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POSITION PAPER

AllergoOncology: Biomarkers and refined classification for research in the allergy and glioma nexus—A joint EAACI-EANO position paper

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Abstract

Epidemiological studies have explored the relationship between allergic diseases and cancer risk or prognosis in AllergoOncology. Some studies suggest an inverse association, but uncertainties remain, including in IgE-mediated diseases and glioma. Allergic disease stems from a Th2-biased immune response to allergens in predisposed atopic individuals. Allergic disorders vary in phenotype, genotype and endotype, affecting their pathophysiology. Beyond clinical manifestation and commonly used clinical markers, there is ongoing research to identify novel biomarkers for allergy diagnosis, monitoring, severity assessment and treatment. Gliomas, the most common and diverse brain tumours, have in parallel undergone changes in classification over time, with specific molecular biomarkers defining glioma subtypes. Gliomas exhibit a complex tumour-immune interphase and distinct immune microenvironment features.

Abbreviations: AAI, allergic airway inflammation; AEC, absolute eosinophil count; AD, atopic dermatitis; AIT, allergen-specific immunotherapy; AR, allergic rhinitis; ARG1, arginase 1; BBB, blood–brain barrier; BRAF, B-raf proto-oncogene; CCL11, eotaxins; CCL22, CC-chemokine ligand-22; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CNS, central nervous system; CSF, cerebrospinal fluid; CSF-1, colony-stimulating factor 1; DHR, drug hypersensitivity reactions; DNA, deoxyribonucleic acid; EGFR, epithelial growth factor receptor; EoE, eosinophilic esophagitis; FcεRI, Fc epsilon RI or high-affinity IgE receptor; FeNO, fractional excretion of nitric oxide; FLG, filaggrin; FOXP3, forkhead box P3; GWAS, genome-wide association study; HGG, high-grade glioma; HLA, human leukocyte antigens; ICS, inhaled corticosteroids; IDH1/2, isocitrate dehydrogenase gene 1/2; IDO, indoleamine-2,3-dioxygenase; IFN-γ, interferon-gamma; Ig, immunoglobulin; IL, interleukin; ILC2, type-2-innate lymphoid cells; LGG, low-grade glioma; LTB4, leukotriene B4; MAT, mast cell activation tests; MCs, mast cells; MGMT, O6-methylguanine DNA methyltransferase; miRNAs, microRNAs; mRNA, messenger RNA; MRGPRX2, MAS-related G protein-coupled receptor-X2; NFκB, nuclear factor 'kappa-light-chain-enhancer' of activated B cell; NTRK, neurotrophic tyrosine receptor kinase; OIT, oral immunotherapy; ORMDL3, ORMDL sphingolipid biosynthesis regulator 3; PBMC, Peripheral blood mononuclear cells; PD-1/PD-L1, programmed cell death (PD)-1 / PD ligand 1; pMAT, passive MC activation testing; RCTs, randomized controlled trials; RNA, ribonucleic acid; sIgE, allergen-specific IgE; sIL10RB, soluble IL-10 receptor subunit beta; SLC40A1, solute carrier family-40 member-1; SNP, single-nucleotide polymorphism; T2, type-2; TERT, telomerase reverse transcriptase; TGF-β, transforming growth factor beta; Th2, T-helper cell type-2; tIgE, total serum IgE; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor; WGS, whole-genome sequencing; WHO, World Health Organisation.

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Immunotherapy and targeted therapy hold promise for primary brain tumour treatment, but require more specific and effective approaches. Animal studies indicate allergic airway inflammation may delay glioma progression. This collaborative European Academy of Allergy and Clinical Immunology (EAACI) and European Association of Neuro-Oncology (EANO) Position Paper summarizes recent advances and emerging biomarkers for refined allergy and adult-type diffuse glioma classification to inform future epidemiological and clinical studies. Future research is needed to enhance our understanding of immune–glioma interactions to ultimately improve patient prognosis and survival.

KEYWORDS
atopy, brain cancer, epidemiology, IgE, neuroimmunology

1 | INTRODUCTION

Numerous epidemiological studies have investigated associations between a history of allergic diseases and cancer risk or prognosis contributing to progress in the field of AllergoOncology.[1–5] Notably, investigations have revealed findings of inverse associations between allergies and cancer risk, in particular for glioma.[6] However, despite these findings, there remain outstanding questions and research gaps for immunoglobulin-E (IgE)-mediated diseases and cancer, including glioma.[7,8]

Allergic diseases and cancer are both influenced by genetic and environmental factors, with potential impacts of allergic inflammation in cancer depending on the tumour subtype and its microenvironment. Several hypotheses have been proposed to define this complex interplay, with pro- and anti-tumoural outcomes integrated into the 'combinatorial hypothesis'.[8] In the cancer initiation phase, the 'prophylaxis hypothesis' suggests that allergic symptoms may decrease tumour risk by expelling environmental carcinogens and stimulating behavioural avoidance. The 'immunosurveillance hypothesis' defines atopy as general enhanced immune responsiveness. The 'chronic inflammation hypothesis' proposes that allergic inflammation, oxidative damage and subsequent gene mutations, increase neoplastic cell risk. Finally, the 'T-helper cell type-2 (Th2)-skewing hypothesis' argues that Type-2 (T2) immune response dominance in allergic disorders potentiates a pro-tumoural microenvironment over anti-tumoural Th1-immunity (Figure 1).[8]

Recent developments in biomedicine techniques allow the integration of omics and non-omics data and have revealed molecular heterogeneity in allergic disorders and glioma, with specific molecular subtypes related to disease severity, prognosis and treatment options.[9–12] There are a range of phenotypes and endotypes for allergic diseases, such as allergic and non-allergic asthma or rhinitis. Advancing neuropathological, cellular and molecular approaches, including deoxyribonucleic acid (DNA) aberrations and methylation profiles, have revealed heterogeneity in glioma classification.[10] Adopting up-to-date molecular and genetic sub-classification approaches is relevant for research in AllergoOncology to further improve understanding of immune–glioma interactions.

In this Position Paper, members of the European Academy of Allergy & Clinical Immunology (EACCI) and the European Association of Neuro-Oncology (EANO) jointly provide an overview of strategies for defining allergic diseases and adult-type diffuse gliomas. The paper summarizes biomarkers for diagnosing and managing both conditions. It provides a narrative review of the epidemiological and pre-clinical evidence on associations between allergy and glioma. Additionally, the paper outlines how emerging allergy biomarkers can be utilized in next-generation AllergoOncology studies to enhance understanding of the aetiology and clinical management of glioma patients.

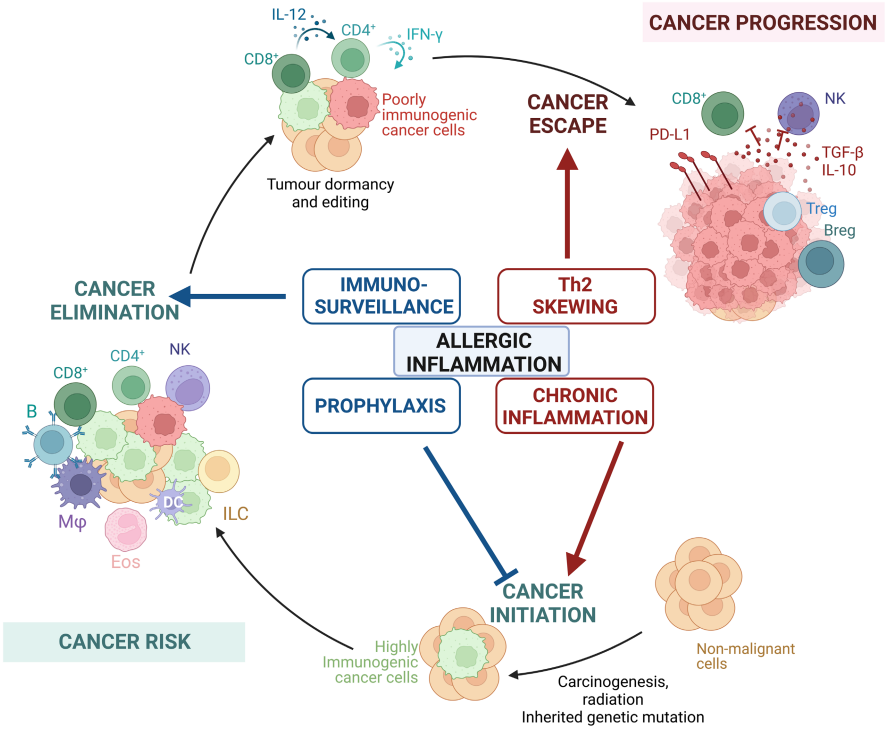

FIGURE 1 Proposed hypotheses of associations between allergic disorders and cancer development and progression within the concept of immunosurveillance and immunoediting. Tumour development involves processes from initiation through progression. Immunogenic transformed cells trigger immune responses, leading to cancer cell elimination via innate and adaptive immunity. This dynamic process generates antigen-specific anti-tumour immunity maintaining dormancy. However, immunoediting and cancer progression can develop poorly immunogenic cells escaping immune surveillance. Hypotheses address the link between allergies and cancers: 'prophylaxis' suggests allergic symptoms reduce risk via carcinogen expulsion, 'chronic inflammation' proposes inflammation-driven mutations, 'immunosurveillance' defines atopy as enhanced immune responsiveness and 'Th2-skewing' argues allergic Th2 dominance promotes a pro-tumoural environment. An arrow indicated activation and a stopped line is used to illustrate inhibition. Breg, regulatory B-cells; DC, dendritic cells; Eos, eosinophils; IFN-γ, interferon-gamma; IL, interleukin; ILC, innate lymphoid cells; Mφ, macrophage; NK, natural killer cells; PD-L1, programmed cell death ligand 1; TGF-β, transforming growth factor beta; Treg, regulatory T-cells. Illustration created with « BioRender.com».

