



Epicutaneous peanut patch device for the treatment of peanut allergy

Alexandra Langlois, François Graham & Philippe Bégin

To cite this article: Alexandra Langlois, François Graham & Philippe Bégin (2019): Epicutaneous peanut patch device for the treatment of peanut allergy, Expert Review of Clinical Immunology, DOI: [10.1080/1744666X.2019.1593138](https://doi.org/10.1080/1744666X.2019.1593138)

To link to this article: <https://doi.org/10.1080/1744666X.2019.1593138>



Accepted author version posted online: 13 Mar 2019.
Published online: 27 Mar 2019.



Submit your article to this journal [↗](#)



Article views: 30



View Crossmark data [↗](#)

DRUG PROFILE



Epicutaneous peanut patch device for the treatment of peanut allergy

Alexandra Langlois^{*a}, François Graham^{*a,b} and Philippe Bégin^{a,b}

^aDepartment of Allergy and Immunology, Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada; ^bDepartment of Allergy and Immunology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montreal, QC, Canada

ABSTRACT

Introduction: Food allergy prevalence has increased in recent decades, which has mobilized efforts to develop treatment alternatives. Epicutaneous immunotherapy (EPIT) is a novel method that involves transdermal administration of peanut allergen with the objective to induce tolerance. Recent clinical trials have shown its efficacy at increasing the eliciting dose in children with a favorable safety profile.

Areas covered: This review covers the proposed mechanism of action of EPIT in murine models and humans, efficacy and safety data from clinical trials with peanut EPIT, and a discussion on its potential role in the future management of peanut allergy.

Expert opinion: With the recent completion of pivotal trials for peanut EPIT and upcoming marketing, the main question for clinicians and food allergic patients is how to define its role in the management of peanut allergy and how it compares to oral immunotherapy (OIT). Like OIT, EPIT seems to promote immunological tolerance over time. However, EPIT could lack the rapid mast-cell desensitization induced by the progressive intake of food in OIT, which explains differences in short-term outcomes and safety profiles. Head-to-head and long-term comparison of real-life efficacy with regards to sustained unresponsiveness will help define its place in the food allergy arsenal.

ARTICLE HISTORY

Received 7 September 2018
Accepted 7 March 2019

KEYWORDS

Epicutaneous immunotherapy; Viaskin® Peanut; peanut; food allergy; anaphylaxis; allergic reaction; desensitization; oral immunotherapy

1. Introduction

Peanut is the food allergen that is most frequently associated with fatal anaphylaxis (55% of cases) [1]. Its prevalence has tripled since the early 1990s, now affecting up to 1% of the general population and up to 2% of children in westernized countries [2–6]. It most often develops in early childhood and tends to persist over time with only 20% of cases resolving naturally by 12 years of age [7]. The burden of the disease derives mostly from the psycho-social impact for patients and families, which is greater than that of type I diabetes or lupus [8]. Even in the absence of reactions, the constant need to check foods and environment can lead to hypervigilance and anxiety, which can significantly limit social interactions [9].

The management of peanut allergy is currently shifting from a relatively passive approach based on avoidance and periodic monitoring of the natural evolution to a more proactive approach aimed at promoting oral tolerance. New guidelines now recommend early peanut introduction in the diet of at-risk children to prevent sensitization and/or development of clinical reactivity [10,11]. Oral immunotherapy, which involves the progressive introduction of minute to regular daily portions of peanut in the patient's diet under medical supervision, is increasingly recognized as an effective method to induce desensitization and possibly even remission in some patients [12,13]. While exciting, these changes in practice come with major challenges in terms of healthcare delivery. The lack of specialized resources is probably the main barrier for effective implementation and universal access. Many specialized

centers are already saturated from the current demand for oral food challenges just to remove false labels of food allergy (either outgrown or misdiagnosed) [14].

In this context, the development of an effective, safe, user-friendly and easily implementable alternative solution to promote oral tolerance to food allergens would be welcome. One such solution could be epicutaneous immunotherapy (EPIT), which consists of the continuous administration of an allergen through the skin using a patch device to induce immunological tolerance. Viaskin® Peanut was developed by DBV Technology in France and is the first EPIT device to have completed a clinical development program with two pivotal phase 3 trials having completed the collection of their primary outcome measures (NCT02916446, NCT02636699). It could potentially become the first product approved by the FDA and the EMA for the treatment of peanut allergy. The goal of this manuscript is to review the proposed mechanism of action of epicutaneous immunotherapy, review the clinical trials, appraise the current evidence for its indication in the treatment of peanut allergy, and discuss its potential role and place in the future arsenal for management of peanut allergy.

2. Historical perspectives

While often perceived as new, the epicutaneous route is, in fact, one of the oldest approaches to immunotherapy. When Edward Jenner first tested his smallpox vaccine through abraded skin in 1796, he himself was replicating the process

of variolation (inoculation with actual smallpox) which had been practiced under various forms in China since the sixteenth century, if not earlier [15,16]. Its first use to treat environmental allergies dates back to 1921, when EPIT to horses was conducted in asthmatic patients by Vallery-Radot [17]. Further work in the 1950s–1960s in France and other European countries used a scarification technique called ‘*quadrille ruling*’ described by Blamoutier [18,19]. It showed superiority over subcutaneous immunotherapy in the treatment of pollen allergy [20]. After a long period of absence from the scientific literature, it was ‘rediscovered’ in the early 2000s for the treatment of environmental and food allergies [21,22]. At that time, one project intended to develop a ready-to-use atopy patch test for delayed milk hypersensitivity [23,24]. This led to the development of what is now used as an EPIT patch device for food allergens [25–27].

3. Proposed mechanisms of action of epicutaneous immunotherapy

3.1. Allergen delivery and capture by antigen presenting cells

3.1.1. Delivery systems

Various systems have been developed for the transdermal administration of antigens, none of which has been compared head-to-head. Examples include solid-in-oil nanodispersion patches [28–30], polyester web patches with adsorbed allergen extract (Medanz Medical GmbH (Starnberg, Germany)) [22] and microarray patches fractionally coated with a powder allergen mixture [31]. The Viaskin® patch consists of an occlusive patch made of an adhesive polyester crown with electrosprayed antigen on its central polyethylene chamber. Once applied on the skin, condensation forms, the allergen is solubilized, and its absorption in the stratum corneum is facilitated (Figure 1) [25,27].

3.1.2. Skin preparation

Skin preparation techniques have been used to increase transdermal uptake of allergens used for EPIT. They include tape-stripping

[21], micro-needles [32], and laser-microperforations [31,33]. With these methods, the allergen rapidly diffuses directly into the dermis [27]. The effect of applying epicutaneous patches on intact vs stripped skin was assessed by Mondoulet et al. [34]. The intact-skin group showed a decrease in peanut-specific IgE and an increase in peanut-specific IgG2a, whereas the stripped-skin group had increased IgE and no change in IgG2a after 8 weeks of treatment. The stripped-skin group also showed significantly more histamine release upon subsequent peanut challenge. The intact-skin group displayed histamine release similar to the naïve and non-sensitized group [34].

3.1.3. Patch application site

These findings reconcile the concept of EPIT with the dual-allergen exposure hypothesis, which stipulates that eczematous skin could be an important source of sensitization to food allergens [35] (Figure 2). If and when approved for clinical use, patients should probably avoid applying the patch on areas of skin with active eczema, as this could theoretically worsen rather than improve their food allergy. The site of application might also hold an important role as demonstrated by comparing inter-scapular upper back, inner upper arm, outer upper thigh and abdomen skin biopsies in healthy individuals [36]. The upper back demonstrated more TH2, Th17, Th22 and Treg markers with the highest concentration of dendritic and Langerhans cell infiltrates.

