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CENTRE FOR SPECIALISED NUTRITION

Universiteit Utrecht
UIPS

Immunopharmacology of non-digestible carbohydrates: a breakthrough for clinical nutrition?

Prof. Dr. Johan Garssen

Zurich
March 20th 2009

Bringing Science to Life

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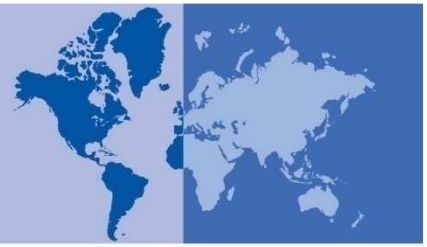

60 - 70% of the current drugs have their origin in edible plants, fruits, vegetables, herbals or ferments

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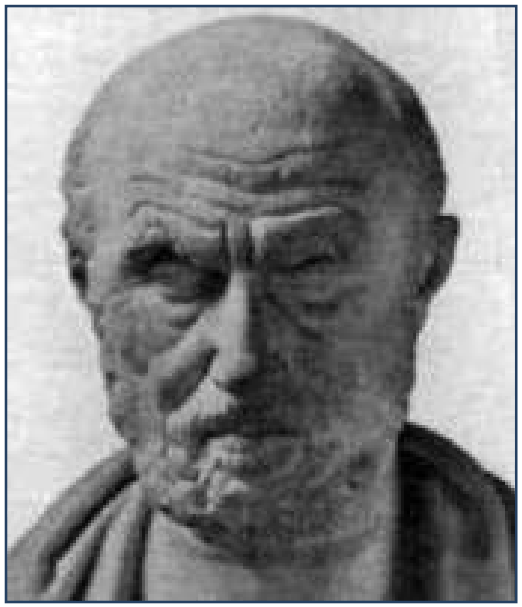
"Let medicine be thy food, and food be thy medicine."

Hippocrates of Cos, Greece
460-377 B.C.



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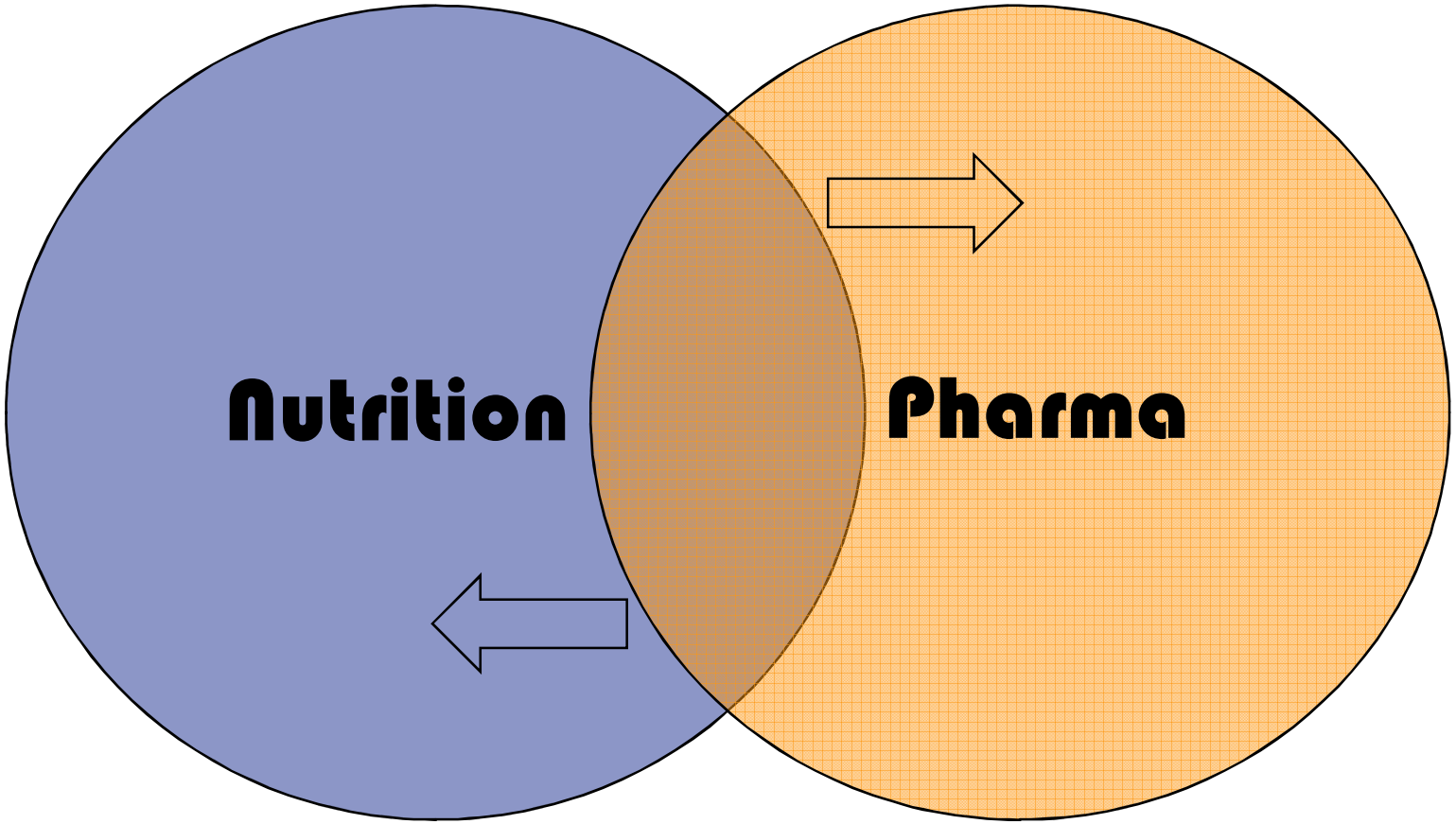
Overlap between Nutrition and Pharma



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Health claims/Immune claims/Reimbursement

- What do we need?
  - Reliable and high quality science
  - Regulation/Guidelines (FDA / medical food/ EFSA / FSMP)
  - Laws and inspection

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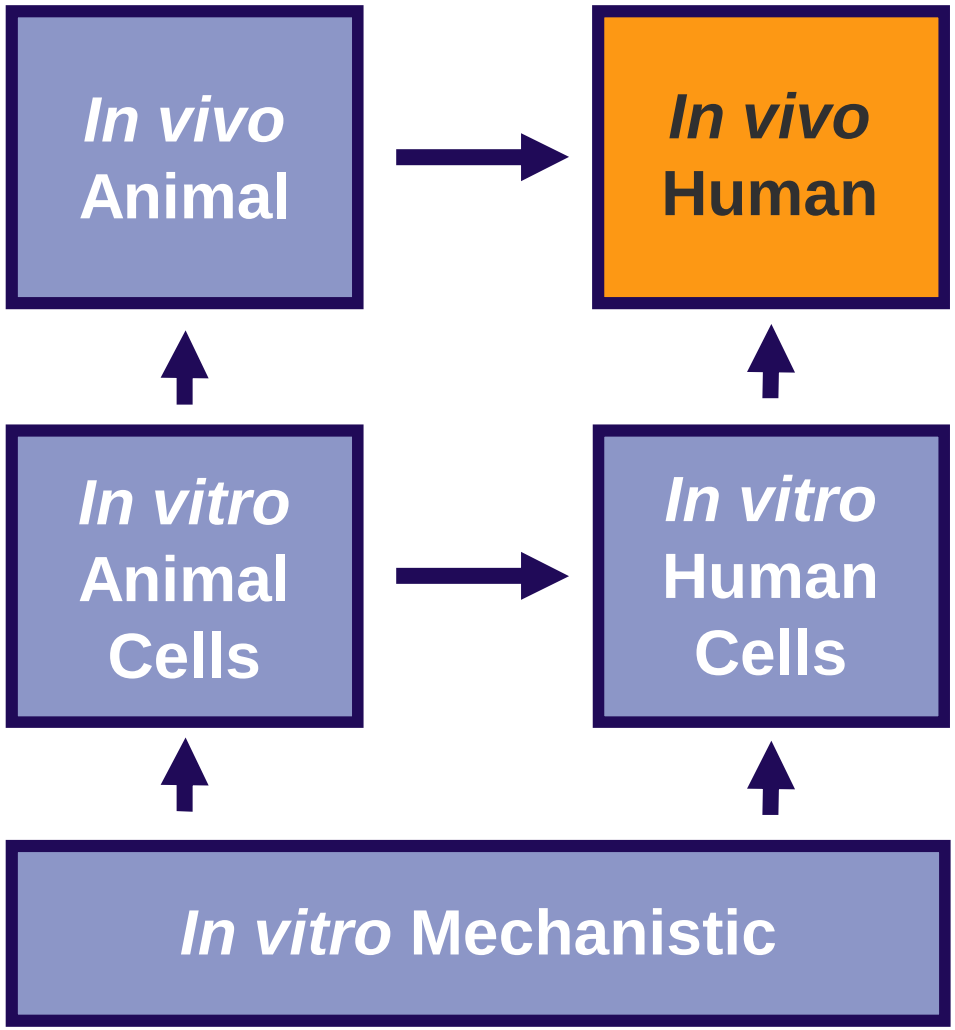
Translational Research – WHO / ILSI / FDA / TIP



