

Sund Vækst

Project kick-off

ØFN-RegionHovedstaden

Copenhagen, 26-8-2008

**Status
on Metabolic
Syndrome and Food****Hagbard**

/ AF CHRIS BROWN



**LIFE, University of Copenhagen
ActiFoods ApS
Aff. Professor, PhD
Peter Olesen**

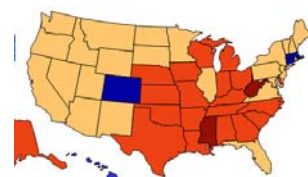
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RegioStars 2008
Winner

**HEALTH/DISEASE: obesity is a very visible phenotype**

Source: Behavioral Risk Factor Surveillance System, CDC.

Prevalence 1986**1996****2006****PARADOX**

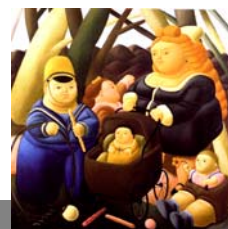
- Increasing problem for children and adolescents
- A rapidly growing global market > 50 bn \$



Family Scene (1969)



Frank Lloyd and his Family on Paradise Island (1972)



The Rich Children (1965)

Fernando Botero

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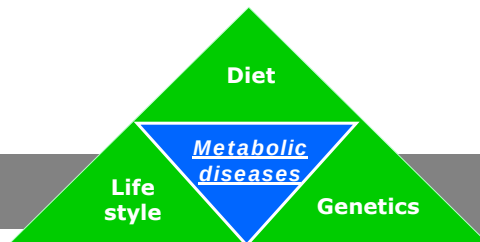




Dr. Louise
Brown,
Unilever

- and part of a less visible but
very serious metabolic syndrome

Urbanisation & metabolic disease



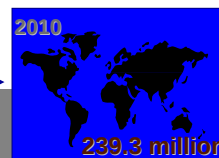
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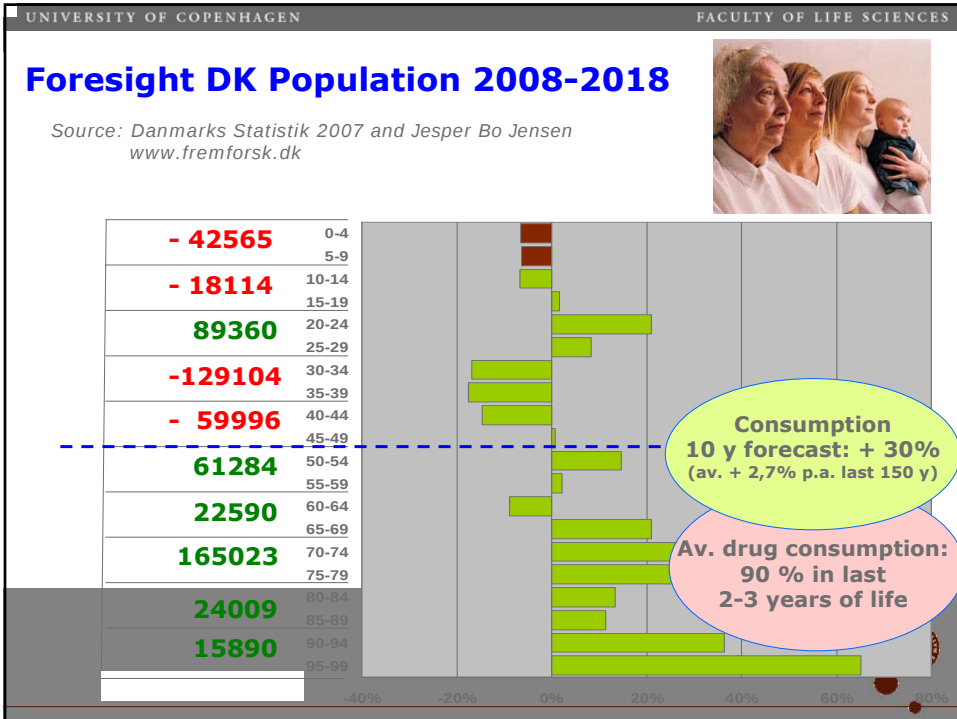


Incidence of diabetes (world wide projections)



