EAACI POSITION PAPER

AllergoOncology: Danger signals in allergology and oncology: A European Academy of Allergy and Clinical Immunology (EAACI) Position Paper

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Abbreviations: AAMP, allergen-associated molecular pattern molecule; DAMP, damage-associated molecular pattern molecule; PAMP, pathogen-associated molecular pattern molecule.

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1 | METHODS

This Position Paper is a product of the EAACI Working Group for AllergoOncology, an expert panel of clinical immunologists, allergists, biochemists and epidemiologists. The topic of the manuscript was identified at the WG workshop in May 2020, and a streamline of relevant subtopics was extensively revised and designated to individual WG members. After following workshops and using a circulation process, the manuscript was recirculated for review to the WG authors, compiled and again recirculated for complete consensus on text, tables and figures. The final manuscript was read and approved by all authors and represents an expert consensus position, with recommendations summarized in the 'Highlights box'.

2 | DATA SOURCES, SEARCH STRATEGY AND STUDY SELECTION

Studies published in English were identified from PubMed. The following keywords were used in the search strategy: (allergy OR atopy) AND (tumor/tumour OR cancer OR malignancy) AND (danger signals OR damp OR pamp) AND (NK cells OR ILC OR mast cells OR granulocytes OR APC OR T cells OR B cells OR clinical applications). References published within the 2000–2020 timeframe that had not been otherwise identified in the initial search were added where relevant. We reviewed approximately 500 published studies relevant to this paper.
OVERVIEW

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The chief danger in life is that you may take too many precautions.
Alfred Adler

I know that every good and excellent thing in the world stands moment by moment on the razor-edge of danger and must be fought for.
Thornton Wilder

PART 1. INTRODUCTION TO DANGER SIGNALS: DAMPS, PAMPS AND AAMPS

4.1 | Part 1a. Introduction to DAMPs and PAMPS in allergology and oncology

Danger is metaphor with deep transcendent meaning for our lives at the cellular, tissue and organisational levels. So-called danger signals can originate from either exogenous (pathogen-associated molecular pattern molecules, PAMPS or allergen-associated molecular pattern molecules, AAMPS), or endogenous (damage-associated molecular pattern molecules, DAMPs). These signals are recognized by the immune system, triggering response in both the innate and adaptive compartments, with varying effects depending on their acuity or chronicity. Charles Janeway introduced the infectious non-self-model, where PAMPS are recognized as infectious non-self. However, this concept could not explain pathogenic self-recognition. Later in 1994, Polly Matzinger introduced the concept of the Danger Model, postulating that the immune system does not distinguish between self and non-self, but discriminates between ‘dangerous’ and ‘safe’ by recognition of pathogens or alarmin signals from injured or stressed tissues. Based on this model, Walter Land et al. proposed the concept of Danger Associated Molecular Patterns (DAMPs).

Pathogen-associated molecular pattern molecules are small molecular motifs well-conserved within a class of microbes. They are recognized by Toll-like receptors (TLRs) and other pattern recognition receptors (PRR) (Table 1). PRR are expressed on the cell surface or on the membrane of intracellular organelles of both innate and adaptive immune cells. PRR also include nucleotide-binding and oligomerization domain NOD-like receptors (NLRs), AIM2-like receptors (ALRs) and retinoid acid-inducible gene-I (RIG)-like receptors (RLRs), intracellular proteins that survey the cytoplasm for signs revealing the presence of not only pathogen-encoded molecules but also of pathogen-encoded activities termed ‘patterns of pathogenesis’. Several types of molecules can act as PAMPS. Bacterial lipopolysaccharides (LPS), consistently present in the cell membranes of Gram-negative bacteria, are considered prototypic PAMPS. LPS are recognized by TLR4 coupled with CD14 and Myeloid Differentiation factor 2 (MD-2). Other PAMPS include (a) bacterial lipoproteins and peptidoglycan recognized by TLR2; (b) parasite...
flagellin recognized by TLR5; (c) lipoteichoic acid from Gram-positive bacteria, recognized by TLR2 and TLR6; (d) nucleic acid variants, usually associated with viruses, such as single-stranded RNA, recognized by TLR7 and TLR8, or double-stranded RNA, recognized by TLR3; (e) unmethylated deoxyctydyl-phosphate-deoxyguanosine (CpG) motifs, recognized by TLR9. Furthermore, the epithelium as a general barrier between an organism’s interior and exterior environments is a critical location, where PRR recognize PAMPs and mount a local immune response.

Damage-associated molecular pattern molecule are endogenous molecules released by degranulating, stressed or dying cells, which undergo necrosis, apoptosis or autophagy. The high-mobility group box 1 (HMGB1) protein is the prototype of DAMPs. HMGB1 is recognized by TLR2, TLR4 and the receptor for advanced glycation end products (RAGE). Other DAMPs are heat shock proteins, reactive oxygen intermediates, extracellular matrix breakdown products such as fibronectin, heparan sulphate, biglycan, fibrinogen, oligosaccharides of hyaluronan and hyaluronan fragments, tenasin-C, cardiac myosin and S100 proteins. Secondary mediators including some neuromediators and cytokines, such as interferons, serve to amplify the response to DAMPs. Non-protein DAMPs include ATP, uric acid, heparan sulphate and denatured DNA. The activation of PRRs by DAMPs is key in the pathogenesis of tissue injury, repair and regeneration in several of acute and chronic inflammatory diseases including allergic disorders, asthma, atherosclerosis, neuroinflammation, and more recently, malignancy.

Accumulating evidence has led to recent advancements designed to manipulate exogenous and endogenous DAMP signal pathways in immunotherapy, both in allergic and oncologic diseases. Table 2 provides an overview of the most relevant danger signals from the areas of allergy and oncology.

In this Position Paper, we provide a comprehensive overview of danger signals in immune responses in allergy and in oncology and we put forward the importance of considering how these should be evaluated to inform both fields. Here, we focus on individual immune cell types. Non-hematopoietic cells, such as epithelial cells, endothelial cells or stromal cells, are considered beyond the scope of this manuscript. We highlight and discuss potential clinical applications addressing danger signals. We also describe new concepts where the homeostasis of different patterns of associated compartments of the immune system may predispose and set a tolerogenic (or oncogenic) or immunogenic (or allergenic) state. This interplay of innate, humoral and cellular compartments may serve to further understand the complex network of immune regulation between danger signals in allergy, oncology and the connection between them (AllergoOncology) (Figure 1A,B).
Part 1b. Allergen-associated molecular pattern (AAMPs): how can allergens introduce ‘danger’?

Recent data suggest that danger signals can be derived from allergens such as from pollen, house dust mite and Staphylococcus aureus enterotoxin B (SEB) (Table 3), inducing antigen-specific IgE production in atopic individuals. How capable a protein is in producing this response is often described as allergenicity and may depend on several factors. Allergens somewhat unusual ability to provoke an immune response is determined by their intrinsic functional properties. During sensitization as well as during the effector phase, it is important that some allergens possess proteolytic functions that breach innate defence barriers, such as epithelial skin layers, leading to an interaction with effector cells such as mast cells, endothelial cells, epithelial cells or stromal cells. This results in inflammation or, when IgE is produced, in typical allergic symptoms such as rhinitis. Examples of allergens with proteolytic functions are dust mite allergens, which are involved in pectin degradation by means of hydrolytic enzymes, or non-hydrolytic enzymes such as the pectin lyase from tree pollen. The major house dust mite allergen Der p 1 exhibits cysteine protease and endopeptidase activity which facilitates barrier disruption leading to activation of caspase-1 activation and induction of IL-1β and IL-18 release. Additionally, house dust mite-induced activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome may play a pivotal role in the pathogenesis of

