Targeting Mast Cells with Biologics

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KEYWORDS

• Mast cell activation • Mastocytosis • Hereditary alpha tryptasemia • Monoclonal • Immunotherapy

KEY POINTS

- Targeting mast cells and the effects of their mediators in individuals with allergic hypersensitivity disorders and reactions is a mainstay of therapy.
- Biologics for the treatment of allergic hypersensitivity and mast cell–associated disorders are emerging as promising second-line interventions.
- There is lack of, and a critical need for, prospective randomized blinded placebo-controlled trials of biologics in disorders where mast cells are central to the pathologic condition.
- Cytoreductive biologics, particularly those targeting neoplastic mast cells, should be reserved for select patients with aggressive and/or pernicious clonal diseases.

INTRODUCTION

Mast cells are bone marrow–derived tissue-resident cells of the myeloid lineage.[1] They reside in large numbers adjacent to blood vessels and near mucosal surfaces where they participate in aspects of both innate and adaptive immune responses and are thought to contribute to the maintenance of connective tissues and potentially other physiologic processes.[2] Mature mast cells harbor abundant secretory granules containing several biologically active preformed mediators that include proteases and histamine, which, along with lipid-derived mediators, are critical to the development of the signs and symptoms of immediate hypersensitivity reactions.[3] Release and generation of such mediators occur during highly regulated degranulation events, resulting canonically from antigen-specific immunoglobulin E (IgE) cross-linking of the

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high-affinity IgE bearing surface receptor FcεRI following exposure to cognate antigen.[4] However, mast cell degranulation may be thought of as a threshold event whereby several potentially additive or even synergistic pathways, including but not limited to cytokine signaling, as well as sensation of temperature, vibration, and stress signals may all contribute.[5,6] Furthermore, mast cells may be activated by cytokines and innate immune pathways to produce inflammatory cytokines independent of degranulation.[2] Many biologics have been developed, or are under development, that target mast cells directly or indirectly through inhibition of cytokines that act upon these cells and/or cytokines and other mediators produced by mast cells. In this review, the authors discuss current and future biologics that may be used to target mast cell disorders and reactions.

ROLE OF MAST CELLS IN ALLERGIC DISEASES AND REACTIONS

Mast cells are thought to be the principal mediators of acute symptoms in type I IgE-mediated immediate hypersensitivity reactions, although blood basophils may also contribute.[7] To accomplish this, mast cells both generate and release several inflammatory mediators, including but not limited to histamine, platelet-activating factor, prostaglandins, leukotrienes, and proteases, such as chymotrypsin and tryptase, the latter of which are stabilized by serglycin-bound heparin and stored within secretory granules.[1–3,7] Mast cells activated following IgE cross-linking by allergen degranulate and release these mediators, leading to vascular leak and pruritus. In addition to their role in the acute phase of allergic hypersensitivity, following activation, mast cells also contribute to the recruitment of other inflammatory cells through the production of chemokines, cytokines, and lipid mediators[8] including the recruitment and activation of eosinophils, which promotes chronic type 2 inflammation.[9] In this way, mast cells are thought to contribute not only to immediate hypersensitivity but also to several chronic allergic diatheses, including eosinophilic gastrointestinal disease (EGID), atopic dermatitis (AD), and food allergy.

CLONAL AND NONCLONAL MAST CELL–ASSOCIATED DISORDERS

In rare instances, mast cells may undergo clonal expansion, most commonly because of the acquired gain-of-function *KIT* p.D816V missense variant,[10,11] which results in constitutive activation and STAT5 phosphorylation independent of ligation by stem cell factor (SCF).[12,13] The net effect of this variant on mast cell homeostasis is at least 2-fold. First, mutant mast cells display indolent, but unrestrained growth, and second, activation of KIT-dependent pathways promotes mast cell reactivity. Together, these result in the clinical entity known as mastocytosis, which may exist in systemic or cutaneous forms as defined through established clinical criteria.[1] Individuals with mastocytosis frequently display recurrent symptoms, such as flushing, pruritus, and systemic anaphylaxis because of episodic mast cell degranulation that may occur following antigen exposure (eg, hymenoptera envenomation) or for unidentified reasons.[14,15] Indeed, individuals with systemic mastocytosis are several times more likely to experience systemic anaphylaxis than individuals in the general population.[15–19] For reasons that are less clear, urticaria and angioedema, symptoms frequently associated with mast cell mediator release, are not common clinical findings among mastocytosis patients.[20]

Symptoms observed in individuals with mastocytosis and associated with mast cell mediator release may not be limited to individuals with identifiable mast cells clones. Idiopathic anaphylaxis (IA) is an extreme example of a mast cell–associated disorder, where affected individuals experience recurrent, often severe, systemic anaphylaxis in

the absence of an identifiable antigenic exposure[21]; some of these individuals may have evidence of clonal disease, but meet only 1 or 2 minor diagnostic criteria or no criteria for the clinical diagnosis of mastocytosis.[22–24] Another example is chronic spontaneous urticaria (CsU), where, as the name suggests, affected individuals have ongoing daily hives of at least 6 weeks' duration without specific provocation.[25] There are also individuals that report recurrent symptoms frequently associated with mast cell mediator release, including, but not limited to, cutaneous flushing, pruritus and/or angioedema, gastrointestinal pain, abdominal distension, vomiting and/or diarrhea, and impairment in energy and/or cognition. Many of these individuals are given the evolving diagnosis of mast cell activation syndrome (MCAS).[23,24] Although criteria for this diagnosis continue to be debated within the medical community, consensus opinion currently generally requires one of 3 clinically measurable mast cell mediators-urine arachidonic acid or histamine metabolites, or serum tryptase- be elevated during an acute symptomatic episode relative to the patient's baseline level, in order to achieve the diagnosis of MCAS.[26–28]

Finally, there are a growing number of heritable genetic conditions that lead to increased mast cell reactivity that thus far have most commonly manifested as physical urticarias.[29,30] One Mendelian genetic trait that bears mention in this context is hereditary alpha tryptasemia (HαT) caused by increased *TPSAB1* copy number encoding alpha-tryptase.[31] It is estimated that this trait may affect up to 5% of the US population and is a common cause for elevated serum tryptase, which can confound the diagnosis of MCAS.[32] Furthermore, up to two-thirds of individuals with this trait have been reported with phenotypes suggestive of mast cell mediator release, and recent mechanistic studies have demonstrated that unique enzymatic properties of alpha-tryptase containing heterotetrameric tryptases may contribute to this association.[33,34]

ALLERGEN IMMUNOTHERAPY: THE FIRST MAST CELL TARGETING BIOLOGIC

Strictly defined, biologics are treatments that are the products of living organisms or contain living organisms within them. Thus, allergen immunotherapy is the first example of the use of a biologic to target mast cell reactivity.