3.1.4. Antigen capture and migration

In 2011, Dioszeghy et al. tracked the absorption steps of Alexa 488-labeled ovalbumin administered with an epicutaneous patch in ovalbumin-sensitized mice [27]. After 2 h of application of the patch, only negligible amounts of ovalbumin could be detected in the dermis or lymph nodes, demonstrating the impermeability of intact skin to the allergen (Figure 2). After 48 h of application, the allergen was detected in the epidermis, dermis and lymph nodes. Over 90% of ovalbumin-positive cells in the epidermis and 99.5% of cells in the dermis were either CD11b, CD11c or B220 positive, showing that the allergen was specifically captured by antigen presenting cells.

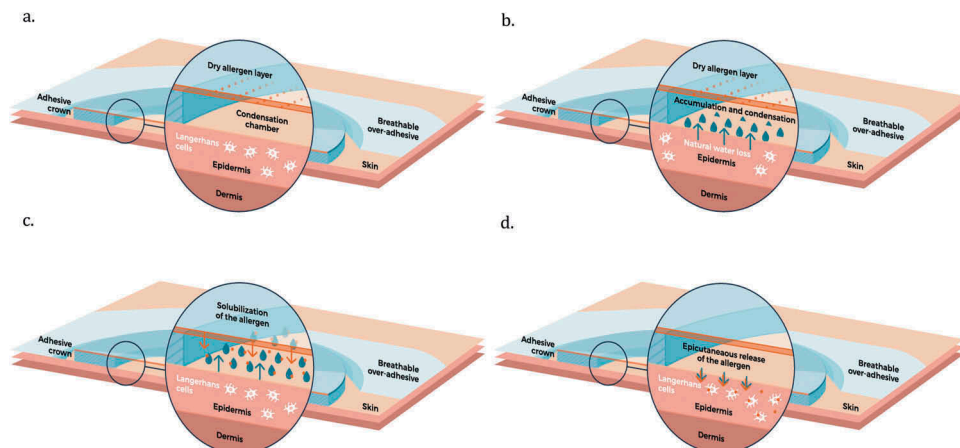


Figure 1. The peanut epicutaneous patch is occlusive and solubilizes the allergen. The allergen is dried and electrosprayed on the surface of the condensation chamber. The skin's natural water loss solubilizes the allergen and facilitates passage through the stratum corneum. Langerhans cells residing in the epidermis will take up and process the allergen, migrate to the lymph node and present it to T cells. Image used with permission from DBV technologies. <https://www.dbv-technologies.com/viaskin-platform>.

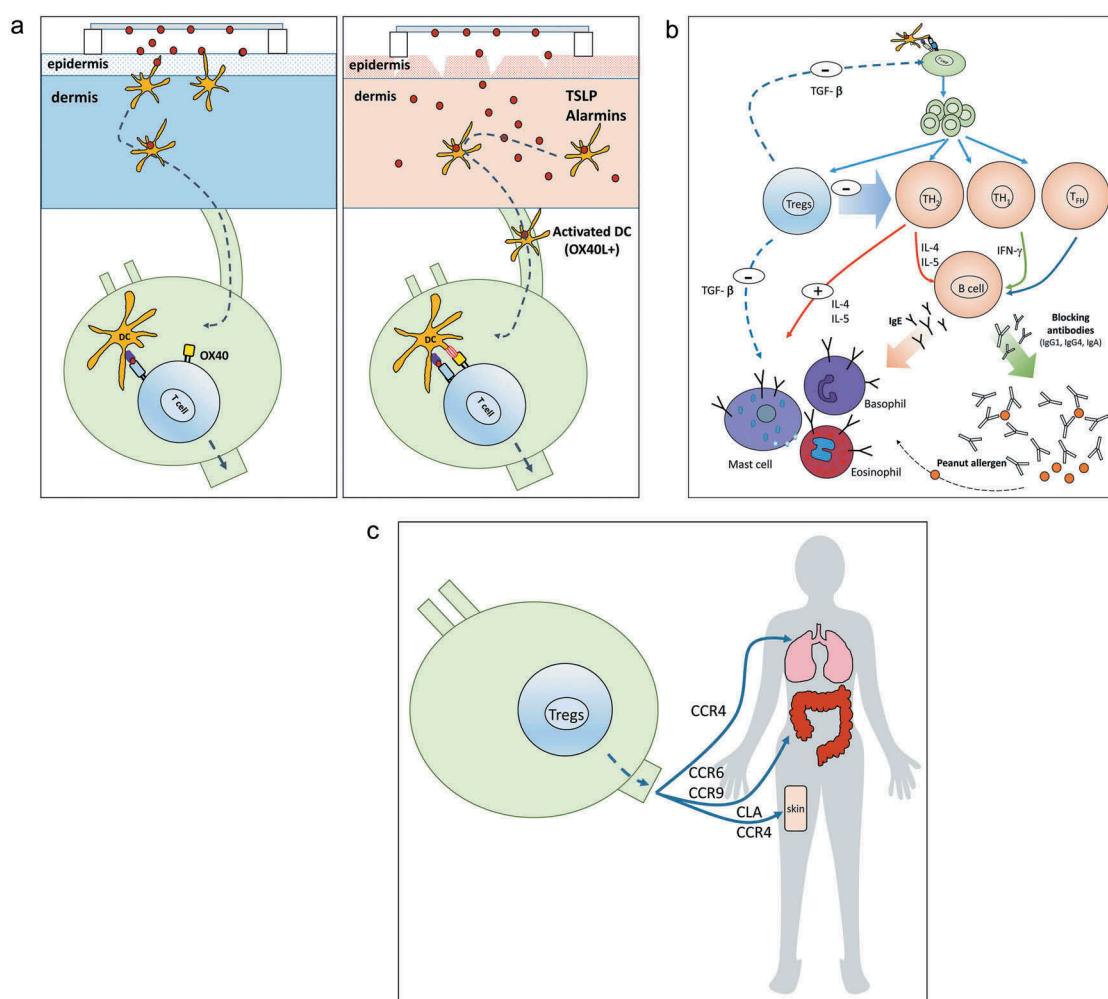


Figure 2. Proposed mechanisms of action in EPIT.

a. Epicutaneous absorption. Left panel: With intact skin, APCs actively take up the antigen across the skin barrier after epicutaneous application and migrate to lymph node for antigen presentation. Right panel: In eczematous skin, skin barrier function is lost, and the allergen readily enters the dermis. Innate inflammatory signals activate DCs before their migration to the lymph node where they will deliver pro-Th2 signaling. **b. Modulation of immune responses.** Over time, EPIT induces proliferation and differentiation of T cells. This gives rise to Tregs that play a key function in immunotherapy and will subsequently modulate different innate cells, T cell subsets (Th1, Th2, and Th17) and memory B cells. Eventually, these B cells will increase production of blocking antibodies (IgG4) and decrease the production of IgE. **c. Migration of regulatory T cells.** Tregs induced by EPIT will exit the lymph node and reach their target organs according to their homing receptors.

Interestingly, dendritic cells (DCs) from sensitized mice were found to capture the allergen faster and more effectively than naïve mice which may reflect effects of histamine-release from degranulating mast cells [37]. The number of ovalbumin-carrying DCs peaked and rapidly decreased in the epidermis at 6 h and then in the dermis at 24 h. They also peaked at 24 h in the lymph nodes and decreased slowly afterward.

