receptors

MDPI

Review

Cross-Organ Differences Between IL-4Rα Blockade and IL-13-Selective Therapy in Immune-Priming and Barrier-Effector Compartments: Implications for Skin, Airway, and Gastrointestinal Diseases

Ryosuke Tanino [1,†] and Takayoshi Komatsu-Fujii [2,*,†]

[1] Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Faculty of Medicine, Shimane University, Izumo 693-8501, Japan; rtanino@med.shimane-u.ac.jp
[2] Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan
* Correspondence: komatsu.fujii.kyoto@gmail.com
† These authors contributed equally to this work.

Highlights

What are the main findings?

- A comprehensive review that compared clinical evidence for IL-4Rα blockade and IL-13-selective therapy across skin, airway, and gastrointestinal diseases.
- Mechanisms of action were organized by linking receptors, responding cells, and clinical endpoints to immune-priming and barrier-effector responses.

What are the implications of the main findings?

- The IL-13-selective antibodies tralokinumab and lebrikizumab improve skin lesions and itch in atopic dermatitis, while cendakimab improves dysphagia, tissue inflammation, and endoscopic findings in eosinophilic esophagitis. Tralokinumab and cendakimab also improve tissue inflammatory and epithelial-differentiation gene signatures.
- IL-4Rα blockade with dupilumab improves itch and skin lesions in prurigo nodularis and reduces exacerbations while improving lung function in asthma and COPD with type 2 inflammation.

Abstract

Antibody therapies targeting the IL-4/IL-13 axis are used in type 2 inflammatory diseases affecting skin, airways, and gastrointestinal tissues. Clinical responses and biomarker behavior differ across organs, complicating trial interpretation and endpoint selection. We propose an IL-4Rα-centered framework that relates these differences to receptor-responsive cells, local cytokine supply, and the compartments sampled by each endpoint. Type I receptors (IL-4Rα/γc) support IL-4-dependent immune priming, including type 2 helper T-cell (Th2) differentiation and immunoglobulin E (IgE) class switching. Type II receptors (IL-4Rα/IL-13Rα1) respond to both IL-4 and IL-13 and are prominent in epithelial and mesenchymal effector programs. Selected immune populations also respond through Type II receptors. We connect receptor biology to organ-specific experimental mechanisms and clinical outcomes, distinguish within-cell receptor expression from tissue cellular composition, and consider IL-13Rα2 as a separate ligand-buffering regulator. These assignments are predominant tendencies rather than exclusive cellular localizations or validated treatment-selection rules. This approach links molecular, tissue, and clinical endpoints while avoiding claims of drug superiority based on cross-trial comparisons.

Check for updates

Academic Editors: Alain Couvineau and Ya-Xiong Tao

Received: 31 January 2026
Revised: 9 October 2026
Accepted: 10 November 2026
Published: 16 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

Keywords: IL-4; IL-13; IL-4Rα; receptor context; type 2 inflammation; barrier tissues; dupilumab; biomarkers; clinical endpoints; OX40

1. Introduction

IL-4Rα-targeted and IL-13-selective antibody therapies have demonstrated benefit in several type 2 inflammatory diseases [1–4], while smaller clinical and tissue studies extend observations to additional skin phenotypes and local immune responses [5–7]. The magnitude and pattern of treatment responses are often organ-dependent. Assessment consequently varies with the endpoints or biomarkers used, including systemic biomarkers and tissue-proximal measures [8,9]. This creates a practical challenge for interpreting trials and selecting endpoints, because the effects of IL-4Rα blockade and IL-13-selective inhibition depend on the responding cells and tissue programs sampled [1,10,11].

We conceptualize Type I and Type II receptor signaling as a functional continuum whose weighting shifts with compartment, disease stage, and cellular composition. In this review, we define the immune-priming compartment as hematopoietic and lymphoid cells, and the barrier-effector compartment as epithelial and mesenchymal structural cells in barrier tissues [12]. In this framework, allergic sensitization and total immunoglobulin E (IgE) mainly reflect immune priming, whereas tissue-proximal endpoints more often reflect effector activity within barrier tissues [8,13,14]. Linking receptor-subunit usage to these immune-priming and barrier-effector compartments helps explain discordance between clinical endpoints and biomarkers across organs. When the term "endotype" is used in this review, it refers to a clinically pragmatic, biomarker-defined construct rather than a fully established molecular category.

Previous reviews have often summarized IL-4/IL-13 biology by cytokine, therapeutic agent, or organ-specific disease area. Here, receptor context provides the organizing principle for interpreting biomarkers and selecting endpoints across organs. In this approach, cell-type-dependent Type I and Type II receptor usage is linked to compartment-specific clinical readouts. Therapeutic responses are then interpreted by asking which receptor complex is available, which cell types express the relevant receptor subunits, and whether the selected endpoint samples immune priming, epithelial activation, mesenchymal remodeling, neuroimmune itch, or mucosal eosinophilic inflammation. Figure 1 summarizes this receptor-context framework by linking ligand–receptor complexes, representative receptor-responsive cell types, biological programs, and endpoint proximity. Accordingly, endpoint selection should prioritize measures that most closely sample the putative receptor-active compartment targeted by therapy.

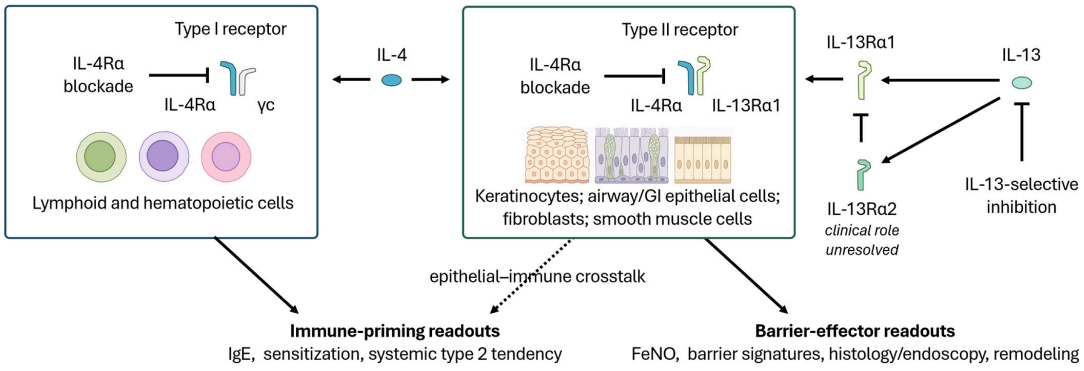


Figure 1. Receptor-context framework linking IL-4Rα blockade and IL-13-selective inhibition to immune-priming and barrier-effector readouts. IL-4 activates Type I (IL-4Rα/γc) and Type II (IL-4Rα/

IL-13Rα1) receptors; IL-13 activates Type II receptors. The depicted cell groups indicate representative tendencies rather than exclusive receptor localization: selected immune populations can also respond through Type II receptors. Cytokine-producing cells and responding cells need not share the same receptor context. IL-4Rα blockade intercepts both receptor contexts, whereas IL-13-selective antibodies inhibit the IL-13-dependent axis. IL-13Rα2 is a separate ligand-binding regulator, not a Type II signaling subunit; its inhibitory symbol denotes reduced ligand availability, not direct inhibition of IL-13Rα1. Local cell density, spatial distribution, ligand exposure, and receptor-subunit availability may shape responses, but no quantitative organ-wide receptor ratio or IL-13Rα2-based clinical selection rule is assumed. Readouts integrate varying contributions from inflammation, epithelial responses, neural signaling, and remodeling; histology and endoscopy are not exclusively epithelial or Type II-specific assays. Abbreviations: γc, common gamma chain; GI, gastrointestinal; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide. Solid and dotted arrows indicate direct and indirect effects, respectively.

2. Receptor Biology and Signaling

2.1. IL-4 and IL-13 Receptor Architecture

We first summarize IL-4 and IL-13 receptor architecture and key signaling features and then apply this framework to skin, airway, and gastrointestinal diseases to explain organ-specific biomarker–endpoint patterns and differential responses to IL-4Rα blockade versus IL-13–selective strategies.

IL-4 and IL-13 share the IL-4Rα subunit and commonly activate the JAK-STAT6 signaling pathway. However, their biological effects differ across organs [12,15,16]. IL-4 signals through both Type I receptor (IL-4Rα/γc) and Type II receptor (IL-4Rα/IL-13Rα1), whereas IL-13 primarily signals through the Type II receptor and can also be regulated by IL-13Rα2-dependent ligand buffering [12,15–18]. The availability of receptor subunits and ligand-dependent receptor assembly are major determinants of the strength, duration, and cellular context of downstream signaling.

Type I receptor signaling is largely enriched in hematopoietic and lymphoid cells, reflecting the lineage-restricted expression pattern of the common γc chain. In contrast, Type II receptor signaling is common in epithelial and mesenchymal cells in barrier tissues such as skin, airways, and the gastrointestinal tract [12,15,16,19–21]. IL-13 initiates signaling by binding IL-13Rα1, followed by recruitment of IL-4Rα; this assembly sequence differs from IL-4-induced Type II receptor assembly [17,18]. Together with the ability of IL-4Rα blockade to intercept both Type I and Type II receptor contexts, this provides a mechanistic basis for broad cross-organ effects [15,22].

2.2. Type I IL-4 Receptor (IL-4Rα/γc)

Upon binding of IL-4 to Type I receptor, JAK1 (associated with IL-4Rα) and JAK3 (associated with γc) are activated and lead to STAT6 phosphorylation [12,15,16]. In some myeloid lineages, IL-4 can activate the PI3K/AKT pathway through adaptor proteins such as insulin receptor substrate 2 (IRS2) [16,18,23].

Functionally, Type I receptor signaling supports upstream immune-priming processes, including Th2 differentiation and IgE class switching, and may contribute to systemic allergic sensitization and comorbidity patterns in type 2 inflammatory diseases [13,24–27]. Because Type I receptor signaling depends on γc availability, variations in γc expression and immune-cell composition can modulate IL-4 sensitivity [18,28]. In addition, SOCS proteins, including SOCS1 and SOCS3, provide negative feedback by attenuating JAK activity and limiting downstream signaling output [29–33].

2.3. Type II Receptor Complex (IL-4Rα/IL-13Rα1)

The Type II receptor complex can be activated by both IL-4 and IL-13 and is widely expressed in epithelial and mesenchymal cells of barrier tissues, such as skin, lung, and gastrointestinal tract [12,15,16,19–21]. Although Type II receptor signaling predominates in structural compartments, receptor engagement can also occur in selected hematopoietic lineages, depending on IL-13Rα1 availability [12,15,16,18–21].

IL-4 initiates Type II receptor signaling by binding IL-4Rα and subsequently recruiting IL-13Rα1, whereas IL-13 binds IL-13Rα1 first and then recruits IL-4Rα [17,18]. These distinct assembly processes can modulate signaling strength and duration in a tissue-dependent manner [17,18]. Type II receptor signaling commonly activates STAT6 through JAK1 associated with IL-4Rα, with context-dependent contributions from other kinases such as JAK2 or TYK2 reported in selected epithelial settings [12,34].

