Epicutaneous immunotherapy, 
a new treatment in life 
threatening food allergies

Lucie Mondoulet, PhD
Disclosure

Deputy CSO, DBV Technologies
The Ontogeny of EPIT®

• **Reference method** for immunotherapy: subcutaneous injection of aero-allergens
• **Food allergy**: subcutaneous injection impossible
• Further attempts with skin: deposition of aero-allergen on heavily scarified skin
• Development of Atopy Patch tests: skin reacts with allergen deposited on intact skin
• **Epicutaneous Immunotherapy**: therapeutic use of the immune reaction triggered by the allergen deposited on the skin
Viaskin®: allergen delivery into the intact skin
Viaskin® patch architecture

- Condensation chamber
- Perspiration and solubilisation
- Proteins/Allergens
  - Epidermis
  - Langerhans Cells
- Dermis
- Skin

Image: Visual representation of the Viaskin® patch architecture with labeled components.
Mechanism of antigen delivery with EPIT®

Fig. 1: Antigen delivery by Viaskin® from epidermis to draining lymph nodes for epicutaneous immunotherapy (EPIT)
DC: dendritic cell; LC: Langerhans cell

Fig. 2: Possible mechanism of action for epicutaneous immunotherapy (EPIT) to treat food allergy.
APC: antigen presenting cell; Baso: Basophil; DC: dendritic cell; Eos: Eosinophils; LC: Langerhans cell; MC: Mast cell; Teff: Effector T cell
Targeting of Langerhans cells: Antigen processing from the epidermis to the draining lymph nodes
Antigen Distribution: Intact Skin vs Stripped Skin

VIASKIN®-OVA-A488 on intact skin

VIASKIN®-OVA-A488 on stripped skin

Specific IgE

Specific IgG2a

EPIT® in non-clinical models
Interaction with the skin immune system
Multi-organ protection
In Vivo POC: Sensitized Mice Exposed to peanut regimen Inducing Esophageal Eosinophilia

**SENSITIZATION**
- peanuts + CT (6 ig for 6 weeks)
- n = 10

**IMMUNOTHERAPY**
- EPIT 100
- n = 10

**SAMPLING**
- Spleen (cell culture)
- Esophagus (histology, mRNA analysis)

**10-DAY-PEANUT-REGIMEN**
- Sham
- n = 10

**Naive**
- EPIT®

Expressed as eosinophils/mm²

- naive
- Sham
- EPIT


Efficacy of EPIT® in Eosinophilic Digestive Disorders

Stomachal samplings blindly analyzed by histology

EPIT® decreases eosinophilic infiltration in stomach

Mondoulet et al, 2013. EAACI meeting
Efficacy of EPIT® against the induction of anaphylaxis and sustainability of the protection

Tordesillas et al., 2015 submitted
Protection Against Esophageal Eosinophilia by Adoptively-Transferred EPIT® Tregs

Tregs TRANSFERT immediately after the end of treatment

SENSITIZATION TO PPE

Naive

Sham

EPIT®

Treg Sham

Treg EPIT

Tregs TRANSFERT 8 WEEKS after the end of treatment

SENSITIZATION TO PPE

Naive

Sham

EPIT®

Treg Sham

Treg EPIT

No transfer

Treg Sham

Treg EPIT

10-DAY-PEANUT-SUSTAINED EXPOSURE

Histology

Splenocytes culture

Dioszeghy et al, 2014. CEA, 44: 867-881
Protection of Esophageal Eosinophilia by Isolated EPIT®-Induced Tregs

Adoptive transfer of Tregs generated immediately or 8 weeks after EPIT® prevents from eosinophilic infiltration into esophagus
Phenotyping of EPIT®-Induced Tregs

Dioszeghy et al, 2014. CEA, 44: 867-881; Dioszeghy et al., submitted

Sampling:

- Spleen cells
  - Tregs analysis:
  - Homing receptor expression

- Lymph node cells
  - Tregs level
  - Homing receptor expression

SENSITIZATION peanuts + CT (6 ig for 6 weeks)

n = 8

D0

IMMUNOTHERAPY

EPIT®

OIT

SLIT

Sham

Naive

D43

D103
EPIT® induces a unique population of Tregs

Dioszeghy et al., 2014. CEA, 44: 867-881; Dioszeghy et al., submitted

- EPIT® induced Foxp3+ Tregs and not IL-10+ Tregs (Tr1)
- EPIT® induced naive and effector Tregs
- EPIT® increased the CTLA-4 expression on Tregs underlying the cell-contact mediation

Dioszeghy et al, 2014. CEA, 44: 867-881; Dioszeghy et al., submitted
Role of Epigenetic Modifications in the Sustainability of EPIT®-Induced Protection

Mondoulet et al, 2014. AAAAI meeting
**EPIT® Induces Sustained Epigenetic Modifications**

Mondoulet et al, 2015. EAACI meeting
Clinical data with EPIT®
Drug development

Feasibility: Milk EPIT® (Dupont et al. JACI 2010)

Safety and efficacy in children with peanut EPIT®: the Arachild study

Pharmaceutical development of peanut EPIT®:
• Phase I study, PEP01
• Phase IIb study, VIPES
• Phase IIb prolongation, OLFUS-VIPES
• Phase III: PEPITES
Viaskin® Peanut patch must be daily applied on the skin for 24 hours on the inter-scapular area of the back of the subjects or the inner side of both upper arms for the adults.
## Product in development in Food Allergy