2 | ALLERGY: CURRENT AND EMERGING BIOMARKERS AND THERAPEUTIC APPROACHES

2.1 | Immune dysregulation

Allergic disease results from a Th2-biased immune response to environmental allergens in genetically predisposed atopic individuals. Trained immunity, characterized by innate immune cells displaying heightened reactivity and memory-like characteristics which occurs through transcriptomic, epigenetic and metabolic reprograming following exposure to specific triggers, may play an important role in this context.[13] Airway epithelium repetitively primed with Th1 (interferon-gamma (IFN-γ)) or Th2 (interleukin-4 (IL-4)) cytokines present imprinted, polarized 'Th1/Th2' gene networks. Human bronchial epithelial cells stimulated with IL-4, but not IFN-γ, produced enhanced levels of IL-24. IL-24 was also increased in allergic rhinitis patients, demonstrating its potential as a biomarker of T2-polarized epithelium and allergic inflammation.[14] Additionally, damaged epithelial barriers result in sensitization to different allergens due to alarmins (thymic stromal lymphopoietin (TSLP), IL-33 and IL-25)[15] that mature $CD4^+$T-cells into Th2-cells and stimulate the overproduction of IL-4, IL-5, IL-9, IL-13 and IL-31. These cytokines promote the Th2-immune response, resulting in IgE isotype switching and involve mechanisms in chronic tissue remodelling during allergic conditions. These include mucus hypersecretion, vascular leakage, smooth muscle cell hypercontraction, neurogenesis and angiogenesis.[16,17] During sensitization, IgE binds to the high-affinity IgE receptor, Fc epsilon RI (FcεRI), on mast cells (MCs) and basophils. Upon allergen exposure, the IgE-bound receptors aggregate, triggering immediate hypersensitivity reactions with various clinical manifestations affecting single or multiple organs with mild–moderate to severe symptoms including anaphylaxis (Figure 2).[16,17] Allergic disorders are heterogeneous, with distinct phenotypes, genotypes and endotypes that differ in pathophysiology (Table 1).[12]

2.2 | Current and emerging biomarkers in diagnosis and treatment

2.2.1 | Clinically used biomarkers

Allergy diagnosis relies on evaluating the history of allergen exposure, symptomatology and tests to determine sensitization.

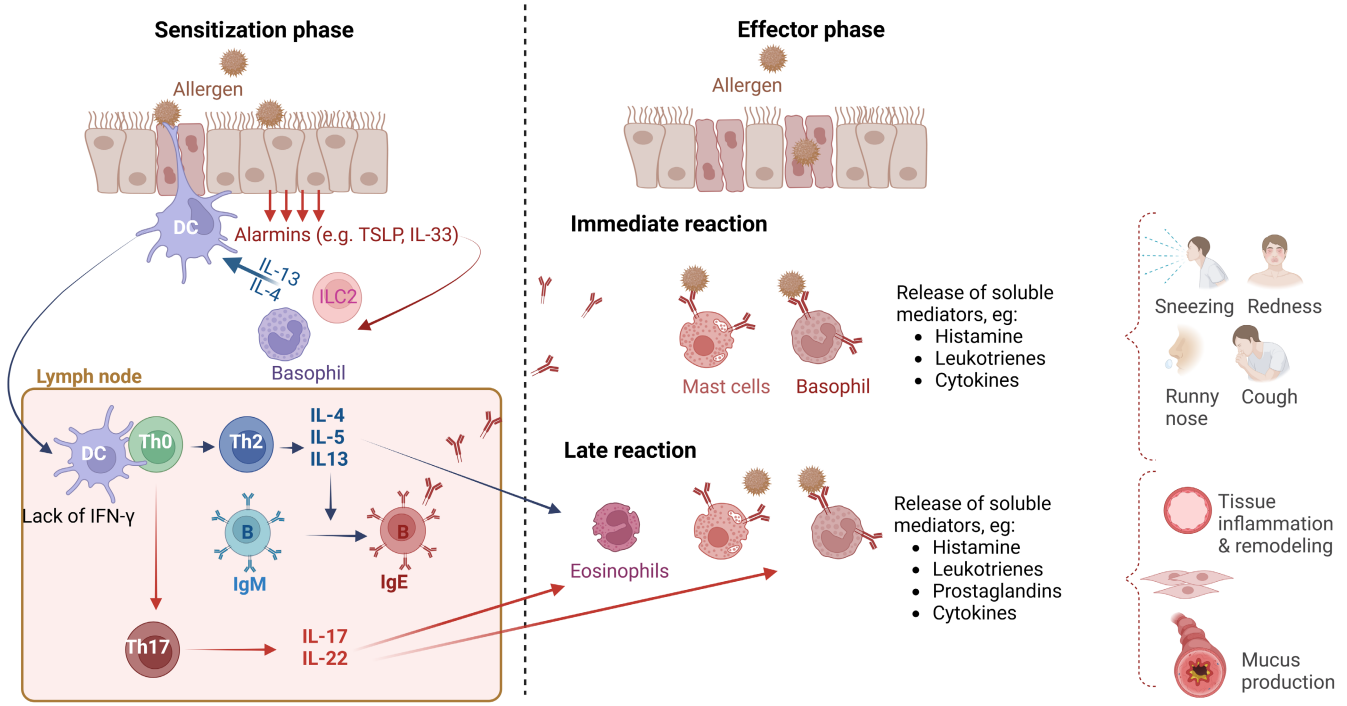

FIGURE 2 Overview of allergic inflammation: cellular and molecular mechanisms. The allergic response consists of two distinct phases. In the early phase or sensitization phase, initial sensitization to an allergen released from an allergen source (brownish spheres) and memory activation to the molecular allergen occur, while in the later phase or effector phase, a response is triggered upon re-exposure to the allergen. During the immediate cell-specific reaction this leads to the release of inflammatory mediators due to the cross-linking of allergen-bound specific IgE on basophils, mast cells and eosinophils. Then, during the late reaction, after re-exposure to allergen specific T-helper cells (Th2 and Th17) further increase local inflammation leading to tissue remodelling and chronicity. B, B-cells; DC, dendritic cells; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cells, Th, T-helper cells; TSLP, thymic stromal lymphopoietin. Illustration created with « BioRender.com».

Elevated total serum IgE (tIgE) is associated with allergic disease, parasitosis and specific immunologic abnormalities. It has traditionally been used as a marker for atopy/allergy, prompting further evaluation.

Allergen-specific IgE (sIgE) is detected on MCs (skin prick testing) and in serum. sIgE can be detected against whole extracts as well as components obtained recombinantly or purified/native. Identifying cross-reactivity and primary sensitization aids treatment decisions such as allergen-specific immunotherapy (AIT).[18] The glycosylation patterns of sIgE (and sIgG) have biomarker potential regarding allergy diagnosis, severity and treatment efficacy (tolerance induction). Sequential epitope-specific IgE-profiling appears valuable in the course of immunotherapy, such as sublingual (SLIT), subcutaneous (SCIT) and peanut oral immunotherapy (OIT).[19,20] Lower sIgE to food allergens at baseline was related to increased efficacy of peanut OIT.[21] Allergen provocation testing is the gold standard when clinical history is inconclusive.[22]

Indirect sIgE-detection can be performed with a flow cytometry-based functional assay that measures basophil activation after allergen exposure (basophil activation test, BAT). This test, among others, discriminates between sensitization and allergy for peanut and red meat allergies.[23–25] The value of BAT extends to diagnosing various conditions, such as drug hypersensitivity, encompassing cases like IgE-based anti-tumour therapy in cancer patients,[26] as well as allergies to hymenoptera venom.[23] BAT has been optimized for broader use.[23] Passive MC activation testing (pMAT) can provide additional information, for example, when basophils are non-responsive to allergens. Ratio analysis of sIgE to tIgE can aid in clinical interpretation.[27]

Serum tryptase is a biomarker for anaphylaxis. Tryptase is released by activated MCs in 30 min to 2 h. Elevated tryptase in the acute phase confirms the diagnosis, but normal levels do not exclude anaphylaxis.[28,29] Basal serum tryptase is also increased in certain MC disorders.

Eosinophilia, or elevated absolute eosinophil count (AEC), is found in atopy, T2-high asthma, atopic dermatitis (AD), eosinophilic gastrointestinal disorders and delayed drug hypersensitivity reactions (DHR), although it is not specific. Eosinophilia is also observed in parasitic infections and autoimmune diseases. T2-high asthma includes, among others, allergic and eosinophilic asthma phenoendotypes. Allergic asthma is characterized by increased circulating allergen-specific IgE, while eosinophilic asthma can be diagnosed based on increased blood (>300/uL) or sputum eosinophil numbers (≥3%). On the other hand, T2-low asthma, including neutrophilic or paucigranulocytic asthma is characterized by low IgE, AEC and allergic symptoms.[30] These phenotypes have different severity and treatment implications in adults and children.[16,31] AEC predicts therapeutic response to biologics in severe asthma (e.g. anti-IL-5).[32,33]

TABLE 1 Selected biomarkers and individual demographics to study links between allergic diseases and gliomas.

