

REVIEW

Past, present, and future of anti-IgE biologics

Pascal Guntern^{1,2,3}  | Alexander Eggel^{2,3} 

¹Graduate School of Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

²Department of BioMedical Research, University of Bern, Bern, Switzerland

³Department of Rheumatology, Immunology and Allergology, University Hospital Bern, Bern, Switzerland

Correspondence

Alexander Eggel, Department of Rheumatology, Immunology and Allergology, University Hospital Bern, Bern, Switzerland. Email: alexander.eggel@dbmr.unibe.ch

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Abstract

About 20 years after the identification of immunoglobulin E (IgE) and its key role in allergic hypersensitivity reactions against normally harmless substances, scientists have started inventing strategies to block its pathophysiological activity in 1986. The initial concept of specific IgE targeting through the use of anti-IgE antibodies has gained a lot of momentum and within a few years independent research groups have reported successful generation of first murine monoclonal anti-IgE antibodies. Subsequent generation of optimized chimeric and humanized versions of these antibodies has paved the way for the development of therapeutic anti-IgE biologics as we know them today. With omalizumab, there is currently still only one therapeutic anti-IgE antibody approved for the treatment of allergic conditions. Since its application is limited to the treatment of moderate-to-severe persistent asthma and chronic spontaneous urticaria, major efforts have been undertaken to develop alternative anti-IgE biologics that could potentially be used in a broader spectrum of allergic diseases. Several new drug candidates have been generated and are currently assessed in pre-clinical studies or clinical trials. In this review, we highlight the molecular properties of past and present anti-IgE biologics and suggest concepts that might improve treatment efficacy of future drug candidates.

KEYWORDS

allergy treatment, anti-IgE, basophils, b cells, biologics, IgE, mast cells

1 | INTRODUCTION

The discovery of immunoglobulin E (IgE) in 1967¹⁻⁹ together with the identification of its central role in the pathogenesis of allergic inflammation (reviewed elsewhere¹⁰⁻¹⁴) has set the stage for the development of therapeutic anti-IgE strategies (Box 1). The generation of detailed knowledge about the molecular and structural characteristics of IgE has further accelerated this process. IgE consists of two identical heavy and light chains. Each heavy chain includes four constant epsilon domains (Cε1-4).¹⁵ Overall, the IgE antibody features high flexibility. Particularly, the IgE-Fc part has been described to undergo important conformational changes depending on its interaction partner. While IgE binding to the high-affinity receptor

FcεRI on allergic effector cells induces an open Fc conformation, low affinity receptor FcεRII/CD23 binding on antigen-presenting cells (APC), airway epithelial cells (AEC) or B-cells forces IgE in a closed Fc conformation and thereby ensures mutually exclusive interaction with the two receptors.¹⁶⁻¹⁸ In addition to the free form of IgE, B cells express membrane IgE (mIgE) that is part of the B-cell receptor (BCR) and contains an extracellular membrane-proximal domain (EMPD).¹⁹⁻²¹ Identification of these features has been key for the development of efficient targeting strategies. Over the last decades, the field of anti-IgE biologics has advanced into a competitive and active field of investigation. Different companies and research institutions are currently assessing approaches to specifically target IgE in pre-clinical studies or clinical trials (Table 1).^{22,23} Here, we provide

a chronological overview on past achievements, present investigations and potential future approaches of anti-IgE strategies.

2 | THE PAST: APPROVED ANTI-IgE BIOLOGICALS

In 1986, Dr Christoph Heusser and his colleagues at the former Swiss pharmaceutical company Ciba-Geigy proposed the development of neutralizing non-anaphylactogenic anti-IgE antibodies.²⁴ Around the same time, the research team of Dr Tse Wen Chang at the US biopharmaceutical company TANOX came up with the idea to generate a monoclonal antibody against IgE that specifically targets and eliminates IgE-secreting B cells.¹⁰ While the group at Ciba-Geigy demonstrated proof-of-concept in different mouse models,^{11,25} TANOX generated the first monoclonal murine anti-human IgE antibody called TES-C21 (Figure 1).²⁶ In 1990, the two companies entered a partnership with the goal to join their anti-IgE programs and to generate a therapeutic anti-IgE antibody that would block the biological activity of IgE based on three criteria: (a) neutralization of free serum IgE, (b) targeting of IgE-producing B cells, and (c) non-reactivity with other IgE-bearing cells. Therefore, they further engineered TES-C21 and developed the chimeric mouse/human monoclonal antibody TESC-2, later renamed to CGP51901.²⁶ In clinical phase I and II trials with allergic rhinitis patients, CGP51901 showed dose-dependent reduction of free serum IgE levels, inhibition of rhinitis symptoms and high tolerability.^{27,28} The cooperation between TANOX and Ciba-Geigy ultimately gave rise to the fully humanized monoclonal anti-IgE antibody CGP56901, also known as TNX-901 or Talizumab.²⁹ Later in 1996, Ciba-Geigy fused with the pharmaceutical company Sandoz to form Novartis. During that time, Genentech has also been generating a murine anti-human IgE antibody called MaE11, which has been further developed into the humanized monoclonal antibody rhuMAB-E25.³⁰ To reduce competition and maximize synergies, Genentech, TANOX, and Novartis formed a tripartite partnership. Despite the fact that both antibody candidates expressed similar key properties,³¹ the three partners decided to select rhuMAB-E25 from Genentech over CGP56901 for further development due to already established manufacturing processes. This collaboration ultimately led to the approval of rhuMAB-E25—today best known as omalizumab (Xolair®)—as the first therapeutic anti-IgE antibody in 2003.¹²

