise for the treatment

of allergic disorders. This approach has already demonstrated substantial potential in effectively controlling allergic inflammation with dupilumab, benralizumab, mepolizumab and reslizumab. By modulating the activity of these cytokines, therapies can significantly reduce symptoms and enhance the quality of life for patients. However, our understanding of type 2 cytokine signaling is still evolving, and there are gaps in knowledge regarding the full range of functions and interactions of these cytokines. Therefore, the long-term safety profile of cytokine-targeted therapies should remain under investigation. While short-term benefits are evident, potential risks associated with chronic use need to be thoroughly evaluated.

By blocking the activity of alarmins, it is possible to disrupt early stages of allergic inflammation. While targeting TSLP signaling pathways has demonstrated successful treatment outcomes, alarmins are also involved in various physiological processes beyond allergic inflammation and their inhibition could potentially disrupt homeostatic immune functions. While generally providing a promising approach, potential risks, such as impaired tissue repair mechanisms should be further evaluated in this context, especially upon long-term treatment.

The identification of allergen-specific IgE as a crucial factor in the pathogenesis of most allergic conditions led to the conceptualization of therapeutic anti-IgE antibodies.^{68,84} Subsequent development efforts mainly focused on generating potentially neutralizing, non-anaphylactogenic monoclonal antibodies, specifically targeting free serum IgE rather than FcεRIα-bound cell surface IgE. The primary goal was to block IgE:FcεRIα interactions, with less emphasis on preventing IgE binding to CD23. The development and approval of omalizumab marked a significant breakthrough in the management of allergic diseases. However, the numerous unsuccessful attempts to develop a next-generation monoclonal anti-IgE antibody suggest that our understanding of the essential functional characteristics for an optimized anti-IgE antibody remains incomplete. For instance, omalizumab's potential to actively disrupt pre-existing IgE:FcεRIα complexes on the surface of allergic effector cells has only recently been described. This raises the question: does the ability to dissociate IgE from its high-affinity receptor contribute to omalizumab's therapeutic efficacy? Remarkably, over 20 years later, omalizumab remains the only approved therapeutic anti-IgE antibody, prompting further questions: Does the weaker inhibitory activity of ligelizumab in blocking IgE:CD23 interactions limit its therapeutic benefit? What role does in vivo biodistribution play in targeting locally produced IgE in different tissues? Are the size and half-life of IgE:anti-IgE complexes important in acting as additional allergen sinks? Future research and development efforts should address these unknowns and pave the way for new therapeutic strategies. At this point, results from basic research strongly suggest that next-generation anti-IgE biologicals will have to optimize more than one mode-of-action to leverage synergistic effects and achieve more complete suppression of the allergic response. It is conceivable that combining those different molecular features into a single antibody

or antibody-like protein could bring the next revolution in allergy disease management.

In conclusion, the continued exploration of the intricate cellular and molecular network involved in allergic responses is crucial for developing next-generation treatments. These advancements hold the potential to provide more effective, safe, and tailored therapeutic options, ultimately improving the quality of life for patients suffering from various allergic diseases. As research progresses, the integration of personalized medicine approaches, leveraging biomarkers to guide treatment selection, will be essential in optimizing clinical outcomes and addressing the diverse needs of allergy patients.

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CONFLICT OF INTEREST STATEMENT

LFP, TSJ and AE are co-founders and shareholders of Excellergy, Inc.—a company developing novel therapeutic molecules to treat allergic disorders. AE is a co-founder and shareholder of ATANIS Biotech AG—a company developing allergy diagnostic tests.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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REFERENCES

- Ishizaka K, Ishizaka T. Identification of gamma-E-antibodies as a carrier of reagenic activity. *J Immunol Baltim Md*. 1967;99(6):1187-1198.
- Stanworth DR, Humphrey JH, Bennich H, Johansson SGO. Specific inhibition of the Prausnitz-Küstner reaction by an atypical human myeloma protein. *Lancet*. 1967;290(7511):330-332. doi:[10.1016/s0140-6736\(67\)90171-7](https://doi.org/10.1016/s0140-6736(67)90171-7)
- Platts-Mills TAE, Heymann PW, Commins SP, Woodfolk JA. The discovery of IgE 50 years later. *Ann Allergy Asthma Immunol*. 2016;116(3):179-182. doi:[10.1016/j.anai.2016.01.003](https://doi.org/10.1016/j.anai.2016.01.003)
- Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature*. 2008;454(7203):445-454. doi:[10.1038/nature07204](https://doi.org/10.1038/nature07204)
- Kopp EB, Agaronyan K, Licona-Limón I, Nish SA, Medzhitov R. Modes of type 2 immune response initiation. *Immunity*. 2023;56(4):687-694. doi:[10.1016/j.immuni.2023.03.015](https://doi.org/10.1016/j.immuni.2023.03.015)
- Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751. doi:[10.1038/s41577-021-00538-7](https://doi.org/10.1038/s41577-021-00538-7)
- Akdis CA. The epithelial barrier hypothesis proposes a comprehensive understanding of the origins of allergic and other chronic noncommunicable diseases. *J Allergy Clin Immunol*. 2022;149(1):41-44. doi:[10.1016/j.jaci.2021.11.010](https://doi.org/10.1016/j.jaci.2021.11.010)
- Ito T, Wang YH, Duramad O, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med*. 2005;202(9):1213-1223. doi:[10.1084/jem.20051135](https://doi.org/10.1084/jem.20051135)
- Murakami-Satsutani N, Ito T, Nakanishi T, et al. IL-33 promotes the induction and maintenance of Th2 immune responses by enhancing the function of OX40 ligand. *Allergol Int*. 2014;63(3):443-455. doi:[10.2332/allergolint.13-0a-0672](https://doi.org/10.2332/allergolint.13-0a-0672)
- Dyken SJV, Nussbaum JC, Lee J, et al. A tissue checkpoint regulates type 2 immunity. *Nat Immunol*. 2016;17(12):1381-1387. doi:[10.1038/ni.3582](https://doi.org/10.1038/ni.3582)
- Gauvreau GM, Bergeron C, Boulet L, et al. Sounding the alarmins—the role of alarmin cytokines in asthma. *Allergy*. 2023;78(2):402-417. doi:[10.1111/all.15609](https://doi.org/10.1111/all.15609)
- Ebina-Shibuya R, Leonard WJ. Role of thymic stromal lymphopoietin in allergy and beyond. *Nat Rev Immunol*. 2023;23(1):24-37. doi:[10.1038/s41577-022-00735-y](https://doi.org/10.1038/s41577-022-00735-y)
- Borowczyk J, Shutova M, Brembilla NC, Boehncke WH. IL-25 (IL-17E) in epithelial immunology and pathophysiology. *J Allergy Clin Immunol*. 2021;148(1):40-52. doi:[10.1016/j.jaci.2020.12.628](https://doi.org/10.1016/j.jaci.2020.12.628)
- Scott IC, Majithiya JB, Sanden C, et al. Interleukin-33 is activated by allergen- and necrosis-associated proteolytic activities to regulate its alarmin activity during epithelial damage. *Sci Rep*. 2018;8(1):3363. doi:[10.1038/s41598-018-21589-2](https://doi.org/10.1038/s41598-018-21589-2)
- Lefrançois E, Duval A, Mirey E, et al. Central domain of IL-33 is cleaved by mast cell proteases for potent activation of group-2 innate lymphoid cells. *Proc Natl Acad Sci*. 2014;111(43):15502-15507. doi:[10.1073/pnas.1410700111](https://doi.org/10.1073/pnas.1410700111)
- Minutti CM, Drube S, Blair N, et al. Epidermal growth factor receptor expression licenses Type-2 helper T cells to function in a T cell receptor-independent fashion. *Immunity*. 2017;47(4):710-722. e6. doi:[10.1016/j.immuni.2017.09.013](https://doi.org/10.1016/j.immuni.2017.09.013)
- Vannella KM, Ramalingam TR, Borthwick LA, et al. Combinatorial targeting of TSLP, IL-25, and IL-33 in type 2 cytokine-driven inflammation and fibrosis. *Sci Transl Med*. 2016;8(337):337ra65. doi:[10.1126/scitranslmed.aaf1938](https://doi.org/10.1126/scitranslmed.aaf1938)
- Verstraete K, Peelman F, Braun H, et al. Structure and antagonism of the receptor complex mediated by human TSLP in allergy and asthma. *Nat Commun*. 2017;8(1):14937. doi:[10.1038/ncomms14937](https://doi.org/10.1038/ncomms14937)
- Liu X, Hammel M, He Y, et al. Structural insights into the interaction of IL-33 with its receptors. *Proc Natl Acad Sci*. 2013;110(37):14918-14923. doi:[10.1073/pnas.1308651110](https://doi.org/10.1073/pnas.1308651110)
- Wilson SC, Caveney NA, Yen M, et al. Organizing structural principles of the IL-17 ligand-receptor axis. *Nature*. 2022;609(7927):622-629. doi:[10.1038/s41586-022-05116-y](https://doi.org/10.1038/s41586-022-05116-y)
- Duchesne M, Okoye I, Lacy P. Epithelial cell alarmin cytokines: frontline mediators of the asthma inflammatory response. *Front Immunol*. 2022;13:975914. doi:[10.3389/fimmu.2022.975914](https://doi.org/10.3389/fimmu.2022.975914)
- Liang HE, Reinhardt RL, Bando JK, Sullivan BM, Ho IC, Locksley RM. Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. *Nat Immunol*. 2012;13(1):58-66. doi:[10.1038/ni.2182](https://doi.org/10.1038/ni.2182)
- Neill DR, Wong SH, Bellosi A, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature*. 2010;464(7293):1367-1370. doi:[10.1038/nature08900](https://doi.org/10.1038/nature08900)
- Price AE, Liang HE, Sullivan BM, et al. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci*. 2010;107(25):11489-11494. doi:[10.1073/pnas.1003988107](https://doi.org/10.1073/pnas.1003988107)
- Bernstein ZJ, Shenoy A, Chen A, Heller NM, Spangler JB. Engineering the IL-4/IL-13 axis for targeted immune modulation. *Immunol Rev*. 2023;320(1):29-57. doi:[10.1111/imr.13230](https://doi.org/10.1111/imr.13230)
- Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signaling through the IL-13 α 2 receptor is involved in induction

