

## REVIEW

# Mast cell silencing: A novel therapeutic approach for urticaria and other mast cell-mediated diseases

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## Abstract

Chronic urticaria (CU) is a mast cell (MC)-dependent disease with limited therapeutic options. Current management strategies are directed at inhibiting IgE-mediated activation of MCs and antagonizing effects of released mediators. Due to the complexity and heterogeneity of CU and other MC diseases and mechanisms of MC activation—including multiple activating receptors and ligands, diverse signaling pathways, and a menagerie of mediators—strategies of MC depletion or MC silencing (i.e., inhibition of MC activation via binding of inhibitory receptors) have been developed to overcome limitations of singularly targeted agents. MC silencers, such as agonist monoclonal antibodies that engage inhibitory receptors (e.g., sialic acid-binding immunoglobulin-like lectin 8 -[Siglec-8] [lirentelimab/AK002], Siglec-6 [AK006], and CD200R [LY3454738]), have reached preclinical and clinical stages of development. In this review, we (1) describe the role of MCs in the pathogenesis of CU, highlighting similarities with other MC diseases in disease mechanisms and response to treatment; (2) explore current therapeutic strategies, categorized by nonspecific immunosuppression, targeted inhibition of MC activation or mediators, and targeted modulation of MC activity; and (3) introduce the concept of MC silencing as an emerging strategy that could selectively block activation of MCs without eliciting or exacerbating on- or off-target, immunosuppressive adverse effects.

## KEYWORDS

allergic, inflammation, inflammatory, mast cell, urticaria

## 1 | INTRODUCTION

Chronic urticaria (CU) is a mast cell (MC)-dependent disease characterized by development of wheals and/or angioedema lasting >6 weeks.<sup>1</sup> Lifetime prevalence of CU is estimated at up to 4.4%, presenting a substantial burden to patients and healthcare systems.

Disease impact spans beyond clinical manifestations, negatively impacting quality of life (QOL), sleep, daily activities, school/work life, and relationships.<sup>2–5</sup>

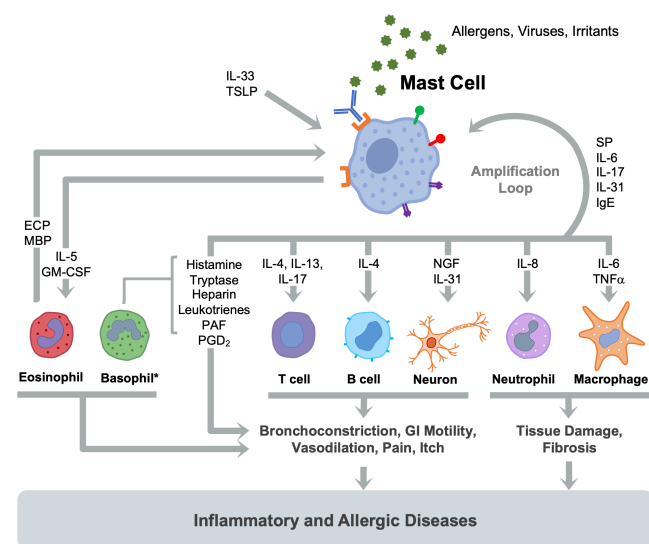
CU is classified into two subtypes: (1) chronic inducible urticaria (CIndU), where symptoms are induced by definite and specific triggers, for example, rubbing/scratching of the skin in symptomatic

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dermographism (SD) or active and passive warming in cholinergic urticaria (CholU); and (2) chronic spontaneous urticaria (CSU), characterized by unpredictable and unprompted wheal and angioedema development.<sup>6</sup> For both, activation of skin MCs is accompanied by release of secretory granules containing preformed mediators (e.g., histamine, proteases, cytokines), secretion of lipid mediators (e.g., leukotrienes, prostaglandin D2 [PGD<sub>2</sub>], platelet-activating factor [PAF]), and de novo synthesis of cytokines, chemokines, and growth factors.<sup>7,8</sup> A complex interplay involving feedback loops between MCs, their downstream effectors, and other skin resident and infiltrating cell types, culminates in the development of CU symptoms. Outside of urticaria, mast cell activation and degranulation in other organs contribute to diverse symptoms including bronchoconstriction, increased gastrointestinal (GI) motility, pain, tissue damage, and/or fibrosis (Figure 1).<sup>9,10</sup>

The goal of treatment for CU is to achieve complete control and to normalize QOL.<sup>1,11,12</sup> Not all underlying causes of CU are known and no cure exists. Spontaneous remission can occur, but is rare and infrequent in early years of disease (CSU estimates: 17% after 1 year, 45% at 5 years, 73% at 20 years<sup>13</sup>), leaving many patients in need of treatment. Therapeutic strategies commonly include trigger avoidance and symptom relief.<sup>1</sup> Second-generation, nonsedating H1-antihistamines are recommended as first-line therapy, with (off-label) dose increases up to fourfold the standard dose for patients who have insufficient responses.<sup>1</sup> Only 39% of CSU patients respond



\*The relative amount of released mediators is much less for basophils than mast cells

**FIGURE 1** Mast cell inflammatory pathways. In response to external stimuli, such as allergens, viruses, or irritants, MCs may be activated via IgE- or IgE-independent mechanisms. Release of preformed granule components (e.g., histamine, tryptase, chymase, carboxypeptidase, heparin) and newly synthesized lipid mediators (i.e., leukotrienes, platelet activating factor [PAF], prostaglandin D2 [PGD<sub>2</sub>]) is followed by an array of cytokines, chemokines, and other molecules. These interactions result in a complex interplay involving recruitment of other immune cells and amplification loops, culminating in a range of diverse symptoms, including bronchoconstriction, increased GI motility, vasodilation, pain, itch, tissue damage, and/or fibrosis.

to standard doses, and 63% of nonresponders improve with higher doses.<sup>14,15</sup> For nonresponders, the anti-IgE monoclonal antibody (mAb) omalizumab is second-line treatment, while later-line (off-label) approaches include omalizumab dose/schedule adjustments or addition of cyclosporin.<sup>1</sup> While current therapies sometimes offer symptomatic relief, treatment failure is common. Patients who continue to suffer uncontrolled and debilitating symptoms have a high unmet need for durable and effective management of their disease.

Growing understanding of the mechanisms and regulation of MC activation and disease pathogenesis has led to substantial progress in development of new strategies for treating CU and other MC diseases.<sup>16</sup> Management of these diseases can be categorized by mechanism of action, including nonspecific immunosuppression to targeted therapies directed at different stages of MC activation. Targets include both extracellular and intracellular molecules required for MC activation, as well as downstream effectors of activated MCs including mediators released during degranulation.<sup>17</sup> Newer strategies have also emerged, with goals to suppress MCs, either by MC depletion or MC silencing (i.e., inhibition of MC activation by binding inhibitory receptors).<sup>16</sup>

In the clinical setting, MC silencing with liletelimab, an anti-Siglec-8 mAb, demonstrated promising efficacy and safety in proof-of-concept studies in patients with CU or allergic conjunctivitis (AC).<sup>18,19</sup> Other MC silencing agents, AK006 and LY3454738, which target Siglec-6 and CD200R, respectively, are being explored in early stages of preclinical and clinical testing.