3.2. Modulation of T cell response

Mice studies have shown that over time, EPIT down-regulates the Th2 response at the site of patch application, in lymph nodes, and systemically. In mice models of ovalbumin EPIT, splenocytes showed a significant decrease in IL-4, IL-5, IL-13, IL-10, and IFN- γ after culture with ovalbumin when compared to sham and control mice [27]. Similar results were found in other studies in mice [25,38–40]. In a study of 74 children and adults treated with peanut-EPIT, Jones et al. used CD154 assay

to identify peanut-specific T cells and while results were not statistically significant, they did report a trend for a decrease in IL-4 and IL-13 in subjects treated with peanut EPIT at a dose of 250 μ g [41].

T cell phenotypic changes following EPIT have been confirmed at the epigenetic level in mice using DNA methylation studies that showed persistent hypermethylation (suppressing expression) of the *Gata3* promoter (marker for Th2 cells) as well as hypomethylation of the T regulatory cell (Treg)-specific determining region (TSDR) of *Foxp3* in CD4⁺ T cells (marker for natural Tregs) [39].

In peanut-sensitized mice, EPIT induces both natural Tregs (CD4⁺CD25⁺Foxp3⁺) as well as Th3, inducible Tregs (CD4⁺CD25⁺TGF β ⁺) [38]. The protective effect of EPIT on oesophageal eosinophilic infiltration after peanut feeding was lost when Tregs were depleted with anti-CD25 antibodies. Conversely, adoptive transfer of CD4⁺CD25⁺Tregs from EPIT-treated mice effectively prevented eosinophilic oesophageal

infiltration in receiving peanut-sensitized mice. These suppressive capacities appeared to be imparted by CTLA-4 and were IL-10 independent [38,42]. Recently it has been reported that Langerhans cells (LCs) play a crucial role in the development of Tregs. Depleting LCs in OVA-sensitized mice prior to ovalbumin epicutaneous immunotherapy failed to induce Tregs. This later translated in anaphylaxis after OVA challenge while the control group did not react [43].

Another similar study demonstrated the lack of successful desensitization with EPIT when it was paired with an anti-TGF- β antibody, supporting a role for LAP⁺Foxp3⁺ Th3 regulatory cells [44]. Importantly, the authors readily showed that transfer of ovalbumin-specific but not of non-specific LAP⁺ Treg cells prevented systemic mast cell degranulation after the oral challenge of mice passively sensitized to ovalbumin. This shows that Tregs can directly suppress mast cell activation in an allergen-specific manner independently of humoral changes with treatment. Interestingly, the LAP⁺Foxp3⁺ Th3 cells exhibited gastrointestinal homing markers CCR6 and CCR9 despite being generated through the skin.

3.3. Modulation of the humoral response

To effectively protect against IgE-mediated anaphylaxis, changes in T cell response must translate to changes in peanut-specific humoral response. The humoral response observed with EPIT to peanut is the same as that seen with all other forms of immunotherapy, regardless of the route or the allergen. It is characterized by an initial increase followed by a decrease in allergen-specific IgE and increases in peanut-specific IgG4 levels and IgG4/IgE ratio. These findings are highlighted in recent clinical trials with peanut EPIT [41,45–48]. The initial rise is possibly due to an expansion of the effector/memory B cell compartment, followed by its progressive depletion, and possible replacement by a new population producing competing protective blocking antibodies (IgG4, IgG1 and IgA) which will increase in parallel to changes in IgE [40,42,49–51]. It is likely that Tregs play a role in this modulation of the humoral response although further studies are needed to elucidate the exact mechanisms surrounding the changes in allergen-specific B cell biology.

3.4. Head-to-head comparison with OIT in mice models

Two recent experiments conducted on peanut-sensitized mice compared EPIT (100 μ g for 8 weeks) to OIT (5 mg maintenance for week 3 to 8) [39,42]. Both approaches induced protection from eosinophilic infiltrate and generation of Tregs. Both approaches also yielded similar changes in IgE and IgG2a levels. However, EPIT induced significantly more Tregs and Th3 cells, and persistent changes in DNA methylation of *Gata3* and *Foxp3* TSDR were also only seen in the EPIT group.

These results must, however, be interpreted with caution as it is difficult to interpret and compare the dosages used in mice to their equivalent in humans. In OIT clinical studies, participants have received up to 3000 mg of peanut protein, which is 12,000 times more than the dosage in peanut epicutaneous patch devices. In this study, the dosage for OIT (5 mg) was only 50 times greater than that of EPIT (100 μ g). It is

therefore unclear whether the differences in Treg phenotype were due solely to the mode of administration or to the dosage.

4. Peanut epicutaneous immunotherapy clinical trials

4.1. Clinical trials: evidence of efficacy

There are five randomized controlled trials (RCTs) assessing the efficacy and safety of peanut EPIT [41,45,46,48,52]. Trials results are summarized in Table 1. Only four of these studies have been published in peer-reviewed journals, one of which provides safety data [52], and three which provide both efficacy and safety data [41,46,48].

Initial efficacy data came from a pilot study by Dupont et al. in France in 2014 published in the form of an abstract (**ARACHILD**) [45]. The study involved 54 patients aged 5 to 17, who were randomly allocated to peanut patch with 100 μ g of peanut protein or placebo for 6 months, with a switch to active treatment in both groups for an additional 12 months. Primary outcome was defined as a 10-fold increase in cumulative reactive dose (CRD) and/or reaching 1000 mg peanut protein CRD at the exit double-blind placebo-controlled food challenge (DBPCFC). Overall, 40% of patients in the active treatment group reached the primary outcome. However, the authors noticed that the subgroup of patients aged 5–11 ($n = 15$) had a higher response rate of 67%. These children also had a significant increase of CRD from 24.27 mg of peanut protein at baseline to 357.7 mg of peanut protein after 18 months ($p < 0.001$).

A second large study funded by the National Institute of Allergy and Infectious Diseases (NIAID) was performed by Jones and colleagues and completed in 2016 (**COFAR 6**) [41]. This was a double-blind placebo-controlled phase 2 RCT involving 74 subjects aged 4 to 25 years in five centers in the USA. Twenty-four were treated with Viaskin 100 μ g (VP100), 25 with Viaskin 250 μ g (VP250), and 25 with placebo. Primary outcome was defined as passing a 5044-mg peanut protein OFC or a 10-fold or greater increase in successfully consumed dose (SCD) compared to baseline after 52 weeks. Three patients (12%) in the placebo group met the primary outcome, 11 (46%) in the VP100 group, and 12 (48%) in the VP250 group ($p = 0.005$ and $P = 0.003$, respectively, when compared to placebo). The median change in SCD was 0, 45, and 130 mg of peanut protein in the placebo group, VP100 group, and VP250 group, respectively, which was statistically significant. In addition, treatment success was higher in patients 11 years or younger with 10 (59%) in the VP100 group, and 11 (61%) in the VP250 group. However, post hoc analysis looking at patients who had an SCD of at least 1044 mg of peanut protein at 52 weeks did not reveal a statistically significant difference between placebo (12%), VP100 (12.5%), and VP250 (28%). A stricter definition involving an SCD of at least 1044 mg of peanut protein in addition to a 10-fold increase in SCD led to only two patients in the placebo group (8%), two in the VP100 group (8.3%), and four in the VP250 group (16%), which was not statistically significant for all comparisons.

Table 1. Randomized controlled trials of peanut epicutaneous immunotherapy.

