The SCIENCE behind the latest recommendations on prebiotics in allergy

20 October 2016 KUALA LUMPUR

Johan Garssen, PhD, MD
Professor “Immunopharmacology”
NCDS ARE THE LEADING CAUSE OF DEATH GLOBALLY

While global health resources are currently focused largely on infectious diseases, Non-Communicable Disease (NCDs) affect more people and are a “silent epidemic” in middle-income countries.

63% OF ALL GLOBAL DEATHS ARE CAUSED BY
NON-COMMUNICABLE DISEASES
- Cardiovascular
- Cancer
- Chronic Lung
- Diabetes

80% OF DEATH OCCUR IN LOW AND MIDDLE-INCOME COUNTRIES
WHO Goal “25 by 25”
25% reduction by 2025 in mortality from non-communicable disease (prevention + treatment).

- CVDs
- Diabetes/Obesity
- Cancer
- COPD/ASTHMA
- Autoimmunity
- IBD
- Brain/Behaviour disorders (autism/parkinsons/alzheimers/depression…)
- Allergies
- HIV (therapy related NCD)
- Ageing/Immunosenescence
- …
Why are NCDs so increasingly common?

No change in genes!!

- Altered environmental diversity (dysbiosis)?
- Altered lifestyle?
- Industrial technologies?
- Altered antigen/allergen exposure?
- Pollution?
- Dietary changes?
- Microbial exposure hypothesis?
- Change in infectious triggers?
- ???

Key role for immune system!!
The Immune System: Your Magic Doctor

A Guide to the Immune System for the Curious of All Ages

by Helen Garvy
Major tasks Immune System

- Defence against pathogens: bacteria, viruses, parasites, fungi
- Assistance in anti-cancer responses
- Removal of foreign / non-self compounds
- Inhibition self-reactive / auto-reactive responsiveness [Impairment of “auto-immunity” (SLE, MS, RA,…)]
- Inhibition “over-activity / allergy” (mucosal and systemic tolerance)
- Regulation metabolism (immuno-metabolism)
- Tissue repair
- Barrier regulation (gut, respiratory tract, brain, placenta, liver, thymus, kidney)
Immune System

Organs
- Thymus
- Spleen
- Lymph nodes
- Bone marrow

Cells
- Epithelial cell
- Granulocyte
- Macrophage / Monocyte
- Dendritic cell
- T Lymphocyte (Th1, Th2, Th3, Tr, ...)
- B Lymphocyte / Antibodies
- Natural Killer Cell
- Neurons, nerves

60-70% of “immune cells” localized in the gastro-intestinal tract
The GUT:
A Complex Neuro-Endocrine-Immune Organ

60 -70% of immune cells
100 million neurons

Dietary intervention as a tool for ‘immune’ regulation (inflammation management)?

Surface of approximately 300m²
100 trillion bacteria “Gut Microbiota”
Immune regulation in the gut
CROSS TALK

Figure 3: TLRs are differentially expressed by neurons and glial cells of the central, peripheral and enteric nervous system. TLRs: toll like receptors

Kraneveld, Nijkamp and Garssen 2009, EJP
Rietdijk, van Wezel, Garssen and Kraneveld 2016, Neuroimmunology Neuroinflammation
Th1 and Th2 activity as function of age

- Genes
- Hygiene
- Antibiotics
- C-section
- Microbiota
- Drugs
- Diets
- Stress
- Hormones
- Infections
- Cancer
- …
Inflammation management

Immune fitness
a healthy balance
Significant increase in immune related disorders:

- Allergies, Asthma
- Autoimmunities
- IBD
- ADHD/AUTISM
- Obesity
- Diabetes
- Metab. syndrome

Programmed early in life?!
Immune dysregulation and NCDs

- HIV
- Autoimmunities
- COPD
- Allergies
- Asthma
- Atopic eczema
- Coeliac disease
- Cystic Fibroses
- Cancer
- Elderly
- Infants

\[\text{Th1} \downarrow, \text{Th2} \uparrow, \text{Th1}/\text{Th2} \downarrow\]

\[\text{Th1} \downarrow \uparrow, \text{Th2} \downarrow \uparrow\]

\[\text{Th1} \uparrow\]

\[\text{Th2} \uparrow (\text{type I allergy})\]

\[\text{Th2} \uparrow\]

\[\text{Th2} \uparrow\]

\[\text{Th1} \uparrow\]

\[\text{Th1} \uparrow?\]

\[\text{Th1} \downarrow\]

\[\text{Th1} \downarrow\]

\[\text{Th1} \downarrow, \text{Th2} \uparrow\]
Immune disorders and NCDs

Hyper immune-responsiveness:
- Allergy
- Autoimmunity
- Chronic inflammatory diseases