In this review, we will (1) review the role of MCs in pathogenesis of CU, highlighting similarities with other MC disorders in disease mechanisms and response to treatment; (2) explore current therapeutic strategies, categorized by nonspecific immunosuppression, targeted inhibition of MC activation and mediators, and targeted modulation of MC activity; and (3) introduce the concept of MC silencing as an emerging strategy that selectively blocks activation of MCs, without eliciting or exacerbating on-/off-target, immunosuppressive adverse effects.

## 2 | ROLE OF MCS IN CU AND OTHER ALLERGIC/INFLAMMATORY DISEASES

MCs are versatile, long-lived, myeloid-lineage, immune effector cells that localize to organs bordering the external environment or barrier tissues, such as the skin and mucosa of the gut and airways.<sup>9,16</sup> In their resting state, MCs might exert a homeostatic function via cell-cell contact or release of soluble mediators, delivering immunoregulatory signals to B cells, T cells, and dendritic cells within their microenvironment.<sup>20</sup> MCs are activated by multiple pathways, of which allergen crosslinking of IgE and its high-affinity receptor, Fc $\epsilon$ RI, is the most widely known.<sup>21,22</sup> In addition to Fc $\epsilon$ RI, MCs possess a myriad of activating cell surface receptors, including G-protein-coupled receptors (e.g., Mas-related G-protein-coupled receptor-X2 [MRGPRX2], chemokine, and complement receptors), cytokine receptors (e.g., KIT, interleukin-3 receptor [IL-3R]), MyD88-dependent

receptors (e.g., IL-33R, toll-like receptors), and pattern recognition receptors that recognize bacterial and viral products.<sup>23,24</sup> In addition to degranulation, activated MCs release inflammatory mediators that orchestrate activity between other immune cells, inducing proinflammatory responses characteristic of acute and chronic MC diseases (Figure 1).<sup>23</sup>

## 2.1 | Spectrum of MC diseases

MC activation and degranulation can occur in any organ system where MCs reside. Due to MC heterogeneity and tissue-specific differences in granule content, cytokine expression, and receptors, MCs exhibit different adaptive homeostatic and physiologic functions, manifested by diverse symptom profiles, including both allergic and nonallergic conditions.<sup>23,25</sup> MC diseases can be categorized according to known contributions of MCs to pathogenesis: MC-dependent diseases, which arise directly from excess MC proliferation and/or activation, and MC-associated diseases, for which MCs have known roles but do not drive pathogenesis (Figure 2).<sup>26</sup>

### 2.1.1 | MC-dependent diseases

Urticaria is a prototypical MC-dependent disease, characterized by complex pathogenesis whereby degranulation of activated skin MCs leads to vasodilation and plasma extravasation, resulting in edema and infiltration of T cells, eosinophils, basophils, and other cells, contributing to local inflammation.<sup>27-31</sup> Nonlesional skin of CSU patients may exhibit mild-to-moderate increase in MCs, sometimes accompanying infiltrating eosinophils, altered cytokine profiles, and increased adhesion molecule expression.<sup>32</sup> MC activation can also affect the local environment by elevated production of nerve growth factor (NGF), which promotes survival, proliferation, and activation of immune cells, including MCs, exacerbating inflammation.<sup>31,33</sup> In CSU, skin MC activation has been attributed to autoimmunity stemming from anti-FcεR1 or anti-IgE autoantibodies or IgE-directed against autoallergens.<sup>34-37</sup>

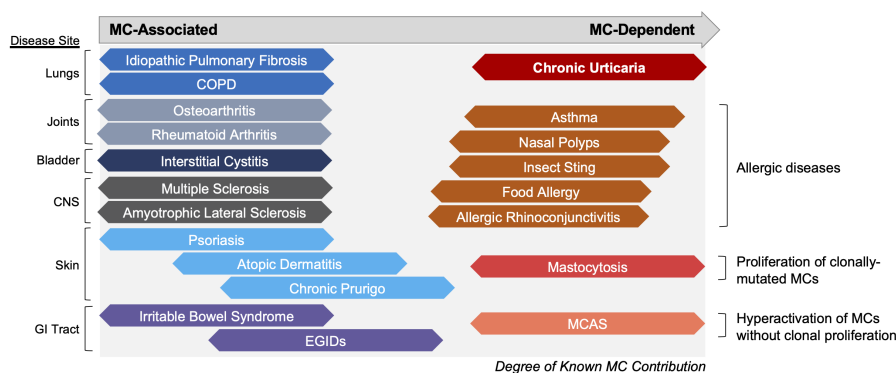
MCs also drive allergic conditions, including asthma, food allergy, allergic rhinitis, anaphylaxis, and chronic sinusitis with nasal polyps (CRSwNP). In allergic asthma, IgE-dependent MC activation contributes to IgE-immune complex formation and recruitment of MC progenitors to the lung, with disease manifested as reversible airway obstruction, hyperactivity, and inflammation.<sup>38,39</sup>

Other MC-dependent disorders include mastocytosis, a disorder characterized by excessive proliferation and accumulation of clonally mutated MCs, and MC activation syndrome (MCAS), caused by increased and inappropriate activation of nonclonal MCs.<sup>40,41</sup> Excessive MC activation leads to a constellation of symptoms across the skin, GI tract, nervous, cardiovascular, respiratory, and musculoskeletal systems.<sup>41,42</sup>

### 2.1.2 | MC-associated diseases

MCs contribute to but do not drive pathogenesis of many diseases. For some MC-associated disorders, MCs contribute to chronic cycles of inflammation, leading to tissue remodeling and fibrosis. For example, in osteoarthritis, a degenerative joint disease, despite non-MC sources of initiation (e.g., trauma, aging, obesity, genetic causes),<sup>43</sup> elevated numbers of degranulated and intact MCs have been detected at disease sites, and studies have suggested roles for NGF, substance P (SP; degranulation trigger), and stem cell factor (SCF)-dependent recruitment of MCs; accumulation of activated MCs correlates with synovial inflammation, cartilage damage, and pain.<sup>44,45</sup>

Similarly, eosinophilic GI disorders (EGIDs) are chronic inflammatory diseases characterized by eosinophilic infiltration of GI mucosa and elevated MC counts.<sup>46-48</sup> The best characterized EGID, eosinophilic esophagitis (EoE), is manifested by esophageal dysfunction and/or fibrosis, leading to dysphagia and esophageal food impaction.<sup>49</sup> While key characteristics include defects in the esophageal epithelial barrier and intraepithelial eosinophil infiltration, there is evidence that inflammatory signals are potentiated by a Th2 response, with TSLP, IL-33, IL-5, and IL-13 activating both eosinophils and MCs, triggering a shift in epithelial gene expression and altering esophageal structure.<sup>49</sup>



**FIGURE 2** Spectrum of mast cell-dependent and -associated diseases. Mast cell diseases fall into a spectrum according to the degree of mast cell involvement. This figure depicts the current known contribution of mast cells to select diseases that fall within the spectrum, with chronic urticaria representing the prototypical mast cell-dependent diseases, whereas mast cells are implicated but not indispensable initiators of pathogenesis in mast cell-associated diseases.

