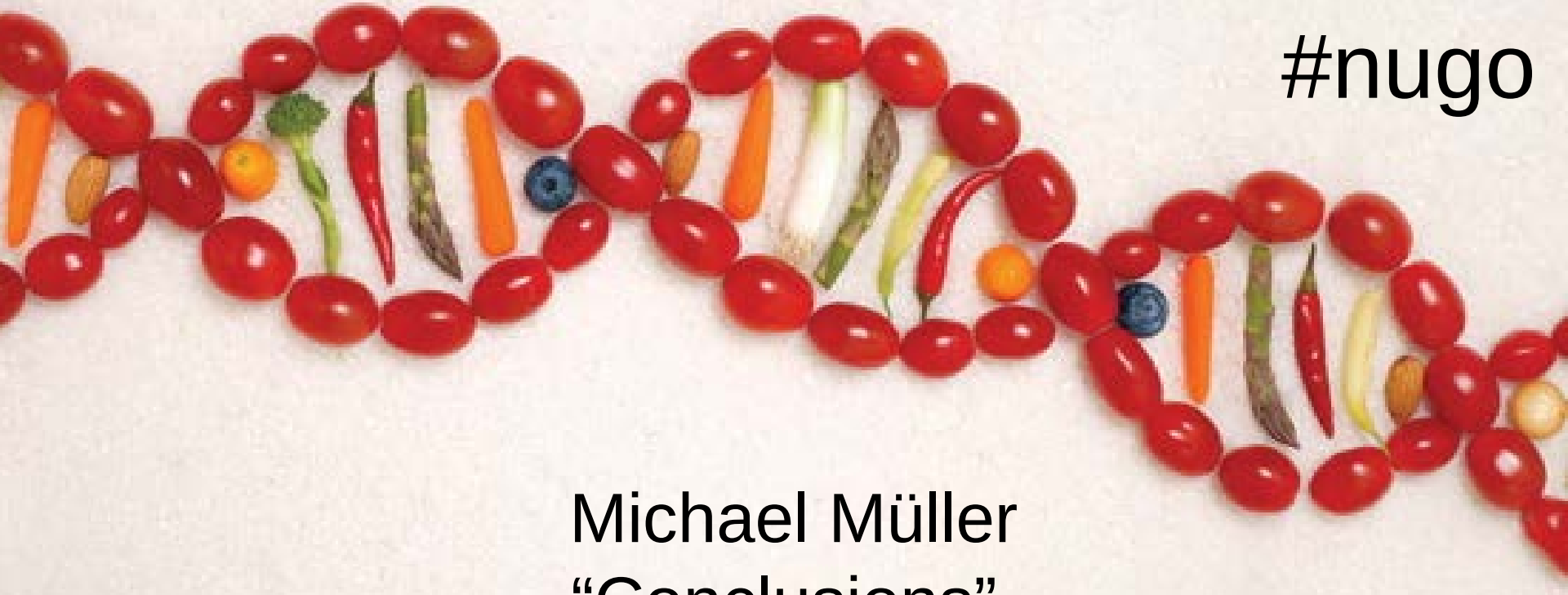
8th NUGO week Wageningen

#nugo