Negative feedback through SOCS1 and SOCS3 can attenuate IL-4/IL-13 signaling in immune and barrier cells, including keratinocytes [29–33,35]. Beyond canonical STAT6 signaling, IL-4/IL-13 stimulation activated ERK and p38 in a human bronchial epithelial cell line, illustrating context-dependent additional outputs [34]. Type II receptor signaling is associated with barrier dysfunction, mucus programs, and remodeling, but these structural-cell effects interact with responses in selected immune lineages and with immune–epithelial feedback [12,15,16].

2.4. IL-13Rα2: Established Ligand Buffering and Unresolved Signaling Roles

IL-13Rα2 is best established as a high-affinity IL-13-binding receptor that buffers ligand availability and limits Type II receptor signaling; the magnitude of this effect likely varies with tissue IL-13Rα2 expression and local IL-13 availability [36].

Additional IL-13Rα2-associated functions require distinction between ligands and experimental contexts. Chitinase 3-like-1 (CHI3L1), rather than IL-13 itself, activated MAPK/ERK and AKT through an IL-13Rα2–TMEM219-associated complex in experimental systems [37,38]. In the TMEM219 study, CHI3L1-associated Wnt/β-catenin activation did not require TMEM219 [38]. These findings should not be conflated with canonical IL-13/Type II receptor signaling. IL-13Rα2-associated TGF-β induction and fibrosis have also been reported in selected experimental models [39,40]; their clinical significance remains unresolved.

These observations raise the possibility that IL-13-selective antibodies differ in ligand handling at the IL-13Rα2 interface. Tralokinumab does not appear to displace IL-13 already bound to IL-13Rα2, whereas IL-13–lebrikizumab complexes can undergo IL-13Rα2-dependent internalization in vitro [41,42]. These differences should be regarded as pharmacologic hypotheses, not established explanations for differential clinical efficacy or safety.

2.5. Therapeutic Implications and Translational Bridge to Clinical Phenotypes

Table 1 summarizes receptor-complex usage rules that are applied to organ-level outcomes in subsequent sections. IL-4Rα integrates Type I signaling in immune lineages and Type II signaling in barrier tissues, providing a mechanistic basis for the broad cross-organ effects of IL-4Rα inhibition [12,15,16]. In contrast, IL-13-selective inhibition may be most mechanistically informative, and potentially most clinically relevant, when IL-13-dependent barrier-effector programs dominate and tissue-proximal endpoints are informative [12,15,16,22]. Residual Type II receptor signaling may persist in IL-4-dominant tissue states because IL-4 can also activate Type II receptor signaling [12,15,16,22]. Within a defined responding cell population, receptor-subunit availability and local IL-13 buffering

may alter cytokine sensitivity. This mechanistic principle should not be extrapolated to an unvalidated organ-wide receptor ratio [17,18,36].

Table 1. Comparison of IL-4 vs. IL-13 receptor-context usage.

Feature	IL-4	IL-13
Signaling receptor	Both Type I (IL-4Rα/γc) and Type II (IL-4Rα/IL-13Rα1) complexes	Type II (IL-4Rα/IL-13Rα1)
Type II assembly	Binding first to IL-4Rα	Binding first to IL-13Rα1
Dominant compartment	Type I: immune-priming compartment, mainly hematopoietic and lymphoid cells	Type II: barrier-effector compartment, mainly epithelial and mesenchymal structural cells
Additional compartment	Type II: barrier-effector compartment, mainly epithelial and mesenchymal structural cells	Type II: selected immune lineages depending on IL-13Rα1 availability
Canonical signaling	Type I: STAT6 via JAK1 associated with IL-4Rα and JAK3 associated with γc	Type II: STAT6 via JAK1 associated with IL-4Rα
IL-13Rα2	Not central to IL-4 signaling.	High-affinity decoy/buffer for IL-13
Translational mapping based on dominant compartment	Upstream immune priming (e.g., Th2 differentiation, IgE class switching)	Barrier-effector programs (e.g., epithelial activation, barrier dysfunction, mucus programs, remodeling)

Abbreviations: γc, common gamma chain; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription. Note: This table summarizes dominant receptor-context tendencies rather than exclusive ligand functions. IL-4 can activate both Type I and Type II receptor complexes, and Type II receptor engagement may occur in selected immune lineages depending on IL-13Rα1 availability. Key references: receptor assembly and structural basis of IL-4/IL-13 receptor complexes [17]; tuning of cytokine sensitivity by IL-4Rα, IL-13Rα1, and γc [18]; IL-13Rα2 buffering and antibody-dependent ligand handling [36,41,42].

From a clinical perspective, IgE and allergic sensitization are more closely aligned with immune-priming outputs associated with Type I receptor context [13,25], whereas barrier tissue-based endpoints, such as fractional exhaled nitric oxide (FeNO), barrier measures, and mucosal histology or endoscopy, are more proximal to Type II-weighted barrier-effector activity [8,9,43]. Blood eosinophil counts are widely used to enrich or monitor type 2 inflammation but are not specific readouts of IL-4/IL-13 receptor activity [44]. Accordingly, interpretation of these biomarkers should consider disease stage, treatment history, and local tissue context, and no single systemic biomarker can be assumed to serve as a universal surrogate for tissue-level receptor activity. In EoE, multidomain histologic scoring assesses epithelial abnormalities in addition to peak eosinophil counts [45].

In the following sections, we apply this receptor-centric framework to skin, airway, and gastrointestinal diseases to interpret organ-level phenotypes and clinical responses across treatment classes [12,15,16]. This framework should therefore be viewed as a testable model for aligning biomarkers and endpoints with receptor-active compartments, rather than as a fixed hierarchy of IL-4 versus IL-13 dominance.

2.6. Cell-Resolved Receptor Expression and Tissue Composition

Experimental human and mouse monocyte, macrophage, and fibroblast studies showed that IL-4Rα, γc, and IL-13Rα1 availability changes cytokine sensitivity [18]. Loss of functional γc markedly reduced IL-4 responses in monocytes and bone-marrow-derived macrophages but had a more modest effect in peritoneal macrophages, illustrating variation even within an immune lineage. Fibroblasts were more sensitive to IL-13. These observations support cell-specific receptor assembly, not a universal skin-to-lung expression ranking. IL-13Rα2 separately regulates ligand availability and is not the subunit defining Type II assembly [17,18,36].

In a tissue biopsy, increased IL2RG may reflect more infiltrating lymphocytes, whereas changes in IL13RA1 or IL13RA2 may reflect structural-cell abundance or altered expression

within those cells. A bulk IL13RA1/IL2RG ratio does not establish coexpression of functional receptor partners on the same cells. Cell density, spatial proximity to cytokine-producing cells, ligand availability, and disease stage must also be considered. Skin keratinocytes, airway epithelial and smooth-muscle cells, and selected immune populations provide different examples of receptor-responsive niches; these are examined below. Cross-organ expression ratios have not been prospectively validated for selecting IL-4Rα versus IL-13-selective therapy. Cell-resolved protein measurements and functional stimulation or inhibition are needed to test that hypothesis [18,36,46,47].

3. IL-4 and IL-13 in Skin Diseases

3.1. Receptor-Centric Mapping and Clinically Tractable Readouts in Type 2 Inflammatory Skin Disease

Skin inflammation involves cytokine-producing immune cells, receptor-responsive keratinocytes and stromal cells, and sensory neurons. IgE and sensitization mainly sample immune priming, while epidermal differentiation and barrier measurements sample structural-cell responses. Itch is a distinct neuroimmune endpoint, rather than a specific assay of keratinocyte Type II signaling [12,18,19,48]. Thymus and activation-regulated chemokine (TARC/CCL17) can reflect skin-associated type 2 inflammation, but it is not specific to atopic dermatitis (AD) or to an epidermal source; dendritic-cell chemokine programs also participate in recruitment of CCR4-positive T cells [47,49–54]. Consequently, both the number and distribution of infiltrating cytokine-producing cells and the state of the surrounding epidermis influence local signaling.

3.2. Atopic Dermatitis: Epidermal Barrier Impairment and Local Immune Circuits

In atopic dermatitis (AD), IL-4 and IL-13 connect immune priming to a keratinocyte barrier defect. Human skin and keratinocyte experiments link these cytokines to reduced filaggrin, loricrin, and involucrin expression, with STAT6 involvement in the latter differentiation programs [55,56]. In structural cells carrying IL-4Rα/IL-13Rα1, this provides a mechanism by which Type II signaling can weaken the epidermal barrier and sustain exposure to inflammatory stimuli. In parallel, IL-4-sensitive lymphoid populations support Th2 differentiation and IgE class switching [12,15]. These processes occur in interacting niches rather than in anatomically separate organs.

The efficacy of dupilumab and IL-13-selective antibodies in AD is compatible with interruption of this epithelial–immune feedback [1,10,11]. Barrier restoration after dupilumab and changes in lesional inflammatory signatures after tralokinumab provide tissue-level readouts in addition to clinical scores [4,52]. However, these observations do not quantify the independent contribution of Type I signaling or establish comparative superiority. Local receptor regulation further complicates the model: scratch injury increased keratinocyte IL-13Rα2 expression, and IL-13Rα2 overexpression attenuated an IL-13-associated differentiation defect in an experimental study [57]. Thus, lichenification and mechanical injury can alter ligand buffering within the epidermal niche; IL-13Rα2 abundance is not a validated predictor of antibody response.

A small human AD biopsy study found IL-13Rα1 expression on inducible T-cell costimulator (ICOS)-positive innate lymphoid cells and reduced density of these cells four weeks after tralokinumab treatment [6]. This associates IL-13 blockade with a local immune-cell change but does not distinguish direct receptor-mediated effects from changes in recruitment or epithelial–immune feedback.

Immune-cell persistence adds a further layer. Komatsu-Fujii et al. associated TNFRSF4-expressing CD4 T cells with type 2-associated resident-memory-like programs in human AD and found that early OX40L blockade reduced resident-memory-phenotype cells and

recall inflammation in a mouse model [54]. OX40 is a distinct costimulatory pathway, not a Type I IL-4 receptor component. These findings support considering the timing and location of cytokine-producing cells; they do not show that IL-4Rα or IL-13 blockade eliminates human tissue-resident memory T cells or establishes durable disease modification.

3.3. Chronic Spontaneous Urticaria: Mast-Cell Dominant Disease with IL-4-Skewed Immune Priming

Chronic spontaneous urticaria (CSU) is driven by mast-cell activation, with heterogeneous IgE-associated and autoimmune pathways [58,59]. IL-4 can influence B-cell IgE production and can also prime mast-cell effector responses. In cord-blood-derived human mast-cell cultures, IL-4 increased FcεRI expression and subsequent IgE-triggered IL-13 production, whereas IL-13 did not reproduce the same surface-receptor effects [60]. This identifies a possible amplification circuit, but those cultured cells are not CSU lesional mast cells and do not establish Type I exclusivity. Indeed, human lung mast cells express IL-13Rα1 and respond to prolonged IL-13 exposure [61], illustrating that immune-lineage responsiveness varies with tissue and cellular state.