Paul Ehrlich first described mast cells (Mastzelle) in his doctoral dissertation in Leipzig in 1878.[35] It was not for another 30 years that the first pioneering trial in allergen immunotherapy was undertaken by Noon and Freeman,[36,37] and nearly another 50 years before the first double-blind, placebo-controlled trial was conducted demonstrating efficacy of allergen immunotherapy.[38] It was around this time, in the late 1940s and early 1950s, that mast cells were also firmly established as the culprit for immediate hypersensitivity symptoms[39,40] caused by allergens and mediated by the transferable "reaginic" substance in blood described decades earlier by Prausnitz and Kustner,[41] and later shown by Ishizaka to be γE antibodies,[42] now known as IgE. Since this pioneering work studying hay fever, there have been a large number of prospective studies using not only environmental allergens but also stinging insect extracts for individuals with venom allergy, and food antigens, administered via several routes, including subcutaneous, oral, sublingual, transdermal, and even intralymphatic.[43–45] Collectively these studies have provided strong evidence that allergen immunotherapy is safe and effective in inducing sustained nonresponsiveness to environmental and stinging insect antigens and in increasing the tolerated mass of food antigen ingestion by food allergic individuals.[44,46] Safety and efficacy of allergen immunotherapy appears to remain largely true among individuals with mast cell–associated disorders. Indeed, a prospective trial in venom allergic patients with indolent systemic mastocytosis (ISM) demonstrated venom immunotherapy (VIT) as safe and effective.[47]

However, the durability of VIT in patients with clonal disease may be diminished, and retrospective data suggest that these patients may require life-long VIT maintenance for protection from anaphylaxis resulting from field stings.[48,49]

BIOLOGICS TARGETING MAST CELL PROLIFERATION AND EFFECTOR FUNCTION

Immunoglobulin E and Allergen-Specific Monoclonal Antibodies

Much in the same way that antigen has been used to suppress mast cell reactivity, so have monoclonal antibodies been developed targeting this pathway (**Fig. 1**, **Table 1**). The first such biologic developed and used clinically was omalizumab, which targets IgE. Omalizumab is a humanized monoclonal IgG1 that binds to the Cε3 region of IgE, preventing association with both high- and low-affinity IgE receptors on mast cells and other cells bearing these receptors.[50] It was first Food and Drug Administration (FDA) approved for the treatment of allergic asthma in 2003.[51] Through additional mechanistic studies it was recognized that in addition to limiting immediate hypersensitivity reactions via sequestration of antigen-specific IgE, omalizumab also led to downregulation of FcεRI and suppression of mast cell reactivity.[52,53] Based in part on these findings, a trial was undertaken to examine the efficacy of omalizumab among individuals with treatment-refractory CsU.[54] Omalizumab provided significant benefit, and in 2014 received an FDA indication for this disorder. Several additional prospective studies have since demonstrated efficacy of omalizumab as an adjunctive therapy for oral and subcutaneous immunotherapy,[55–57] and still others are ongoing (NCT03881696).

Based upon these successes and the proof-of-concept that omalizumab can promote mast cell quiescence, omalizumab is frequently used in patients with mast cell–associated disorders in clinical practice. Although a relatively large number of case reports, series, and retrospective cohort studies have been largely positive on the use of omalizumab in mast cell–associated disorders,[21,58,59] including in ISM,

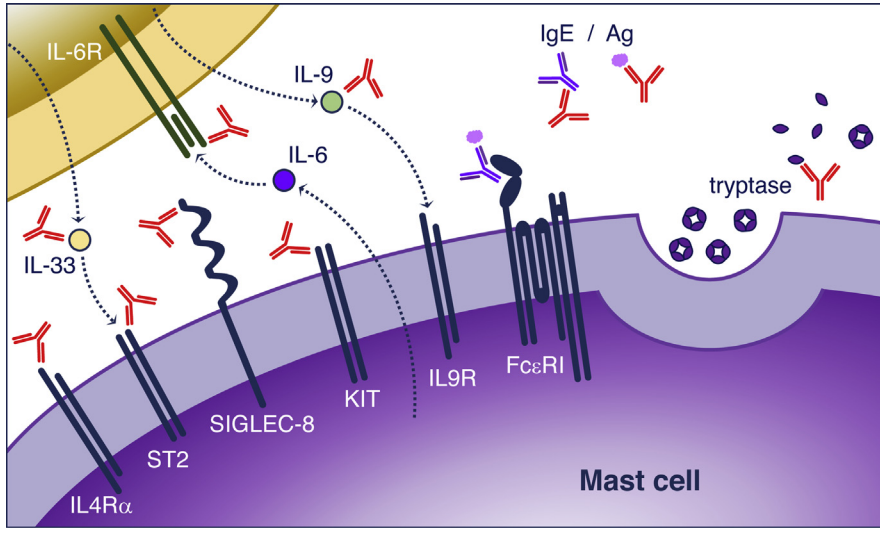

Fig. 1. Biologics targeting mast cell proliferation and effector function. Monoclonal antibodies (*red*) currently FDA approved or in phase 2/3 clinical trials that can target mast cell activation, proliferation, and/or effector functions.

Table 1
Current and future monoclonal antibodies targeting mast cell signaling and mediators

Target	FDA-Indication (I)/Disease Population Under Study (S)	Biologic
KIT	(S) KIT^+ solid tumors	CDX-0158 (formerly KTN0158)
IgE	(I) Allergic asthma, (I) CsU; (S) IA, (S) OIT	Omalizumab, ligelizumab
Allergens	(S) Allergic rhinoconjunctivitis	REGN1908-1909 (Fel d 1); REGN5713-5714-5715 (Bet v 1)
SIGLEC-8	(S) EGID, (S) allergic kerato/conjunctivitis, (S) urticarias, (S) ISM	Antolimab (AK002)
IL4Rα	(I) AD, (I) asthma, (I) CRSwNP; (S) EGID	Dupilumab
IL6R	(I) RA, (I) SJIA, (I) PJIA, (I) GCA, (I) CRS; (S) ISM[a]	Tocilizumab, sarilumab
IL-9	(F) Asthma	Enokizumab (MEDI-528)
IL-33	(S) Food allergy, (S) AD, (S) asthma, (S) CRSwNP	Etokimab (ANB-020), REGN3500, MEDI 3506
ST2	(S) Asthma,	MSTT1041A, GSK3772847
Tryptase	(S) Asthma ± allergic fungal airway disease, (S) AD, (S) COPD	MTPS9579A

Abbreviations: CRS, cytokine release syndrome; GCA, giant cell arteritis; OIT, oral immunotherapy; PJIA, polyarticular juvenile idiopathic arthritis; RA, rheumatoid arthritis; SJIA, systemic juvenile idiopathic arthritis.

[a] There are a large number of studies underway in other rheumatologic conditions using anti-IL6R.

MCAS, and IA, as well as in HαT,[60] to date only 1 randomized double-blind placebo-controlled trial in patients with IA has been undertaken to objectively examine efficacy in any of these populations (NCT00890162). The complete results are not yet published; although preliminary reported data suggest a positive effect, the study was underpowered to achieve its primary endpoint in part owing to the rigorous nature of the inclusion criteria limiting recruitment. While the preponderance of the literature would suggest that in a manner similar to that seen in patients with CsU, omalizumab has efficacy in some patients with mast cell-associated diseases, the trials to demonstrate a broader use have yet to be undertaken, and which endotypes may most benefit from this biologic remain speculative.