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**BOX 1 Examples of unknown mechanisms of danger signal interactions with immune cells in allergy and oncology**

| Unmet needs |
|-------------|
| 2: NK cells and ILC |
| **a: Allergology** |
| To decipher the function of allergens with their AAMP, PAMP and DAMP signals on modulating expression of activating and inhibitory molecules of NK cells and ILCs. How epithelial stress and damage at the mucosal interface can interact with DAMP receptors (IL-33R/ST2) and TSLPR on ILC and NK cell functions for better preventive measurements. |
| **b: Oncology** |
| Contrasting pro- or anti-tumoral activities of innate cells when activated by DAMPs appear to be dictated by the individual microenvironment and specifically cancer type, histology. The mechanism of how DAMPs regulate innate arms of immunity to enhance their anti-tumour functions require further study in specific patient settings. Innate cells play two predominant roles in the tumour microenvironment, the initial as ‘first responders’, allowing rapid sensing of tissue damage or injury, and recruiting and maturing an adaptive immune response. The latter is as entrained effectors, responding to adaptive effectors, amplifying and enhancing antitumour effects. |
| 3: Mast cells and granulocytes |
| **a: Allergology** |
| To further identify granulocyte mediators with potential defensive responses against danger signals. |
| **b: Oncology** |
| To further elucidate the mechanism by which DAMPs (e.g., IL-33, ATP, DNA/CpG motifs, HMGB1, GM-CSF) in the clinical setting influence tumour growth by promoting survival of granulocytes and modulating adaptive immune cells within the tumour. |
| 4: Antigen-presenting cells |
| **a: Allergology** |
| To further investigate how the response of DCs and macrophages to AAMPs, PAMPs and DAMPs influence allergic sensitization, and the resolution of the allergic inflammation. For instance, how danger signals modulate M2/M2b polarization and, in concert, the tissue microenvironment. |
| **b: Oncology** |
| DCs and TAMs exhibit both anti- and a pro-tumoral effects, influenced by the different status of activation and by the TME. To overcome tumour evasion and reset the DC and TAM immune responses against tumours, it is necessary to understand which and how PAMPs and DAMPs repolarise these APCs towards a DC1- and M1- like phenotype, respectively, and consequently drive a tumoricidal TME. |
| 5: T cells and B cells |
| **a: Allergology** |
| To understand the role of type-2 alarmins and their differences as well as yet undiscovered elements between B and T cells and the epithelial barrier. |
| **b: Oncology** |
| In response to danger signals stimulation, B cells, as other immune cells, can have pro or antitumour effects depending on the cancer type and especially on the immune context. At present, there is a significant need for more studies aiming to get a holistic view of the immune infiltrate in cancer, which may be achieved using the recently developed high throughput methods for proteogenomics and spatial proteogenomics. The most recent insights in tumour immunobiology and response to checkpoints suggest that B cells, at the very least as sentinels of so-called tertiary lymphoid structures (TLS), portend a favorable prognosis. |

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Mutagens in skin cancer models have also been demonstrated to provoke γδ T-cell-dependent IgE production, suggesting an unusual linkage between atopy and oncology. Lack of barrier-protective factors may act in this sense as immune adjuvants. Examples are mutations in the filaggrin protein in AD in which percutaneous allergen exposure, and thus sensitization, may occur; and MHC haplotype variability, which may alter or amplify T-cell activating signals, thus increasing the likelihood of developing allergic responses.

| Allergy involvement                                                                 | Type of ‘danger signal’                                      | Oncology involvement                                                                 |
|------------------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Activates mast cells and eosinophil inflammation. Studies with anti-TSLP are underway. ILC2 cells express alarmin receptors: IL-33R/ST2 (suppression of tumorigenicity 2), TSLPR. | TSLP                                                        | Pro-tumorigenic in some models, anti-tumorigenic in other studies                     |
| Activates mast cells and eosinophil inflammation.                                   | ATP                                                         | ATP from dying cells also activates P2X7R in DCs, leading to pro-inflammatory IL-1β secretion through the NLRP3 inflammasome, again targeting CD8+ T cells |
| Activates mast cells and eosinophil inflammation. Studies with anti-IL-33 are used as treatment in various allergy models. | IL-33                                                        | Pro-tumorigenic in some models, anti-tumorigenic in other studies                     |
| Allergenic lipocalin peptides bind DAMP formyl peptide receptors 3 (FPR3) expressed by monocyte-derived DCs and stimulate the Th2 microenvironment | Formyl peptide receptors 3 (FPR3)                          | Reactive oxygen species-dependent Epidermal growth factor receptor (EGFR) tyrosine phosphorylation |
| Triggers the production of CCL2, a Th2-related chemokine                           | HMGB1                                                       | Leads to production of pro-inflammatory cytokines, regulates monocyte recruitment, angiogenesis and immune suppression. May also lead to NK cell activation. HMGB1-induced TLR4 activation on Tregs decreases IL-10, forkhead box P3 (FOXP3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression |
| n.d.                                                                               | HSP27                                                       | Allows the formation of the metastatic niche for secondary tumour growth             |
| Promotes pulmonary type 2 immunity to mite allergens at mucosal surfaces           | Serum amyloid 3 and A1 (SAA1)                               | Allows the formation of the metastatic niche for secondary tumour growth             |
| Induce specific IgE production                                                     | Different allergens (pollens, house dust mites)             | n.d.                                                                               |
| Activates mast cells and eosinophils                                               | Papain                                                      | Inhibition of NFκB/AMPK signalling and p- AKT, p- ERK, p- Stat3                        |
| Activates mast cells and eosinophils                                               | Staphylococcus aureus enterotoxin B                         | Downregulates the expression of Transforming Growth Factor-Beta (TGF-β) signalling transducers |
| Enhances influx of inflammatory cells in lung epithelia in allergic mouse models   | Adenosine                                                   | Stimulation of the DAMP adenosine and its receptor A2A on B cells can block signalling downstream of TLR4 and the B-cell receptor (BCR) which inhibit B-cell survival and can also promote VEGF-C expression, leading angiogenesis and metastasis |
| Induction of strong Th1 immune response to counterbalance allergen-driven Th2 response | DNA/CpG motifs                                              | TLR9 dependent activation of antigen-specific anti-cancer immune responses via plasmacytoid DC |
| Modulates the immune response from Th2 to Th17 to Treg                            | LPS                                                         | Required for DC activation, which can then sense DAMPs released through the activation of specific cell surface receptors. LPS activation of TLR4 in Tregs enhances their immunosuppressive activity and proliferation |

Abbreviation: N.d., not determined yet

Allergens seem to possess particular features that facilitate immune activation. Most allergens are 5–100 kDa size proteins or glycoproteins but are clustered in very few protein families (Table 3). Many are dimers, oligomers or tend to form aggregates, thereby forming the so-called AAMPs. Thereby, they can interact with soluble pattern recognition receptors, such as the hexameric serum amyloid A, and initiate inflammation. The potential sources of allergens are numerous, from foods to plants and arthropod faeces. Some proteins contribute to adjuvant functions.
Enterotoxin produced by staphylococcal bacteria plays a role in AD via breaching the innate barrier by forming pores in cell membranes. It acts as a superantigen to non-specifically activate adaptive immunity. Others are proteins involved in innate defence and specifically target immune cells. Animal-derived lipocalins or the pathogenesis-related protein 10 (PR-10) proteins possess immune regulatory properties when they transport ligands such as flavonoids, lipids, vitamins and steroids, but initiate danger signals in their unbound form. The heat shock proteins which are an other allergenic protein family eliciting immunological danger and being allergenic.

Allergens may carry danger signals that support allergenicity. Examples are pollen-associated lipid mediators (PALMs) released by pollen grains, which attract and may activate eosinophils and neutrophils and modulate dendritic cell (DC) function, and HMGB1, which binds to RAGE. Advanced glycation end products (AGEs), which RAGE recognizes, are also present in foods such as cooked meat, oils, cheese and other foods with high sugar content. A combination of potential food allergens and AGEs may thus lead to sensitization and food allergies.