DONOR/PATIENT INFORMATION					
Demographics		**Genotype**			
Gender Age Ethnicity Socio-economic Exposome characteristic		Whole-genome sequencing (WGS) SNPs			
ALLERGIC DISORDERS		**ADULT DIFFUSE GLIOMAS**			
Phenotype	**Endotype**	**Histological phenotype**	**Location**	**Molecular testing**	
Allergic type(s)	**Clinically used**	Diffuse astrocytic	Midline	*IDH1* , *IDH2*	
Allergic asthma	Clinical manifestation (or diagnosis)	Oligodendroglial	Hemispheric	Chromosome 1p/19q	
Allergic rhinitis	Concentration of serum total IgE	Mixed		*CDKN2A/B*	
Conjunctivitis	Definition and concentration of serum sIgE			*TERT* promoter, *EGFR* and/or +7/-10	
Urticaria	Skin testing			*MGMT* promoter methylation	
Atopic dermatitis	Basophil activation test	**Integrated diagnosis**			
Food allergy	Eosinophil count in blood	Astrocytoma, IDH-mutant, WHO grade 2, 3 or 4			
Drug allergy	FeNO (respiratory allergies asthma)	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 2 or 3			
Anaphylaxis	Serum tryptase (anaphylaxis)	Glioblastoma, IDH-wildtype, WHO grade 4			
Clinical Characteristics	**Emerging Biomarkers**	**Clinical characteristics**			
Severity	Cell count of Th2-cells	Age at the diagnosis			
Persistency	Th2	Progression free survival			
Onset age	MC	Overall survival			
Sensitisation sources	ILC2	Karnofsky Performance Scale			
Anti-allergic drugs (type & posology)	Concentration of Th2-related cytokines & proteins	Neurological Assessment of Neuro-Oncology Scale			
AIT	IL-4	Age at recurence			
	IL-5	Description of the therapeutic regimens: surgical resection (radical/partial); chemotherapy (YES/NO), Radiation (YES/NO)			
	IL-10	Usage of steroid before, after, during treatment			
	IL-13				
	IL-33				
	TSLP				
	TGF-β				
	CCL22				
	CCL11				
	Eicosanoids				
	Leukotriene B4				
	Lipocalin-2				
	Genetic and molecular omics biomarkers				
	HLA-typing				
	miRNA				
	SNPs (GWAS)				
	ORMDL3 gene				
	Iron deficiency				
	Serum MRGPRX2 levels				
	Sphingosine				
	Filaggrin				

Note: The grey shade represents DONOR/PATIENT INFORMATION. The blue shade corresponds to ALLERGIC DISORDERS related information. The yellow shade indicates ADULT DIFFUSE GLIOMAS related information.

Abbreviations: AIT, Allergen Immunotherapy; CCL, C-C chemokine ligand; CDKN2A/B, Cyclin-dependent kinase inhibitor 2A/B; EGFR, Epidermal growth factor receptor; FeNO, Fraction exhaled nitric oxide; GWAS, Genome-wide association study; HLA, human leukocyte antigen; IDH, Isocitrate dehydrogenase; IL, Interleukin; ILC2, type-2-innate lymphoid cells; MC, Mast cells; MGMT, O6-methylguanine-DNA methyltransferase; miRNA, micro ribonucleic acid; MRGPRX2, Mas-Related G Protein-Coupled Receptor-X2; SNPs, Single nucleotide polymorphisms; TERT, Telomerase reverse transcriptase; TGF-β, Transforming growth factor; Th2, T-helper cell type-2; TSLP, Thymic Stromal Lymphopoietin; WHO, World Health Organization.

Fractional excretion of nitric oxide (FeNO) is a reproducible and non-invasive indirect biomarker of IL-13-mediated T2-airway inflammation. Higher values of FeNO are found in T2-high compared with T2-low asthma and help confirm diagnosis in adults and children. It predicts response to inhaled corticosteroids (ICS).[34] Elevated FeNO values during ICS therapy do not support ICS dose reduction. Low FeNO values alone do not exclude bronchial asthma. FeNO levels vary with different asthma biologics.[35]

2.2.2 | Emerging cellular markers

Allergen-specific Th2A-cells, found in allergic individuals, are $CD4^{+}CRTH2^{+}CD161^{high}HPGDS^{+}CD27^{low}CD49d^{high}ST2^{high}$ memory cells that play a pathogenic role in AD, food allergy, asthma and eosinophilic esophagitis (EoE).[36] Th2A-cell frequency inversely correlates with treatment efficacy. $CD38^{+}$Th2A-cells are an emerging clinical biomarker in T2-high asthma, with CD38 upregulation in Th2A-cells and downregulation with immunotherapy treatment.[37]

MCs are activated in allergic diseases like asthma and AD, with MAS-related G protein-coupled receptor-X2 (MRGPRX2) being a new biomarker for allergic disorders such as asthma and drug allergy. Serum MRGPRX2 levels are elevated in allergic asthma, especially in those responding well to ICS.[38] This receptor is expressed on cutaneous MCs in patients with severe chronic spontaneous urticaria.[39] Some reactions to specific drugs such as fluoroquinolone antibiotics or neuromuscular blocking agents have been postulated to be induced by MC MRGPRX2-mediated mechanisms.[40] MC activation tests (MAT) are being developed to aid diagnosis and monitoring of allergic diseases.[41] However, MC activation is not always present, requiring differential diagnosis.

T2-innate lymphoid cells (ILC2) contribute to inflammation in allergic disorders, such as allergic rhinitis (AR), chronic sinusitis, asthma and AD, by enhancing the activity of Th2-cells, eosinophils and their cytokines. ILC2 are increased in the blood, lung and skin of individuals with these conditions and are related to disease severity and treatment response.[42] Notably, AIT reduced frequencies of sputum ILC2s in patients with grass pollen allergic rhinitis and asthma.[43]

2.2.3 | Emerging Type-2 cytokines and proteins

Allergic patients generally present higher serum T2-cytokine levels compared to healthy individuals. However, they are not routinely used as clinical biomarkers in allergy due to usually low serum detectable levels.[44] Elevated IL-4 differentiates T2-high from T2-low asthma, while elevated IL-4 and IL-5 distinguishes asthma persistence in adults and children, respectively. IL-13 and IL-33 correlate with asthma severity, while thymic stromal lymphopoietin (TSLP) levels are increased in the skin of AD patients and in the airways of patients with severe asthma. Decreased T2-cytokines are associated with treatment success.[44,45]

Elevated blood levels of CC-chemokine ligand-22 (CCL22) have been detected in AD patients compared to controls and are associated with disease severity.[44] Eotaxins (CCL11) are proposed biomarkers for AR, asthma and AD.[44] Periostin is a biomarker of T2-inflammation in adults; however, its levels vary in children until bone growth stops.[46] Eicosanoids play a role in allergy pathomechanisms. Levels of leukotriene B4 (LTB4) were increased in patients with asthma.[34] Increased lipocalin-2 after sublingual immunotherapy was associated with clinical benefit.[47] Additionally, prostaglandin E2 (PGE2) was upregulated in untreated allergic rhinitis and asthma patients with a significant decrease observed after AIT. Notably, PGE2 levels correlated with T2-inflammation and clinical markers, such as IL-13, sputum eosinophil counts and symptom scores.[43] Lastly, decorin, an extracellular matrix proteoglycan participates in the pathogenesis of allergic asthma by reducing bioavailability of transforming growth factor beta (TGF-β).[48]

2.2.4 | Emerging genetic and molecular omics markers

Genomic loci, such as 17q21 are associated with allergic diseases. This region is associated with gene expression of ORMDL sphingolipid biosynthesis regulator 3 (*ORMDL3*), an inhibitor of de novo sphingolipid synthesis, a mediator in severe allergic asthma.[49] *ORMDL3* is expressed in airway smooth muscle cells, airway epithelium, $CD4^+$ T-cells and eosinophils. *ORMDL3*

TABLE 2 Biological drugs targeting molecules relevant for atopic/allergic disease pathomechanisms.

Target	Indication	Drug
IL-5 receptor (CD125)	Asthma	Benralizumab
Inhibits the dimerization of IL-13Rα1 and IL-4Rα	Asthma + AD	Lebrikizumab[a]
IL-5	Asthma	Mepolizumab
IL-5 Rα	Asthma	Reslizumab
IgE	Asthma + Urticaria	Omalizumab
IL-4 Rαsubunit	AD, Asthma, CRSwNP	Dupilumab
IL-9	Asthma	Enokizumab[a]
IL-13	AD	Tralokinumab
IL-33	AD	Etokimab
IL-31 receptor A	AD	Nemolizumab
TSLP	Tezepelumab	Tezepelumab
IgE	Chronic urticaria	Ligelizumab
IgE	Chronic urticaria, asthma, CRSwNP	Omalizumab
Lectin 8	Asthma	Lirentelimab
Inhibits JAK1 and JAK2	AD	Baricitinib
JAK1 inhibitor	AD	Upadacitinib
JAK1 inhibitor	AD	Abrocitinib
A CRTH2 antagonist	Th2-mediated inflammation	AMG853[a]
A CRTH2 antagonist	Th2-mediated inflammation	OC000459[a]
A CRTH2 antagonist	Th2-mediated inflammation	BI671800[a]
Inhibitor of GSNOR	Th2-mediated inflammation	N6022[a]
Plasma kallikrein	Hereditary angioedema	Lanadelumab

Note: Adapted from Gülsen et al. (2020),[32] modified and updated.[33]

Abbreviations: AD, atopic dermatitis; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; CRSwNP, chronic rhinosinusitis with nasal polyposis; GSNOR, S-nitrosoglutathione reductase; IgE, immunoglobulin E; IL, interleukin; JAK, Janus kinase; TSLP, thymic stromal lymphopoietin.