A second anti-IgE drug, ligelizumab, which is a humanized IgG that functions in a manner very similar to omalizumab, recently demonstrated efficacy in patients with CsU based on standardized validated symptom scores in a phase 2b study[61] and is currently in 2 phase 3 studies for CsU (NCT03907878, NCT03580356). Interestingly, in the phase 2b study, ligelizumab was reported to have greater efficacy compared with omalizumab in improving symptom scores and resolving patients' hives. However, baseline weight and total IgE were not stratified for or taken into account post hoc, and thus it is not clear whether this difference is due to a failure to meet the 0.016 mg/kg/IgE (IU/mL) therapeutic threshold for omalizumab, or if the observed increase in efficacy will be reproduced in larger ongoing trials.

Like omalizumab, the binding site of ligelizumab is in the Cε3 region of IgE, which is inaccessible once IgE is bound to FcεRI,[62] thus preventing unwanted cross-linking of receptor-bound IgE that would result in signaling and mast cell degranulation. Despite this design, between 0.09% and 0.2% of individuals who receive omalizumab develop systemic anaphylaxis,[63] typically on the first few administrations, and thus

omalizumab has a black box warning associated with this risk. The mechanism underlying these rare reactions is unclear. Several hypotheses have been proposed, including non-IgE–mediated hypersensitivity to polysorbate,[64,65] an excipient contained in omalizumab preparations, and the presence of preexisting antibodies directed against some portion of omalizumab,[66] although neither has been definitely demonstrated to be the culprit. Because of this uncertainty, it is recommended that all individuals receiving this medication be observed by a medical group capable of treating anaphylaxis for 2 hours on the first 3 injections, and for 30 minutes with each subsequent injection.[66]

Recently, an alternative strategy to allergen immunotherapy has been developed whereby neutralizing monoclonal antibodies targeting major allergen components have been developed to limit immediate hypersensitivity reactions resulting from exposure. Two such targets have biologics in development. Two pooled monoclonal $IgG4^P$ antibodies (REGN1908 and REGN1909)- the modified isotype nomenclature indicating the presence of IgG1 sequence at the hinge-region rendering the monoclonal antibody more stable- targeting the major cat allergen Fel d 1, have completed a phase 1 study.[67] In this study, a single injection of both of the 2 noncompetitive monoclonal inhibitors given to cat-allergic individuals resulted in significant improvement in total nasal symptom scores (TNSS) following nasal provocation. Both TNSS and wheal size in response to skin-prick testing to cat hair extract was reduced for up to 85 days after injection. The mechanism underlying the potential durability of this intervention is unclear.

Using a similar strategy, another pool of 3 noncompetitive monoclonal antibodies targeting the major birch allergen Bet v 1 (REGN5713, REGN 5714, REGN5715) is currently under investigation in a 2-part phase 1 randomized, double-blind, placebo-controlled study (NCT03969849) with the same primary endpoints at the Fel d 1 study: evaluating safety and tolerability in part 1, and assessing TNSS and skin prick testing (SPT) responses to birch in part 2.

Stem Cell Factor Receptor KIT

The development of mast cell precursors in the bone marrow as well as the maintenance of long-lived mature mast cells in tissue is dependent on SCF signaling via its cognate tyrosine kinase receptor KIT. Because gain-of-function variants in *KIT* as well as exogenous administration of SCF to humans promote mast cell activation,[68,69] targeting this pathway to limit symptoms of immediate hypersensitivity has long been of interest. Complicating this strategy is the fact that SCF is also crucial for normal hematopoietic stem cell maturation.[70] Thus, identifying ways to inhibit this pathway while limiting marrow suppression and toxicity has been of paramount importance.

Although several small molecules have been developed to inhibit tyrosine kinase activity generally, including imatinib, nilotinib, dasatinib, midostaurin, masitinib, ibrutinib, and avapritinib, few have been KIT-specific, and most have had significant and limiting toxicity.[71] One KIT-specific biologic CDX-0158 (formerly KTN0158), a humanized monoclonal antibody that has inhibitory activity against both wild-type and mutant KIT, completed a phase 1 trial for KIT-positive advanced solid tumors in mid-2019 (NCT02642016). Although these first-in-human data are not yet available, in preclinical studies CDX-0158 reduced mast cell degranulation, mast cell number in tissues, and mast cell tumor size in canines.[72] In dogs, this monoclonal antibody resulted in anemia in 1 animal, suggesting marrow suppression may occur.

An additional intriguing strategy for targeting this pathway has been described by Garcia and colleagues.[73] They have engineered an SCF-analogue with partial agonistic activity that preferentially activates hematopoietic progenitors and does not promote mast

cell activation in vitro or in mouse models. Whether such a partial agonist could be developed and applied to mast cell–associated disorders in humans remains to be seen.

Sialic Acid–Binding Immunoglobulin-Type Lectin-8

Sialic acid–binding immunoglobulin-type lectins (SIGLECs) are a family of immunoglobulin-like carbohydrate-binding molecules present primarily on the plasma membrane of immune cells that recognize specific sialic acid residues.[74] Each of the 15 known human SIGLECs display different tissue distributions and serve diverse functions. Although these molecules may contribute to cellular signaling, adhesion, and phagocytosis, most contain an intracytoplasmic domain bearing one or more immunoreceptor tyrosine-based inhibitory motif (ITIM) motifs and serve to limit immune cell activation. SIGLEC-8 was first cloned from a human with idiopathic hypereosinophilic syndrome[75] and is known to be expressed only on human allergic effector mast cells and eosinophils, and to a lesser extent on basophils.[76] Engagement of SIGLEC-8 by the endogenous ligand 6′sulfo-sialyl-Lewis-X induces eosinophil apoptosis and inhibits IgE-mediated mast cell calcium flux and degranulation.[77,78] Thus, an agonist or suicide immunoglobulin that could direct antibody-dependent cell-mediated cytotoxicity (ADCC) of allergic effector cells could be an effective treatment for mast cell–associated disorders.

Antolimab (formerly AK002) is a nonfucosylated IgG1 monoclonal antibody targeting SIGLEC-8 under study for several clinical indications. This molecule is currently given as an infusion, and owing to the lack of fucosylation, induces ADCC of blood eosinophils. In humanized mouse models, it limits systemic anaphylaxis as well as eosinophilic inflammation of the gut.[79] Ostensibly it is this ADCC activity that results in first infusion reactions, which have been described in unpublished reports of early phase studies; extension phase studies are ongoing (NCT03664960). This drug is currently being evaluated in several ongoing or recently completed clinical trials, including EGID (NCT03496571, NCT03664960), treatment-refractory urticarias, including CsU, cholinergic urticaria, and symptomatic dermatographism (NCT03436797), and a phase 1b study of severe allergic conjunctivitis (atopic keratoconjunctivitis, vernal keratoconjunctivitis, and perennial allergic conjunctivitis refractory to topical treatments) (NCT03379311). Finally, an open-label phase 1 dose-finding study in patients with ISM was also recently completed (NCT02808793). Although the preliminary data reported in these studies have thus far been positive, the results currently remain unpublished.

Cytokine and Cytokine-Receptor Blockade

In addition to the effects of SCF on mast cell reactivity and homeostasis, there are many biologics available or in development targeting other cytokines that contribute to the pathogenesis of type I hypersensitivity reactions.