Atopic dermatitis (AD), interstitial cystitis (IC), and chronic prurigo are conditions where interactions between MC mediators and sensory neurons appear to facilitate localized inflammation.<sup>50</sup> In AD skin, MCs accumulate proximally to neuropeptide-containing nerve bundles,<sup>51</sup> along with elevated expression of SP and its receptor MRGPRX2<sup>52</sup> and aberrant activation of thymic stromal lymphopoietin (TSLP; priming factor for SP-induced degranulation).<sup>53,54</sup> In IC, urothelial damage significantly correlates with elevated MCs,<sup>55</sup> while in chronic prurigo, MRGPRX2-dependent MC activation may be exacerbated by chronic cycles of neurogenic inflammation, pain, and itch.<sup>56,57</sup> In chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis, IL-33/ST2-dependent MC activation induces nonallergic inflammation, including immune cell infiltration, tissue remodeling, and fibrosis.<sup>58,59</sup>

Central nervous system diseases, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), have shown localized inflammation and cellular destruction at sites where MCs have been detected.<sup>60,61</sup> In MS, characterized by inflammatory demyelination in the brain and spinal cord, aberrant MC activation has been detected at disease sites,<sup>61</sup> while in spinal cords of ALS patients, degranulating MCs accumulate at motor axons and neuromuscular junctions at sites of motor neuron damage.<sup>60</sup>

### 3 | THERAPEUTIC STRATEGIES FOR MC DISEASES

MC-related disorders currently have no curative therapy, and conventional treatments are often insufficient for symptom control.<sup>62</sup> Outside of trigger avoidance or elimination of triggers,<sup>1,3</sup> the focus for therapeutic intervention has been on the MC itself, with targets found at each step of MC activation, signaling, and degranulation, as well as MC proliferation and survival (Figure 3).

#### 3.1 | Nonspecific immunosuppression

Short courses of (off-label) oral corticosteroids (e.g., prednisone) have helped to reduce disease duration or activity in acute urticaria and acute exacerbations of CSU,<sup>63,64</sup> and cyclosporine is recommended as a late-line (off-label) measure for CU,<sup>1</sup> but neither is recommended for long-term use due to adverse effects.<sup>1,65</sup>

MC stabilizers, disodium cromoglycate and nedocromil sodium (discontinued), are well tolerated and have shown activity in mastocytosis and AC/asthma, respectively,<sup>66</sup> but require high doses and frequent intervals yielding inconsistent or negligible MC inhibitory effects.<sup>23,67</sup> They have not been effective in CU.<sup>68</sup>

#### 3.2 | Targeted therapies

Targeted therapies for CU and other MC diseases can be categorized into those that (1) antagonize MC activation; (2) block the effects of

MC mediators; (3) deplete MCs; and (4) silence MCs via binding of MC inhibitory receptors (Tables 1 and 2; Figure 4).

##### 3.2.1 | Antagonists of MC activation

MC activation antagonists include agents that block ligands of activating MC receptors, including omalizumab, an anti-IgE mAb, and tezepelumab, an anti-TSLP mAb. Omalizumab is indicated for CSU, moderate-to-severe asthma, allergic asthma, and nasal polyps. Omalizumab inhibits both MC and basophil activation by reducing free IgE and decreases expression of FcεRI and FcεRI-bound IgE on MCs and basophils, targets of autoantibodies in autoimmune CSU.<sup>72</sup> Tezepelumab, which inhibits the MC-activating cytokine TSLP, is indicated for add-on maintenance treatment of asthma and is under evaluation in a Phase 2 trial in CSU.<sup>73,74</sup>

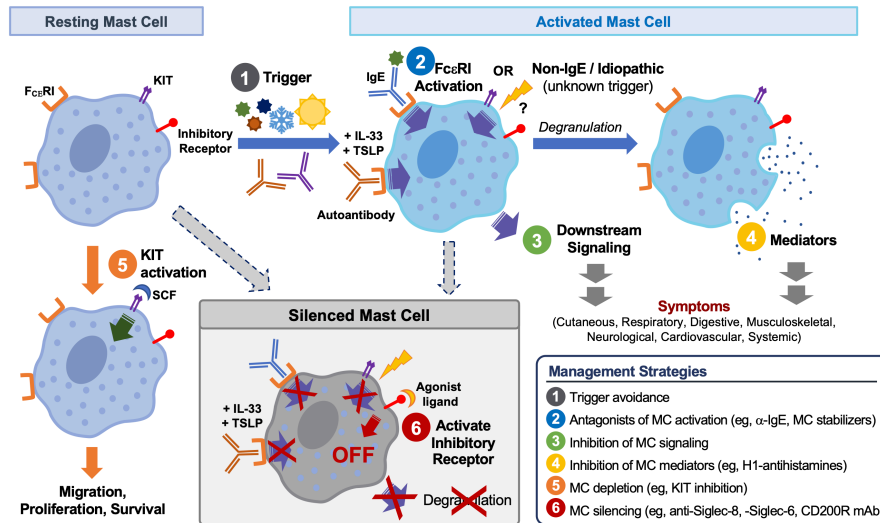
JAK-STAT is a MC signaling pathway activated downstream of IgE, IL-3, or SCF receptors, with important roles in MC homeostasis via regulation of proliferation, survival, and release of mediators.<sup>75</sup> JAK-STAT activation is associated with polarization toward Th2, B cell isotype switching to IgE production, and IgE-dependent degranulation and cytokine release.<sup>75</sup> Several JAK inhibitors have been approved for AD (Table 1), having demonstrated inhibition of MC degranulation and symptom reduction in models of allergic disease.<sup>76</sup> JAK inhibitors have also inhibited allergen-specific activation of basophils in response to peanut.<sup>77</sup>

Other MC activation antagonists include investigational anti-IgE and anti-IL-33 mAbs that block extracellular activating molecules and agents targeting intracellular signaling molecules, such as Bruton's tyrosine kinase (BTK), required for FcεRI-mediated MC activation,<sup>78</sup> and spleen tyrosine kinase (SYK), which promotes MC degranulation and histamine release.<sup>79</sup> Safety signals from on-target BTK inhibition have resulted from broad expression of these kinases,<sup>80</sup> but newer agents (e.g., remibrutinib, rilzabrutinib) have shown better tolerability.<sup>81-83</sup>