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>INDICATION</th>
<th>COMMERCIAL RIGHTS</th>
<th>DEVELOPMENT STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viaskin Peanut</td>
<td>Peanut Allergy</td>
<td>DBV Worldwide</td>
<td>DISCOVERY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FDA Fast Track and Breakthrough Therapy</td>
</tr>
<tr>
<td>Viaskin Milk</td>
<td>Cow’s Milk Protein Allergy (CMPA)</td>
<td>DBV Worldwide</td>
<td>DISCOVERY</td>
</tr>
<tr>
<td>Viaskin Egg</td>
<td>Hen’s Egg</td>
<td>DBV Worldwide</td>
<td>DISCOVERY</td>
</tr>
</tbody>
</table>
Viaskin® Peanut Development Plan

Core Development Plan

Phase I

Phase IIb
VIPES
OLFUS-VIPES

Phase III

Registration

Academic collaborations

Phase Ila
Arachild

Phase II
CoFAR 6

Biomarkers and MoA

Proof of Concept
VIPES Phase IIb & OLFUS-VIPES: largest study ever in peanut allergy

**Study Design**

**Phase IIb**
- 221 patients, 22 centers, 5 countries*

**Food challenges:**
- Completed
- Ongoing
- Planned

**Study Population**
- Age: 6 -55 years old
- Peanut allergic patients (positive peanut-specific IgE and SPT)
- Highly sensitive subjects: DBPFC reactive dose at baseline (M0) \(\leq 300 \text{ mg peanut protein}\)

**Efficacy Endpoints**
- Primary endpoints: ‘responder rate’ defined as patients reaching \(\geq 1,000 \text{ mg reactive dose or } \geq 10 \times \text{ initial reactive dose at M12 DBPCFC}\)
- Main secondary endpoints: efficacy in patient populations (CRD, LS Mean, and other measures in children, adolescents, adults), change from baseline in sIgE, sIgG4

* US, Canada, The Netherlands, France, Poland
VIPES, Phase IIb
Primary Efficacy Endpoint Met

Response rate across doses after 12 months

<table>
<thead>
<tr>
<th>Dose</th>
<th>% of responders (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25.0% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>50 µg</td>
<td>45.3% (95% CI)</td>
<td>0.0292</td>
</tr>
<tr>
<td>100 µg</td>
<td>41.1% (95% CI)</td>
<td>0.1074</td>
</tr>
<tr>
<td>250 µg</td>
<td>50.0% (95% CI)</td>
<td>0.0108</td>
</tr>
</tbody>
</table>

All population

Response rate in children across doses after 12 months

<table>
<thead>
<tr>
<th>Dose</th>
<th>% of responders (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>19.4% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>50 µg</td>
<td>57.1% (95% CI)</td>
<td>0.0035</td>
</tr>
<tr>
<td>100 µg</td>
<td>46.2% (95% CI)</td>
<td>0.0453</td>
</tr>
<tr>
<td>250 µg</td>
<td>53.6% (95% CI)</td>
<td>0.0076</td>
</tr>
</tbody>
</table>

Children
Children
Increased Criteria Stringency Supports Strong Efficacy

Proportion of strong responders in children (both x10 and 1,000 mg increase in ED)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Responders</th>
<th># of Children with No Objective Symptoms during Highest Dose of M12 DBPCFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>50 µg</td>
<td>17.9%</td>
<td>0</td>
</tr>
<tr>
<td>100 µg</td>
<td>26.9%</td>
<td>1</td>
</tr>
<tr>
<td>250 µg</td>
<td>32.1%</td>
<td>4</td>
</tr>
</tbody>
</table>

p = 0.0005
p = 0.0196
p = 0.0025

# of children with no objective symptoms during highest dose of M12 DBPCFC
Children
Immunological Changes Confirm Treatment Effect

Peanut-specific IgE (kU/L)

Peanut-specific IgG4 (mg/L)

Viaskin Peanut 250 µg, n=28
Viaskin Peanut 100 µg, n=26
Viaskin Peanut 50 µg, n=28
Placebo, n=31
Perspectives

Early intervention during the « window of opportunity »
Role of EPIT®-induced Tregs in the protection against anaphylaxis to further allergens

SENSITIZATION To milk

Naive mice

No transfer

Treg EPIT

Sensitization to peanut (1 SC. + 1 ig.)

Treg EPIT

Treg Sham

Treg Sham

No transfer/no sensitization

IV challenge to Peanut

Body temperature mMCP1 in blood

Mondoulet et al, 2015, JACI, 135(6): 1546-1557
EPIT®-induced Tregs are responsible for protection against anaphylaxis to further allergens.

Drop in temperature

Plasma mMCP1

Mondoulet et al, 2015, JACI, 135(6): 1546-1557
EPIT® Opens a New Pathway for Treatment of Immune Diseases

- Epicutaneous pathway: **Safety of administration** (no passive passage into bloodstream) and **efficacy** (targeting of LCs)
- Continuous antigen exposure triggers sustained tolerization leading to a potential treatment for allergies: Induction of FoxP3+ **naive** and **effector Tregs** and deeper **epigenetic modifications**
- Validation of the **safety** and **efficacy of EPIT®** in the treatment of **peanut allergy** in a large Phase II clinical trial
- **Pivotal Phase III** in 260 children (4-11) expected to initiate **before** end of 2015
- Prevention of allergic disease evolution **by allowing an early intervention during the “window of opportunity”** in animal model