Interleukin-4 (IL-4) is an early and potent driver of Th2 immune responses, contributing to skin barrier dysfunction and promoting IgE class-switching in humans.[80,81] IL-4 shares a coreceptor IL4Rα, with IL-13, which has been shown to be important for generation of high-affinity IgE associated with strong mast cell activation and severe allergic reactions in mice,[82,83] and is an important effector cytokine in allergic inflammatory responses. Both of these cytokines are generated by activated mast cells, and IL4Rα is present on the cell surface.[84–86] IL4Rα has also been shown to contribute to IL-33–associated histamine release in mouse models.[87]

Dupilumab is a fully human IgG4 monoclonal antibody that blocks receptor activation by IL-4 or IL-13. It is FDA approved for the treatment of individuals older than 12 years of age with moderate to severe AD or moderate to severe asthma, and in adults with chronic rhinosinusitis with nasal polyposis chronic rhinosinusitis with nasal

polyps (CRSwNP) refractory to standard-of-care interventions.[88–90] Although it is thought that some of the efficacy observed in these atopic disorders may result from reduced activity of mast cell–derived IL-4 and IL-13 as well as reduced IL4Rα--signaling in mast cells, the mast cell–specific contribution to the pathogenesis or improvement of these diseases remains undefined in humans.

IL-6 has been demonstrated to increase proliferation and IgE-dependent activation of cultured human mast cells in vitro.[91] Individuals with ISM have been shown to have elevated levels of serum IL-6, which may contribute to several clinical symptoms, including mast cell reactivity.[92–95] Heightened serum levels in these individuals are associated with the presence of the *KIT* p.D816V gain-of-function missense variant, which promotes constitutive overexpression of IL-6 in vitro.[95] There are 2 currently FDA-approved IL-6 receptor inhibitors: tocilizumab, a humanized monoclonal IgG1, and sarilumab, a fully human monoclonal IgG1, both of which are approved for the treatment of autoimmune disease. Tocilizumab also has an indication for the treatment of cytokine release syndrome associated with chimeric antigen receptor T-cell therapy, which is thought to be a result of exuberant cytokine release from activated macrophages. Although mast cells have been implicated in the pathogenesis of joint destruction in disorders such as rheumatoid arthritis,[96] it is generally thought that other immune cells are principal drivers of autoimmune inflammation. However, the observed effects of IL-6 on the mast cell compartment among patients with ISM have led to an investigator-initiated phase 2 double-blind placebo-controlled trial of sarilumab in patients with this disorder (NCT03770273). Results are not yet available, but primary outcome measures include safety and quality of life as measured by a validated questionnaire.

IL-9 is a pleiotropic cytokine produced by several immune cell lineages, including many lymphocytes as well as mast cells.[97] Among the identified activities of this cytokine, it has been demonstrated that IL-9 can promote mast cell proliferation in vitro,[98] contributes to tissue recruitment of mast cells to sites of allergic inflammation in vitro,[99] and IL-9 produced both by mucosal mast cell and tissue homing/infiltrating Th2 cells may promote allergic phenotypes, such as AD and food allergy. Enokizumab (formerly MEDI-528) is a humanized IgG1 targeting IL-9. Despite the associations between allergic inflammation, mast cells, and IL-9, it failed in a phase 2b study of adults with uncontrolled asthma whereby no difference was seen in the Asthma Control Questionnaire-6 score, forced expiratory volume in 1 second (FEV1), or rate of exacerbation.[100]

IL-33 is a member of the IL-1 superfamily of cytokines and is expressed predominantly by cells of ectodermal and myeloid origin, including epithelia and mast cells.[101] This cytokine is produced following epithelial damage or stress and contributes to allergic inflammation via signaling through its cognate receptor ST2 found on mast cells, eosinophils, ILC2s, and Th2 lymphocytes. In this context, mast cells both produce and respond to IL-33. Etokimab (ANB020) is a humanized IgG1 anti-IL-33 monoclonal antibody that has been evaluated in phase 2a trials for AD and food allergy.[102] In the AD study, all subjects received a placebo infusion followed 1 week later by a single infusion of study drug. AD severity significantly improved as measured by a reduction in Eczema Area and Severity Index core, with maximal improvement occurring between day 29 and 57. This improvement appeared to persist in some individuals out to 150 days after infusion. Although the mast cell compartment was not evaluated in this study, another similarly sized placebo-controlled phase 2a study examined the efficacy of etokimab in peanut allergic adults.[103] In this study, 11/15 peanut-allergic individuals who received a single infusion of drug and failed an oral food challenge (OFC) at baseline were able to pass OFC at day 15, and 4 remained tolerant at day 45 after infusion. None of those receiving placebo were able to pass OFC. Despite

this clinical result, there was no detectable difference in SPT responses to peanut during the study. In vivo and in vitro data suggest that short-term exposure to IL-33 can increase both IgE-dependent and -independent mast cell activation,[104,105] potentially without clear provocation in a manner dependent on IL4Rα-mediated signaling.[87]

Taken together, these results thus suggest that IL-33 blockade may be a viable therapy for prevention of mast cell activation generally, and there are several clinical trials recently completed or underway evaluating the effect of IL-33/ST2 blockade on several allergic and pulmonary diseases where mast cells may contribute. A phase 2 study of etokimab in patients with severe eosinophilic asthma (NCT03469934) was recently completed, and another in patients with CRSwNP is still recruiting (NCT03614923). Phase 2 studies of another fully human $IgG4^P$ anti-IL-33 monoclonal antibody REGN3500 (formerly SAR440340) in patients with AD (NCT03112577) and allergic asthma (NCT02999711) alone, or in combination with dupilumab, have recently been completed, and a third phase 2 study in chronic obstructive pulmonary disease (COPD) (NCT03546907) has also completed recruitment. A third anti-IL-33 monoclonal antibody MEDI 3506 is also recruiting adults with moderate to severe AD for a phase 2 safety and efficacy study (NCT04212169).

Within the same pathway, GSK3772847 (formerly CNTO 7160), a human IgG2 anti-ST2 monoclonal antibody, has completed a phase 2 study designed to determine efficacy in adults with moderate to severe asthma (NCT03207243) and has completed recruitment in another phase 2 study of individuals with moderate to severe asthma with concomitant allergic fungal airway disease (NCT03393806). A second anti-ST2 candidate, MSTT1041A (formerly AMG 282 and RG6149), a defucosylated fully human monoclonal antibody, has completed phase 1 study in patients with allergic asthma (NCT01928368) and CRSwNP (NCT02170337); phase 2 studies in moderate to severe AD (NCT03747575), severe asthma (NCT02918019), and COPD (NCT03615040) have also either recently been completed or have finished recruiting. Published results from all of these trials are not yet available.