McCarty and Zimmet - ISBN 0 646 20244 8



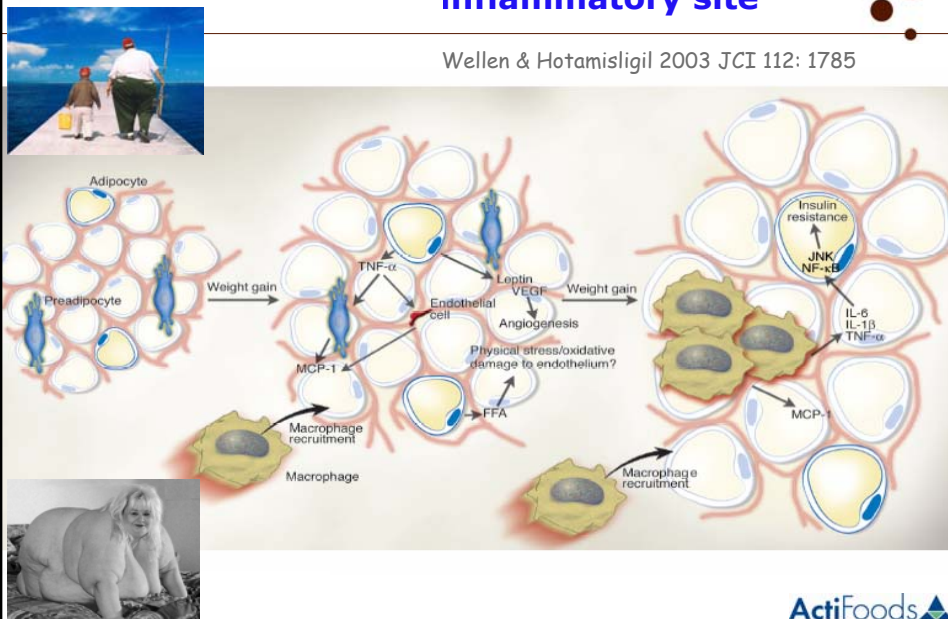


Lifestyle and metabolic diseases

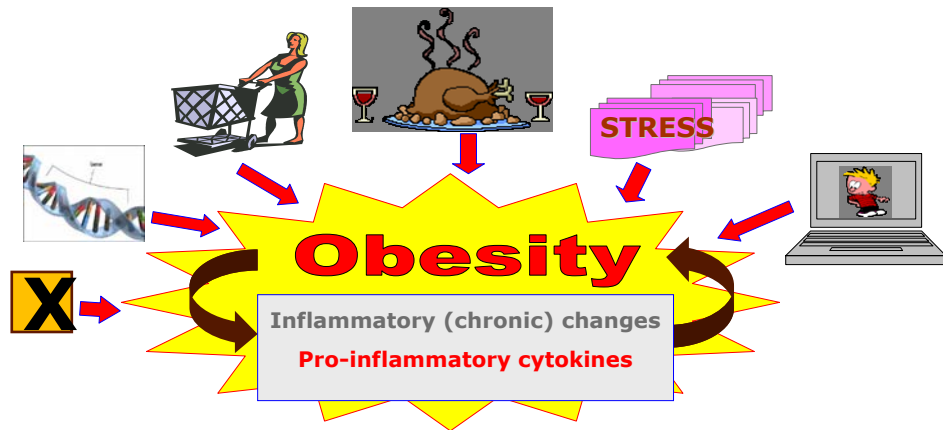


Adipose tissue becomes inflammatory site

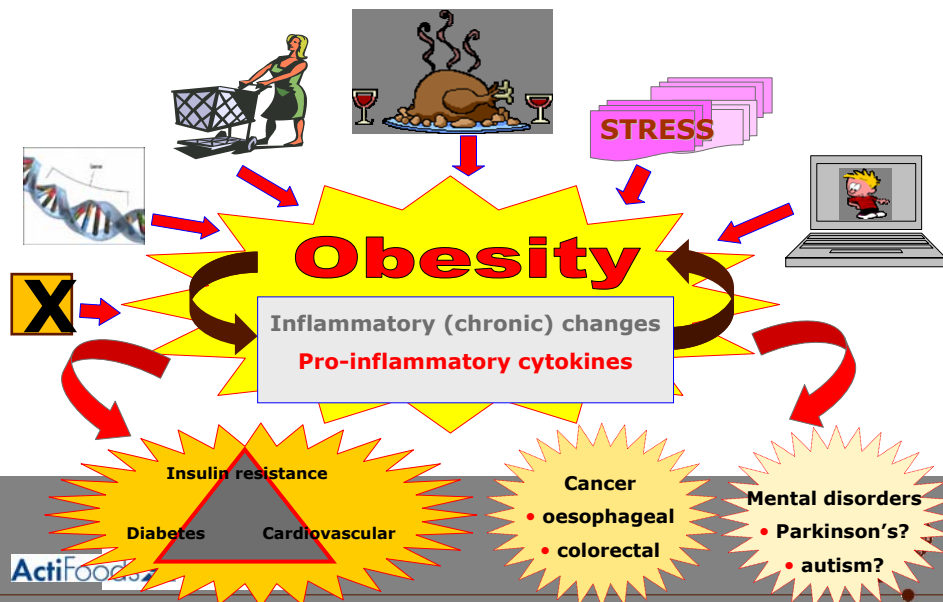
Wellen & Hotamisligil 2003 JCI 112: 1785

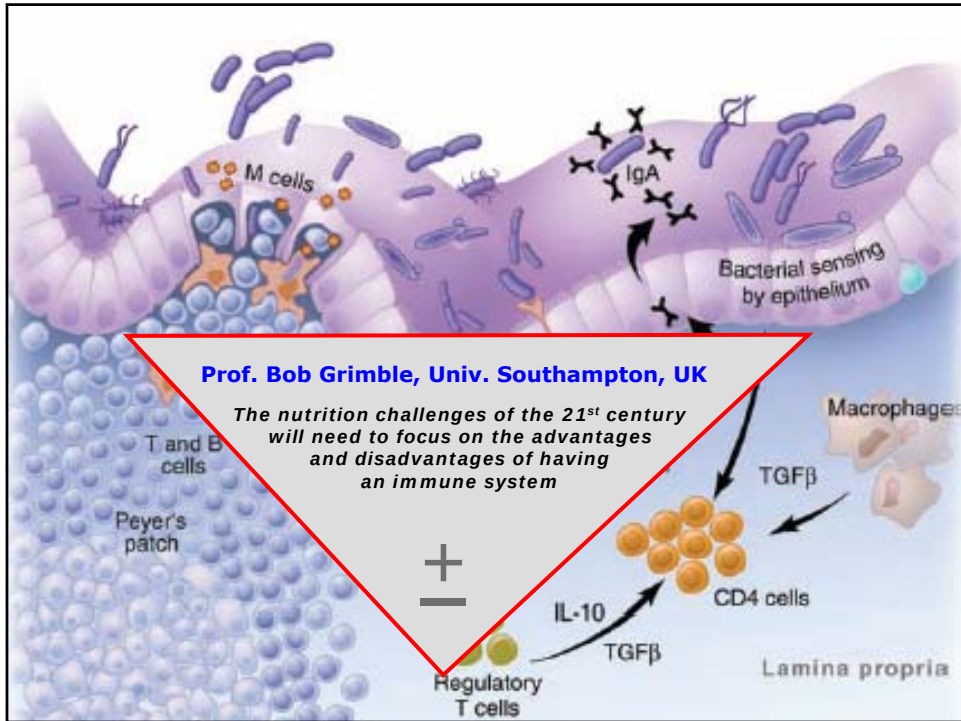


Lifestyle and metabolic diseases



Lifestyle and metabolic diseases





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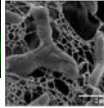
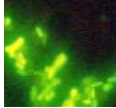
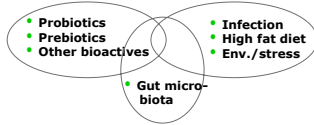
The human gut: layers of complexity...