In LIBERTY-CSU CUPID Study A, dupilumab improved symptoms in omalizumab-naïve patients; Study B, involving omalizumab-intolerant patients or those with an incomplete response, did not meet its primary endpoint [59]. Improvement across baseline IgE strata further cautions against treating total IgE as a necessary surrogate for the mechanism of response [58]. A proposed connection between IL-4-sensitive immune priming, mast-cell activation thresholds, and urticaria therefore needs direct lesional receptor and functional studies. Urticaria activity and itch scores remain clinical outputs of this circuit, rather than measurements of Type I receptor abundance.

3.4. Prurigo Nodularis: Neuroimmune Itch Amplification and Epidermal Remodeling

Prurigo nodularis (PN) combines chronic itch with epidermal and dermal remodeling [62]. Experimental work demonstrated responses to IL-4/IL-13 in sensory neurons and showed that neuron-specific disruption of IL-4Rα or JAK1 reduced chronic itch in mouse models [48]. This supplies a direct neuroimmune mechanism for separating itch from epidermal barrier endpoints. The experiments do not establish the relative necessity of Type I and Type II complexes in human PN lesions; JAK1 is shared across several signaling pathways, and itch intensity cannot identify a receptor complex.

Dupilumab improved both itch and skin lesions in PRIME and PRIME2 [62]. These outcomes are compatible with combined neuronal, inflammatory, and structural effects of IL-4Rα blockade, including secondary interruption of the itch–scratch cycle. Lesion reduction consequently should not be equated with direct inhibition of a single keratinocyte program. Evidence for IL-13-selective therapy in PN remains insufficient for a mechanistic comparison; paired assessment of itch, lesion remodeling, and cell-resolved receptor expression would distinguish these domains.

3.5. Practical Summary in Dermatologic Disease

AD demonstrates that IL-13-sensitive epithelial programs can be clinically relevant alongside IL-4-dependent immune priming. CSU emphasizes mast-cell activation and heterogeneous upstream pathways, while PN emphasizes neuronal sensitization and the itch–scratch cycle. These differences arise from the cells and circuits sampled by each endpoint, rather than a proven organ-wide receptor ratio (Tables 2 and 3) [1,10,19,48,58–60,62].

Table 2. Cell compartments, mechanistic evidence, and endpoint interpretation across organs.

Disease	Responding and Supplying Compartments	Mechanistic Connection	Endpoint and Evidence Limit
AD	Keratinocytes beside inflammatory T-cell, dendritic-cell, and ILC niches	Loss of differentiation proteins; injury-associated IL-13Rα2 regulation; local IL-13Rα1-positive ILC changes [6,55–57].	Barrier function is proximal; EASI and itch integrate several compartments. OX40 evidence does not establish memory-cell elimination by cytokine blockade [54].
CSU	B-cell priming and mast-cell effector responses	IL-4 priming altered FcεRI and IgE-triggered IL-13 production in cultured human mast cells [60].	Urticaria and itch are clinical outputs; culture findings do not establish receptor dependence in CSU lesions [58,59].
PN	Sensory neurons and epidermal/dermal responses to scratching	Neuronal IL-4Rα/JAK1 perturbation reduced chronic itch in mice [48].	Distinguish itch from lesion reduction; receptor-complex necessity in human PN remains unresolved [62].
Asthma	Bronchial epithelium, smooth muscle, and local mast cells	IL-13–SPDEF mucus program; smooth-muscle responses; IL-13Rα1-positive mast cells and smooth-muscle-localized mast-cell density [61,63–65].	Molecular mucus/FeNO changes differ from FEV1 and exacerbations. Cross-trial discordance does not isolate an IL-4 contribution [22,66].
CRSwNP	Basal/progenitor and differentiated epithelium within inflamed polyps	Altered epithelial composition and retained type 2-associated progenitor programs [67].	Polyp size and smell integrate multiple processes; treated-cell findings from one individual remain exploratory [67,68].
COPD with type 2 inflammation	Airway epithelium within mixed injury/inflammatory states	Type 2 epithelial signatures occur in subsets; relative Type I/II contributions remain unresolved [69].	Blood eosinophils enrich trial populations. FEV1 and exacerbations do not measure receptor stoichiometry [70–72].
EoE	Mucosal epithelium, recruited eosinophils, and remodeling compartments	Epithelial CCL26 and differentiation programs link cytokine responses to local inflammation [73,74].	Both drug classes have multidomain trial evidence; histology/endoscopy are mixed-cell outputs, not Type II-specific assays [75–77].
Non-EoE EGIDs	Segment-dependent mucosal and inflammatory populations	New EoG/EoD trials support cytokine-sensitive histologic activity; mechanisms vary by segment [78–80].	Separate tissue improvement from symptom benefit; no direct comparative Type I contribution is established [79,80].
UC	Colonic epithelium and heterogeneous mucosal immune populations	IL-13 impaired barrier resistance, with claudin-2 and apoptosis changes in an epithelial-cell model [81,82].	Anti-IL-13 trials missed primary endpoints; receptor-expression enrichment tests remain unvalidated [83–87].

Abbreviations: AD, atopic dermatitis; CSU, chronic spontaneous urticaria; PN, prurigo nodularis; CRSwNP, chronic rhinosinusitis with nasal polyps; COPD, chronic obstructive pulmonary disease; EoE, eosinophilic esophagitis; EGIDs, eosinophilic gastrointestinal disorders; EoG/EoD, eosinophilic gastritis/duodenitis; UC, ulcerative colitis; ILC, innate lymphoid cell; EASI, Eczema Area and Severity Index; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FcεRI, high-affinity IgE receptor; SPDEF, SAM pointed domain-containing ETS transcription factor. Notes: FeNO is steroid- and context-sensitive (e.g., upper airway inflammation, smoking, infection). Blood eosinophils enrich type 2 inflammation but are not IL-4/IL-13 specific and may not reliably reflect tissue activity, particularly in GI disease. Key references: receptor-context framework/complex biology [12,15–18]; FeNO and context sensitivity [8,9,43]; biomarker considerations (including eosinophils) [44]; tissue-aligned endpoints in EoE (endoscopy/histology) [14,45].

Table 3. Putative receptor-context alignment of biomarker and endpoint classes; assignments are not validated tests of receptor dependence.

Disease	IgE/Sensitization	FeNO	Blood Eosinophils †	Local Tissue Histology/Organ-Proximal Pathology	Barrier/Epithelial Signatures
Atopic dermatitis	I-aligned	—	Mixed	Mixed	II-aligned
Chronic spontaneous urticaria	I-aligned	—	Mixed	—	Mixed
Prurigo nodularis	Mixed	—	Mixed	Mixed	Mixed
Asthma (type 2-high)	I-aligned	II-aligned	Mixed	Mixed	II-aligned
CRSwNP	I-aligned	—	Mixed	Mixed	II-aligned
COPD with type 2 inflammation	Mixed	Mixed	Mixed ‡	—	Mixed
Eosinophilic esophagitis	I-aligned	—	Mixed	Mixed	II-aligned
Non-esophageal EGIDs (EoG/EoD/EGE)	I-aligned	—	Mixed	Mixed	II-aligned
Ulcerative colitis	Mixed	—	Mixed	Mixed	Mixed

Abbreviations: IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; CRSwNP, chronic rhinosinusitis with nasal polyps; COPD, chronic obstructive pulmonary disease; EGIDs, eosinophilic gastrointestinal disorders; EoG, eosinophilic gastritis; EoD, eosinophilic duodenitis; EGE, eosinophilic gastroenteritis. Notes: I-aligned and II-aligned denote putative proximity to Type I (IL-4Rα/γc) and Type II (IL-4Rα/IL-13Rα1) contexts, not receptor-specific measurements. Mixed indicates contributions from several cells, pathways, disease stages, or treatment effects; — indicates an insufficiently established organ-specific use. Tissue histology includes infiltrates and remodeling as well as epithelial responses. TARC/CCL17 and itch are not exclusive epithelial Type II readouts. † Blood eosinophils enrich type 2 inflammation but are not specific to IL-4/IL-13 signaling or to either receptor type and may not reflect tissue activity, especially in gastrointestinal disease. ‡ In COPD, blood eosinophils are an operational trial-enrichment criterion and remain auxiliary for inferring Type I versus Type II dominance; FeNO is context- and corticosteroid-sensitive. Key references: receptor-context framework and compartment mapping [12,15–18]; FeNO as an epithelial/type 2 readout (context sensitive) [8,9,43]; inflammatory biomarker considerations (including eosinophils) [44]; tissue-aligned endpoints in EoE (endoscopy/histology scoring) [14,45].

The assignments in Tables 2 and 3 describe mechanistic alignment, not receptor-specific assays. Clinical scores integrate several compartments, and neither an epithelial transcript signature nor response to dupilumab proves that a particular endpoint is exclusively Type II-dependent.

4. IL-4 and IL-13 in Airway Disease

4.1. Receptor-Centric Mapping and Biomarkers in United Airway Disease

Asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) link epithelial injury and alarmin release to cytokine production by Th2 cells, ILC2s, and other inflammatory populations [19,88–91]. Cytokine production must be distinguished from receptor responsiveness: IL-13-producing immune cells can drive Type II responses in adjacent epithelium without themselves being predominantly Type II responsive. Changes in immune-cell infiltration and in basal, secretory, and ciliated epithelial populations can therefore change whole-tissue receptor expression [67]. FeNO samples an epithelial nitric-oxide program influenced by corticosteroids and clinical context; it does not measure all airway inflammation or the separate contribution of IL-4 versus IL-13 [8,9,43].

4.2. Asthma (Type 2-High Endotype)

In type 2-high asthma, a direct epithelial mechanism links IL-13 stimulation to SPDEF-dependent goblet-cell differentiation and MUC5AC expression. Targeting SPDEF in primary human bronchial epithelial cells prevented IL-13-induced impairment of mucociliary trans-

port, connecting a cytokine-responsive structural-cell program to mucus retention [63]. Human airway smooth-muscle cultures also express IL-4Rα and IL-13Rα1 and show IL-13-associated STAT6 activation and changes in agonist-evoked calcium responses [64]. These epithelial and mesenchymal responses provide distinct routes to airflow obstruction alongside immune priming and inflammatory recruitment.

Human lung mast cells express IL-13Rα1 and responded to prolonged IL-13 exposure with increased FcεRI and IgE-triggered histamine release [61]; cord-blood-derived mast-cell cultures did not show equivalent IL-13 surface-receptor effects [60]. Bronchial submucosal mast cells also showed higher IL-13Rα1 positivity in asthma than in healthy controls [61], providing disease-site protein evidence of variation within a responding immune population. Cytokine pretreatment altered smooth-muscle responsiveness in ways not explained by IL-13Rα2 alone [64]. Hematopoietic identity therefore does not establish Type I restriction.