Tryptase Neutralization

Although targeting mast cell mediators using antihistamines, leukotriene antagonists, and mast cell stabilizers is the mainstay of treatment of individuals with mast cell disorders, there is currently no FDA-approved biologic other than immunotherapy with allergen that targets these inflammatory molecules. However, there is renewed interest in targeting tryptase to treat allergic diseases. Human tryptases are a family of serine proteases that have only recently evolved and share only modest homology with orthologs, even those present in nonhuman primates.[106] There are 5 known tryptase loci, with *TPSAB1* and *TPSB2* encoding the known common secreted forms α- and/or β-tryptase.[107] Enzymatically active tryptases exist as tetrameric complexes stabilized in mast cell granules by heparin.[108] In a humanized mouse model, neutralization of enzymatically active human tryptase has been shown to reduce the severity of IgE-dependent systemic anaphylaxis.[109] Furthermore, post hoc analysis reexamining the treatment benefits of omalizumab in patients with allergic asthma suggests that a greater number of the enzymatically active β-tryptase isoform is associated with a failure to respond to this IgE-directed therapy. Based on these observations, a phase 2a, randomized, placebo-controlled, double-blind, multicenter, 2-arm study is underway to evaluate the safety and efficacy of a humanized antitryptase IgG4 monoclonal antibody (MTPS9579A) as an add-on therapy in patients with uncontrolled moderate to severe asthma (NCT04092582). The primary composite endpoint is the time to first asthma exacerbation or diary worsening. Several additional objective clinical and laboratory measures will be evaluated as secondary endpoints. Although clinical efficacy

data are not yet available, targeting tryptase in mast cell–associated disorders may be of benefit as mature tryptases- in particular heterotetrameric αβ-tryptase- may contribute to many clinical phenotypes reported.[33]

BIOLOGICS TARGETING NEOPLASTIC MAST CELLS

In addition to targeting dysregulated physiologic processes that lead to enhanced mast cell activation, proliferation, or reactivity, several additional targets have been identified on neoplastic mast cells that can be targeted to eliminate mast cells (**Fig. 2**). Generally, these biologics are cytotoxic, either bearing a conjugated poisonous payload to cells they target or exhibiting strong ADCC activity (**Table 2**). Thus, these agents carry significant off-target effects and should be reserved for individuals with advanced disease or those with associated hematologic malignancies and given by physicians experienced in the care of such patients.

CD25

IL-2 is an essential cytokine for immune function.[110] Failure of IL-2 signaling, principally in T lymphocytes, because of autosomal or X-linked recessive loss-of-function mutations in one of the 3 heterotrimeric IL-2R subunits, results in combined or severe combined immunodeficiency.[111–114] IL-2 is also important for maintenance of immune tolerance, and impairment in signaling has been shown to result in loss of peripheral and self-tolerance in humans. *IL2RA* encodes the alpha subunit, which is also commonly known as CD25, which is aberrantly expressed on the surface of neoplastic mast cells,[115] where it is able to bind IL-2, but unable to signal because of the absence of IL-2Rβ. Daclizumab is an anti-CD25 humanized IgG1 monoclonal antibody approved for adults with relapsing forms of multiple sclerosis.[116] In 1 small case series, 4 patients with refractory aggressive systemic mastocytosis were treated open and off-label with daclizumab. Only 1 individual demonstrated evidence of a temporary partial clinical response with improvement in pleural effusions, ascites, flushing, emesis, diarrhea, fatigue, and joint pain over the weeks following administration of daclizumab. At that time, changes were also observed on bone marrow section, which suggested mast cell destruction. However, disease fully recurred within 1 month, and none of the other 3 individuals demonstrated benefit.[117] This drug has since been

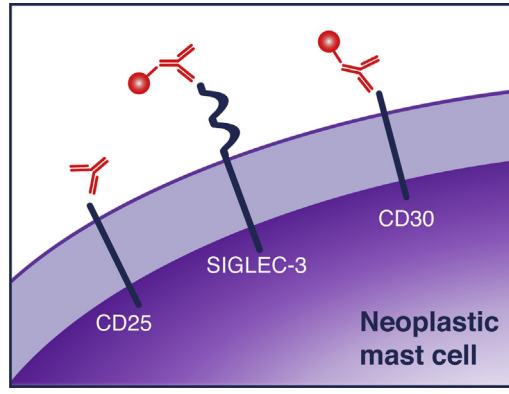

Fig. 2. FDA-approved biologics that can target neoplastic mast cells. Monoclonal antibodies (*red*) FDA approved for malignancy or immunosuppression that have shown some efficacy in case reports of patients with advanced or aggressive clonal mast cell disease.

Table 2
Food and Drug Administration–approved monoclonal antibodies that can target neoplastic mast cells

Target	Indication	Normal Tissue Distribution	Biologic
CD25	Allograft rejection prophylaxis; multiple sclerosis	Lymphocytes and activated granulocytes	Basiliximab, daclizumab[a]
CD30	Hodgkin or anaplastic lymphoma; $CD30^+$ T-cell lymphomas	Lymphocytes and granulocytes	Brentuximab vedotin
SIGLEC-3 (CD33)	AML	Myeloid lineage cells and precursors; activated T lymphocytes	Gemtuzumab ozogamicin

[a] Voluntarily withdrawn by the manufacturer over safety concerns.

voluntarily withdrawn from the market over safety concerns.[118] Basiliximab is a chimeric IgG1 monoclonal antibody that also targets CD25 and is indicated for the acute organ rejection prophylaxis following renal transplantation.[119] This biologic has not been studied in mast cell diseases.

CD30

Tumor necrosis factor receptor superfamily member 8, or CD30, is normally expressed on the cell surface of activated T, B, and NK lymphocytes, and at a lower level in some myeloid cells, such as activated monocytes and eosinophils.[120] Ligation of CD30 by CD30L leads to NF-κB activation that can promote cellular proliferation or death. Brentuximab vedotin is a chimeric IgG1 monoclonal antibody targeting CD30 conjugated to monomethyl auristatin E (vedotin) that disrupts microtubule formation. It has several clinical indications, including advanced and high-risk Hodgkin lymphomas, systemic or cutaneous anaplastic large cell lymphoma, or other CD30-expressing peripheral T-cell lymphomas.[121] Treatment of CD30-positive systemic mastocytosis in 1 case series involving 4 patients with aggressive systemic mastocytosis (ASM) or ISM was associated with evidence of reduced disease burden in 2 patients.[122] One individual experienced partial remission with resolution of pancytopenia such that growth factor support was no longer necessary, and the patient was continued for 44 monthly cycles of drug.

Sialic Acid–Binding Immunoglobulin-Type Lectin-3 (CD33)

SIGLEC-3, or CD33, belongs to the same family of sialic acid–binding lectins as SIGLEC-8, the promising therapeutic target present on nonneoplastic mast cells.[74] In healthy individuals, CD33 is found on the surface of many myeloid lineage cells, including mast cells, as well as on activated T lymphocytes, where it serves as an inhibitory receptor regulating signaling. Gemtuzumab ozogamicin is a humanized IgG4 monoclonal antibody against CD33 that has been conjugated to a cytotoxic agent (*N*-acetyl gamma calicheamicin dimethyl hydrazide) approved for the treatment of CD33-positive acute myeloid leukemia (AML) in adults and reserved for relapsed or refractory CD33-positive AML in children.[123] In 1 case report, an individual with mast cell leukemia refractory to several agents, including imatinib, cladribine, and midostaurin, was treated with gemtuzumab ozogamicin resulting in complete histologic remission out to 7 months of follow-up.[124]

DISCUSSION

The utilization of biologics, in the form of allergen-specific immunotherapy, to target mast cells and their mediators in order to treat and even prevent immediate hypersensitivity symptoms and reactions has been part of clinical practice for over a century. Recent advances in technologies have massively expanded the number of monoclonal antibodies that may be used in a similar manner. Although published randomized prospective blinded placebo-controlled trials evaluating efficacy of the expanding number of biologics are generally lacking, many of these molecules hold significant promise for mast cell–associated diseases and reactions.