Study (year)	Study population			Intervention		Efficacy			
	Name of study Design N	Phase	Age (years)	Median peanut specific IgE (kU/L)	Maintenance dose (µg)	Duration	Primary endpoint	ITT Primary endpoint results	Safety data (Summary)
Dupont et al. ⁴⁵ (2014) ARACHILD * RCT N = 54 T: 25 P: 29	2	5–17	NA	100	18 months	CRD>10-fold basal CRD or reaching > 1000 mg pp on DBPCFC	40% overall 67% in 5–11 years group	NA	-Local adverse reactions increased in active treatment group vs placebo (84% vs 60%). Most mild to moderate. -No severe TEAEs. -No epinephrine used. -WR: T: 3/80 (3.75%), P: 1/20 (5%) -WR due to TEAEs: P:1/20 (5%), T:2/80 (2.5%). -Increased local reactions in treatment group (VP250 and VP100) vs placebo (79.7, 79.8 vs 14.4% respectively) – mainly grade 1 or 2. -No severe TEAEs. -No epinephrine used. -WR: P: 3/25 (12%), T: 3/59 (6.1%). -WR due to TEAEs: P: 0/25 (0%), T: 1/49 (2%). -TEAEs related to patch 2x more frequent in T group and mainly in year 1 of study. -Local reactions most common TEAE (grade 1 to 3) – mainly 3 first months. -25% with more generalized TEAEs. -20 serious TEAEs, none related to study drug. -1 patient with non-serious moderate anaphylaxis possibly related to therapy. -WR: P: 2/56 (3.6%), T: 12/165 (7.3%) -WR due to TEAEs: P: 0/56 (0%), T: 3/165 (1.8%) -OLFUS-VIPES WR: -m24 WR: 22/171 (12.9%), due to TEAEs: 3/171 (1.75%). -m36 WR: 54/171 (32%). Due to TEAEs: 3/171 (1.75%).
Jones et al. ⁵² (2016) PEP01.09 RCT N = 100 T: 80 P: 20	1b	6–50	T: 9.89 P: 21.75	20, 150, 250 or 500 (adults only)	2 weeks	NA (safety study)	NA (safety study)	NA	
Jones et al. ⁴¹ (2017) COFAR 6 RCT N = 74 T: 49 P: 25	2	4–25	78.2	100 or 250	52 weeks	Passing a 5044-mg pp DBPCFC or 10-fold or greater increase in SCD from baseline	250 µg: 48% (12/25) 100 µg: 46% (11/24) P: 12% (3/25)		
Sampson et al. ⁴⁶ (2017)** VIPES RCT N = 221 T: 165 P: 56	2b	6–55	250 µg: 79.9 100 µg: 66.1 50 µg: 83 P: 68.5	50, 100 or 250	12 months	pp ED 10-times increase above baseline or post treatment ED >1000 mg pp on DBPCFC	250 µg: 50% (23/46) P: 25% (14/56)		
Sampson et al. ⁴⁶ (2017)** OLFUS-VIPES Open-label study N = 171 T: 171 P: none	2b follow-up	6–55		250	24 months (continuation of VIPES)	Overall: 24 m: 59.7% (89/149) 36 m: 65.5% (80/124) Age 6–11: 24 m: 63.3% (57/90) 36 m: 68.4% (56/79) Ages 6–11 on 250 µg patch 24 m: 80% (16/20) 36: 83.3% (15/18)			

(Continued)

Table 1. (Continued).

Study (year)	Study population		Intervention		Efficacy				
	Name of study Design	Phase	Age (years)	Median peanut specific IgE (kU/L)	Maintenance dose (µg)	Duration	Primary endpoint	ITT Primary endpoint results	Safety data (Summary)
Fleischer et al. ⁴⁸ (2019)	PEPITES RCT	3	4–11	NA	250	12 months	Subjects with pp ED>300 mg (baseline ED<10 mg) or >1000 mg (baseline ED>10 mg) at Month 12 DBPCFC	T: 35.3% P:13.6% CRD increase after 12 m: T: 144 mg pp -> 444 mg pp P: 144 mg pp -> 144 mg pp	- Mild/moderate local adverse reactions most common adverse events. -Serious TEAEs: P: 6/118 (5.1%), T: 10/238 (4.2%). 4 moderate anaphylactic reactions related to patch in 3 patients. - Epinephrine use: P: 4/118 (3.4%), T: 22/238 (9.2%). -WR: P: 11/118 (9.3%), T: 25/238 (10.5%). -WR due to TEAEs: P: 0/118 (0%), T: 4/238 (1.7%).

Legend:

- * Abstract
- ** Same study
- CRD = cumulative reactive dose
- DBPCFC = Double-blind, placebo-controlled food challenge
- ED = Eliciting dose
- m = months
- N = number of patients
- NA = not available
- P = placebo
- pp = peanut protein
- RCT = randomized controlled trial
- SCD = successfully consumed dose
- T = treatment group
- TEAEs = treatment emergent adverse events
- VP 100 = Viaskin peanut patch with 100 µg of peanut protein
- VP 250 = Viaskin peanut patch with 250 µg of peanut protein
- WR = Withdrawal rate

In 2017, Sampson et al. published results from a phase 2b RCT involving 221 subjects aged 6 to 55 from 22 tertiary referral centers in North America and Europe (**VIPES**) [53]. Patients had peanut allergy confirmed by a DBPCFC to peanut with an eliciting dose of 300 mg of peanut protein or less. Patients were randomly allocated to use a daily Viaskin peanut patch containing 50 µg (n = 53), 100 µg (n = 56), or 250 µg (n = 56) of peanut protein or placebo (n = 56). Primary outcome was defined as a 10-fold increase in eliciting dose and/or reaching 1000 mg of peanut protein at DBPCFC after 12 months. Fourteen patients (25%) in the placebo group met the primary outcome, and 28 in the VP250 group (50%), which was a significant difference (p = 0.01). Stratified analysis by age revealed that 53.6% of children in the group 6 to 11 years with the 250 µg patch responded at 12 months compared to 19.4% with the placebo patch (p = 0.008). When looking at adolescent and adult age groups there was no significant difference when comparing the treatment group (250 µg patch) to placebo. Of note, the 25% response in the placebo group was much higher than expected (projected rate of 10%) in this study. The authors question whether the 10-fold increase in eliciting dose primary outcome may not have been stringent enough, considering possible variability of individual eliciting doses in patients with low peanut thresholds, especially when starting with very low quantities of peanut protein as in the PRACTALL food challenge protocol (1 mg of peanut protein) [54].

The same centers completed an open-label 2-year extension involving 97 children and 74 adolescents/adults of the original study (**OLFUS-VIPES**) [46,53]. All patients enrolled were transitioned to the 250 µg patch. Per protocol response rate at 12 and 24 months was, respectively, 89/149 (59.7%) and 80/124 (64.5%). Of note, 31.6% of patients in the extension discontinued for various reasons (withdrawal of consent, loss to follow-up, investigator's decision, noncompliance), including two (1.2%) because of adverse events. In the children subgroup, the per-protocol response rate at 12 and 24 months was, respectively, 63.3% and 68.4%. Twenty-one children 6 to 11 underwent treatment with the 250 µg for 3 consecutive years (phase 2b trial and 2-year extension) with a response rate of 57.1% at 1 year, 80% at 2 years, and 83.3% at 3 years. At the end of the study, 61% of these children had an eliciting dose of at least 1000 mg of peanut protein. Although additional years of treatment with peanut EPIT seem to be of additional benefit, interpretation requires caution since there was no placebo group after 1 year. This said, from a conceptual point of view, it is quite plausible considering that the sustained tolerogenic effects of most other methods of allergen immunotherapy occur over years [55–57].