The diagram shows a 3D rendering of the human gut. A cross-section of the gut wall is shown, with the 'Gut lumen' (the space inside the gut) and the 'Gut epithelium (mucosa)' (the lining of the gut). 'Commensal bacteria (microbiota)' are shown as blue dots in the lumen. A red box highlights a section of the gut wall, which is shown in a larger, more detailed view on the right. This detailed view shows the 'Gut epithelium (mucosa)' and the 'Commensal bacteria (microbiota)' in more detail.

1-2 kg complex microbial ecosystem
 - 100X # genes in human genome
 - 100X # cells in human body

FOCUS: epithelial barrier & immune response

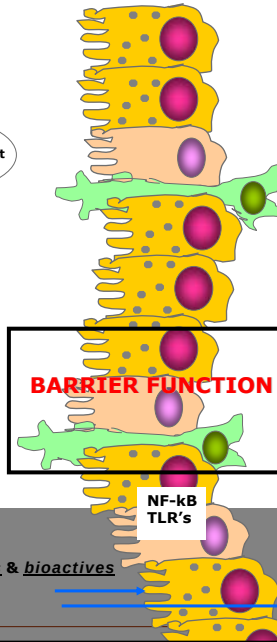
GUT LUMEN



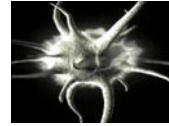
FOOD

- metabolism
- fermentation
- bioconversion
- uptake/signalling *nutrients & bioactives*

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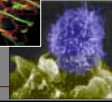


Dendritic cells: sensing luminal factors (cells, bioactives)

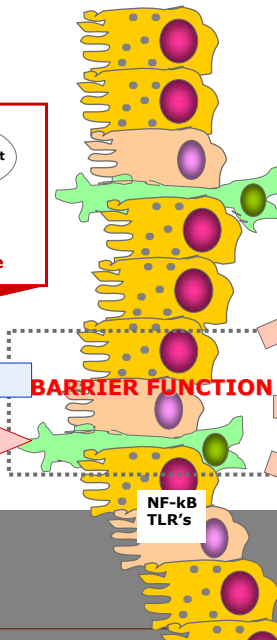
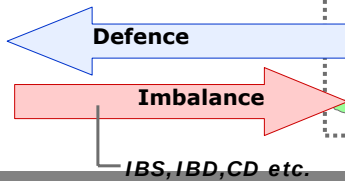
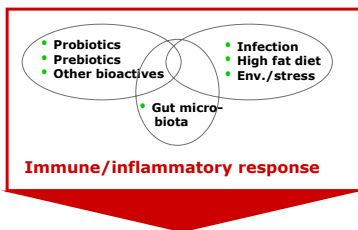


MUCOSAL / SUBMUCOSAL LAYERS

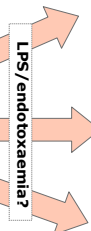
- connective tissue
- immune cells: macrophages, DC's, T_{reg}, T_{help} etc.
- nerve cells
- vascular