Cell location adds information beyond an overall inflammatory count. In human bronchial biopsies, asthma and eosinophilic bronchitis had similar submucosal eosinophilia, but asthma showed greater mast-cell density within airway smooth-muscle bundles [65]. This associated a specific immune-cell niche with abnormal airway function. It does not establish an IL-4/IL-13 receptor ratio or a causal comparative treatment effect but illustrates why local immune-cell distribution can alter the structural compartment exposed to inflammatory signals.

Dupilumab improved exacerbation and lung-function outcomes in QUEST and reduced oral glucocorticoid requirements in VENTURE [2,92]. LAVOLTA I and II showed inconsistent primary exacerbation results with lebrikizumab [66], while a post hoc reanalysis identified benefit in selected patients with elevated blood eosinophils or FeNO and prior exacerbations [22]. These results do not isolate an IL-4-dependent contribution: population selection, exposure, concomitant treatment, and endpoint composition also matter. Molecular epithelial responses and exacerbation outcomes are related but not interchangeable [66,93].

4.3. Chronic Rhinosinusitis with Nasal Polyps

CRSwNP offers a human example of changes in the composition and state of a receptor-responsive epithelial niche. Single-cell and ex vivo studies identified expanded basal-cell populations, altered epithelial differentiation, and retained IL-4/IL-13-associated inflammatory programs in progenitor cells [67]. An exploratory analysis from one dupilumab-treated individual suggested altered epithelial states; it does not establish reversal of inflammatory memory across patients. Local inflammatory-cell density and proximity to progenitors may sustain cytokine exposure even when bulk receptor abundance appears similar.

Polyp size, nasal obstruction, and smell reflect integrated changes in epithelium, edema, inflammatory infiltrates, and remodeling [94]. Dupilumab improved these domains and reduced systemic corticosteroid use and surgery in randomized studies [68,95,96]. The mechanistic bridge is interruption of cytokine-responsive epithelial–immune feedback, not a demonstrated Type II-only origin of the polyp score. Paired tissue profiling could test whether epithelial-state changes and local immune-cell redistribution account for discordance between circulating IgE and clinical improvement [67,97].

4.4. Chronic Obstructive Pulmonary Disease with Type 2 Inflammation (Biomarker-Defined)

Chronic obstructive pulmonary disease (COPD) with type 2 inflammation is a biomarker-defined subgroup within a heterogeneous disease. Primary transcriptomic studies identified asthma-associated type 2 signatures in airway epithelium from subsets of patients with COPD [69]. This supplies a tissue-level link between cytokine-responsive

epithelial programs and phenotype but does not establish the relative contribution of γc-dependent immune signaling versus Type II signaling in individual patients. Smoking-related injury, infection, and changes in inflammatory-cell and epithelial composition can coexist with these programs.

BOREAS and NOTUS enrolled patients with blood eosinophils ≥ 300 cells/μL and demonstrated benefits of add-on dupilumab for exacerbations and lung function despite maintenance inhaled treatment [70–72]. Blood eosinophils operationally enriched a responsive population; they did not measure airway receptor stoichiometry or identify the cells responsible for benefit. Linking clinical response to epithelial differentiation, mucus biology, and spatially resolved immune-cell niches is therefore a translational hypothesis, rather than an established explanation for the superiority of one receptor-targeting strategy [69].

4.5. Practical Summary in Airway Disease

Airway endpoints sample different parts of the same circuit: FeNO and epithelial mucus signatures are relatively proximal molecular outputs, while FEV1, exacerbations, polyp scores, and smell integrate structural and inflammatory processes [2,8,9,43,68]. Receptor availability, ligand supply, and the distribution of responding cells provide a mechanistic explanation to test; they are not established comparative treatment-selection rules. The variable results of IL-13-selective asthma trials and the benefits of IL-4Rα blockade should be interpreted with trial design and biomarker enrichment in view [22,66,92,93].

5. IL-4 and IL-13 in Gastrointestinal Diseases

5.1. Receptor-Centric Mapping and Biomarkers in Type 2 Inflammatory Gastrointestinal Disease

Gastrointestinal type 2 inflammation involves epithelial barrier dysfunction, local immune responses, and remodeling [98]. IL-4 can support immune priming through Type I receptors, whereas IL-13-sensitive Type II programs include epithelial chemokine production and differentiation. Mucosal eosinophil density, epithelial transcripts, and endoscopic findings sample different components of this circuit: tissue eosinophils are an inflammatory infiltrate, not a receptor-specific epithelial assay. Systemic IgE and blood eosinophils may therefore diverge from mucosal or symptomatic outcomes [45,99,100].

5.2. Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) features cytokine-responsive epithelial programs linked to mucosal inflammation. A conserved transcript signature identified increased eotaxin-3 (CCL26) expression and its association with tissue eosinophilia [73]. This connects a local epithelial chemokine program to inflammatory recruitment. Cendakimab-treated biopsies showed changes in CCL26, epithelial differentiation genes, and remodeling-associated transcripts [74], providing molecular readouts alongside clinical outcomes. Histology and endoscopy should be assessed with symptoms, and multidomain histologic scoring can capture epithelial and structural abnormalities beyond peak eosinophil counts [14,45].

Dupilumab improved histologic and symptomatic outcomes through 52 weeks, and cendakimab improved dysphagia, histologic response, and endoscopic features in its phase 3 program [3,75,76]. Both classes therefore have evidence of multidomain benefit. These trials support the clinical relevance of IL-13-sensitive tissue programs, but differences in study design and endpoints prevent a ranking of receptor-pathway contributions or comparative efficacy. Histology and endoscopy measure mixed mucosal outputs and should be interpreted alongside symptoms [14,45,77].

5.3. Non-Esophageal Eosinophilic Gastrointestinal Disorders: Segment-Specific Responses and Endpoint Discordance

Non-esophageal eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic gastritis (EoG), duodenitis (EoD), and gastroenteritis (EGE), vary by gastrointestinal segment, layer involvement, and disease stage [78,101]. Histologic assessment requires site-appropriate sampling because eosinophilic infiltration may be patchy and endoscopic findings can be nonspecific [101,102]. This heterogeneity limits extrapolation of an esophageal epithelial mechanism to every non-esophageal disorder.

An early phase 2 anti-Siglec-8 trial showed improvement in tissue eosinophilia and symptoms, illustrating eosinophil/mast-cell targeting rather than directly testing an IL-4/IL-13 receptor complex [103,104]. Randomized evidence for cytokine blockade has since expanded. In the 41-patient phase 2 DEGAS trial, dupilumab improved gastric eosinophil counts, histologic scores, and endoscopic features at week 12, while the symptom-score difference was not significant; the study was not powered for symptoms [79]. A phase 3 trial in 48 Japanese patients with eosinophilic gastritis and/or duodenitis found that cendakimab reduced gastrointestinal eosinophil counts at week 16, with histologic effects maintained at week 48 and numerically improved symptom domains [80]. These results support cytokine-sensitive mucosal inflammation but do not establish equal symptom benefit, generalizability to every gastrointestinal segment, or a comparative Type I contribution. Clinical and tissue endpoints must be assessed separately.

5.4. Ulcerative Colitis: Mechanistic Signals Without Consistent Clinical Efficacy

Ulcerative colitis (UC) is not a uniformly type 2-driven disease. Mucosal studies identified IL-13-producing nonclassical natural killer T cells in an atypical Th2-associated response [81]. In a colonic epithelial-cell model expressing IL-4Rα and IL-13Rα1, IL-13 increased claudin-2 and apoptosis and impaired barrier resistance and restitution, whereas IL-4 did not reproduce the resistance effect under the tested conditions [82]. This illustrates distinct ligand responses despite shared receptor components; it does not establish a universal IL-13-dependent UC endotype. Tralokinumab and anrukinzumab phase IIa trials did not significantly improve their primary endpoints [83,84]. A positive secondary remission signal with tralokinumab and evidence of anrukinzumab target binding consequently do not establish consistent population-level efficacy. Transcriptomic heterogeneity and eosinophil-associated findings motivate exploratory tissue stratification [85–87], but mucosal receptor expression, barrier signatures, and eosinophil-rich histology have not been validated as predictive tests for selecting anti-IL-13 treatment in UC.

5.5. Practical Summary in Gastrointestinal Disease

Gastrointestinal response assessment should combine symptoms with segment-appropriate histology and endoscopy because these domains can diverge [3,14]. EoE has multidomain evidence for both IL-4Rα and IL-13 blockade [3,73,75–77]. New eosinophilic gastritis/duodenitis trials further support cytokine-sensitive histologic activity while demonstrating the need to evaluate symptoms separately [79,80]. In UC, mechanistic epithelial findings coexist with negative primary trial results; proposed tissue enrichment markers remain exploratory [82–87].

6. Discussion

6.1. Safety Considerations

Clinical trials and follow-up studies of IL-4/IL-13 pathway inhibitors generally support a favorable safety profile without evidence of broad immunosuppression [105–109].

Reported adverse events include injection-site reactions, conjunctivitis, and transient eosinophilia. Safety patterns nevertheless depend on agent, disease, and follow-up duration. The 48-week cendakimab EoE trial reported more overall adverse events in active-treatment groups than with placebo, underscoring the need for agent-specific interpretation [76].

In dermatologic practice, ocular surface disease represents a clinically recognized organ-specific off-tissue effect of IL-4/IL-13 pathway inhibition. Conjunctivitis and related events, including keratitis, blepharitis, eye pruritus, and dry eye, have been reported in AD patients treated with IL-4Rα or IL-13 pathway inhibitors [110,111]. Because AD itself predisposes patients to ocular surface inflammation, these events are best interpreted as a drug–disease interaction and a barrier-mucosal safety signal rather than as nonspecific toxicity alone.

Overall, these safety findings are consistent with targeting a type 2-high signaling axis (IL-4Rα-dependent receptor complexes) rather than broadly suppressing host defense. However, long-term and real-world pharmacovigilance is still important to detect uncommon events, guide monitoring in patients with multi-organ disease, and clarify differences in safety patterns between IL-4Rα and IL-13-selective inhibition. Direct comparative safety data also remain limited.

6.2. Disease Modification and Long-Term Outcomes

Whether IL-4/IL-13 inhibition changes the long-term disease course beyond controlling symptoms remains unresolved. Type II-responsive structural-cell programs include barrier function, mucus production, and epithelial differentiation [17–19]. Tralokinumab AD biopsies and cendakimab EoE biopsies showed normalization of inflammatory, differentiation, and remodeling-associated transcripts [52,74]. Changes in remodeling-associated gene expression should not be equated with proven reversal of structural fibrosis or durable disease modification after treatment withdrawal.

To determine whether IL-4/IL-13 inhibition leads to durable disease modification, future studies should incorporate longer follow-up and endpoints capturing structural biology, alongside symptoms and exacerbations. IL-13Rα2 handling is included as a mechanistic gap rather than as a proven clinical discriminator (Table 4).

Table 4. Comparison of agents targeting IL-4Rα and IL-13 in receptor context.