Interestingly, there were 29 participants (21 children and 8 adolescents/adults) who were unresponsive to an eliciting dose of ≥ 1000 mg peanut protein. Of these, 25 were enrolled in a sustained unresponsiveness study, where they discontinued the patch, were instructed to keep avoiding peanut for 2 months and repeated the DBPCFC [58]. Twenty (80%) were still unresponsive to the cumulative dose of ≥ 1000 mg and the remaining five (20%) reached a cumulative dose of 1000 mg

before reacting. The immunological changes in peanut-specific IgE and IgG4 remained unchanged after stopping the patch for 2 months.

Finally, results from a large phase 3 RCT (**PEPITES**) were recently published [48]. This was a DBPC phase 3 RCT involving 356 peanut-allergic subjects age 4 to 11 recruited in Australia, Europe, and North America. All patients had positive DBPCFC with an eliciting dose (ED) ≤ 300 mg peanut protein and were randomized (2:1) to VP250 or placebo for 12 months. Primary endpoint was the difference in response rate between placebo and VP250 group, defined as patients with ED ≥ 300 mg peanut protein (baseline ED ≤ 10 mg peanut protein) or ED ≥ 1000 mg peanut protein (baseline ED > 10 mg peanut protein) at 12-month DBPCFC. The placebo group had a response rate of 13.6% compared to 35.3% for the active treatment group (p = 0.00001). Baseline median CRD was 144 mg peanut protein in both groups and increased significantly to 444 mg peanut protein in the VP250 group after 12 months of treatment, compared to no change (144 mg peanut protein) in the placebo group (p < 0.001). An open-label extension of this study is currently underway to assess long-term efficacy and safety outcomes in this larger cohort (PEOPLE study, NCT03013517).

4.2. Clinical trials: evidence of safety

Four major RCTs have assessed the safety of peanut epicutaneous patches for a total of over 500 patients in the treatment group (Table 1) [41,46,48,52], with the majority of reactions being local and mild, and decreasing over time. Rarely, mild to moderate systemic reactions related to the peanut patch have been described [41,46,48]. Overall withdrawal rates due to treatment emergent adverse events (TEAEs) are around 1–2% [41,46,48,52]. For comparison, withdrawal rates due to adverse events vary between 10% and 20% in peanut OIT trials [59–64].

Jones et al. performed a phase 1b safety study in 2016 that included 100 peanut-allergic subjects between 6 and 50 years of age at five clinical sites in the USA (**PEP01.09**) [52]. Eighty patients were randomized to apply Viaskin® peanut patches with 20, 100, 250, and 500 µg of peanut protein and 20 received placebo. Only adults received the 500 µg dose. Patches were placed for 24 or 48-h intervals for a period of 2 weeks. Doses were increased sequentially using an interactive Web-based response system. Eighty-four percent (84%) and 60% of patients on active treatment and placebo, respectively, reported at least one local adverse reaction. The majority of local reactions were mild to moderate and lasted longer in the treatment group compared to the placebo group. The main local reactions at the site of patch application involved pruritus (82.5% in treatment compared to 50% in placebo), erythema (70% in treatment group compared to 25% in placebo), edema (47.5% in treatment group compared to 5% in placebo), and urticaria (50% in treatment group compared to 15% in placebo). Two patients in the active treatment group had systemic symptoms related to the peanut patch. No severe TEAEs were reported and no epinephrine was used.

Withdrawal rate due to TEAEs in the placebo group was 1/20 (5%) compared to 2/80 (2.5%) in the treatment group.

In Sampson et al.'s phase 2b RCT (**VIPES**) [46] involving 221 peanut-allergic patients, the percentage of patients with any TEAEs was similar among patients with 50 µg patch (100%), 100 µg patch (98.2%), 250 µg patch (100%), and placebo (92.9%). TEAEs related to the investigational drug were twice as frequent in the treatment group (96.4% in the 250 µg group) when compared to the placebo group (48.2%). Twenty serious TEAEs were recorded in 17 patients, although none were related to the study drug. Local skin reactions were the most frequent reactions, generally occurring during the first months of treatment and decreasing over time. Twenty-five percent (25%) of patients had more generalized TEAEs, mainly cutaneous reactions extending beyond the border of the patch. One patient presented non-serious anaphylaxis possibly related to therapy. Discontinuation rate due to TEAEs in the treatment group was 3/165 (1.8%) in the phase 2b trial: one for an AE unrelated to peanut patch, and the two others (1.2%) for local dermatitis at patch site application.

In the 74 participants of COFAR 6 [41], 79.8% of doses (VP100 and VP250) caused TEAEs compared to 14.4% of placebo doses. Most reactions were local grade 1 or grade 2 reactions, meaning they did not significantly extend beyond the patch area. The median percentage of doses causing local patch site reactions per participant was 1.6% for placebo, 92.8% for the VP100 group, and 96.1% for the VP250 group. Some reactions extended around the patch site in 1.5% of placebo doses compared to 8.9% of VP100 doses and 16% of VP250 doses. One patient in the VP100 presented systemic urticaria, which responded to antihistamines and lasted 2–4 h. No epinephrine was used. Three severe adverse events were unrelated to the study drug. Withdrawal rate due to TEAEs related to investigational product was low, with no patients in the placebo group and 1/49 (2%) in the treatment group.

Similarly, the most common TEAEs in the PEPITES trial [48] were local application site reactions (mainly grade 1 or 2), which were generally observed during the first month of application and decreased subsequently. Five (2.1%) participants in the treatment group had grade 4 reactions. TEAEs were balanced between the treatment (95.4% of patients) and placebo group (89% of patients). Overall, systemic reactions were identified in both treatment (7.6%) and placebo groups (6.8%) and described as mild to moderate intensity (no cardiovascular or respiratory compromise). Three patients in the treatment group presented mild to moderate anaphylaxis treated with epinephrine at home (serious TEAEs); these reactions were deemed treatment-related by investigators, and two of these patients discontinued the study. Discontinuation rate was 10.5% in the treatment group and 9.3% in the placebo group; 1.7% of withdrawals in the treatment group were due to TEAEs.

4.3. Clinical trials: evidence on quality of life

Although Quality of Life (the Food Allergy Quality of Life Questionnaire (FAQLQ)/Food Allergy Independent Measure (FAIM)) at Month 12 and Month 24 compared to Day 1 was

assessed in OLFUS-VIPES (NCT01955109) results have not been published yet.

A recent study reporting results of the semi-structured interview with caregivers of patients undergoing OIT and EPIT suggested that increasing peanut threshold to protect against accidental reactions would improve quality of life [65].

4.4. Ongoing studies

Multiple studies are ongoing to provide additional data on the efficacy and safety profile of peanut EPIT in different age groups.

- PEOPLE is an open-label extension study of patients who completed the PEPITES study (NCT03013517). Patients will undergo treatment with VP250 for 2 years if already on active treatment or for 3 years if previously on placebo in the PEPITES study. The primary endpoint will be to evaluate the percentage of patients achieving an ED $\geq$ 1,000 mg after 24 months of additional treatment.
- REALISE is an ongoing phase 3 RCT (NCT02916446) to evaluate the safety of Viaskin® peanut in children 4–11 years. Subjects are randomized to placebo or VP250 for 6 months, followed by active treatment for up to 3 years. The primary outcome measures of the study are adverse events (AEs), TEAEs and SAEs.
- EPITOPE is a phase 3 multi-center RCT (NCT03211247) that aims to determine the efficacy of Viaskin® peanut in children 1–3 years of age after 12 months of treatment.

5. Conclusion

EPIT is an emerging modality of peanut immunotherapy which has shown efficacy in increasing peanut reaction threshold in children over time. The underlying mechanism most likely relies on the generation of Tregs and modulation of innate, cellular and humoral immunity. Clinical trials to date have shown an excellent safety profile with low withdrawal rates albeit only a modest increase in CRD after 12 months of treatment.