Extrinsic microenvironmental factors, which alter normal defence mechanisms may also contribute to allergenicity. Bacterial LPS, an example of a Th1 adjuvant, acts through PRR including TLRs, nucleotide-binding oligomerization domain-containing proteins (NOD), Dectin and DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN/CD209). Helminth-derived molecules, an example of a Th2 adjuvant, may also skew the immune system towards Th2.
| Allergen-family | Paradigms (alphabetic) | Source | Mechanism of danger signal | Physiological function |
|-----------------|------------------------|--------|----------------------------|------------------------|
| With transport function | | | | |
| PR-10 | • Aln g 1  
• Bet v 1  
• Cor a 1  
• Fag s 1  
• Pla a 1  
• Api g 1  
• Ara h 8  
• Cor a 1  
• Dau c 1  
• Fra a 1  
• Gly m 4  
• Mal d 1 | Alder  
Birch trees  
Hazelnut  
Beech  
Platane-reactive plant food:  
Celery  
Peanut  
Hazelnut  
Carrot  
Strawberry  
Soy  
Apple | Exposure of AAMPs by dimer formation  
Like lipocalins, PR-10 pollen allergens sequester iron and are produced in response to plant stress, like microbial attack. Their withdrawal of iron from immune cells favours the survival of Th2 cells.  
Their withdrawal of iron from immune cells favours the survival of Th2 cells.  
Some lipid ligands hinder proteolytic digestion of food allergens, promote their thermal stability and absorption (e.g., Ara h 8) | Pathogenesis-related |
| Lipocalins | • Bos d 2,5  
• Can f 1,2,4,6  
• Cav p 1  
• Equ c 1  
• Fel d 4,7  
• Mus m 1  
• Ory c 1  
• Phod s 1 | Cattle  
Dog  
Guinea pig  
Horse  
Cat  
Mouse  
Rabbit  
Hamster | AAMPs by dimer formation  
These innate defence molecules sequester iron from the environment, thereby skewing immune cells towards Th2, as Th1 are more susceptible to iron deficiency.  
Lipid binding protects against degradation and enhances LPS/TLR4 signalling | Transport function |
| Subgroup of lipocalins: fatty acid binding proteins (FABPs) | • Der p 13  
• Der f 13  
• Blo t 13 | Mites | AAMP bind to hexameric Serum amyloid A, the complex activates the SAA1-binding receptor, formyl peptide receptor 2 (FPR2). | Function: transport and metabolism of large-chain fatty acids |
| Secreto-globulin, Utero-globin | • Can f Fel d 1-like  
• Fel d 1  
• Ory c 3 | Dog  
Cat  
Rabbit | Yet not clear, potentially binding TLR4 ligands and Th2 activation via TLR4 and TLR2. | Hormone binding |
| (Beta)-Expansins | • Cyn d 1  
• Lol p 1  
• Phil p 1  
• Phil p 2 | Bermuda grass  
Ryegrass  
Timothy grass | n.d. | Xylan-binding  
Cell wall relaxation  
Fruit ripening  
Antimicrobial |
| NPC2 (Niemann-Pick type C2) | • Can f 2  
• Cat NPC2  
• Der p 2  
• Der f 2 | Dog  
Cat  
house dust mite  
storage mite | Lipid binding molecules  
Replace MD-2 subunit from TLR4 complex, initiate Th2 signals | Nutrient transfer |
| Parvalbumins (α and β) | • Cyp c 1  
• Clu h 1  
• Dal s 1  
• Gad m 1  
• Raj c  
• Sco s 1 | Carp  
Herring  
Salmon  
Codfish  
Ray  
Mackerel | Calcium sequestration | Participate in muscle relaxation  
Regulator of neuronal signal transmission |
| Ole e 1  
Ole e 1-like | • Frau e 1  
• Lig v 1  
• Ole e 1  
• Pla l 1 | Ash  
Privet  
Olive  
plantain | AAMPs by dimer formation.  
Zn2+ binding  
Signal transduction during germination and growth  
Immune activator | |
| Tropomyosins | • Ani s 3  
• Blo t 10  
• Pen m 1  
• Per a 7 | Anisakids  
Blomia tropic.  
Black Tiger Shrimp  
Cockroach | AAMPs by repetitive epitope display  
Troponin/Actin binding  
Regulator of muscle contraction | |

(Continues)
| Allergen-family | Paradigms (alphabetical) | Source | Mechanism of danger signal | Physiological function |
|-----------------|--------------------------|--------|----------------------------|------------------------|
| Troponins       | Cra c 6                  | Brown shrimp | AAMPs by repetitive epitope display | Calcium binding, Tropomyosin/Actin binding, Regulator of muscle contraction |
| Polcalcin       | Ain g 4, Phi p 7         | Alder, Tim. Grass | n.d. | Calcium binding, Growth regulation |
| Profilins       | Polen, Plant food        | n.d. | Calcium binding, Actin binding, Locomotion and shape regulator |
| Manganese superoxide dismutase | Alt a MnSOD, Asp f 6, Mala s 11, Pis v 4 | Alternaria, Aspergillus, Malassezia, Pistachio | n.d. | Manganese-binding, Anti-inflammatory, Transform reactive oxygen species into molecular oxygen |
| Oleosins        | Ara h 15, Cor a 12       | Peanut, Hazelnut | Bind phospholipids, creating an oil body—potentially supporting mucosal uptake | n.d. |
| Cysteine proteases | Der p 1, Der f 1, Papain, Bla g 1 | House dust, storage mites, Plant food, German cockroach frass proteases | Direct lytic effect: Degrade extracellular matrix proteins and lead to an inflammasome response in the skin and release of IL-33. | n.d. |
| Aspartate proteases | Bla g 2 | Cockroach, Alternaria fungus | Aspartate protease activation of protease-activated receptor (PAR)-2 | n.d. |
| Arginine kinases | Der p 20, Bla g 9, Pen m 2 | House dust mite, Black tiger shrimps | n.d. | Mg2+ binding, Couple energy production with cellular function |
| Alpha-Gal (mammalian meat allergy) | α-Gal | Cat Fel d 5, Ticks bite, Red meat | Presumably AAMPs by repetitive epitope display | n.d. |
| 2S-Albumins     | Ana o 3, Ara h 2, Ara h 6, Ber e 1, Cor a 14, Fag e 2, Gly m 8, Jug r 1, Maci S2 albumin, Pap S2 albumin, Pis v 1, Ses i 1, Sin a 1 | Cashew nut, Peanut, Peanut, Brazil nut, Hazelnut, Buckwheat, Soy, Walnut, Macadamia nut, Poppy, Pistachio, Sesame, Mustard | Destabilization of membranes resulting in leakage, Presumably, the lipids inside may act on innate cells (iNKTs) | Lipid binding, Seed storage, Pathogenesis-related |
| 7/11S Globulins (vicilins/legumins) | Ara h 1, Cor a 11, Gly m 5, Jug r 2, Jug r 6, Pis v 3 | Peanut, Hazelnut, Soy, Walnut, Walnut, Pistachio | Exposure of AAMPs by trimer/hexamer formation, Destabilization of membranes resulting in leakage, Globulins interact with phosphatidylcholine, which hinders their digestion and activates DCs |
Additionally, irritants may serve as adjuvants. This is the case for environmental pollutants including particulate matter, such as diesel exhaust particles (DEPs) and viral infections. These may alter the development of allergic sensitization through immunomodulatory effects such as altering antigen-presenting cell (APC) functions and influencing cytokine profiles. The concept of allergens expressing AAMPs may open new opportunities for therapeutic interventions targeting AAMP/receptor downstream signalling, in an analogy to danger signals currently being investigated and already applied in anti-tumour treatment.