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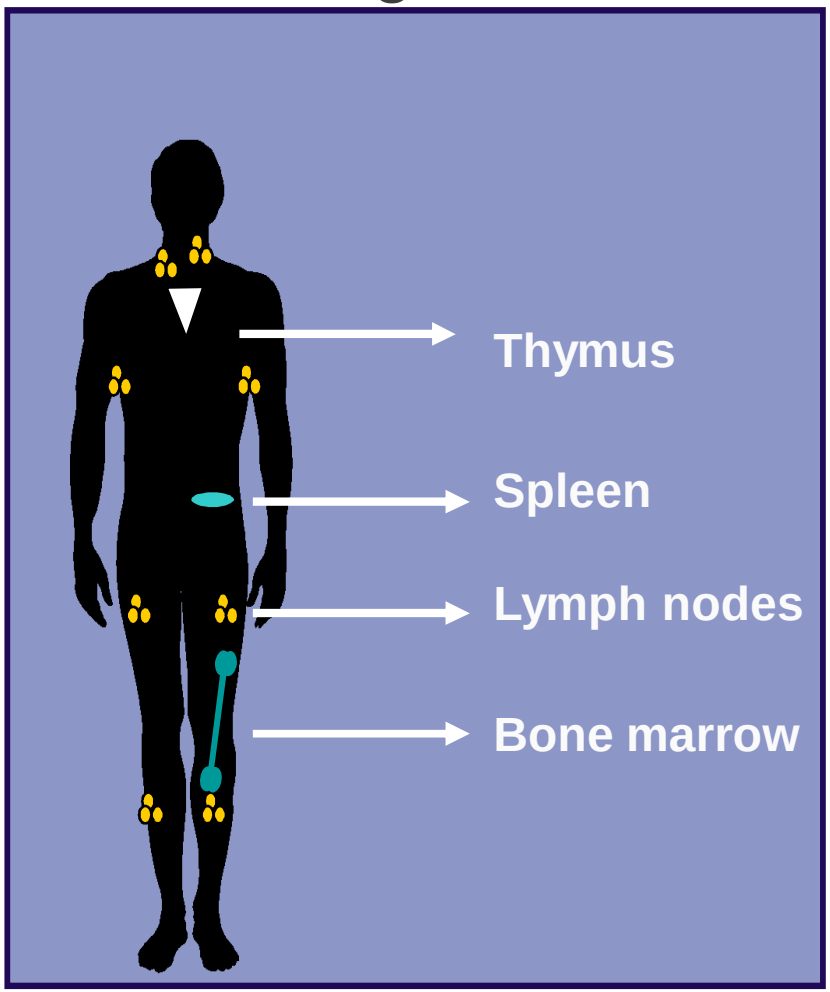
Organs



Cells

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

60 – 70 % of immune cells in the gastro- intestinal tract !!

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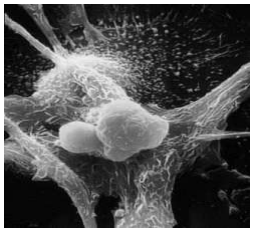
Immune system

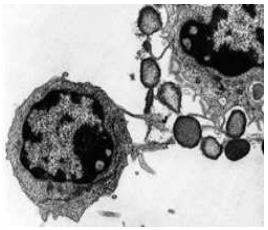
Innate immune system
1st line of defense (Non-specific)

Adaptive immune system
2nd line of defense (Specific)

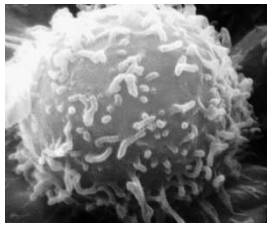
Cells



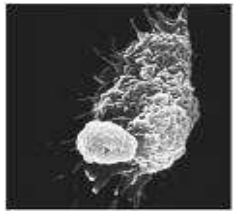
Macrophage



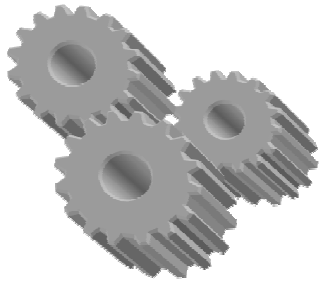
Natural Killer (NK) cell



T lymphocyte



B lymphocyte



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Immune system

Hyper immune- responsiveness:

Allergy

Autoimmunity

Chronic inflammatory diseases

Hypo immune- responsiveness:

Infections

Tumors/metastasis

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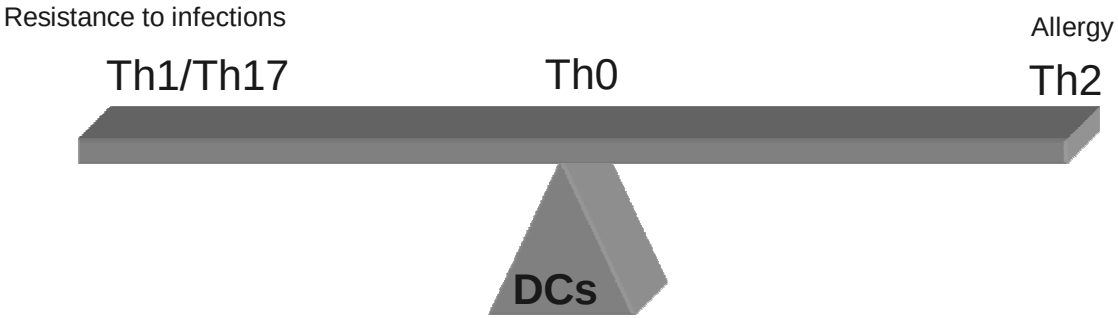
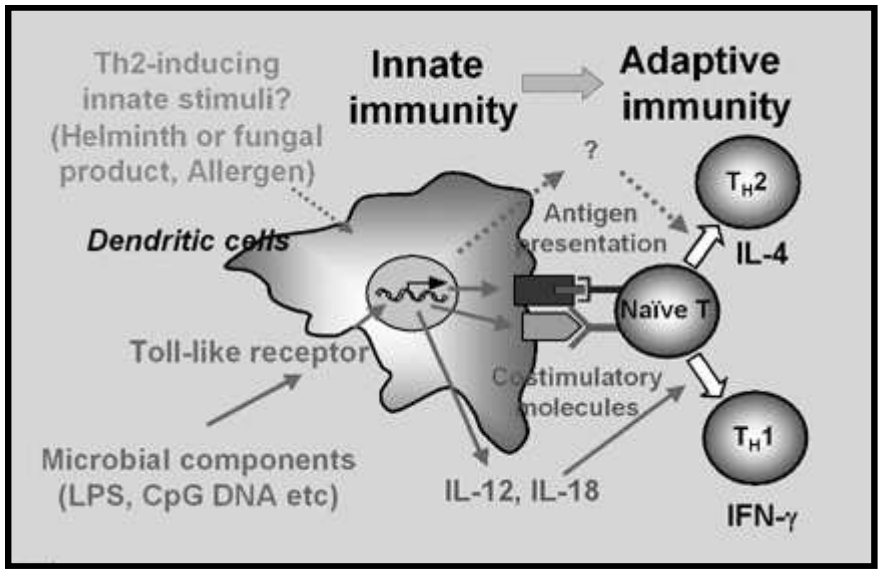
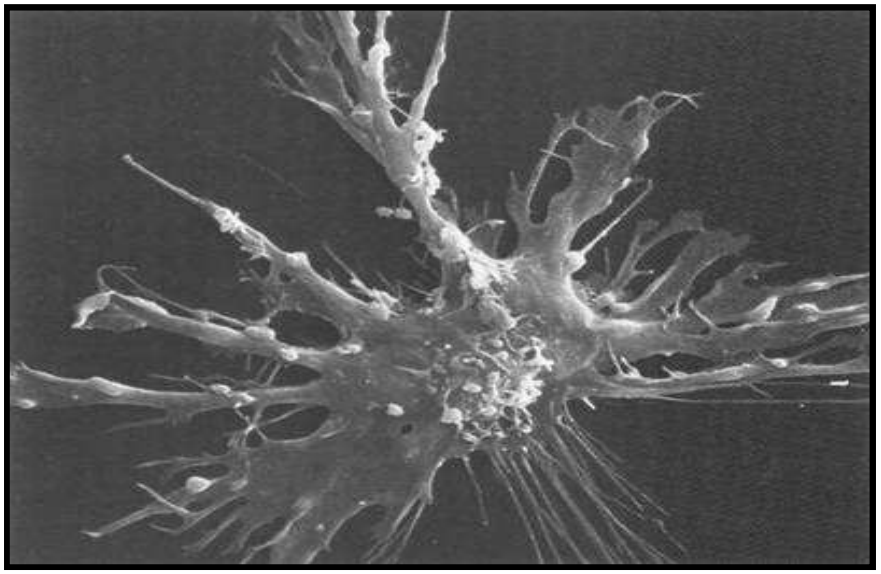
Immune regulation







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Immune regulation

Cellular immunity:

Th1:	IL-2, IL-3, IL-12, IFN-γ, IL-7, IL-15, IL-23
Th2:	IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13
Tr/Th3:	IL-10, TGF-β1 (inhibitory cytokines)

Humoral Immunity:

Th1:	IgG1, IgG3
Th2:	IgG2, IgE
Tr/Th3:	IgG4

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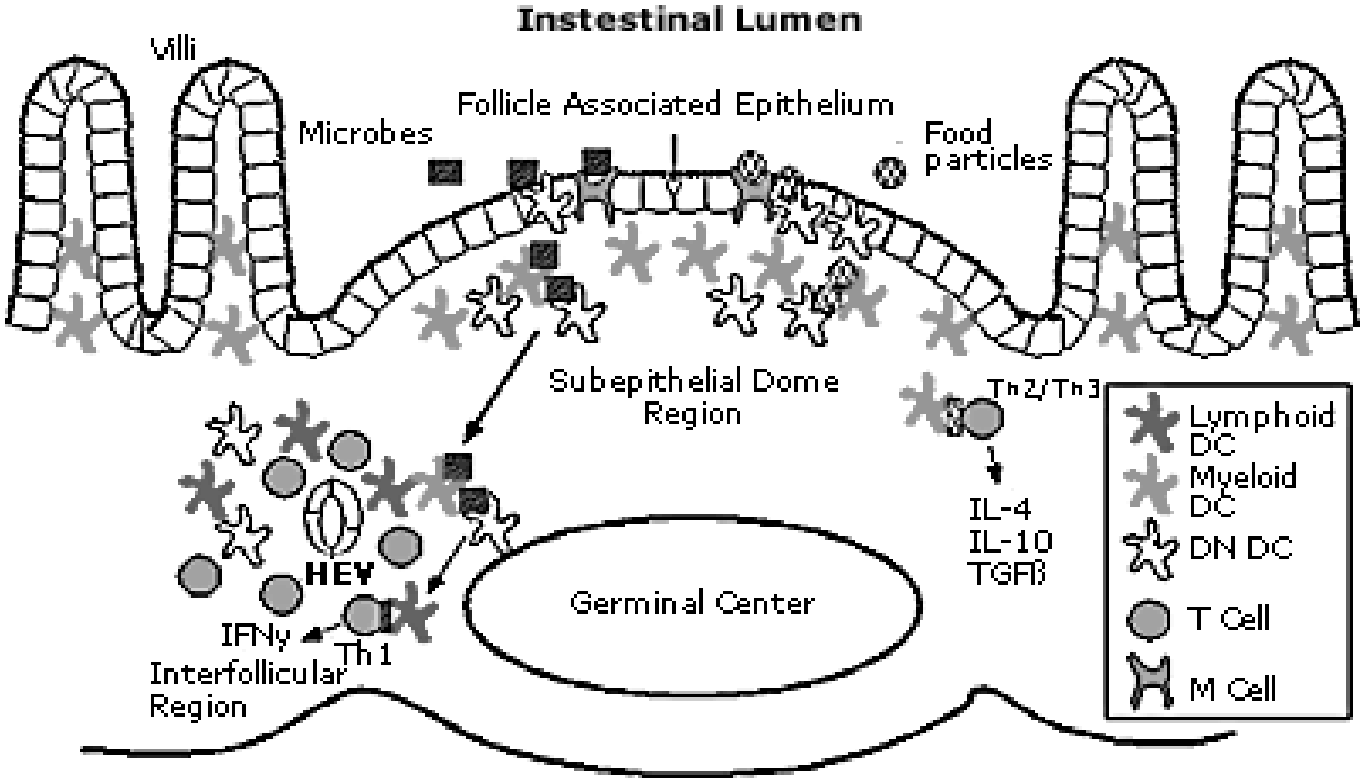
Immune regulation in the intestine:
a bridge to systemic immunity