6. Expert opinion

With the upcoming marketing of EPIT products, determining their place in the management of food allergy will likely prove a challenge to clinicians and patients. While studies have demonstrated the efficacy of peanut EPIT at raising the reaction threshold, its clinical role in real life setting is still undetermined. Importantly, it is unclear how it compares to other emerging options such as oral immunotherapy. The lack of head-to-head trials makes it hard to compare the two approaches, as different studies may use different endpoints or DBPCFC stopping rules. Another problem is that response is generally defined by the change in threshold, which may be due to a combination of different mechanisms with different clinical significances. The lack of a universal vocabulary to describe these concepts makes it even more difficult to present a theoretical framework to discuss the interpretation of

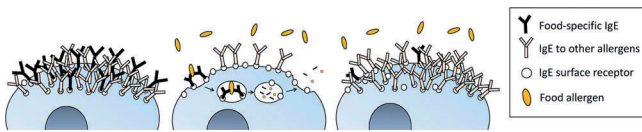


Figure 3. Mast cell desensitization. With progressive exposure to the allergen, food-specific IgE are internalized and degraded. IgE to other allergens bind the high-affinity IgE receptor (FcεR) now vacant on mast cell surface. On further exposure to the food allergen, there is insufficient food-specific IgE to trigger a reaction.

the available data. For instance, the word desensitization can be used to describe both the internalization of IgE on mast cells (Figure 3) with exposure to allergens or the clinical state of increased reaction threshold regardless of underlying mechanism.

In the following discussion, we will refer to end-organ mast cell desensitization as the immune mechanism by which allergen-IgE complexes are internalized by mast cells and basophils when membrane-bound IgE encounter their specific allergen [66]. This is assumed to be the main mechanism implicated in rush desensitization procedures for IgE-mediated allergy (e.g. penicillin or carboplatin) and is well described in mouse models of food allergy [66]. Once internalized, the IgE-allergen complex is digested and the empty Fcε receptor is recycled to the surface (Figure 3). Mast cells can carry between 200,000 and 500,000 IgE antibodies on their surface and binding of 2000 of these will generally lead to 50% degranulation [67]. The key is to start the allergen low enough not to trigger degranulation. With IgE internalization, the reaction threshold increases thus allowing progression to the next dose and so on, until mast cells are sufficiently disarmed of the specific IgE to tolerate the target maintenance dose. This is a temporary state because with discontinuation of allergen doses, circulating IgE will be able to rearm mast cells and basophils in sufficient density to trigger reactions again.

End-organ mast cell desensitization is presumably the main mechanism responsible for the initial rapid increase in threshold seen in the first months of OIT. Clinically, this protection can be captured by an early decrease in allergen-specific basophil activation, which precedes changes in IgE and IgG4 [68]. And just as would be expected with desensitization procedures to antibiotics, constant exposure is required to maintain this temporary state of protection.

Over time, changes in the cellular and humoral responses can be seen in most individuals undergoing OIT, which suggests the underlying allergy itself has changed. Similarly to environmental allergen or hymenoptera venom immunotherapy, the key waiting period to see most of these changes seems to be 3–5 years, although the clinical impact is variable [69–71]. In their NEJM paper on egg OIT, Burks and colleagues report that after 2 years, only 28% of participants achieved sustained unresponsiveness (SU), which was defined as a lack of reaction to a 10 g challenge (two eggs) after discontinuing daily dosing for 4–6 weeks [72]. However, one should note that all subjects could tolerate a greater dose than on their initial challenge at study entry. This suggests that, even if not fully ‘unresponsive’, at least part of the acquired tolerance remains sustained for a majority of patients [72]. In these patients, oral tolerance is probably the result of a mix of end-

organ mast-cell desensitization (temporary) and active immune modulation (sustained).

In view of the current gaps in the literature, it is interesting to consider EPIT data with this theoretical framework in mind. With EPIT, there is no or very little systemic exposure to the allergen and the dose (250 µg) does not increase over time. The only basophil activation test (BAT) data available shows limited suppression of basophil activation in the first year [41]. Considering this, end-organ mast cell desensitization does not seem to play a major role in the mechanism of EPIT. At best, one could say that it induces local mast cell desensitization directly under the patch. This is supported by the rapid decrease in local urticaria at the patch site observed in the first few weeks of treatment.

The corollary is that, if changes in reaction threshold in EPIT are not explained by end-organ mast-cell desensitization, then it follows that they are probably the result of immune modulation. And if changes in threshold from EPIT are indeed the result of active immune changes, then one would expect these changes to be sustained with treatment discontinuation. It is unfortunate that SU was not systematically tested in all previous EPIT trials, but there is one publication (OLFUS) to that regard which is encouraging. In the only report to evaluate SU in EPIT, of 25 treatment responders (CRD >1000 mg), 20 (80%) maintained their reaction threshold above 1000 mg after discontinuing treatment for 2 months and the remaining 5 did reach 1000 mg on the challenge before reacting [58].

While more data is needed to confirm this hypothesis, if EPIT did induce a sustained change in the allergic response rather than temporary desensitization, the implication would be important. This would mean that rather than looking at the evolution of the reaction threshold, the more appropriate comparator between OIT and EPIT would be rates of SU. Interestingly, just as with SU in OIT, the success rate of EPIT have been shown to increase significantly after 3 years of treatment (OLFUS-VIPES) [46]. This said, this was based on a small number of patients who underwent the uncontrolled extension of the phase 2 trial. It remains to be seen whether these results will be confirmed in currently ongoing long-term open-label studies.

While the lack of systemic exposure to peanut allergen in EPIT potentially explains the lack of end-organ mast cell desensitization, it also explains its good safety profile, which is its main advantage. Another significant advantage is the low amount of clinical resources it requires. Drastically higher success rates of peanut OIT reported in toddlers suggest there may be a window of opportunity early after diagnosis where an immunotherapy program could be more effective at inducing SU [60]. Because of this knowledge, there is a significant pressure on allergist and parents to start treatment early, but current resources and treatment capacity are insufficient. Peanut EPIT might allow to safely and rapidly initiate therapy in those young children, potentially even before consultation with an allergist. Ongoing trials focusing on this population should provide valuable insight. This may be particularly relevant in areas where there are significant issues with access to specialized care [73].

For subjects above 11 years of age, efficacy has been lower. This could be explained by dosage considerations, different

stage in disease evolution, or the fact that the patch was applied at a different, potentially less immunogenic site in this age group (upper inner arm). New studies will be needed for this age group.

While the limited need for specialized care is a potential advantage of EPIT, another important gap of knowledge is how to best monitor treatment response in the real-life setting. Periodic challenges would defeat the advantage of EPIT of 'not needing specialized resources'. This said, if the response is not monitored, the patients cannot know whether they are protected or not. The benefit of quality of life and decreased hypervigilance then become less clear. Worse, it could lead to over-confidence in the patch's protective effect and unsafe voluntary exposure to the allergen. Eventual use of BAT assay in the clinic to follow change from baseline reactivity could be an interesting avenue, but more data are needed before it can be used in this particular setting.

In the end, the decision between OIT and EPIT will most likely depend on patients/parents' objectives. If their goal is to achieve rapid protection or introduction of high amounts of peanut in the diet, desensitization with OIT would appear to be the best option at the moment. However, for those with safety concerns or logistic limitations who wish to increase their threshold over time with minimal risks of systemic allergic reactions, EPIT could become a valid option.

Finally, an interesting question to answer will be how OIT and EPIT can work together rather than compete. One potential such application would be in patients with particularly severe allergies for which the allergist or the patient is not ready to undertake OIT. EPIT could potentially offer a safe bridge to decrease baseline reactivity, potentially generating blocking antibodies or peanut-specific Tregs, before attempting desensitization with OIT.