### TABLE 3 (Continued)

| Allergen-family | Paradigms (alphabetic) | Source | Mechanism of danger signal | Physiological function |
|-----------------|------------------------|--------|---------------------------|-----------------------|
| LTPs (Lipid transfer proteins) | • Fra a 3 | • Plants, nuts, fruits | • Destabilization of membranes resulting in leakage | • Lipid binding  
• Trafficking |
| nsLTPs (nonspecific Lipid transfer proteins) | • Pru p 3, Api g 2 | • Fruits, vegetables | • Destabilization of membrane | • Lipid binding  
• Signal transduction regulation  
• Cell wall organization  
• Antimicrobial activity |
| Phospho-lipases | • Ves v 1 (PLA1), Ves v 2 (PLA2) | • Wasp | • Cleaves fatty acids, important for downstream activation of the inflammatory arachidonic acid pathway  
• Potential interaction with cell membranes of inflammatory cells | • Ca2+ binding |
| Pectate lyases | • Amb a 1, Cup a 1, Cry j 1 | • Ragweed, Arizona cypress, Jap. Cedar | • AAMPs by repetitive epitope display | • Calcium binding  
• Pectate lyase activity |

Abbreviations: AAMPs, Allergen-Associated Molecular Patterns; N.d., not determined yet.

5. PART 2: DANGER SIGNALS IN INNATE LYMPHOID CELLS (ILCs) AND NATURAL KILLER (NK) CELLS

5.1. Part 2a. Allergology

While there is controversial evidence for a role of ILC1 and NK cells in asthma, ILC2 are now known to be an integral part of the type 2 response that occurs in allergic diseases. ILC2 are key players sensing epithelial stress and damage occurring at the mucosal interface through expression of DAMP receptors (IL-33R/ST2) suppression of tumorigenicity 2 and TSLPR). Together with basophils and mast cells, ILC2 provide early signals to other cell types involved downstream in the allergic response (DC, eosinophils, macrophages). Furthermore, IL-17-derived ILC3 have been associated with asthma exacerbation in obese individuals (Figure 2A).

5.2. Part 2b. Oncology

ILCs have been reported in many tumour types and have been shown to exert both tumour-protective and tumour-promoting capabilities. These functions likely depending on their specific subsets (ILC1, ILC2, ILC3 or LTi), in a way that is similar to the different CD4+ T helper cell subsets. Since ILCs display high plasticity, their functions are determined mainly on their immediate environment, such as the organ/tissue type, the cancer type and the nature of immune cells they are in contact with (reviewed by).

ILCs express a variety of sensors for danger signals such as ST2, IL-17RB or TSLPR. The DAMP IL-33, known for its modulation of tumour-associated ILC2, is the most documented activator of ILCs. IL-33-mediated ILC2 expansion conferred effective anti-tumour immunity against pancreatic cancer, particularly in combination with PD-1 checkpoint blockade. Furthermore, tumour models genetically manipulated to secrete endogenous IL-33 showed increased accumulation of ILC2s secreting CXCL2/1 which promoted tumour apoptosis via CXCR2 activation. In contrast, in a breast cancer model, a time-dependent increase of endogenous IL-33 in primary tumours and development of metastases was associated with an increase IL-13-producing ILC2 and immunosuppressive cells including M2 macrophages in the tumour microenvironment (TME). The IL-33-related immunosuppressive properties of ILC2 were also demonstrated to depend on the ecto-enzyme CD73 which in concert with CD39, converts extracellular ATP to adenosine, an inhibitor of anti-tumoral immunity. Similar effects were described during chemotherapy and radiation therapy before allogeneic hematopoietic stem cell transplantation. As such, therapy-mediated tissue damage induced extracellular ATP release, sensed by resident ILC3 expressing the ecto-enzymes CD73/CD39, results in immune tolerance manifested by reduced graft-versus-host disease (GvHD).

NK cells also play pivotal roles in anti-tumour innate immune responses via cytotoxic functions and cytokine and chemokine secretion. PAMP and DAMP signals can modulate the expression of activating and inhibitory ligands of NK cells, resulting in disparate, anti-tumour or pro-tumour effects, respectively. For example, TLR5 stimulation
via entolimod, a TLR5 agonist, improved survival in a murine model of colorectal cancer metastasis to the liver. These anti-tumour effects were associated with increased NK cell homing to the liver and NK cell-mediated activation of DCs, which in turn stimulated CD8+ T cells.34 In a glioma mouse model, HMGB1 release induced by the immunogenic chemotherapeutic cyclophosphamide resulted in NK cell activation.35 Furthermore, stress-, radiotherapy- or chemotherapy-induced membrane and exosome-associated HSP70 could act as DAMPs to activate NK cell-mediated cytotoxicity in vitro and in vivo.36 Conversely, the anti-inflammatory DAMP, adenosine, decreases NK cell maturation and cytotoxic functions, by impairing perforin and IFNγ release, resulting in tumour growth and metastatic spread36 (Figure 2B).
Mast cells (MCs), eosinophils (Eos), neutrophils and basophils are armed with an array of PRRs (e.g., TLRs, NLRs, RLRs, ALRs, C-lectin receptors). MCs are key sentinels of danger signals because of their presence in nearly all body barrier tissues, while Eos seemingly share this function mainly in the gut. IL-33 derived from epithelial cells bound to MC via its specific ST2 receptor plays a crucial role in the exacerbation of allergic diseases.\(^\text{37}\) Mast cell activation is fundamental for the recruitment and activation of blood granulocytes, especially in allergic reactions. Allergens bind to IgE /FcεR1 complexes on MCs and basophils, resulting in cellular activation and release of a vast array of preformed and newly formed mediators. Additionally, some allergens (‘pseudoallergens’) can cause ‘direct’ MC and granulocyte activation. For example, MCs and Eos can be activated by SEB binding to CD48 and TLR2,\(^\text{38}\) and papain binding to protease-activated receptor 2 (PAR-2),\(^\text{39}\) thereby modelling the danger mechanism of mite allergen Der p 1.\(^\text{40}\) Interestingly, neutrophils, which do not play a major role in Th2 immunity, are recruited to the airways by direct binding of pollen or animal dander to TLR4, MD-2 and CXCR2.\(^\text{41}\) Moreover, MCs and blood granulocytes can be activated by DAMPs released from epithelial cells following cell damage, an event that occurs in allergic reactions. Epithelial-derived molecules that may activate MCs and granulocytes include D AMPs, such as TSLP, ATP and IL-33.\(^\text{42,43}\) In regard to allergic immune responses, TSLP is released by skin, gut and lung epithelial cells in response to danger signals and has been linked to MC activation and eosinophilic inflammation.\(^\text{44}\) Basophils can also be activated by epithelial cell release of D AMPs that either directly activate basophils or synergize with IgE-driven activation on the basophil surface to trigger IL-4 and IL-13 production.\(^\text{45,46}\) Furthermore, B-cell-derived IgD binds to mast cells and basophils to activate these cells to produce antimicrobial factors mounting an respiratory immune defence.\(^\text{47,48}\) Importantly, MCs and blood granulocytes contain potent preformed pro-inflammatory mediators in their cytoplasmic granules that can promptly mount a ‘defensive’ response against danger signals such as Staphylococcus aureus enterotoxin B.\(^\text{49}\) Examples include tumour necrosis factor α (TNFα) and proteases for MCs, eosinophil peroxidase (EPO) for Eos and myeloperoxidase for neutrophils (Figure 3A).