[a]Studies ongoing.

expression is related to exaggerated T2-inflammation, increased expression of adhesion molecule ICAM-1, enhanced glycolysis and pro-inflammatory cytokine production (IL-6 and IL-18) in both structural lung cells and infiltrating immune cells in the lungs.[50] Filaggrin (FLG) genetic variations are genetic biomarkers in eosinophilic asthma[51] and AD,[52] related to a higher risk of presenting Th2 multimorbidity.

Polygenic risk scores combining 41 genetic polymorphisms show significant associations with asthma risk.[53] Human leukocyte antigens (HLA)-DR1 is abundant in cat allergy, while HLA-DR4 is associated with Alt a 1 responsiveness in *Alternaria* allergy.[54] Notably, single-nucleotide polymorphism (SNP) on D2HGDH (rs34290285) demonstrated significance in both asthma and allergic diseases.[55] HLA-B alleles are related to drug hypersensitivity.[56,57] Forty-two genetic loci are associated with AR.[57] MicroRNAs (miRNAs) are small non-coding RNA molecules involved in gene expression regulation. Several miRNAs play a role in allergic diseases and have been proposed as potential biomarkers of both disease pathology and therapy outcomes.[58] miR-155 plays a role in AR, AD and asthma.[58] miR-3935, the predicted target of PGE2 receptor (PTGER3), was upregulated during AIT in patients with allergy.[43] The detailed role of miRNAs in allergy and asthma is reviewed elsewhere.[58]

Iron metabolism is involved in childhood allergic asthma. Downregulated solute carrier family-40 member-1 (SLC40A1) expression correlates with T2-inflammation in the lung and is used to classify patients into T2-low and T2-high subgroups. Decreased SLC40A1 results in reduced iron levels in the airways.[59]

Omics technologies can further explore allergy pathobiology, define specific endotypes and refine disease classification and treatment.[12]

2.3 | Therapeutic approaches

Antihistamines, decongestants and corticosteroids relieve allergy symptoms. AIT shifts the Th2-response to a Th1-response, and induces regulatory T-(Tregs) and B-cells (IL-10$^+$ B-cells), subsequently promoting tolerance to allergens and providing long-term symptom relief.[60] AIT is effective across all age groups, requiring a minimum of 3 years of treatment.[33] Several randomized controlled trials (RCTs) demonstrated AIT's efficacy,[61–64] including in children (≥5 years) and older patients (>65 years).[65] Individual molecular sensitization profiles influence AIT effectiveness.[66] AIT is the only treatment with maintained efficacy after stopping treatment. AIT can be combined with biological therapies (treatment antibodies) for 'difficult-to-treat' allergic asthma or to increase tolerability.[67] Biological therapies targeting IgE, interleukins, IL-receptors or TSLP (Table 2) are used to treat various allergic disorders.[32,33] Desensitization protocols effectively prevent DHR, maintaining first-line treatment when no equivalent alternatives exist in drug allergy patients.[68]

3 | GLIOMA: UPDATED CLASSIFICATION, IMMUNE BIOMARKERS AND THERAPEUTIC APPROACHES

3.1 | Diagnosis and classification

Gliomas are the most common and varied tumours originating from the central nervous system (CNS) parenchyma. When reviewing the literature on glioma it is important to acknowledge changes in their classification (and clinical diagnosis) over time (Figure 3). Since the 2016 World Health Organisation (WHO) CNS tumour classification (revised fourth edition),[69,70] particular molecular alterations are part of the definition of multiple gliomas, including adult-type diffuse gliomas. These latter tumours are characterised by extensive infiltration of tumour cells in the surrounding CNS parenchyma and constitute the bulk of adult neuro-oncology practice. The taxonomy of adult-type diffuse gliomas is now largely based on the presence/absence of a hotspot mutation in isocitrate dehydrogenase gene 1 or 2 (IDH1 or IDH2) and of combined, complete loss of the short arm of chromosome 1 and of the long arm of chromosome 19 (1p/19q codeletion). In the 2021 or fifth edition of the WHO CNS tumour classification,[10] three tumour types are recognized in this family: diffuse astrocytoma, IDH-mutant (Grade 2, 3 or 4); oligodendroglioma, IDH-mutant and 1p/19q-codeleted (Grade 2 or 3); and glioblastoma, IDH-wildtype, which is not only the most malignant (Grade 4), but also the most frequent in adults. Elucidation of molecular differences between adult- and paediatric-type diffuse gliomas has allowed for recognizing these as distinct groups of tumours. The 2021 WHO classification now lists (next to adult-type diffuse gliomas) a family of low-grade and high-grade paediatric-type diffuse gliomas (Table S1).

In the 2016 classification, only histological features such as mitotic activity, necrosis and florid microvascular proliferation were used for assigning malignancy grade to adult-type diffuse gliomas. More recently, cIMPACT-NOW presented a compilation of the evidence that particular molecular characteristics substantially improve the prognostic impact of grading of these neoplasms.[71,72] According to the 2021 classification, even in the absence of, for example, microvascular proliferation and necrosis, an IDH-mutant astrocytoma with cyclin-dependent kinase inhibitor 2A/B *(CDKN2A/B)* homozygous deletion is considered as Grade 4. Similarly, in adult patients with a histologically low(er)-grade, IDH-wildtype diffuse glioma, the presence of one or more of the following three genetic characteristics is now sufficient for a diagnosis of glioblastoma, IDH-wildtype (Grade 4): telomerase reverse transcriptase *(TERT)* promoter mutation, epithelial growth factor receptor *(EGFR)* gene amplification and +7/−10 (i.e. the gain of whole chromosome 7 and loss of whole chromosome 10).[10] These developments in classification necessitated updated guidelines for the clinical management of patients (Table 1).[73]

Glioblastoma can be further classified into molecular subtypes, informing disease progression and clinical practice. Wang et al. identified

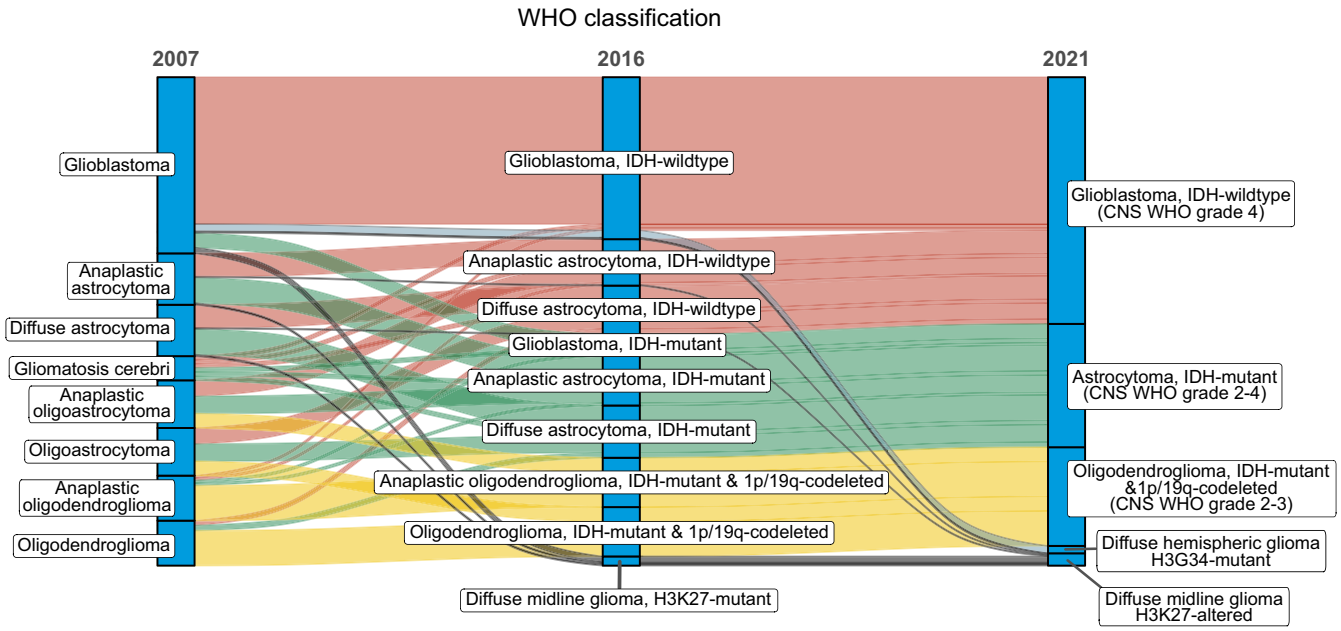

FIGURE 3 WHO classification of gliomas over time. Sankey plot displaying an overview of how the taxonomy of diffuse gliomas has changed over time; the size of the strips provides an indication of the relative frequency of the different tumour types. Since 2016 molecular characteristics are part of the definition of multiple gliomas. As a result, (anaplastic) oligoastrocytoma and gliomatosis cerebri are now generally recognized as another diffuse glioma type and their diagnosis has almost disappeared. Of note, different grades of glioma still had their own entry in the 2007 and 2016 classification (e.g. anaplastic astrocytoma = WHO grade 3), but in the 2021 classification grades are assigned within types. Last but not least, after the introduction of diffuse midline glioma, H3K27-mutant in 2016, since 2021 more paediatric-type diffuse gliomas are included as separate tumour types in the classification. For the sake of clarity only diffuse midline glioma, H3K27-altered and diffuse hemispheric glioma, H3G34-mutant (both CNS WHO grade 4) are included in this diagram. The reader is referred to Table S1 for all gliomas as listed in the WHO 2007, 2016 and 2021 classification of CNS tumours, respectively. CNS, central nervous system; H3G34, histone 3 G34; H3K27, histone 3 lysine 27; IDH, isocitrate dehydrogenase; WHO, World Health Organisation.

