Michael Müller
“Conclusions”
What is health?
You are what you eat
What's healthy?
What is health?

- WHO 1946: “..a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity…”
- The ability to adapt…
- The ability to fully recover from diseases…
2 Meals a day
work as long as possible
& embrace challenges

Walter Breuning (1896 - 2011)
The Nutrigenomics Challenge
Identify the chronic “two hit stress”:

(a) Nutrients (dietary signals) → Signalling through sensor mechanisms → Genes (normal genotype) → Normal phenotype → Homeostasis

(b) Nutrients (dietary signals) → Signalling through sensor mechanisms → Genes (sensitive genotype) → Sensitive phenotype → Onset of disease

‘Hit 1’ Metabolic stress ‘Hit 2’ Proinflammatory stress

‘Healthy’ signatures

‘Stress’ signatures
Metabolic homeostasis & syndrome

**Metabolic Homeostasis**
- Normal hormone response
- Normal nutrient sensing
- Normal hormonal load
- Normal gastrointestinal activity
- Normal sympathetic nervous system function
- Normal visceral adipose tissue function
- Normal immune response

**Metabolic Syndrome**
- Abnormal hormone response
- Abnormal nutrient sensing
- Abnormal visceral adipose tissue function
- Abnormal immune response

**Definition (IDF):**
- Central obesity (usually BMI > 30 kg/m²)
- Plus 2 of the following:
  - Total cholesterol > 150 mg/dl
  - HDL < 40-60 mg/dl
  - Blood pressure ≥ 120/80 mmHg
  - Hyperglycemia

**Complications of Chronic Diabetes:**
- Chronic kidney disease
- Cardiovascular disease
- Peripheral nerve damage
- Eye disease & blindness
- Non-healing skin ulcers, usually leading to amputations
- Non-alcoholic fatty liver disease, which can lead to cirrhosis

**Systemic Inflammation**
- Increased release of inflammatory cytokines
- Increased insulin resistance
- Increased risk of developing chronic diseases

**Systemic Hypertension**
- Increased blood pressure
- Increased risk of developing cardiovascular diseases

**Systemic Lipid Abnormalities**
- Increased cholesterol levels
- Increased triglyceride levels
- Increased risk of developing atherosclerosis

**Systemic Glucose Metabolism**
- Increased glucose uptake
- Increased risk of developing type 2 diabetes

**Conclusion:**
- Metabolic syndrome is a complex condition that requires a multidisciplinary approach for management.

**Nature Medicine**
- Literature review
- Clinical guidelines
- Research advances

**Additional Resources:**
- Textbooks on endocrinology and metabolism
- Online databases on metabolic diseases
- Professional journals on clinical medicine
Controllability of complex networks

- Naturally occurring networks, such as those involving gene regulation, are surprisingly hard to control.
- To fully control a gene regulatory network, roughly 80% of the nodes should be driver nodes. (in contrast to social networks)
- To a certain extent this is reassuring, because it means that such networks are fairly immune to hostile takeovers: a large fraction of the network's nodes must be directly controlled for the whole of it to change.
- By contrast, engineered networks are generally much easier to control, which may or may not be a good thing, depending on who is trying to control the network.
- This may explain also the big difference between “food & mono-target drugs”.

Yang-Yu Liu, Jean-Jacques Slotine & Albert-László Barabási

Diseases as network perturbations
Mutation leading to the gene regulatory network malfunctioning
Network-based disease classification

• A network-based disease classification uncovers the gaps in our experimental and theoretical knowledge.

• It demonstrates that only an integrated programme has the potential to provide a useful framework, by defining disease susceptibility, predicting disease outcome and identifying tailored therapeutic strategies.
METABOLIC SYNDROME

- Increased endocannabinoid tone:
  - Food intake ↑
  - Lipogenesis ↑
- Low-grade systemic inflammation
- Impaired insulin response:
  - Reduced glucose uptake
  - Enhanced FFA release
- High levels of pro-inflammatory cytokines (TNFα, IL-6, MCP-1)
- Adipokines:
  - Adiponectin
  - Leptin
  - Resistin
  - Rbp4
  - Sfrp5
  - Adipsin
- Glucotoxicity
- Lipotoxicity
- Severe complications of chronic diabetes:
  - Diabetic nephropathy
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic skin ulcers