##### 3.2.2 | Inhibition of MC mediators

Among therapies that target MC mediators, non-sedating H1-antihistamines are most frequently prescribed for initial treatment of CU.<sup>84</sup> However, most patients respond poorly even at higher-than-standard doses, likely because of the numerous mediators released with MC activation.<sup>84</sup> Leukotriene receptor blockers (montelukast, zafirlukast) are used to treat mastocytosis<sup>85,86</sup> and have been applied in asthma, chronic hyperplastic rhinosinusitis, AD, and irritable bowel syndrome.<sup>87,88</sup>

Other MC mediator targets include IL-4 and IL-13, cytokines which promote Th2 inflammation, IgE production, and recruitment of inflammatory cells.<sup>23</sup> The anti-IL-4Rα mAb dupilumab, currently in Phase 3 trials for CSU, is approved for moderate-to-severe AD, severe asthma (eosinophilic phenotype), corticosteroid-dependent asthma, CRSwNP, EoE, and prurigo nodularis.<sup>89,90</sup>



**FIGURE 3** Therapeutic targets for management of mast cell diseases. The stepwise activation of MCs enables therapeutic targeting at each stage of activation: (1) MCs are activated upon interaction with triggers that may be avoided when known. (2) Activation of MCs occur via IgE-dependent activation of FcεRI or IgE-independent activating receptors, which may be blocked by IgE inhibitors and inhibitors of other activating molecules, respectively. (3) Activated MCs secrete lipid mediators (e.g., leukotrienes, prostaglandin, platelet-activating factor), cytokines, chemokines, and growth factors and (4) undergo degranulation of secretory granules containing preformed mediators (e.g., histamine, proteases, cytokines); these extracellular mediators may be blocked after secretion to inhibit downstream processes that result in inflammation. (5) MC migration, proliferation, and survival are dependent on KIT, an SCF-binding receptor whose activation may be blocked with KIT inhibitors, thus suppressing MCs via MC depletion. (6) Blocking of MC activation via agonist ligand binding to inhibitory receptors, such as Siglec-8, may be exploited for MC silencing strategies.

### 3.2.3 | MC depletion

MC depleters suppress global MC function and may be suitable alternatives to inhibition of individual targets. KIT (CD117) is a primary regulator of MCs, contributing to their differentiation, tissue migration, adhesion, maturation, survival, and activation.<sup>91,92</sup> Inhibition of KIT reduces MC burden, achieving systemic MC suppression independent of activating triggers. However, inhibition of KIT on hematopoietic stem cells, melanocytes, and germ cells, have led to hair depigmentation, myelosuppression, impaired erythroid and myeloid progenitor cell function, and impaired spermatogenesis.<sup>93</sup> Imatinib mesylate, avapritinib, and midostaurin are small molecule KIT inhibitors approved for treatment of aggressive systemic mastocytosis. No MC depleters have yet been approved for CU. An ongoing Phase 2 study of the anti-KIT mAb barzolvolimab in CSU demonstrated sustained improvement in mean urticaria control test (UCT7) score and depletion of cutaneous MCs.<sup>94,95</sup> Other investigational KIT inhibitors include nilotinib and bezclastinib, both in ongoing Phase 1/2 trials in systemic mastocytosis.

### 3.2.4 | MC silencing—An emerging class of therapies

The complex dynamics of the immune system are held in check by mechanisms that regulate the intensity of the immune response to foreign antigens.<sup>96</sup> Inhibitory receptors on immune cells serve as gatekeepers, functioning in a negative feedback loop that counters the dangers of an overactive immune response and helps resolve

inflammation. Therapeutic targeting of inhibitory receptors has demonstrated proof-of-concept in rheumatoid arthritis (RA) and COVID-19. In RA, peresolimab (a humanized anti-PD-1 mAb that stimulates PD-1-dependent immune inhibitory pathways) significantly improved disease activity scores versus placebo in a Phase 2 study.<sup>97</sup> In COVID-19 patients, treatment with CD24Fc (a fusion protein that suppresses proinflammatory signaling by binding Siglec-10) reduced risk of death and respiratory failure in a Phase 3 trial of hospitalized COVID-19 patients on oxygen support.<sup>98</sup>

A new class of agents, known as MC silencers, engage immunomodulatory transmembrane receptors to broadly inhibit MC activation, blocking multiple pathways that drive MC activation.<sup>16,99</sup> Several inhibitory receptors have been identified on the surface of MCs, with roles in modulating activation and degranulation of MCs, or coaggregation with FcεRI to inhibit downstream signaling and degranulation.<sup>100,101</sup> Of the two superfamilies, the Ig-like superfamily (Allergin-1, Gp49B1, FcγRIIB, SIRPα, KIR, PECAM-1, CD300, and Siglecs) have been explored to varying degrees, whereas the C-type lectin superfamily (MAFA, CD72) appears to have limited therapeutic potential.<sup>102</sup>

The Siglecs are a family of Type I transmembrane proteins that contain N-terminal binding domains.<sup>99</sup> Siglecs serve as immune checkpoints, using signaling motifs such as the intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM) to deliver inhibitory signals to attenuate or terminate activating signals. These ITIMs recruit phosphatases (e.g., SHP-1, SHP-2, SHIP1) via their Src Homology 2 (SH2) domains, which in turn, dephosphorylate tyrosine kinases responsible for IgE-dependent and -independent signaling, enabling broad inhibitory effects. Based on promising findings in

TABLE 1 Approved therapies in MC disease indications, categorized by treatment strategy.<sup>69</sup>

Treatment category	Mechanism of action	Examples	Approved MC disease indication
<i>Nonspecific therapies</i>			
	MC stabilizer	Nedocromil sodium Disodium cromoglycate	Allergic conjunctivitis (discontinued) Mastocytosis
	Immunosuppressant	Corticosteroid/prednisone Cyclosporine	Atopic dermatitis, drug hypersensitivity, seasonal/perennial allergic rhinitis, asthma Atopic dermatitis <sup>a,b</sup>
<i>Antagonists of MC activation</i>			
	Anti-IgE mAb	Omalizumab	Moderate to severe persistent asthma, nasal polyps, CSU
	Anti-TSLP mAb	Tezepelumab	Asthma
	JAK inhibitors	Abrocitinib Baricitinib Upadacitinib Ruxolitinib Delgocitinib	Moderate-to-severe atopic dermatitis (systemic) Moderate-to-severe atopic dermatitis (systemic) <sup>b</sup> Moderate-to-severe atopic dermatitis (systemic) Mild-to-moderate atopic dermatitis (topical) Atopic dermatitis (topical) <sup>b</sup>
	Inhibitor of TRPV2	Tranilast	Allergic rhinitis, asthma, atopic dermatitis <sup>b</sup>
<i>Inhibitors of MC mediators</i>			
	Anti-IL-4R $\alpha$ mAb	Dupilumab	Moderate-to-severe atopic dermatitis, severe asthma (eosinophilic phenotype), corticosteroid-dependent asthma; chronic rhinosinusitis w/nasal polyps; EoE; prurigo nodularis
	Anti-IL-13 mAb	Tralokinumab	Moderate-to-severe atopic dermatitis
	H1 antihistamines	Ketotifen Cetirizine Levocetirizine Fexofenadine Loratadine Desloratidine Rupatadine Ebastine <sup>b</sup> Bilastine <sup>b</sup>	Allergic conjunctivitis (ophthalmic solution); allergic rhinitis <sup>b,c</sup> Seasonal/perennial allergic rhinitis, CSU
	Leukotriene receptor antagonists	Montelukast Zafirlukast	Asthma, allergic rhinitis Asthma
<i>MC depletion</i>			
	KIT inhibitors	Imatinib Avapritinib Midostaurin	Aggressive systemic mastocytosis without (or unknown) D816V <i>c-KIT</i> mutation; hypereosinophilic syndrome and/or chronic eosinophilic leukemia Advanced systemic mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm, and mast cell leukemia <sup>d</sup> Aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, MC leukemia