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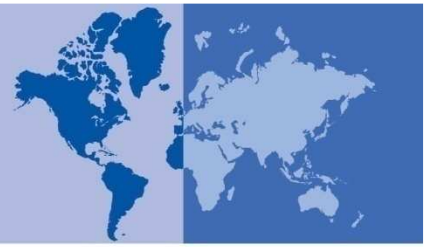

Immune disorders

HIV	**Th1 ↓, Th2 ↑, Th1/Th2 ↓**
COPD	**Th1 ↑**
Allergies	**Th2 ↑ (type I allergy)**
Asthma	**Th2 ↑**
Atopic eczema	**Th2 ↑**
Coeliac disease	**Th1 ↑**
Cystic Fibroses	**Th1 ↑?**
Cancer	**Th1 ↓**
Elderly	**Th1 ↓**
Infants	**Th1 ↓, Th2 ↑**

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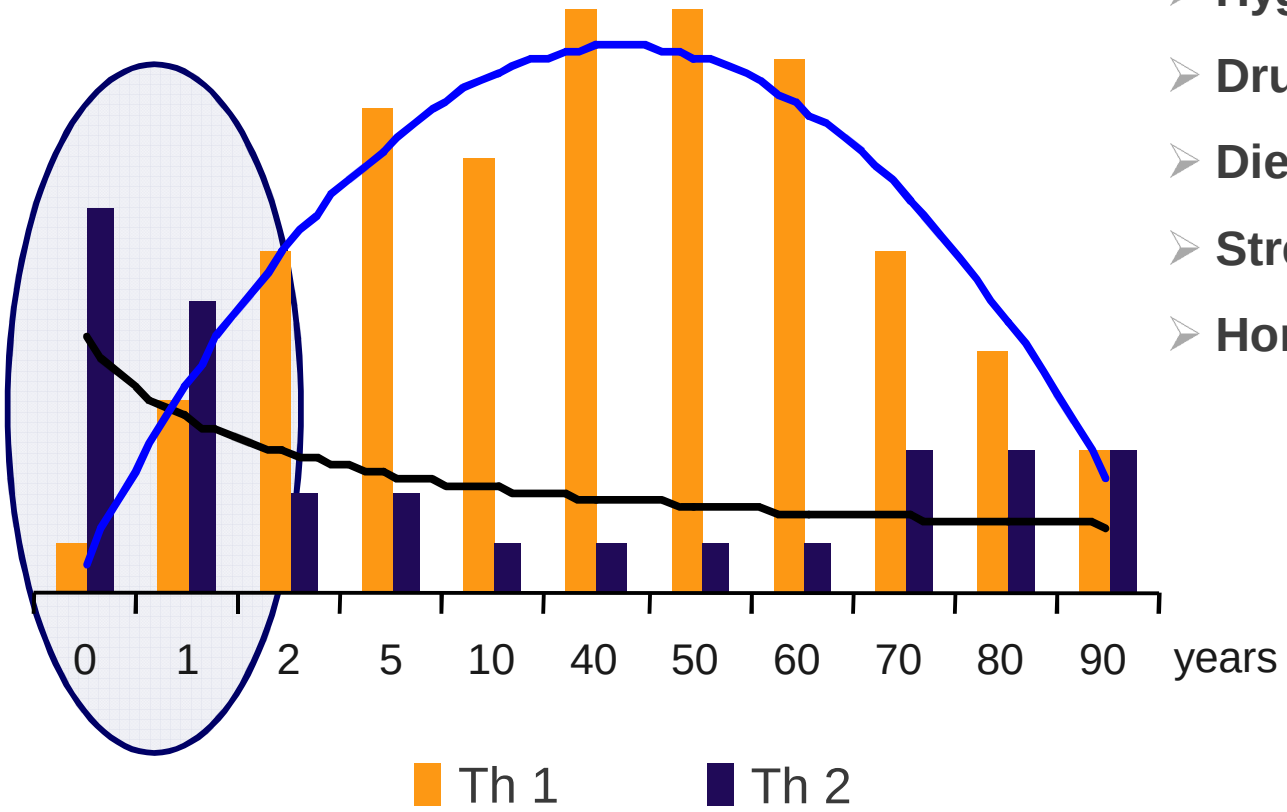
Th1 and Th2 activity as a function of age

- Genes
- Hygiene
- Drugs
- Diets
- Stress
- Hormones



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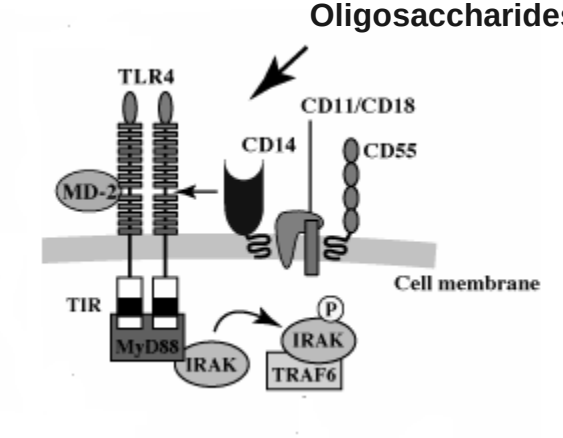
Compounds with immunological properties in human milk

Anti-microbial compounds
Immunoglobiuines: sIgA, SIgG, SIgM
Lactoferrin, lactoferrin B and H
Lysozyme
Lactoperoxidase
Nucleotide-hydrolizing Antibodies
κ-casein and α-lactalbumin
Haptocorrin
Mucins
Lactadherin
Free secretory component
Oligosaccharides and pre-biotics
Fatty acids
Maternal leukocytes and Cytokines
sCD14
Complement and complement receptors
β-defensin-1
Toll-like receptors
Bifidus factor
Tolerance/priming compounds
Cytokines: Il10 and TGFβ
Anti-idiotypic antibodies

Immune development compounds
Macrophages
Neutrophils
Lymphocytes
Cytokines
Growth factors
Hormones
Milk peptides
Long-chain polyunsaturated fatty acids
Nucleotides
Adhesion molecules

Anti-inflammatory compounds
Cytokines: Il-10 and TGFβ
Il-1 receptor anatagonist
TNFα and Il-6 receptors
sCD14
Adhesion molecules
Long-chain polyunsaturated fatty acids
Hormones and growth factors
Osteoprotegerin
Long-chain polyunsaturated fatty acids
Hormones and growth factors

Oligosaccharides



Field J Nutr 2005

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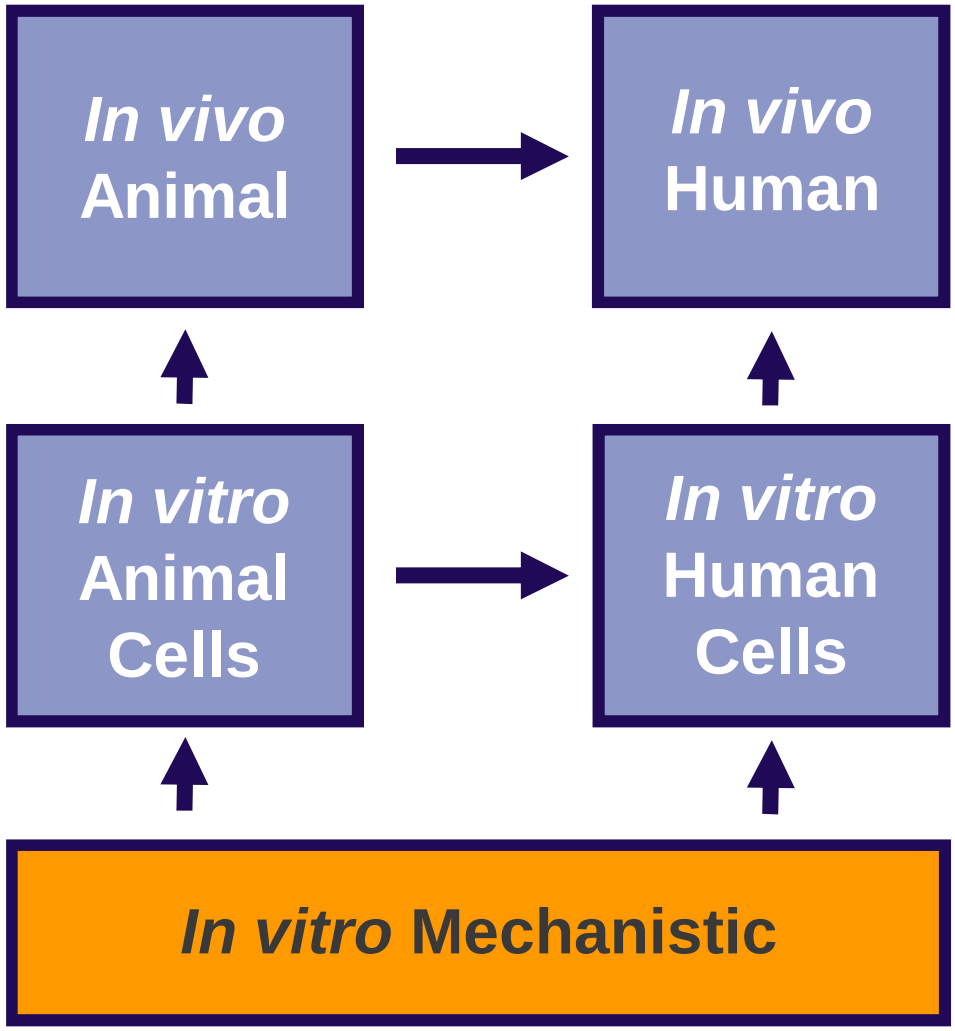
Translational research – WHO/ILSI/FDA/TIP