Until now, omalizumab is still the only approved therapeutic anti-IgE antibody. Despite its restricted indication for the treatment of moderate-to-severe persistent asthma and chronic spontaneous urticaria (CSU), omalizumab is frequently used off-label in allergic rhinitis, food allergies, and allergen-specific immunotherapy.^{32–34} Several meta-analyses have assessed the efficacy of omalizumab treatment in allergic asthma and CSU. These studies came to the conclusion that omalizumab efficiently reduces asthma exacerbations, leads to overall improvement in quality of life, and allows the reduction or withdrawal of inhaled corticosteroids.^{35–39} However, the use of omalizumab in severe eosinophilic asthma in corticosteroid-resistant patients is controversially discussed.^{19,35,40} Further

studies on this subject are needed, especially since there are other approved biologics that might be superior to omalizumab in this context.⁴¹ The primary mode-of-action of this humanized monoclonal anti-IgE antibody of IgG1 subclass is the neutralization of free IgE. It binds with nanomolar affinity ($K_D \sim 7 \times 10^{-9}$ M)⁴² to the Cε3 domain of IgE. Recent analysis of crystal structures composed of omalizumab Fab fragments and IgE-Fc₃₋₄ variants revealed that omalizumab-mediated inhibition of IgE binding to FcεRI does not occur via direct competition for binding sites on IgE as stated in many previous reports.⁴³ Omalizumab shares only minor overlap with FcεRIα-binding epitopes on IgE and mainly inhibits IgE receptor binding via steric inhibition (Figure 2A).^{43,44} On the other hand, the binding footprints of omalizumab and CD23 on IgE show a high degree of overlap.^{43,44} Therefore, the inhibition of IgE:CD23 interactions is primarily dependent on direct binding competition. Importantly, omalizumab inhibits IgE receptor interactions with both, FcεRI and CD23 (Figure 2B) and does not aggregate receptor-bound IgE ensuring its non-anaphylactogenic profile.⁴³ In rare cases (~0.1%), however, treatment with omalizumab has induced adverse reactions including skin inflammation and anaphylaxis in the absence of anti-drug antibodies.^{45–47} Recent studies have provided strong evidence that omalizumab can bind and cross-link IgE-Fc₃₋₄:FcεRIα complexes due to the missing Cε2 domain, which in the intact IgE molecule masks the omalizumab-binding epitope on IgE.⁴³ Whether IgE-Fc₃₋₄:FcεRIα complexes exist in vivo and whether such binding events might play a role in the limited cases of omalizumab-induced anaphylaxis are currently not known. Another study revealed that omalizumab-IgE immune complexes activate human neutrophils that may induce skin inflammation and anaphylaxis in humanized mice by engaging activating Fc-gamma receptors and binding of complement factors.⁴⁸ Although this is an interesting finding, it does not explain the rarity of such omalizumab-induced adverse reactions in humans.

As first discovered by Dr Donald MacGlashan in 1997^{49,50} and confirmed by several studies with omalizumab, anti-IgE treatment reduces FcεRI levels on allergic effector cells such as mast cells and basophils.⁵¹ This beneficial side effect is a consequence of free IgE clearance, which leads to the lack of IgE-mediated FcεRI stabilization on the surface of these cells.⁵² Additionally, omalizumab has been described to accelerate the dissociation of IgE from FcεRI⁵³ and CD23⁴⁴ (Figure 2C). Recently, an alternative omalizumab Fab fragment has been generated by introducing three mutations in the variable and constant light chain. This so-called FabXol3 antibody fragment showed superior activity in dissociating IgE from FcεRIα than the original full length antibody.⁵⁴ Whether the increased disruptive efficacy of omalizumab would result in an additional treatment benefit still requires careful evaluation.

There is emerging evidence that omalizumab in addition to its primary mode-of-action has the ability to decrease IgE production by targeting mIgE-positive B-cells.^{55,56} Several studies have shown reduced B-cell numbers and IgE secretion upon long-term omalizumab treatment (Figure 2D).^{57–59} While these observations are

TABLE 1 Past, present, and future anti-IgE biologicals

Anti-IgE name	Format	Target	Indication	Clinical status	Company	Published
Omalizumab	Antibody	IgE, mIgE	Asthma, CSU	Approved	Novartis, Genentech	1993 ³⁰
Ligelizumab	Antibody	IgE, mIgE, CD23-IgE	CSU	Phase III	Novartis	1999 ¹¹⁶
Quilizumab	Antibody	mIgE	CSU	Phase II	Genentech	2010 ⁶⁵
MEDI4212	Antibody	IgE, mIgE	n.a.	Phase I	MedImmune	2014 ⁷⁷
XmAb7195	Antibody	IgE, mIgE	n.a.	Phase I	Xencor	2012 ⁸⁰
8D6	Antibody	IgE, CD23-IgE	n.a.	Pre-clinical	—	2012 ⁹¹
GE2	Fc-fusion protein	FcεRI/ CD23, FcγRII,	n.a.	Pre-clinical	—	2002 ⁹⁹
DE53-Fc	DARPin	IgE, FcεRI-IgE, FcγRIIb	n.a.	Pre-clinical	—	2011 ¹⁰⁵
bi53_79	DARPin	IgE, FcεRI-IgE	n.a.	Pre-clinical	—	2014 ⁹⁰
026 sdab	Nanobody	IgE, FcεRI-IgE	n.a.	Pre-clinical	Ablynx	2018 ¹⁰⁹