Under the influence of IL-33, MCs and basophils can indirectly favour neoplastic development via modulation of tumour-resident myeloid cells. In a mouse model of gastric cancer, MCs responded to tumour-derived IL-33 through the release of other factors such as GM-CSF, CCL3 and IL-6, attracting macrophages that supported tumour growth.\(^\text{50}\) Similarly, under the influence of IL-33 and GM-CSF, lung-resident basophils promoted polarization of alveolar macrophages towards anti-inflammatory phenotypes with tumour-supporting potential.\(^\text{51}\) Conversely, basophils can be activated by IL-33, along with IL-3 and IL-18 to secrete CCL3 and CCL4, which can attract CD8 T-cells into tumours, resulting in increased rejection of melanoma tumours in vivo.\(^\text{52}\) Several studies revealed that IL-33 can directly activate cytolytic eosinophil function against cancer cells in multiple murine models of cancer, such as hepatocellular,\(^\text{53}\) breast\(^\text{53}\) and colorectal\(^\text{54}\) cancer. This activity is associated with the ability of eosinophils to clear DAMPs through the release of potent peroxidases. In addition to these potential roles of IL-33, inflammatory proteases released by MCs and neutrophils can cleave secreted IL-33, modulating its biological activity and its subsequent influence on tumour immunity,\(^\text{55}\) and mounting a ‘defensive’ response.\(^\text{49}\) HMGB1 secretion by neoplastic cells can trigger the recruitment and pro-tumoral functions of neutrophils. HMGB1 release by ultraviolet-damaged keratinocytes supported melanoma genesis and promoted lung metastases, a mechanism dependent on the recruitment and the subversion of neutrophils towards a pro-angiogenic state via TLR4 activation.\(^\text{56}\) In addition, hypoxia promoted the release of HMGB1 by primary tumours favouring lung metastasis through the activation of CD62L\(^\text{dim}\) neutrophils in a mouse model of triple-negative breast cancer. TLR2 signalling pathway activation by HMGB1 directed CD62L\(^\text{dim}\) neutrophils to produce and release neutrophil extracellular traps, which in turn promoted cancer metastasis.\(^\text{57}\) Neutrophils respond to cell death and the release of D AMPs by limiting the immune role of T cells; this may constitute a means by which the tumour adapts to cell death signals that promote reparative proliferation to exert local immunosuppression (Figure 3B).

7  |  Part 4a. Allergology

DCs and macrophages initiate and maintain allergen-driven Th2 immune responses in the airways, with IL-4 as a key driver for alternative activation of macrophages and for the pathogenesis of asthma.\(^\text{58}\) Macrophage features and functions are insufficiently studied in human allergic diseases (most studies so far have been conducted in murine models). Allergic asthma is associated with increased infiltration of alveolar macrophages (AM) with an alternatively activated (M2) rather than the classically activated (M1) phenotype.\(^\text{59}\) Damage and activation of the respiratory epithelium through D AMPs, such as those induced by viruses\(^\text{60}\) and uric acid\(^\text{61}\) generated during tissue damage, probably induce ingestion of DCs from the bone marrow.
FIGURE 3 Implication of Danger signals in Mast cells and Granulocytes in Allergology and Oncology. (A) Schematic depicting allergic diseases progression driven by mast cells, basophils, eosinophils and neutrophils activated by allergens (AAMP) and epithelial damage (DAMP) through the FcεRI and ‘direct’ activation (Part 3A of the Position Paper). (B) Schematic depicting oncologic disease progression and suppression by mast cells, basophils, eosinophils and neutrophils activity based on their interaction with DAMPS such as IL-33, ATP, DNA/CpG motifs and HMGB1 with different behaviour determined by cancer type; for example, pro-angiogenic activity of neutrophils in melanoma and the release of extracellular TRAPS in triple-negative breast cancer: the tumour grow activity of MCs stimulated by IL-33 in gastric cancer; the cytolytic function of eosinophils in various cancer types and basophils activated by IL-33, recruiting CD8+ T cells inducing rejection of tumour cells in melanoma (Part 3B of the Position Paper). ATP, Adenosine 5′-triphosphate; BAS, Basophil; CCL3, C-C Motif Chemokine Ligand 3; CXCR2, Chemokine (C-X-C motif) receptor 2; Eos, Eosinophil; FcεRI, Fc epsilon RI or high-affinity IgE receptor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HMGB1, High-mobility group box protein 1; IL, Interleukin; IgE, Immunoglobulin E; MC, Mast cell; MD-2, Myeloid differentiation factor 2; M2, M2 polarized Macrophage; Neu, Neutrophil; SEB, Staphylococcus aureus enterotoxin B; TME, tumour microenvironment; TLR, Toll-like receptor 2/4; TNBC, Triple-negative breast cancer; ST2, Suppression of tumorigenicity 2.
PAMPs, such as LPS, are required for DC activation and triggering immune responses.\textsuperscript{62,63} In atopic dermatitis (AD), TLR2-mediated sensing of Staphylococcus (S) aureus is strongly impaired in Langerhans cells and inflammatory DCs and contributes to immune deviation in AD and lack of S. aureus clearance.\textsuperscript{64}

DCs and macrophages can sense DAMPs released through the activation of specific cell surface receptors (Table 1). For example, P2X7R expression is higher in M2-type than in M1-type AMs; P2X7R activation by ATP can induce M2-type AM polarization and inhibit M1 AM polarization, while blocking of P2X7R has the opposite effect.\textsuperscript{65} However, DAMP signals are also involved in the polarization of macrophages towards an immunoregulatory, that is, M2b phenotype. Increased production of HMGB1, a Th1-associated DAMP, in the plasma of severely burned patients during the acute phase can trigger the production of CCL2, a Th2-related chemokine. CCL2 can stimulate macrophages towards M2b-like polarization,\textsuperscript{66} the same phenotype involved in IgG4-related tolerance induced by allergen immunotherapy (AIT).\textsuperscript{67} (Figure 4A). APCs express a wide variety of PPRs (for DAMPs, PAMPs and AAMPs). Investigation of homeostatic versus allergic states can help identify targets to inhibit inflammation associated with allergy.

### 7.2 | Part 4b. Oncology

Modulation of antigen-presenting capacity by various danger signals is starting to be understood as an important feature of tumour evasion. Harold Dvorak’s comparison of the TME to an impaired wound healing process placed DAMPs into the limelight as prime modulators of APC functions during tumour defence. Tumour proliferation triggers substantial cell death-associated DAMPs, and DCs and tumour-associated macrophages (TAMs) frequently orchestrate the downstream immune response.\textsuperscript{68,69} The main consequences of DAMP-mediated modulation of antigen presentation in tumours are as follows: (i) shifting of primary T-cell responses, (ii) modulating effector T-cell responses and/or (iii) influencing the APC-derived cytokine milieu. This response can either manifest as immunogenic cell death (ICD), whereby DAMP engagement of APCs induces antigen-specific anti-cancer immunity; or alternatively, as tolerogenic cell death (TCD), through immunologically silent clearance of cancer cells and their associated antigens.\textsuperscript{68} The balance between these two states is delicate and frequently influenced by the phenotype of the APCs engaging DAMPs.\textsuperscript{70–72}

In the context of triggering immunogenic cell death, chronic exposure to DAMPs within the TME can contribute to the migration and maturation of DCs, which induce anti-cancer responses by presenting cancer antigens to T cells.\textsuperscript{73} Dying cancer cells release nucleic acids sensed by PRR on DCs, that trigger RIG-I/MDA5 and cGAS-STING pathway activation, leading to IFN secretion and DC cross-priming of naïve CD8+ T cells in tumour-draining lymph nodes.\textsuperscript{74} Furthermore, ATP from dying cells stimulates tumour and immune cells to release further ATP which activates P2X7R and the NLR-NLRP3 inflammasome in both macrophages and DCs, leading to pro-inflammatory IL-1β and TNF secretion and increasing Th1 and CD8+ T-cell immunity.\textsuperscript{75,76}

In contrast, DAMPs can establish a pro-tumorigenic response, by inducing macrophage polarization to M2-like phenotypes resulting in poor cancer prognosis. HMGB1, with its thiol group in a reduced state, binding to CXCL12 expressed by TAMs, induces chemotaxis via CXCR4 and regulates monocyte recruitment, angiogenesis and immune suppression.\textsuperscript{77} Moreover, HMGB1, interacting with RAGE,\textsuperscript{70,72} or via the HMGB1-TLR2-NOX2-autophagy axis,\textsuperscript{71} promotes the monocyte differentiation to anti-inflammatory pro-tumour M2-like macrophages, allowing the formation of a metastatic niche for secondary tumour growth. This has been described in lung cancer with released HSP27 interacting with macrophage-associated TLR3, and in breast cancer by induction of serum amyloid A3 (SAA3) interacting with TLR4.\textsuperscript{77} Furthermore, M2 TAM subsets exhibit high expression of ectonucleotidases, CD39 and CD73, which scavenge ATP and hydrolyse it to adenosine,\textsuperscript{76} promoting immunosuppression by driving a TCD response, and potentiating TAM pro-tumour functions, such as vascular endothelial growth factor (VEGF)-mediated angiogenesis.\textsuperscript{76} (Figure 4B). After chemotherapy or radiotherapy, tumour-derived DAMPs activate innate cells that produce pro-inflammatory cytokines. However, chronic inflammation on the one hand leads to autoimmunity, while on the other hand ultimately increases the population of immunosuppressive cells in the tumour microenvironment.\textsuperscript{77} It was shown that infiltration of leukaemia cells into the bone marrow rewires the tissue environment to inhibit the phagocytic capacity of macrophages. Resistance to macrophage-mediated killing can be overcome by combination of therapeutic antibodies and chemotherapy.\textsuperscript{79} Besides, tumour-derived DAMPs elevate the expression of immune checkpoint molecules that allow tumours to evade immune responses.

