

# Developments allergy in 2019 through the eyes of clinical and experimental allergy, part I mechanisms

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## Abstract

In the first of two linked articles, we describe the development in the mechanisms underlying allergy as described by Clinical & Experimental Allergy and other journals in 2019. Experimental models of allergic disease, basic mechanisms, clinical mechanisms and allergens are all covered.

## KEYWORDS

allergens, basic mechanisms, clinical mechanisms, experimental models

In this article, we described the development in the field of allergy as described by Clinical and Experimental Allergy and other journals in 2019. Experimental models of allergic disease, basic mechanisms, clinical mechanisms and allergens are all covered.

## 1 | EXPERIMENTAL MODELS OF ALLERGIC DISEASE

### 1.1 | Development of oral tolerance

To prevent the development of systemic immune responsiveness to dietary protein antigens, the immune system has developed mechanisms of local and systemic immune unresponsiveness termed "oral tolerance".<sup>1-3</sup> Soluble dietary protein antigens within the gastrointestinal tract are acquired by small intestine (SI) lamina propria (LP) antigen-presenting cells [CX3CR1<sup>+</sup> macrophages and CD103<sup>+</sup> migratory dendritic cells (DCs)] and are presented via cognate interaction to naive CD4<sup>+</sup> T cells.<sup>4-6</sup> CD103<sup>+</sup> DC-derived retinoic acid, indolamine 2,3-dioxygenase and transforming growth factor (TGF- $\beta$ ) promote de novo Foxp3 expression and generation of peripheral Regulatory T cells (Tregs).<sup>5-8</sup> These newly derived CD4<sup>+</sup> Treg cells traffic back to the SI LP where they maintain a tolerant homeostatic environment through secretion of the cytokines, TGF- $\beta$  and IL-10.<sup>9</sup> The FoxP3<sup>+</sup> CD4<sup>+</sup> Treg cells are maintained and supported by additional regulatory cells positioned within the SI mucosa, including MHCII<sup>+</sup> CX3CR1<sup>Hi</sup> IL-10 producing macrophages, gut resident ILC3s and B regulatory cells.<sup>9-12</sup>

### 1.2 | Development of food allergy

In food allergic individuals, food allergen exposure leads to the production of the pro-type 2 epithelial derived cytokines IL-25, IL-33 and thymic stromal lymphopoiectin (TSLP)<sup>13</sup> which drive a CD4<sup>+</sup> Th2 response and food sensitization.<sup>14</sup> The pro-type-2 cytokines are thought to act on CD103<sup>+</sup> DC cells to promote OX40L expression which drives the IL-4-dependent CD4<sup>+</sup> Th2 cells. The CD4<sup>+</sup> Th2 cells stimulate CD4<sup>+</sup> Th9 cells<sup>15-17</sup>; ILC2-derived cytokines (IL-5 and IL-13), isotype switching and induction of IgE<sup>+</sup> plasma cells in the GI compartment and expansion of basophils, mast cells and suppresses Treg function.<sup>18,19</sup>

### 1.3 | Targeted immunotherapy

Recently, there has been significant interest in developing immunotherapy approaches targeting DCs, B and CD4<sup>+</sup> T cells to efforts switch the pro-Type-2 allergic response to promote immune regulatory function and suppress allergic disease phenotype, in particular, DC vaccine approaches to stimulate TGF $\beta$ 1 and IL-10 producing immune regulatory DCs to facilitate induction of FoxP3<sup>+</sup> CD4<sup>+</sup> Treg cells.<sup>20</sup> DEC-205 (CD205) is a 205 kDa endocytotic receptor

predominantly expressed by DCs and thymic epithelial cells and is thought to act as a cell surface receptor for CpG oligonucleotides and promote DC immunoregulatory activity.<sup>21-23</sup> Xu and colleagues constructed a fusion protein consisting of an epitope of the ovalbumin (OVA) molecule and a segment of the anti-DEC205 antibody, scFv.<sup>24</sup> The fusion protein termed chimeric Ag peptide (CAP), specifically, binds DEC205 and present on the surface of DCs. The authors show that exposure of bone marrow-derived DCs to scFv-IC fusion protein led to DC uptake of scFv-IC and also surface expression. Presentation of the scFv-IC on surface DCs was associated with immune regulatory phenotype including expression of CD80 and CD86 as well as the regulatory cytokines, IL-6, IL-23 and TGF $\beta$ . In vivo studies revealed that transfer of CAP-DCs or injection of scFv-IC induced antigen (Ag)-specific IL-17<sup>+</sup> FoxP3<sup>+</sup> iTreg response in gastrointestinal tract of food allergic mice. Notably, the iTregs showed immune suppressive activity, suppressing Ag-specific CD4<sup>+</sup> Th2 response and ameliorating food allergy via an IL-17-dependent mechanism. These studies show that scFv-IC chimeric DC technology can ameliorate FA response by inducing Ag-specific IL-17<sup>+</sup> FoxP3<sup>+</sup> iTregs and maybe a therapeutic technology to treat allergic diseases.