three subtypes based on molecular features: pro-neural, mesenchymal and classical.[74] Neftel et al. utilized single-cell ribonucleic acid (RNA)-sequencing to identify four cellular states within glioblastoma,[75] showing intra-tumoural heterogeneity. The signatures of individual tumour cells were categorized into neural progenitor-like, oligodendrocyte progenitor-like, astrocyte-like and mesenchymal-like.[74]

Although molecular knowledge has enabled more precise clinical diagnosis, the translation into more effective therapeutic approaches is lagging behind. Further elucidation of the pathobiology of these tumours through single-cell expression profiling studies,[76] longitudinal multiplatform analyses[77] and of inherited genetic aspects[78,79] may be helpful in this regard.[80]

3.2 | Immune response and biomarkers

Gliomas are characterized by a complex immune tumour microenvironment (TME), with up to 50% of tumour composition consisting of immune cells (mainly microglia and glioma-associated macrophages). In much lower quantities, tumour-infiltrating lymphocytes, monocytes, MCs, eosinophils and neutrophils are also present.[81,82] These innate and adaptive immune cell types directly and indirectly interact with tumour cells and resident glial cells, neurons and vascular cells. The immune landscape of gliomas is highly immunosuppressive with immunologically quiet macrophages and sparse lymphocytic infiltration, with a shift to Th2.[83,84] IDH-mutant gliomas display even less lymphocytes than IDH-wildtype tumours.[85] The complex dynamic interplay of the various cell types involves the expression of a multitude of immunoregulatory factors, partly with tumour-promoting features, such as cytokines and chemokines (e.g. IL-4, IL-10 and TGF-β), colony-stimulating factor 1 (CSF-1), immune checkpoint molecules (e.g. programmed cell death (PD)-1/PD ligand 1 (PD-L1)-dependent signalling, CD39) among others.[81,86] The inflammatory cytokine profile of glioblastoma (diagnosed via histopathological features) is a valuable prognostic indicator, with increased levels of immunosuppressive molecules such as TGF-β related to decreased survival.[87] Genotypes of Th2-related IL-4Rα and IL-13 have also been related to prognosis.[88]

Angiogenic (vascular endothelial growth factor (VEGF)), metabolic (e.g. indoleamine-2,3-dioxygenase (IDO), arginase 1 (ARG1)) and dietary factors[89] influence the inflammatory microenvironment and immunogenicity of glial brain tumours. Presumably, the local immune reaction in gliomas is connected to the systemic immune system via meningeal lymphatic vessels and lymphatic CNS drainage to cervical lymph nodes[90–93] (Figure 4). CNS immunological dysregulation in the context of allergy and/or glioma has been examined in multiple studies but remains poorly characterized (Figure 5 and Box 1).

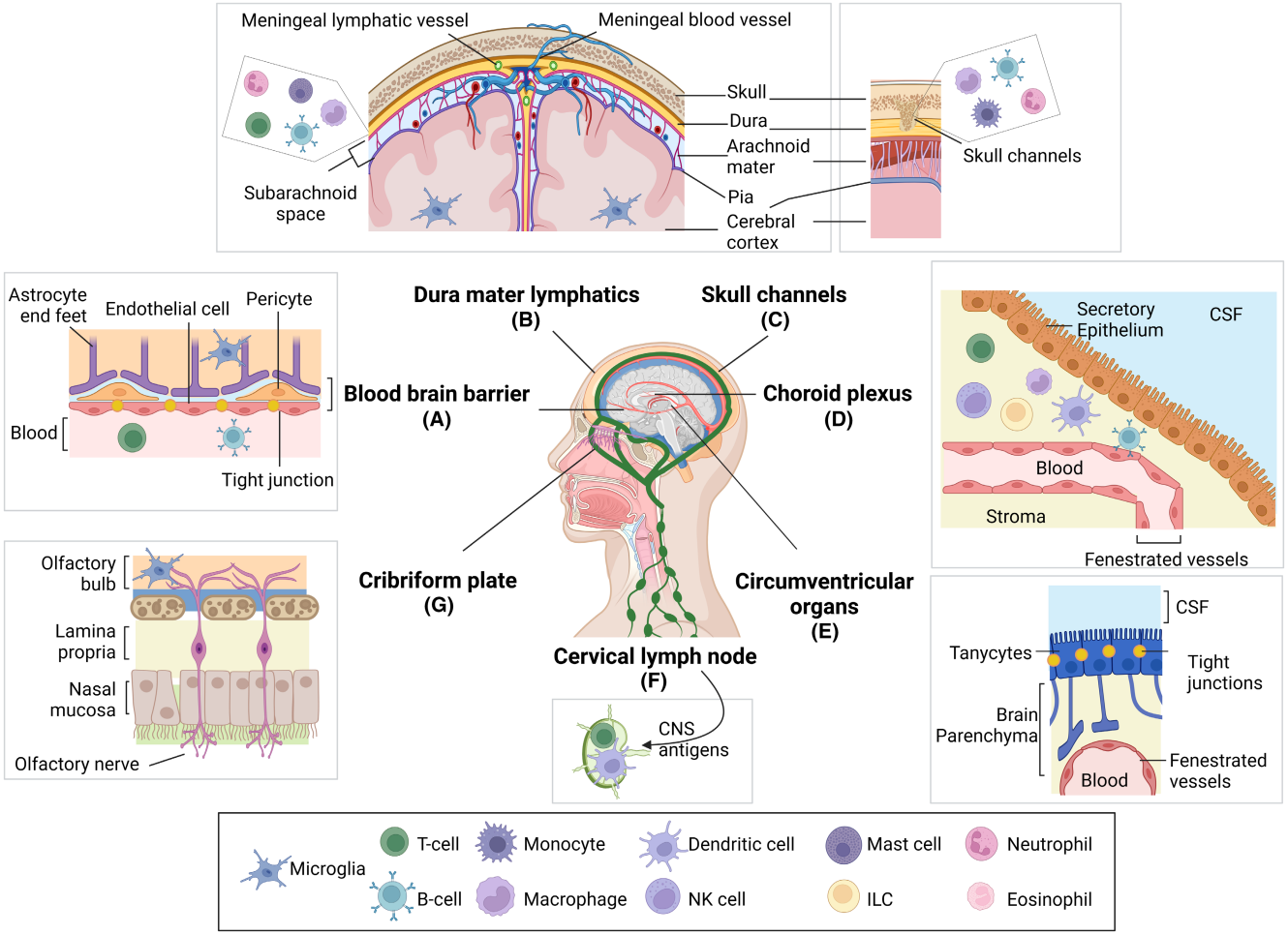

FIGURE 4 The border-associated immune compartments of the brain. Even though peripheral inflammation, such as allergic airway inflammation, can be far from the brain parenchyma, there are many ways through which the immune system can communicate with the brain. (A) The blood–brain barrier (BBB) is a semipermeable membrane composed of endothelial cells of the capillary wall, pericytes, with astrocytic end feet encircling the capillary. The BBB restricts access and immune cells can only cross this barrier during inflammation. However, recent discoveries found that other entry points into the brain make communication between the brain parenchyma and the peripheral immune system more dynamic than previously thought. (B) Meningeal lymphatic vessels found in the meningeal layer of the dura mater, allow surveillance of antigens and transport of immune cells in the dura. The main immune cells here are neutrophils, MCs, multiple stages of B-cells, monocytes and T-cells (C) During extensive neuroinflammation recruited myeloid cells and neutrophils can take a shortcut to the brain. They can migrate via microscopic channels crossing the inner skull cortex and end up in dura. B-cells can also enter the dura from the skull bone marrow. (D) The choroid plexus located in the ventricles consists of secretory epithelium producing CSF and is an important site for immune surveillance and this barrier allows circulating immune cells to communicate with resident choroid plexus macrophages and NK cells. (E) The circumventricular organs (CVO) are highly vascularized areas located in the third and fourth ventricle. There is a communication via the blood, brain parenchyma and CSF in the CVOs. (F) The deep cervical lymph nodes are important drainage routes for CNS antigens, where DCs sample antigens and may present these antigens to T-cells. (G) The cribriform plate is pierced with small holes in the ethmoid bone. This, together with lymphatic vessels, trigeminal nerves and olfactory nerves, is believed to allow the transport of CNS antigens and entry of immune cells into the CNS. The subarachnoid lymphatic-like membrane (SLYM)[94] which is a fourth meningeal layer, completing the dura, arachnoid and pia mater, that compartmentalises the subarachnoid space in the mouse and human brain is not depicted in this figure. Created with « BioRender.com». BBB, blood–brain barrier CSF, cerebrospinal fluid; CNS, central nervous system.