Agent	Molecular Target	Affected Receptor-Context Signaling	Clinical Evidence Context	Mechanistic Gap
Dupilumab	IL-4Rα	IL-4-driven Type I, IL-4-driven Type II, IL-13-driven Type II	AD, asthma, PN, CSU, CRSwNP, EoE, type 2-enriched COPD; EoG (phase 2)	Endpoint-specific Type I vs. Type II contribution remains unresolved
Tralokinumab	IL-13	IL-13-driven Type II	AD	Clinical significance of IL-13Rα2 ligand handling remains unproven
Lebrikizumab	IL-13	IL-13-driven Type II	AD	No definitive head-to-head mechanistic validation versus tralokinumab
Cendakimab	IL-13	IL-13-driven Type II	EoE; EoG/EoD (Japanese phase 3 trial)	Structural remodeling, symptom benefit in non-EoE EGIDs, and broader generalizability require further evaluation

Note: Clinical evidence context summarizes trial-supported effects, not regulatory approval in every jurisdiction or comparative efficacy. CSU results vary with prior omalizumab exposure. Non-EoE EGID trials showed histologic effects with less certain symptom benefit; cendakimab findings are from a small Japanese trial. IL-13Rα2 ligand-handling differences remain mechanistic hypotheses [58,59,76,79,80].

6.3. Cross-Organ Therapeutic Implications

For patients with multiple type 2 inflammatory diseases, receptor context offers a framework for interpreting the cells and processes sampled by each endpoint. Tables 2 and 3 relate candidate compartments to evidence and readouts, without treating the assignments as validated receptor-specific tests. Tissue histology and endoscopy assess local mucosal inflammation and structural change [14,45], whereas circulating IgE is more closely aligned with immune-priming processes [13,25]. Neural sensitization, cellular recruitment, epithelial responses, and remodeling can contribute together. Antibody-specific IL-13 handling at the IL-13Rα2 interface provides a further hypothesis for response heterogeneity, but direct clinical causality and comparative treatment-selection value remain unproven [41,42].

6.4. Refining Endotypes, Biomarkers, and Limitations

Progress will require cell-specific measurements of IL-4/IL-13 activity and prospective validation of clinically useful biomarkers. Single-cell and spatial transcriptomics can map receptor transcripts and candidate epithelial–immune relationships to disease phenotypes [46,47]; they do not directly measure receptor-complex engagement. Local cytokine supply, receptor-responsive cell states, and upstream inflammatory circuits may contribute to organ-specific effects. IgE and sensitization reflect immune-priming processes, while epithelial signatures sample structural-cell programs; neither identifies a unique receptor complex [8,9,43,44]. Head-to-head trials remain scarce, and study populations, endpoints, drug exposure, and concomitant treatment differ across trials. These limitations constrain mechanistic interpretation of apparent cross-drug efficacy differences. Prospective studies should combine receptor–protein measurements, functional perturbation, local cellular composition, and molecular, tissue, and clinical outcomes.

7. Conclusions

Cross-organ differences in type 2 inflammatory disease can be interpreted with attention to local cytokine supply, receptor availability within responding cells, cellular distribution, and the processes sampled by each endpoint. Type I receptors support IL-4-dependent immune priming, while Type II receptors mediate structural-cell programs and responses in selected immune populations. This framework links mechanistic evidence to molecular, tissue, and clinical readouts while preserving the limits of each evidence level.

IL-4Rα blockade covers IL-4-driven Type I and Type II signaling and IL-13-driven Type II signaling. IL-13-selective inhibition targets the IL-13-dependent component while leaving IL-4-mediated signaling available. The clinical contribution of that difference varies with disease context and cannot be inferred directly from cross-trial efficacy patterns because head-to-head and comparative mechanistic data remain limited.

These observations suggest three priorities for prospective studies. First, cell-resolved abundance and coexpression of IL-4Rα, γc, and IL-13Rα1, combined with the density and proximity of cytokine-producing immune cells, may help explain organ-specific molecular responses. Bulk IL13RA1/IL2RG ratios cannot substitute for these measurements. Second, local IL-13Rα2-mediated buffering may influence ligand availability, requiring direct in vivo pharmacodynamic validation. Third, molecular, structural, and clinical endpoints should be measured together to distinguish target engagement from whole-organ benefit. These hypotheses require prospective validation and comparative studies rather than inference from cross-trial efficacy alone.

Author Contributions: Conceptualization, T.K.-F.; writing—original draft preparation, R.T. and T.K.-F.; writing—review and editing, T.K.-F.; visualization, R.T. and T.K.-F.; supervision, T.K.-F., R.T. and T.K.-F. contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: ChatGPT (GPT-6) was used during revision to assist with language editing. The authors retain responsibility for the scientific content and final approval.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Blauvelt, A.; de Bruin-Weller, M.; Gooderham, M.; Cather, J.C.; Weisman, J.; Pariser, D.; Simpson, E.L.; Papp, K.A.; Hong, H.C.; Rubel, D.; et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): A 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* **2017**, *389*, 2287–2303. [CrossRef] [PubMed]
2. Castro, M.; Corren, J.; Pavord, I.D.; Maspero, J.; Wenzel, S.; Rabe, K.F.; Busse, W.W.; Ford, L.; Sher, L.; FitzGerald, J.M.; et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N. Engl. J. Med.* **2018**, *378*, 2486–2496. [CrossRef] [PubMed]
3. Dellon, E.S.; Rothenberg, M.E.; Collins, M.H.; Hirano, I.; Chehade, M.; Bredenoord, A.J.; Lucendo, A.J.; Spergel, J.M.; Aceves, S.; Sun, X.; et al. Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis. *N. Engl. J. Med.* **2022**, *387*, 2317–2330. [CrossRef] [PubMed]
4. Berdyshev, E.; Goleva, E.; Bissonnette, R.; Bronova, I.; Bronoff, A.S.; Richers, B.N.; Garcia, S.; Ramirez-Gama, M.; Taylor, P.; Praestgaard, A.; et al. Dupilumab significantly improves skin barrier function in patients with moderate-to-severe atopic dermatitis. *Allergy* **2022**, *77*, 3388–3397. [CrossRef] [PubMed]
5. Komatsu-Fujii, T.; Nonoyama, S.; Ogawa, M.; Fukumoto, T.; Tanabe, H. Rapid effects of dupilumab treatment on papuloerythroderma of Ofuji. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, e739–e741. [CrossRef] [PubMed]
6. Kogame, T.; Yonekura, S.; Lovato, P.; Hirata, M.; Takimoto-Ito, R.; Takegami, T.; Komatsu-Fujii, T.; Kambe, N.; Nomura, T.; Røpke, M.A.; et al. Interleukin-13 inhibition by tralokinumab reduces inducible T-cell costimulator-positive innate lymphoid cells in skin lesions of atopic dermatitis. *Br. J. Dermatol.* **2023**, *188*, 146–148. [CrossRef] [PubMed]
7. Komatsu-Fujii, T.; Cho, R.; Nomiyama, T.; Yamamoto, Y.; Kogame, T.; Kabashima, K. Clinical outcome of alopecia areata in patients with atopic dermatitis treated with dupilumab combined with topical immunotherapy: A case series. *Eur. J. Dermatol.* **2025**, *35*, 519–526. [CrossRef] [PubMed]
8. Maniscalco, M.; Fuschillo, S.; Mormile, I.; Detoraki, A.; Sarnelli, G.; Paulis, A.; Spadaro, G.; Cantone, E.; PATH-2 TASK FORCE. Exhaled Nitric Oxide as Biomarker of Type 2 Diseases. *Cells* **2023**, *12*, 2518. [CrossRef] [PubMed]
9. Murugesan, N.; Saxena, D.; Dileep, A.; Adrish, M.; Hanania, N.A. Update on the Role of FeNO in Asthma Management. *Diagnostics* **2023**, *13*, 1428. [CrossRef] [PubMed]
10. Silverberg, J.I.; Toth, D.; Bieber, T.; Alexis, A.F.; Elewski, B.E.; Pink, A.E.; Hijnen, D.; Jensen, T.N.; Bang, B.; Olsen, C.K.; et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: Results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *Br. J. Dermatol.* **2021**, *184*, 450–463. [CrossRef] [PubMed]
11. Silverberg, J.I.; Guttman-Yassky, E.; Thaçi, D.; Irvine, A.D.; Stein Gold, L.; Blauvelt, A.; Simpson, E.L.; Chu, C.Y.; Liu, Z.; Gontijo Lima, R.; et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. *N. Engl. J. Med.* **2023**, *388*, 1080–1091. [CrossRef] [PubMed]
12. Junttila, I.S. Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes. *Front. Immunol.* **2018**, *9*, 888. [CrossRef] [PubMed]
13. Wang, W.; Wang, L.; Zha, B. The roles of STAT6 in regulating B cell fate, activation, and function. *Immunol. Lett.* **2021**, *233*, 87–91. [CrossRef] [PubMed]
14. Hirano, I.; Moy, N.; Heckman, M.G.; Thomas, C.S.; Gonsalves, N.; Achem, S.R. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: Validation of a novel classification and grading system. *Gut* **2013**, *62*, 489–495. [CrossRef] [PubMed]