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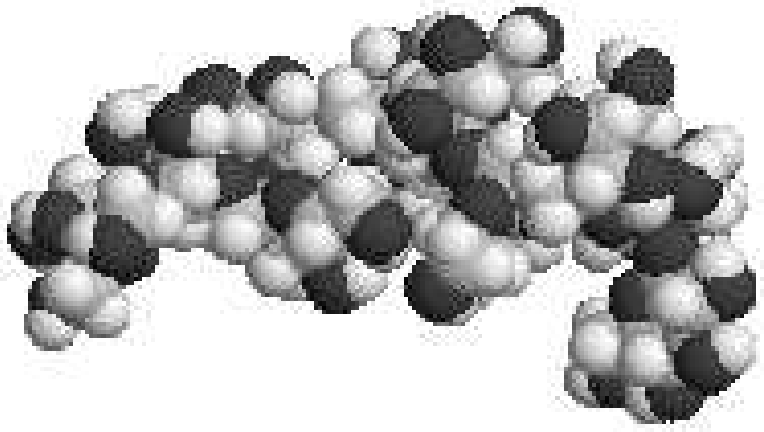
scGOS e.g. DP3

Gal(β1-4)Gal(β1-4)Glc

lcFOS e.g. DP10

$[Frc(\beta 2\text{-}1)]_8Frc(\beta 2\text{-}1)Glc$



90 % GOS: short-chain β-**G**alacto-**O**ligo**S**accharides from lactose

10 % FOS: long-chain β-**F**ructo-**O**ligo**S**accharides from chicory

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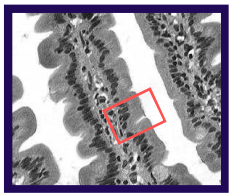
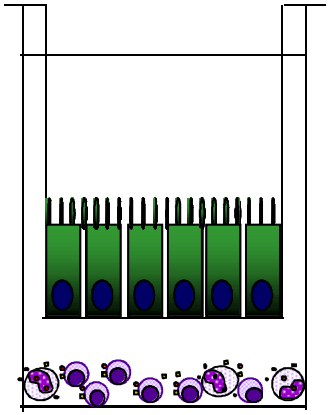
Improvement gut barrier? – First line defense

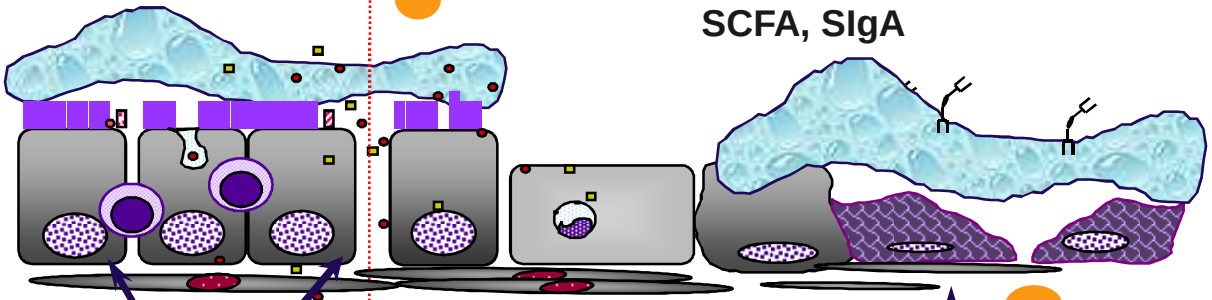


Epithelial Function and Regeneration



Permeability

Mucus
SCFA, SIgA



Mesenchym

Inflammation induced tissue destruction

Intestinal Immune Cell activity

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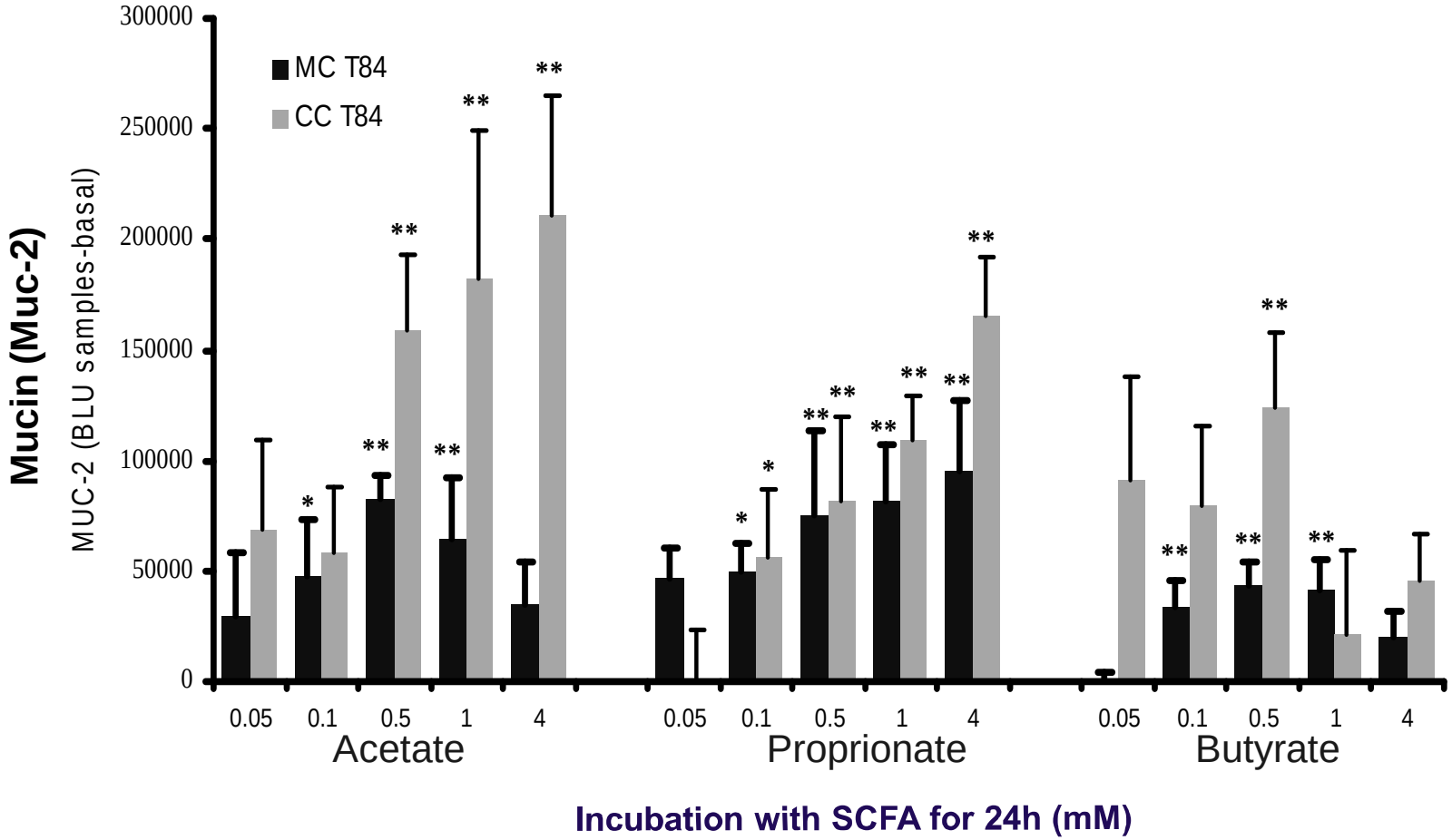
Oligosaccharides

SCFA differentially stimulate mucin production: mono and co-cultures



Linette Willemsen et al, Gut 2003

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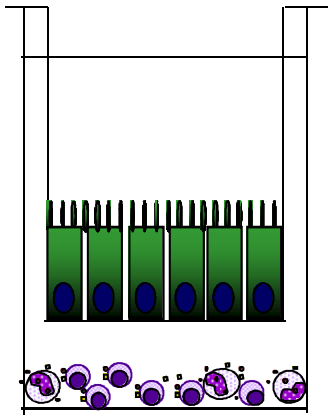
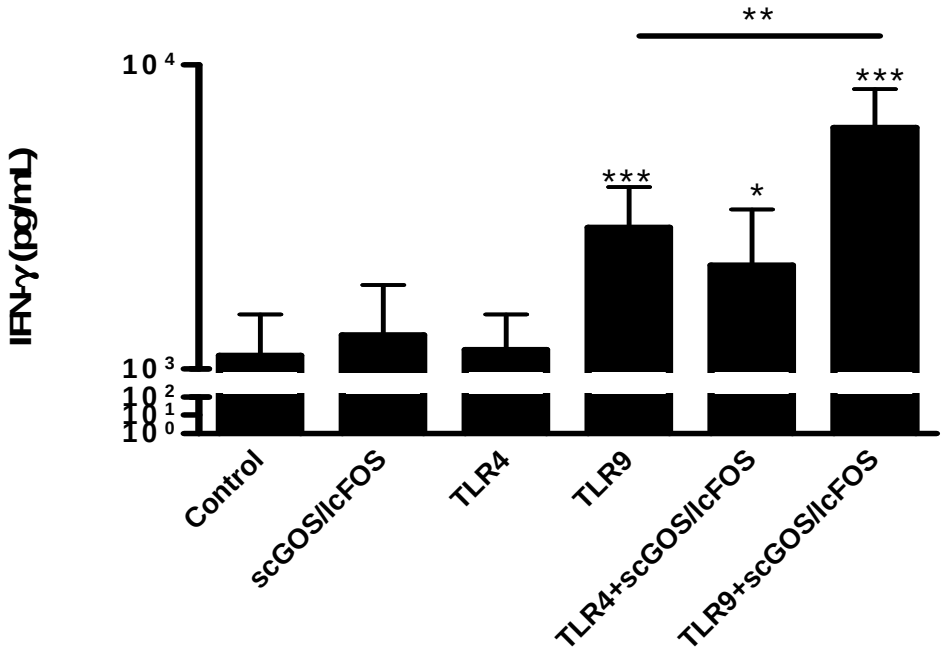
scGOS/lcFOS stimulates TLR9 induced IFN-γ production by human blood cells in co-culture systems with human gut epithelial cells





