Can we prevent allergic diseases?

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Allergy - contributors

- GENES
- ENVIRONMENT
  (- life style)
  - Allergen exposure
  - Microbes
  - Viruses
  - Pollution
  - Dietary factors
Genetic spectrum of allergy

... in theory!

Healthy

Mild to moderate allergic constitution

Severe allergy

= manipulable

IL1RL1
STAT6
FOXP3
FLG
Others...
SECOND WAVE... in food allergy and eczema in the last 10 years

Mullins, MJA 2007; 186: 618-621 (Australian data)
GUSTO: Positive SPT at 18 and 36 months

n = 848
Food allergy in Singapore (in 2015)

- Infants: EGG
- Preschoolers: PEANUT
- Older children: SEAFOOD
Increasing diseases in children

- Obesity
- Allergic diseases
- Auto-immune diseases (diabetes, NS)
- Myopia – autism
- Kawasaki Disease
Causes?

- Hygiene Hypothesis

- Wrong Life Style Hypothesis

- Overprotection – overtreatment

- Paracetamol? Vaccinations? Other?
Allergen exposure

new concepts...
Allergen exposure!

Different routes

- eating, drinking
- inhaling – smelling
- transcutaneous (eczema)
- prenatal
- through breast milk

UNMEASURABLE
Classical preventive measures
- recent conclusions -

- Bacterial products may prevent eczema
- HA-milks may prevent CMA / eczema
- Early pet exposure may prevent allergy
- Early moisturizing may prevent eczema
- Early food exposure may prevent food allergy (Leap study)
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*
**Figure 2. Primary Outcome.**

The prevalence of peanut allergy at 60 months of age is shown among participants who had a negative result on the skin-prick test at baseline, among those who had a positive result at baseline, and in both groups combined, in the intention-to-treat analysis (Panel A) and the per-protocol analysis (Panel B). Among the 640 participants who underwent randomization, peanut-allergy status was determined by means of an oral food challenge in 617 (96.4%) and by means of a diagnostic algorithm in 11 (1.7%). Peanut allergy could not be evaluated with the use of the diagnostic algorithm in 2 participants (0.3%). A total of 10 participants (1.6%) voluntarily withdrew or were lost to follow-up. The worst-case imputation analysis (Panel C) assumes that participants with missing data in the peanut-consumption group would have been allergic to peanuts and that participants with missing data in the peanut-avoidance group would have been nonallergic. *P* values are based on chi-square analyses.
To prevent a food allergy: expose!
Prevention of respiratory allergy?

- Anti-viral (RSV – HRV)
- HDM allergy = consequence of early viral infections (?)
- Pregnancy: role of URTI during pregnancy
Early moisturizing prevents eczema

JACI October 2014 - 2 studies

Atopic dermatitis and skin disease

Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

Eric L. Simpson, MD, MCR, Joanne R. Chalmers, PhD, Jon M. Hanifin, MD, Kim S. Thomas, PhD, Michael J. Cork, PhD, FRCP, W. H. Irwin McLean, FRSE, FMedSci, Sara J. Brown, MRCP, MD, Zunqiu Chen, MS, Yiyi Chen, PhD, and Hywel C. Williams, DSc, FMedSci

Portland, Ore, and Nottingham, Sheffield, and Dundee, United Kingdom

Application of moisturizer to neonates prevents development of atopic dermatitis

Kenta Horimukai, MD, Kumiko Morita, MD, Masami Narita, MD, PhD, Mai Kondo, MD, Hiroshi Kitazawa, MD, PhD, Makoto Nozaki, MD, Yukiko Shigematsu, MD, Kazue Yoshida, MD, PhD, Hironori Niizeki, MD, PhD, Ken-ichi Motomura, MD, Haruhi Sago, MD, PhD, Tetsuya Takimoto, MD, PhD, Eisuke Inoue, PhD, Norio Kamemura, PhD, Hiroshi Kido, MD, PhD, Junzo Hisatsune, PhD, Motoyuki Sugai, DDS, PhD, Hiroyuki Murota, MD, PhD, Ichiro Katayama, MD, PhD, Takashi Sasaki, PhD, Masayuki Amagai, MD, PhD, Hideaki Morita, MD, PhD, Akio Matsuda, PhD, Kenji Matsumoto, MD, PhD, Hirohisa Saito, MD, PhD, and Yukihiro Ohya, MD, PhD

Tokyo, Tokushima, Hiroshima, and Osaka, Japan
Effects of nonpathogenic gram-negative bacterium *Vitreoscilla filiformis* lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study

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N = 75 – DBPC local treatment

Results: improvement in symptoms (SCORAD) improvement in TEWL
Idea for a new study!

Early moisturizing with probiotic-containing cream
Breastfeeding in the prevention of allergy

- Breast milk is the best
- Breast milk is the only living milk
- No other formula milk will ever be better for babies than breast milk

How to make it more anti-allergic?
A systematic review of the importance of milk TGF-β on immunological outcomes in the infant and young child

range of immunological outcomes in infancy and early childhood, such as wheeze, atopy, eczema and the immunoglobulin switch. Twelve human studies were included in the review and 67% showed a positive association with TGF-β1 or TGF-β2 demonstrating protection against allergy-related outcomes in infancy and early childhood. High
Supplementation with *Lactobacillus rhamnosus* or *Bifidobacterium lactis* probiotics in pregnancy increases cord blood interferon-γ and breast milk transforming growth factor-β and immunoglobulin A detection


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Primary prevention...

1. Early bacterial products *(start earlier?)*
   *(cfr Bifidobacteriaceae dynamics in pregnancy)*

2. Early moisturizer

3. Breast-feeding *(increase anti-allergic features)*

4. Early exposure to allergenic foods

**FUTURE: early IT (?)**
Early Immunotherapy

The future?