### 1.4 | Metainflammation and eosinophilic oesophagitis

Emerging clinical studies have revealed that lifestyle factors such as sedentary lifestyle and diet high in fat and simple sugars can promote chronic metabolic inflammation termed metainflammation<sup>25-27</sup> which modulate immune mediated disease processes including allergic diseases.<sup>28-30</sup> The metabolic overload as a consequence of excess nutrients and their metabolites leads to the release of metabolism-associated molecular patterns (MAMPs) such as oxidized low-density lipoproteins (OxLDLs), free fatty acids (FFAs), glucose, advanced glycation end products (AGEs) and cholesterol.<sup>31</sup> These danger signals activate pattern recognition receptors (PRRs) downstream NF $\kappa$ B, MAPK and NLRP3-inflammaosome pathways in macrophages (IL-6, TNF $\alpha$  and IL-1 $\beta$ ), CD4<sup>+</sup> Th1 cells (IFN $\gamma$ ) and CD4<sup>+</sup> Th17 cells (IL-17) leading to chronic low-grade inflammation.<sup>31,32</sup> The molecular basis of how chronic low-grade inflammation alters the allergic phenotypes is not yet fully elucidated.<sup>30</sup>

Silva and colleagues utilizing a murine model of eosinophilic oesophagitis (EoE) examined the effect of obesity on EoE in mice.<sup>33</sup> The authors induced obesity and associated increase in body mass index (BMI), greater perigonadal fat accumulation and serum total cholesterol, LDL cholesterol and triglycerides in BALB/c male mice by feeding the mice high fat diet (HFD). Increased levels of these MAMPs were associated with metainflammation as evidenced by heightened systemic leptin and TNF $\alpha$  levels. The authors show that HFD alone was sufficient to promote a systemic allergic phenotype characterized by a significant mast cell and eosinophil accumulation in the oesophagus, trachea, gut and lung. Induction of the EoE phenotype in lean and obese mice revealed that obesity aggravated the histopathological characteristics EoE including increased

eosinophils and mast cells, Th2 cytokines (IL5 and TSLP) and systemic CD4<sup>+</sup> Th2 response.<sup>33</sup> Clinical studies have revealed that the presence of eosinophils and eosinophil granule proteins correlates with histologic features of EoE including intercellular oedema, basal zone hyperplasia, lamina propria elongation and lamina propria fibrosis.<sup>34</sup> Given the exaggerated inflammatory cell infiltrate in obese mice, one would predict increased oesophageal epithelial remodelling and disease severity; however, this was not examined. Despite these limitations, the study demonstrates that obesity can exacerbate allergic inflammatory responses and be an important risk and aggravating factor for EoE.

### 1.5 | Metainflammation and asthma

Schroder and colleagues examined the effect of short-term HFD, mild weight gain on the induction of the asthma phenotype in mice.<sup>35</sup> In these studies, the author show that female (C57BL6JRJ) mice feed HFD to induce mild increase in body weight accompanied by mild metabolic alterations develop a less severe asthma phenotype. Moreover, the asthma phenotype in chow diet fed mice was associated with more severe airway inflammation and AHR response compared to HFD-fed mice. Analyses of the immune phenotype revealed the reduced asthma phenotype was associated with decreased OVA-induced DC and CD4<sup>+</sup> T-cell recruitment. Mechanistic analyses revealed that the pulmonary CD11b<sup>+</sup> DCs phenotype from the HFD-fed mice was markedly different with reduced MHC-II and CD40 expression. These findings suggest that short-term HFD feeding attenuates the development of AHR, airway inflammation, pulmonary DC recruitment and MHC-II/CD40 expression leading to diminished Th1/17 but unchanged Th2 differentiation. Thus, short-term HFD feeding and associated metabolic alterations may have protective effects in allergic asthma development.