Abbreviations: CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; IgE, immunoglobulin E; IL, interleukin; mAb, monoclonal antibody; MC, mast cell; TRPV, transient receptor potential vanilloid.

<sup>a</sup>Cyclosporine is an immunosuppressant indicated for organ transplant, RA, and psoriasis, included in guideline recommendations for off-label use as add-on therapy for CSU after omalizumab failure.

<sup>b</sup>Approved ex-US.

<sup>c</sup>Discontinued for allergic rhinitis in some countries.

<sup>d</sup>Also approved for GIST with PDGFRA exon 18 mutation.

preclinical studies, mAbs against Siglec-8 and Siglec-6 have entered or are entering clinical trials for several MC-related diseases.<sup>103</sup>

In the preclinical setting, mechanisms other than antibody-based inhibition have been explored with Siglec-8. For example, liposomal nanoparticles displaying synthetic glycan ligands for Siglec-8 have demonstrated inhibition of degranulation and desensitization to

antigen exposure in murine MCs.<sup>104</sup> Siglecs have also been shown to be internalized upon antibody engagement, a property that has been leveraged on selectively expressed Siglecs, such as Siglec-8, to deplete MCs via a payload-conjugated antibody. Indeed, conjugating saporin to an internalizing Siglec-8 antibody caused extensive cell death in human mast cells.<sup>105</sup>

**TABLE 2** Investigational agents in CU and other MC diseases, categorized by treatment strategy and trial status.<sup>70</sup>

Category	MOA	Examples	Stage of clinical development	NCT identifier
<i>Antagonists of MC activation</i>				
	Anti-TSLP mAb	Tezepelumab	Phase 2 in CSU	NCT04833855
	Anti-IgE mAb	Ligelizumab	Phase 3 in CSU, CIndU <sup>a</sup> peanut allergy	NCT03580369, NCT03580356, NCT03907878, NCT05024058 <sup>a</sup> , NCT04984876
		UB-221	Phase 2 in CSU	NCT05298215
		UCB8600	Phase 1 in CSU <sup>a</sup>	NCT04444466 <sup>a</sup>
	Anti-IL-33 mAb	Tozorakimab	Phase 3 in COPD; Phase 2 in AD <sup>a</sup>	NCT05166889, NCT05158387, NCT04212169
		Itepekimab	Phase 3 in COPD; Phase 2 in moderate-to-severe asthma (plus dupilumab)	NCT04701983, NCT04751487, NCT03387852
		Etokimab	Phase 2 in peanut allergy, CRSwNP, severe eosinophilic asthma, and AD <sup>a</sup>	NCT02920021, NCT03614923, NCT03469934, NCT03533751
	MGRPX2 modulator	EVO756	Pre-IND	NA
	Tyrosine kinase inhibitor	Masitinib	Phase 3 in ISM	NCT04333108, NCT00814073
			Phase 3 in Severe Asthma	NCT03771040, NCT01449162
			Phase 2 in MCAS	NCT05449444
	BTK Inhibitors	Remibrutinib/LOU064	Phase 3 in CSU, Phase 2 in peanut allergy	NCT05032157, NCT05030311, NCT05048342, NCT05432388
		Fenebrutinib	Phase 2 in CSU <sup>a</sup>	NCT03137069
		Tirabrutinib	Phase 2 in CSU <sup>a</sup>	NCT04827589 <sup>a</sup>
		Rilzabrutinib	Phase 2 in CSU, moderate-to-severe asthma, moderate-to-severe AD	NCT05107115, NCT05104892, NCT05018806
		TAS5315	Phase 2 in CSU	NCT05335499
	SYK inhibitor	GSK2646264	Phase 1 in CSU	NCT02424799
<i>Inhibitors of MC mediators</i>				
	Anti-IL-4R $\alpha$ mAb	Dupilumab	Phase 3 in CSU; Phase 2 in peanut allergy, atopic keratoconjunctivitis	NCT05526521, NCT03793608, NCT04296864
	Anti-IL-1 mAb	Canakinumab	Phase 2 in CSU <sup>a,b</sup>	NCT01635127
	IL-1 blocker	Rilonacept	Phase 2 in CIndU-cold urticaria <sup>b</sup>	NCT02171416
	TNF blockers	Adalimumab	Phase 2 in asthma <sup>a,b</sup>	NCT00512863
		Etanercept	Phase 2–3 in CSU <sup>a,b</sup>	NCT01030120
		Infliximab	Phase 2 EoE <sup>b</sup>	NCT00523354
	H2 antihistamines	Ranitidine	Phase 2 (+ desloratadine) in allergy <sup>b</sup>	NCT01601522
	Tryptase inhibitor	MTPS9579A	Phase 2 in CSU <sup>a</sup> , asthma	NCT05129423 <sup>a</sup> , NCT04092582

(Continues)

TABLE 2 (Continued)

Category	MOA	Examples	Stage of clinical development	NCT identifier
<i>MC depletion</i>				
	KIT inhibitors	Nilotinib	Phase 1/2 in systemic mastocytosis <sup>b</sup>	NCT00109707
		Avapritinib	Phase 2 in ISM or advSM	NCT03731260, NCT03580655
		BLU 263	Phase 2/3 in ISM	NCT04910685
		Bezuclastinib/ CGT9486	Phase 2 in SM (advSM/ISM)	NCT05186753, NCT04996875
		Barzolvolimab/ CDX-0159	Phase 2 CSU, CIndU	NCT05368285, NCT05405660
<i>MC silencing</i>				
	Anti-Siglec-8 mAb	Lirentelimab/AK002	Phase 3 in EG/EoD <sup>a</sup>	NCT04856891, NCT04322604, NCT05152563
			Phase 2/3 in EoE <sup>a</sup>	NCT04322708
			Phase 2 in CSU	NCT05528861
			Phase 2 in AD	NCT05155085
			Phase 1b in allergic conjunctivitis	NCT03379311
			Phase 1 in ISM	NCT02808793
	Anti-Siglec-6 mAb	AK006	Phase 1 planned <sup>71</sup>	Not available
	CD200R agonist	LY3454738	Phase 2 in CSU <sup>a</sup>	NCT04159701
			Phase 1 in AD	NCT03750643

Note: Table includes key clinical studies at time of drafting the manuscript and neither includes discontinued or negative studies, nor represents a comprehensive list.