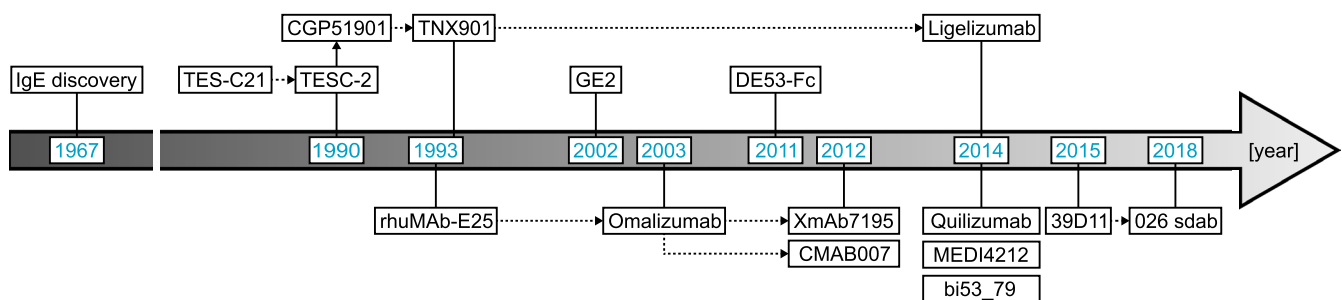


FIGURE 1 Chronological appearance of anti-IgE compounds. Following the discovery of IgE, various anti-IgE compounds have been reported. The years of their appearance (blue) are marked on the timeline (gray arrow). The inter-relationship between different anti-IgE compounds is highlighted with arrows (dotted black). TES-C21: monoclonal murine anti-IgE antibody; TESC-2/ CGP51901: monoclonal chimeric mouse/human anti-IgE antibody; TNX-901: humanized monoclonal anti-IgE antibody; rhuMab-E25/ omalizumab: humanized monoclonal anti-IgE antibody; GE2: fusion protein of IgG1-Fc₃₋₄ and IgE-Fc₂₋₄; DE53-Fc: fusion protein of anti-IgE DARPin and IgG1-Fc₃₋₄; XmAb7195: humanized affinity matured version of parental omalizumab antibody; CMAB007: omalizumab biosimilar; ligelizumab: high-affinity version of TNX-901; quilizumab: afucosylated humanized monoclonal anti-IgE (EMPD) antibody; MEDI4212: afucosylated monoclonal anti-IgE antibody; bi53_79: bispecific disruptive anti-IgE DARPin; 39D11: anti-IgE nanobody; and 026 sdab: humanized affinity matured anti-IgE nanobody

highly interesting, the exact mechanisms underlying omalizumab-dependent regulation of IgE production are not fully understood yet.

3 | THE PRESENT: MONOCLONAL ANTI-IgE ANTIBODIES IN CLINICAL TRIALS

So far, the field of anti-IgE biologicals has largely been dominated by monoclonal antibody approaches and different companies have successfully reached the stage of clinical trials with their anti-IgE candidates. However, none of these have been approved for therapeutic application in the last two decades. One of the highly anticipated antibodies that is still under active investigation in clinical trials is ligelizumab (QGE031) from Novartis. This is a high-affinity version of TNX-901 that was originally “put on ice” in the collaboration between Genentech, TANOX, and Novartis. To our current knowledge, all other anti-IgE programs discussed in this section have been

discontinued due to strategic decisions or failure to achieve primary endpoints in clinical trials.

3.1 | Monoclonal anti-IgE antibody ligelizumab

While omalizumab was successfully developed in the tripartite collaboration with Novartis and Genentech, TANOX still proceeded to test the original anti-IgE antibody TNX-901 in a phase II clinical trial with peanut allergic subjects.^{60,61} However, this program had to be stopped after an extensive legal debate with Genentech and Novartis. Recently, a high-affinity version of TNX-901, generated by TANOX, has been developed by Novartis under the name ligelizumab (QGE 031) and is currently in a phase III clinical investigation for the treatment of CSU (NCT03580356). Ligelizumab is a humanized monoclonal IgG1 antibody that binds IgE with an affinity of $\sim 1.4 \times 10^{-10}$ M but does not interact with FcεRIα-bound IgE.²² Unlike omalizumab, it does not accelerate dissociation of pre-formed FcεRIα:IgE complexes and recent structural