3.3 | Immunotherapeutic approaches

Immunotherapy and targeted therapy are leading areas of innovation for the treatment of primary brain tumours in adults and children. Numerous efforts have been made to integrate immunotherapy into current standards of care for glioblastoma that consists of neurosurgical resection as feasible followed by involved-field radiotherapy and concomitant and maintenance temozolomide alkylating agent chemotherapy.[73] In selected patients, treatments targeting specific molecular tumour alterations such as B-raf proto-oncogene (BRAF) mutations or neurotrophic tyrosine receptor kinase (NTRK) fusions may be considered.[11] Importantly, a recent Phase 3 trial has shown the efficacy of the IDH1/2 inhibitor vorasidenib in IDH-mutant Grade 2 glioma.[112]

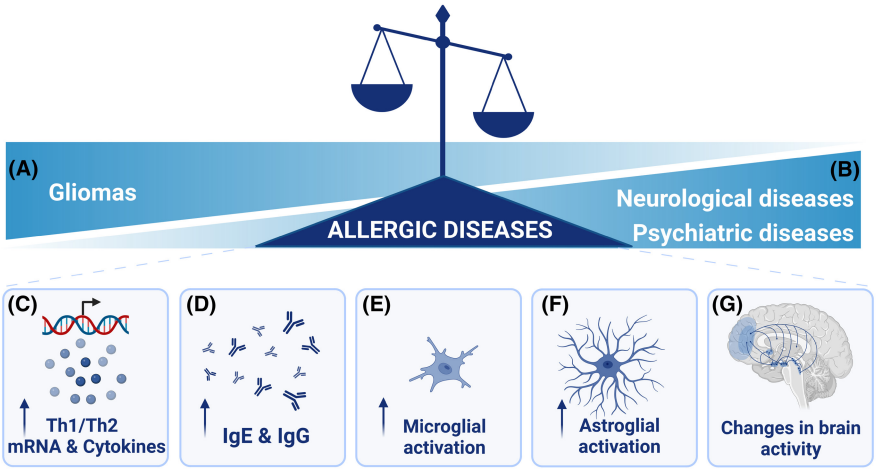

FIGURE 5 Allergic inflammation modulation of central nervous system (CNS) homeostasis. (A) Allergic diseases have typically been inversely related to the risk of glioma development, and (B) conversely, positively related to the risk of neurological or psychiatric diseases. (C–F) An extended knowledge of allergy's impact on the brain was unearthed using rodent models of allergic disorders. (C) These studies demonstrated that allergic inflammation could increase the level of mRNA and cytokines from Th1/Th2 immunity, (D) as well as of IgE and IgG in brain lysates compared to controls. In parallel, allergic inflammation was shown to lead to activation of brain-specific cells, such as (E) microglia and (F) astrocytes. (G) Changes in the resting state of spontaneous brain activity demonstrate allergic inflammation can modulate brain homeostasis in humans. Created with « BioRender.com». Ig, immunoglobulin; mRNA, messenger RNA; Th, T-helper cells.

BOX 1 Allergic inflammation and brain physiology.

- The blood–brain barrier (BBB) is no longer the only specialised border contributing to controlling neuro-immune crosstalk and brain immunosurveillance (Figure 4).[93]
- Similar roles have recently been attributed to the circumventricular organs (CVO), skull bone marrow channels, the meningeal lymphatic system, choroid plexus, cribriform plate and more recently the subarachnoid lymphatic-like membrane (SLYM).[94]
- In these structures, blood-borne resident immune cells create specialised immune niches involved in brain development, homeostasis and protection.
- Immune cells associated with T2-immunity, such as MCs, ILC2, B-cells and Th2-cells, can be found in these barriers.[95]
- IL-33, IL-13, and IL-4, which are T2-immunity-related soluble factors, play a role in immune-related mechanisms associated with neuroprotection and neuroinflammation,[95] such as modulating synaptic remodelling and activity.[96,97]
- Existing evidence suggests that peripheral allergic inflammation affects brain homeostasis (Figure 5).[98]
- Allergic sensitization in rodent models leads to rapid activation of neuronal pathways,[99,100] as well as Th1- and Th2-related gene expression,[101,102] and accumulation of IgG and IgE in the brain parenchyma.[103,104]
- Studies have shown that peripheral allergic inflammation in mouse models can activate microglia into a pro-inflammatory state induced with either timothy grass pollen,[105] ovalbumin,[106] fungal allergens[107] or house dust mite.[108]
- Mice with asthma or AD demonstrate increased activation of microglia and astrocytes in the spinal cord.[106]
- Epigenetic changes have been detected in microglia obtained from the offspring of mothers with allergic asthma.[109]
- Emerging studies are investigating differences in brain activity between allergic and non-allergic individuals.[110,111]

Efforts focusing on the antagonism of glioma-associated immunosuppression alone, for example, blocking the TGF-β pathway[113] or PD-1/PD-L1-dependent signalling have not been successful. Three randomized Phase 3 trials have explored the PD-1 antibody nivolumab in newly diagnosed or recurrent[114] glioblastoma with[115] or without[116] O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation and all were negative. For newly diagnosed patients, whose tumours are lacking *MGMT* promoter methylation and thus are resistant to chemotherapy, nivolumab, an immune checkpoint inhibitor, did not work better than temozolomide.[116] It was also not superior to placebo in patients with tumours with *MGMT* promoter methylation who may exhibit higher mutational burden because of chemosensitivity.[115] Promising findings for survival were observed when anti-PD-1 antibody, pembrolizumab, was administered in a 'neoadjuvant' setting before salvage surgery

for recurrent glioblastoma,[117] though findings await confirmation in a larger study.

Various vaccination approaches have been tested, including single peptide-based vaccines like rindopepimut[118] or dendritic cell-based vaccines such as ICT-107[119] or DCVax,[120] without clear efficacy. Novel approaches include recombinant fusion protein composed of a human antibody fragment and human tumour necrosis factor (L19TNF) that use antibodies directed against embryonal fibronectin to target cytokines to the tumour site.[121] Finally, chimeric antigen receptor (CAR) T cells hold promise but in primary brain tumours have not yet shown striking activity seen in some liquid cancers, primarily because of the lack of suitable highly expressed and tumour-specific antigens.

4 | EPIDEMIOLOGICAL, CLINICAL AND PRE-CLINICAL STUDIES OF ALLERGY AND GLIOMA

4.1 | Studies of allergy and glioma risk

Several epidemiological studies and meta-analyses reported an approximate 30–40% decreased glioma risk associated with an allergy history (Figure 5A), with stronger findings for high-grade glioma.[7,122-124] Studies were often based on self-report or self-reported physician-diagnosed allergies, which may be limited by patient or proxy recall biases, temporal variability of allergy symptoms or reverse causality in retrospective research.[125] These studies often took into consideration a history of any allergy and/or specific allergies. In contrast, in some, but not all,[126] studies based in hospital, healthcare, or population registries of allergy patients or medication users, there was either no clear association with primary brain or CNS tumours overall (including gliomas),[127] or there were positive associations observed.[127-129] Krishnamachari et al. demonstrated inverse associations of self-reported atopy history and glioma which varied by ethnicity.[130] There were no clear associations between self-reported allergy history and brain tumour risk in recent studies in children and adolescents.[131]

There are also studies of allergy biomarkers, such as total and/or sIgE and glioma. For example, pre-diagnosis concentrations of tIgE were inversely associated with glioma occurrence.[132-134] However, regular intake of some types of antihistamines in allergic populations has been reported to be associated with increased risk of glioma, although this has not been borne out in all studies, a phenomenon that may be dependent on the different types of antihistamines evaluated.[135] Histamine-H4 blocking drugs may moderate $CD4^+$ T-cell functions away from classical allergy-associated Th2 features and support forkhead box P3-positive ($FOXP3^+$) Tregs.[136,137] This could result in reduced production of cytokines such as IL-4, IL-5, IL-13, reduced B-cell class switching to IgE, which together would otherwise support inflammation and surveillance including to the CNS and against glioma.[132,138,139] Consistent with this possibility are studies reporting key roles for IL-4 and activated eosinophils in glioma suppression, and systemic treatment with IL-4 transduced glioma cells engendering anti-tumour immunity against intracranial tumours.[140-142] A nested case–control study by Schwartzbaum et al. reported that elevated IL-4 and soluble IL-4 receptor alpha (sIL-4RA) prior to diagnosis was associated with a reduced glioma and glioblastoma risk, and that early gliomagenesis affects circulating immune function proteins.[138] In allergic state robust IL-4 and IL-13 responses could function via T-cell help to support class switching of B-cells to IgE, something that may be influenced by long-term exposure to some types of antihistamines. In accordance, a meta-analysis reported that increased concentrations of total and respiratory allergen sIgE before tumour diagnosis were inversely associated with glioma risk.[143] Zhou et al. reported significant inverse associations between CCL22 and glioma risk; however, CCL22 was not associated with self-reported allergy or IgE.[144] Another study by Schwartzbaum et al. reported positive associations of soluble IL-10 receptor subunit beta (sIL10RB), VEGF, beta-catenin and CCL22 and glioma risk among the 277 pre-diagnostic cytokines evaluated.[145] Collectively, studies may point to a potential contribution of classical Th2-immune features in some level of protective immune surveillance from glioma and CNS tumours.