15. Keegan, A.D.; Zamorano, J.; Keselman, A.; Heller, N.M. IL-4 and IL-13 Receptor Signaling From 4PS to Insulin Receptor Substrate 2: There and Back Again, a Historical View. *Front. Immunol.* **2018**, *9*, 1037. [CrossRef] [PubMed]
16. Keegan, A.D.; Leonard, W.J.; Zhu, J. Recent advances in understanding the role of IL-4 signaling. *Fac. Rev.* **2021**, *10*, 71. [CrossRef] [PubMed]
17. LaPorte, S.L.; Juo, Z.S.; Vaclavikova, J.; Colf, L.A.; Qi, X.; Heller, N.M.; Keegan, A.D.; Garcia, K.C. Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. *Cell* **2008**, *132*, 259–272. [CrossRef] [PubMed]
18. Junttila, I.S.; Mizukami, K.; Dickensheets, H.; Meier-Schellersheim, M.; Yamane, H.; Donnelly, R.P.; Paul, W.E. Tuning sensitivity to IL-4 and IL-13: Differential expression of IL-4Ralpha, IL-13Ralpha1, and gammac regulates relative cytokine sensitivity. *J. Exp. Med.* **2008**, *205*, 2595–2608. [CrossRef] [PubMed]
19. Akdis, C.A.; Arkwright, P.D.; Brüggen, M.C.; Busse, W.; Gadina, M.; Guttman-Yassky, E.; Kabashima, K.; Mitamura, Y.; Vian, L.; Wu, J.; et al. Type 2 immunity in the skin and lungs. *Allergy* **2020**, *75*, 1582–1605. [CrossRef] [PubMed]
20. Hocke, A.C.; Ermert, M.; Althoff, A.; Brell, B.; N'Guessan, P.D.; Suttorp, N.; Ermert, L. Regulation of interleukin IL-4, IL-13, IL-10, and their downstream components in lipopolysaccharide-exposed rat lungs. Comparison of the constitutive expression between rats and humans. *Cytokine* **2006**, *33*, 199–211. [CrossRef] [PubMed]
21. Yoshikawa, M.; Nakajima, T.; Tsukidate, T.; Matsumoto, K.; Iida, M.; Otori, N.; Haruna, S.; Moriyama, H.; Saito, H. TNF-alpha and IL-4 regulate expression of IL-13 receptor alpha2 on human fibroblasts. *Biochem. Biophys. Res. Commun.* **2003**, *312*, 1248–1255. [CrossRef] [PubMed]
22. Corren, J.; Szefler, S.J.; Sher, E.; Korenblat, P.; Soong, W.; Hanania, N.A.; Berman, G.; Brusselle, G.; Zitnik, R.; Natalie, C.R.; et al. Lebrikizumab in Uncontrolled Asthma: Reanalysis in a Well-Defined Type 2 Population. *J. Allergy Clin. Immunol. Pract.* **2024**, *12*, 1215–1224.e3. [CrossRef] [PubMed]
23. Kubota, T.; Inoue, M.; Kubota, N.; Takamoto, I.; Mineyama, T.; Iwayama, K.; Tokuyama, K.; Moroi, M.; Ueki, K.; Yamauchi, T.; et al. Downregulation of macrophage Irs2 by hyperinsulinemia impairs IL-4-indeuced M2a-subtype macrophage activation in obesity. *Nat. Commun.* **2018**, *9*, 4863. [CrossRef] [PubMed]
24. Goenka, S.; Kaplan, M.H. Transcriptional regulation by STAT6. *Immunol. Res.* **2011**, *50*, 87–96. [CrossRef] [PubMed]
25. Karpathiou, G.; Papoudou-Bai, A.; Ferrand, E.; Dumollard, J.M.; Peoc'h, M. STAT6: A review of a signaling pathway implicated in various diseases with a special emphasis in its usefulness in pathology. *Pathol. Res. Pract.* **2021**, *223*, 153477. [CrossRef] [PubMed]
26. Brunner, P.M.; Silverberg, J.I.; Guttman-Yassky, E.; Paller, A.S.; Kabashima, K.; Amagai, M.; Luger, T.A.; Deleuran, M.; Werfel, T.; Eyerich, K.; et al. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. *J. Investig. Dermatol.* **2017**, *137*, 18–25. [CrossRef] [PubMed]
27. Khan, A.H.; Gouia, I.; Kamat, S.; Johnson, R.; Small, M.; Siddall, J. Prevalence and Severity Distribution of Type 2 Inflammation-Related Comorbidities Among Patients with Asthma, Chronic Rhinosinusitis with Nasal Polyps, and Atopic Dermatitis. *Lung* **2023**, *201*, 57–63. [CrossRef] [PubMed]
28. Leonard, W.J.; Lin, J.X.; O'Shea, J.J. The γc Family of Cytokines: Basic Biology to Therapeutic Ramifications. *Immunity* **2019**, *50*, 832–850. [CrossRef] [PubMed]
29. Haque, S.J.; Harbor, P.C.; Williams, B.R. Identification of critical residues required for suppressor of cytokine signaling-specific regulation of interleukin-4 signaling. *J. Biol. Chem.* **2000**, *275*, 26500–26506. [CrossRef] [PubMed]
30. Canfield, S.; Lee, Y.; Schröder, A.; Rothman, P. Cutting edge: IL-4 induces suppressor of cytokine signaling-3 expression in B cells by a mechanism dependent on activation of p38 MAPK. *J. Immunol.* **2005**, *174*, 2494–2498. [CrossRef] [PubMed]
31. Dickensheets, H.; Vazquez, N.; Sheikh, F.; Gingras, S.; Murray, P.J.; Ryan, J.J.; Donnelly, R.P. Suppressor of cytokine signaling-1 is an IL-4-inducible gene in macrophages and feedback inhibits IL-4 signaling. *Genes Immun.* **2007**, *8*, 21–27. [CrossRef] [PubMed]
32. Ratthé, C.; Pelletier, M.; Chiasson, S.; Girard, D. Molecular mechanisms involved in interleukin-4-induced human neutrophils: Expression and regulation of suppressor of cytokine signaling. *J. Leukoc. Biol.* **2007**, *81*, 1287–1296. [CrossRef] [PubMed]
33. McCormick, S.M.; Gowda, N.; Fang, J.X.; Heller, N.M. Suppressor of Cytokine Signaling (SOCS)1 Regulates Interleukin-4 (IL-4)-activated Insulin Receptor Substrate (IRS)-2 Tyrosine Phosphorylation in Monocytes and Macrophages via the Proteasome. *J. Biol. Chem.* **2016**, *291*, 20574–20587. [CrossRef] [PubMed]
34. Ip, W.K.; Wong, C.K.; Lam, C.W. Interleukin (IL)-4 and IL-13 up-regulate monocyte chemoattractant protein-1 expression in human bronchial epithelial cells: Involvement of p38 mitogen-activated protein kinase, extracellular signal-regulated kinase 1/2 and Janus kinase-2 but not c-Jun NH2-terminal kinase 1/2 signalling pathways. *Clin. Exp. Immunol.* **2006**, *145*, 162–172. [CrossRef] [PubMed]
35. Morelli, M.; Madonna, S.; Albanesi, C. SOCS1 and SOCS3 as key checkpoint molecules in the immune responses associated to skin inflammation and malignant transformation. *Front. Immunol.* **2024**, *15*, 1393799. [CrossRef] [PubMed]
36. Chandriani, S.; DePianto, D.J.; N'Diaye, E.N.; Abbas, A.R.; Jackman, J.; Bevers, J.; Ramirez-Carrozzi, V.; Pappu, R.; Kauder, S.E.; Toy, K.; et al. Endogenously expressed IL-13Rα2 attenuates IL-13-mediated responses but does not activate signaling in human lung fibroblasts. *J. Immunol.* **2014**, *193*, 111–119. [CrossRef] [PubMed]

37. He, C.H.; Lee, C.G.; Ma, B.; Kamle, S.; Choi, A.M.K.; Elias, J.A. N-Glycosylation Regulates Chitinase 3-like-1 and IL-13 Ligand Binding to IL-13 Receptor α2. *Am. J. Respir. Cell Mol. Biol.* **2020**, *63*, 386–395. [CrossRef] [PubMed]
38. Lee, C.M.; He, C.H.; Nour, A.M.; Zhou, Y.; Ma, B.; Park, J.W.; Kim, K.H.; Dela Cruz, C.; Sharma, L.; Nasr, M.L.; et al. IL-13Rα2 uses TMEM219 in chitinase 3-like-1-induced signalling and effector responses. *Nat. Commun.* **2016**, *7*, 12752. [CrossRef] [PubMed]
39. Fichtner-Feigl, S.; Strober, W.; Kawakami, K.; Puri, R.K.; Kitani, A. IL-13 signaling through the IL-13alpha2 receptor is involved in induction of TGF-beta1 production and fibrosis. *Nat. Med.* **2006**, *12*, 99–106. [CrossRef] [PubMed]
40. Brunner, S.M.; Schiechl, G.; Kesselring, R.; Martin, M.; Balam, S.; Schlitt, H.J.; Geissler, E.K.; Fichtner-Feigl, S. IL-13 signaling via IL-13Rα2 triggers TGF-β1-dependent allograft fibrosis. *Transplant. Res.* **2013**, *2*, 16. [CrossRef] [PubMed]
41. Tollenaere, M.A.X.; Mølck, C.; Henderson, I.; Pollack, S.; Addis, P.; Petersen, H.H.; Norsgaard, H. Tralokinumab Effectively Disrupts the IL-13/IL-13Rα1/IL-4Rα Signaling Complex but Not the IL-13/IL-13Rα2 Complex. *JID Innov.* **2023**, *3*, 100214. [CrossRef] [PubMed]
42. Okragly, A.J.; Ryuzoji, A.; Wulur, I.; Daniels, M.; Van Horn, R.D.; Patel, C.N.; Benschop, R.J. Binding, Neutralization and Internalization of the Interleukin-13 Antibody, Lebrikizumab. *Dermatol. Ther.* **2023**, *13*, 1535–1547. [CrossRef] [PubMed]
43. Escamilla-Gil, J.M.; Fernandez-Nieto, M.; Acevedo, N. Understanding the Cellular Sources of the Fractional Exhaled Nitric Oxide (FeNO) and Its Role as a Biomarker of Type 2 Inflammation in Asthma. *Biomed. Res. Int.* **2022**, *2022*, 5753524. [CrossRef] [PubMed]
44. Sim, S.; Choi, Y.; Park, H.S. Update on Inflammatory Biomarkers for Defining Asthma Phenotype. *Allergy Asthma Immunol. Res.* **2024**, *16*, 462–472. [CrossRef] [PubMed]
45. Collins, M.H.; Martin, L.J.; Alexander, E.S.; Boyd, J.T.; Sheridan, R.; He, H.; Pentiuk, S.; Putnam, P.E.; Abonia, J.P.; Mukkada, V.A.; et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis. Esophagus* **2017**, *30*, 1–8. [CrossRef] [PubMed]
46. Xia, D.; Wang, Y.; Xiao, Y.; Li, W. Applications of single-cell RNA sequencing in atopic dermatitis and psoriasis. *Front. Immunol.* **2022**, *13*, 1038744. [CrossRef] [PubMed]
47. Mitamura, Y.; Reiger, M.; Kim, J.; Xiao, Y.; Zhakparov, D.; Tan, G.; Rückert, B.; Rinaldi, A.O.; Baerenfaller, K.; Akdis, M.; et al. Spatial transcriptomics combined with single-cell RNA-sequencing unravels the complex inflammatory cell network in atopic dermatitis. *Allergy* **2023**, *78*, 2215–2231. [CrossRef] [PubMed]
48. Oetjen, L.K.; Mack, M.R.; Feng, J.; Whelan, T.M.; Niu, H.; Guo, C.J.; Chen, S.; Trier, A.M.; Xu, A.Z.; Tripathi, S.V.; et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. *Cell* **2017**, *171*, 217–228.e13. [CrossRef] [PubMed]
49. Komatsu-Fujii, T.; Chinuki, Y.; Niihara, H.; Hayashida, K.; Ohta, M.; Okazaki, R.; Kaneko, S.; Morita, E. The thymus and activation-regulated chemokine (TARC) level in serum at an early stage of a drug eruption is a prognostic biomarker of severity of systemic inflammation. *Allergol. Int.* **2018**, *67*, 90–95. [CrossRef] [PubMed]
50. Komatsu-Fujii, T.; Kaneko, S.; Chinuki, Y.; Suyama, Y.; Ohta, M.; Niihara, H.; Morita, E. Serum TARC levels are strongly correlated with blood eosinophil count in patients with drug eruptions. *Allergol. Int.* **2017**, *66*, 116–122. [CrossRef] [PubMed]
51. Komatsu-Fujii, T.; Ohta, M.; Niihara, H.; Morita, E. Usefulness of rapid measurement of serum thymus and activation-regulated chemokine level in diagnosing drug-induced hypersensitivity syndrome. *Allergol. Int.* **2015**, *64*, 388–389. [CrossRef] [PubMed]
52. Guttman-Yassky, E.; Kabashima, K.; Staumont-Salle, D.; Nahm, W.K.; Pauser, S.; Da Rosa, J.C.; Martel, B.C.; Madsen, D.E.; Røpke, M.; Arlert, P.; et al. Targeting IL-13 with tralokinumab normalizes type 2 inflammation in atopic dermatitis both early and at 2 years. *Allergy* **2024**, *79*, 1560–1572. [CrossRef] [PubMed]
53. Bakker, D.; de Bruin-Weller, M.; Drylewicz, J.; van Wijk, F.; Thijs, J. Biomarkers in atopic dermatitis. *J. Allergy Clin. Immunol.* **2023**, *151*, 1163–1168. [CrossRef] [PubMed]
54. Komatsu-Fujii, T.; Asahina, R.; Hasegawa, T.; Nakamizo, S.; Nakajima, S.; Kogame, T.; Kabashima, K. Initial OX40-OX40L Signaling Promotes a Skin-Resident Memory T-Cell Reservoir in Atopic Dermatitis. *Allergy* **2026**, *Online ahead of print*. [CrossRef] [PubMed]
55. Howell, M.D.; Kim, B.E.; Gao, P.; Grant, A.V.; Boguniewicz, M.; Debenedetto, A.; Schneider, L.; Beck, L.A.; Barnes, K.C.; Leung, D.Y. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J. Allergy Clin. Immunol.* **2007**, *120*, 150–155. [CrossRef] [PubMed]
56. Kim, B.E.; Leung, D.Y.; Boguniewicz, M.; Howell, M.D. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin. Immunol.* **2008**, *126*, 332–337. [CrossRef] [PubMed]
57. Ulzii, D.; Kido-Nakahara, M.; Nakahara, T.; Tsuji, G.; Furue, K.; Hashimoto-Hachiya, A.; Furue, M. Scratching Counteracts IL-13 Signaling by Upregulating the Decoy Receptor IL-13Rα2 in Keratinocytes. *Int. J. Mol. Sci.* **2019**, *20*, 3324. [CrossRef] [PubMed]
58. Maurer, M.; Casale, T.B.; Saini, S.S.; Ben-Shoshan, M.; Laws, E.; Maloney, J.; Bauer, D.; Radin, A.; Makhija, M. Dupilumab Reduces Urticaria Activity, Itch, and Hives in Patients with Chronic Spontaneous Urticaria Regardless of Baseline Serum Immunoglobulin E Levels. *Dermatol. Ther.* **2024**, *14*, 2427–2441. [CrossRef] [PubMed]
59. Maurer, M.; Casale, T.B.; Saini, S.S.; Ben-Shoshan, M.; Giménez-Arnau, A.M.; Bernstein, J.A.; Yagami, A.; Stjepanovic, A.; Radin, A.; Staudinger, H.W.; et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials. *J. Allergy Clin. Immunol.* **2024**, *154*, 184–194. [CrossRef] [PubMed]