FOCUS: epithelial barrier & immune response

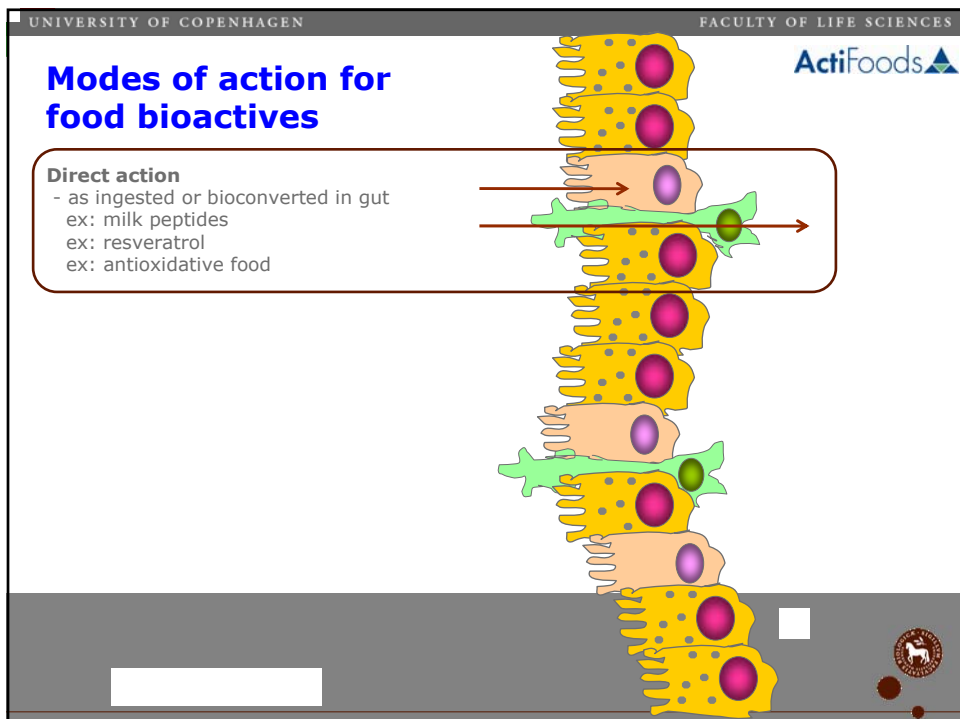
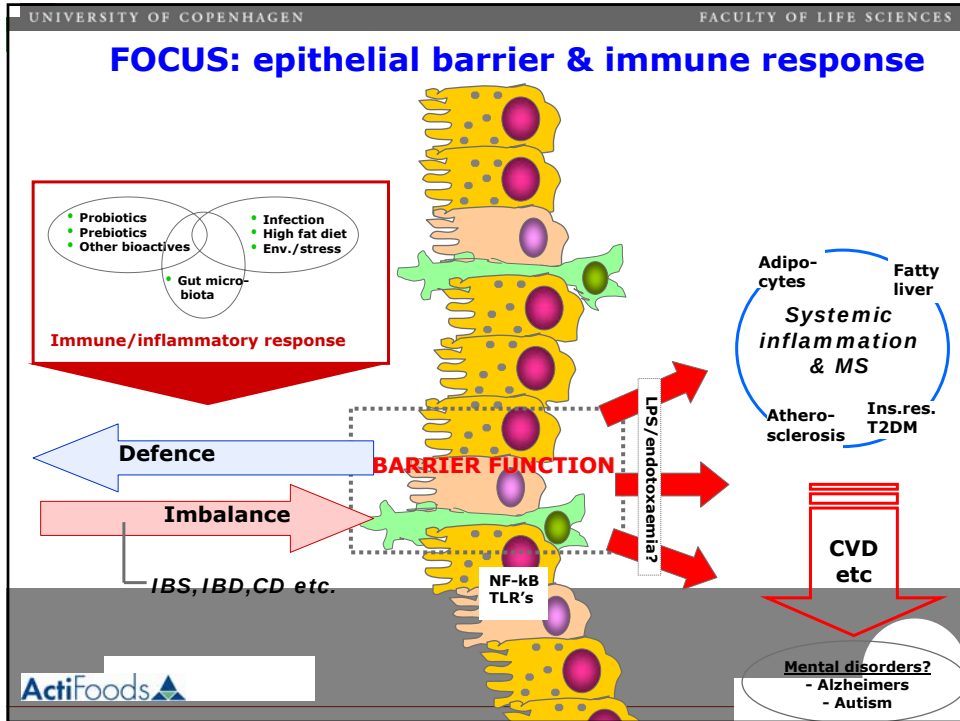


The advantage/
disadvantage
balance



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The gut is our largest endocrine organ – contains 80% of all antibody producing cells (~ 40 mg IgA/kg/day)



Evolus® – Lowers blood pressure and improves the vascular health

Evolus

Courtesy of Dr. Tiina Mattila-Sandholm, Valio (Finland)



Iceland, Portugal, Spain, Korea, Chile, Mexico, Argentina, Brasil

During Evolus Drink fermentation, milk proteins are degraded into peptides (smaller protein units) whose effect is to lower blood pressure: **they act as an ACE inhibitor**

The mineral composition of Evolus is beneficial for blood pressure:

- sodium, calcium and potassium

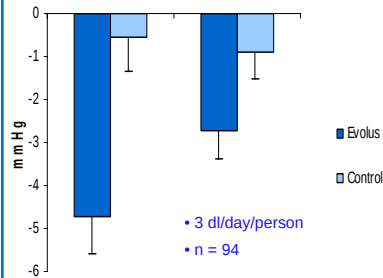
ActiFoods

Evolus

Clinical effects

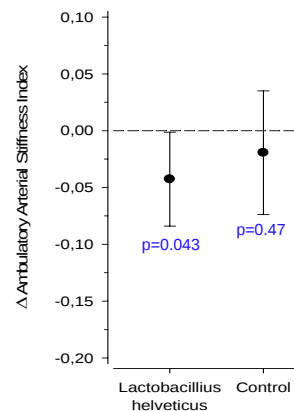


Changes in systolic and diastolic blood pressure



Jauhiainen et al. Am J Hypertens 2005
Tuomilehto et al. J Hum Hypertens 2004
Seppo et al. Am J Clin Nutr 2003
Seppo et al. Milk Sci Int 2002.

Evolus reduces arterial stiffness



Jauhiainen et al. Int Dairy J 2007

ActiFoods

Courtesy of Dr. Tiina Mattila-Sandholm, Valio (Finland)

Dr. Tiina
M-Sandholm
Valio, SF

Yes - it works!

SBP – 6 mmHg

DBP – 3 mmHg

OR

SBP – 5 mmHg

DBP – 4 mmHg

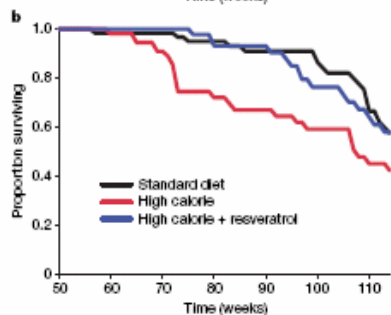
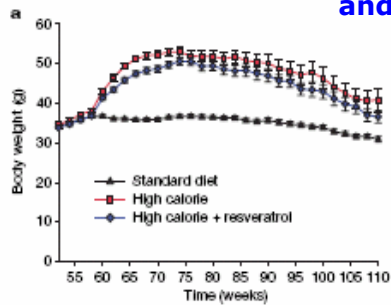


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Dr. Joseph
A. Baur
Harvard Med. School

**Resveratrol – a plant polyphenol
and anti-oxidant – is anti-inflammatory**

Effect of resveratrol on obese mice



Decrease in:

- Inflammation
- Fat accumulation
- Diabetes development
- Liver damage

Increase in:

- Endurance



Links between type of caloric intake (food components), oxidative & inflammatory stress and metabolic syndrome

Dr. Paresh Dandona
University
New York

J Clin Endocrin & Met. 2000, **85**: 2970-72

Am J Clin Nutr 2002, **75**: 767-72

Am J Clin Nutr 2004, **79**: 682-90

Am J Clin Nutr 2004, **80**: 51-57

Diabetes care March 2007

Diabetes is associated with increased ROS generation, oxidative injury (lipids, proteins, DNA) and obesity

Glucose challenge stimulates ROS generation by plasma leucocytes (PMNL's and MNC's)

Increased ROS generation (oxidation) and lipid peroxidation are key events in atherogenesis (arterial plaque formation)

Lipid and protein intake stimulates increased generation of ROS in plasma leucocytes

Glucose intake stimulates an increase in NF- κ B and two other pro-inflammatory transcription factors

Caloric intake in the form of orange juice and fructose does not induce either oxidative or inflammatory stress

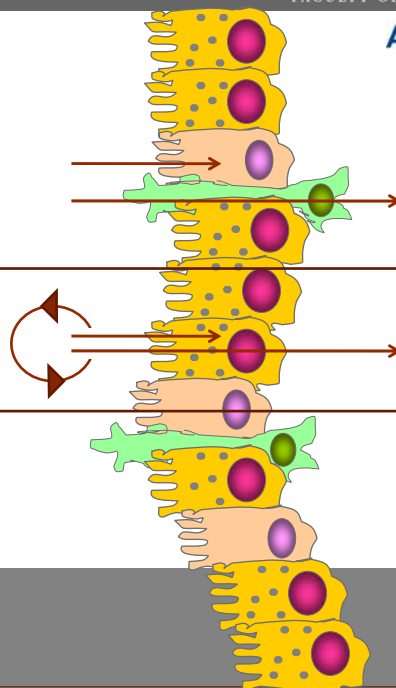
Modes of action for food bioactives

Direct action

- as ingested or bioconverted in gut
- ex: milk peptides
- ex: resveratrol
- ex: antioxidative food

Microbiota

- diversity and dynamics
- ex: chicken flora
- ex: probiotic effects
- ex: prebiotic / synbiotic effects



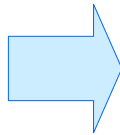
Human DC's show differential *in vitro* responses to different probiotic bacteria



Dr. Hans
van Noort
TNO, NL

LPS
L. acidophilus NCFM
L. acidophilus La-5
B. lactis Bb-12
B. lactis BI-07

- activation of pattern-recognition receptors on DC's incl. TLR's
- powerful induction of DC maturation
- early cytokine & chemokine responses are often similar, indicating common activation of NF-κB
- other cytokine responses are quantitatively very different
- late DC responses diverge and indicate differential induction by bacteria of many growth and differentiation factors



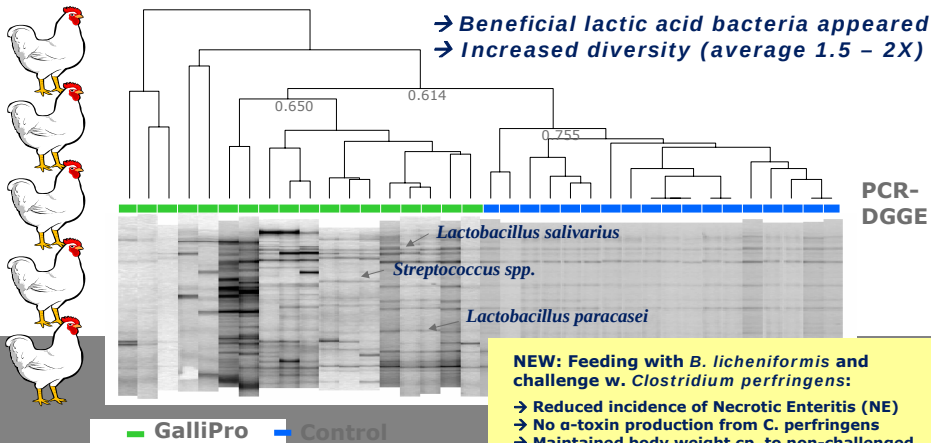
The *in vitro* response of human DC's to probiotics involve secretion of several immune regulatory and/or health-promoting factors

Feeding GalliPro (*Bacillus subtilis*) to broiler chicken alters the bacterial community in the ileum and enhances growth

N Milora et al. 2008 J Prob Preb Res (in press):

Dice coefficient analysis of the ileal profiles from control birds and birds fed GalliPro resulted in a grouping associated with the dietary treatment

- ➔ **Beneficial lactic acid bacteria appeared**
- ➔ **Increased diversity (average 1.5 – 2X)**



NEW: Feeding with *B. licheniformis* and challenge w. *Clostridium perfringens*:

- ➔ Reduced incidence of Necrotic Enteritis (NE)
- ➔ No α-toxin production from *C. perfringens*
- ➔ Maintained body weight cp. to non-challenged