Abbreviations: AD, atopic dermatitis; advSM, advanced systemic mastocytosis; AS, ankylosing spondylitis; CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSM, chronic systemic mastocytosis; CSU, chronic spontaneous urticaria; CU, chronic urticaria; EG, eosinophilic gastritis; EoD, eosinophilic duodenitis; EoE, eosinophilic esophagitis; GIST, gastrointestinal stroma tumor; GPR35, G-protein-coupled receptor 35; IgE, immunoglobulin E; IL, interleukin; IND, investigational new drug; ISM, indolent systemic mastocytosis; mAb, monoclonal antibody; MC, mast cell; PsA, psoriatic arthritis; RA, rheumatic arthritis; siglec, sialic acid-binding immunoglobulin-like lectin; TRPV, transient receptor potential vanilloid.

<sup>a</sup>Trial withdrawn, terminated, or had negative results.

<sup>b</sup>Approved in non-MC indications.

Other than lirentelimab and AK006, to our knowledge, the only other inhibitory receptor agonist in clinical trials in MC-related diseases is LY3454738, an agonist of CD200R, which does not contain an ITIM. Instead, CD200-CD200R signals via activation of Dok2 and RasGAP, which result in Ras inhibition, downstream suppression of PI3K and Erk, and inhibition of NF- $\kappa$ B and its pro-inflammatory signals.<sup>106</sup> Findings from studies of lirentelimab, AK006, and LY3454738 are described below.

## 4 | MC SILENCERS IN CLINICAL DEVELOPMENT

### 4.1 | Lirentelimab, a Siglec-8 agonist antibody

Lirentelimab is a humanized Siglec-8 antibody under investigation for treatment of allergic and inflammatory diseases involving MCs and eosinophils. It has shown activity in both clinical and non-clinical studies of allergic and nonallergic inflammatory diseases,

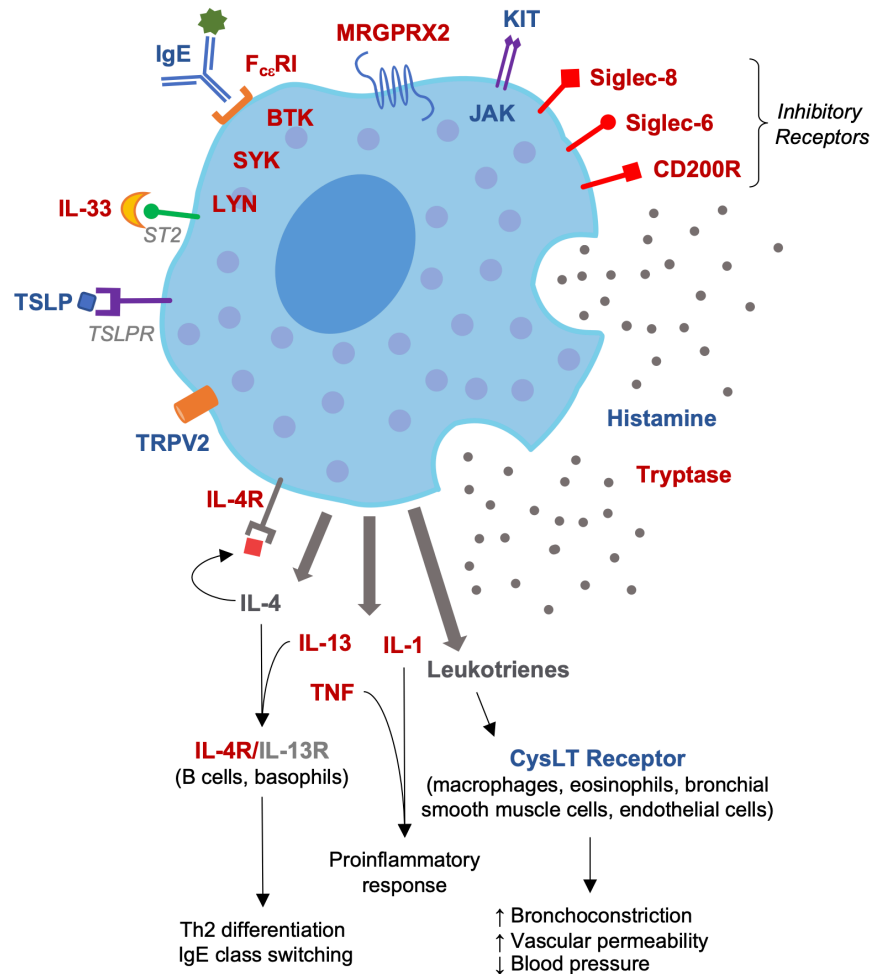
including a Phase 2a study in CSU, and is currently under clinical evaluation for treatment of CSU, AD, AC, mastocytosis, and EGIDs.

#### 4.1.1 | Preclinical studies of Siglec-8 and lirentelimab

Siglec-8 has broad inhibitory effects across several MC activating pathways, including those initiated by ligand/receptor interactions of IgE/Fc $\epsilon$ RI, IL-33/ST2L, and SP/MRGPRX2.<sup>107-109</sup> Development of therapeutic anti-Siglec-8 mAbs followed in a series of studies evaluating the effects of Siglec-8 engagement by anti-Siglec-8 mAbs in mouse models of IgE-dependent and IgE-independent disease, using transgenic mice expressing human Siglec-8.<sup>110</sup> First, in a mouse model of eosinophilic gastroenteritis, treatment with anti-Siglec-8 mAbs significantly reduced eosinophils and MCs in the stomach, small intestine, and mesenteric lymph nodes, and decreased Type 2 immune-associated, IgE-dependent, inflammatory



FIGURE 4 Mast cell targets of approved and investigational therapies.



cytokines and chemokines (CCL17, CCL2, CCL5) important for MC recruitment.<sup>111</sup> Given that inhibitory rather than apoptotic effects on MCs were observed, the authors proposed that decreased intestinal MC recruitment was the mechanism for intestinal MC reduction.<sup>110</sup>

Anti-Siglec-8 mAbs were also evaluated in IgE-independent, non-allergic diseases, mouse models of cigarette smoke-induced COPD, bleomycin-induced lung injury, and MC-dependent, IL-33-induced inflammation.<sup>107</sup> In COPD and lung injury models, anti-Siglec-8 mAbs inhibited MC activation and reduced immune cell recruitment, airway inflammation, and lung fibrosis. In the IL-33 inflammation model, anti-Siglec-8 mAbs inhibited MCs, suppressing neutrophil influx and cytokine production, including IL-33-induced TNF signaling via NF- $\kappa$ B.<sup>107</sup>