60. Toru, H.; Pawankar, R.; Ra, C.; Yata, J.; Nakahata, T. 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*, 491–502. [CrossRef] [PubMed]
61. Kaur, D.; Hollins, F.; Woodman, L.; Yang, W.; Monk, P.; May, R.; Bradding, P.; Brightling, C.E. Mast cells express IL-13R alpha 1: IL-13 promotes human lung mast cell proliferation and Fc epsilon RI expression. *Allergy* **2006**, *61*, 1047–1053. [CrossRef] [PubMed]
62. Yosipovitch, G.; Mollanazar, N.; Ständer, S.; Kwatra, S.G.; Kim, B.S.; Laws, E.; Mannent, L.P.; Amin, N.; Akinlade, B.; Staudinger, H.W.; et al. Dupilumab in patients with prurigo nodularis: Two randomized, double-blind, placebo-controlled phase 3 trials. *Nat. Med.* **2023**, *29*, 1180–1190. [CrossRef] [PubMed]
63. Koh, K.D.; Siddiqui, S.; Cheng, D.; Bonser, L.R.; Sun, D.I.; Zlock, L.T.; Finkbeiner, W.E.; Woodruff, P.G.; Erle, D.J. Efficient RNP-directed Human Gene Targeting Reveals SPDEF Is Required for IL-13-induced Mucostasis. *Am. J. Respir. Cell Mol. Biol.* **2020**, *62*, 373–381. [CrossRef] [PubMed]
64. Moynihan, B.J.; Tolloczko, B.; El Bassam, S.; Ferraro, P.; Michoud, M.C.; Martin, J.G.; Laberge, S. IFN-gamma, IL-4 and IL-13 modulate responsiveness of human airway smooth muscle cells to IL-13. *Respir. Res.* **2008**, *9*, 84. [CrossRef] [PubMed]
65. Brightling, C.E.; Bradding, P.; Symon, F.A.; Holgate, S.T.; Wardlaw, A.J.; Pavord, I.D. Mast-cell infiltration of airway smooth muscle in asthma. *N. Engl. J. Med.* **2002**, *346*, 1699–1705. [CrossRef] [PubMed]
66. Hanania, N.A.; Korenblat, P.; Chapman, K.R.; Bateman, E.D.; Kopecky, P.; Paggiaro, P.; Yokoyama, A.; Olsson, J.; Gray, S.; Holweg, C.T.; et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): Replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir. Med.* **2016**, *4*, 781–796. [CrossRef] [PubMed]
67. Ordovas-Montanes, J.; Dwyer, D.F.; Nyquist, S.K.; Buchheit, K.M.; Vukovic, M.; Deb, C.; Wadsworth, M.H.; Hughes, T.K.; Kazer, S.W.; Yoshimoto, E.; et al. Allergic inflammatory memory in human respiratory epithelial progenitor cells. *Nature* **2018**, *560*, 649–654. [CrossRef] [PubMed]
68. Bachert, C.; Han, J.K.; Desrosiers, M.; Hellings, P.W.; Amin, N.; Lee, S.E.; Mullol, J.; Greos, L.S.; Bosso, J.V.; Laidlaw, T.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*, 1638–1650. [CrossRef] [PubMed]
69. Christenson, S.A.; Steiling, K.; van den Berge, M.; Hijazi, K.; Hiemstra, P.S.; Postma, D.S.; Lenburg, M.E.; Spira, A.; Woodruff, P.G. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2015**, *191*, 758–766. [CrossRef] [PubMed]
70. Bhatt, S.P.; Rabe, K.F.; Hanania, N.A.; Vogelmeier, C.F.; Bafadhel, M.; Christenson, S.A.; Papi, A.; Singh, D.; Laws, E.; Patel, N.; et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. *N. Engl. J. Med.* **2024**, *390*, 2274–2283. [CrossRef] [PubMed]
71. Bhatt, S.P.; Rabe, K.F.; Hanania, N.A.; Vogelmeier, C.F.; Cole, J.; Bafadhel, M.; Christenson, S.A.; Papi, A.; Singh, D.; Laws, E.; et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. *N. Engl. J. Med.* **2023**, *389*, 205–214. [CrossRef] [PubMed]
72. Bhatt, S.P.; Rabe, K.F.; Hanania, N.A.; Vogelmeier, C.F.; Bafadhel, M.; Christenson, S.A.; Papi, A.; Singh, D.; Laws, E.; Dakin, P.; et al. Dupilumab for chronic obstructive pulmonary disease with type 2 inflammation: A pooled analysis of two phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir. Med.* **2025**, *13*, 234–243. [CrossRef] [PubMed]
73. Blanchard, C.; Wang, N.; Stringer, K.F.; Mishra, A.; Fulkerson, P.C.; Abonia, J.P.; Jameson, S.C.; Kirby, C.; Konikoff, M.R.; Collins, M.H.; et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J. Clin. Investig.* **2006**, *116*, 536–547. [CrossRef] [PubMed]
74. Caldwell, J.M.; Ballaban, A.Y.; Li, J.; Maddux, R.; Harris, S.; Dellon, E.S.; Rothenberg, M.E. Cendakimab (anti-IL-13) administration improves esophageal gene expression in eosinophilic esophagitis. *J. Allergy Clin. Immunol.* **2026**, *157*, 118–130.e7. [CrossRef] [PubMed]
75. Rothenberg, M.E.; Dellon, E.S.; Collins, M.H.; Hirano, I.; Chehade, M.; Bredenoord, A.J.; Lucendo, A.J.; Spergel, J.M.; Sun, X.; Hamilton, J.D.; et al. Efficacy and safety of dupilumab up to 52 weeks in adults and adolescents with eosinophilic oesophagitis (LIBERTY EoE TREET study): A multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol. Hepatol.* **2023**, *8*, 990–1004. [CrossRef] [PubMed]
76. Dellon, E.S.; Charriez, C.M.; Zhang, S.; Falk, G.W.; Oliva, S.; Ma, C.; Siffledeen, J.; Schroeder, S.; Philpott, H.; Vanuytsel, T.; et al. Cendakimab in Adults and Adolescents with Eosinophilic Esophagitis. *NEJM Evid.* **2025**, *4*, EVIDoa2500095. [CrossRef] [PubMed]
77. Hirano, I.; Collins, M.H.; Assouline-Dayan, Y.; Evans, L.; Gupta, S.; Schoepfer, A.M.; Straumann, A.; Safroneeva, E.; Grimm, M.; Smith, H.; et al. RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis. *Gastroenterology* **2019**, *156*, 592–603.e10. [CrossRef] [PubMed]
78. Shoda, T.; Taylor, R.J.; Sakai, N.; Rothenberg, M.E. Common and disparate clinical presentations and mechanisms in different eosinophilic gastrointestinal diseases. *J. Allergy Clin. Immunol.* **2024**, *153*, 1472–1484. [CrossRef] [PubMed]