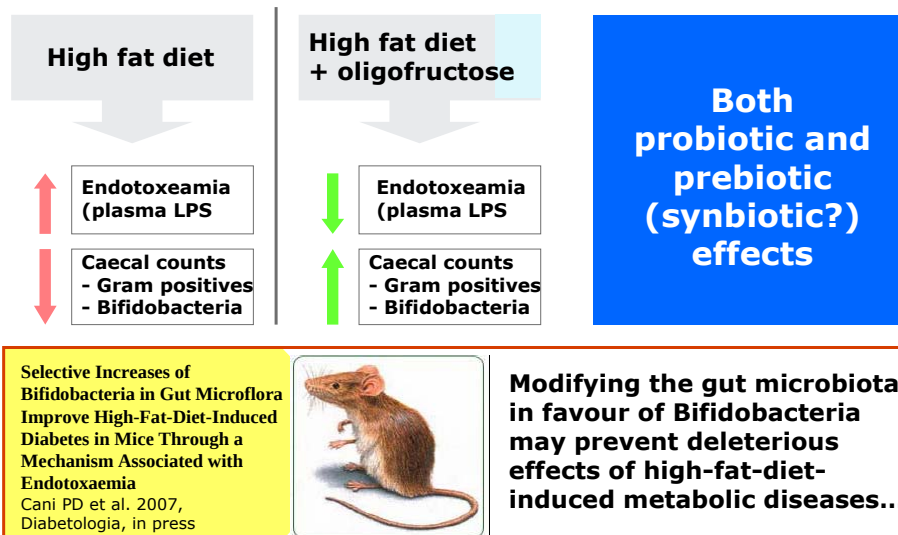
Summary probiotics



Probiotics work together with the microbiota and the immune system
 -with great potentials for development and maintenance of a healthy balance
→ DISEASE RISK REDUCTION AND PREVENTION

- Composition and maturation of microbiota: pre- & postnatal window
- Maintaining a healthy microbiota: stability, restoration, function (transit, bloating etc.)
- Protecting against infections: viruses (rota, cold, flu) and some pathogens (H. pylori, E. coli EHEC / O 157 etc.)
- Inflammatory gut diseases: IBS, IBD (UC and maybe CD)
- Chronic inflammation levels that would otherwise induce metabolic diseases: insulin resistance, T2DM, obesity etc.
- Immune disturbances like atopic dermatitis (eczema) and certain allergies

Can Bifidobacteria help prevent development of metabolic syndrome?



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Complex communications

- bioactives/microbiota/host immune cells
- ex: microbial symbiosis factor
- ex: epithelial response factor

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Microbial signals can elicit host responses involved in maintaining a healthy balance

A 'fishy' story about Intestinal Alkaline Phosphatase, IAP

Source:
Guillemin K et al. 2007: *Cell Host & Microbe* (Dec 13, 2007) & commentary *Science* 318: 1853 (Dec 21, 2007).

Balancing act.
Fish intestines (green) use a detoxifying enzyme to tolerate normal gut microbes (red)

CONCLUSION: IAP dampens LPS mediated inflammatory response to normal microbiome = host tolerance

Intestinal inflammation in mice can be tamed by bacterial sugars

Source:
Mazmanian K et al. 2008: *Nature* Vol 453/29 May 2008, 620-25.
A microbial symbiosis factor prevents intestinal inflammatory disease

Experimental colitis induced by *Helicobacter hepaticus* (a murine commensal) can be abolished by a single microbial molecule (polysaccharide A, PSA) produced by e.g. *Bacteroides fragilis* (a human commensal).

"Intestinal inflammation in mice can be tamed by bacterial sugars"



A microbial symbiosis factor prevents intestinal inflammatory disease

Mazmanian SK et al. Nature vol 453/May 2008, 620-25.

- ❖ Experimental colitis induced by *Helicobacter hepaticus* (a murine commensal) can be abolished by a single microbial molecule (polysaccharide A, PSA) produced by e.g. *Bacteroides fragilis* (a human commensal).
- ❖ PSA seems to suppress pro-inflammatory IL-17 production in intestinal immune cells a.o. *in vitro* cell cultures
- ❖ PSA protection is based upon a functional requirement for IL-10 producing CD4+ T-cells.
- ❖ Germ-free mice have defects in CD4+ T-cell development and human *B. fragilis* can correct the deficiency through PSA expression



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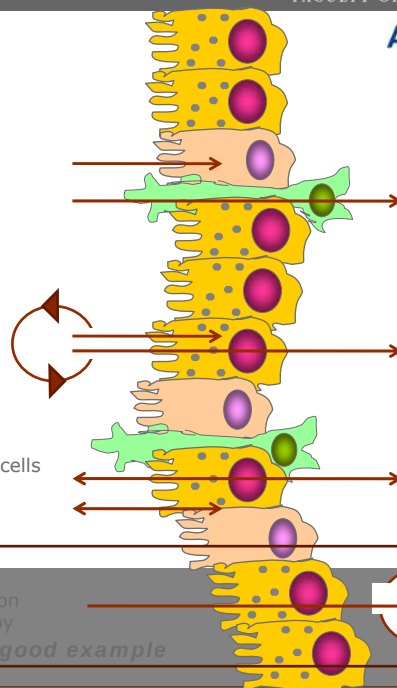
Complex communications

- bioactives/microbiota/host immune cells
- ex: microbial symbiosis factor
- ex: epithelial response factor

Drug interference

- bioactive improving antibiotic function
- ex: flavonoid compounds and TB therapy

NOTE! Not related to MS – but good example



Drug interference from a food ingredient improves tuberculosis therapy

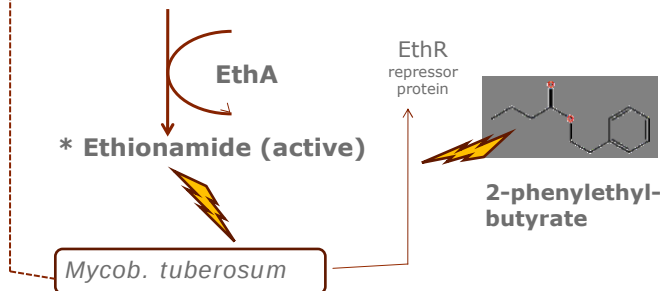


TB strikes back (WHO data):



- 9.000.000 new cases each year
- 50.000.000 infected with Rifampicin and Isoniazid resistant strains of *Mycobacterium tuberculosis*
- Ethionamid only effective remedy, but fatally toxic at high doses

Ethionamide (prodrug)



An approved food ingredient

A floral flavor (pheromone) compound from plants – orchids, citrus, old sherry etc.