### 8 | PART 5 DANGER SIGNALS IN T CELLS AND B CELLS

#### 8.1 | Part 5a. Allergology

TLRs are expressed by adaptive immune cells, such as B cells, CD4+ and CD8+, γδ T cells and CD4+CD25+ regulatory T-cell (Treg) populations.\textsuperscript{80} There is a concentration dependency leading to an immune outcome. For example, an increase in the levels of TLR ligands such as LPS can change the immune outcome from Th2 to Th17 to Th1.\textsuperscript{81} Similarly, TLR ligands can directly modulate adaptive immune cell functions. Bacterial lipopeptides Pam3CSK4 (TLR1/TLR2), flagellin (TLR5), and R-848 (TLR7/8) can co-stimulate proliferation and cytokine secretion in human memory CD4+ T cells, whereas TLR3 ligand poly(I:C) and TLR2 ligands increase IFN-γ and IL-6 secretion in T-cell receptor (TCR)-stimulated γδ T cells. TLR
ligands have also been implicated in the survival and modulation of the suppressive capacity of Tregs.

In B cells, B-cell receptor (BCR)-mediated and TLR signalling pathways interact and synergize to enable T-cell-independent class switching. Importantly for allergic diseases, danger signals are translated by epithelial cells which then produce serum amyloid A and the DAMPs TSLP and IL-33 to drive Th2 immune responses. Epithelial cells are also capable of responding to other environmental triggers from changes in ion or oxygen concentration, metabolites from food or microbiome or even sunlight. Interestingly, epithelial cells also commit to a type 1 or type 2 polarized expression profile, which is characterized by distinct functions. They respond by release of IL-33 which exerts its effects by activating the ST2/IL-1aR receptor, expressed constitutively on Tregs, MCs, Th2 and ILC2 cells, the predominant ILC population in the lung. After binding to its receptor, IL-33 activates NF-κB, which likely regulates the outcome of diseases such as atopic dermatitis (Figure 5A).

The danger model according to Polly Matzinger reflects the integration of the adaptive and innate immunity in immune regulation, where APCs activate T and B cells, leading to production of specific antibodies. Those antibodies recognize foreign antigens, which may act as danger to the organism. As such, immunoglobulins play a central role in danger-associated immune responses. As discussed in our previous Position Paper, IgE is not only associated with allergic disorders, parasitosis and specific immunological abnormalities but also epidemiologic and mechanistic evidence indicates a role for IgE-mediated immune surveillance and protection from tumour growth. A less well-studied antibody class, immunoglobulin D (IgD), is upregulated in the bronchial mucosa in asthma, and the IgD repertoire shows a high level of somatic hypermutation. Bioinformatics analyses of the IgD repertoire indicate that the somatic mutations in IgD are antigen driven, although less so compared to other isotypes. Clinical studies demonstrate an association between asthma and infection of the bronchial mucosa.
with the common commensal bacteria, Moraxella catarrhalis and atypical Haemophilus influenzae. These bacteria express IgD-binding proteins that induce the polyclonal proliferation of naive IgD+ B cells and heavy-chain class switch recombination. Class switch recombination and somatic hypermutation are catalysed by the same enzyme (activation-induced cytidine deaminase or AID) and occur together in germinal centre reactions involving both processes of genetic recombination, unique to immunoglobulin genes and TCRs. We suggest that the antigens recognized by IgD antibodies may include local proteins in the bronchial mucosa, such as those expressed by bacteria in asthma patients. It is proposed that the mutual antagonism between the antigens and antibodies signifies a standoff between the bacteria and host in commensalism. IgD is an isotype that is known to interact with innate immune proteins, such as Galectin-9 and CD44 on basophils. It may therefore not only deliver a stimulus for switching to IgE, but can also amplify Th2 responses and cause the exacerbation of asthma and other inflammatory diseases affecting the lungs, for example, autoimmunity and cancer.

8.2 Part 5b. Oncology

Danger signals in cancer are employed by tumour cells, including dying tumour cells and the surrounding ones, to orchestrate the TME and create immune tolerance and dysfunction by interacting with APC or T cells directly. The prototypic danger signal HMGB1, found in many tumours, triggers TLR-mediated induction of tumour antigen-specific T cells, which in turn recruit tumour-promoting macrophages or retain CD8+ cytotoxic T cells in an anergic state. Moreover, tumour-derived DAMPs induce tumour-specific Tregs directly or via DC and mount a strong tumour tolerance to engineer an escape from immune control. The enzyme indoleamine 2,3-dioxygenase (IDO) (produced by immune cells or cancer cells) causes degradation of tryptophan, thereby suppressing proliferation and differentiation of effector T cells and provoking enhanced suppressor activity of Tregs.

B cells in the TME can have anti-tumour activity, however, regulatory B cells (Bregs) support pro-tumour immune responses. In cancer, stressed and dying cancer cells can release DAMPs and, in some
cases, there could be loss of barrier integrity with consequent flux of PAMPs. DAMPs and PAMPs can shape adaptive immunity, potentiating anti-tumour or pro-tumour B-cell phenotypes.\(^9\) Stimulation of the DAMP adenosine and its receptor A2A on B cells can block signalling downstream of TLR4 and the BCR which inhibit B-cell survival and can also promote VEGF-C expression, leading to angiogenesis and metastasis.\(^9\) The PAMP and TLR9 ligand CpG can induce anti-tumour B-cell phenotypes and repolarize Bregs into B effector cells.\(^9\) In contrast, immunogenic chemotherapeutic oxalipatin treatment was associated with increased tumour-infiltrating IgA+PD-L1+IL-10+ B cells which inhibited oxaliplatin-induced tumour regression and anti-tumour CTL in a murine model of prostate cancer.\(^9\) Furthermore, HMGB1 stimulated Bregs ex vivo suppressed CD8+ T-cell activity.\(^9\)

Also, LPS can activate B cells via TLR4-dependent signalling, while cytokine secretion by T cells seems to be unaffected or may have their functions impaired. Unlike the engagement of TLR1/2, LPS activation of TLR4 in Tregs enhances their immunosuppressive activity and proliferation. In contrast, HMGB1-induced TLR4 activation on Tregs decreases IL-10, forkhead box P3 (FOXP3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression. The activation of similar kinds of TLRs may thus have a pro-tumour or anti-tumour effect in different types of cancers.

B cells differentiate into plasma cells, which in allergic patients produce high levels of allergen-specific IgE. While elevated serum IgE is generally associated with allergic/atopic conditions, very low or absent IgE may hamper anti-tumour surveillance, indicating the importance of a balanced IgE-mediated immune function. Epidemiologic studies indicate that IgE has a surveillance function in cancer, and since solid tumours are infiltrated by IgE receptor-expressing immune cells, anti-tumour IgE may result in antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP) of cancer cells \(^{27}\) (Figure 5B). On the other hand, the impact of anti-IgE therapies (used to treat allergic diseases), in the development of malignant diseases is yet unclear and must be further investigated.