- of TGF- β 1 production and fibrosis. *Nat Med*. 2006;12(1):99-106. doi:[10.1038/nm1332](https://doi.org/10.1038/nm1332)
27. He JS, Subramaniam S, Narang V, et al. IgG1 memory B cells keep the memory of IgE responses. *Nat Commun*. 2017;8(1):641. doi:[10.1038/s41467-017-00723-0](https://doi.org/10.1038/s41467-017-00723-0)
 28. Caveney NA, Rodriguez GE, Pollmann C, et al. Structure of the interleukin-5 receptor complex exemplifies the organizing principle of common beta cytokine signaling. *Mol Cell*. 2024;84(10):1995-2005.e7. doi:[10.1016/j.molcel.2024.03.023](https://doi.org/10.1016/j.molcel.2024.03.023)
 29. Dagher R, Kumar V, Copenhaver AM, et al. Novel mechanisms of action contributing to benralizumab's potent anti-eosinophilic activity. *Eur Respir J*. 2022;59(3):2004306. doi:[10.1183/13993003.04306-2020](https://doi.org/10.1183/13993003.04306-2020)
 30. Borkowski TA, Jouvin MH, Lin SY, Kinet JP. Minimal requirements for IgE-mediated regulation of surface fc epsilon RI. *J Immunol*. 2001;167(3):1290-1296. <http://www.jimmunol.org/cgi/content/full/167/3/1290>
 31. Greer AM, Wu N, Putnam AL, et al. Serum IgE clearance is facilitated by human Fc ϵ RI internalization. *J Clin Invest*. 2014;124(3):1187-1198. doi:[10.1172/jci68964](https://doi.org/10.1172/jci68964)
 32. Holdom MD, Davies AM, Nettlehip JE, et al. Conformational changes in IgE contribute to its uniquely slow dissociation rate from receptor Fc ϵ RI. *Nat Struct Mol Biol*. 2011;18(5):571-576. doi:[10.1038/nsmb.2044](https://doi.org/10.1038/nsmb.2044)
 33. Lua WH, Su CTT, Yeo JY, et al. Role of the IgE variable heavy chain in Fc ϵ RI α and superantigen binding in allergy and immunotherapy. *J Allergy Clin Immunol*. 2019;144(2):514-523.e5. doi:[10.1016/j.jaci.2019.03.028](https://doi.org/10.1016/j.jaci.2019.03.028)
 34. Blank U, Ra CS, Kinet JP. Characterization of truncated alpha chain products from human, rat, and mouse high affinity receptor for immunoglobulin E. *J Biol Chem*. 1991;266(4):2639-2646. doi:[10.1016/s0021-9258\(18\)52292-4](https://doi.org/10.1016/s0021-9258(18)52292-4)
 35. Kiyoshi M, Caaveiro JMM, Kawai T, et al. Structural basis for binding of human IgG1 to its high-affinity human receptor Fc γ RI. *Nat Commun*. 2015;6(1):6866. doi:[10.1038/ncomms7866](https://doi.org/10.1038/ncomms7866)
 36. Lawrence MG, Woodfolk JA, Schuyler AJ, Stillman LC, Chapman MD, Platts-Mills TAE. Half-life of IgE in serum and skin: consequences for anti-IgE therapy in patients with allergic disease. *J Allergy Clin Immunol*. 2017;139(2):422-428.e4. doi:[10.1016/j.jaci.2016.04.056](https://doi.org/10.1016/j.jaci.2016.04.056)
 37. Kubo S, Nakayama T, Matsuoka K, Yonekawa H, Karasuyama H. Long term maintenance of IgE-mediated memory in mast cells in the absence of detectable serum IgE. *J Immunol*. 2003;170(2):775-780. doi:[10.4049/jimmunol.170.2.775](https://doi.org/10.4049/jimmunol.170.2.775)
 38. Hoh RA, Boyd SD. Gut mucosal antibody responses and implications for food allergy. *Front Immunol*. 2018;9:2221. doi:[10.3389/fimmu.2018.02221](https://doi.org/10.3389/fimmu.2018.02221)
 39. Schryver ED, Devuyst L, Derycke L, et al. Local immunoglobulin E in the nasal mucosa: clinical implications. *Allergy, Asthma Immunol Res*. 2015;7(4):321-331. doi:[10.4168/air.2015.7.4.321](https://doi.org/10.4168/air.2015.7.4.321)
 40. Hjort C, Schiøtz PO, Ohlin M, Würtzen PA, Christensen LH, Hoffmann HJ. The number and affinity of productive IgE pairs determine allergen activation of mast cells. *J Allergy Clin Immunol*. 2017;140(4):1167-1170.e2. doi:[10.1016/j.jaci.2017.04.014](https://doi.org/10.1016/j.jaci.2017.04.014)
 41. Christensen LH, Holm J, Lund G, Riise E, Lund K. Several distinct properties of the IgE repertoire determine effector cell degranulation in response to allergen challenge. *J Allergy Clin Immunol*. 2008;122(2):298-304. doi:[10.1016/j.jaci.2008.05.026](https://doi.org/10.1016/j.jaci.2008.05.026)
 42. Hoh RA, Joshi SA, Lee JY, et al. Origins and clonal convergence of gastrointestinal IgE⁺ B cells in human peanut allergy. *Sci Immunol*. 2020;5(45). doi:[10.1126/sciimmunol.aay4209](https://doi.org/10.1126/sciimmunol.aay4209)
 43. Eckl-Dorna J, Pree I, Reisinger J, et al. The majority of allergen-specific IgE in the blood of allergic patients does not originate from blood-derived B cells or plasma cells. *Clin Exp Allergy*. 2012;42(9):1347-1355. doi:[10.1111/j.1365-2222.2012.04030.x](https://doi.org/10.1111/j.1365-2222.2012.04030.x)
 44. Yoshida T, Usui A, Kusumi T, et al. A quantitative analysis of cedar pollen-specific immunoglobulins in nasal lavage supported the local production of specific IgE, not of specific IgG. *Microbiol Immunol*. 2005;49(6):529-534. doi:[10.1111/j.1348-0421.2005.tb03758.x](https://doi.org/10.1111/j.1348-0421.2005.tb03758.x)
 45. Gauvreau GM, Arm JP, Boulet LP, et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. *J Allergy Clin Immunol*. 2016;138(4):1051-1059. doi:[10.1016/j.jaci.2016.02.027](https://doi.org/10.1016/j.jaci.2016.02.027)
 46. Henault J, Riggs JM, Karnell JL, et al. Self-reactive IgE exacerbates interferon responses associated with autoimmunity. *Nat Immunol*. 2016;17(2):196-203. doi:[10.1038/ni.3326](https://doi.org/10.1038/ni.3326)
 47. Henningsson F, Ding Z, Dahlin JS, et al. IgE-mediated enhancement of CD4⁺ T cell responses in mice requires antigen presentation by CD11c⁺ cells and not by B cells. *PLoS One*. 2011;6(7):e21760. doi:[10.1371/journal.pone.0021760](https://doi.org/10.1371/journal.pone.0021760)
 48. López-Abente J, Benito-Villalvilla C, Jaumont X, Pfister P, Tassinari P, Palomares O. Omalizumab restores the ability of human plasmacytoid dendritic cells to induce Foxp3⁺Tregs. *Eur Respir J*. 2021;57(1):2000751. doi:[10.1183/13993003.00751-2020](https://doi.org/10.1183/13993003.00751-2020)
 49. Burton OT, Oettgen HC. Beyond immediate hypersensitivity: evolving roles for IgE antibodies in immune homeostasis and allergic diseases. *Immunol Rev*. 2011;242(1):128-143. doi:[10.1111/j.1600-065x.2011.01024.x](https://doi.org/10.1111/j.1600-065x.2011.01024.x)
 50. Burton OT, Rivas MN, Zhou JS, et al. Immunoglobulin E signal inhibition during allergen ingestion leads to reversal of established food allergy and induction of regulatory T cells. *Immunity*. 2014;41(1):141-151. doi:[10.1016/j.immuni.2014.05.017](https://doi.org/10.1016/j.immuni.2014.05.017)
 51. Baravalle G, Greer AM, LaFlam TN, Shin JS. Antigen-conjugated human IgE induces antigen-specific T cell tolerance in a humanized mouse model. *J Immunol*. 2014;192(7):3280-3288. doi:[10.4049/jimmunol.1301751](https://doi.org/10.4049/jimmunol.1301751)
 52. Yang PC, Berin MC, Yu LCH, Conrad DH, Perdue MH. Enhanced intestinal transepithelial antigen transport in allergic rats is mediated by IgE and CD23 (Fc ϵ RII). *J Clin Invest*. 2000;106(7):879-886. doi:[10.1172/jci9258](https://doi.org/10.1172/jci9258)
 53. Tu Y, Salim S, Bourgeois J, et al. CD23-mediated IgE transport across human intestinal epithelium: inhibition by blocking sites of translation or binding. *Gastroenterology*. 2005;129(3):928-940. doi:[10.1053/j.gastro.2005.06.014](https://doi.org/10.1053/j.gastro.2005.06.014)
 54. Palaniyandi S, Tomei E, Li Z, Conrad DH, Zhu X. CD23-dependent Transcytosis of IgE and immune complex across the polarized human respiratory epithelial cells. *J Immunol*. 2011;186(6):3484-3496. doi:[10.4049/jimmunol.1002146](https://doi.org/10.4049/jimmunol.1002146)
 55. Palaniyandi S, Liu X, Periasamy S, et al. Inhibition of CD23-mediated IgE transcytosis suppresses the initiation and development of allergic airway inflammation. *Mucosal Immunol*. 2015;8(6):1262-1274. doi:[10.1038/mi.2015.16](https://doi.org/10.1038/mi.2015.16)
 56. Getahun A, Hjelm F, Heyman B. IgE enhances antibody and T cell responses in vivo via CD23⁺ B cells. *J Immunol*. 2005;175(3):1473-1482. doi:[10.4049/jimmunol.175.3.1473](https://doi.org/10.4049/jimmunol.175.3.1473)
 57. Heyman B, Tianmin L, Gustavsson S. In vivo enhancement of the specific antibody response via the low-affinity receptor for IgE. *Eur J Immunol*. 1993;23(7):1739-1742. doi:[10.1002/eji.1830230754](https://doi.org/10.1002/eji.1830230754)
 58. Ding Z, Dahlin JS, Xu H, Heyman B. IgE-mediated enhancement of CD4⁺ T cell responses requires antigen presentation by CD8 α ⁻ conventional dendritic cells. *Sci Rep*. 2016;6(1):28290. doi:[10.1038/srep28290](https://doi.org/10.1038/srep28290)
 59. Martin RK, Brooks KB, Henningsson F, Heyman B, Conrad DH. Antigen transfer from exosomes to dendritic cells as an explanation for the immune enhancement seen by IgE immune complexes. *PLoS One*. 2014;9(10):e110609. doi:[10.1371/journal.pone.0110609](https://doi.org/10.1371/journal.pone.0110609)