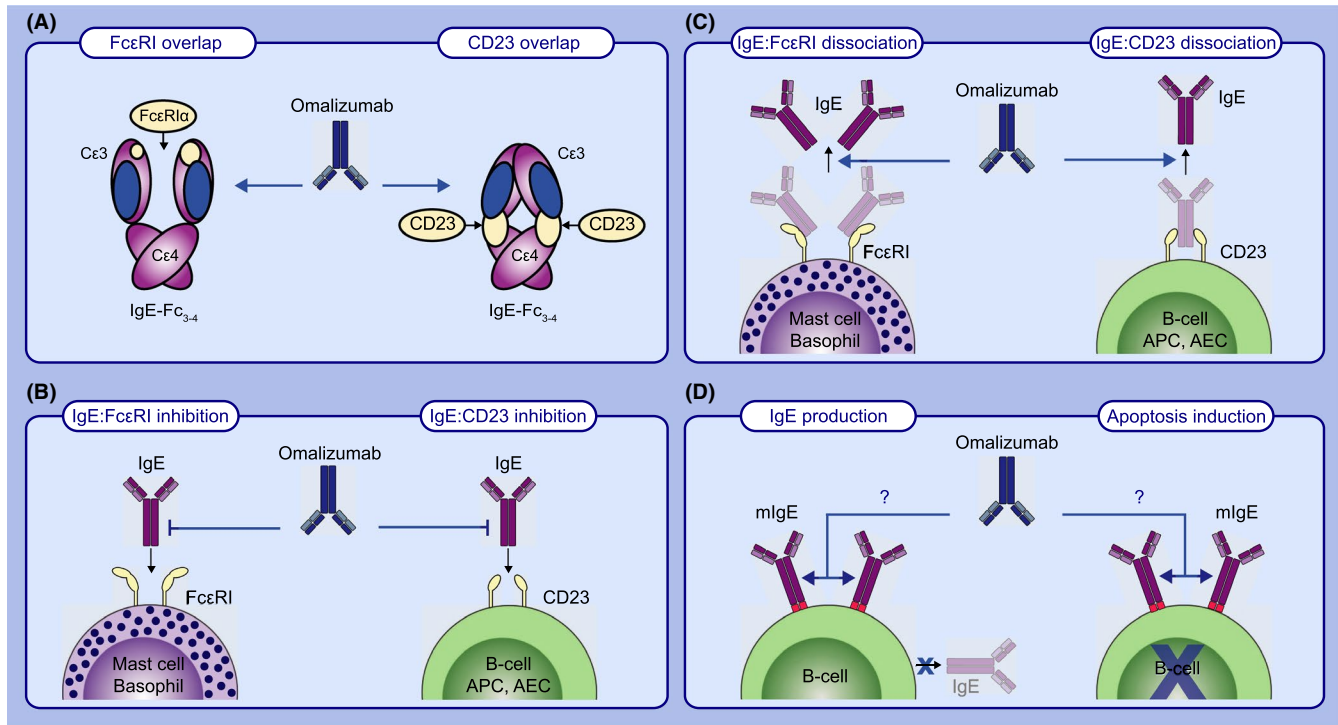


FIGURE 2 Binding characteristics and modes-of-action of omalizumab. A, Schematic overview of omalizumab (blue)-, FcεRIα (left panel)- and FcεRII/CD23 (right panel)-binding sites as well as their relative overlap on IgE-Fc₃₋₄ (purple). B, Omalizumab-mediated inhibition of free IgE binding to FcεRI or CD23. C, Omalizumab-mediated accelerated dissociation of pre-formed IgE:FcεRI and IgE:CD23 complexes. D, Potential mechanisms leading to suppression of IgE production by omalizumab

BOX 1 Major milestone discoveries

Discovery of mast cells in 1878 and basophils in 1879^{1,2}
 Discovery of anaphylaxis in 1902³
 Introduction of the allergy concept in 1906⁴
 Discovery of the "atopic reagent" in serum transfer experiments in 1923⁵
 Introduction of the atopy theory in 1923⁶
 Classification of hypersensitivity reactions in 1963⁷
 Discovery of IgE in 1967^{8,9}
 First anti-IgE concept 1986/87 with development of antibody prototype in 1990^{10,11}
 Market approval of first anti-IgE antibody omalizumab in 2003¹²

analysis revealed that ligelizumab recognizes a distinct IgE epitope, only partially overlapping with that of omalizumab.⁴⁴ Ligelizumab binds to both Cε3 domains across the IgE-Fc dimer and favors the recognition of IgE in an open Fc conformation. It shares significantly more overlap with the binding epitope of FcεRI on IgE than omalizumab and is superior in inhibiting this interaction. On the other hand, ligelizumab shows almost no overlap with the CD23-binding site and is therefore less efficient than omalizumab in blocking IgE:CD23 interactions (Figure 3A).⁴⁴ This distinct receptor inhibition profile might play an important role for its

treatment efficacy in certain diseases. Based on these findings, ligelizumab is predicted to have a therapeutic advantage over omalizumab in FcεRI-driven allergic disorders. Indeed, ligelizumab showed significantly better symptom control in comparison with omalizumab in a phase IIb dose-finding trial for CSU last year.⁶² It was also superior to omalizumab in the inhibition of primary human basophil activation and a passive systemic anaphylaxis mouse model.⁴⁴ On the other hand, it might be less suitable for the treatment of allergic disorders that heavily rely on CD23-dependent processes including antigen presentation or trans-epithelial transport (eg, eosinophilic lung inflammation).⁶³ Further, the distinct receptor inhibition profile provides a plausible explanation as to why ligelizumab lacked superior efficacy over omalizumab treatment in a phase II clinical trial with allergic asthma patients (NCT02075008). In line with a recent clinical trial that revealed a surprisingly long suppression of free serum IgE levels in atopic patients upon single-dose injection,⁴² it has been demonstrated that ligelizumab can suppress IgE production most likely by interacting with CD23-bound IgE on human B cells.⁴⁴ However, this secondary mode-of-action that might increase treatment efficacy of ligelizumab over omalizumab in various atopic disorders needs to be further investigated.

3.2 | Monoclonal anti-IgE antibody quilizumab

Another extensively investigated approach for the treatment of allergic disorders is the specific targeting of IgE-producing B cells