SUMMARY

Several biologics exist that hold promise for mast cell–associated diseases. However, only allergen immunotherapy, IgE-blocking monoclonal antibodies, and more recently, anti-IL33, have been shown to be effective in clinical trials involving clinical phenotypes resulting from mast cell activation, namely, IgE-mediated immediate hypersensitivity or CsU. Although additional studies have been completed and published results should be forthcoming, the only prospective studies of biologics in mast cell–associated disorders in the literature currently are trials of anti-IgE monoclonal therapies for CsU and VIT in ISM. Thus, prospective randomized placebo-controlled clinical trials of biologics in mast cell–associated diseases are critically needed because efficacy in CsU or other allergic diseases, such as asthma and AD, may not translate to the mast cell compartment.

CLINICAL CARE POINTS

- Diagnostic criteria for MCAS are incompletely defined and unevenly applied by physicians, making the care and study of individuals with this diagnosis very challenging.
- VIT is safe and effective but potentially less durable in patients with ISM who may require lifelong maintenance to ensure protection from field stings.
- Anti-IgE therapy is effective for antihistamine-refractory CsU, but case reports and cohort studies suggest it may not effectively treat many other symptoms frequently attributed to mast cell activation.
- There are no prospective studies to support off-label use of any monoclonal antibody in clonal or non-clonal mast cell–associated diseases.
- Cytoreductive biologics should be reserved for patients with aggressive clonal mast cell disease and administered only by physicians experienced in caring for these complex patients.

DISCLOSURE

The authors declare no competing or conflicting interests.

REFERENCES

1. Metcalfe DD. Mast cells and mastocytosis. Blood 2008;112(4):946–56.
2. Olivera A, Beaven MA, Metcalfe DD. Mast cells signal their importance in health and disease. J Allergy Clin Immunol 2018;142(2):381–93.
3. Wernersson S, Pejler G. Mast cell secretory granules: armed for battle. Nat Rev Immunol 2014;14(7):478–94.

4. Turner H, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonRI. Nature 1999;402(6760 Suppl):B24–30.
5. Halova I, Ronnberg E, Draberova L, et al. Changing the threshold-signals and mechanisms of mast cell priming. Immunol Rev 2018;282(1):73–86.
6. Gilfillan AM, Peavy RD, Metcalfe DD. Amplification mechanisms for the enhancement of antigen-mediated mast cell activation. Immunol Res 2009; 43(1–3):15–24.
7. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med 2012;18(5): 693–704.
8. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation. Biochim Biophys Acta 2012;1822(1):21–33.
9. Shakoory B, Fitzgerald SM, Lee SA, et al. The role of human mast cell-derived cytokines in eosinophil biology. J Interferon Cytokine Res 2004;24(5):271–81.
10. Longley BJ, Tyrrell L, Lu SZ, et al. Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. Nat Genet 1996;12(3):312–4.
11. Nagata H, Worobec AS, Oh CK, et al. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci U S A 1995;92(23):10560–4.
12. Furitsu T, Tsujimura T, Tono T, et al. Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. J Clin Invest 1993; 92(4):1736–44.
13. Baumgartner C, Cerny-Reiterer S, Sonneck K, et al. Expression of activated STAT5 in neoplastic mast cells in systemic mastocytosis: subcellular distribution and role of the transforming oncoprotein KIT D816V. Am J Pathol 2009;175(6): 2416–29.
14. Kors JW, van Doormaal JJ, de Monchy JG. Anaphylactoid shock following Hymenoptera sting as a presenting symptom of systemic mastocytosis. J Intern Med 1993;233(3):255–8.
15. Bonadonna P, Zanotti R, Muller U. Mastocytosis and insect venom allergy. Curr Opin Allergy Clin Immunol 2010;10(4):347–53.
16. Gulen T, Hagglund H, Dahlen B, et al. High prevalence of anaphylaxis in patients with systemic mastocytosis - a single-centre experience. Clin Exp Allergy 2014;44(1):121–9.
17. Brockow K, Jofer C, Behrendt H, et al. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63(2):226–32.
18. Sheikh A, Hippisley-Cox J, Newton J, et al. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. J R Soc Med 2008;101(3):139–43.
19. Wood RA, Camargo CA Jr, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol 2014;133(2):461–7.
20. Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010;125(6): 1269–78.e2.

21. Carter MC, Akin C, Castells MC, et al. Idiopathic anaphylaxis yardstick: practical recommendations for clinical practice. Ann Allergy Asthma Immunol 2020;124(1):16–27.
22. Valent P, Akin C, Metcalfe DD, et al. 2016 updated WHO classification and novel emerging treatment concepts. Blood 2017;129(11):1420–7.
23. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140(2):349–55.
24. Picard M, Giavina-Bianchi P, Mezzano V, et al. Expanding spectrum of mast cell activation disorders: monoclonal and idiopathic mast cell activation syndromes. Clin Ther 2013;35(5):548–62.
25. Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. Immunol Allergy Clin North Am 2014;34(1):33–52.
26. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126(6):1099–104.e4.
27. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157(3):215–25.
28. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. J Allergy Clin Immunol Pract 2019;7(4):1125–33.e1.
29. Ombrello MJ, Remmers EF, Sun G, et al. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. N Engl J Med 2012;366(4):330–8.
30. Boyden SE, Desai A, Cruse G, et al. Vibratory urticaria associated with a missense variant in ADGRE2. N Engl J Med 2016;374(7):656–63.
31. Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016;48(12):1564–9.
32. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. Immunol Allergy Clin North Am 2018;38(3):483–95.
33. Le QT, Lyons JJ, Naranjo AN, et al. Impact of naturally forming human alpha/beta-tryptase heterotetramers in the pathogenesis of hereditary alpha-tryptasemia. J Exp Med 2019;216(10):2348–61.
34. Lyons JJ, Chovanec J, O'Connell MP, et al. Heritable risk for severe anaphylaxis associated with increased α-tryptase-encoding germline copy number at TPSAB1. J Allergy Clin Immunol 2020.
35. Beiträge PE. Zur Theorie und Praxis der histologischen Färbung [doctoral thesis]. Germany: University of Leipzig; 1878. Available at: https://www.worldcat.org/title/beitrage-fur-theorie-und-praxis-der-histologischen-farbung/oclc/63372150.
36. Prophylactic LN. Innoculation against hay fever. Lancet 1911;177(4580):2. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)78276-6/fulltext.
37. Freeman J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. Lancet 1911;178(4594):4.
38. Frankland AW, Augustin R. Prophylaxis of summer hay-fever and asthma: a controlled trial comparing crude grass-pollen extracts with the isolated main protein component. Lancet 1954;266(6821):1055–7.
39. Rocha e Silva M, Scroggie AE, Fidlar E, et al. Liberation of histamine and heparin by peptone from the isolated dog's liver. Proc Soc Exp Biol Med 1947;64(2):141–6.
40. Riley JF, West GB. Histamine in tissue mast cells. J Physiol 1952;117(4):72P–3P.