To evaluate effects of anti-Siglec-8 mAbs in IgE-induced passive systemic anaphylaxis (PSA), a humanized strain of mice was engrafted with human thymus, liver, and hematopoietic stem cells, which produce mature, Siglec-8-expressing, human MCs. An anti-Siglec-8 mAb prevented IgE-induced PSA via MC inhibition, based on lack of change in body temperature and clinical symptoms (scratching, breathing, edema, motility).<sup>112</sup>

Finally, intracellular signaling pathways of Siglec-8-mediated MC inhibition were elucidated by phospho-proteomic profiling of primary murine MCs treated with anti-Siglec-8 mAbs, revealing ITIM-dependent Siglec-8 inhibition of Fc $\epsilon$ RI-induced intracellular signaling, regulation of Fc $\epsilon$ RI-mediated kinase activity, and attenuation of degranulation and mediator release in a concentration-dependent fashion.<sup>113</sup> Findings from the study led to a model in which Siglec-8 regulation of proximal Fc $\epsilon$ RI-induced phosphorylation is regulated by SH2-containing phosphatase recruitment, leading to global MC inhibition.

#### 4.1.2 | Clinical studies of lirentelimab

To date, the safety and efficacy of lirentelimab has been evaluated in clinical trials for several MC diseases, including indolent systemic mastocytosis, CSU, ChOI, SD, and severe AC, where patients reported substantial improvements in disease symptoms.<sup>18,99,114</sup> Lirentelimab has also been evaluated in eosinophilic gastritis (EoG) and/or eosinophilic duodenitis (EoD). Promising findings in EoG/EoD in the initial Phase 2 ENIGMA trial<sup>115</sup> were met by disappointing results in Phase

2/3 and Phase 3 studies (ENIGMA 2, KRYPTOS, EoDyssey), which met their histologic co-endpoints, but did not achieve statistical significance on patient-reported symptomatic endpoints.<sup>116,117</sup>

Lirentelimab was evaluated in a Phase 2a trial (CURSIG; NCT03436797) in 45 patients with omalizumab-naïve and omalizumab-refractory CSU, ChoIU, and SD.<sup>18</sup> Among omalizumab-naïve and -refractory CSU patients who received 6 intravenous doses of lirentelimab, urticaria disease activity (UAS7) was reduced by 75% and 61% at Week 22, respectively, with 54% of omalizumab-naïve patients achieving UAS7=0, and 92% and 57% of patients, respectively, achieved disease control (UCT  $\geq$ 12).<sup>18</sup> Among patients with ChoIU, all (seven of seven) evaluable patients who received 6 doses of lirentelimab had negative responses to exercise provocation testing by pulse-controlled ergometry, and 82% achieved well-controlled disease by UCT. Among those with SD, 50% had complete itch resolution, and 40% had complete hive resolution as assessed by FricTest provocation.<sup>18</sup>

Evaluation of lirentelimab in a Phase 1b study (KRONOS, NCT03379311) in patients with severe and chronic forms of AC showed improvements in ocular symptom scores and reduced levels of cytokines and chemokines (IL-4, IL-10, IL-13, IL-17A, IL-23, CCL5, CCL11, CCL26).<sup>19</sup> Patients with concomitant atopic comorbidities, also showed a reduction in symptoms of -55%, -50%, and -63% for AD, allergic asthma, and allergic rhinitis, respectively.<sup>19</sup>

Across all studies to date, lirentelimab has been well tolerated, the most common adverse events (AEs) being infusion-related reactions typically associated with the initial infusion.<sup>18,19,114</sup> Subcutaneously administered lirentelimab is being evaluated in two ongoing Phase 2, randomized, double-blind, placebo-controlled studies (MAVERICK [NCT05528861], ATLAS [NCT05155085]) in H1-antihistamine-refractory CSU and moderate-to-severe AD, respectively.<sup>118,119</sup>

## 4.2 | AK006, a Siglec-6 agonist antibody

Siglec-6 is an inhibitory receptor expressed predominantly on MCs, and at lower levels on basophils, select populations of B cells, and placental trophoblasts.<sup>120,121</sup> Siglec-6 is constitutively expressed on mucosal and connective tissue MC subtypes.<sup>121,122</sup> In contrast to Siglec-8, is upregulated in IgE- and SCF-activated MCs, suggesting Siglec-6 may play a greater role in activated MCs.<sup>120</sup> Anti-Siglec-6 mAbs appear to mediate broad inhibition of IgE-dependent and -independent MC activation and degranulation through multiple routes, including FcεRI, complement component 5a receptor, and MRGPRX2 pathways.<sup>121</sup> Consistent with the inhibitory function of Siglec-6, mutation of both the ITIM and ITIM-like domains abrogate anti-Siglec-6-mediated MC inhibition by preventing SHP-1 and SHP-2 phosphatase recruitment.<sup>122</sup>

In humanized mice, anti-Siglec-6 mAbs reduced degranulation and soluble mediator production of activated human MCs *in vitro* and inhibited IgE-mediated systemic anaphylaxis.<sup>122</sup> MC inhibition via Siglec-6 has also been observed to undergo antibody-dependent cellular phagocytosis in the presence of activated macrophages,

suggesting dual roles of MC inhibition and depletion.<sup>122</sup> Notably, *ex vivo* human MC activation assays have shown that the human therapeutic anti-Siglec-6 mAb, AK006, inhibits degranulation to a greater extent than lirentelimab, suggesting Siglec-6 may have more potent inhibitory activity compared to Siglec-8.<sup>123</sup> First-in-human clinical studies of AK006 in healthy volunteers and in patients with MC-dependent diseases are planned, initiating the second half of 2023.<sup>71</sup>

## 4.3 | LY3454738, an anti-CD200R antibody

CD200R is an inhibitory receptor in the Ig supergene family, expressed predominantly on myeloid cells including MCs and basophils. Unlike most other myeloid inhibitory receptors, CD200R lacks an ITIM, therefore utilizes a novel mechanism for inhibition upon binding CD200.<sup>124</sup> In animal studies, CD200R activation with an mCD200-mIgG2a fusion protein inhibited or alleviated severity of several inflammatory disease models, including arthritis, islet xenograft rejection, and experimental autoimmune encephalitis. Additionally, CD200R inhibits basophil activation through interaction with CD200 proteins.<sup>125</sup> Engagement of CD200R with anti-CD200R antibodies also reduced disease severity in mouse models of arthritis, influenza, and autoimmune uveitis.<sup>126-128</sup>

LY3454738, a humanized anti-CD200R mAb, potently inhibited MC degranulation and cytokine secretion upon binding to agonist antibodies or ligands *in vitro*, blocked FcγR-induced cytokine secretion from a human myeloid cell line, and inhibited activation of primary MCs.<sup>129,130</sup> *In vivo*, LY3454738 has shown activity in a mouse model of contact hypersensitivity and in a *Cynomolgus* monkey model of passive cutaneous anaphylaxis.<sup>131</sup>