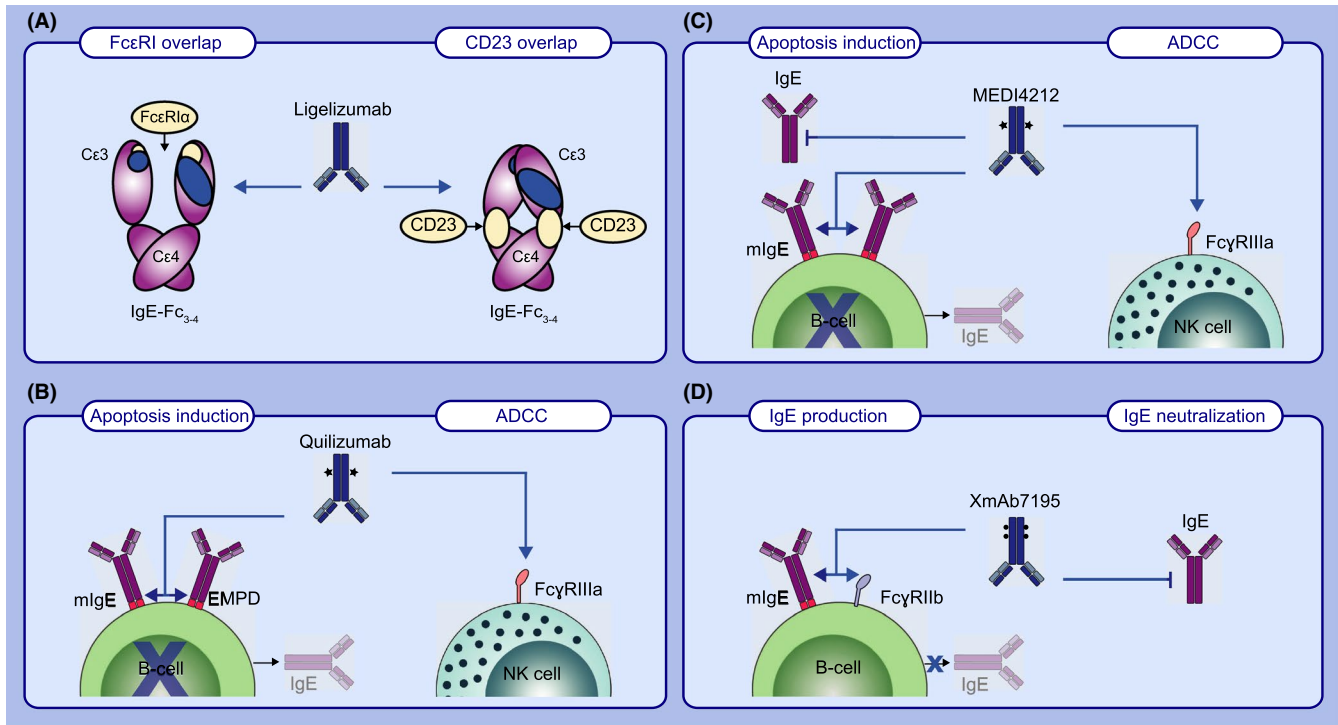


FIGURE 3 Binding characteristics and modes-of-action of different anti-IgE antibodies. A, Schematic overview of ligelizumab (blue)-, FcεRIα (left panel)- and FcεRII/CD23 (right panel)-binding sites as well as their relative overlap on IgE-Fc₃₋₄ (purple). B, Two mechanisms of quilizumab-mediated suppression of IgE production through induction of B-cell apoptosis or antibody-dependent cellular cytotoxicity (ADCC). Afucosylation of quilizumab is indicated with stars. C, Mechanisms of MEDI4212 mediated neutralization of free IgE and suppression of IgE production through induction of B-cell apoptosis or antibody-dependent cellular cytotoxicity (ADCC). Afucosylation of MEDI4212 is indicated with stars. D, XmAb7195-mediated neutralization of free IgE and suppression of IgE production through co-aggregation of mIgE and FcγRIIb on B-cells. Mutations in the antibody Fc-part are indicated with dots

displaying mIgE on their surface.⁶⁴ Genentech has developed the monoclonal mouse anti-human IgE antibody 47H4, which recognizes the EMPD of IgE.⁶⁵ 47H4 has been shown to reduce serum IgE levels and the number of IgE-producing plasma cells in vivo in genetically modified mice that carry the human EMPD in the mouse IgE locus. The authors have concluded that 47H4 most likely induces apoptosis in mIgE-positive B-cells.⁶⁵ Following these studies, an afucosylated humanized version of the antibody, known as quilizumab, has been generated. The removal of fucose from the IgG antibody increases the binding affinity to FcγRIIIa.⁶⁶ This modification enhances the mechanism of antibody-dependent cellular cytotoxicity (ADCC) by NK cells and in the case of quilizumab increased its efficacy to kill mIgE-positive B cells (Figure 3B).⁶⁶ In a phase I clinical trial for allergic rhinitis (NCT01160861) and a phase II clinical trial for allergen-induced asthma (NCT01196039), quilizumab treatment reduced both total and allergen-specific IgE levels by 35% and 40%, respectively, and resulted in a slight amelioration of allergen-induced asthmatic airway responses.⁶⁷ Surprisingly, these results did not translate into phase II clinical trials with allergic asthma patients (NCT01582503) or CSU patients (NCT01987947), as quilizumab treatment only partially reduced serum IgE levels and did not significantly improve the clinical outcome.^{68,69} The disappointing results of these trials might be due to the low frequency and transient abundance of mIgE-positive B cells⁷⁰ as well as the growing evidence that most of the

secreted IgE derives from IgG-producing B cells undergoing sequential isotype switching to IgE.⁷¹⁻⁷⁶

3.3 | Monoclonal anti-IgE antibody MEDI4212

A monoclonal anti-IgE antibody with the aim of combining two modes-of-action, namely the neutralization of free IgE and the enhanced killing of mIgE-positive B cells via ADCC has been developed by MedImmune. MEDI4212 has been selected using phage display technology and targeted mutagenesis of the V_H and V_L chains for affinity maturation.⁷⁷ It binds IgE with an affinity of K_D ~2 pM and does not interact with FcεRI-bound IgE.⁷⁷ To maximize MEDI4212-mediated induction of ADCC in mIgE-positive B cells, an afucosylated version of the antibody has been produced (Figure 3C).⁷⁸ Crystal structure analysis of the MEDI4212 Fab with IgE-Fc₃₋₄ revealed a binding epitope within the Cε3 and Cε4 domains of IgE. It shows a substantial overlap with the FcεRI-binding sites on IgE and thus blocks IgE binding to FcεRI through direct competition. In contrast, MEDI4212 has no obvious overlap with CD23 epitopes on IgE, but still inhibits binding to CD23. The authors concluded that steric or even allosteric inhibition might be involved.⁷⁷ A phase I study with atopic patients (NCT01544348) has been conducted with MEDI4212 in 2013. The results looked promising as MEDI4212 treatment led to more pronounced reduction of free

IgE than omalizumab. However, IgE levels returned to baseline faster in the subjects treated with MEDI4212 than with omalizumab. This has most likely been due to the short serum half-life of the afucosylated antibody.⁷⁹ So far, no clinical follow-up study has been conducted.

3.4 | Monoclonal anti-IgE antibody XmAb7195

The anti-IgE antibody XmAb7195 is a humanized, affinity matured version of the murine parental antibody of omalizumab (MaE11) with a mutated Fc-part for increased binding to the inhibitory receptor FcγRIIb.^{80,81} It has been developed by Xencor with the aim of neutralizing free serum IgE and suppressing IgE production through aggregation of FcγRIIb and mIgE on B-cells (Figure 3D). Indeed, XmAb7195 has been shown to reduce free IgE levels and to inhibit the formation of IgE-secreting plasma cells in a severe combined immunodeficiency (SCID) mouse model engrafted with human PBMCs.⁸⁰ The benefit of this dual-targeting approach has also been evaluated in a phase Ia clinical trial with healthy volunteers and adults with elevated IgE levels (NCT02148744). A second phase Ib clinical trial (NCT02881853) has been completed in 2017. However, the results of these studies have not been published.