2-phenylethyl-butyrate

Weber W et al. (2008) A synthetic mammalian gene circuit reveals antituberculosis compounds
<http://www.pnas.org/content/105/29/9994>

Clinical efficacy a major shortcome

3-4 main categories of food bioactives known to have health-promoting (and disease prevention) functionalities, BUT.....

Probiotics & Prebiotics

- GI stability
- Inflammatory gut diseases
- Anti-inflammatory
- Anti-infective
- Immune stimulating
- Anti-allergic
- Satiating /anti-obesigenic)

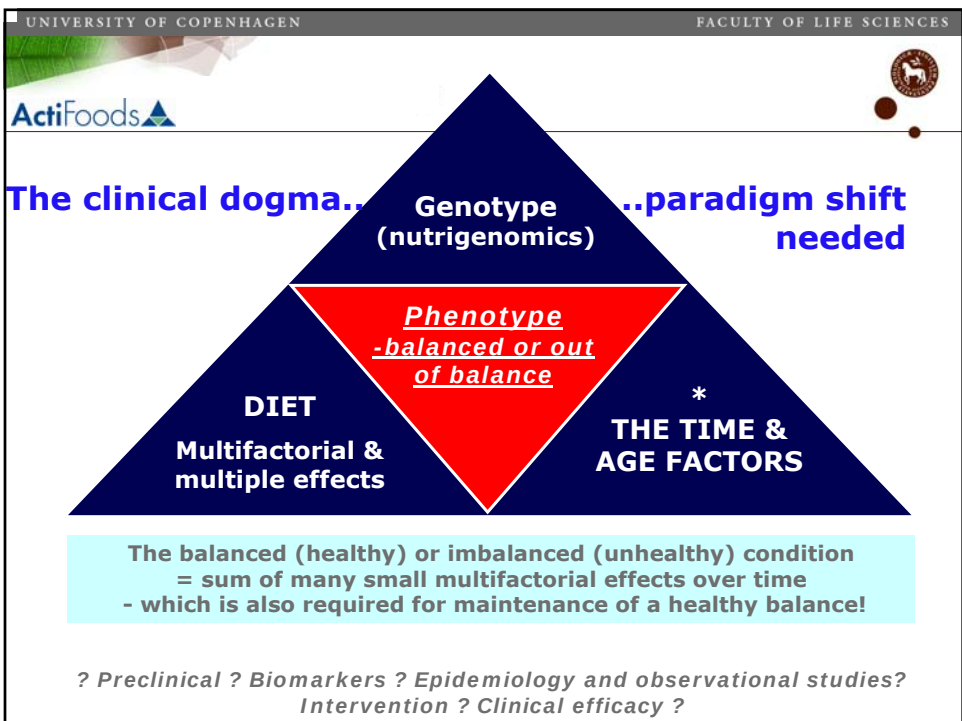
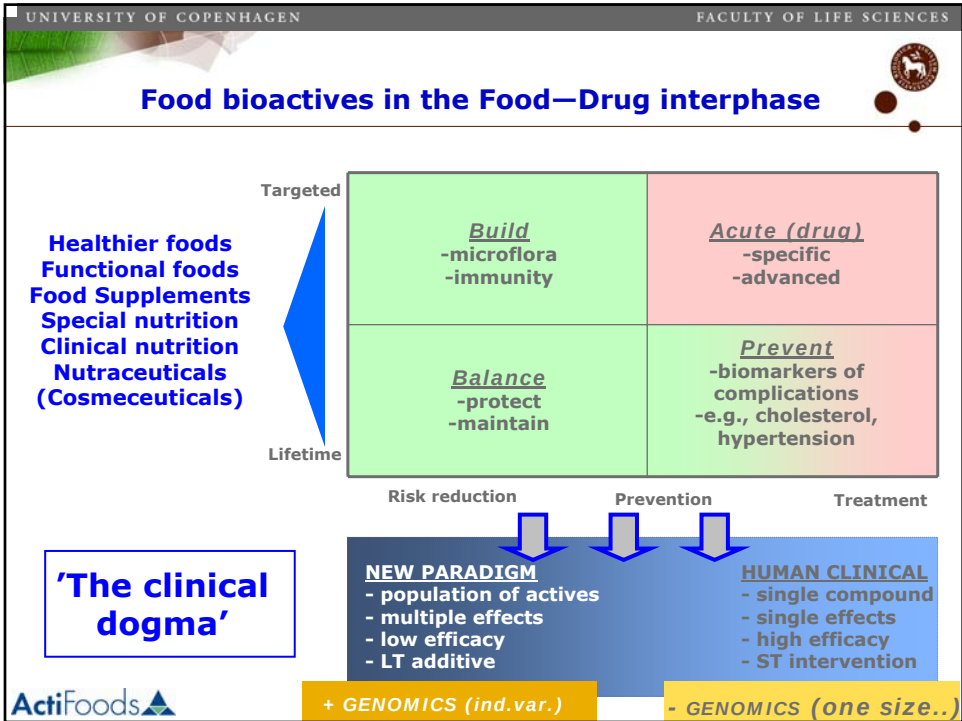
(Fermented) Milk Peptides

- Anti-hypertensive
- Anti-arrhythmic
- Anti-cholesterolaemic
- Anti-atherosclerotic
- Anti-inflammatory
- Satiating (anti-obesigenic)

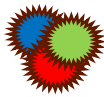
Resveratrol a.o. Plant Phenolics

- Anti-oxidant
- Anti-inflammatory
- Anti-diabetic
- Anti-obesigenic
- Liver protecting
- Energy (endurance)
- Anti-carcinogenic