The two studies clearly show that metainflammation can alter allergic disease susceptibility and severity and that further in-depth studies will be required to fully decipher the mechanism of action.

### 1.6 | Sex switching in asthma risk at puberty

Another factor that has been recently shown to be linked with allergic phenotypes, particularly asthma is sex hormones.<sup>36</sup> The prevalence of asthma in prepubescent boys is higher than that observed in girls, with boys having increased wheeze, serum IgE levels and use of asthma medications.<sup>37</sup> During puberty, the sex disparity is switched with girls having increased asthma incidence which is maintained in adulthood.<sup>38,39</sup> This has led to the concept that female sex hormones such as oestrogen (E2) plays a role in immune regulation and susceptibility to allergic disease phenotypes. Experimental studies have shown that female sex hormones modulate multiple immune cell populations including DC, B cells and alter balance in Th1/Th2 immunity.<sup>36,40,41</sup> However, the contribution of E2 to development of

the asthma phenotype (eosinophilic inflammation, airway remodelling and AHR) is not fully elucidated.

Lauzon-Joset and colleagues employed a rat model of experimental atopic asthma to gain insight into the role of E2 in experimental atopic asthma.<sup>42</sup> The authors use two rat strains, which express highly dichotomous Th2<sup>high</sup> (Brown Norway, BN) versus Th2<sup>low</sup> (Piebald Virol Glaxo, PVG) immunophenotypes that model the human IgE responsiveness spectrum. The authors show that the male and female rats of the pro-allergic BN rat strain demonstrate different immune cell composition phenotype at baseline. Moreover, BN females displayed increased number of BAL cells including macrophages, neutrophils, lymphocytes and a marked increase in eosinophils. Furthermore, female BN rats displayed significantly higher peripheral blood eosinophil levels and total IgE titres compared to their male counterparts. Implantation of male BN rats with E2-releasing pellets which induced serum E2 concentrations that were comparable to female levels induced a heightened baseline CD4<sup>+</sup> Th2 phenotype characterized by increased pulmonary neutrophils and eosinophils and total serum IgE titres suggesting that E2 may contribute to driving the elevated systemic Th2 response observed in female BN rats. Employing an antigen model system in BN female and male rats transplanted with E2 releasing pellets the authors show that E2 perpetuates the activation of the CD4<sup>+</sup> Th2 response in the pulmonary compartment. Importantly, these effects of E2 were not replicated in the Th2<sup>low</sup> PVG rat strain, suggesting the involvement of Th2-promoting cofactors within the Th2<sup>high</sup> background in the potentiation of the E2-dependent effects. Collectively, these studies show that E2 can alter the eosinophilic component of pre-existing Th2-high immunophenotype and modulate the asthma phenotype. These findings suggest E2 may contribute to increasing the risk of asthma development in females.

### 1.7 | Weight gain and asthma risk

The reported association between weight gain and asthma in females, but not in males, suggests that there may also be interaction between metabolic syndromes and sex hormones that exacerbates allergic disease phenotypes.<sup>43</sup>

To test this concept of interaction between weight gain and sex in allergic disease phenotypes, e-Lacerda and colleagues examined allergic pulmonary inflammatory responses in female and male mice independently on a HFD regime.<sup>44</sup> The authors show that HFD led to 36% and 27% increase in body weight and elevated levels of metabolic parameters, glucose, triglycerides and total cholesterol in male and females, respectively, in comparison to their standard chow fed counterparts. Notably, HFD alone was sufficient to increase total BAL leucocyte levels in both males and females. Induction of allergic pulmonary inflammatory response revealed that HFD enhanced antigen-induced accumulation of leucocytes in BAL of males which was a predominantly caused by increased eosinophil numbers. In contrast, antigen challenge did not increase BAL leucocyte levels in HFD-fed female mice. However, examination of leucocyte infiltrate

in lung tissue demonstrated a completely different picture. HFD alone did not alter total BAL leucocyte levels in both males and females. Furthermore, HFD had no impact on antigen-induced lung tissue leucocyte counts in male mice. However, HFD alone was sufficient to enhance lung tissue leucocyte counts in female mice with macrophage, neutrophil and eosinophil counts significantly higher than the control chow diet feed female mice. HFD did not alter antigen-induced pulmonary inflammation of the lung tissue in female mice. With respect to pulmonary tissue remodelling, HFD did not impact antigen-induced collagen deposition or presence of pro-fibrotic BAL TGF $\beta$ 1 levels in male mice; however, HFD exacerbated antigen-induced collagen deposition and pro-fibrotic BAL TGF $\beta$ 1 levels in female mice.