Kievit and Willemsen, 2009

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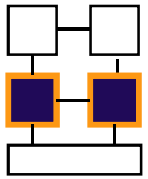
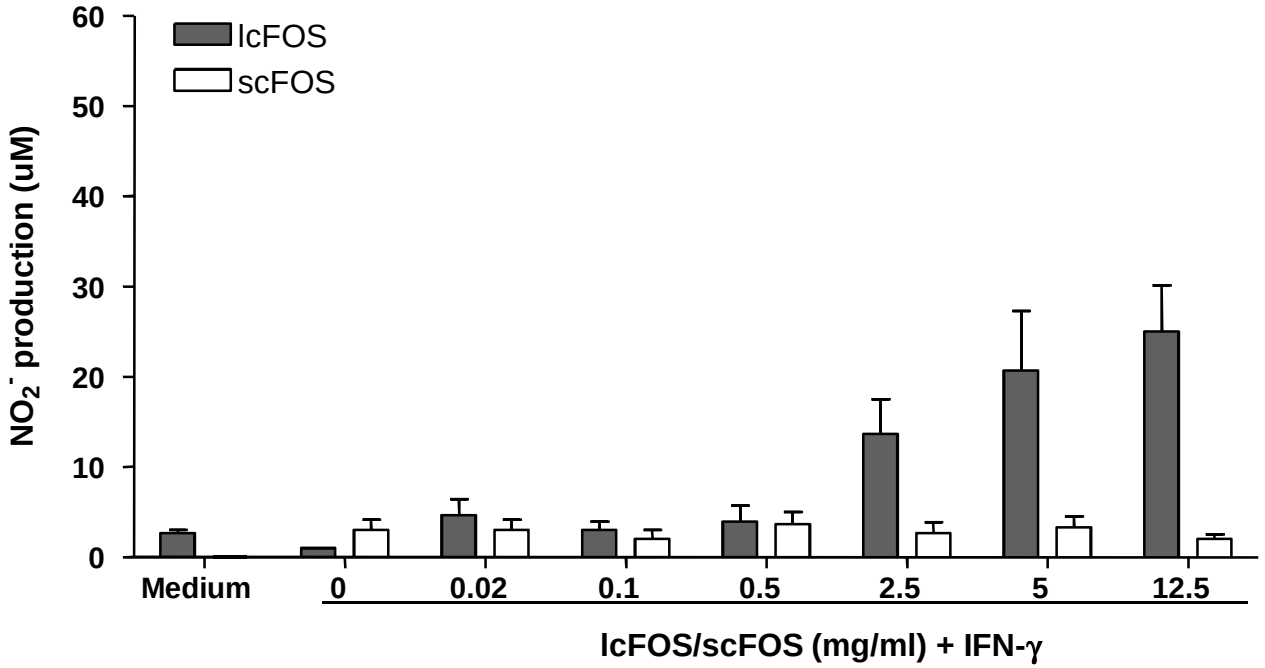
lcFOS stimulates NO_2 production by murine MØ





Jeurink et al, unpublished observations

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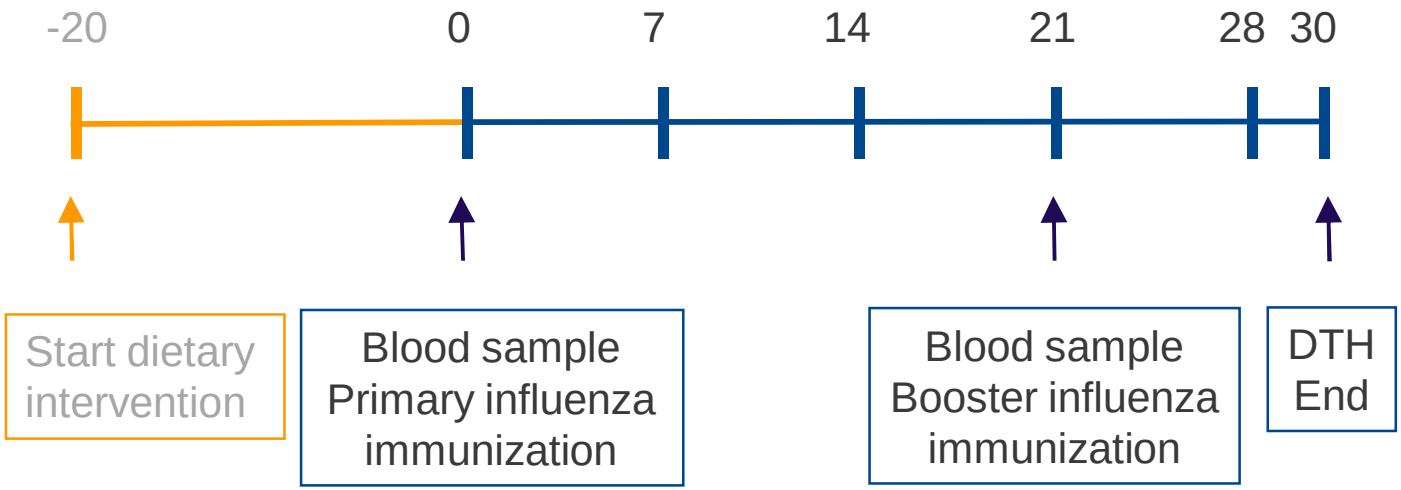
Vaccination model

Study parameters:

- DTH
- Influenza specific antibody titers
- Ex-vivo lymphocyte restimulation



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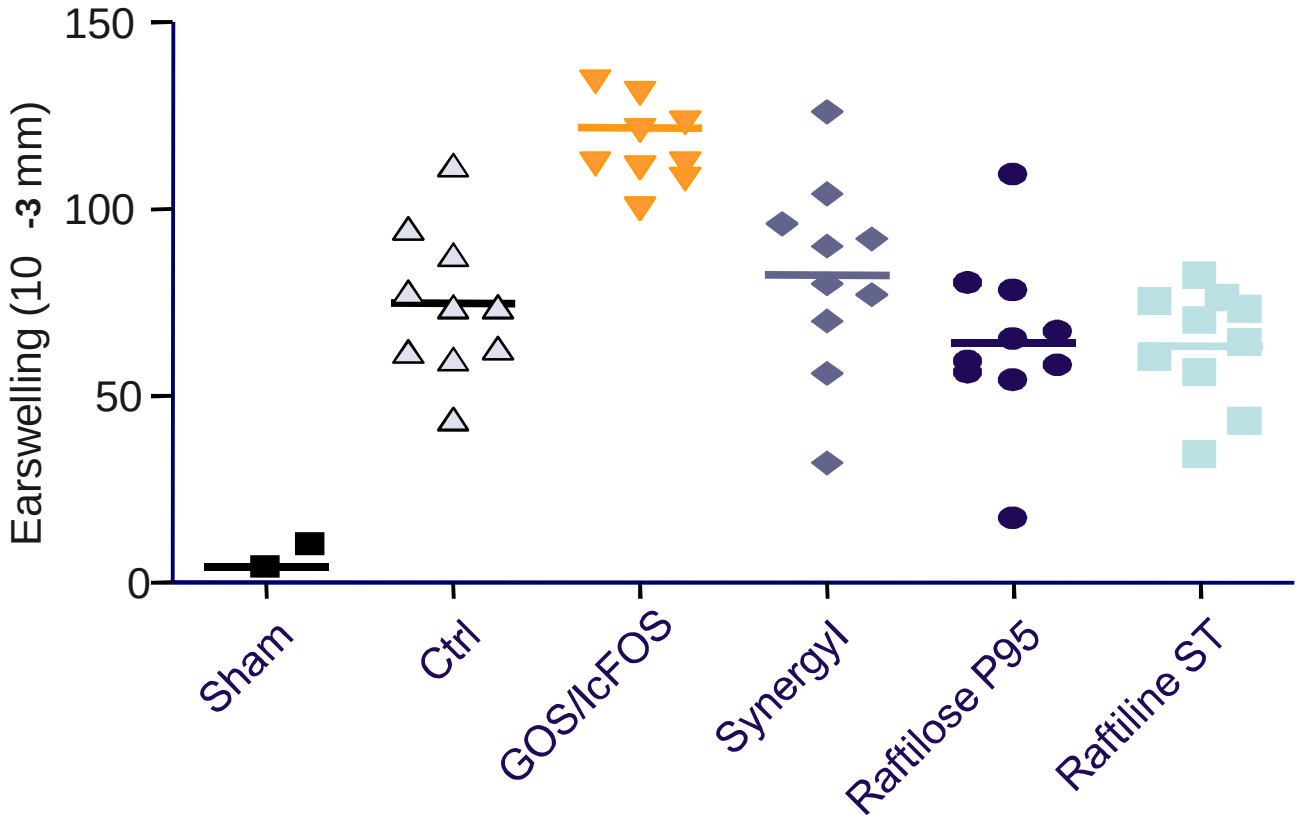
GOS/lcFOS improves vaccination



Vos et al, 2006, International Immunopharmacology 6: 1277-1286

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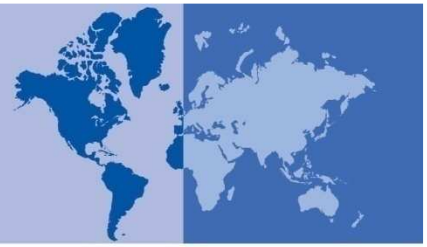

Conclusions so far

- ✓ GOS/lcFOS can affect systemic immunity (Th1/Th2)
- ✓ Regular T cells play a crucial role
- ✓ There is synergy between different types of oligosaccharides
- ✓ Not all oligosaccharides affect the immune system

- What about improved resistance to infections
- What about reduced risk for IgE mediated allergy

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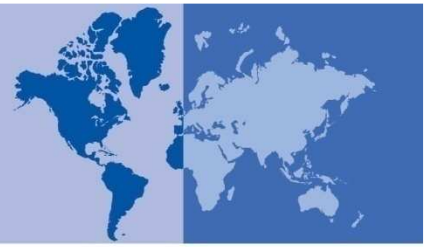