3.5 | Omalizumab biosimilars

The patents for omalizumab have recently expired in the United States and Europe. Therefore, various companies have started developing biosimilars. Even though the generation of an omalizumab biosimilar might be faster and less cost intense than generating a novel anti-IgE antibody from scratch, this process requires laborious

optimization and thorough testing.⁸² To get approval by official authorities, biosimilars are expected to feature a similar safety and efficacy profile as the original biological. Typically, at least one phase I and one phase III clinical trial will be required to gather this information. One of the most advanced biosimilars of omalizumab is the monoclonal anti-IgE antibody CMAB007,⁸³ which is developed by the National Engineering Research Center of Antibody Medicine of China. Besides minor changes, it shares the same amino acid sequence as omalizumab. CMAB007 has completed a phase I clinical trial in China with promising results similar to omalizumab⁸³ and is currently undergoing a multi-center, randomized, double-blind, placebo-controlled phase III clinical trial for patients with allergic asthma in China (NCT03468790). Since omalizumab has only recently been approved for the treatment of moderate-to-severe asthma in China in 2017, it will be interesting to see what will happen to CMAB007. There are several additional omalizumab biosimilars, which are currently evaluated at different stages of clinical trials (Table 2).

4 | THE FUTURE: ANTI-IG E BIOLOGICALS IN PRE-CLINICAL EVALUATION

Based on the lessons learned from past anti-IgE approaches, various novel strategies are currently evaluated in pre-clinical studies. Some of these next-generation anti-IgE variants deviate from the classical monoclonal antibody framework and aim to be either more specific than the classical anti-IgE antibody strategies or to feature multi-functionality (Box 2). Whether any of the alternative anti-IgE variants will make it into clinics and whether they will bring superior patient benefit remain to be seen.

4.1 | Anti-IgE designed ankyrin repeat proteins

In 2010, a set of new anti-IgE binders based on designed ankyrin repeat protein (DARPin) scaffolds has been published.⁸⁴ DARPins are genetically engineered alternative scaffold proteins consisting of a repetitive consensus sequence derived from naturally occurring ankyrin repeat proteins.⁸⁵ DARPin libraries with either two or three internal repeats have been generated by randomizing variable positions in the scaffold. For the selection of specific DARPins, these libraries are screened using ribosome display.⁸⁶ Their simple structure, small size and high solubility, allows expression at high

BOX 2 Future research perspectives

Alternative binding scaffolds instead of monoclonal anti-IgE antibodies.

Disruptive IgE inhibitors for active desensitization.

Active suppression of allergic effector cells by targeting inhibitory receptors.

Multi-level targeting approaches to optimize treatment efficacy.

TABLE 2 Omalizumab biosimilars in development

Anti-IgE name	Format	Indication	Clinical status	Company	Year
CMAB007	Antibody	Asthma	Phase III	Mabpharm	2012
STI-004	Antibody	Asthma	Phase III	Sorrento Therapeutics	2015
FB317	Antibody	Asthma, CIU	Phase I	Fountain Biopharma	2016
GBR 310	Antibody	Asthma, CSU	Phase II	Glenmark	2018
CTP-39	Antibody	n.a.	Phase I	Celltrion	2019
BP001	Antibody	Asthma, CU	Phase I	Biosana	2019

quantities in *E. coli*.⁸⁷ Selected DARPins can be genetically joined by suitable linkers to create multivalent or even multi-specific binders.⁸⁸ Multiple DARPins against human IgE were selected, and some of them have been reported to bind to the constant heavy chain of human IgE with high specificity and affinity. DARPIn clone E2_79 showed the highest affinity and prominently inhibited IgE binding to FcεRI. Moreover, it suppressed allergen-mediated degranulation of human FcεRI expressing rat basophilic leukemia cells to the same degree as omalizumab.⁸⁴ In a follow-up study, E2_79 has been found to feature a novel mode-of-action, which led to the definition of a new class of anti-IgE molecules, termed “disruptive IgE inhibitors.” Namely, in addition to neutralizing free IgE, E2_79 actively removes IgE that is pre-bound to FcεRI by a facilitated dissociation mechanism.⁸⁹ The disruptive efficacy could be further enhanced by fusing E2_79 to a non-disruptive anti-IgE DARPIn E3_53 that recognizes FcεRI-bound IgE and thus serves as an anchoring moiety in the resulting bispecific DARPIn bi53_79 (Figure 4A).⁹⁰ In the meantime, several pre-clinical studies have highlighted the therapeutic potential of DARPIn bi53_79. It has been demonstrated to efficiently desensitize human basophils ex vivo, to prevent passive cutaneous anaphylaxis in human FcεRIα transgenic mice in vivo⁹⁰ and to inhibit mast cell-dependent early airway responses in viable human atopic

lung tissue ex vivo.⁹⁰ The possibility to desensitize allergic effector cells by actively removing IgE from the cell surface opens new therapeutic approaches that might impact the development strategies of future anti-IgE drug candidates. Particularly, such an approach might allow acute treatment, which is different to “classical” anti-IgE antibodies that have a rather slow onset of action. Overall, DARPins feature many favorable characteristics including ease of production, high stability and solubility, small molecular size, and the possibility to generate multi-specific binders.⁸⁷ On the other hand, they need to be carefully optimized to warrant low immunogenicity and long serum half-life. Phase III trials with other DARPIn-based drug candidates are currently ongoing (NCT02462486), and it will be interesting to see when the first DARPIn-based biological will be approved for clinical use.