Other key points:
- M2 macrophages (anti-inflammatory)
- M1 macrophages (pro-inflammatory)
- Impaired vascularization: Hypoxic conditions
- Increased inflammation:
  - M1 macrophages ↑
  - Mast cells ↑
  - Tregs ↑
  - B cells ↑
  - CLS (crown-like structures)
  - Fibrosis
  - Mast cells

The diagram illustrates the complex interplay between various metabolic and inflammatory processes, highlighting the role of insulin resistance, adipokine signaling, mitochondrial dysfunction, and endocannabinoid tone in the development of metabolic syndrome.
Organ-specific gene expression signatures of the early phase (metabolic stress) & the late phase of metabolic syndrome
Phenotype plasticity

Phenotypic plasticity is the ability of an organism to change its phenotype in response to changes in the environment (e.g. nutrition).
1 Genotype => 5 nutritional phenotypes

Stuart Howell’s amazing weight loss journey from 24st 4.5lbs in January 2008 to 11st 13.5lbs in July 2010

155 kg  76 kg
Genotype-phenotype plasticity
Understanding Nutrition
How nutrients regulate our genes: via sensing molecular switches

Improved organ capacity by PUFAs

References:
- J Clin Invest. 2004;114:94-103
- J Biol Chem. 2006;28:934-44
- Endocrinology. 2006;147:1508-16
- Physiol Genetics. 2007;30:192-204
- Endocrinology. 2007;148:2753-63
- BMC Genetics 2007; 8:267
- Arterioscler Thromb Vasc Biol. 2007;27:2420-7
- PLOS ONE 2008;3(2):e1681
- BMC Genetics 2008; 9:231
- BMC Genetics 2008; 9:262
- J Biol Chem. 2008;283:22620-7
- Plos One 2009;4(8):e6796
- HEPATOLOGY 2010;51:511-522
- Mol Cell Biology 2009;29:6257-67
- Am J Clin Nutr. 2010;91:208-17
- BMC Genetics 2009
- Physiol. Genomics 2009
- Circulation 2010
- Diabetes 2010
- Cell Metabolism 2010
Intestinal PPAR target genes are largely regulated by dietary PUFAS/MUFAs

<table>
<thead>
<tr>
<th>6h after oral gavage</th>
<th>OA 18:1</th>
<th>EPA 20:5</th>
<th>DHA 22:6</th>
<th>WY14643</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>508</td>
<td>874</td>
<td>894</td>
<td>1218</td>
</tr>
</tbody>
</table>
Intestine
Comparison intestine / liver
Dose-dependent effects of dietary fat on development of obesity in relation to intestinal differential gene expression in C57BL/6J mice

![Graph showing weight gain (g) for different dietary fat percentages: 10 E%, 20 E%, 30 E%, 45 E% with significant differences indicated by letters a, ab, bc, c.]
Robust & concentration dependent effects in small intestine
Differentially regulated intestinal genes by high fat diet

Number of differentially expressed genes

<table>
<thead>
<tr>
<th></th>
<th>proximal</th>
<th>middle</th>
<th>distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-10E%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-10E%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-10E%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PLOS one 2011
Heat map diagrams of fat-dose dependently regulated genes, categorized according to their biological function.
Cellular localization and specific lipid metabolism-related function of fat-dose dependently regulated genes

Cytoplasm (e.g. lipid hydrolysis & intracellular lipid transport)
- Abhd5
- Acot1
- Acot12
- Adefp
- Fabp1
- Fabp2
- Glpdp2
- Hsd17b11
- Akr1b7
- Ddh1d1
- Osbp1f

Mitochondrion (e.g. fatty acid oxidation & ketogenesis)
- Acaa2
- Acad1
- Acad2
- Acad3
- Acadv1
- Acs13
- Hmgcs2
- Pgs1
- Hsd3b2
- Oxsm
- Pccb
- Ocxt1

Cell membrane (e.g. lipid transport)
- Adipo2
- Arv1
- Cad36
- Daglb
- Plcb3
- Abca1
- Abcg5
- Abcg8
- Npc1l1