Immune disorders

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Cancer	**Th1 ↓**
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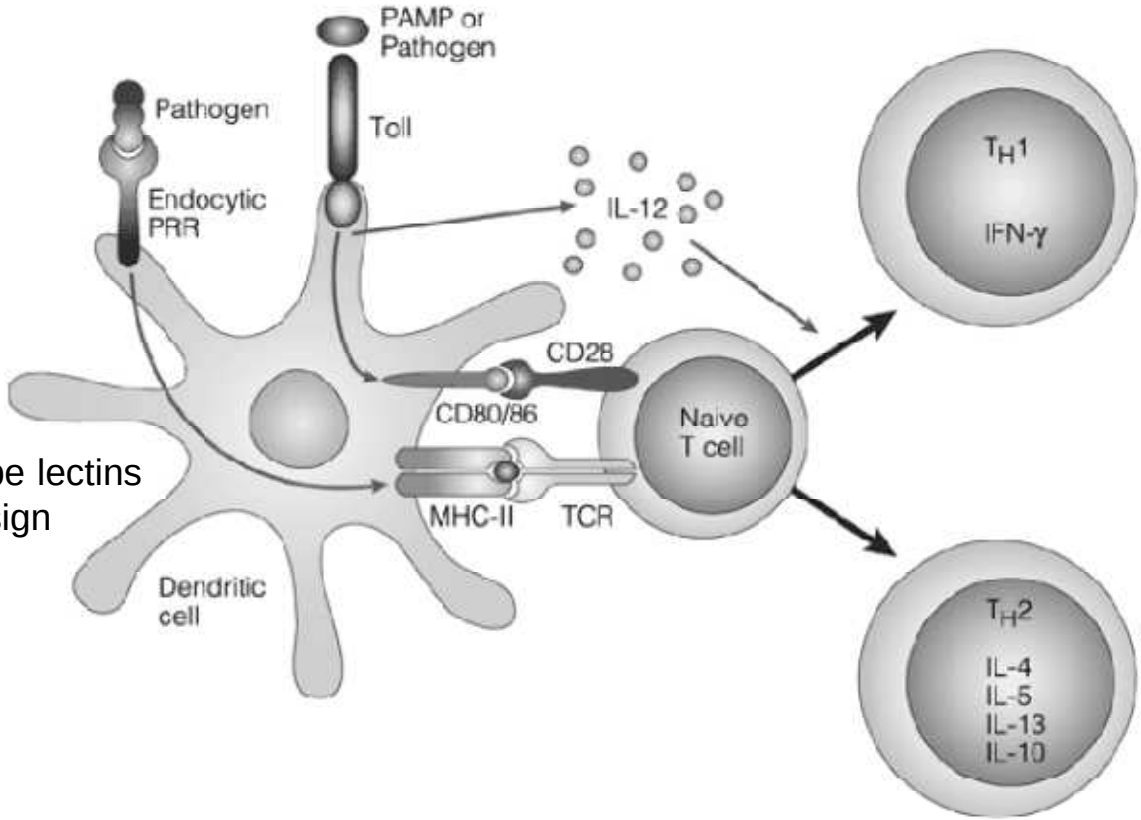
Immune skewing

microbes → TLRs

oligosaccharidess → C-type lectins
DC-sign



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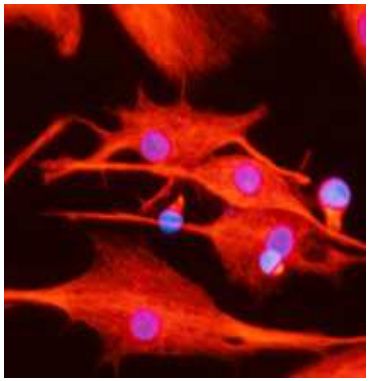
scGOS/lcFOS affects Th1/Th2 via DC/T-cell interaction



Stimulation of anti-allergic profile

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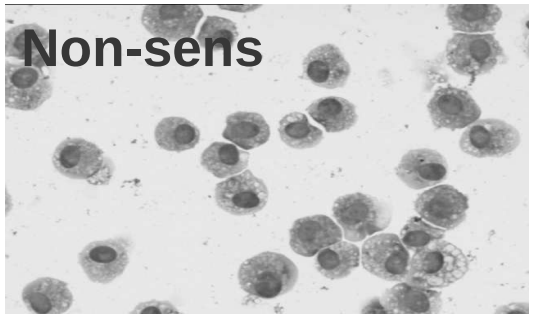
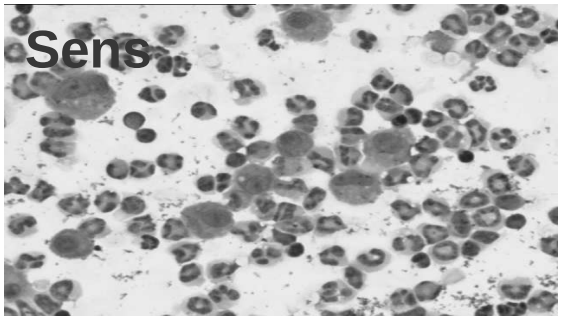
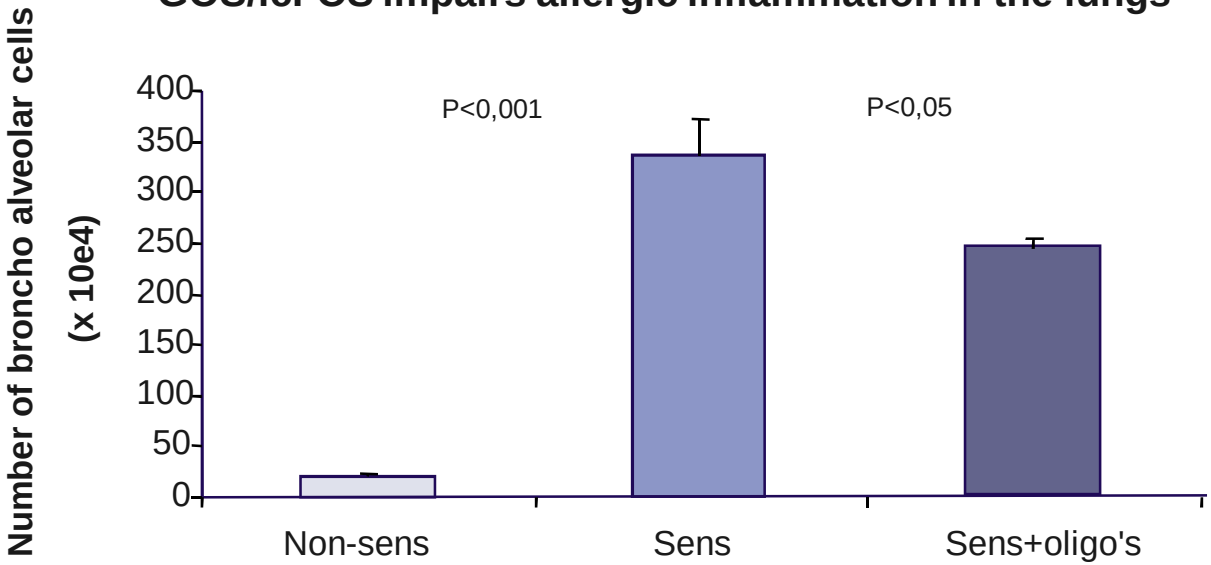
Allergy (respiratory)





GOS/IcFOS impairs allergic inflammation in the lungs



P.Vos, G. Folkerts, B. van Esch, G. Hofman, J. Garssen International Immunopharmacology 2007; 7(12):1582-1587.

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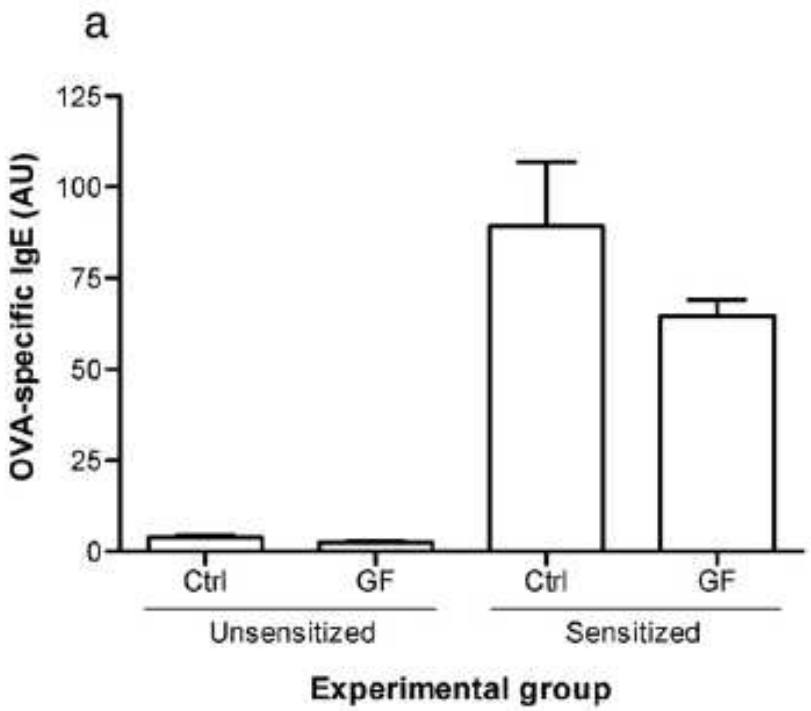
Allergy (respiratory)

GOS/lcFOS impairs IgE in serum



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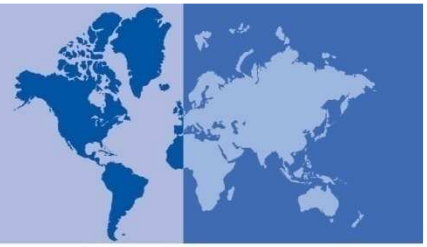

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Coeliac disease	Th1 ↑
Cystic Fibroses	Th1 ↑?
Cancer	Th1 ↓
Elderly	Th1 ↓
Infants	Th1 ↓, Th2 ↑