Hypo immune-responsiveness:
- Infections
- Tumors/metastasis

Inflammation (management)

Global Health-WUN
Why are NCDs so increasingly common?

- Altered environmental diversity (dysbiosis)?
- Altered lifestyle?
- Industrial technologies?
- Altered antigen/allergen exposure?
- Pollution?
- Dietary changes?
- Microbial exposure hypothesis?
- Change in infectious triggers?
- ???
Increased pro-inflammatory diet?

Decreased microbial diversity?

Inhaled pollutants?

S. Prescott, Perth, Australia
PREVENTION OF NCDs

Early life: Setting the Right Course for Later Life

-9m to 24m
Critical window of opportunity to support healthy later life

CONCEPTION

TODDLERHOOD

ADULTHOOD

HEALTHY

DISEASE

Immune Programming

Altered growth and development
Stunting
Allergy
Obesity
Coronary heart disease
Diabetes
Cognitive decline

Immune Programming
Th1 and Th2 activity as function of age

Belinda Van’t Land, Günther Boehm, Johan Garssen:
Breast milk: components with immune modulating potential and their possible role in immune mediated disease resistance.

- Genes
- Hygiene
- Microbiota
- Drugs
- Diets
- Stress
- Hormones
- Infections
- Cancer
- …
Immune fitness/balance
Ability to Adapt

**Activation**
Pro-inflammation
Pathogenic bacteria
Viruses
Parasites

**Th1/Th2**
Th17

**Tregs**

**Activation**

**Oral** Tolerance
Anti-inflammation
Commensal bacteria (microbiota)
Food antigens
Environmental antigens
The protective effects of breastfeeding on chronic non-communicable diseases in adulthood: A review of evidence

The Breastfed Baby

Immune system.
Responds better to vaccinations. Human milk helps to mature immune system. Decreased risk of childhood cancer.

Skin.
Less allergic eczema in breastfed infants.

Joints and muscles.
Juvenile rheumatoid arthritis is less common in children who were breastfed.

Throat.
Children who are breastfed are less likely to require tonsillectomies.

Urine tract.
Fewer infections in breastfed infants.

Digestive system.
Less diarrhea, fewer gastrointestinal infections in babies who are breastfeeding. Six months or more of exclusive breastfeeding reduces risk of food allergies. Also, less risk of Crohn’s disease and ulcerative colitis in adulthood.

Eyes.
Visual acuity is higher in babies fed human milk.

Ears.
Breastfed babies get fewer ear infections.

Appendix.
Children with acute appendicitis are less likely to have been breastfed.

Kidneys.
With less salt and less protein, human milk is easier on a baby’s kidneys.

Respiratory system.
Breastfed babies have fewer and less severe upper respiratory infections, less wheezing, less pneumonia and less influenza.

Heart and circulatory system.
Breastfed children have lower cholesterol as adults. Heart rates are lower in breastfed infants.

Higher IQ.
Cholesterol and other types of fat in human milk support the growth of nerve tissue.

Endocrine system.
Reduced risk of getting diabetes.
COMPOSITION & BENEFITS OF HUMAN MILK

An Orchestra of Complex Functions in a Complex Matrix

- HMOS (Human Milk Oligosaccharides)
  - Microbiota
  - Immunity
  - Digestion

- Bacteria
  - Microbiota
  - Immunity
  - Digestion

- Fat / LCPUFA
  - Energy
  - Immunity
  - Brain

- Hormones
  - Growth
  - Mood
  - Immunity

- Vitamins
  - Growth
  - Immunity

- Minerals
  - Growth
  - Bone & Teeth
  - Blood

- Nucleotides
  - Growth
  - Immunity
  - Brain

- Proteins
  - Immunity
  - Signaling
  - Growth
  - Immunity

- Lactose
  - Energy

- Hydration
  - + 88% Water

- Living Cells
  - Immunity

Universiteit Utrecht
New nutritional concepts for immune development/inflammation management early in life