Collectively, these studies identify a complex interaction between sex and weight gain in the progression of allergic asthma in mice with females developing airway remodelling at a much earlier stage than males. Additional studies will be required to tease apart the individual contribution and the complex interaction between these pathways in the exacerbation of the allergic phenotypes and how life events (eg pregnancy) can alter disease phenotypes. Despite this, these studies contribute to a better understanding of the clinical differences in the development and severity of allergic asthma observed between men and women of reproductive age.

## 1.8 | New model of eosinophilic oesophagitis

While there has been increased understanding of the underlying immunological processes that drive the immunopathophysiology of EoE,<sup>45</sup> a limitation has been the lack of suitable models of EoE. With a vast array of readily available immunological tools coupled with excellent understanding of immunological systems, the mouse has been the standard model of investigation for immunopathology of disease processes. However, the oesophagus of the mouse is anatomically different to human (keratinized versus non-keratinized) which greatly limits interpretation and translatability of studies derived from using this animal model system.<sup>46</sup> Plundrich and colleagues examined whether food (hen egg white protein) induced allergy in young pigs induced an EoE like phenotype.<sup>47</sup> The advantage of the pig system is that pig oesophagus is anatomically similar to humans, non-keratinized and display oesophageal submucosal glands and is similar in size to the human oesophagus allowing for the use of endoscopy.<sup>48</sup> The authors showed that challenge of hen egg white protein (HEWP)-sensitized pigs by gavage with HEWP induced clinical signs of food allergy including diarrhoea, emesis, and skin rash. Endoscopic analyses revealed clinical signs of oesophagitis including oedema, granularity, furrowing, while histological assessment showed evidence of oedema, immune cell infiltration including a dominant eosinophilic infiltrate and oesophageal epithelial remodelling including basal zone hyperplasia, dilated intercellular spaces. Limitations of this model were the authors did not observe large numbers of eosinophils in the intraepithelial region nor layering of eosinophils which is often used observed in humans.

Collectively, these studies suggest that the pig may be an effective model to study immunological processes that drive some EoE-associated oesophageal epithelia remodelling features and to study the role of the underlying oesophageal inflammatory component in EoE with endoscopic features.

## 2 | BASIC MECHANISMS UNDERPINNING ALLERGY

### 2.1 | Mast cells

Tissue-resident mast cells are key mediators of inflammation, with their rapid degranulation and release of proinflammatory molecules upon activation being central to many of the hallmark pathological features of allergic diseases.<sup>49,50</sup> Recent studies have described populations of mast cell precursors in the circulation,<sup>51</sup> which are recruited to the airways upon allergen challenge.<sup>52</sup> Salomonsson and colleagues have now investigated whether these circulating mast cell progenitors are linked with the severity of atopic asthma.<sup>53</sup> Studying 38 asthmatics and 29 controls, the authors found that increased circulating mast cell progenitors were associated with reduced lung function, indicating these cells might play an active role in the severity of asthma and strengthening their potential use as biomarkers of disease.<sup>53</sup>

The impact of mast cells certainly goes beyond asthma, with medication allergies, for example against antibiotics or chemotherapies, posing threats to both appropriate clinical treatment and inducing severe adverse reactions.

In a study by Killoran and colleagues, the authors used a mouse model to investigate the potential of rush desensitization, a process where short-term exposure to an allergen can provide a window of tolerance, to protect against diverse allergens. Although rush desensitization with a single model allergen resulted in sustained subclinical degranulation of mast cells, mice were then also protected against a second, unrelated, model allergen.<sup>54</sup> These data, although needing further investigation, highlight a potentially valuable future intervention approach whereby poly-sensitized allergic individuals might be afforded a window of tolerance against multiple allergens.

### 2.2 | Airway remodelling in asthma

Airway remodelling in asthma is aligned with disease severity, and in part, is linked with the responsiveness of airway epithelial cells to allergen exposure.<sup>55</sup> Through the use of both an in vitro human epithelial cell culture system and a mouse model, Labram and colleagues reported that *Aspergillus fumigatus* antigens led to endothelin-1 production, which was associated with extensive inflammation and tissue remodelling.<sup>56</sup> Administration of an endothelin-1 antagonist protected against airway wall remodelling,<sup>56</sup> highlighting endothelin-1 as a key player in this disease process, and potentially, an excellent therapeutic target.