### 9 | PART 6 CLINICAL APPLICATIONS
ADDRESSING DANGER SIGNALS

#### 9.1 | Part 6a. Allergy and clinical immunology

Individual pathways through which danger signals contribute to the pathophysiology of various allergic and immunologic disorders have been described. For instance, several studies have recently demonstrated an important role of endogenous danger signals at the inception and maintenance phase of allergic disease.\(^{62}\) For example, generation of danger signals by the reactive drug metabolites represents a proposed mechanism for certain drug-induced cutaneous reactions. Danger signals result in lymphocyte activation with damage of the target cell, whereas in the absence of the stress signal, no activation is provided and tolerance of the drug results.\(^{98,99}\) In addition, since HMGB1 levels are significantly increased in allergic rhinitis,\(^{10}\) while promoting smooth muscle contraction via TLR4 in the upper airways in allergic asthma,\(^{101}\) a potential therapeutic intervention targeting HMGB1 has been proposed.\(^{102}\)

Therapeutic strategies to target HMGB1 by binding and neutralizing extracellular HMGB1 currently include small molecule drugs and antibodies which antagonize TLR4 and RAGE (extracellular HMGB1 receptors), as well as decoy receptors.\(^{103}\) Some drugs such as metformin which is approved for the treatment of type 2 diabetes, have off-target effects by directly binding HMGB1.\(^{104}\) Other drugs designed to target HMGB1 have only been tested preclinically in different inflammatory diseases.\(^{105}\) With regard to allergy treatment, some data exist on the HMGB1 binding compound glycyrrhizin (GLT), a natural anti-inflammatory and antiviral triterpene in clinical use, which inhibits the chemotactic and mitogenic activities of HMGB1.\(^{106}\) Topical glycyrrhizin application reduced the content of HMGB1 in nasal fluid of rhinitis patients as well as decreased the number of eosinophils, which would normally release high amounts of HMGB1.\(^{102}\)

Auto-inflammatory disorders, such as hereditary periodic fevers (HFPs) or cryopyrin-associated periodic syndrome (CAPS), involve mutations in the gene coding for NLRP3, characterized by aberrant inflammasome hyperactivity and constitutive IL-1β production. These patients present with unexplained and recurrent fever, severe inflammation, arthropathy, chronic urticaria or central nervous system involvement. IL-1β inhibitor treatment results in dramatic improvement of symptoms.\(^{107}\) Interestingly, activation by apolipoprotein E (a concentration-dependent pulmonary danger signal) of the NLRP3 inflammasome and subsequent IL-1β secretion by bronchoalveolar fluid macrophages has been observed in asthmatic subjects.\(^{108}\) Moreover, NLRP3 inhibitors in asthma models decrease pulmonary inflammation, making NLRP3 a potential therapeutic target in severe asthma.\(^{109}\) Similarly, activation of the NLRP3 inflammasome by AAMP danger signals originated from dust mites has also been also described in the pathogenesis of atopic dermatitis.\(^{14}\)

IL-33 is considered to be a key factor in the development of different allergic disorders, especially asthma\(^{110}\) and atopic dermatitis.\(^{111}\) Anti-IL-33 and anti-TSLP agents are being studied as treatments in various allergy models. For example, a phase 2a study of etokimab, an IgG1 anti-IL-33 monoclonal antibody, showed significant clinical improvement in patients with moderate-to-severe atopic dermatitis. Treatment was associated with decreased peripheral eosinophilia and reduction in skin neutrophil infiltration.\(^{112}\) Stimulation of individual cells by alarmins results in production of IL-4 and IL-13.\(^{46}\) As such, dupilumab, the monoclonal antibody targeting the IL-4 and IL-13 pathways is used in the treatment for asthma, atopic dermatitis and chronic rhinosinusitis with nasal polyps.\(^{113}\)

Allergen immunotherapy (AIT) is the only disease-modifying therapy for allergic rhinoconjunctivitis, asthma and other allergic conditions. Several adjuvants are used to induce a more rapid, potent and long-lasting AIT immune response, by acting as immunostimulatory agents: aluminium hydroxide, calcium phosphate, microcrystalline tyrosine (MCT) and (monophosphoryl lipid A MPL).\(^{114}\)
If aluminium hydroxide is used as an adjuvant in certain subcutaneous immunotherapy (SCIT) protocols, the damaged tissue releases endogenous signals, such as uric acid which may stimulate the NLRP3 inflammasome, a caspase-1 activating complex that induces inflammation. Contrastingly, specific allergen tolerance is achieved through sublingual-specific immunotherapy (SLIT) in the absence of danger signals, where the effector cells are biased towards induction of Th1 and IL-10 producing CD4+ Tregs, resulting in tolerance as opposed to inflammation.^{115}

Peptide immunotherapy (PIT) is a new type of allergen-specific immunotherapy, aimed at increasing clinical tolerance to the allergen while reducing the potential risk of systemic allergic reactions. Through PIT, the administered ‘immunodominant’ peptides from specific allergens in the absence of danger signals (e.g., in the absence of LPS and/or an adjuvant), can generate T-cell tolerance. This is the opposite of administering the same peptide with an adjuvant, which promotes an inflammatory/immunogenic response. Soluble peptides administered by intranasal, oral, intravenous, subcutaneous and intradermal routes, all have the potential to induce tolerance.^{116} Another approach towards allergen immunotherapy with potential lower side effects than the currentAIT may be administering a mixture of allergens together with immunostimulatory oligodeoxynucleotide sequences (ISS-ODN). These sequences are bacterial DNA motifs containing unmethylated cytosine residues in the sequence CpG, which act via the cytosolic TLR9 receptor in DC and serve as adjuvants that promote a Th1 response.^{117}

### 9.2.2 | Treatment-associated immune-related adverse effects in patients with cancer

Danger signals in oncology can also impair the delivery of first-line therapies to cancer patients. Close to one third of women with ovarian cancer receiving carboplatin present with allergic and anaphylactic reactions after 6–8 exposures to the drugs, precluding their continued treatment.^{120} The presence of BRCA1/2 mutations seems to induce earlier and more severe reactions.^{121} Allergic and anaphylactic reactions can occur on first exposure in patients reactive to cremophor or polysorbate 80, which can activate complement, such as observed with taxanes.^{122} Biomarkers such as MC-released beta-tryptase can be detected in blood during type I IgE and non-IgE mast cell-mediated reactions and IL-6 is elevated in cytokine-storm like reactions.^{123,124} A novel procedure has been successfully developed to address danger signals in oncology, rapid drug desensitization (RDD), applicable to all chemotherapies, small molecules and monoclonal antibodies, including checkpoint inhibitor immunotherapies.^{125} RDD can address individual reaction phenotypes, such as type I cytokine-storm like reactions, mixed reactions and delayed reactions, but it cannot address serum sickness-like or delayed severe cutaneous adverse reactions.^{123} The mechanisms of RDD implicate MC inhibitory pathways, blocking extracellular calcium influx and the release of acute and delayed mediators, stabilizing FceRI/IgE/antigen complexes on the cell surface, preventing their internalization.^{126}