41. Prausnitz CKH. Studien über die Überempfindlichkeit. Centralbl Bakterio 1921; 86:160.
42. Ishizaka K, Ishizaka T. Identification of gamma-E-antibodies as a carrier of reaginic activity. J Immunol 1967;99(6):1187–98.
43. Gunawardana NC, Durham SR. New approaches to allergen immunotherapy. Ann Allergy Asthma Immunol 2018;121(3):293–305.
44. Wood RA. Food allergen immunotherapy: current status and prospects for the future. J Allergy Clin Immunol 2016;137(4):973–82.
45. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. J Allergy Clin Immunol 2005;115(3):439–47 [quiz: 48].
46. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. World Allergy Organ J 2015;8(1):17.
47. Bonadonna P, Gonzalez-de-Olano D, Zanotti R, et al. Venom immunotherapy in patients with clonal mast cell disorders: efficacy, safety, and practical considerations. J Allergy Clin Immunol Pract 2013;1(5):474–8.
48. Bonadonna P, Zanotti R, Pagani M, et al. Anaphylactic reactions after discontinuation of hymenoptera venom immunotherapy: a clonal mast cell disorder should be suspected. J Allergy Clin Immunol Pract 2018;6(4):1368–72.
49. Oude Elberink JN, de Monchy JG, Kors JW, et al. Fatal anaphylaxis after a yellow jacket sting, despite venom immunotherapy, in two patients with mastocytosis. J Allergy Clin Immunol 1997;99(1 Pt 1):153–4.
50. Pennington LF, Tarchevskaya S, Brigger D, et al. Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. Nat Commun 2016;7:11610.
51. Busse WW. Anti-immunoglobulin E (omalizumab) therapy in allergic asthma. Am J Respir Crit Care Med 2001;164(8 Pt 2):S12–7.
52. Gomez G, Jogie-Brahim S, Shima M, et al. Omalizumab reverses the phenotypic and functional effects of IgE-enhanced Fc epsilonRI on human skin mast cells. J Immunol 2007;179(2):1353–61.
53. Beck LA, Marcotte GV, MacGlashan D, et al. Omalizumab-induced reductions in mast cell Fce psilon RI expression and function. J Allergy Clin Immunol 2004; 114(3):527–30.
54. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368(10):924–35.
55. Brandstrom J, Vetander M, Sundqvist AC, et al. Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents. Clin Exp Allergy 2019;49(10):1328–41.
56. Takahashi M, Soejima K, Taniuchi S, et al. Oral immunotherapy combined with omalizumab for high-risk cow's milk allergy: a randomized controlled trial. Sci Rep 2017;7(1):17453.
57. Yee CSK, Albuhairi S, Noh E, et al. Long-term outcome of peanut oral immunotherapy facilitated initially by omalizumab. J Allergy Clin Immunol Pract 2019; 7(2):451–61.e7.
58. Broesby-Olsen S, Vestergaard H, Mortz CG, et al. Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: efficacy and safety observations. Allergy 2018;73(1):230–8.
59. Lemal R, Fouquet G, Terriou L, et al. Omalizumab therapy for mast cell-mediator symptoms in patients with ISM, CM, MMAS, and MCAS. J Allergy Clin Immunol Pract 2019;7(7):2387–95.e3.
60. Mendoza Alvarez LB, Barker R, Nelson C, et al. Clinical response to omalizumab in patients with hereditary alpha-tryptasemia. Ann Allergy Asthma Immunol 2020;124(1):99–100.e1.

61. Maurer M, Gimenez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. N Engl J Med 2019;381(14):1321–32.
62. 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):165.
63. Lieberman PL, Jones I, Rajwanshi R, et al. Anaphylaxis associated with omalizumab administration: risk factors and patient characteristics. J Allergy Clin Immunol 2017;140(6):1734–6.e4.
64. Lieberman P. The unusual suspects: a surprise regarding reactions to omalizumab. Allergy Asthma Proc 2007;28(3):259–61.
65. Perino E, Freymond N, Devouassoux G, et al. Xolair-induced recurrent anaphylaxis through sensitization to the excipient polysorbate. Ann Allergy Asthma Immunol 2018;120(6):664–6.
66. Cox L, Platts-Mills TA, Finegold I, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol 2007;120(6):1373–7.
67. Orengo JM, Radin AR, Kamat V, et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. Nat Commun 2018;9(1):1421.
68. Costa JJ, Demetri GD, Harrist TJ, et al. Recombinant human stem cell factor (kit ligand) promotes human mast cell and melanocyte hyperplasia and functional activation in vivo. J Exp Med 1996;183(6):2681–6.
69. Moskowitz CH, Stiff P, Gordon MS, et al. Recombinant methionyl human stem cell factor and filgrastim for peripheral blood progenitor cell mobilization and transplantation in non-Hodgkin's lymphoma patients–results of a phase I/II trial. Blood 1997;89(9):3136–47.
70. Broudy VC. Stem cell factor and hematopoiesis. Blood 1997;90(4):1345–64.
71. Bibi S, Arock M. Tyrosine kinase inhibition in mastocytosis: KIT and beyond KIT. Immunol Allergy Clin North Am 2018;38(3):527–43.
72. London CA, Gardner HL, Rippy 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):2565–74.
73. Ho CCM, Chhabra A, Starkl P, et al. Decoupling the functional pleiotropy of stem cell factor by tuning c-Kit signaling. Cell 2017;168(6):1041–1052 e18.
74. Macauley MS, Crocker PR, Paulson JC. Siglec-mediated regulation of immune cell function in disease. Nat Rev Immunol 2014;14(10):653–66.
75. Kikly KK, Bochner BS, Freeman SD, et al. Identification of SAF-2, a novel siglec expressed on eosinophils, mast cells, and basophils. J Allergy Clin Immunol 2000;105(6 Pt 1):1093–100.
76. Kiwamoto T, Kawasaki N, Paulson JC, et al. Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. Pharmacol Ther 2012;135(3):327–36.
77. Nutku E, Aizawa H, Hudson SA, et al. Ligation of Siglec-8: a selective mechanism for induction of human eosinophil apoptosis. Blood 2003;101(12):5014–20.
78. Yokoi H, Choi OH, Hubbard W, et al. Inhibition of FcepsilonRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. J Allergy Clin Immunol 2008;121(2):499–505.e1.