60. Engeroff P, Fellmann M, Yerly D, Bachmann MF, Vogel M. A novel recycling mechanism of native IgE-antigen complexes in human B cells facilitates transfer of antigen to dendritic cells for antigen presentation. *J Allergy Clin Immunol*. 2017;23:557-568.e6. doi:[10.1016/j.jaci.2017.09.024](https://doi.org/10.1016/j.jaci.2017.09.024)
61. Lennartsson J, Rönnstrand L. Stem cell factor receptor/c-kit: from basic science to clinical implications. *Physiol Rev*. 2012;92(4):1619-1649. doi:[10.1152/physrev.00046.2011](https://doi.org/10.1152/physrev.00046.2011)
62. Yuzawa S, Opatowsky Y, Zhang Z, Mandiyan V, Lax I, Schlessinger J. Structural basis for activation of the receptor tyrosine kinase KIT by stem cell factor. *Cell*. 2007;130(2):323-334. doi:[10.1016/j.cell.2007.05.055](https://doi.org/10.1016/j.cell.2007.05.055)
63. Tsai M, Valent P, Galli SJ. KIT as a master regulator of the mast cell lineage. *J Allergy Clin Immunol*. 2022;149(6):1845-1854. doi:[10.1016/j.jaci.2022.04.012](https://doi.org/10.1016/j.jaci.2022.04.012)
64. Crocker PR, Paulson JC, Varki A. Siglecs and their roles in the immune system. *Nat Rev Immunol*. 2007;7(4):255-266. doi:[10.1038/nri2056](https://doi.org/10.1038/nri2056)
65. Macauley MS, Crocker PR, Paulson JC. Siglec-mediated regulation of immune cell function in disease. *Nat Rev Immunol*. 2014;14(10):653-666. doi:[10.1038/nri3737](https://doi.org/10.1038/nri3737)
66. Smiljkovic D, Herrmann H, Sadovnik I, et al. Expression and regulation of Siglec-6 (CD327) on human mast cells and basophils. *J Allergy Clin Immunol*. 2023;151(1):202-211. doi:[10.1016/j.jaci.2022.07.018](https://doi.org/10.1016/j.jaci.2022.07.018)
67. Schanin J, Korver W, Brock EC, et al. Discovery of an agonistic Siglec-6 antibody that inhibits and reduces human mast cells. *Commun Biol*. 2022;5(1):1226. doi:[10.1038/s42003-022-04207-w](https://doi.org/10.1038/s42003-022-04207-w)
68. Chang TW. The pharmacological basis of anti-IgE therapy. *Nat Biotechnol*. 2000;18(2):157-162. doi:[10.1038/72601](https://doi.org/10.1038/72601)
69. Presta LG, Lahr SJ, Shields RL, et al. Humanization of an antibody directed against IgE. *J Immunol*. 1993;151(5):2623-2632. doi:[10.4049/jimmunol.151.5.2623](https://doi.org/10.4049/jimmunol.151.5.2623)
70. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med*. 1997;155(6):1828-1834. doi:[10.1164/ajrccm.155.6.9196082](https://doi.org/10.1164/ajrccm.155.6.9196082)
71. Boulet LP, Chapman KR, Côté J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med*. 1997;155(6):1835-1840. doi:[10.1164/ajrccm.155.6.9196083](https://doi.org/10.1164/ajrccm.155.6.9196083)
72. Milgrom H, Fick RB, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAB-E25 study group. *N Engl J Med*. 1999;341(26):1966-1973. <http://content.nejm.org/cgi/content/abstract/341/26/1966>
73. Barnes PJ. Anti-IgE therapy in asthma: rationale and therapeutic potential. *Int Arch Allergy Immunol*. 2000;123(3):196-204. doi:[10.1159/000024444](https://doi.org/10.1159/000024444)
74. Saini SS, MacGlashan DW, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. *J Immunol*. 1999;162(9):5624-5630. <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=10228046&retmode=ref&cmd=prlinks>
75. MacGlashan DW, Bochner BS, Adelman DC, et al. Down-regulation of f(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol*. 1997;158(3):1438-1445. <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9013989&retmode=ref&cmd=prlinks>
76. Saini SS, Richardson JJ, Wofsy C, Lavens-Phillips S, Bochner BS, MacGlashan DW. Expression and modulation of FcepsilonRIalpha and FcepsilonRIbeta in human blood basophils. *J Allergy Clin Immunol*. 2001;107(5):832-841. <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=11344350&retmode=ref&cmd=prlinks>
77. Pennington LF, Tarchevskaya S, Brigger D, et al. Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. *Nat Commun*. 2016;7(1):11610. doi:[10.1038/ncomms11610](https://doi.org/10.1038/ncomms11610)
78. Davies AM, Allan EG, Keeble AH, et al. Allosteric mechanism of action of the therapeutic anti-IgE antibody omalizumab. *J Biol Chem*. 2017;292(24):9975-9987. doi:[10.1074/jbc.m117.776476](https://doi.org/10.1074/jbc.m117.776476)
79. Eggel A, Baravalle G, Hobi G, et al. Accelerated dissociation of IgE-FcεRI complexes by disruptive inhibitors actively desensitizes allergic effector cells. *J Allergy Clin Immunol*. 2014;133(6):1709-1719.e8. doi:[10.1016/j.jaci.2014.02.005](https://doi.org/10.1016/j.jaci.2014.02.005)
80. Gasser P, Tarchevskaya SS, Guntern P, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun*. 2020;11(1):1-14. doi:[10.1038/s41467-019-13815-w](https://doi.org/10.1038/s41467-019-13815-w)
81. Pennington LF, Gasser P, Brigger D, Guntern P, Eggel A, Jardetzky TS. Structure-guided design of ultrapotent disruptive IgE inhibitors to rapidly terminate acute allergic reactions. *J Allergy Clin Immunol*. 2021;148(4):1049-1060. doi:[10.1016/j.jaci.2021.03.050](https://doi.org/10.1016/j.jaci.2021.03.050)
82. Racine-Poon A, Botta L, Chang TW, et al. Efficacy, pharmacodynamics, and pharmacokinetics of CGP 51901, an anti-immunoglobulin E chimeric monoclonal antibody, in patients with seasonal allergic rhinitis. *Clin Pharmacol Ther*. 1997;62(6):675-690. doi:[10.1016/s0009-9236\(97\)90087-4](https://doi.org/10.1016/s0009-9236(97)90087-4)
83. Davis FM, Gossett LA, Pinkston KL, et al. Can anti-IgE be used to treat allergy? *Springer Semin Immunopathol*. 1993;15(1):51-73. doi:[10.1007/bf00204626](https://doi.org/10.1007/bf00204626)
84. Heusser C, Jardieu P. Therapeutic potential of anti-IgE antibodies. *Curr Opin Immunol*. 1997;9(6):805-813. <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9492982&retmode=ref&cmd=prlinks>
85. Kolbinger F, Saldanha J, Hardman N, Bendig MM. Humanization of a mouse anti-human IgE antibody: a potential therapeutic for IgE-mediated allergies. *Protein Eng Des Sel*. 1993;6(8):971-980. doi:[10.1093/protein/6.8.971](https://doi.org/10.1093/protein/6.8.971)
86. Leung DYM, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med*. 2003;348(11):986-993. doi:[10.1056/nejmoa022613](https://doi.org/10.1056/nejmoa022613)
87. Leung DYM, Shanahan WR, Li XM, Sampson HA. New approaches for the treatment of anaphylaxis. *Novartis Found Symp*. 2004;257:248-260. discussion 260-4, 276-285.
88. Maurer M, Ensina LF, Gimenez-Arnau AM, et al. Efficacy and safety of ligelizumab in adults and adolescents with chronic spontaneous urticaria: results of two phase 3 randomised controlled trials. *Lancet*. 2024;403(10422):147-159. doi:[10.1016/s0140-6736\(23\)01684-7](https://doi.org/10.1016/s0140-6736(23)01684-7)
89. Trischler J, Bottoli I, Janocha R, et al. Ligelizumab treatment for severe asthma: learnings from the clinical development programme. *Clin Transl Immunol*. 2021;10(3):e1255. doi:[10.1002/cti2.1255](https://doi.org/10.1002/cti2.1255)
90. Maurer M, Giménez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous Urticaria. *N Engl J Med*. 2019;381(14):1321-1332. doi:[10.1056/nejmoa1900408](https://doi.org/10.1056/nejmoa1900408)
91. Coyle AJ, Wagner K, Bertrand C, Tsuyuki S, Bews J, Heusser C. Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. *J Exp Med*. 1996;183(4):1303-1310. doi:[10.1084/jem.183.4.1303](https://doi.org/10.1084/jem.183.4.1303)
92. Selb R, Eckl-Dorna J, Twaroch TE, et al. Critical and direct involvement of the CD23 stalk region in IgE binding. *J Allergy Clin Immunol*. 2017;139(1):281-289.e5. doi:[10.1016/j.jaci.2016.04.015](https://doi.org/10.1016/j.jaci.2016.04.015)
93. Selb R, Eckl-Dorna J, Neunkirchner A, et al. CD23 surface density on B cells is associated with IgE levels and determines IgE-facilitated allergen uptake, as well as activation of allergen-specific T cells.