4.2 | Monoclonal anti-IgE antibody 8D6

In 2012, another monoclonal anti-IgE antibody, called 8D6, which binds to the Cε3 domain of IgE with high affinity ($K_D \sim 20$ pmol/L) was generated.^{91,92} 8D6 features a special binding characteristic that has not been described before. It inhibits the interaction of

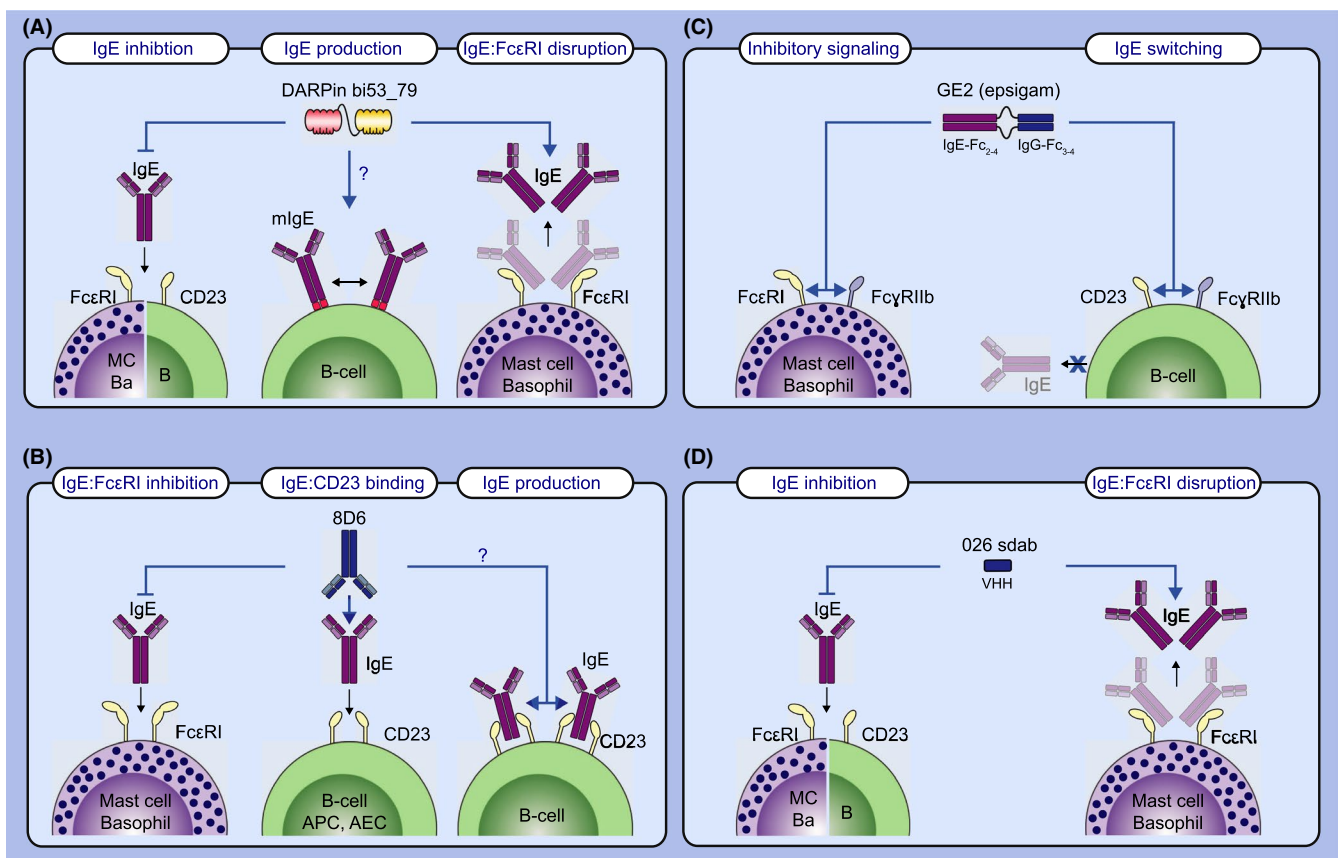


FIGURE 4 Modes-of-action of potential future anti-IgE drug candidates. A, Mechanisms of DARPIn bi53_79 mediated inhibition of IgE-binding to FcεRI and CD23, suppression of IgE production and active disruption of pre-formed IgE:FcεRI complexes. B, 8D6 mediated inhibition of IgE binding to FcεRI, binding of IgE complexes to CD23 and suppression of IgE production. C, GE2 mediated suppression of allergic effector cell activation through co-aggregation of FcεRI with FcγRIIb and suppression of IgE production by co-aggregation of CD23 with FcγRIIb. D, 026 sdab mediated inhibition of IgE-binding to FcεRI and CD23 and active disruption of pre-formed IgE:FcεRI complexes

IgE with FcεRI but does not interfere with IgE-binding to CD23. Similar to ligelizumab, 8D6 recognizes CD23-IgE complexes on the cell surface. However, unlike ligelizumab pre-formed 8D6:IgE immune complexes still bind to CD23.⁹¹ Because aggregation of CD23 on B cells has been claimed to reduce IgE production,^{93,94} it has been speculated that 8D6 could potentially mimic this activity by cross-linking CD23-bound IgE in addition to block sensitization of allergic effector cells.^{91,95} However, this has not been experimentally confirmed so far.

4.3 | IgG-Fc-fusion proteins

An alternative strategy to suppress allergic reactions besides interfering with IgE-binding to FcεRI is to leverage the inhibitory function of FcγRIIb on allergic effector cells.^{96–98} A fusion protein consisting of the human IgG1-Fc₃₋₄ and the human IgE-Fc₂₋₄ parts, known as GE2 (or epsigam), has been generated to aggregate FcεRI with FcγRIIb on allergic effector cells and thereby exploit this mechanism of inhibition (Figure 4C).⁹⁹ GE2 has been shown to inhibit IgE-mediated degranulation of sensitized primary human basophils⁹⁹ and cord blood-derived human mast cells.⁹⁷ Further, it suppresses passive cutaneous anaphylaxis in human FcεRIα transgenic mice,⁹⁹ reduces IL-16 production in Langerhans-like dendritic cells (LLDCs),¹⁰⁰ decreases isotype switching of peripheral human B-cells to IgE,¹⁰¹ inhibits dust mite allergen-induced allergic skin reaction in rhesus monkeys dose-dependently,¹⁰² and showed positive results in a non-human primate model of allergic asthma with cynomolgus monkeys.¹⁰³ Unfortunately, repeated injections of GE2 led to the production of anti-drug antibodies resulting in acute anaphylaxis-like reactions in monkeys.¹⁰³ Multiple modified versions of GE2 failed to improve efficacy to inhibit allergic effector cell activation or its safety profile.¹⁰⁴ Nevertheless, GE2 has been patented by Tunitas Therapeutics in 2015. It will be interesting to see, whether GE2 will be further developed.