IMPACT FOR ALLERGIES

1. Microbiome management (Pro-, Pre-, Syn-, Post-biotics)
2. Epitopes
3. Antigens/Allergens
4. lcPUFAs
5. Exosomes/lipid vesicles
6. Amino-acids
7. Enzymes
8. Peptides
9. …
PRE-PRO-BIOTICS & PEDIATRICS ≈ 130 Y

1886
CHO in milks differ
Eschbach
Deniges

1900s
T Escherich
Microbiota
in BF infants

1920s
E Moro
H Tissier
Bifidus
in BF infants

1950s
First separation
of HMOS
Kuhn

1960s
3 groups
of HMOS
Kobata

1970s
Characterisation
of sc HMOS
Montreuil
Kobata

1980s
Egge
FAB MS

1990s
Kunz HPAEC
Thurl HPAEC
Stahl MALDI for OS
Stahl sc/lc HMOS
Thurl 4 groups

2000s
Morrow Anti-infection
Kunz Immunmodulation
Newburg Anti-infection
Martin Bifidus and Lb in HM
Sela Bifidus enzymes.....

1886
1900s
1920s
1950s
1960s
1970s
1980s
1990s
2000s

Adapted from:
Bode L, Review, Glycobiology vol. 22 no. 9 pp. 1147–1162, 2012

Scientific Knowledge Coevolution
with Clinical findings
Analytics & Nutritional concepts

© Nutricia Research
A PRE-biotic is non-digestible food ingredient that, when consumed in sufficient amounts, selectively stimulates the growth and/or activity of one or a limited number of microbes in the colon resulting in documented health benefits.

Examples:
- Galacto-Oligosaccharides
- Fructo-Oligosaccharides
- Inulin
- HMOS
- ...
DRY MATTER OF HUMAN MILK

adapted from:
Newburg DS, Neubauer SH: In: RG Jensen (ed):
Human milk composition Academic Press 1995; 273-349
HMOS: ESTIMATED > 1000 STRUCTURES

Immune dysregulation and NCDs

- HIV
- Autoimmunities
- COPD
- Allergies
- Asthma
- Atopic eczema
- Coeliac disease
- Cystic Fibroses
- Cancer
- Elderly
- Infants

Th1 ↓, Th2 ↑, Th1/Th2 ↓

Th1 ↓ ↑, Th2 ↓ ↑

Th1 ↑

Th2 ↑ (type I allergy)

Th2 ↑

Th1 ↑

Th1 ↑?

Th1 ↓

Th1 ↓

Th1 ↓, Th2 ↑
Experimental Setup

NOD/ShiLtJ mouse

Weeks

0  4  10  30

Monitoring diabetes incidence ONCE a week from week 6 to week 29

Control diet

HMOS diet  Control diet

!!!
HMOS reduces diabetes incidence in later life

**Diabetes development**

**Urine glucose score results**

- **Diabetes-free survival (%)**
  - **Control (n=19)**
  - **HMOS (n=20)**
  - \( p = 0.026 \)

- **Dietary intervention**

- **Normalized score (range 0-4)**
  - **Control HMOS**
  - \( p < 0.001 \)

Food intake & body weight were similar between experimental groups
What Are the Possible Mechanisms?

Genetics

T1D Immune System

Adaptive Innate

HMOS

Gut Microbiota
Reduced Overall Immune Hyperactivation
Induction of Immune fitness
What Are the Possible Mechanisms?