7. Five-year view

With results from ongoing trials, and the marketing of a first EPIT product for peanut, the next five years will be highly determinant for the future of EPIT in food allergy. By then, real-life head-to-head trials with OIT and large cohorts tested for SU will surely help better define its role and place in the management of peanut allergy. Market cost of this new product, which is unknown at the moment, will be determinant in establishing its place in the food allergy management arsenal.

Key issues

- Preliminary data from RCTs indicate that peanut EPIT may be a promising avenue to increase peanut reaction threshold in peanut allergic children.
- Animal models have shown that the efficacy is dependent on the generation of allergen-specific T regulatory cells.
- Potential advantages of EPIT over OIT:
 - more favorable safety profile with low rate of systemic reactions.
 - low withdrawal rates.
 - minimal clinical resources required.
- Potential disadvantages of EPIT compared to OIT:
 - longer treatment needed to achieve comparable levels of protection.
 - lack of clinical indicator of when protection is achieved (self-evident with OIT as daily dose increases).
 - lack of data concerning improvement in Quality of Life.
- More data is needed to determine optimal age group for initiation of therapy, application site, duration of treatment, and effect on quality of life.

Funding

This paper was not funded.

Declaration of interest

P Bégin is an investigator on clinical trials sponsored by DBV technologies for which he has declined all personal honoraria. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed that their institution has received grant funding from DBV Technologies and Aimmune Therapeutics. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose. DBV Technologies provided a scientific accuracy review at the request of the journal editor.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol.* **2001**;107(1):191–193.
2. Soller L, Ben-Shoshan M, Harrington DW, et al. Overall prevalence of self-reported food allergy in Canada. *J Allergy Clin Immunol.* **2012**;130(4):986–988.
3. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol.* **2018**;141(1):41–58.
4. Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and pre-determined challenge criteria in infants. *J Allergy Clin Immunol.* **2011**;127(3):668–676. e661–e662.
5. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, et al. Peanut allergy prevalence among school-age children in a US cohort not selected for any disease. *J Allergy Clin Immunol.* **2014**;134(3):753–755.
6. Sicherer SH, Munoz-Furlong A, Godbold JH, et al. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol.* **2010**;125(6):1322–1326.
7. Bégin P, Paradis L, Paradis J, et al. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. *J Allergy Clin Immunol Pract.* **2013**;1(5):528–530. e521–e524.
8. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy.* **2000**;30(8):1135–1143.
9. Muraro A, Polloni L, Lazzarotto F, et al. Comparison of bullying of food-allergic versus healthy schoolchildren in Italy. *J Allergy Clin Immunol.* **2014**;134(3):749–751.
10. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med.* **2015**;372(9):803–813.

11. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of allergy and infectious diseases-sponsored expert panel. *J Allergy Clin Immunol*. **2017**;139(1):29–44.
12. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. **2017**;72(8):1133–1147.
13. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. **2018**;73(4):799–815.
14. Okada Y, Yamashita T, Kumagai H, et al. Accurate determination of childhood food allergy prevalence and correction of unnecessary avoidance. *Allergy Asthma Immunol Res*. **2017**;9(4):322–328.
15. Murphy KW, Weaver C. *Janeway's immunobiology*. New York (NY): Garland Science; **2017**.
16. Stewart AJ, Devlin PM. The history of the smallpox vaccine. *J Infect*. **2006**;52(5):329–334.
17. Vallery-Radot PHJ. [Equine Asthma. Desensitization trials by repeated skin scarifications]. *Bull Soc Méd Hôp Paris*. **1921**;1921(45):1251–1260.
18. Blamoutier P, Blamoutier J, Guibert L. [Treatment of pollinosis with pollen extracts by the method of cutaneous quadrille ruling]. *La Presse medicale*. **1959**;67:2299–2301.
19. Eichenberger H, Storck H. Co-seasonal desensitization of pollinosis with the scarification-method of Blamoutier. *Acta Allergol*. **1966**;21(3):261–267.
20. Martin-DuPan R, Buser F, Neyroud M. [Treatment of pollen allergy using the cutaneous checker square method of Blamoutier and Guibert]. *Schweizerische Rundschau für Medizin Praxis = Revue suisse de médecine Praxis*. **1971**;60(44):1469–1472.
21. Senti G, Graf N, Haug S, et al. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. *J Allergy Clin Immunol*. **2009**;124(5):997–1002.
22. Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol*. **2012**;129(1):128–135.
23. Kalach N, Soulaïnes P, de Boissieu D, et al. A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow's milk allergy in children. *J Allergy Clin Immunol*. **2005**;116(6):1321–1326.
24. Soury D, Barratt G, Ah-Leung S, et al. Skin localization of cow's milk proteins delivered by a new ready-to-use atopy patch test. *Pharm Res*. **2005**;22(9):1530–1536.
25. Mondoulet L, Dioszeghy V, Ligouis M, et al. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. *Clin Exp Allergy*. **2010**;40(4):659–667.
26. Mondoulet L, Dioszeghy V, Vanoirbeek JA, et al. Epicutaneous immunotherapy using a new epicutaneous delivery system in mice sensitized to peanuts. *Int Arch Allergy Immunol*. **2011**;154(4):299–309.
27. Dioszeghy V, Mondoulet L, Dhelft V, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. *J Immunol (Baltimore, Md: 1950)*. **2011**;186(10):5629–5637.
28. Tahara Y, Kamiya N, Goto M. Solid-in-oil dispersion: a novel core technology for drug delivery systems. *Int J Pharm*. **2012**;438(1–2):249–257.
29. Kitaoka M, Wakabayashi R, Kamiya N, et al. Solid-in-oil nanodispersions for transdermal drug delivery systems. *Biotechnol J*. **2016**;11(11):1375–1385.
30. Kong Q, Kitaoka M, Wakabayashi R, et al. Transcutaneous immunotherapy of pollinosis using solid-in-oil nanodispersions loaded with T cell epitope peptides. *Int J Pharm*. **2017**;529(1–2):401–409.
31. Kumar MNK, Zhou C, Wu MX. Laser-facilitated epicutaneous immunotherapy to IgE-mediated allergy. *J Control Release*. **2016**;235:82–90.
32. Spina L, Weisskopf M, von Moos S, et al. Comparison of microneedles and adhesive-tape stripping in skin preparation for epicutaneous allergen delivery. *Int Arch Allergy Immunol*. **2015**;167(2):103–109.
33. Herve PL, Dhelft V, Plaquet C, et al. Epidermal micro-perforation potentiates the efficacy of epicutaneous vaccination. *J Control Release*. **2019**;298:12–26.
34. Mondoulet L, Dioszeghy V, Puteaux E, et al. Intact skin and not stripped skin is crucial for the safety and efficacy of peanut epicutaneous immunotherapy (EPIT) in mice. *Clin Transl Allergy*. **2012**;2(1):22.
- **This preclinical study showed that Viaskin® Peanut applied on stripped skin induces Th2 polarization and negatively affects outcome and safety.**
35. Du Toit G, Sampson HA, Plaut M, et al. Food allergy: update on prevention and tolerance. *J Allergy Clin Immunol*. **2018**;141(1):30–40.
36. Duca ED, Pavel AB, Dubin C, et al. Major differences in expression of inflammatory products in skin from different body sites of healthy individuals. *Exp Dermatol*. **2018**;27:29. *Conference: 3rd Inflammatory Skin Disease Summit-The Translational Revolution. Austria.*
37. Jawdat DM, Albert EJ, Rowden G, et al. IgE-mediated mast cell activation induces Langerhans cell migration in vivo. *J Immunol (Baltimore, Md: 1950)*. **2004**;173(8):5275–5282.
38. Dioszeghy V, Mondoulet L, Dhelft V, et al. The regulatory T cells induction by epicutaneous immunotherapy is sustained and mediates long-term protection from eosinophilic disorders in peanut-sensitized mice. *Clin Exp Allergy*. **2014**;44(6):867–881.
- **This preclinical mechanistic study uses anti-CD25 antibodies coupled with EPIT and adoptive transfer of Tregs to prove Tregs contribution to immunotherapy.**
39. Mondoulet L, Dioszeghy V, Busato F, et al. Gata3 hypermethylation and Foxp3 hypomethylation are associated with sustained protection and bystander effect following epicutaneous immunotherapy in peanut-sensitized mice. *Allergy*. **2019**;74(1):152–164.
- **This mechanistic study explores the epigenetic changes in Tregs induced by EPIT.**
40. Mondoulet L, Dioszeghy V, Ligouis M, et al. Epicutaneous immunotherapy compared with sublingual immunotherapy in mice sensitized to pollen (phleum pratense). *ISRN Allergy*. **2012**;375735:2012.
41. Jones SM, Sicherer SH, Burks AW, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol*. **2017**;139(4):1242–1252. e1249.
42. Dioszeghy V, Mondoulet L, Puteaux E, et al. Differences in phenotype, homing properties and suppressive activities of regulatory T cells induced by epicutaneous, oral or sublingual immunotherapy in mice sensitized to peanut. *Cell Mol Immunol*. **2017**;14(9):770–782.
43. Dioszeghy V, Mondoulet L, Laoubi L, et al. Antigen uptake by langerhans cells is required for the induction of regulatory t cells and the acquisition of tolerance during epicutaneous immunotherapy in OVA-sensitized mice. *Front Immunol*. **2018**;9:1951.
44. Tordesillas L, Mondoulet L, Blazquez AB, et al. Epicutaneous immunotherapy induces gastrointestinal LAP(+) regulatory T cells and prevents food-induced anaphylaxis. *J Allergy Clin Immunol*. **2017**;139(1):189–201. e184.
45. Dupont C, Bourrier T, de Blay F, et al. Peanut epicutaneous immunotherapy (EPIT) in peanut-allergic children: 18 months treatment in the arachid study. *J Allergy Clin Immunol*. **2014**;133(2):AB102.
- **This abstract reports an increase in the cumulative reactive dose after 18 months of EPIT in a pilot study.**
46. Sampson HA, Shreffler WG, Yang WH, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. *JAMA*. **2017**;318(18):1798–1809.
- **This RCT is the largest to date and assessed dose-responses to peanut-EPIT while showing safety and efficacy with the VP250.**
47. Fleischer DM, Lloyd Sussman G, Begin P, et al. Effect of epicutaneous immunotherapy on inducing peanut desensitization in