A range of studies of SNPs of genes related to allergy reported some association with either glioma or glioblastoma risk and outcome.[146] Genetic variation of HLA was related to glioblastoma risk in a Korean study.[147] A recent genome-wide association study (GWAS) study by Eckel-Passow et al. examined specific molecular subtypes of glioma based on IDH mutation, *TERT* mutation, and 1p/19q codeletion status.[148] There were two new regions associated with specific glioma subtypes including a region in *D2HGDH* (which is also associated with allergy and asthma) that was associated with IDH-mutant but not IDH-wildtype glioma.[148] Mendelian randomization studies of genetically predicted allergic disease or serum tIgE generally reported no clear associations with glioma risk; one study reported a positive association with glioblastoma.[149-151] Ostrom et al. reported inverse correlations of the genetic architecture of autoimmune conditions and glioma, with increased activation of acquired immune traits (T-cells, NK-cells, myeloid cells) mediating susceptibility to glioma; however, there was no association of glioma and eosinophil count or percentage, or with allergic/atopic traits (asthma, hay fever and eczema) which had lower heritability.[152] They suggested that previous findings of protective effects of atopic traits may be driven by environmental factors.

4.2 | Studies of allergy and glioma prognosis

Two studies reported better prognosis among glioma patients with a history of allergy; in one of these studies, this was shown to be independent of tumour mutational status (IDH).[153,154] Prior history of asthma in patients with glioma was associated with higher mortality

risk,[149] while elevated, versus normal or borderline, serum IgE levels were linked with longer survival. Furthermore, higher rates of positive penicillin skin tests and higher eosinophil counts were reported in patients with glioma compared with healthy controls.[155,156]

Elevated serum IgE levels and past history of allergies were less frequent in patients with glioma compared with healthy subjects.[88,132,157,158] The levels of plasma IgE were lower and especially in low-grade glioma compared with healthy controls, and increased plasma IgE during treatment correlated with better outcomes.[152]

Associations between allergy-related cytokines/chemokines and prognosis are generally restricted to gene polymorphisms, including in IL-4Rα and IL-13.[88,159] Allergy-related IL4R rs1805016 and 1805015 (TT genotypes) were associated with long-term survival in high-grade glioma[159] while IL-4Rα AA genotypes conferred survival advantages in glioblastoma.[88] Inverse correlations were reported between specific complement proteins and immunoglobulins in relation to glioma grade.[160] Aberrant expression of some allergy-associated (e.g. IL-33)[161] or anti-inflammatory cytokines (e.g. IL-10 and[162] TGF-β[87]), corresponded with poor prognosis. Circulating CCL22 levels were associated with improved glioma survival, but were unrelated to allergy history or post-diagnosis IgE.[144]

Overexpression of Th2-associated genes corresponding to Th2 cell infiltration in GBM, were linked to worse glioma prognosis, while lower Th2-cell infiltration was associated with better prognosis.[163] AEC also appears to hold roles in predicting prognosis. Eosinophil-based indices in glioblastoma were altered compared to controls and AEC were higher in groups with more favourable prognosis,[164] although a separate study found prognostic value of AEC only in low-grade glioma (LGG).[165] Eosinophil activation has been positively linked to improved overall survival (OS)[166]; and increased AEC predicted shorter treatment duration with anti-VEGF antibody and more favourable progression-free survival.[167] Accordingly, lower AEC correlated with shorter OS[168] and AEC falls rapidly as glioma grade increases.[169] Observations for basophils are inconsistent and limited to a few studies.[164,170] MC activation was positively linked to OS,[166] including prognostic MC-related genes in predicting survival.[171] However, increased infiltrating MCs are detectable in GBM compared to LGG.[172]

Antihistamine usage was reported to have little impact on survival or prognosis, although further research is required.[135] Cancer patients' OS rates suffer when first-line treatment options are restricted because of drug-related hypersensitivity reactions. However, there is little information regarding glioma patients with drug allergies to their initial treatment compared with non-allergic glioma patients. Continuing carboplatin and temozolomide treatment after a hypersensitivity reaction using a drug desensitization protocol is safe and effective.[173]

Overall, higher IgE levels and past history of allergies were less frequent in patients with glioma, while allergy history, higher serum levels of IgE, certain polymorphisms to IL-4Rα, eosinophils, activated eosinophils and MCs appeared to be linked to more favourable prognosis in patients. Contrastingly, asthma, Th-2-associated cell and mediator genes such as IL-33 were linked to worse clinical outcomes. One limitation lies with the variable allergy assessment method. Further prospective research using additional established and emerging allergy biomarkers are required (Box 2).

BOX 2 Research questions for new studies in allergy and glioma risk, prognosis and treatment.

- What are the most relevant and promising new allergy biomarkers for future AllergoOncology studies in glioma?
- What is the most relevant allergic phenotype, genotype or endotype for glioma?
- Is the association of allergy and glioma most relevant for a specific glioma subtype?
- What is the association of allergy and glioma in large-scale prospective studies with comprehensive and objectively measured allergy biomarkers across the lifecourse using both systematic and agnostic analysis methods?
- Are tIgE and/or sIgE involved in glioma immunosurveillance and or immunoediting? What are the optimal threshold of IgE concentration?
- What is the association of allergy and glioma in broader geographically diverse populations with different genetic backgrounds and environmental exposures?
- What is the impact of climate-related changes in allergen exposure, allergy and glioma?
- What is the impact of anti-allergic therapies (including AIT), including their interactions, in allergy and glioma?
- What are the most relevant allergy biomarkers for monitoring immune–glioma interactions and treatment response?
- Can next-generation AllergoOncology research develop an allergy-related immunoscore for the prediction of recurrence and/or response to therapeutics?
- How can patient records, registries and databases capture the most relevant AllergoOncology data for future research?
- What is the impact of allergy on brain immunology in the context of glioma?
- Does the phenomenon of trained immunity, which is associated with the initiation of allergic diseases or influenced by allergic responses, exhibit a distinguishable and specific role in the process of glioma elimination? Can improved allergy and glioma therapeutic options be developed based on findings in AllergoOncology?
- Is research and knowledge of allergic disorders and glioma relevant to other priority cancer types?

4.3 | Pre-clinical studies of allergy and glioma

Two recent studies reported that allergic airway inflammation (AAI) could delay the progression of experimental LGG[174] and high-grade gliomas (HGG).[108] Chatterjee et al. used a genetically engineered mouse model of neurofibromatosis type-1-associated optic pathway gliomas (NF1-OPGs) and showed that experimental asthma induction inhibited glioma formation via reduced expression of the microglia-produced optic glioma mitogen, CCL5. Inhibition of CCL5 synthesis by microglia was mediated through increased T-cell expression of decorin. Decorin inhibited CCL5 production through reduced microglia nuclear factor 'kappa-light-chain-enhancer' of activated B-cell (NFκB) signalling.[174]

Poli et al. demonstrated that AAI delays glioblastoma progression in GL261-bearing mice, increasing survival and providing an alternative preclinical model to study the impact of allergy.[108] AAI establishment led to the activation of microglia into pro-inflammatory and antigen-presenting cells, as well as increased infiltration of $CD4^+$