Genetics

Immune System

T1D

Adaptive

Innate

HMOS

Gut Microbiota

?
Time points of fecal sample collection

Dietary intervention start
4 weeks after dietary intervention
20 weeks after dietary intervention

- First point
- Second point
- End point

Weeks of follow-up

Diabetes-free survival (%)

- Control (n=19)
- HMOS (n=20)

p = 0.026
Changes of phylum distribution of fecal samples over time

Control diet

First point
- Verrucomicrobia: 13%
- Proteobacteria: 0%
- Firmicutes: 42%
- Bacteroidetes: 45%

Second point
- Verrucomicrobia: 17%
- Proteobacteria: 0%
- Firmicutes: 39%
- Bacteroidetes: 44%

End point
- Verrucomicrobia: 12%
- Proteobacteria: 0%
- Firmicutes: 46%
- Bacteroidetes: 42%

HMOS diet

First point
- Verrucomicrobia: 16%
- Proteobacteria: 0%
- Firmicutes: 43%
- Bacteroidetes: 41%

Second point
- Verrucomicrobia: 20%
- Proteobacteria: 0%
- Firmicutes: 44%
- Bacteroidetes: 38%

End point
- Verrucomicrobia: 13%
- Proteobacteria: 4%
- Firmicutes: 57%
- Bacteroidetes: 26%
The Ratio of Firmicutes/Bacteroidetes declined over time in the individuals who developed T1D, while the inverse pattern was observed in the healthy individuals.

Negative correlation between this ratio and the glucose levels in children with T1D.
Hypothetical interplay between gut microbiota and intestinal immune system by HMOS

- HMOS activate Tregs with anti-inflammatory properties.
- HMOS decrease antigen exposure to the mucosal system.
- HMOS beneficially induce tolerogenic DCs differentiation.
- HMOS increase mucin synthesis therefore maintain gut integrity and inhibit pathogen adhesion.
Conclusions

- Early HMOS diet suppresses autoimmune diabetes development in NOD mice later in life.

- Associated with milder insulitis, lower induction of Th1 cells, overall immune activation markers expression and down-regulation of serum IL-17.

- Maybe related to regulation of intestinal microbiota.

- HMOS in early life modulate T1D in later life: an example of immunological programming.

WIRM award 2016 DAVOS
NOT ALL PREBIOTICS ARE THE SAME

Cellular immunity (DTH)
Flu vaccination response (10^2-mm)

Unique oligosaccharides  PROMOTE HEALTHY  BACTERIA & pH

Bifidus

Change in stool pH

Log 10 of CFU/g wet faeces (median, IQR)

Reference range (IQR) of breastfed infants (n=15)

Group difference according to Mann-Whitney U-test:
* p<0.05 vs. 0.0, # vs. 0.4

Reference range (IQR) of breastfed infants (n=15)

Change in stool pH day 28 vs. day 0 (means ± SD)

* p<0.01 vs. 0.0, # vs. 0.4 according to ANOVA and Fisher post-hoc-test

CRITERIA FOR THE SELECTION OF PREBIOTICS

- Safe, Food-Grade Source
- Approved as Food or Food Ingredient
- Exact Characterization
- Chemical and Physical Properties
  (No Negative Effect Like: Complexing of Minerals, Vitamins and Fats)
- Physiologic Parameters Like: Digestibility, Taste & Texture
- Clinical Evidence for Prebiotic Effect