Preventing the development of asthma and airway remodelling would ultimately be the most impactful approach. The cytokine, IL-17, is a potent driver of neutrophil recruitment and plays a complex role in both initiation and suppressing type 2 inflammatory responses, such as those seen in allergic asthma.<sup>57</sup> A study by de-Oliveira and colleagues investigated the rules governing the localization of IL-17-producing gamma-delta T cells in the airways of mice.<sup>58</sup> Specifically, the authors found that offspring of mice that had been immunized with an antigen, and subsequently developed a specific IgG response, exhibited a reduced number of IL-17 producing gamma-delta cells in the airways.<sup>58</sup> The mechanism was linked to the maternal IgG binding the gamma-delta T cells, and the phenomenon was evident in both mice and human cells.<sup>58</sup> This previously unrecognized role of IgG in modulating gamma-delta cell IL-17-producing cells could lead to both preventative strategies (via maternal tolerance) and new IgG-based therapeutics.

### 3 | CLINICAL MECHANISMS

#### 3.1 | Mediators driving granulocytes function in inflamed airways

Several articles published on clinical mechanisms emphasized the cellular mechanisms of disease. Two of these focused on mediators that may impact the recruitment or function of granulocytes in the inflamed airways. In addition to basophils, both neutrophils and eosinophils are implicated in the pathogenesis of chronic inflammatory processes in the upper and lower airways. Cao et al presented evidence to support a role for LL-37, in promoting the formation of neutrophil extracellular traps (NETs) in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).<sup>59</sup> LL37, a cathelicidin-derived anti-microbial peptide, is produced by NETs and was already known to aid in NET formation as an innate defence mechanism. The present report advances knowledge, by linking LL-37 to NET formation in CRSwNP, and supporting a pathogenic role for extracellular traps beyond asthma, possibly influenced by the airway microbiome or else microbial exposures.

Other work in the journal added another mediator to the list of those implicated in eosinophil recruitment to the airways. This area of study continues to be a major focus in the field, since it may inform targeted interventions in a variety of eosinophilic diseases.<sup>60</sup>

In their report, Kobayashi and colleagues found that the chemokine macrophage inflammatory protein 1 $\beta$ /CCL4 was chemotactic for eosinophils in vitro, and that neutralization of CCL4 attenuated infiltration of eosinophils into the airways in an OVA challenge mouse model.<sup>61</sup>

Other work examined eosinophils in order to address mechanisms of glucocorticoid (GC) resistance in non-myeloid hypereosinophilic syndromes (HES). That report found no differences in GC receptor isoforms that might explain GC resistance based on a comparison of mRNA expression levels in eosinophils from GC-resistant versus GC-sensitive patients with HES.<sup>62</sup> However, elevated levels

of serum IL-5 in a subset of patients who were GC-resistant raised an alternative theory wherein the actions of IL-5 on eosinophils may serve to counter GC-mediated eosinophil apoptosis. Such variability in IL-5 levels across patients warrants further work to identify additional mechanisms of GC resistance.

#### 3.2 | Single-cell approaches to understanding allergy

The variability in cellular responses in allergic patients poses challenges to understanding immune mechanisms of disease. With this in mind, there has been a shift towards experimental platforms that enable the discovery of new immunophenotypes based on the ability to collect large amounts of data at the single-cell level.

One such method, high-dimensional mass cytometry, was used to identify B-cell signatures linked to red meat allergy.<sup>63</sup> The hallmark of this increasingly recognized disease is the production of IgE to an oligosaccharide ("alpha-gal") found in the tissues of all non-primate animals.<sup>64</sup> In their work in the journal, Cox and colleagues identified atypical B-cell types in meat allergic patients that were present in the naïve B-cell population, as opposed to the isotype-switched memory subset. These B cells secreted IgE specific for alpha-gal when activated in vitro and displayed the chemokine receptors CXCR4 and CCR6 on their surface, which might indicate gut-homing. Further work is needed to understand the mode of differentiation of these B cells into IgE-secreting cells, and whether or not the production of IgE to alpha-gal requires T-cell help, as is the case for protein allergens.

#### 3.3 | Advances in food allergy

Three opinion articles were also published related to food allergy. These focused on the need for psychological services for food allergy in the UK<sup>65</sup>; identifying and managing patients at risk of severe allergic reactions to food<sup>66</sup>; and evidenced-based approaches to the application of precautionary allergen labelling.<sup>67</sup> The latter two papers were the result of reports from workshops related to the Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM) held in 2016 and 2018. These reports outlined the work the iFAAM project has done in each area, including the development of a Food Allergy Severity Score and a tiered risk approach for allergen labelling designed to better inform the allergic consumer.