YES!
Allergen Immunotherapy

AR > AA > AD...

U. Wahn, Stallergenes Symposium, EAACI, June 2014
Allergen Immunotherapy

• Is effective (30% - 40%)
• But... *doesn’t cure*
• Changes immune direction (Th2 → Th1)
• Adjuvants are needed to induce a strong (and permanent Th1-booster / T-reg-booster)
Immunotherapy → change direction and go in the new direction!
Future of IT

ALLERGEN + ADJUVANTS = Th1 – Treg BOOST

- Bacterial antigens (toxins)
- Probiotics - prebiotics
- Helminthic proteins
**Immunotherapy: role of adjuvants**

*Escherichia coli* Heat-Labile Detoxified Enterotoxin Modulates Dendritic Cell Function and Attenuates Allergic Airway Inflammation

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**Abstract**

Various mutant forms of *Escherichia coli* heat-labile enterotoxin (LT) have been used as a mucosal adjuvant for vaccines, as it enhances immune responses to specific antigens including antigen-specific IgA antibodies when administrated intranasally or orally. We hypothesized that a detoxified mutant form of LT, LTS61K, could modulate dendritic cell (DC) function and alleviate allergen-induced airway inflammation. Two protocols, preventative and therapeutic, were used to evaluate the effects of LTS61K in a *Dermatophagoides pteronyssinus* (Der p)-sensitized and challenged murine model of asthma. LTS61K or Der p-primed bone marrow-derived dendritic cells (BMDCs) were also adoptively transferred into Der p-sensitized and challenged mice. Intranasal inoculations with LTS61K or LTS61K/Der p decreased allergen-induced airway inflammation and alleviated systemic Th2-type immune responses. Bronchoalveolar lavage fluid (BALF) and sera from LTS61K/Der p-treated mice also had higher concentrations of Der p-specific immunoglobulin (Ig) A than those of other groups. In vitro, BMDCs stimulated with Der p underwent cellular maturation and secreted proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)α. In contrast, Der p-stimulated BMDCs that were pretreated with LTS61K showed decreased IL-6 and TNFα production and were less mature. Intratracheal adoptive transfer of LTS61K- or LTS61K/Der p-primed BMDCs into Der p-sensitized mice reduced inflammatory cell infiltration and Th2-type chemokines in BALF and alleviated airway inflammation in treated mice. LTS61K influenced DC maturation and decreased inflammatory cytokine production. Moreover, LTS61K/Der p induced increased Der p-specific IgA production to decrease allergic Th2 cytokine responses and alleviated airway inflammation in Der p-sensitized mice. These results suggest that the immunomodulatory effects of LTS61K may have clinical applications for allergy and asthma treatment.
Administration of a probiotic with peanut oral immunotherapy: a randomized trial.

*Mimi Tang et al. JACI 2015*

- DBPC trial (2 groups) of the probiotic Lactobacillus rhamnosus CGMCC 1.3724 and peanut OIT, in 62 children → 56 reached the study’s end.

- Possible sustained unresponsiveness was achieved in 82.1% receiving PPOIT and 3.6% receiving placebo (P < .001) (i.e. 9 children need to be treated for 7 to achieve sustained unresponsiveness)

- Criticism: no OIT group
Fungal immunomodulatory proteins
(example: FIP-fve)

Golden Needle Mushroom
(Flammulina velutipes)
**Effect on RSV infections**

Alleviation of respiratory syncytial virus replication and inflammation by fungal immunomodulatory protein FIP-fve from *Flammulina velutipes*

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**ABSTRACT**

Respiratory syncytial virus (RSV) causes bronchiolitis in children followed by inflammation and asthma-like symptoms. The development of preventive therapy for this virus continues to pose a challenge. Fungal immunomodulatory proteins (FIPs) exhibit anti-inflammatory function. FIP-fve is an immunomodulatory protein isolated from *Flammulina velutipes*. To determine whether FIP-fve affects the infection or consequence of immunity of RSV, we investigated viral titers of RSV and inflammatory cytokine levels in vivo and in vitro. Oral FIP-fve decreased RSV-induced airway hyperresponsiveness (AHR), airway inflammation, and IL-6 expression in bronchoalveolar lavage fluid (BALF) of BALB/c mice. RSV replication and interleukin 6 (IL-6) levels in RSV-infected HEp-2 cells were compared before and after FIP-fve treatment. FIP-fve inhibited viral titers on plaque assay and Western blot, as well as inhibited RSV-stimulated expression of IL-6 on ELISA and RT-PCR. The results of this study suggested that FIP-fve decreases RSV replication, RSV-induced inflammation and respiratory pathogenesis. FIP-fve is a widely used, natural compound from *F. velutipes* that may be a safe agent for viral prevention and even therapy.

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SLIT in the future

50% of AD patients develop asthma later in life
SLIT as preventive treatment of allergy.

FUTURE

Pregnancy

Early infancy
Conclusions: In our model, maternal allergen exposures during pregnancy prevented later allergen-mediated sensitization and airway inflammation by allergen-specific tolerance induction in the offspring.
Interventions – overview.

• Early bacterial products
• Breast feeding (4 – 6 months)
• Weaning = should be tailored
• Early moisturizing (new creams?)
• New types of immunotherapy *(FUTURE)*

→ We need studies in our Asian children!
The tools are available

... we have to use them in the appropriate construction

*Primary prevention: we are looking at it and don’t see it?*
Conclusion

- Prevention becomes more and more a reality.

- Prevention should be safe and natural.