A fusion protein (DE53-Fc) consisting of an IgG1-Fc and the anti-IgE anchor DARPIn E3_53 has also been reported to inhibit allergic effector cells by co-engagement of FcεRI and FcγRIIb on allergic effector cells.¹⁰⁵ Compared with GE2, DE53-Fc recognizes FcεRI-bound IgE in a non-competitive manner. Moreover, a mutated version of DE53-Fc (DE53-Fc mut+) with increased affinity for FcγRIIb showed even higher efficacy to inhibit basophil activation.¹⁰⁶

4.4 | Anti-IgE nanobodies

Another alternative scaffold, known as nanobody or single-domain antibody (sdab), has been used to generate specific binders against IgE. These antibody fragments are derived from camelids (eg, camels, dromedaries, and llamas) or cartilaginous fishes (eg, nurse shark and wobbegong), which produce functional antibodies devoid of light chains.¹⁰⁷ Using phage display, nanobody libraries have been screened on cynomolgus IgE and selected clones tested for

cross-reactivity to human IgE as well as for their efficacy to inhibit IgE-binding to FcεRI. 39D11 is one of the identified anti-IgE clones, which has undergone additional rounds of affinity maturation and sequence optimization (humanization).¹⁰⁸ The resulting anti-IgE nanobody IgE026 or 026 sdab is patented by Ablynx. An independent study has shown that 026 sdab binds across the Cε3 and Cε4 domain of human IgE overlapping with the CD23 binding epitope and thus inhibiting IgE-CD23 interactions by steric hindrance.¹⁰⁹ On the other hand, there is virtually no overlap with the FcεRI-binding epitope on IgE. Nevertheless, 026 sdab still inhibits the interaction of IgE with FcεRI, which has been explained by conformational hindrance,¹⁰⁹ as the IgE-Fc adopts a closed conformation in complex with 026 sdab, which is incompatible with FcεRI binding. Consequently, 026 sdab also inhibits mediator release of human FcεRI-expressing RBL-SX38 cells.¹⁰⁹ 026 sdab belongs to the novel class of disruptive IgE inhibitors, as it has been shown to displace IgE from FcεRI (Figure 4D).¹⁰⁹ Nanobodies share many common features with DARPins such as small size, high stability, and solubility as well as the possibility to generate multi-specific binders.¹¹⁰ However, due to the lack of the Fc-part, they also require optimization of pharmacokinetics.¹⁰⁷

5 | CONCLUSIONS

The classical anti-IgE approach using intact humanized monoclonal antibodies for the neutralization of IgE has led to the generation of potent IgE inhibitors such as omalizumab. Despite the successful use of the current anti-IgE therapy for the treatment of severe allergic asthma and CSU, there is certainly still a lot of room for improvement. It seems that an important aspect in the development of monoclonal anti-IgE biologicals has been underestimated so far - namely, that anti-IgE antibodies often feature fundamentally distinct receptor inhibition profiles depending on their particular binding epitopes, steric effects, and the ability to induce conformational changes in IgE upon binding. Obviously, their modes-of-action will heavily depend on these features. It seems that too much emphasis has been assigned to affinity optimization of anti-IgE biologicals in the past. Careful assessment of the efficacy to inhibit IgE-binding to CD23 or FcεRI and the generation of structural information is key to identify their potential modes-of-action. This knowledge will facilitate determination of suitable therapeutic indications and ultimately increase chances of success in clinical trials. IgE-driven conditions, in which CD23-mediated processes are known to play an important role (eg, allergic asthma^{111,112}) should therefore be primarily treated with anti-IgE biologicals that provide strong inhibition of CD23: IgE complex formation, as shown in a model of pulmonary inflammation quite some time ago.⁶³ On the other hand, IgE-dependent conditions like CSU^{113,114} or food allergies¹¹⁵ that heavily rely on FcεRI-mediated processes require treatments with compounds that feature the corresponding inhibition profile. As already mentioned earlier in this review, the specific receptor inhibition profile could be an important reason why ligelizumab treatment did not

show superior efficacy compared with omalizumab treatment in patients with allergic asthma (NCT02075008), however was well superior for the treatment of CSU patients.⁶² While the line between FcεRI- and CD23-mediated pathogenesis cannot always be drawn strictly, this concept should still be kept in mind for the development of future anti-IgE drug candidates.

Another aspect that is likely to impact the generation of new anti-IgE biologicals is the discovery of disruptive IgE inhibitors.^{90,109} The possibility to actively desensitize allergic effector cells might potentially shorten the onset of action and the degree of treatment benefit. Such disruptive IgE inhibitors might also be of great value for rapid desensitization prior to or during allergen-specific immunotherapy (AIT). Combinatorial treatment with a disruptive IgE inhibitor could potentially enhance the outcome, reduce adverse reactions, and increase the overall safety of AIT.

Taken together, we suggest that future anti-IgE biologicals should aim at targeting the involved pathomechanisms at multiple levels to get maximal treatment efficacy.²² An ideal IgE inhibitor should therefore in addition to neutralizing free IgE, actively disrupt IgE:FcεRI complexes on allergic effector cells and suppress IgE production in B cells through engagement of either mIgE, CD23-bound IgE or inhibitory co-receptors. First steps into multi-level targeting have been taken with the development of XmAb7195⁸⁰ or MEDI1412.⁷⁷ However, as clinical trials have demonstrated, there is still much room for improvement of such approaches. While recent studies clearly suggest that more tailored anti-IgE approaches for different indications are required, the question whether a universal anti-IgE biological that shows high treatment efficacy in a multitude of allergic disorders could be developed by broadening the activity profile and following a multi-level IgE targeting strategy remains to be investigated.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ORCID

Pascal Guntern  <https://orcid.org/0000-0001-8840-8577>

Alexander Eggel  <https://orcid.org/0000-0001-8746-3339>

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