- peanut-allergic children: topline peanut epicutaneous immunotherapy efficacy and safety (PEPITES) randomized clinical trial results. *J Allergy Clin Immunol.* **2018**;141(2):AB410.
- **This abstract reports data from a phase 3 RCT of VP250 and shows a difference in response rate, an increase in cumulative reactive dose and a good safety profile.**
48. Fleischer DM, Greenhawt M, Sussman G. et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *JAMA.* **2019**;321(10):946–955.
 - **This phase 3 RCT enrolled the most patients and demonstrated a significant percentage difference in responders at 12 months (21.7%) but failed to meet the prespecified lower bound of the confidence interval set at 15%.**
 49. Berings M, Karaaslan C, Altunbulakli C, et al. Advances and highlights in allergen immunotherapy: on the way to sustained clinical and immunologic tolerance. *J Allergy Clin Immunol.* **2017**;140(5):1250–1267.
 50. Burks AW, Sampson HA, Plaut M, et al. Treatment for food allergy. *J Allergy Clin Immunol.* **2018**;141(1):1–9.
 51. Vickery BP, Lin J, Kulis M. et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. *J Allergy Clin Immunol.* **2013**;131(1):128–134. e121–e123.
 52. Jones SM, Agbotounou WK, Fleischer DM. et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: A phase 1 study using the Viaskin patch. *J Allergy Clin Immunol.* **2016**;137(4):1258–1261. e1210.
 - **This randomized, double-blind, placebo-controlled phase 1b study showed mostly local cutaneous reactions and established a good safety profile.**
 53. Shreffler WG, Nadeau KC, Leonard SA, et al. Efficacy and safety of long-term epicutaneous immunotherapy (EPIT) treatment of peanut allergy with viaskin peanut: results of the two-year extension of the vipes phase IIb clinical trial. *J Allergy Clin Immunol.* **2017**;139(2):AB377.
 - **This follow-up study showed that with a 36-month treatment with VP250, the eliciting dose increased over the 1000 mg threshold in a majority of participants.**
 54. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of allergy, asthma & immunology-European Academy of allergy and clinical immunology PRACTALL consensus report. *J Allergy Clin Immunol.* **2012**;130(6):1260–1274.
 55. Durham SR, Emminger W, Kapp A. et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol.* **2010**;125(1):131–138. e131–e137.
 56. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med.* **1999**;341(7):468–475.
 57. Jones SM, Burks AW, Keet C. et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol.* **2016**;137(4):1117–1127. e1110.
 58. Brown-Whitehorn T, de Blay F, Sampson H. Sustained unresponsiveness following long term epicutaneous immunotherapy (EPIT) with VIASKIN® Peanut: results of the OLFUS-VIPES phase IIb study. *Allergy.* **2018**;73(S105):1–903.
 59. Investigators PGoC, Vickery BP, Vereda A. et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med.* **2018**;379(21):1991–2001.
 60. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol.* **2017**;139(1):173–181 e178.
 61. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol.* **2011**;127(3):654–660.
 62. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol.* **2010**;126(1):83–91 e81.
 63. Wasserman RL, Factor JM, Baker JW, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. *J Allergy Clin Immunol Pract.* **2014**;2(1):91–96.
 64. Virkud YV, Burks AW, Steele PH. et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol.* **2017**;139(3):882–888. e885.
 65. Greenhawt M, Marsh R, Gilbert H, et al. Understanding caregiver goals, benefits, and acceptable risks of peanut allergy therapies. *Ann Allergy Asthma Immunol.* **2018**;121(5):575–579.
 66. Oka T, Rios EJ, Tsai M, et al. Rapid desensitization induces internalization of antigen-specific IgE on mouse mast cells. *J Allergy Clin Immunol.* **2013**;132(4):922–932. e921–e916.
 67. MacGlashan DW Jr., Savage JH, Wood RA, et al. Suppression of the basophil response to allergen during treatment with omalizumab is dependent on 2 competing factors. *J Allergy Clin Immunol.* **2012**;130(5):1130–1135. e1135.
 68. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol.* **2014**;133(2):500–510.
 69. Tabar AI, Arroabarren E, Echechipia S, et al. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol.* **2011**;127(1):57–63. 63e51–63e53.
 70. Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy.* **1996**;51(6):430–433.
 71. Golden DB, Kwiterovich KA, Kagey-Sobotka A, et al. Discontinuing venom immunotherapy: outcome after five years. *J Allergy Clin Immunol.* **1996**;97(2):579–587.
 72. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med.* **2012**;367(3):233–243.
 73. Fox AT, Turner P, Ewan PW. Towards excellence in paediatric allergy care for all. *Clin Exp Allergy.* **2019**;49(3):266–268.