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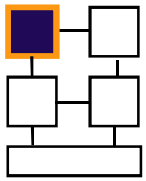
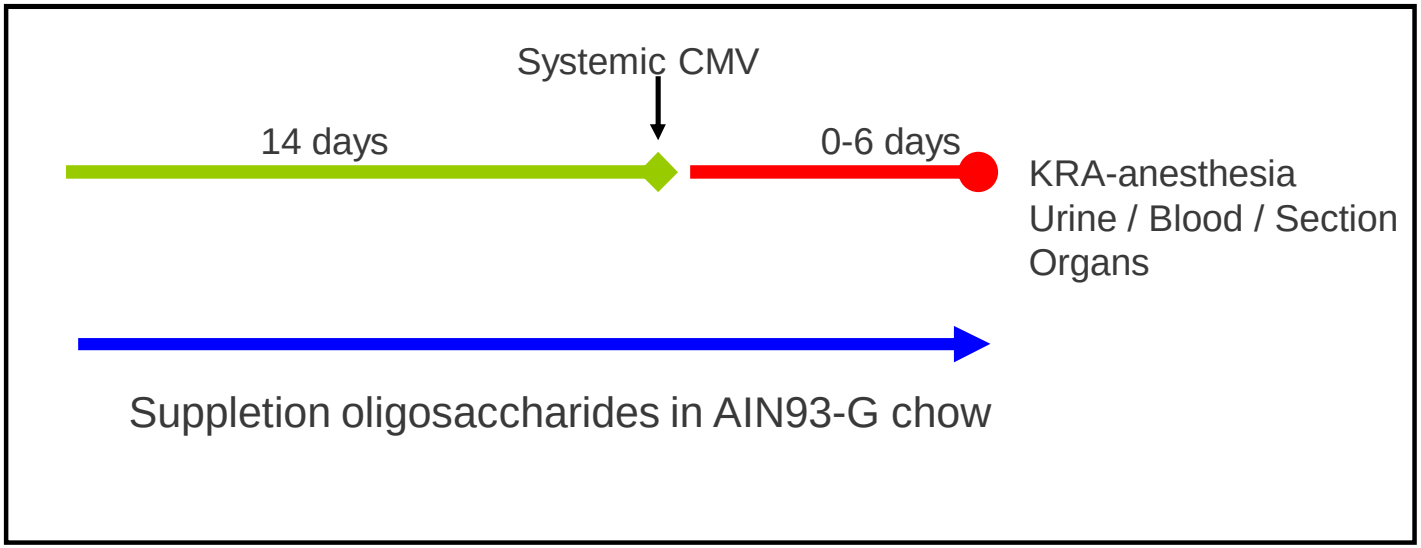
Cytomegalo virus infection model in mice
(systemic infection)





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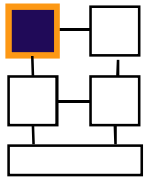
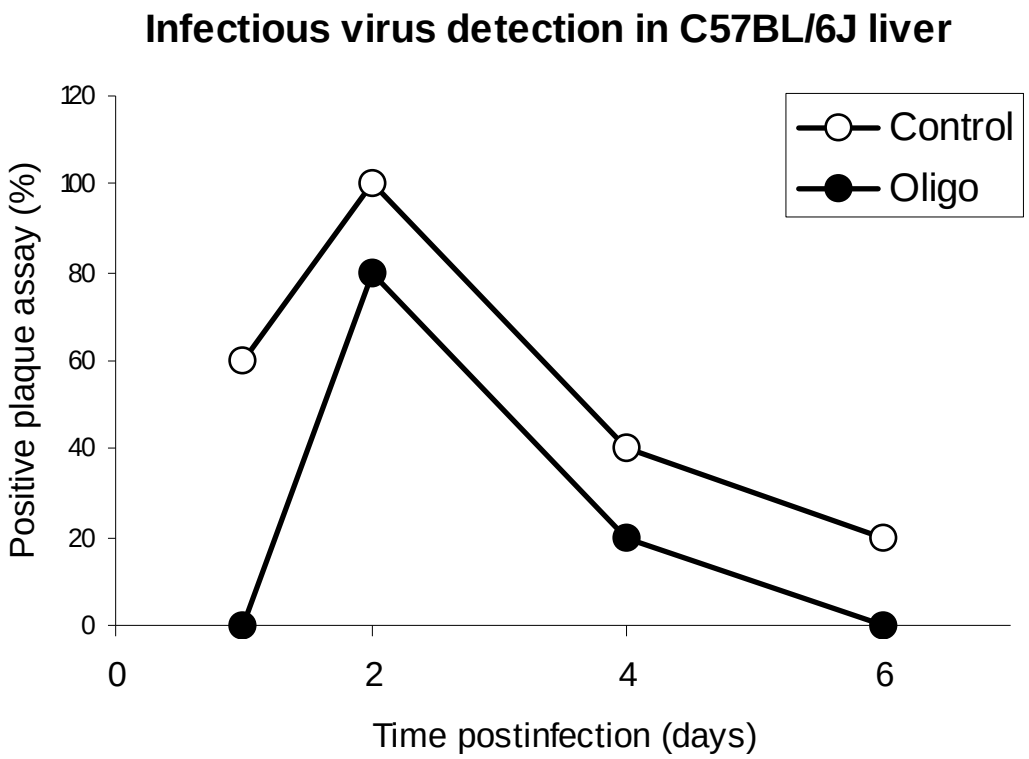
Oligosaccharides decrease MCMV load *in vivo*





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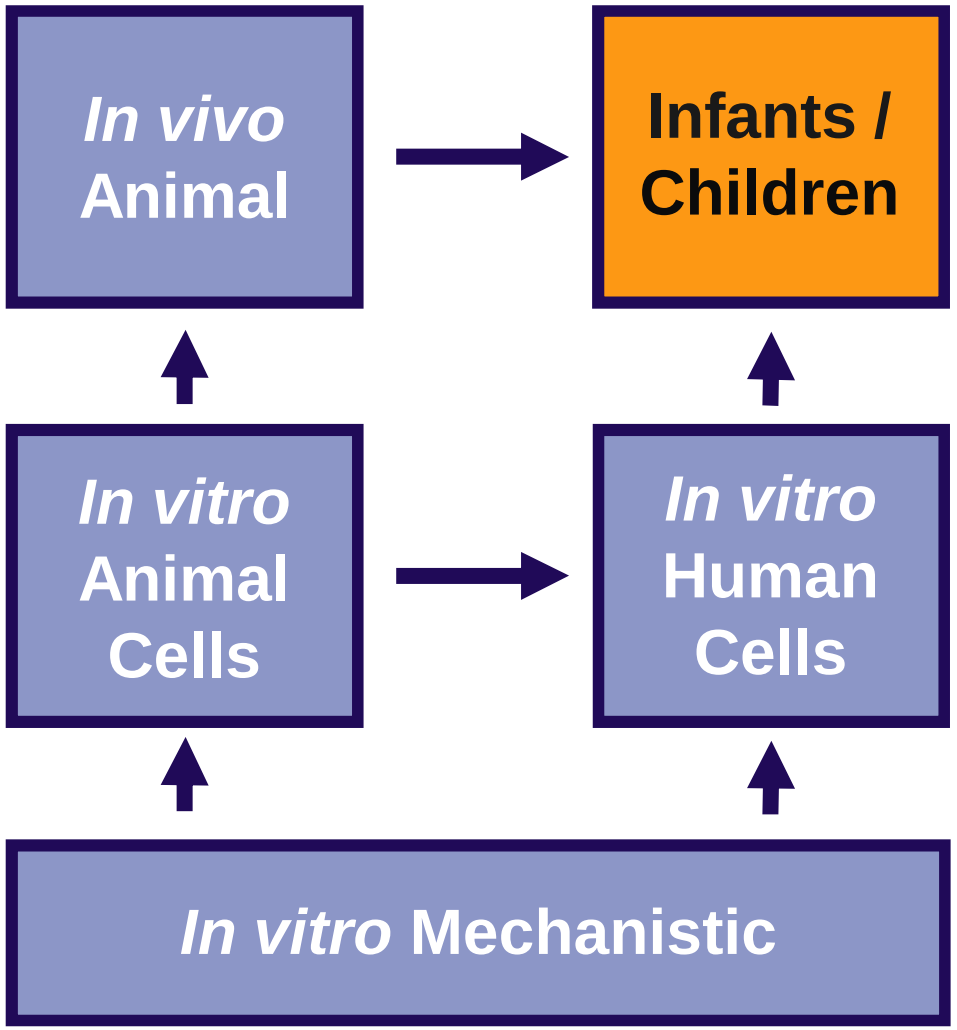
Translational research – WHO/ILSI/FDA/TIP



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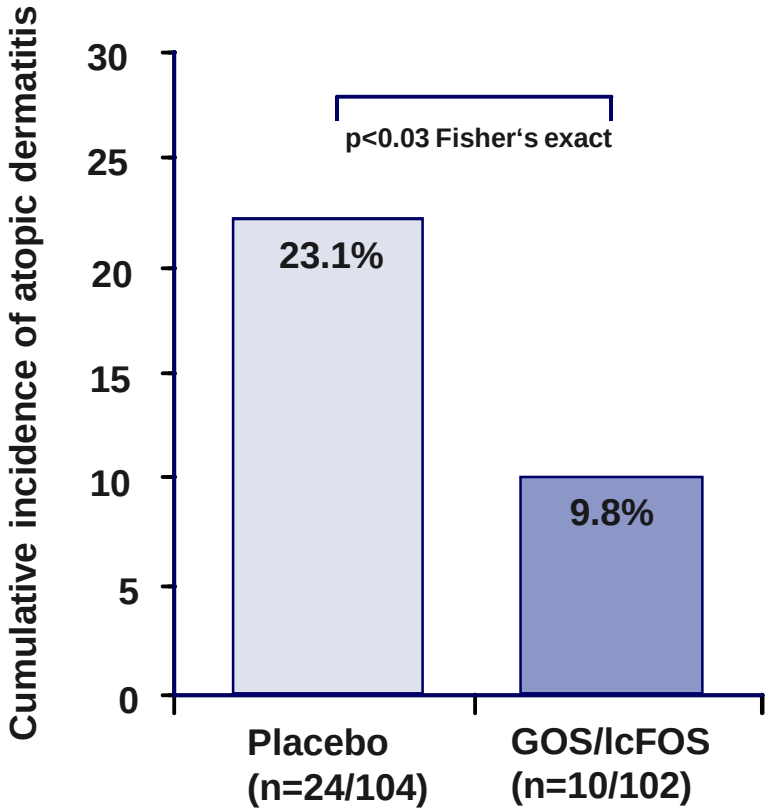
Atopic Dermatitis
in high-risk infants at 6 months