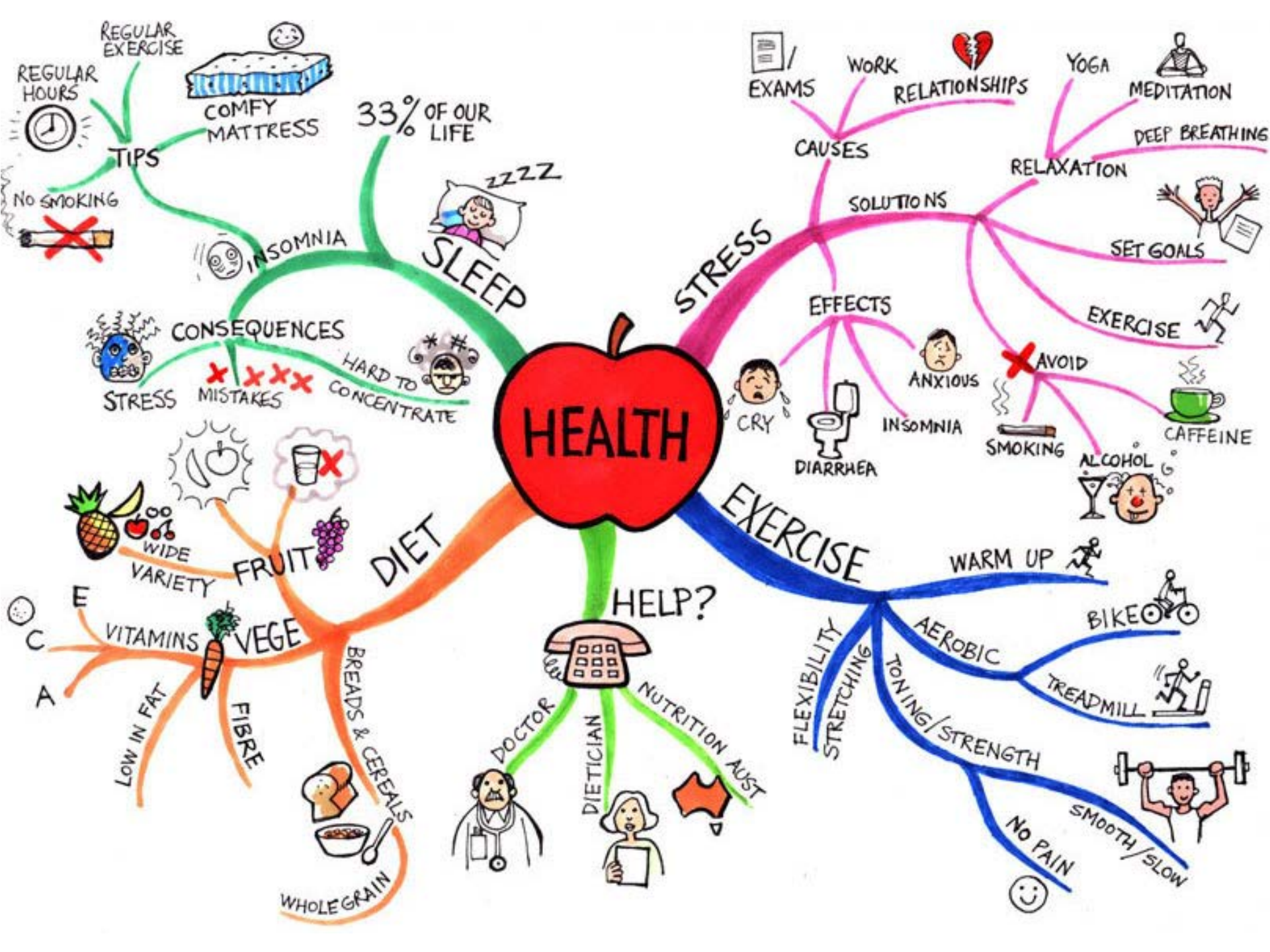
Michael Müller

"Conclusions"

What is health?