79. Gonsalves, N.P.; Dellon, E.S.; Kliewer, K.L.; Shoda, T.; Yearout, R.; Aceves, S.S.; Arva, N.C.; Besse, J.A.; Caldwell, J.M.; Chehade, M.; et al. Dupilumab versus placebo in adults and adolescents with eosinophilic gastritis (DEGAS): A double-blind, placebo-controlled, phase 2, multicentre, randomised controlled trial. *Lancet Gastroenterol. Hepatol.* **2026**, *11*, 672–688. [CrossRef] [PubMed]
80. Kinoshita, Y.; Oka, S.; Matsushima, K.; Kataoka, M.; Sanuki, T.; Fujiwara, Y.; Arai, K.; Midorikawa, S.; Hatai, H.; Charriez, C.M.; et al. Cendakimab for Eosinophilic Gastritis and Duodenitis in Japanese Adults and Adolescents: Results From a Phase 3 Randomized Controlled Trial. *Am. J. Gastroenterol.* **2026**, *Advance online publication*. [CrossRef] [PubMed]
81. Fuss, I.J.; Heller, F.; Boirivant, M.; Leon, F.; Yoshida, M.; Fichtner-Feigl, S.; Yang, Z.; Exley, M.; Kitani, A.; Blumberg, R.S.; et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J. Clin. Investig.* **2004**, *113*, 1490–1497. [CrossRef] [PubMed]
82. Heller, F.; Florian, P.; Bojarski, C.; Richter, J.; Christ, M.; Hillenbrand, B.; Mankertz, J.; Gitter, A.H.; Bürgel, N.; Fromm, M.; et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology* **2005**, *129*, 550–564. [CrossRef]
83. Danese, S.; Rudziński, J.; Brandt, W.; Dupas, J.L.; Peyrin-Biroulet, L.; Bouhnik, Y.; Kleczkowski, D.; Uebel, P.; Lukas, M.; Knutsson, M.; et al. Tralokinumab for moderate-to-severe UC: A randomised, double-blind, placebo-controlled, phase IIa study. *Gut* **2015**, *64*, 243–249. [CrossRef] [PubMed]
84. Reinisch, W.; Panés, J.; Khurana, S.; Toth, G.; Hua, F.; Comer, G.M.; Hinz, M.; Page, K.; O'Toole, M.; Moorehead, T.M.; et al. Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: Efficacy and safety from a phase IIa randomised multicentre study. *Gut* **2015**, *64*, 894–900. [CrossRef] [PubMed]
85. Mo, S.; Jin, B.; Tseng, Y.; Lin, L.; Lin, L.; Shen, X.; Song, H.; Kong, M.; Luo, Z.; Chu, Y.; et al. A precise molecular subtyping of ulcerative colitis reveals the immune heterogeneity and predicts clinical drug responses. *J. Transl. Med.* **2023**, *21*, 466. [CrossRef] [PubMed]
86. Linggi, B.; Filice, M.; Sangiorgi, B.; Smith, M.I.; Teft, W.; Jairath, V.; Ma, C.; Vande Casteele, N. Metabolism and response to stress gene signatures reveal ulcerative colitis heterogeneity and identify patients with increased response to therapy. *J. Crohns Colitis* **2025**, *19*, jjaf092. [CrossRef] [PubMed]
87. Mookhoek, A.; Haasnoot, M.L.; Bredenoord, A.J.; Ma, C.; Jairath, V.; Pai, R.K. The Clinical Significance of Eosinophils in Ulcerative Colitis: A Systematic Review. *J. Crohns Colitis* **2022**, *16*, 1321–1334. [CrossRef] [PubMed]
88. Håkansson, K.; Bachert, C.; Konge, L.; Thomsen, S.F.; Pedersen, A.E.; Poulsen, S.S.; Martin-Bertelsen, T.; Winther, O.; Backer, V.; von Buchwald, C. Airway Inflammation in Chronic Rhinosinusitis with Nasal Polyps and Asthma: The United Airways Concept Further Supported. *PLoS ONE* **2015**, *10*, e0127228. [CrossRef] [PubMed]
89. Mullol, J.; Maldonado, M.; Castillo, J.A.; Miguel-Blanco, C.; Dávila, I.; Domínguez-Ortega, J.; Blanco-Aparicio, M. Management of United Airway Disease Focused on Patients With Asthma and Chronic Rhinosinusitis With Nasal Polyps: A Systematic Review. *J. Allergy Clin. Immunol. Pract.* **2022**, *10*, 2438–2447.e9. [CrossRef] [PubMed]
90. Duchesne, M.; Okoye, I.; Lacy, P. Epithelial cell alarmin cytokines: Frontline mediators of the asthma inflammatory response. *Front. Immunol.* **2022**, *13*, 975914. [CrossRef] [PubMed]
91. Gauvreau, G.M.; Bergeron, C.; Boulet, L.P.; Cockcroft, D.W.; Côté, A.; Davis, B.E.; Leigh, R.; Myers, I.; O'Byrne, P.M.; Sehmi, R. Sounding the alarmins-The role of alarmin cytokines in asthma. *Allergy* **2023**, *78*, 402–417. [CrossRef] [PubMed]
92. Rabe, K.F.; Nair, P.; Brusselle, G.; Maspero, J.F.; Castro, M.; Sher, L.; Zhu, H.; Hamilton, J.D.; Swanson, B.N.; Khan, A.; et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N. Engl. J. Med.* **2018**, *378*, 2475–2485. [CrossRef] [PubMed]
93. Corren, J.; Lemanske, R.F.; Hanania, N.A.; Korenblat, P.E.; Parsey, M.V.; Arron, J.R.; Harris, J.M.; Scheerens, H.; Wu, L.C.; Su, Z.; et al. Lebrikizumab treatment in adults with asthma. *N. Engl. J. Med.* **2011**, *365*, 1088–1098. [CrossRef] [PubMed]
94. Bachert, C.; Bhattacharyya, N.; Desrosiers, M.; Khan, A.H. Burden of Disease in Chronic Rhinosinusitis with Nasal Polyps. *J. Asthma Allergy* **2021**, *14*, 127–134. [CrossRef] [PubMed]
95. Bachert, C.; Mannent, L.; Naclerio, R.M.; Mullol, J.; Ferguson, B.J.; Gevaert, P.; Hellings, P.; Jiao, L.; Wang, L.; Evans, R.R.; et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients with Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. *JAMA* **2016**, *315*, 469–479. [CrossRef] [PubMed]
96. Desrosiers, M.; Mannent, L.P.; Amin, N.; Canonica, G.W.; Hellings, P.W.; Gevaert, P.; Mullol, J.; Lee, S.E.; Fujieda, S.; Han, J.K.; et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. *Rhinology* **2021**, *59*, 301–311. [CrossRef] [PubMed]
97. Bachert, C.; Corren, J.; Lee, S.E.; Zhang, H.; Harel, S.; Cunoosamy, D.; Khan, A.H.; Jacob-Nara, J.A.; Siddiqui, S.; Nash, S.; et al. Dupilumab efficacy and biomarkers in chronic rhinosinusitis with nasal polyps: Association between dupilumab treatment effect on nasal polyp score and biomarkers of type 2 inflammation in patients with chronic rhinosinusitis with nasal polyps in the phase 3 SINUS-24 and SINUS-52 trials. *Int. Forum Allergy Rhinol.* **2022**, *12*, 1191–1195. [CrossRef] [PubMed]

98. O'Shea, K.M.; Aceves, S.S.; Dellon, E.S.; Gupta, S.K.; Spergel, J.M.; Furuta, G.T.; Rothenberg, M.E. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology* **2018**, *154*, 333–345. [CrossRef] [PubMed]
99. Furuta, E.J.M.; Furuta, G.T.; Shandas, R. Minimally Invasive Approaches to Diagnose and Monitor Eosinophilic GI Diseases. *Curr. Allergy Asthma Rep.* **2024**, *24*, 269–279. [CrossRef] [PubMed]
100. Noble, S.L.; Tyrrell, R.; Mules, T.C.; Inns, S. Non-invasive biomarkers to diagnose and monitor eosinophilic esophagitis: A systematic review. *Front. Med.* **2025**, *12*, 1607306. [CrossRef] [PubMed]
101. Collins, M.H.; Capocelli, K.; Yang, G.Y. Eosinophilic Gastrointestinal Disorders Pathology. *Front. Med.* **2017**, *4*, 261. [CrossRef] [PubMed]
102. Turner, K.O.; Collins, M.H.; Walker, M.M.; Genta, R.M. Quantification of Mucosal Eosinophils for the Histopathologic Diagnosis of Eosinophilic Gastritis and Duodenitis: A Primer for Practicing Pathologists. *Am. J. Surg. Pathol.* **2022**, *46*, 557–566. [CrossRef] [PubMed]
103. Dellon, E.S.; Peterson, K.A.; Murray, J.A.; Falk, G.W.; Gonsalves, N.; Chehade, M.; Genta, R.M.; Leung, J.; Khoury, P.; Klion, A.D.; et al. Anti-Siglec-8 Antibody for Eosinophilic Gastritis and Duodenitis. *N. Engl. J. Med.* **2020**, *383*, 1624–1634. [CrossRef] [PubMed]
104. Dellon, E.S.; Spergel, J.M. Biologics in eosinophilic gastrointestinal diseases. *Ann. Allergy Asthma Immunol.* **2023**, *130*, 21–27. [CrossRef] [PubMed]
105. Schneeweiss, M.C.; Kim, S.C.; Wyss, R.; Schneeweiss, S.; Merola, J.F. Dupilumab and the risk of conjunctivitis and serious infection in patients with atopic dermatitis: A propensity score-matched cohort study. *J. Am. Acad. Dermatol.* **2021**, *84*, 300–311. [CrossRef] [PubMed]
106. Beck, L.A.; Bissonnette, R.; Deleuran, M.; Nakahara, T.; Galus, R.; Coleman, A.; Gherardi, G.; Xiao, J.; Dingman, R.; Xu, C.; et al. Dupilumab in Adults With Moderate to Severe Atopic Dermatitis: A 5-Year Open-Label Extension Study. *JAMA Dermatol.* **2024**, *160*, 805–812. [CrossRef] [PubMed]
107. Langley, R.G.; Gherardi, G.; Coleman, A.; Ardeleanu, M.; Rodríguez-Marco, A.; Levy, S.; Bansal, A.; Chen, Z.; Rossi, A.B.; Shumel, B.; et al. The Safety Data of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Infants, Children, Adolescents, and Adults. *Am. J. Clin. Dermatol.* **2025**, *26*, 981–1002. [CrossRef] [PubMed]
108. Guttman-Yassky, E.; Weidinger, S.; Simpson, E.L.; Gooderham, M.; Irvine, A.D.; Spelman, L.; Silverberg, J.I.; ElMaraghy, H.; DeLuca-Carter, L.; Piruzeli, M.L.B.; et al. Two-Year Efficacy and Safety of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis: A Long-Term Extension (ADjoin). *Dermatol. Ther.* **2025**, *15*, 2217–2232. [CrossRef] [PubMed]
109. Reich, K.; Langley, R.G.; Silvestre Salvador, J.F.; Staumont-Sallé, D.; Costanzo, A.; Pink, A.E.; Paller, A.S.; Katoh, N.; Wollenberg, A.; Warren, R.B.; et al. Safety of tralokinumab in patients with moderate-to-severe atopic dermatitis followed for up to 4.5 years: An integrated analysis of eight clinical trials. *Br. J. Dermatol.* **2026**, *194*, 225–235. [CrossRef] [PubMed]
110. Achten, R.E.; Van Luijk, C.; Van der Rijst, L.; Bakker, D.; Spekhorst, L.; Zuithoff, N.; Schuttelaar, M.; Romeijn, G.; Voorberg, A.; Kamsteeg, M.; et al. Identification of Risk Factors for Dupilumab-associated Ocular Surface Disease in Patients with Atopic Dermatitis. *Acta Derm. Venereol.* **2022**, *102*, adv00666. [CrossRef] [PubMed]
111. Wollenberg, A.; Beck, L.A.; de Bruin Weller, M.; Simpson, E.L.; Imafuku, S.; Boguniewicz, M.; Zachariae, R.; Olsen, C.K.; Thyssen, J.P. Conjunctivitis in adult patients with moderate-to-severe atopic dermatitis: Results from five tralokinumab clinical trials. *Br. J. Dermatol.* **2022**, *186*, 453–465. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.