Moro et al., Arch. Dis. Child, 2006

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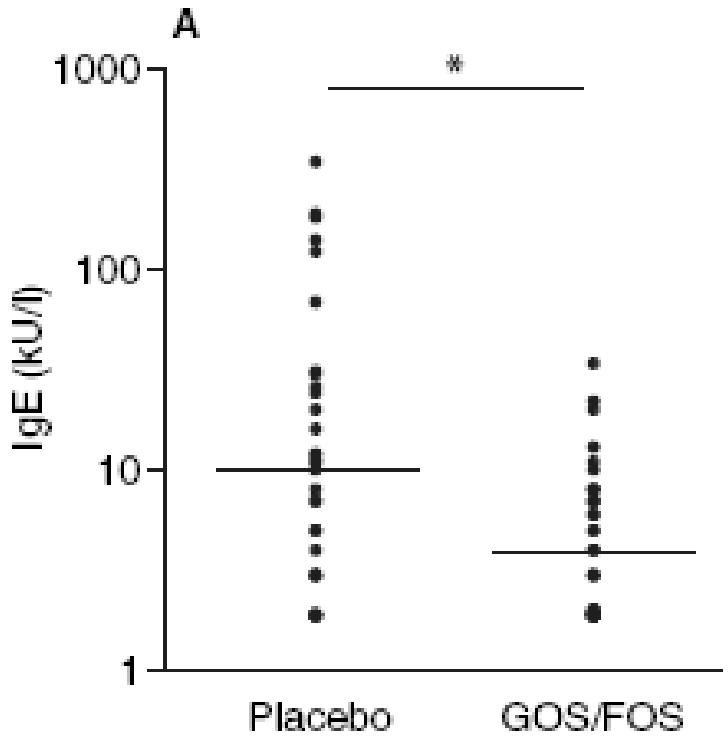
GOS/lcFOS decrease serum IgE
in high-risk infants at 6 months



E. Van Hoffen et al., Allergy 2009

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Early dietary intervention with a mixture of prebiotic oligosaccharides reduce the incidence of infections during the first 2 years of life

	Placebo	scGOS/lcFOS
	episode/infant	
n	68	66
Physician-diagnosed infections		
Overall (any kind of infection)**	5.9 ± 4.1	4.1 ± 3.1
URTI†	3.2 ± 2.2	2.1 ± 1.8
Lower respiratory tract infections	1.3 ± 0.8	0.9 ± 1.1
Otitis media	0.7 ± 1.2	0.5 ± 1.0
Gastrointestinal infections	0.6 ± 0.9	0.4 ± 0.7
Urinary tract infections	0.1 ± 0.5	0.0 ± 0.0
Infections requiring antibiotic prescriptions*	2.7 ± 2.4	1.8 ± 2.3
Fever episodes recorded by parents‡	3.9 ± 2.5	2.2 ± 1.9

[1] Values are means ± SD. *Different from placebo, $P < 0.05$, **$P = 0.01$, †$P < 0.01$, ‡$P < 0.0001$.

Arslanoglu et al., 2008, J. of Nutr. 138:1091-1095

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Early dietary intervention with a mixture of prebiotic oligosaccharides reduce the incidence of acute diarrhoea and protect from recurrent URTI

Table.2 Primary outcomes (intention to treat analysis)

	GOS/FOS group	Formula Standard group	P value
Gastrointestinal infections			
Number of episodes of diarrhea	22	44	**.02**
Number of children with 1 episode of diarrhea	19/169	37/173	**.0129**
Upper respiratory tract infections			
Number of episodes of URTI	241	302	**NS**
Number of children with at least 1URTI	84/169	87/173	**NS**
Number of children with > 3 URTI	22/169	36/173	**.06**
Use of antibiotics for URTI			
Number of antibiotic courses/URTI	123/241	190/302	**NS**
Number of children with at least 1 antibiotic course	65/84	78/87	**.038**
Number of children with ≥2 antibiotic courses	32/84	59/87	**.0001**
Number of children with ≥3 antibiotic courses	14/84	34/87	**.0012**

Bruzzesse et al., 2009, Clinical Nutrition, in press

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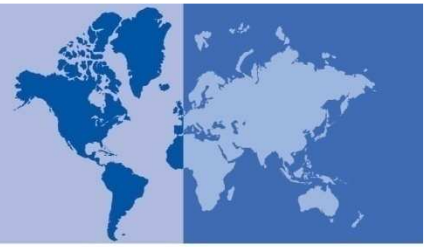

Immune disorders

HIV	**Th1 ↓, Th2 ↑, Th1/Th2 ↓**
COPD	**Th1 ↑**
Allergies	**Th2 ↑ (type I allergy)**
Asthma	**Th2 ↑**
Atopic eczema	**Th2 ↑**
Coeliac disease	**Th1 ↑**
Cystic Fibroses	**Th1 ↑?**
Cancer	**Th1 ↓**
Elderly	**Th1 ↓**
Infants	**Th1 ↓, Th2 ↑**

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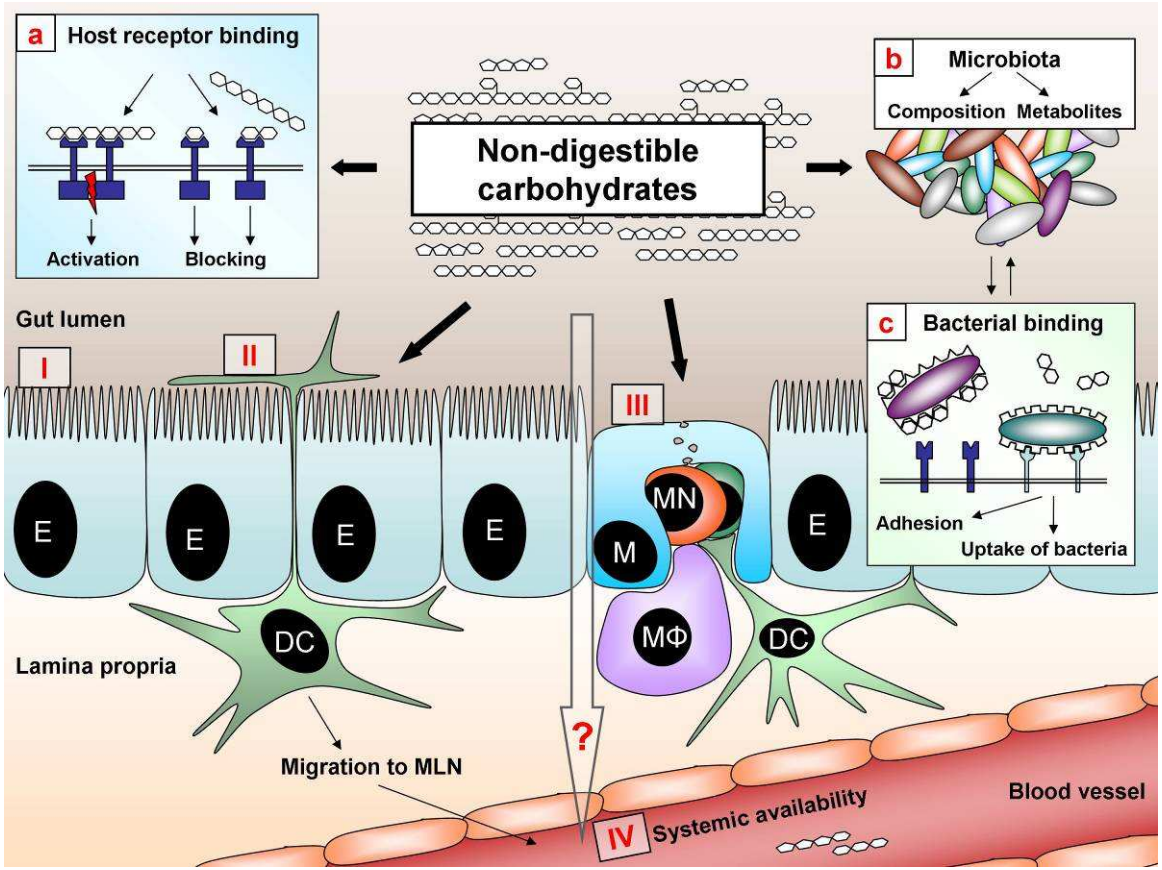
Summary



From invited review on oligosaccharides: critical reviews immunology: Paul Vos et al., 2007

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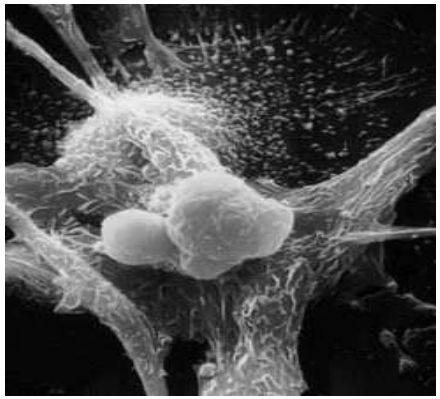
Conclusion (1)

- 60 - 70% of the immune cells are present in the gastro-intestinal tract
- There is a crucial interaction between gut associated and systemic immunity
- Non-digestible carbohydrates can affect the immune system both locally as well as systemically (less infections, less allergic inflammation) > a new chapter in immuno-pharmacology



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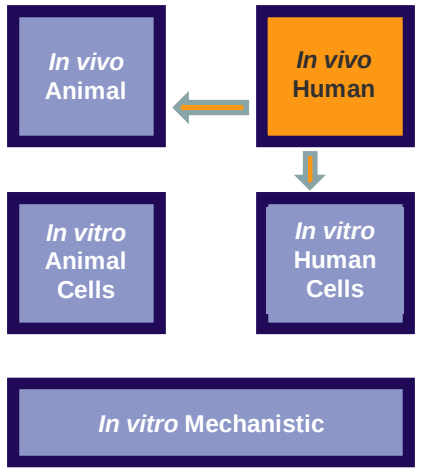
Conclusion (2)

- Non-digestible carbohydrates are a promising tool to improve immune responsiveness in immuno-compromised individuals (cancer, HIV, elderly,..)
- Food immunology is one of the most promising new life sciences at the interface between food and pharma
- Translational bi-directional research is essential



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"There is a reason behind everything in nature."

Aristoteles