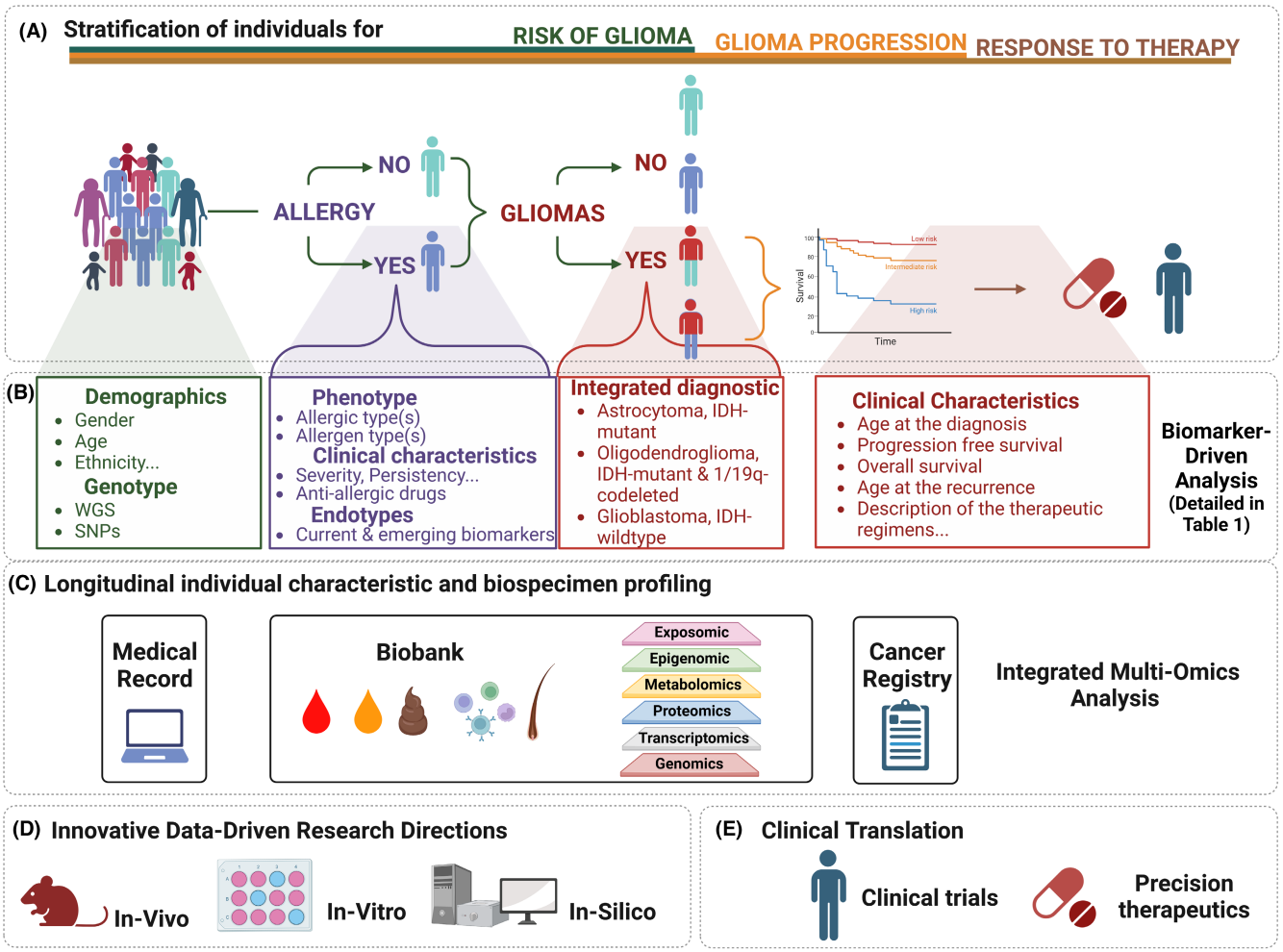

FIGURE 6 Future research in AllergoOncology. (A) This panel highlights potential directions for future investigations into the relationship between allergies and brain immunology in the context of gliomagenesis. Emphasis is placed on studying glioma risk, prognosis and treatment response. (B) Biomarker-driven analysis, utilizing current and upcoming clinically relevant markers for allergies, can aid in defining patient phenotypes and endotypes. Coupled with the sub-classification of gliomas based on integrated diagnosis (refer to Table 1), this approach holds the potential to address various unanswered questions in the field (as described in Box 2). (C) Next-generation AllergoOncology studies could incorporate the use of relevant biomarkers for allergy and glioma classification, particularly in large patient cohorts. It is essential to establish high-resolution epidemiological cohorts with comprehensive individual characteristics (including demographics, medical records with comorbidity and treatment information), as well as biospecimens (such as blood, serum, faeces, PBMC and hair) collected over the lifetime or at aetiologically relevant time points. This will enable integrated multi-omics analysis. (D) Innovative in vitro and in vivo models are necessary to further elucidate the causative molecular mechanisms underlying AllergoOncology. Stratification approaches can play a crucial role in fulfilling these research needs. (E) The ultimate objective is to sustain the development of innovative clinical trials aimed at advancing new therapeutics in the field of AllergoOncology. Created with « BioRender.com». IDH, isocitrate dehydrogenase; SNP, single-nucleotide polymorphisms; WGS, whole-genome sequencing. PBMC, Peripheral blood mononuclear cells.

T-cells in the TME. In addition, mice with deficient adaptive immunity (RAG1-KO) indicated abrogation of allergic protection effects against glioblastoma.[108]

These findings suggest an interplay between the local innate immune system, specifically microglia, and the systemic adaptive immune system, particularly T-cell responses, in eradicating cancerous cells that develop in the brain in the context of allergic inflammation.

5 | FUTURE RESEARCH IN ALLERGOONCOLOGY

Opportunities exist for future investigation of allergy and glioma risk, prognosis and treatment response (Box 2, Figure 6A). More studies using clinically relevant allergy biomarkers and updated subclassification information on gliomas are needed to define patient phenotypes, endotypes and genotypes (Figure 6B, Table 1).

Future large-scale prospective studies with comprehensive allergy biomarkers measured over the lifecourse are necessary to examine relevant points in aetiology (Figure 6C). Integrating exposome approaches may be particularly valuable.[175] The concept of the exposome highlights the critical need for more complete environmental exposure assessment in epidemiological studies, that is, the broad context of 'non-genetic' environmental factors. It complements the genome by providing a comprehensive description of lifelong exposure history.

It is unclear whether the reported inverse associations between allergy and glioma will be confirmed in additional prospective studies and whether they are specific to particular allergic disorders and/or allergens or glioma subtypes. Further understanding will be required to define the most relevant allergy biomarkers during early glioma formation and response to treatment, and for which types of gliomas or subtypes. Harmonizing and pooling data from new and existing studies would enhance the power to explore associations, especially given glioma's rarity. There are also other emerging AllergoOncology biomarkers including deficiency of IgE[5] or serum IgG4/IgE ratios[176] that may be relevant to monitor in glioma. Existing epidemiological studies are primarily conducted in Europe and North America, necessitating research in diverse geographical settings to account for environmental/allergen exposures and population profiles. Future studies are needed to clarify the prognostic role and personalized implications of allergy for patients with glioma. To achieve this, targeted patient cohorts with information on allergy and allergy-related biomarkers are needed to evaluate the prognostic value of different types of allergies and their effect on anti-cancer therapy response. This is especially relevant regarding immunotherapy response or cancer vaccines, exemplified in a recent study reporting that the allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1.[177]

Finally, in-depth understanding of cellular and molecular effects that may be shared between allergic diseases and gliomas is needed. Innovative in vitro and in vivo models are needed to further elucidate potential causative molecular mechanisms and stratification in AllergoOncology in relation to glioma (Figure 6D). Understanding the mechanisms of allergic inflammation on brain homeostasis is limited, with few studies investigating the influence of systemic Th2 allergic immune response on CNS dysfunction (Box 1 and Figure 5). Studies indicate that allergy may impact brain homeostasis and induce neuro-inflammation that subsequently could result in a range of neurological effects, including those of relevance for glioma risk and progression. Inflammatory manifestations in the brain during viral infections, such as long COVID, are documented.[178] Further studies on the intricate relationship between allergic inflammation and various brain border immune niches is crucial for comprehending the impact of allergies on brain function and may point to potential therapeutic strategies for CNS disorders including glioma. While the synergy between the immune system, the peripheral and CNS is increasingly appreciated as a regulator of both allergic diseases[179] and glioma,[180] the impact of immune cells with regard to the association between both pathologies remains to be explored.

6 | CONCLUSION

In this Position Paper, we review recent advances in allergy and glioma heterogeneity, underlining innovative opportunities for translational research. Future epidemiological AllergoOncology research could capitalise upon modern atopy-related biomarkers for assessment in glioma development and clinical outcomes and potentially elucidate underlying molecular and cellular mechanisms. Efforts to systematically record real-world data and novel biomarkers relevant to allergy and cancer risk are needed, including in cohorts, registries and in medical records. Collecting atopy-related data for monitoring immunosuppression-related changes in cancer patients is also needed. Relevant studies accounting for immune system heterogeneity, glioma diversity and specific allergic conditions may provide improved insights into the complex allergy–glioma relationship.

AUTHOR CONTRIBUTIONS

Conceptualisation: AP, MCT, EJJ, SK. **Writting- Abstract**: AP, MCT, SK, EJJ, PW; **Introduction**: AP, MCT, UR, LC, GN, SK; **Allergy: Current and emerging biomarkers, and therapeutic approaches**: AP, MME, UR, UJ, DEF, MPa, EI, SK, LV, EJJ, ChB; **Glioma: Updated classification, immune biomarkers, and therapeutic approaches**: PW, MPr, SN, MW, AP; **Epidemiological, clinical, and pre-clinical studies of allergy and glioma**: MCT, AMC, AP, SK; **Future research in AllergoOncology**: All authors; **Conclusion**: All authors. **Figure 1**: AP, NRU. **Figure 2**: AP. **Figure 3**: PW, RT. **Figure 4**: AP, FLH. **Figure 5**: AP. **Figure 6**: AP, MCT. **Box 1**: AP, FLH, AS. **Box 2**: AP, MCT, EJJ, SNK. **Table 1**: All authors. **Table 2**: UJ, ChB. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have read and approved the Position Paper. AMC, AM, AP, AS, ClB, DF; FLM, EI, GN, LC, LV, MCT, MPa, MO, MVH, MW, NRU, SPN, PVN, PW, RT, RB and UR declare no conflict of interest. CB received honoraria for presentations from Allergy Therapeutics, Bencard, HAL Allergy and SCS. EJJ declares inventorship in patents on allergen immunotherapy formulation with Biomedical International R+D, Vienna, Austria, of which she is a shareholder. She received honoraria for presentations from Allergy Therapeutics, AllergoPharma, Bencard, Meda, Roxall, ThermoFisher, and consulted previously for MediGene, Germany, Novartis, for Allergy Therapeutics and Dr. Schär. MME has received honoraria from lectures from the following companies: Stallegenes Greer, Diater and GSK. MPr has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Servier. SNK is founder and shareholder of Epsilogen Ltd. (formerly IGEM Therapeutics Ltd.) and has received funds from IGEM Therapeutics Ltd/Epsilogen Ltd. HJB is employed through a fund provided by Epsilogen Ltd. SNK and HJB are inventors of patents on antibody technologies. AJM is supported by the UK Medical Research Council (MR/R015643/1) and King's College London member of the MRC Doctoral Training Partnership in Biomedical Sciences. UJ has received a hotel accommodation and catering for a lecture and chairing of a workshop organized by ALK Abello. The honorarium went to her institution, the RCB. Her research on molecular allergology is funded by the Federal Ministry of Education and Science, the Federal Ministries of Technology, Economy and Technology, Food and Agriculture (BMEL), the German Research Foundation and the Kanert Foundation. MW has received research grants from Quercis and Versameb, and honoraria for lectures or advisory board participation or consulting from Bayer, Curevac, Medac, Novartis, Novocure, Orbus, Philogen, Roche and Sandoz.

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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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