LY3454738 demonstrated safety and tolerability in a Phase 1 study of healthy participants, with no dose-limiting safety issues after single or repeat doses.<sup>132</sup> A Phase 2 study of LY3454738 in adults with CSU (NCT04159701) was terminated early for lack of efficacy after an interim analysis.<sup>133,134</sup> According to results posted by the study sponsor on [clinicaltrials.com](https://clinicaltrials.com), LY3454738 did not show superiority to placebo in efficacy outcomes.<sup>135</sup> For the primary outcome, mean change in UAS7 from baseline to Week 12 was -6.4 with LY3454738 versus -9.3 with placebo. For secondary outcomes, mean change in itch severity and hive severity scores was -2.9 and -3.5, respectively, for LY3454738, versus -4.2 and -5.2, respectively, for placebo; the percentage of patients with UAS7  $\leq$  6 was 15.4% for LY3454738 versus 23.1% for placebo. Overall incidence of AEs was higher with placebo than LY3454738 (31% vs. 10%, first 12 weeks; 39% vs. 13%, second 12 weeks).<sup>135</sup> A Phase 1 study of LY3454738 in patients with AD (NCT03750643) has been completed, with results pending.<sup>136</sup>

## 5 | CLINICAL PERSPECTIVE

Several approaches have been used to mitigate the impact of MCs in human disease, including blockade of MC-derived mediators and

activation receptors, reduction of MC numbers, and more recently, silencing of MCs.<sup>57</sup> Targeting a single step in the MC activation pathway can confer clinical benefit, but effects are often limited, as MC activity involves contributions of multiple effectors and mediators.<sup>23,137</sup> Blocking individual pathways of MC activation also has limitations due to the heterogeneous spectrum of endotypes within and across MC diseases.<sup>138</sup> Furthermore, given that MCs can be activated via multiple pathways through different activating receptors and ligands, inhibition of one activating pathway does not prohibit activation by another.<sup>9</sup> MC depletion and MC silencing are novel approaches that have demonstrated potential in overcoming limitations of single pathway-targeted therapies. MC depleters bind to extracellular MC receptors (i.e., KIT) required for survival and suppress function by reducing MC numbers, whereas MC silencers engage inhibitory receptors, such as Siglec-8, Siglec-6, and CD200R, to prevent MC activation.<sup>16,139</sup> Other inhibitory receptors (i.e., CD300a, FcγRIIb) in early stages of preclinical testing warrant further investigation.

While both strategies ultimately prohibit MCs from their pathogenic function, there are some advantages and disadvantages to each approach. For example, KIT is not limited to MC expression, but found on multiple cell types, including embryonic, spermatogonial, and hematopoietic stem cells, as well as in differentiated cells such as melanocytes, neurons, and testicular Leydig cells, and has recently shown roles in cardiac development and regeneration.<sup>140,141</sup> Given its broad distribution, MC depletion with KIT inhibitors could have on-target class effects, such as known impacts on hematology, spermatogenesis, hair depigmentation, or taste changes.<sup>94</sup> In addition, small molecule inhibitors carry risk of off-target side effects, such as myelosuppression, which has been reported in cancer patients receiving imatinib or midostaurin.<sup>93</sup> Although Siglec-8 and Siglec-6 expression has been reported in some cancers and in placental trophoblasts, respectively,<sup>142,143</sup> high MC expression of Siglec-8 and Siglec-6 make these inhibitory receptors attractive targets with potentially fewer off-target or immunosuppressive side effects than MC depleters. Degree of off-target effects by Siglec antibodies will be determined in clinical studies.

Suppression of MC activation does not significantly reduce MC counts, leaving inactivated or resting MCs available, thus potentially preserving their physiological role in homeostasis. Frossi et al. has described MCs as having a “rheostatic” function—that is, having the ability to modulate intensity of its response based on signaling within their microenvironment.<sup>20</sup> Rather than the traditional view of MCs having a binary “all-or-nothing” effector function, MCs are thought to be more adaptive, even in their inactivated state, modulating activities of other immunoregulatory cells and altering fluid flow, permeability, secretion, and contraction of blood vessels, lymphatics, epithelial surfaces, and smooth muscle in response to local stimuli.<sup>20,144</sup> Moreover, humans lacking MCs have not been found, suggesting they may have a fundamental physiological role during development (with the alternative explanation that MCs are vestigial remnants of the immune system).<sup>145</sup> MC silencing therefore may offer an advantage over MC depletion if they indeed leave underlying functions of inactivated MCs intact.

Conversely, although speculative, if inactivated MCs are responsible for certain disease manifestations, MC silencing may be less effective at full containment of disease. Furthermore, given the heterogeneity of MCs across different MC diseases and between patients, MC silencing therapies may not be one-size-fits-all and could require fine-tuning of dosing regimens or biomarker-based patient selection for a given disease.

## 6 | CONCLUSION

Mitigation of pathogenic MC activity by MC silencing provides a compelling new approach that may offer the benefit of suppressing MC function, but with potentially greater selectivity and less toxicity than MC depletion. Findings from early clinical trials have been encouraging and provide hope to patients who aspire for a better life without the debilitating effects of MC-dependent disease.

### AUTHOR CONTRIBUTIONS

All authors contributed to the writing and revision of the manuscript, and all approved the final draft of the paper.

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### CONFLICT OF INTEREST STATEMENT

Martin Metz has received honoraria as a speaker and/or consultant for Amgen, argenX, AstraZeneca, Celldex, Escient, GSK, Novartis, Roche, Sanofi-Aventis, and Third Harmonic Bio. Pavel Kolkhir has received honoraria as a speaker and/or consultant for Novartis, ValenzaBio, and Roche. Sabine Altrichter is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, AstraZeneca, Biocryst, CSL Behring, Moxie, Novartis, Pharvaris, Sanofi/Regeneron, Takeda, and Thermo Fisher. Frank Siebenhaar is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Blueprint, Celldex, Cogent, Escient, Granular, GSK, InveaTx, Moxie, Novartis, Sanofi/Regeneron, Third Harmonic Bio, and Uriach. Francesca Levi-Schaffer is a consultant for Hi-Bio. Bradford A. Youngblood is a current employee of Allakos and owns stock in Allakos. Martin K. Church has been a speaker or consultant for Almirall, FAES Farma, Menarini, Moxie, MSD, Novartis, Sanofi-Aventis, UCB, and Uriach. Marcus Maurer recently was a speaker and/or advisor for and/or has received research funding from Allakos, Alnylam, Amgen, Aralez, argenx, AstraZeneca, Astria, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Dyax, FAES, Genentech, GI Innovation, GSK, Innate Pharma, KalVista, Kyowa Kirin, LEO Pharma, Lilly, Menarini, Moxie, Novartis, Pfizer, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, Third Harmonic Bio, UCB, and Uriach.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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