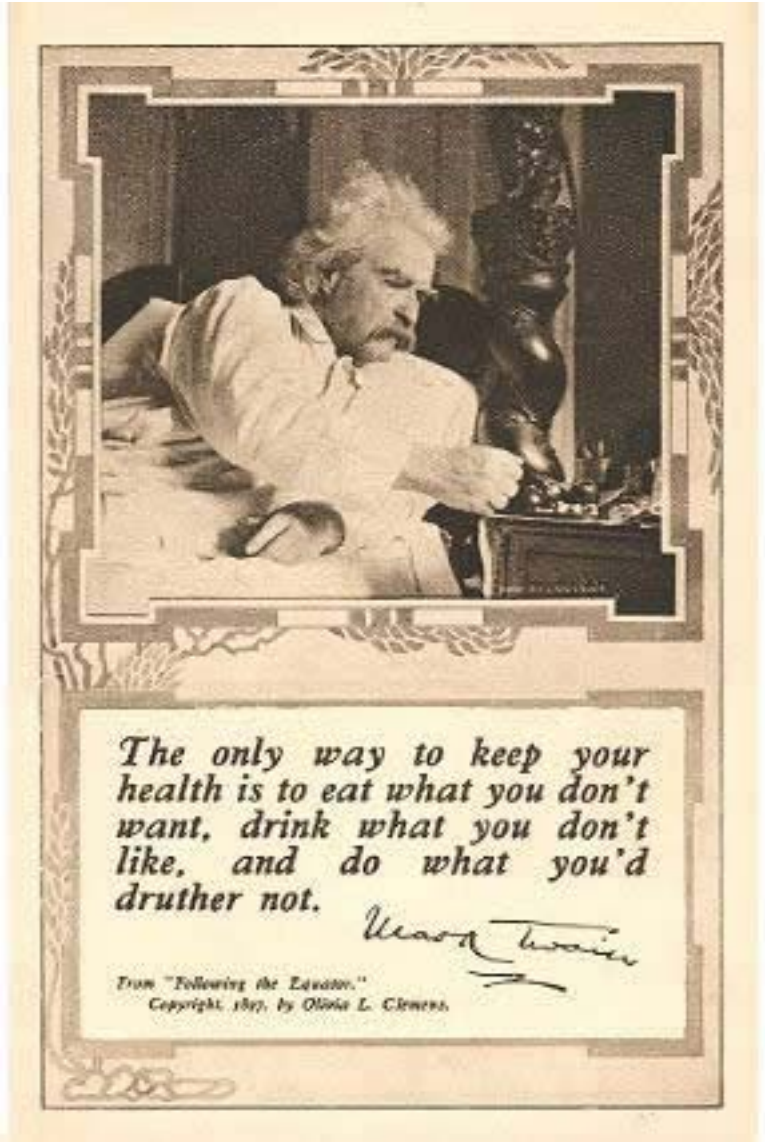
You are what you eat

What's healthy?


HEALTH
SLEEP
33% OF OUR LIFE
TIPS
REGULAR EXERCISE
REGULAR HOURS
COMFY MATTRESS
NO SMOKING
INSOMNIA
CONSEQUENCES
STRESS
MISTAKES
HARD TO CONCENTRATE
STRESS
CAUSES
EXAMS
WORK
RELATIONSHIPS
SOLUTIONS
RELAXATION
YOGA
MEDITATION
DEEP BREATHING
SET GOALS
EXERCISE
AVOID
CAFFEINE
ALCOHOL
SMOKING
EFFECTS
CRY
DIARRHEA
INSOMNIA
ANXIOUS
DIET
FRUIT
WIDE VARIETY
VEGE
VITAMINS
A
C
E
LOW IN FAT
FIBRE
BREADS & CEREALS
WHOLEGRAIN
HELP?
DOCTOR
DIETICIAN
NUTRITION AUST
EXERCISE
WARM UP
AEROBIC
BIKE
TREADMILL
TONING/STRENGTH
FLEXIBILITY
STRETCHING
SMOOTH/SLOW
NO PAIN

What is health?