#### 3.4 | Mechanisms underlying hereditary angioedema and atopic dermatitis

Finally, two articles focused on mechanisms of diseases with skin manifestations. The first one probed the genetic basis of hereditary angioedema (HAE) arising from mutation of the angiotensin-converting enzyme 1 gene (ANGPT1), a phenomenon that was only recently described.<sup>68</sup> The

authors presented evidence to support the view that heterozygous forms of the A119S mutation impact the endothelial barrier through loss of function of angiopoietin arising from haploinsufficiency.<sup>69</sup> Using in vitro assays, data were presented to support the inability for the heterozygous state to counteract the damaging effects of critical mediators of HAE, bradykinin and VEGF, on integrity of the epithelial barrier.

The other paper related to skin explored how the skin microbiome is influenced by the alpine climate in patients with atopic dermatitis (AD).<sup>70</sup> This paper built on earlier reports describing the benefits of an alpine climate on skin condition. Notable findings included increased microbial diversity in both lesional and non-lesional skin, and a decrease in the load of *S aureus* in lesional skin of patients in an alpine climate versus a moderate maritime climate. Whether such differences reflect the presence of decreased environmental triggers, changes in the immune response, or both, remain important questions.

## 4 | ALLERGENS

### 4.1 | The increasing number of peanut and tree nut allergen components

A number of articles in 2019 focused on peanut allergen components. Hazebrouck and colleagues looked at the cross-reactivity between peanut 2S-albumins Ara h2 and Ara h 6.<sup>71</sup> They identified low rates of cross-reactivity but, importantly, low affinity cross-reactivity appeared to be leading to diagnostic inaccuracy due to these antibodies being unable to trigger mast cell degranulation. They suggested that testing IgE binding to a mixture of 2S-albumins might be a more efficient diagnostic approach. The storage 2S albumins are also important allergens in the tree nuts that may be responsible for allergic symptoms to more than one type. For example, Bueno-Diaz and colleagues demonstrated that allergic sensitization to the 2S albumins (Pis v 1 and Ana o 3) results in allergy to pistachio and/or cashew but not the other nuts.<sup>72</sup> Finally back to peanut with Ara h 7 isoforms. Three have been identified with differing potential to degranulate basophils in an ex vivo system. Ehlers and colleagues found that they have similar linear epitopes and so they must therefore differ in terms of their conformational epitopes.<sup>73</sup>

### 4.2 | Tree pollen allergens

There are a number of variants of the birch pollen Bet v 1 component which may have therapeutic implications. Von Loetzen and colleagues compared the serum IgE and IgG binding to these variants.<sup>74</sup> They found eight recombinant Bet v 1 variants that showed similar specific IgE binding to Bet v 1. A number of papers focused on Pru p 7 sensitization. Klingebiel and colleagues found a Pru p 7 related pollen protein in three Cupressaceae species.<sup>75</sup> They presented data

suggesting that primary sensitization to the tree pollen was leading to symptoms of allergy in 51 peach allergy individuals. Their paper led to some interesting correspondence.<sup>76,77</sup>

### 4.3 | Other aeroallergens and food allergens

Allergy healthcare professionals are often asked whether there are “hypoallergenic” animals. Victor and colleagues looked at levels of horse allergen in the dander and saliva of 10 different breeds.<sup>78</sup> There was a lot of variability but both between and within breeds. Much higher levels were found in stallions than mares and geldings, independent of breed. So there is not a “hypoallergenic” horse.

In other papers from 2019, Pulsawat and colleagues demonstrated that the house dust mite Der p5 allergen can trigger an allergic reaction via a TLR-2 dependent mechanism,<sup>79</sup> Yang and colleagues identified crab IgE epitopes,<sup>80</sup> Safi and colleagues demonstrated that non-specific lipid transfer protein Tri tu 14 is a risk factor for wheat exercise-dependent allergy<sup>80</sup> and Kern and colleagues mapped the soy bean IgE epitopes.<sup>81</sup>

## 5 | CONCLUSIONS

The year 2019 provided further advances in the mechanism underlying allergy. In the related paper, we look at more clinical aspects.<sup>82</sup> We look forward to publishing more interesting observations in 2021.

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