Peroxisome (e.g. fatty acid oxidation)
- Acot4
- Hsd17b4
- Acot8
- Acox2
- Pex13
- Phyc
- Slc27a2
- Hac1
- Agps

Endoplasmatic reticulum (e.g. lipid hydrolysis)
- Ebp
- Hsd17b2
- Hsd17b6
- Pla2g12b
- Pnpla8
- Slc27a5
- Ces3

Lipoprotein particles (e.g. extracellular lipid transport)
- Apoa2
- Apoa4
- Apoc2
- Apob

PLOS one 2011
The intestinal tube model for lipid absorption

4 cm

C1 C2 C3 C4 C5 C6 C7 C8 C9 C10

10% FAT

45% FAT

60% FAT

?
Effect of Fish Oil Supplementation on Quality of Life in a General Population of Older Dutch Subjects: A Randomized, Double-Blind, Placebo-Controlled Trial

Ondine van de Rest, MSc,* Johanna M. Geleijnse, PhD,* Frans J. Kok, PhD,* WiJa A. van Staveren, PhD,* Marcel G.M. OldeRikkert, MD, PhD, † Aartjan T.F. Beekman, MD, PhD, † and Lisette C.P.G.M. de Groot, PhD*

OBJECTIVES: To investigate the effect of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) supplementation on quality of life (QOL).

DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING: Independently living individuals from the general older Dutch population.

PARTICIPANTS: Three hundred two individuals aged 65 and older without depression or dementia.

INTERVENTION: 1,800 mg/d EPA-DHA (n = 96), 400 mg/d EPA-DHA (n = 100), or placebo capsules (n = 106) for 26 weeks.


Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial1–3

Ondine van de Rest, Johanna M Geleijnse, Frans J Kok, WiJa A van Staveren, Willibrord H Hoefnagels, Aartjan TF Beekman, and Lisette CPGM de Groot

Conclusions: In this randomized, double-blind, placebo-controlled trial we observed no effect of EPA+DHA supplementation for 26 wk on mental well-being in the general older population studied. This trial was registered at clinicaltrials.gov as NCT00124852. Am J Clin Nutr 2008;88:706–13.
Fish-oil supplementation induces anti-inflammatory gene expression profiles in human blood mononuclear cells

Less inflammation & decreased pro-arteriosclerosis markers = Anti-immuno-senescence

NUGO week 2011

C Buettner

CNS regulation
Satiety signals

H Vidal
M Ryden
Ling Qi

Energy absorption
Fat digestion and absorption

Energy storage
Long-term fat storage
Fat mobilization

Energy expenditure
Fat oxidation

W d Vos
C Wijmenga

Energy storage and conversion
Short-term fat storage
Fat oxidation

P Schrauwen

N Stefan
NUGO 2011:
Metabolic health = plasticity / flexibility

- The personal genome is the starting point & we can get comprehensive information about it (D. Mac Arthur, J Hoeijmakers, P vd Spek) => don’t forget “bioinformatics & databasing”
- Health is dynamic: The property to adapt to metabolic perturbations / challenges (M Huber)
- Feeding / fasting => autophagy => cellular homeostasis & “exercise” (R Singh)
- Caloric restriction => chromatin “exercise” (L Fontana)
- Food bioactives that modulate transcription (e.g. via nuclear receptors) or chromatin activity (nutri-epigenome) => cell & organ “exercise” (C Cummins)
So how to keep our metabolic health

• Identify chronic (non-resolving) stress using systems “perturbation” tests & deep genomics-based phenotyping (E Holmes, R Gerszten)

• Solve it!
  – Less Inflammation
  – Less Metabolic Stress (sat. fat, lipogenic foods)
  – More Exercise (muscle & other organs) with a “challenging” lifestyle & food pattern
  – Eat less from time to time

This will be the future of Nutrigenomics research.
Sander Kersten
Linda Sanderson
Natasha Georgiadi
Mark Bouwens
Lydia Afman
Guido Hooiveld
Rinke Stienstra
Wilma Steegenga
Meike Bunger
Philip de Groot
Mark Boekschoten
Nicole de Wit
Mohammad Ohid Ullah
Susan van Dijk
Diederik Esser &….

Christian Trautwein
Folkert Kuipers
Ben van Ommen + many more

THANKS