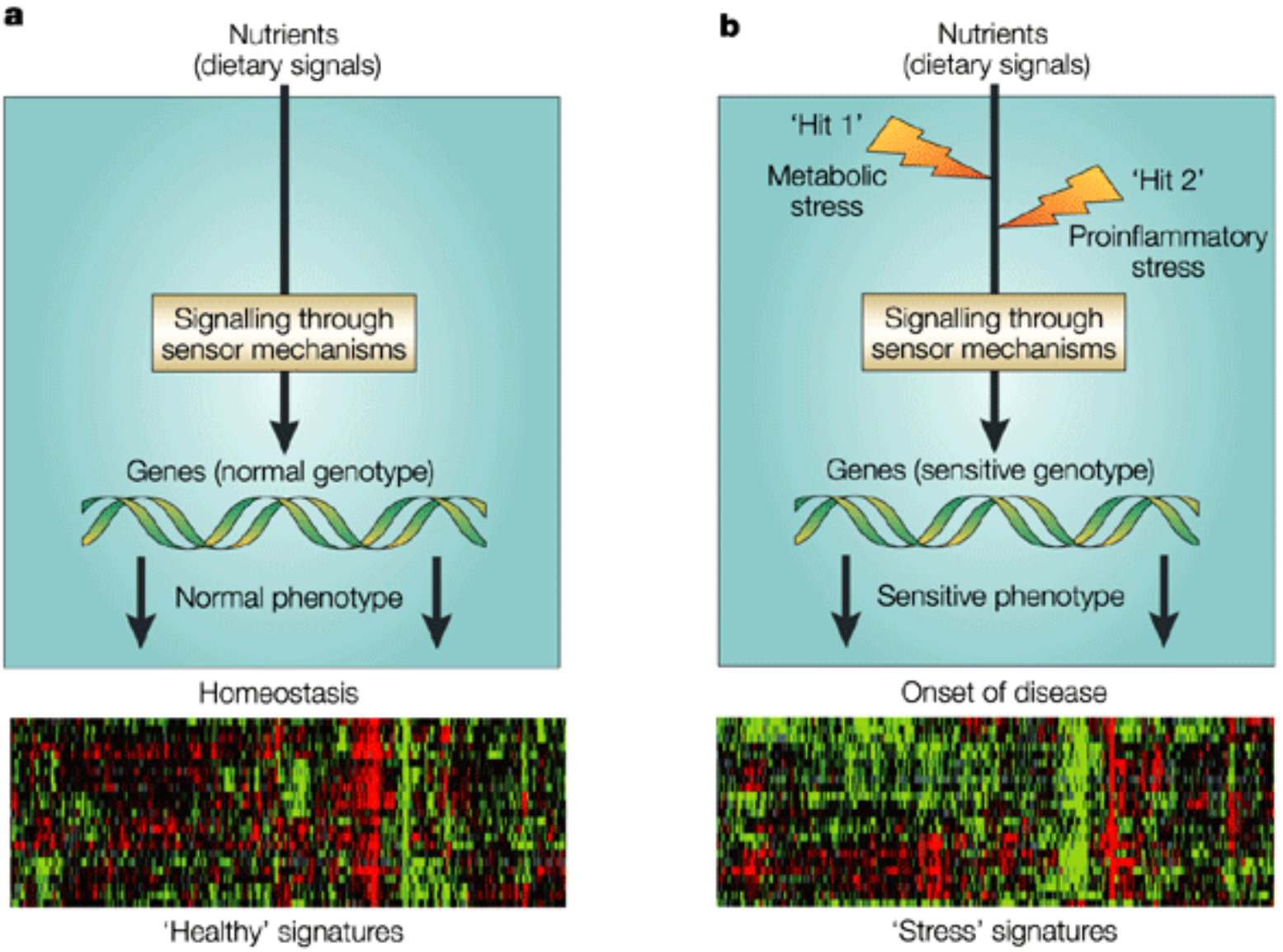
- WHO 1946: "..a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity…"
- The ability to adapt…
- The ability to fully recover from diseases…



2 Meals a day
work as long as possible
& embrace challenges

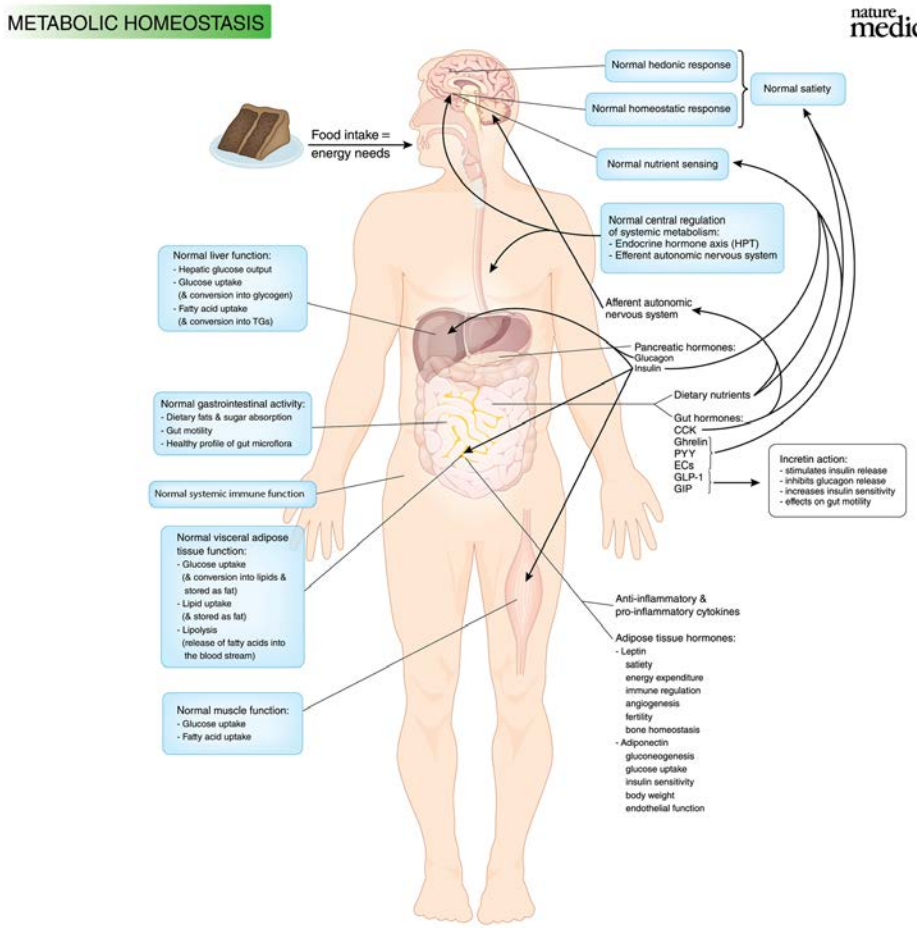
Walter Breuning (1896 - 2011)