- J Allergy Clin Immunol.* 2017;139(1):290-299.e4. doi:[10.1016/j.jaci.2016.03.042](https://doi.org/10.1016/j.jaci.2016.03.042)
94. Assayag M, Moshel S, Kohan M, Berkman N. The effect of omalizumab treatment on the low affinity immunoglobulin E receptor (CD23/fc epsilon RII) in patients with severe allergic asthma. *Allergy Asthma Proc.* 2017;39(1):36-42. doi:[10.2500/aap.2018.39.4106](https://doi.org/10.2500/aap.2018.39.4106)
 95. Yu LCH, Montagnac G, Yang PC, Conrad DH, Benmerah A, Perdue MH. Intestinal epithelial CD23 mediates enhanced antigen transport in allergy: evidence for novel splice forms. *Am J Physiol-Gastrointest Liver Physiol.* 2003;285(1):G223-G234. doi:[10.1152/ajpgi.00445.2002](https://doi.org/10.1152/ajpgi.00445.2002)
 96. Bevilacqua C, Montagnac G, Benmerah A, et al. Food allergens are protected from degradation during CD23-mediated Transepithelial transport. *Int Arch Allergy Immunol.* 2004;135(2):108-116. doi:[10.1159/000080653](https://doi.org/10.1159/000080653)
 97. Li H, Nowak-Węgrzyn A, Charlop-Powers Z, et al. Transcytosis of IgE-antigen complexes by CD23a in human intestinal epithelial cells and its role in food allergy. *Gastroenterology.* 2006;131(1):47-58. doi:[10.1053/j.gastro.2006.03.044](https://doi.org/10.1053/j.gastro.2006.03.044)
 98. Aubry JP, Pochon S, Graber P, Jansen KU, Bonnefoy JY. CD21 is a ligand for CD23 and regulates IgE production. *Nature.* 1992;358(6386):505-507. doi:[10.1038/358505a0](https://doi.org/10.1038/358505a0)
 99. Bonnefoy JY, Gauchat JF, Life P, Graber P, Aubry JP, Lecoanet-Henchos S. Regulation of IgE synthesis by CD23/CD21 interaction. *Int Arch Allergy Immunol.* 1995;107(1-3):40-42. doi:[10.1159/000236924](https://doi.org/10.1159/000236924)
 100. Putnam WS, Li J, Haggstrom J, et al. Use of quantitative pharmacology in the development of HAE1, a high-affinity anti-IgE monoclonal antibody. *AAPS J.* 2008;10(2):425-430. doi:[10.1208/s12248-008-9045-4](https://doi.org/10.1208/s12248-008-9045-4)
 101. Mortensen DL, Prabhu S, Stefanich EG, et al. Effect of antigen binding affinity and effector function on the pharmacokinetics and pharmacodynamics of anti-IgE monoclonal antibodies. *MAbs.* 2012;4(6):724-731. doi:[10.4161/mabs.22216](https://doi.org/10.4161/mabs.22216)
 102. Pennington LF, Gasser P, Kleinboelting S, et al. Directed evolution of and structural insights into antibody-mediated disruption of a stable receptor-ligand complex. *Nat Commun.* 2021;12(1):7016-7069. doi:[10.1038/s41467-021-27397-z](https://doi.org/10.1038/s41467-021-27397-z)
 103. Liour SS, Tom A, Chan Y, Chang TW. Treating IgE-mediated diseases via targeting IgE-expressing B cells using an anti-CemX antibody. *Pediatr Allergy Immunol.* 2016;27(5):446-451. doi:[10.1111/pai.12584](https://doi.org/10.1111/pai.12584)
 104. Laffleur B, Duchez S, Tarte K, et al. Self-restrained B cells Arise following membrane IgE expression. *Cell Rep.* 2015;10(6):900-909. doi:[10.1016/j.celrep.2015.01.023](https://doi.org/10.1016/j.celrep.2015.01.023)
 105. Ramadani F, Bowen H, Upton N, et al. Ontogeny of human IgE-expressing B cells and plasma cells. *Allergy.* 2016;72(1):66-76. doi:[10.1111/all.12911](https://doi.org/10.1111/all.12911)
 106. Chen JB, Wu PC, Hung AFH, et al. Unique epitopes on C epsilon mX in IgE-B cell receptors are potentially applicable for targeting IgE-committed B cells. *J Immunol.* 2010;184(4):1748-1756. doi:[10.4049/jimmunol.0902437](https://doi.org/10.4049/jimmunol.0902437)
 107. Brightbill HD, Jeet S, Lin Z, et al. Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice. *J Clin Invest.* 2010;120(6):2218-2229. doi:[10.1172/jci40141](https://doi.org/10.1172/jci40141)
 108. Chu HM, Wright J, Chan YH, Lin CJ, Chang TW, Lim C. Two potential therapeutic antibodies bind to a peptide segment of membrane-bound IgE in different conformations. *Nat Commun.* 2014;5:3139. doi:[10.1038/ncomms4139](https://doi.org/10.1038/ncomms4139)
 109. Brightbill H, Lin Y, Lin Z, et al. Quilizumab is an Afucosylated humanized anti-M1 prime therapeutic antibody. *Clin Anti-Inflamm Anti-Allergy Drugs.* 2014;1(1):24-31. doi:[10.2174/22127038114019990003](https://doi.org/10.2174/22127038114019990003)
 110. Gauvreau GM, Harris JM, Boulet LP, et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Sci Transl Med.* 2014;6(243):243ra85. doi:[10.1126/scitranslmed.3008961](https://doi.org/10.1126/scitranslmed.3008961)
 111. Harris JM, Maciuga R, Bradley MS, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. *Respir Res.* 2016;17(1):29. doi:[10.1186/s12931-016-0347-2](https://doi.org/10.1186/s12931-016-0347-2)
 112. Koenig JFE, Knudsen NPH, Phelps A, et al. Type 2-polarized memory B cells hold allergen-specific IgE memory. *Sci Transl Med.* 2024;16(733):eadi0944. doi:[10.1126/scitranslmed.adi0944](https://doi.org/10.1126/scitranslmed.adi0944)
 113. Ota M, Hoehn KB, Fernandes-Braga W, et al. CD23+IgG1+ memory B cells are poised to switch to pathogenic IgE production in food allergy. *Sci Transl Med.* 2024;16(733):eadi0673. doi:[10.1126/scitranslmed.adi0673](https://doi.org/10.1126/scitranslmed.adi0673)
 114. Saban R, Haak-Frendscho M, Zine M, et al. Human FcERI-IgG and humanized anti-IgE monoclonal antibody MaE11 block passive sensitization of human and rhesus monkey lung. *J Allergy Clin Immunol.* 1994;94(5):836-843. doi:[10.1016/0091-6749\(94\)90151-1](https://doi.org/10.1016/0091-6749(94)90151-1)
 115. Chu SY, Vostiar I, Karki S, et al. Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcγRIIb with fc-engineered antibodies. *Mol Immunol.* 2008;45(15):3926-3933. doi:[10.1016/j.molimm.2008.06.027](https://doi.org/10.1016/j.molimm.2008.06.027)
 116. Chu SY, Horton HM, Pong E, et al. Reduction of total IgE by targeted coengagement of IgE B-cell receptor and FcγRIIb with fc-engineered antibody. *J Allergy Clin Immunol.* 2012;129(4):1102-1115. doi:[10.1016/j.jaci.2011.11.029](https://doi.org/10.1016/j.jaci.2011.11.029)
 117. Shiung YY, Chiang CY, Chen JB, et al. An anti-IgE monoclonal antibody that binds to IgE on CD23 but not on high-affinity IgE.Fc receptors. *Immunobiology.* 2012;217(7):676-683. doi:[10.1016/j.imbio.2011.11.006](https://doi.org/10.1016/j.imbio.2011.11.006)
 118. Kuo BS, Li CH, Chen JB, et al. IgE-neutralizing UB-221 mAb, distinct from omalizumab and ligelizumab, exhibits CD23-mediated IgE downregulation and relieves urticaria symptoms. *J Clin Invest.* 2022;132(15). doi:[10.1172/jci157765](https://doi.org/10.1172/jci157765)
 119. An SB, Yang BG, Jang G, et al. Combined IgE neutralization and Bifidobacterium longum supplementation reduces the allergic response in models of food allergy. *Nat Commun.* 2022;13(1):5669. doi:[10.1038/s41467-022-33176-1](https://doi.org/10.1038/s41467-022-33176-1)
 120. Ye YM, Park JW, Kim SH, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of YH35324, a novel Long-acting high-affinity IgETrap-fc protein in subjects with atopy: results from the first-in-human study. *Int Immunopharmacol.* 2024;130:111706. doi:[10.1016/j.intimp.2024.111706](https://doi.org/10.1016/j.intimp.2024.111706)
 121. Fujiwara H, Kikutani H, Suematsu S, et al. The absence of IgE antibody-mediated augmentation of immune responses in CD23-deficient mice. *Proc Natl Acad Sci.* 1994;91(15):6835-6839. doi:[10.1073/pnas.91.15.6835](https://doi.org/10.1073/pnas.91.15.6835)
 122. Sarfati M, Delespesse G. Possible role of human lymphocyte receptor for IgE (CD23) or its soluble fragments in the in vitro synthesis of human IgE. *J Immunol (Baltim, Md: 1950).* 1988;141(7):2195-2199.
 123. Bonnefoy J, Shields J, Mermod J. Inhibition of human interleukin 4-induced IgE synthesis by a subset of anti-CD23/FcεRII monoclonal antibodies. *Eur J Immunol.* 1990;20(1):139-144. doi:[10.1002/eji.1830200120](https://doi.org/10.1002/eji.1830200120)
 124. Wakai M, Pasley P, Stoecker ZM, et al. Anti-CD23 monoclonal antibodies: comparisons of epitope specificities and modulating capacities for IgE binding and production. *Hybridoma.* 1993;12(1):25-43. doi:[10.1089/hyb.1993.12.25](https://doi.org/10.1089/hyb.1993.12.25)
 125. Nakamura T, Kloetzer WS, Brams P, et al. In vitro IgE inhibition in B cells by anti-CD23 monoclonal antibodies is functionally dependent on the immunoglobulin fc domain. *Int J Immunopharmacol.* 2000;22(2):131-141. <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=10684997&retmode=ref&cmd=prlinks>
 126. Campbell KA, Lees A, Finkelman FD, Conrad DH. Co-crosslinking FcεRII/CD23 and B cell surface immunoglobulin modulates B cell