Prebiotic concept for infant nutrition.
EFFECTS ON STOOL CHARACTERISTICS

<table>
<thead>
<tr>
<th>Author</th>
<th>Age group</th>
<th>Dose</th>
<th>n</th>
<th>Outcome</th>
<th>Result in scGOS/LcFOS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costalos 2008</td>
<td>Term</td>
<td>0.4 g/100 mL</td>
<td>140 (2 groups)</td>
<td>Stool frequency</td>
<td>Statistically significant increase after 10 wk of intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool consistency</td>
<td>Statistically significant softer stools after 10 wk of intervention</td>
</tr>
<tr>
<td>Moro 2002</td>
<td>Term</td>
<td>0.4/0.8 g/100 mL</td>
<td>90 (3 groups)</td>
<td>Stool frequency</td>
<td>Statistically significant increase after 4 wk of intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool consistency</td>
<td>Statistically significant softer stools after 4 wk of intervention</td>
</tr>
<tr>
<td>Veereman 2011</td>
<td>Term</td>
<td>0.8 g/100 mL</td>
<td>76 (5 groups)</td>
<td>Stool frequency</td>
<td>No statistically significant differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool consistency</td>
<td>Statistically significant softer stools after 2 and 4 wk of intervention</td>
</tr>
<tr>
<td>Bisceglia 2009</td>
<td>Term</td>
<td>0.8 g/100 mL</td>
<td>76 (2 groups)</td>
<td>Stool frequency</td>
<td>Statistically significant increase throughout 4 wk of intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool consistency</td>
<td>Not measured</td>
</tr>
<tr>
<td>Boehm 2002</td>
<td>Preterm</td>
<td>1.0 g/100 mL</td>
<td>42 (3 groups)</td>
<td>Stool frequency</td>
<td>Statistically significant increase after 4 wk of intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool consistency</td>
<td>Statistically significant softer stools after 4 wk of intervention</td>
</tr>
<tr>
<td>Mihatsch 2006</td>
<td>Preterm</td>
<td>1.0 g/100 mL</td>
<td>20 (2 groups)</td>
<td>Stool frequency</td>
<td>No statistically significant differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stool consistency</td>
<td>Results not provided</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viscosity</td>
<td>Statistically significant lower viscosity after 2 wk of intervention</td>
</tr>
<tr>
<td>Modi 2010</td>
<td>Preterm</td>
<td>0.8 g/100 mL</td>
<td>150 (2 groups)</td>
<td>Stool frequency</td>
<td>No statistically significant differences</td>
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<td></td>
<td></td>
<td>Stool consistency</td>
<td>No statistically significant differences</td>
</tr>
</tbody>
</table>

scGOS/LcFOS: Short chain galacto-oligosaccharides and long-chain fructo-oligosaccharides.

Scholtens, PAMJ, Goossens DAM, Staiano A
Prebiotic Effect: Established Scientific Fact

FREE ACCESS
Review on Prebiotics by ILSI-Europe Task Force

GRAS Notice (GRN) No.477
http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticelInventory/default.htm

COMMISSION DIRECTIVE 2006/141/EC 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC
...the WAO guideline panel suggests using prebiotic supplementation in not-exclusively breastfed infants ....
Potential Mechanisms for Immune Fitness by unique oligosaccharides

Vos AP, M’rabet L, Stahl B, Boehm G, Garssen J.
Critical Reviews. Immunology 2007
What about clinical relevance/health benefits??

What about NCDs??
Immune dysregulation and NCDs

- HIV
- COPD
- Allergies
- Asthma
- Atopic eczema
- Coeliac disease
- Cystic Fibroses
- Cancer
- Elderly
- Infants

A model for NCDs?

TH1↓, TH2↑, TH1/TH2↓

TH1↑

TH2↑ (type I allergy)

TH2↑

TH1↑

TH1↑?

TH1↓

TH1↓, TH2↑
Altered gut microbiota in HIV infected individuals

Prebiotic Oligo’s improve the Gut Microbiota of HIV infected Adults

Stimulation of bifidobacteria

Expressed as median (range)

Reduction of C. histolyticum cluster

Expressed as mean ± se
Changes from baseline in activated CD4+ T cells (% CD4+CD25+) during the 52-week intervention period in the intention-to-treat population from a BITE pilot study (*P = .036, change from baseline).

Immune dysregulation and NCDs

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Th1 ↓, Th2 ↑, Th1/Th2 ↓
Th1 ↓↑ , Th2 ↓↑
Th1 ↑
Th2 ↑ (type I allergy)
Th2 ↑
Th1 ↑
Th1 ↑?
Th1 ↓
Th1 ↓
Th1 ↓, Th2 ↑
Protection Against Allergy-prevention Atopic Dermatitis (infants at risk)

After 6 months

- scGOS/lcFOS (n=102): 9.8%
- Control (n=104): 23.1%

P = 0.014 (Fisher test)

After 24 months

- scGOS/lcFOS (n=66): 13.6%
- Control (n=68): 27.9%

P < 0.05 (Fisher test)

Significant decrease in biomarkers for allergy (serum IgE, IgG1 and CMA IgG1 in High-Risk Infants at 6 Months) (first preliminary indications for tolerance induction-IgG4/Treg)

Hoffen et al., 2009 Allergy
Plasma cells

IgE

IgG

IgLC

Mast cell

F_{c\varepsilon}RI/RII

Fc_{\gamma}RI

Allergen challenge: cross-linking surface-bound Ig

Allergic response

Inflammation response

- Anti-histamines
- Leukotriene antagonists
- NSAID’s
- Corticosteroids
- Anti-cytokines