COMMON FEATURES: small, additive, multiple/multifactorial effects
COMMON CHALLENGE: impressive laboratory and pre-clinical data
 – BUT human clinical trials often inconclusive



Some research priorities for documentation of preventional effects of food



1. Validation of early biomarkers - metabolomics that can be added/consolidated for documentation of small, multifactorial effects over time - typical for anti-inflammatory and anti-oxidant functions etc. - **the clinical dogma.**



2. Dynamics of the microbiome – genomics/metagenomics
healthy/nonhealthy profiles and the way composition may be changed into a more healthy balance as a result of dietary changes (involving pro- and prebiotic 'interventions')



3. The Pre/Postnatal window – investing in health
Principles and processes (biochemical and molecular) that determine the development and maturation of a healthy microbiota, immune system – and **taste & metabolic imprinting**

NB! Ongoing more classical mode-of-action and intervention studies will continue deliver valuable knowledge – but a strong OMICS approach is highly needed for more substantial new knowledge → INNOVATION.

The pre/postnatal window and metabolic and taste imprinting



We are born naked...

- Microbiota

- Immune system

...but



Taste preferences etc.

- Sweet & fat are native preferences
+ imprint from mother's diet

- Bitter & acid tastes of healthy bioactives in foods and ingredients may be 'trained' (imprinted) via breast milk and umbilical cord

Helene Hausner et al. PhD-project af IFS KU-Life
-Physiology and Behaviour, DOI: 1016/j.physb.2008.05.007
-New Scientist, 23 July 2008 p. 14

Also for big men and their cars - The recent trucker study



18 truckers followed over 12 days, 2 groups with different diets

HTM diet:

Carbohydrates 55-60%
(max 10% simple)
Protein 10-15%
Fat 25-30%
(10-15% polyuns. & 15-20% sat.)

Hypertension:
52% (5 needing treatment)

Cholesterol:
74% too high

ATM diet:

Carbohydrates 45-55%
(0% simple)
Protein 10-20%
Fat 30-40%
(60-70% polyuns. & 30-40% sat.)

Hypertension:
30% (2 needing treatment)

Cholesterol:
39% too high

The omics ('holistic') approach

The genome

The transcriptome

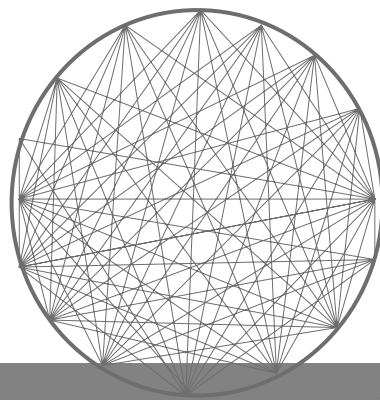
- response to diet
- individuals
- metagenome(s)

The metabolome

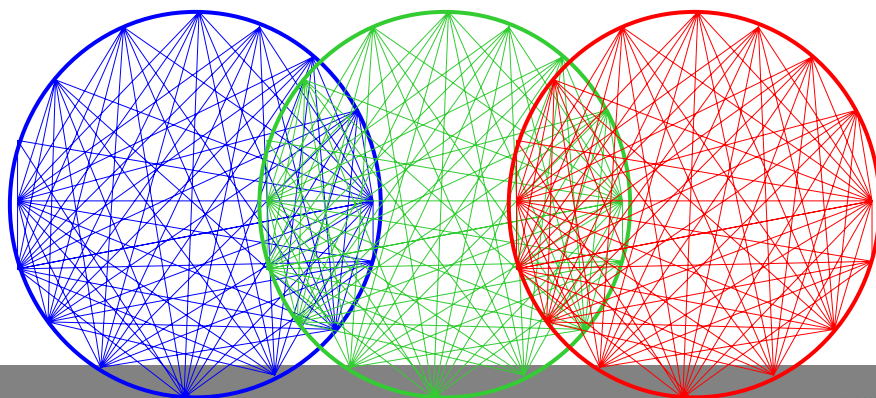
- lipidome, proteome
- 'urinome'

Other 'omes'?

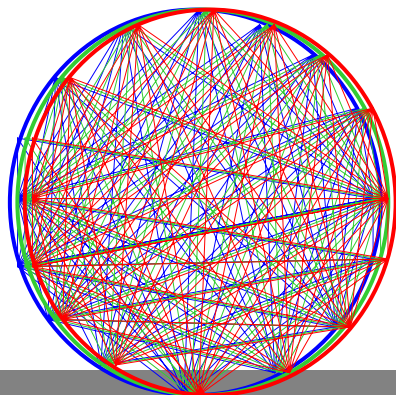
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A (very) complicated pattern profiling



A (very) complicated pattern profiling



DOABLE?

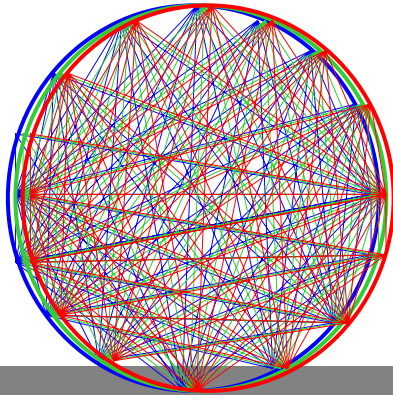
Analytical chemistry

Bioinformatics

New advanced
technologies

-
-

A (very) complicated pattern profiling



DOABLE? - YES!

Analytical chemistry

Bioinformatics

New advanced
technologies

-



*- Members of the microflora and the gut
epithelial/immune cells do it all the time*



**Thank you
- for inviting
me**



**- and for your
attention!**

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