- activation. *Eur J Immunol.* 1992;22(8):2107-2112. doi:[10.1002/eji.1830220822](https://doi.org/10.1002/eji.1830220822)
127. Sherr E, Macy E, Kimata H, Gilly M, Saxon A. Binding the low affinity fc epsilon R on B cells suppresses ongoing human IgE synthesis. *J Immunol.* 1989;142(2):481-489. <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/eflink.fcgi?dbfrom=pubmed&id=2521348&retmode=ref&cmd=prlinks>
 128. Flores-Romo L, Shields J, Humbert Y, et al. Inhibition of an in vivo antigen-specific IgE response by antibodies to CD23. *Science.* 1993;261(5124):1038-1041. doi:[10.1126/science.8351517](https://doi.org/10.1126/science.8351517)
 129. Rosenwasser LJ, Busse WW, Lizambri RG, Olejnik TA, Totoritis MC. Allergic asthma and an anti-CD23 mAb (IDEC-152) results of a phase I, single-dose, dose-escalating clinical trial. *J Allergy Clin Immunol.* 2003;112(3):563-570. doi:[10.1016/s0091-6749\(03\)01861-x](https://doi.org/10.1016/s0091-6749(03)01861-x)
 130. Awan FT, Hillmen P, Hellmann A, et al. A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia. *Br J Haematol.* 2014;167(4):466-477. doi:[10.1111/bjh.13061](https://doi.org/10.1111/bjh.13061)
 131. Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): two randomized, double-blind, placebo-controlled, phase 3 trials. *J Allergy Clin Immunol.* 2024;154(1):184-194. doi:[10.1016/j.jaci.2024.01.028](https://doi.org/10.1016/j.jaci.2024.01.028)
 132. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018;378(26):2486-2496. doi:[10.1056/nejmoa1804092](https://doi.org/10.1056/nejmoa1804092)
 133. Spekhorst LS, van der Rijst LP, de Graaf M, et al. Dupilumab has a profound effect on specific-IgE levels of several food allergens in atopic dermatitis patients. *Allergy.* 2023;78(3):875-878. doi:[10.1111/all.15591](https://doi.org/10.1111/all.15591)
 134. Prætorius K, Henriksen DP, Schmid JM, et al. Indirect comparison of efficacy of dupilumab versus mepolizumab and omalizumab for severe type 2 asthma. *ERJ Open Res.* 2021;7(3):306-2021. doi:[10.1183/23120541.00306-2021](https://doi.org/10.1183/23120541.00306-2021)
 135. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor α mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol.* 2010;125(6):1344-1353.e2. doi:[10.1016/j.jaci.2010.04.004](https://doi.org/10.1016/j.jaci.2010.04.004)
 136. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med.* 2016;111:21-29. doi:[10.1016/j.rmed.2016.01.003](https://doi.org/10.1016/j.rmed.2016.01.003)
 137. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2115-2127. doi:[10.1016/s0140-6736\(16\)31324-1](https://doi.org/10.1016/s0140-6736(16)31324-1)
 138. Pavord ID, Menzies-Gow A, Buhl R, et al. Clinical development of Mepolizumab for the treatment of severe eosinophilic asthma: on the path to personalized medicine. *J Allergy Clin Immunol: Pract.* 2020;9:1121-1132.e7. doi:[10.1016/j.jaip.2020.08.039](https://doi.org/10.1016/j.jaip.2020.08.039)
 139. Leckie MJ, Brinke A t, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet (Lond, Engl).* 2000;356(9248):2144-2148. doi:[10.1016/s0140-6736\(00\)03496-6](https://doi.org/10.1016/s0140-6736(00)03496-6)
 140. Flood-Page P, Swenson C, Faierman I, et al. A study to evaluate safety and efficacy of Mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med.* 2012;176(11):1062-1071. doi:[10.1164/rccm.200701-085oc](https://doi.org/10.1164/rccm.200701-085oc)
 141. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13):1198-1207. doi:[10.1056/nejmoa1403290](https://doi.org/10.1056/nejmoa1403290)
 142. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet.* 2002;360(9347):1715-1721. doi:[10.1016/s0140-6736\(02\)11679-5](https://doi.org/10.1016/s0140-6736(02)11679-5)
 143. Khurana S, Brusselle GG, Bel EH, et al. Long-term safety and clinical benefit of Mepolizumab in patients with the Most severe eosinophilic asthma: the COSMEX study. *Clin Ther.* 2019;41(10):2041-2056.e5. doi:[10.1016/j.clinthera.2019.07.007](https://doi.org/10.1016/j.clinthera.2019.07.007)
 144. Pavord ID, Bel EH, Bourdin A, et al. From DREAM to REALITI-A and beyond: Mepolizumab for the treatment of eosinophil-driven diseases. *Allergy.* 2022;77(3):778-797. doi:[10.1111/all.15056](https://doi.org/10.1111/all.15056)
 145. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med.* 2015;3(5):355-366. doi:[10.1016/s2213-2600\(15\)00042-9](https://doi.org/10.1016/s2213-2600(15)00042-9)
 146. Liddament M, Husten J, Estephan T, et al. Higher binding affinity and in vitro potency of Reslizumab for Interleukin-5 compared with Mepolizumab. *Allergy, Asthma Immunol Res.* 2018;11(2):291-298. doi:[10.4168/air.2019.11.2.291](https://doi.org/10.4168/air.2019.11.2.291)
 147. Hoy SM. Tezepelumab: First Approval. *Drugs.* 2022;82(4):461-468. doi:[10.1007/s40265-022-01679-2](https://doi.org/10.1007/s40265-022-01679-2)
 148. Jonathan C, Parnes JR, Liangwei W, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med.* 2017;377(10):936-946. doi:[10.1056/nejmoa1704064](https://doi.org/10.1056/nejmoa1704064)
 149. Corren J, Pham T, Gil EG, et al. Baseline type 2 biomarker levels and response to tezepelumab in severe asthma. *Allergy.* 2022;77(6):1786-1796. doi:[10.1111/all.15197](https://doi.org/10.1111/all.15197)
 150. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med.* 2021;384(19):1800-1809. doi:[10.1056/nejmoa2034975](https://doi.org/10.1056/nejmoa2034975)
 151. Maurer M, McLaren J, Chon Y, et al. Sustained improvement in UAS7 after 16-week treatment with Tezepelumab in biologic-Naïve adults with CSU: results of the phase 2b INCEPTION study. *J Allergy Clin Immunol.* 2024;153(2):AB373. doi:[10.1016/j.jaci.2023.11.894](https://doi.org/10.1016/j.jaci.2023.11.894)
 152. Ultsch M, Bevers J, Nakamura G, et al. Structural basis of signaling blockade by anti-IL-13 antibody Lebrikizumab. *J Mol Biol.* 2013;425(8):1330-1339. doi:[10.1016/j.jmb.2013.01.024](https://doi.org/10.1016/j.jmb.2013.01.024)
 153. Moyle M, Cevikbas F, Harden JL, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis: the era of biologics and emerging therapeutic approaches. *Exp Dermatol.* 2019;28(7):756-768. doi:[10.1111/exd.13911](https://doi.org/10.1111/exd.13911)
 154. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med.* 2016;4(10):781-796. doi:[10.1016/s2213-2600\(16\)30265-x](https://doi.org/10.1016/s2213-2600(16)30265-x)
 155. Corren J, Szefer SJ, Sher E, et al. Lebrikizumab in uncontrolled asthma: reanalysis in a well-defined type 2 population. *J Allergy Clin Immunol: Pr.* 2024;12(5):1215-1224.e3. doi:[10.1016/j.jaip.2024.02.007](https://doi.org/10.1016/j.jaip.2024.02.007)
 156. Silverberg JI, Guttman-Yassky E, Thaçi D, et al. Two phase 3 trials of Lebrikizumab for moderate-to-severe atopic dermatitis. *N Engl J Med.* 2023;388(12):1080-1091. doi:[10.1056/nejmoa2206714](https://doi.org/10.1056/nejmoa2206714)
 157. Keam SJ. Lebrikizumab: First Approval. *Drugs.* 2024;84(3):347-353. doi:[10.1007/s40265-024-02000-z](https://doi.org/10.1007/s40265-024-02000-z)
 158. Zhang Y, Yan B, Shen S, et al. Efficacy and safety of CM310 in severe eosinophilic chronic rhinosinusitis with nasal polyps (CROWNS-1): a multicentre, randomised, double-blind, placebo-controlled phase 2 clinical trial. *eClinicalMedicine.* 2023;61:102076. doi:[10.1016/j.eclinm.2023.102076](https://doi.org/10.1016/j.eclinm.2023.102076)
 159. Wynne CJ, Cole A, Lemech C, et al. Safety, pharmacokinetics and preliminary efficacy of IL4-R α monoclonal antibody AK120 in both healthy and atopic dermatitis subjects: A phase I, randomized, two-part, double-blind, placebo-controlled, dose-escalation,