Redegeld et al., Curr. Opin. Invest. Drugs, 2009
Redegeld et al., Nature Med 2002
Schouten et al. JACI 2010
atopic dermatitis: higher levels of Ig-FLC in serum

oligosaccharides down-regulates Ig-FLC in infants at risk for allergy
Early dietary intervention with a mixture of prebiotic oligosaccharides reduce the incidence of allergic manifestations during the first 2 years of life

Arslanoglu et al., 2008, J. of Nutr. 138:1091-1095
Protection Against Allergy
5 year follow-up

Arslanoglu S, et al 2011
Oligosaccharides reduce incidence of Atopic Dermatitis in infants not at risk (prevention)

Gruber et al. JACI 2010

Cumulative incidence of atopic dermatitis

- Placebo
- scGOS/LcFOS/AOS
- Breastfed

Age (weeks)

p<0.0469
Study formula was provided from the moment the mother decided to stop or supplement breastfeeding. Part of the original study population (38%) was followed up until 3-5 years of age.

Boyle, Tang et al. Allergy 2016
Beneficial effect of HP + prebiotics related to the timing of introduction of weaning foods and long-term allergy development.

18 month eczema development

5 year allergic manifestations in subgroup not weaned <18 weeks

*Boyle, Tang et al. Allergy 2016*

*Manuscript in preparation*
Indication of immune-modulatory capacities of HP + prebiotics

long-term reduction of sensitization marker

Boyle, Tang et al. Allergy 2016, manuscript in preparation

Ovalbumin-specific immunoglobulins A and G levels at age 2 years are associated with the occurrence of atopic disorders

A. K. Kukkonen1, E. M. Savička2, T. Haashtela1, E. Savilahti3 and M. Kuitunen1

1Skin and Allergy Hospital, University of Helsinki, Helsinki, Finland and 2Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

Relation between IgG antibodies to foods and IgE antibodies to milk, egg, cat, dog and/or mite in a cross-sectional study

P. E. D. Eysink*, M. H. De Jong†, P. J. E. Bindels‡, V. T. M. Scharp-Van der Linden†, C. J. De Groot†, S. O. Stapel‡ and R. C. Alberse‡

*Department of General Practice, Division Public Health, Academic Medical Center, University of Amsterdam, †Department of Pediatrics, Emma Children’s Hospital, Academic Medical Center, University of Amsterdam and, ‡Department of Allergy, Central Laboratory of the Blood Transfusion Service of the Netherlands Red Cross, The Netherlands
Biomarkers for “immune tolerance-immune fitness” upregulated

Boyle, Tang et al. Allergy 2016
A **PRO-**biotic is a live microorganism which when administered in adequate amounts confer a health benefit on the host (WHO/FAO 2002)

**Examples:**
- Lactobacillus
- Bifidobacterium
- ...
Isolation of Bifidobacteria from Breast Milk and Assessment of the Bifidobacterial Population by PCR-Denaturing Gradient Gel Electrophoresis and Quantitative Real-Time PCR

Rocio Martin,1, Esther Jimenez,2 Hans Heilig,1 Leonides Fernandez,2 Maria L. Marin,2 Erwin G. Zoetendal,1 and Juan M. Rodriguez2,*

FIG. 1. Relative abundances (percentages) of the different bifidobacterial species isolated from infant feces (A) and breast milk samples (B) or detected in the clone library obtained from breast milk samples (C). a, B. adolescentis; b, B. longum; c, B. bifidum; d, B. breve; e, B. pseudocatenulatum; f, B. dentium; g, Bifidobacterium spp.
Probiotics: strain selection is essential!! (new concepts for allergic inflammation)

Total number of cells in BALF (x 10^4)

- Lymphocytes
- Neutrophils
- Macrophages
- Eosinophils

A synbiotics is the combination of both pro- and prebiotics

Example:

😊 Galacto-Oligosaccharides
😊 Fructo-Oligosaccharides
😊 B breve M16V

😊 Fructo-Oligosaccharides
😊 B breve M16V
Synbiotics prevent acute response for cow’s milk allergy in vivo (preclinical studies)