79. 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):e126219.
80. Paul WE. History of interleukin-4. Cytokine 2015;75(1):3–7.
81. Sehra S, Yao Y, Howell MD, et al. IL-4 regulates skin homeostasis and the predisposition toward allergic skin inflammation. J Immunol 2010;184(6):3186–90.
82. Fallon PG, Emson CL, Smith P, et al. IL-13 overexpression predisposes to anaphylaxis following antigen sensitization. J Immunol 2001;166(4):2712–6.
83. Gowthaman U, Chen JS, Zhang B, et al. Identification of a T follicular helper cell subset that drives anaphylactic IgE. Science 2019;365(6456):eaaw6433.
84. Burton OT, Darling AR, Zhou JS, et al. Direct effects of IL-4 on mast cells drive their intestinal expansion and increase susceptibility to anaphylaxis in a murine model of food allergy. Mucosal Immunol 2013;6(4):740–50.
85. McLeod JJ, Baker B, Ryan JJ. Mast cell production and response to IL-4 and IL-13. Cytokine 2015;75(1):57–61.
86. Toru H, Pawankar R, Ra C, et al. Human mast cells produce IL-13 by high-affinity IgE receptor cross-linking: enhanced IL-13 production by IL-4-primed human mast cells. J Allergy Clin Immunol 1998;102(3):491–502.
87. Komai-Koma M, Brombacher F, Pushparaj PN, et al. Interleukin-33 amplifies IgE synthesis and triggers mast cell degranulation via interleukin-4 in naive mice. Allergy 2012;67(9):1118–26.
88. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019;394(10209):1638–50.
89. 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):2486–96.
90. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375(24):2335–48.
91. Desai A, Jung MY, Olivera A, et al. IL-6 promotes an increase in human mast cell numbers and reactivity through suppression of suppressor of cytokine signaling 3. J Allergy Clin Immunol 2016;137(6):1863–71.e6.
92. Brockow K, Akin C, Huber M, et al. IL-6 levels predict disease variant and extent of organ involvement in patients with mastocytosis. Clin Immunol 2005;115(2):216–23.
93. Mayado A, Teodosio C, Garcia-Montero AC, et al. Increased IL6 plasma levels in indolent systemic mastocytosis patients are associated with high risk of disease progression. Leukemia 2016;30(1):124–30.
94. Theoharides TC, Boucher W, Spear K. Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. Int Arch Allergy Immunol 2002;128(4):344–50.
95. Tobio A, Bandara G, Morris DA, et al. Oncogenic D816V-KIT signaling in mast cells causes persistent IL-6 production. Haematologica 2020;105(1):124–35.
96. Shin K, Nigrovic PA, Crish J, et al. Mast cells contribute to autoimmune inflammatory arthritis via their tryptase/heparin complexes. J Immunol 2009;182(1):647–56.
97. Goswami R, Kaplan MH. A brief history of IL-9. J Immunol 2011;186(6):3283–8.
98. Hultner L, Druez C, Moeller J, et al. Mast cell growth-enhancing activity (MEA) is structurally related and functionally identical to the novel mouse T cell growth factor P40/TCGFIII (interleukin 9). Eur J Immunol 1990;20(6):1413–6.

99. Sehra S, Yao W, Nguyen ET, et al. TH9 cells are required for tissue mast cell accumulation during allergic inflammation. J Allergy Clin Immunol 2015; 136(2):433–40.e1.
100. Oh CK, Leigh R, McLaurin KK, et al. A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma. Respir Res 2013;14:93.
101. Liew FY, Girard JP, Turnquist HR. Interleukin-33 in health and disease. Nat Rev Immunol 2016;16(11):676–89.
102. Chen YL, Gutowska-Owsiak D, Hardman CS, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. Sci Transl Med 2019;11(515):eaax2945.
103. Chinthrajah S, Cao S, Liu C, et al. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight 2019;4(22):e131347.
104. Joulia R, L'Faqihi FE, Valitutti S, et al. IL-33 fine tunes mast cell degranulation and chemokine production at the single-cell level. J Allergy Clin Immunol 2017;140(2):497–509 e10.
105. Wang Z, Guhl S, Franke K, et al. IL-33 and MRGPRX2-triggered activation of human skin mast cells-elimination of receptor expression on chronic exposure, but reinforced degranulation on acute priming. Cells 2019;8(4):341.
106. Trivedi NN, Tong Q, Raman K, et al. Mast cell alpha and beta tryptases changed rapidly during primate speciation and evolved from gamma-like transmembrane peptidases in ancestral vertebrates. J Immunol 2007;179(9):6072–9.
107. Caughey GH. Tryptase genetics and anaphylaxis. J Allergy Clin Immunol 2006; 117(6):1411–4.
108. Schwartz LB, Lewis RA, Austen KF. Tryptase from human pulmonary mast cells. Purification and characterization. J Biol Chem 1981;256(22):11939–43.
109. Maun HR, Jackman JK, Choy DF, et al. An allosteric anti-tryptase antibody for the treatment of mast cell-mediated severe asthma. Cell 2019;179(2): 417–31.e19.
110. Malek TR. The biology of interleukin-2. Annu Rev Immunol 2008;26:453–79.
111. Fernandez IZ, Baxter RM, Garcia-Perez JE, et al. A novel human IL2RB mutation results in T and NK cell-driven immune dysregulation. J Exp Med 2019;216(6): 1255–67.
112. Schmalstieg FC, Leonard WJ, Noguchi M, et al. Missense mutation in exon 7 of the common gamma chain gene causes a moderate form of X-linked combined immunodeficiency. J Clin Invest 1995;95(3):1169–73.
113. Sharfe N, Dadi HK, Shahar M, et al. Human immune disorder arising from mutation of the alpha chain of the interleukin-2 receptor. Proc Natl Acad Sci U S A 1997;94(7):3168–71.
114. Zhang Z, Gothe F, Pennamen P, et al. Human interleukin-2 receptor beta mutations associated with defects in immunity and peripheral tolerance. J Exp Med 2019;216(6):1311–27.
115. Sotlar K, Horny HP, Simonitsch I, et al. CD25 indicates the neoplastic phenotype of mast cells: a novel immunohistochemical marker for the diagnosis of systemic mastocytosis (SM) in routinely processed bone marrow biopsy specimens. Am J Surg Pathol 2004;28(10):1319–25.
116. Baldassari LE, Rose JW. Daclizumab: development, clinical trials, and practical aspects of use in multiple sclerosis. Neurotherapeutics 2017;14(4):842–58.
117. Quintas-Cardama A, Amin HM, Kantarjian H, et al. Treatment of aggressive systemic mastocytosis with daclizumab. Leuk Lymphoma 2010;51(3):540–2.

118. The L. End of the road for daclizumab in multiple sclerosis. Lancet 2018; 391(10125):1000.
119. Salis P, Caccamo C, Verzaro R, et al. The role of basiliximab in the evolving renal transplantation immunosuppression protocol. Biologics 2008;2(2):175–88.
120. van der Weyden CA, Pileri SA, Feldman AL, et al. Understanding CD30 biology and therapeutic targeting: a historical perspective providing insight into future directions. Blood Cancer J 2017;7(9):e603.
121. Donato EM, Fernandez-Zarzoso M, Hueso JA, et al. Brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma: an evidence-based review. Onco Targets Ther 2018;11:4583–90.
122. Borate U, Mehta A, Reddy V, et al. Treatment of CD30-positive systemic mastocytosis with brentuximab vedotin. Leuk Res 2016;44:25–31.
123. Laszlo GS, Estey EH, Walter RB. The past and future of CD33 as therapeutic target in acute myeloid leukemia. Blood Rev 2014;28(4):143–53.
124. Alvarez-Twose I, Martinez-Barranco P, Gotlib J, et al. Complete response to gemtuzumab ozogamicin in a patient with refractory mast cell leukemia. Leukemia 2016;30(8):1753–6.