- first-in-human clinical study. *Dermatol Ther.* 2023;13(10):2357-2373. doi:[10.1007/s13555-023-01010-1](https://doi.org/10.1007/s13555-023-01010-1)
160. Silverberg JI, Strober B, Feinstein B, et al. Efficacy and safety of rademikibart (CBP-201), a next-generation mAb targeting IL-4R α , in adults with moderate to severe atopic dermatitis: A phase 2 randomized trial (CBP-201-WW001). *J Allergy Clin Immunol.* 2024;153(4):1040-1049.e12. doi:[10.1016/j.jaci.2023.11.924](https://doi.org/10.1016/j.jaci.2023.11.924)
 161. Singh D, Fuhr R, Bird NP, et al. A phase 1 study of the long-acting anti-IL-5 monoclonal antibody GSK3511294 in patients with asthma. *Br J Clin Pharmacol.* 2022;88(2):702-712. doi:[10.1111/bcp.15002](https://doi.org/10.1111/bcp.15002)
 162. Paller AS, Flohr C, Cork M, et al. Efficacy and safety of Tralokinumab in adolescents with moderate to severe atopic dermatitis. *JAMA Dermatol.* 2023;159(6):596-605. doi:[10.1001/jamadermatol.2023.0627](https://doi.org/10.1001/jamadermatol.2023.0627)
 163. Blauvelt A, Guttman-Yassky E, Lynde C, et al. Cendakimab in patients with moderate to severe atopic dermatitis: A randomized clinical trial. *JAMA Dermatol* Published online. 2024. doi:[10.1001/jamadermatol.2024.2131](https://doi.org/10.1001/jamadermatol.2024.2131)
 164. Kabashima K, Matsumura T, Komazaki H, Kawashima M, Group NJS. Trial of Nemolizumab and topical agents for atopic dermatitis with pruritus. *N Engl J Med.* 2020;383(2):141-150. doi:[10.1056/nejmoa1917006](https://doi.org/10.1056/nejmoa1917006)
 165. Sindher SB, Long A, Chin AR, et al. Food allergy, mechanisms, diagnosis and treatment: innovation through a multi-targeted approach. *Allergy.* 2022;77(10):2937-2948. doi:[10.1111/all.15418](https://doi.org/10.1111/all.15418)
 166. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of Itepekimab in patients with moderate-to-severe asthma. *N Engl J Med.* 2021;385(18):1656-1668. doi:[10.1056/nejmoa2024257](https://doi.org/10.1056/nejmoa2024257)
 167. England E, Rees DG, Scott IC, et al. Tozorakimab (MEDI3506): an anti-IL-33 antibody that inhibits IL-33 signalling via ST2 and RAGE/EGFR to reduce inflammation and epithelial dysfunction. *Sci Rep.* 2023;13(1):9825. doi:[10.1038/s41598-023-36642-y](https://doi.org/10.1038/s41598-023-36642-y)
 168. Gauvreau G, Hohlfeld J, Boulet LP, et al. Late breaking abstract - efficacy of CSJ117 on allergen-induced asthmatic responses in mild atopic asthma patients. *Airw Pharmacol Treat.* 2020;3690. doi:[10.1183/13993003.congress-2020.3690](https://doi.org/10.1183/13993003.congress-2020.3690)
 169. Weidinger S, Bieber T, Cork MJ, et al. Safety and efficacy of amlitelimab, a fully human nondepleting, noncytotoxic anti-OX40 ligand monoclonal antibody, in atopic dermatitis: results of a phase IIa randomized placebo-controlled trial. *Br J Dermatol.* 2023;189(5):531-539. doi:[10.1093/bjd/ljad240](https://doi.org/10.1093/bjd/ljad240)
 170. Morita H, Matsumoto K, Saito H. Biologics for allergic and immunologic diseases. *J Allergy Clin Immunol.* 2022;150(4):766-777. doi:[10.1016/j.jaci.2022.08.009](https://doi.org/10.1016/j.jaci.2022.08.009)
 171. Tan HTT, Sugita K, Akdis CA. Novel biologicals for the treatment of allergic diseases and asthma. *Curr Allergy Asthma Rep.* 2016;16(10):70. doi:[10.1007/s11882-016-0650-5](https://doi.org/10.1007/s11882-016-0650-5)
 172. London CA, Gardner HL, Rippey S, et al. KTN0158, a humanized anti-KIT monoclonal antibody, demonstrates biologic activity against both Normal and malignant canine mast cells. *Clin Cancer Res.* 2017;23(10):2565-2574. doi:[10.1158/1078-0432.ccr-16-2152](https://doi.org/10.1158/1078-0432.ccr-16-2152)
 173. Reshetnyak AV, Nelson B, Shi X, et al. Structural basis for KIT receptor tyrosine kinase inhibition by antibodies targeting the D4 membrane-proximal region. *Proc Natl Acad Sci.* 2013;110(44):17832-17837. doi:[10.1073/pnas.1317118110](https://doi.org/10.1073/pnas.1317118110)
 174. Alvarado D, Maurer M, Gedrich R, et al. Anti-KIT monoclonal antibody CDX-0159 induces profound and durable mast cell suppression in a healthy volunteer study. *Allergy.* 2022;77(8):2393-2403. doi:[10.1111/all.15262](https://doi.org/10.1111/all.15262)
 175. Terhorst-Molawi D, Hawro T, Grekowitz E, et al. Anti-KIT antibody, barzolvolimab, reduces skin mast cells and disease activity in chronic inducible urticaria. *Allergy.* 2023;78(5):1269-1279. doi:[10.1111/all.15585](https://doi.org/10.1111/all.15585)
 176. Maurer M, Kobielusz-Gembala I, Mitha E, et al. Barzolvolimab significantly decreases chronic spontaneous Urticaria disease activity and is well tolerated: top line results from a phase 2 trial. *J Allergy Clin Immunol.* 2024;153(2):AB366. doi:[10.1016/j.jaci.2023.11.873](https://doi.org/10.1016/j.jaci.2023.11.873)
 177. Legrand F, Cao Y, Wechsler JB, et al. Sialic acid-binding immunoglobulin-like lectin (Siglec) 8 in patients with eosinophilic disorders: receptor expression and targeting using chimeric antibodies. *J Allergy Clin Immunol.* 2019;143(6):2227-2237.e10. doi:[10.1016/j.jaci.2018.10.066](https://doi.org/10.1016/j.jaci.2018.10.066)
 178. Youngblood BA, Brock EC, Leung J, et al. AK002, a humanized sialic acid-binding immunoglobulin-like Lectin-8 antibody that induces antibody-dependent cell-mediated cytotoxicity against human eosinophils and inhibits mast cell-mediated anaphylaxis in mice. *Int Arch Allergy Immunol.* 2019;180(2):91-102. doi:[10.1159/000501637](https://doi.org/10.1159/000501637)
 179. Kerr SC, Gonzalez JR, Schanin J, et al. An anti-siglec-8 antibody depletes sputum eosinophils from asthmatic subjects and inhibits lung mast cells. *Clin Exp Allergy.* 2020;50(8):904-914. doi:[10.1111/cea.13681](https://doi.org/10.1111/cea.13681)
 180. Youngblood BA, Brock EC, Leung J, et al. Siglec-8 antibody reduces eosinophils and mast cells in a transgenic mouse model of eosinophilic gastroenteritis. *JCI Insight.* 2019;4(19). doi:[10.1172/jci.insight.126219](https://doi.org/10.1172/jci.insight.126219)
 181. Robida PA, Rische CH, Morgenstern NBB, et al. Functional and phenotypic characterization of Siglec-6 on human mast cells. *Cells.* 2022;11(7):1138. doi:[10.3390/cells11071138](https://doi.org/10.3390/cells11071138)
 182. Feske S, Gwack Y, Prakriya M, et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature.* 2006;441(7090):179-185. doi:[10.1038/nature04702](https://doi.org/10.1038/nature04702)
 183. Vig M, DeHaven WI, Bird GS, et al. Defective mast cell effector functions in mice lacking the CRACM1 pore subunit of store-operated calcium release-activated calcium channels. *Nat Immunol.* 2008;9(1):89-96. doi:[10.1038/ni1550](https://doi.org/10.1038/ni1550)
 184. Aki A, Tanaka K, Nagaoka N, et al. Anti-ORAI1 antibody DS-2741a, a specific CRAC channel blocker, shows ideal therapeutic profiles for allergic disease via suppression of aberrant T-cell and mast cell activation. *FASEB BioAdvances.* 2020;2(8):478-488. doi:[10.1096/fba.2020-00008](https://doi.org/10.1096/fba.2020-00008)
 185. Holm JG, Thomsen SF. Omalizumab for atopic dermatitis: evidence for and against its use. *G Ital di Dermatol e Venereol.* 2019;154(4):480-487. doi:[10.23736/s0392-0488.19.06302-8](https://doi.org/10.23736/s0392-0488.19.06302-8)
 186. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr.* 2011;170(11):1471-1474. doi:[10.1007/s00431-011-1540-4](https://doi.org/10.1007/s00431-011-1540-4)
 187. Altrichter S, Giménez-Arnau AM, Bernstein JA, et al. Benralizumab does not elicit therapeutic effect in patients with chronic spontaneous urticaria: results from the phase IIb multinational randomized double-blind placebo-controlled ARROYO trial. *Br J Dermatol.* 2024;191(2):187-199. doi:[10.1093/bjd/ljae067](https://doi.org/10.1093/bjd/ljae067)
 188. Guttman-Yassky E, Bahadori L, Brooks L, et al. Lack of effect of benralizumab on signs and symptoms of moderate-to-severe atopic dermatitis: results from the phase 2 randomized, double-blind, placebo-controlled HILLIER trial. *J Eur Acad Dermatol Venereol.* 2023;37(10):e1211-e1214. doi:[10.1111/jdv.19195](https://doi.org/10.1111/jdv.19195)
 189. Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2022;149(4):1309-1317.e12. doi:[10.1016/j.jaci.2021.08.030](https://doi.org/10.1016/j.jaci.2021.08.030)
 190. Rothenberg ME, Dellon ES, Collins MH, et al. Eosinophil depletion with Benralizumab for eosinophilic esophagitis. *N Engl J Med.* 2024;390(24):2252-2263. doi:[10.1056/nejmoa2313318](https://doi.org/10.1056/nejmoa2313318)
 191. Dellon ES, Peterson KA, Mitlyng BL, et al. Mepolizumab for treatment of adolescents and adults with eosinophilic oesophagitis: a multicentre, randomised, double-blind, placebo-controlled clinical trial. *Gut.* 2023;72(10):1828-1837. doi:[10.1136/gutjnl-2023-330337](https://doi.org/10.1136/gutjnl-2023-330337)

192. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012;129(2):456-463.e3. doi:[10.1016/j.jaci.2011.11.044](https://doi.org/10.1016/j.jaci.2011.11.044)
193. Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. *J Am Acad Dermatol*. 2019;80(4):1013-1021. doi:[10.1016/j.jaad.2018.11.059](https://doi.org/10.1016/j.jaad.2018.11.059)
194. Szefer SJ, Roberts G, Rubin AS, et al. Efficacy, safety, and tolerability of lebrikizumab in adolescent patients with uncontrolled asthma (ACOUSTICS). *Clin Transl Allergy*. 2022;12(7):e12176. doi:[10.1002/ctt2.12176](https://doi.org/10.1002/ctt2.12176)
195. Rogers L, Jesenak M, Bjermer L, Hanania NA, Seys SF, Diamant Z. Biologics in severe asthma: A pragmatic approach for choosing the right treatment for the right patient. *Respir Med*. 2023;218:107414. doi:[10.1016/j.rmed.2023.107414](https://doi.org/10.1016/j.rmed.2023.107414)
196. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologics (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAAACI guidelines-recommendations on the use of biologics in severe asthma. *Allergy*. 2020;75(5):1023-1042. doi:[10.1111/all.14221](https://doi.org/10.1111/all.14221)
197. Agache I, Akdis CA, Akdis M, et al. EAAACI biologics guidelines—recommendations for severe asthma. *Allergy*. 2021;76(1):14-44. doi:[10.1111/all.14425](https://doi.org/10.1111/all.14425)
198. Levy ML, Bacharier LB, Bateman E, et al. Key recommendations for primary care from the 2022 global initiative for asthma (GINA) update. *Npj Prim Care Respir Med*. 2023;33(1):7. doi:[10.1038/s41533-023-00330-1](https://doi.org/10.1038/s41533-023-00330-1)
199. Agache I, Song Y, Alonso-Coello P, et al. Efficacy and safety of treatment with biologics for severe chronic rhinosinusitis with nasal polyps: A systematic review for the EAAACI guidelines. *Allergy*. 2021;76(8):2337-2353. doi:[10.1111/all.14809](https://doi.org/10.1111/all.14809)
200. Zuberbier T, Latiff AHA, Abuzakouk M, et al. The international EAAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734-766. doi:[10.1111/all.15090](https://doi.org/10.1111/all.15090)
201. Wollenberg A, Thomsen SF, Lacour JP, Jaumont X, Lazarewicz S. Targeting immunoglobulin E in atopic dermatitis: A review of the existing evidence. *World Allergy Organ J*. 2021;14(3):100519. doi:[10.1016/j.waojou.2021.100519](https://doi.org/10.1016/j.waojou.2021.100519)
202. Muñoz-Bellido F, Moreno E, Dávila I. Dupilumab: A review of present indications and off-label uses. *J Investig Allergy Clin Immunol*. 2022;32(2):97-115. doi:[10.18176/jiaci.0682](https://doi.org/10.18176/jiaci.0682)
203. Kau AL, Korenblat PE. Anti-interleukin 4 and 13 for asthma treatment in the era of endotypes. *Curr Opin Allergy Clin Immunol*. 2014;14(6):570-575. doi:[10.1097/aci.0000000000000108](https://doi.org/10.1097/aci.0000000000000108)
204. Pelaia C, Paoletti G, Puggioni F, et al. Interleukin-5 in the pathophysiology of severe asthma. *Front Physiol*. 2019;10:1514. doi:[10.3389/fphys.2019.01514](https://doi.org/10.3389/fphys.2019.01514)
205. Pham DD, Lee JH, Kwon HS, et al. Prospective direct comparison of biologic treatments for severe eosinophilic asthma findings from the PRISM study. *Ann Allergy Asthma Immunol*. 2024;132(4):457-462.e2. doi:[10.1016/j.anai.2023.11.005](https://doi.org/10.1016/j.anai.2023.11.005)
206. Bateman ED, Khan AH, Xu Y, et al. Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma. *Respir Med*. 2022;191:105991. doi:[10.1016/j.rmed.2020.105991](https://doi.org/10.1016/j.rmed.2020.105991)
207. Nopsopon T, Lassiter G, Chen ML, et al. Comparative efficacy of tezepelumab to mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: A Bayesian network meta-analysis. *J Allergy Clin Immunol*. 2023;151(3):747-755. doi:[10.1016/j.jaci.2022.11.021](https://doi.org/10.1016/j.jaci.2022.11.021)
208. Wood RA, Togias A, Sicherer SH, et al. Omalizumab for the treatment of multiple food allergies. *N Engl J Med* Published online. 2024;390:889-899. doi:[10.1056/nejmoa2312382](https://doi.org/10.1056/nejmoa2312382)
209. Mitropoulou AN, Ceska T, Heads JT, et al. Engineering the fab fragment of the anti-IgE omalizumab to prevent fab crystallization and permit IgE-fc complex crystallization. *Acta Crystallogr Sect F*. 2020;76(Pt 3):116-129. doi:[10.1107/s2053230x20001466](https://doi.org/10.1107/s2053230x20001466)
210. Liu P, Pan Z, Gu C, et al. An Omalizumab biobetter antibody with improved stability and efficacy for the treatment of allergic diseases. *Front Immunol*. 2020;11:596908. doi:[10.3389/fimmu.2020.596908](https://doi.org/10.3389/fimmu.2020.596908)
211. Robbie GJ, Criste R, Dall'acqua WF, et al. A novel investigational fc-modified humanized monoclonal antibody, Motavizumab-YTE, has an extended half-life in healthy adults. *Antimicrob Agents Chemother*. 2013;57(12):6147-6153. doi:[10.1128/aac.01285-13](https://doi.org/10.1128/aac.01285-13)
212. Jabs F, Plum M, Laursen NS, et al. Trapping IgE in a closed conformation by mimicking CD23 binding prevents and disrupts FcεRI interaction. *Nat Commun*. 2018;9(1):7. doi:[10.1038/s41467-017-02312-7](https://doi.org/10.1038/s41467-017-02312-7)
213. Wurzburg BA, Garman SC, Jardetzky TS. Structure of the human IgE-fc Cε3-Cε4 reveals conformational flexibility in the antibody effector domains. *Immunity*. 2000;13(3):375-385. doi:[10.1016/s1074-7613\(00\)00037-6](https://doi.org/10.1016/s1074-7613(00)00037-6)
214. Guntern P, Eggel A. Past, present, and future of anti-IgE biologics. *Allergy*. 2020;3(87):166-2502. doi:[10.1111/all.14308](https://doi.org/10.1111/all.14308)
215. Roberts G, Pfaar O, Akdis CA, et al. EAAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2018;73(4):765-798. doi:[10.1111/all.13317](https://doi.org/10.1111/all.13317)
216. Tsai M, Mukai K, Chinthrajah RS, Nadeau KC, Galli SJ. Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE. *J Allergy Clin Immunol*. 2020;145(3):885-896.e6. doi:[10.1016/j.jaci.2019.10.038](https://doi.org/10.1016/j.jaci.2019.10.038)
217. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133(2):468-475.e6. doi:[10.1016/j.jaci.2013.11.007](https://doi.org/10.1016/j.jaci.2013.11.007)
218. Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2002;109(2):274-280. doi:[10.1067/mai.2002.121949](https://doi.org/10.1067/mai.2002.121949)
219. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. *Clin Exp Allergy*. 2018;48(3):232-240. doi:[10.1111/cea.13084](https://doi.org/10.1111/cea.13084)
220. Božek A, Fischer A, Bogacz-Piasieczynska A, Canonica GW. Adding a biologic to allergen immunotherapy increases treatment efficacy. *ERJ Open Res*. 2023;9(2):00639-02022. doi:[10.1183/23120541.00639-2022](https://doi.org/10.1183/23120541.00639-2022)
221. Zhang Y, Zhang M, Zhang J, Li Q, Lu M, Cheng L. Combination of omalizumab with allergen immunotherapy versus immunotherapy alone for allergic diseases: A meta-analysis of randomized controlled trials. *Int Forum Allergy Rhinol*. 2024;14(4):794-806. doi:[10.1002/alr.23268](https://doi.org/10.1002/alr.23268)
222. Larenas-Linnemann D, Wahn U, Kopp M. Use of omalizumab to improve desensitization safety in allergen immunotherapy. *J Allergy Clin Immunol*. 2014;133(3):937-937.e2. doi:[10.1016/j.jaci.2013.12.1089](https://doi.org/10.1016/j.jaci.2013.12.1089)
223. Wood RA, Chinthrajah RS, Spergel AKR, et al. Protocol design and synopsis: Omalizumab as monotherapy and as adjunct therapy to multiallergen OIT in children and adults with food allergy (OUMATCH). *J Allergy Clin Immunol: Glob*. 2022;1(4):225-232. doi:[10.1016/j.jacig.2022.05.006](https://doi.org/10.1016/j.jacig.2022.05.006)
224. Chaker AM, Shamji MH, Dumitru FA, et al. Short-term subcutaneous grass pollen immunotherapy under the umbrella of