Synbiotics reduce acute allergic reaction

Synbiotic effect correlated with increased galectin-9

Schouten et al. J Nutr 2009

de Kivit et al. Allergy 2012
Non-digestible oligosaccharides + B breve M16V reduce Asthma Markers in Adults (treatment)

Van de Pol et al, Allergy, 2011
Non-digestible oligosaccharides + B breve M16 V reduce atopic dermatitis in children (treatment)

Table 5. Effect of synbiotics on the severity of IgE-associated AD

<table>
<thead>
<tr>
<th></th>
<th>Synbiotics (n = 24)</th>
<th>Placebo (n = 24)</th>
<th>Difference Syn vs. plac (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORAD change week 4 – baseline, EMM±SE</td>
<td>$-5.2 \pm 2.1$</td>
<td>$-3.5 \pm 2.2$</td>
<td>$-1.7 \ (-7.9 \text{ to } 4.4)$</td>
<td>0.57</td>
</tr>
<tr>
<td>SCORAD change week 8 – baseline, EMM±SE</td>
<td>$-13.7 \pm 2.2$</td>
<td>$-9.3 \pm 2.3$</td>
<td>$-4.4 \ (-10.6 \text{ to } 2.0)$</td>
<td>0.17</td>
</tr>
<tr>
<td>SCORAD change week 12 – baseline, EMM±SE</td>
<td>$-18.1 \pm 1.6$</td>
<td>$-13.5 \pm 1.6$</td>
<td>$-4.6 \ (-9.1 \text{ to } -0.1)$</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Univariate analysis of variance with cofactors treatment, topical steroid use at baseline and previous use of hydrolysate formula and covariate SCORAD score at baseline.
EMM, estimated marginal mean; AD, atopic dermatitis; SCORAD, SCORing Atopic Dermatitis; Syn, synbiotics; Plac, placebo.

Van de Aa et al, Clin Exp All, 2010
Synbiotics increase serum galectin-9 in infants with atopic dermatitis (*van der Aa study*)

*de Kivit et al. Allergy 2012*
At risk for Asthma/Respiratory allergy?
Non-digestible oligosaccharides + B breve M16V reduce respiratory symptoms in children (sec. prevention)

Noisy breathing apart from colds

Frequent wheezing

\[ p = 0.001 \]

Lower Prevalence of Asthma like Symptoms in the Synbiotic group at 1 year Follow Up

Less asthma medication

Van de Aa et al, Allergy, 2011
PREVENTION of NCDs
Early life: Setting the Right Course for Later Life

-9 months Birth +48 months

Disease
Health

Programming
Imprinting
Dietary intervention
Prebiotics

Allergy
Obesity
Coronary Heart Disease
Diabetes
Autoimmunity
NCDs

Healthy Life
Role in metabolic disorders/diabetes/syndrome X/obesity: immunometabolism

Role in cachexia/sarcopenia

Role in neurological disorders: Autism, Alzheimer, Depression, Hyperactivity Syndrome, ...

Hyper immune-responsiveness:
- Allergy
- Autoimmunity
- Chronic inflammatory diseases

Hypo immune-responsiveness:
- Infections
- Tumors/metastasis

Immune disorders and NCDs

Global Health-WUN

IMMUNE FITNESS
FIT FOR LIFE
New nutritional concepts for allergy management

1. **Microbiome management (Pro-, Pre-, Syn-, Post-biotics)**
2. Epitopes
3. Antigens/Allergens
4. lCPUFAs
5. Exosomes/lipid vesicles
6. Amino-acids
7. Enzymes
8. Peptides
9. …
MAJOR CONCLUSIONS

1. Selective prebiotics inhibit the onset and severity of allergy related disorders early and later in life. PROGRAMMING.
2. Specific prebiotics induce immune biomarkers for immune fitness and tolerance.
3. Underlying mechanisms indicate a role for gut integrity, microbiome diversity, immune tolerance, Tregs, and galectin 9
Acknowledgements/Conflicts of interest

Immune modulatory mechanisms, allergy, inflammation, obesity, autoimmunity, infections, NCDs, ...

Ongoing collaborations

Grants & industry

PYRAMID OF EVIDENCE

CFA
Center food allergy

Ministry VWA

Nederlandse Vereniging Voor Immunologie