### 10 | PART 7. UNMET NEEDS AND CONCLUSION

Undoubtedly, danger signals impact the pathologies of both allergy and oncology. Here, we propose that danger signals form part of the links between allergy and oncology and are key topics in AllergoOncology (Box 2). Not only that the PAMPs or DAMPs may influence the immune response but also allergens such as AAMP can act as danger signals, generating different immune responses. Delineating the nature and the broader effects of individual danger signals allows a novel understanding of allergy development and treatment. For example, in light of new discoveries regarding DAMPs, it is possible to re-consider the hygiene hypothesis in genetically susceptible subjects exposed to allergens: in the presence of low-dose DAMP (as well as PAMP and AAMP), there is an enhancement of the allergic response induced by DC and macrophage activation; in the presence of high-dose DAMP (and PAMP) exposure (for example, as occurs on livestock farms, in rural environments in developing countries and in traditional lifestyles), there is a shift towards allergenic tolerance.^{127,128} (Figure 1A). Along these lines, these questions may also be relevant with regard to allergen immunotherapy: it is yet unclear whether danger signal molecules may support the induction of tolerance to specific allergens, at what doses and what is the most effective route of administration of immunotherapies. These considerations still require extensive study (Box 2). In the cancer field, on the other hand, danger signals should be considered not only in relation to a history of allergy, chronic inflammation and autoimmunity linked to the risk of developing cancer but...
also with regard to clinical responses to targeted treatments and to immunotherapy. It is possible that danger signals can trigger or be the result immunogenic cell death (ICD). Harnessing ICD-triggering danger signals may be a desirable mechanism, which can be used as an add on therapy for cancer. For example, antibody-drug conjugates able to induce ICD may be employed in combination with checkpoint inhibitors as potent strategy for cancer treatment. However, the balance of cell death, tissue remodelling and immunogenicity to cancer antigens in the presence or absence of additional danger signals is unknown. TLR ligands, TSLP, IL-33 and HMGB1 can influence a range of immune cells and their activation states towards adopting either pro- or anti-tumour roles in different malignant states. These danger signals thus have the capability to shape the local and systemic inflammatory milieu. It is possible that fine tuning of danger signals

### BOX 2  Examples of unmet needs on the interphase between danger signals and immunity in allergy and oncology to inform patient treatment

| Danger signals | Clinical unknowns |
|----------------|-------------------|
| AAMPs and their roles in the development of allergy and cancer | - Can AAMPs as danger signals generate different immune responses in allergy and in cancer? |
| Low-dose versus high-dose exposure to DAMPs, PAMPs, AAMPs in allergic/malignant diseases | - Is there an enhancement of the sensitization process in allergy with low-dose exposure?  
- Is there a shift towards tolerance rather with high-dose exposure?  
- Could these pathways be better targeted in allergen immunotherapy?  
- What are the implications of AIT for anti-cancer immunity? |
| Danger signals and immunogenic cell death | - Is there a link between danger signals and immunogenic cell death (ICD)?  
- How does this influence the development of allergy?  
- Can this be an immune protective signal in cancer?  
- Could drugs be combined to achieve and enhance the effects of danger signals in triggering and enhancing ICD in cancer (e.g., triggering danger signals +antibody/checkpoint inhibitors)? |
| PAMPs (TLR ligands)  
DAMPs (HMGB1, TSLP, IL−33) | - How do these influence immune cells and their activation states in different environments and anatomic locations?  
- How will these shape the local and systemic inflammatory milieu in allergy and in cancer?  
- Could these serve as biomarkers in different disease settings? |
| Allergen versus cancer immunotherapy with or without danger signals and clinical outcomes | - What are the outcomes of immunotherapy given with or without danger signals (e.g., LPS) in allergy and in cancer?  
- Could clinical tolerance to an allergen be induced with the right level of a danger signal or rather in the absence of danger signal? Could the opposite be achieved in a cancer vaccine to promotes an inflammatory/immunogenic response to an antigen?  
- How does the route of administration of immunotherapies (intranasal, oral, intravenous, subcutaneous and intradermal) and associated danger signals influence their potential to induce tolerance or immune activation?  
- Can danger signals influence response to cancer immunotherapy e.g., checkpoint inhibitors? |
| AAMPs, DAMPs, PAMPs and cancer risk | - What are the contributions of internal or external danger signals including of AAMPs on cancer risk and on cancer survival? Need for validated measures of allergy history including biomarkers of allergy and immune function, i.e., AAMPs, DAMPs PAMPs, mast cell and other immune cell mediators, IgE levels, MCs, ILC. |
| Roles of danger signals in tolerance induction to chemotherapies | - Platins/platinum drugs are haptons which require protein conjugation and repeated exposures to induce antigen-specific IgE production, which can lead to severe allergic reactions including anaphylaxis once crosslinked by drug antigen on IgE bound to mast cells. How can Th2 responses towards small molecules such as platins be elicited in the context of immune dormancy and tolerance of cancer antigens through activation of PD1/PDL1 pathways?  
- Outcomes of desensitized patients with IgE against platins may be more favourable than non-allergic, non-desensitized patients? Could a Th2 phenotype increase immune surveillance?  
- Could IgE desensitization of mast cells generate a favourable environment for tumour recognition and control? |
signals such as targeting TLRs or cancer-released DAMPs either as a stand-alone strategy or in combination with targeted therapeutic interventions might turn the odds in favour of anti-tumour immunity. For example, Li et al. have published intriguing data on antihistamines, taken by patients with melanoma, who received checkpoint inhibitor immunotherapy\(^\text{12}\)(Figure 1B).

After reviewing different danger signals collectively and their respective recognizing receptors in different subtypes of immune cells, this Position Paper stresses the notion that an individual’s immune system can act as a relay station between the body and external or internal threats in a defined manner. An urgent need is evident to understand how these processes are regulated, the relationship between them, and how they can be manipulated in the context of various pathological states. It is important to consider allergens and their DAMP-induced signalling as potential targets to overcome inflammatory responses in allergy. The field of AllergoOncology offers the chance to evaluate how a range of danger signals trigger different immune responses with juxtaposing clinical outcomes in allergy and cancer and how dissecting different clinical phenotypes of common DAMP pathways may lead improvements of the clinical management of these diseases. These considerations may open the door to new therapeutic approaches for allergic and malignant diseases.

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**CONFLICT OF INTEREST**
All authors have read and approved the Position Paper. Any potential conflicts of interest are listed here: CB: Christoph Bergmann received honoraria for presentations from Allergy Therapeutics, Bencard, HAL Allergy and SCS. CSW: Carsten Schmidt-Weber has received speaker honoraria from Bencard and Allergopharma and has a patent on nasal secretions that is pending. EJJ: Erika Jensen-Jarolim declares inventorship in patents on allergen immunotherapy formulation with Biomedical International R+D, Vienna, Austria, of which she is 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. EHS: Esther Steveling has received funds from Bencard and ALK. HJB: Heather J. Bax is employed through a fund provided by Epsilogen Ltd. (formerly IGEM Therapeutics Ltd.) and holds patents on anti-tumour IgE antibodies. DHJ: Debra H Josephs holds patents on anti-tumour IgE antibodies. GJ: Galateja Jordakieva has received lecture honoraria by Bencard Allergie GmbH and Thermo Fisher Scientific. KH: Karin Hartmann has received research funding from Thermo Fisher and consultancy or lecture fees from Allergopharma, ALK-Abello, Blueprint, Deciphera, Leo Pharma, Menarini, Novartis, Pfizer, Takeda and Thermo Fisher. MC: Marianna Castells is Principal Investigator for Blueprint PIONEER and HARBOR clinical trials, Editorial Board Annals of Allergy Asthma and Immunology, Author UpToDate, Board of Directors ABAI. MTL: Michael Lotze is currently Chief Cell Therapy Officer at Nurix Biotherapeutics and has an invention disclosure with the University of Pittsburgh relating IgE to γδ T cells. FRW: Franziska Roth-Walter declares main inventorship on patent EP2894478 (applicant Biomedical International R+D GmbH, Vienna, Austria) and received research funding from Biomedical International R+D GmbH, Vienna, Austria and Bencard Allergie GmbH, Munich, Germany. Moreover, she received lecture honoraria by FOMF, VAEM, Bencard Allergie GmbH, Munich, Germany and Vienna, Austria, and Allergy Therapeutics, Worthing, UK. SNK: Sophia N. Karagiannis is founder and shareholder of Epsilogen Ltd. (formerly IGEM Therapeutics Ltd.) and has received funds from IGEM Therapeutics Ltd/Epsilogen Ltd. Sophia N. Karagiannis holds patents on anti-tumour IgE antibodies. AP, DD, DR, DHJ, DF, EF, EI, EU, FLS, FR, GO, HJJ, IA, LV, MJ, MP, MCT, MS, RB and SC declare no conflict of interest.

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