- anti-IL-4: A randomized controlled trial. *J Allergy Clin Immunol*. 2016;137(2):452-461.e9. doi:[10.1016/j.jaci.2015.08.046](https://doi.org/10.1016/j.jaci.2015.08.046)
225. Bumma N, Richter J, Jagannath S, et al. Linvoseltamab for treatment of relapsed/refractory multiple myeloma. *J Clin Oncol Off J Am Soc Clin Oncol* Published online. 2024;42:JCO2401008. doi:[10.1200/jco.24.01008](https://doi.org/10.1200/jco.24.01008)
 226. Limnander A, Kaur N, Asrat S, et al. A therapeutic strategy to target distinct sources of IgE and durably reverse allergy. *Sci Transl Med*. 2023;15(726):eadf9561. doi:[10.1126/scitranslmed.adf9561](https://doi.org/10.1126/scitranslmed.adf9561)
 227. Altman MC, Lenington J, Bronson S, Ayars AG. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol: Pr*. 2017;5(4):1137-1139. doi:[10.1016/j.jaip.2017.01.013](https://doi.org/10.1016/j.jaip.2017.01.013)
 228. Dedaj R, Unsel L. Case study: A combination of Mepolizumab and Omaluzimab injections for severe asthma. *J Asthma*. 2019;56(5):473-474. doi:[10.1080/02770903.2018.1471706](https://doi.org/10.1080/02770903.2018.1471706)
 229. Ortega G, Tongchinsub P, Carr T. Combination biologic therapy for severe persistent asthma. *Ann Allergy Asthma Immunol*. 2019;123(3):309-311. doi:[10.1016/j.anai.2019.06.013](https://doi.org/10.1016/j.anai.2019.06.013)
 230. Domingo C, Pomares X, Morón A, Sogo A. Dual monoclonal antibody therapy for a severe asthma patient. *Front Pharmacol*. 2020;11:587621. doi:[10.3389/fphar.2020.587621](https://doi.org/10.3389/fphar.2020.587621)
 231. Fox HM, Rotolo SM. Combination anti-IgE and anti-IL5 therapy in a pediatric patient with severe persistent asthma. *J Pediatr Pharmacol Ther*. 2021;26(3):306-310. doi:[10.5863/1551-6776-26.3.306](https://doi.org/10.5863/1551-6776-26.3.306)
 232. Briegel I, Felicio-Briegel A, Mertsch P, Kneidinger N, Haubner F, Milger K. Hypereosinophilia with systemic manifestations under dupilumab and possibility of dual benralizumab and dupilumab therapy in patients with asthma and CRSwNP. *J Allergy Clin Immunol: Pr*. 2021;9(12):4477-4479. doi:[10.1016/j.jaip.2021.07.049](https://doi.org/10.1016/j.jaip.2021.07.049)
 233. Pitlick MM, Pongdee T. Combining biologics targeting eosinophils (IL-5/IL-5R), IgE, and IL-4/IL-13 in allergic and inflammatory diseases. *World Allergy Organ J*. 2022;15(11):100707. doi:[10.1016/j.waojou.2022.100707](https://doi.org/10.1016/j.waojou.2022.100707)
 234. Lommatzsch M, Suhling H, Korn S, et al. Safety of combining biologics in severe asthma: asthma-related and unrelated combinations. *Allergy*. 2022;77(9):2839-2843. doi:[10.1111/all.15379](https://doi.org/10.1111/all.15379)
 235. Matsumoto T, Sakurai Y, Tashima N, et al. Dual biologics for severe asthma and atopic dermatitis: synopsis of two cases and literature review. *Respirol Case Rep*. 2024;12(1):e01266. doi:[10.1002/rcr2.1266](https://doi.org/10.1002/rcr2.1266)
 236. Azzano P, Dufresne É, Poder T, Bégin P. Economic considerations on the usage of biologics in the allergy clinic. *Allergy*. 2021;76(1):191-209. doi:[10.1111/all.14494](https://doi.org/10.1111/all.14494)
 237. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJT. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov*. 2010;9(4):325-338. doi:[10.1038/nrd3003](https://doi.org/10.1038/nrd3003)
 238. Liu X, Pop LM, Vitetta ES. Engineering therapeutic monoclonal antibodies. *Immunol Rev*. 2008;222(1):9-27. doi:[10.1111/j.1600-065x.2008.00601.x](https://doi.org/10.1111/j.1600-065x.2008.00601.x)
 239. Hudson PJ, Souriau C. Engineered antibodies. *Nat Med*. 2003;9(1):129-134. doi:[10.1038/nm0103-129](https://doi.org/10.1038/nm0103-129)
 240. Kelley B. Developing therapeutic monoclonal antibodies at pandemic pace. *Nat Biotechnol*. 2020;38(5):540-545. doi:[10.1038/s41587-020-0512-5](https://doi.org/10.1038/s41587-020-0512-5)
 241. Shukla AA, Thömmes J. Recent advances in large-scale production of monoclonal antibodies and related proteins. *Trends Biotechnol*. 2010;28(5):253-261. doi:[10.1016/j.tibtech.2010.02.001](https://doi.org/10.1016/j.tibtech.2010.02.001)

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