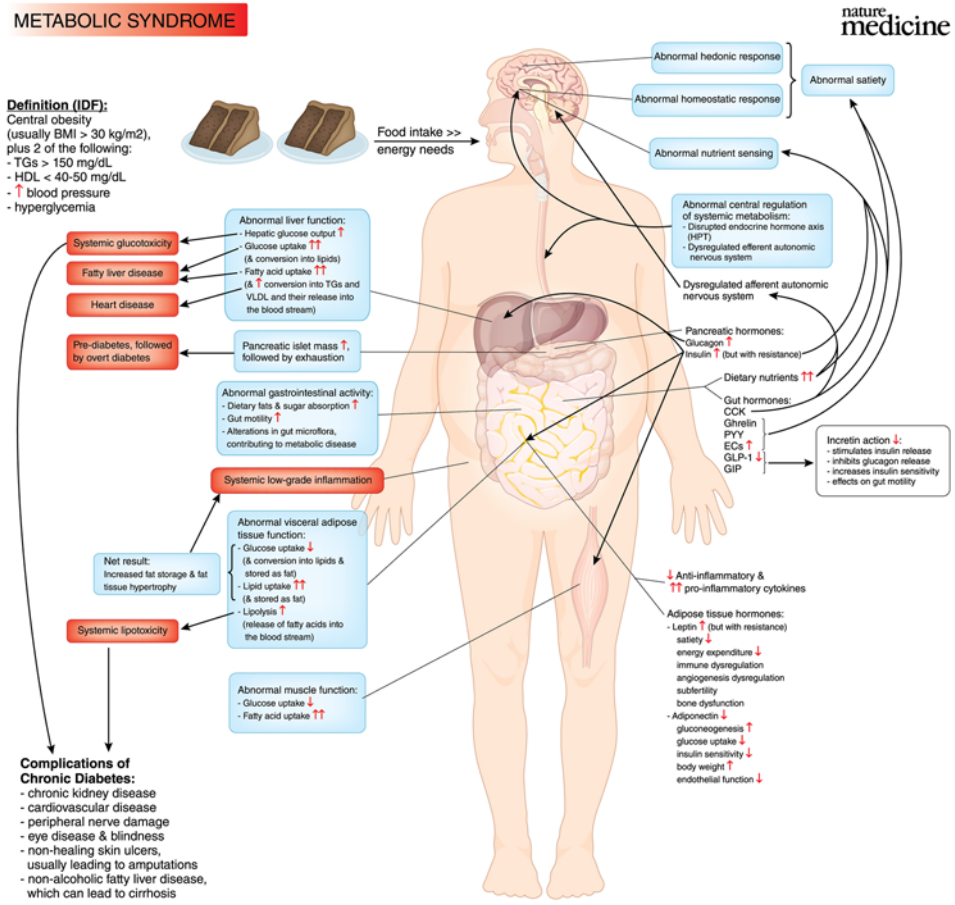
The Nutrigenomics Challenge
Identify the chronic "two hit stress":



Nature Reviews | Genetics 2003

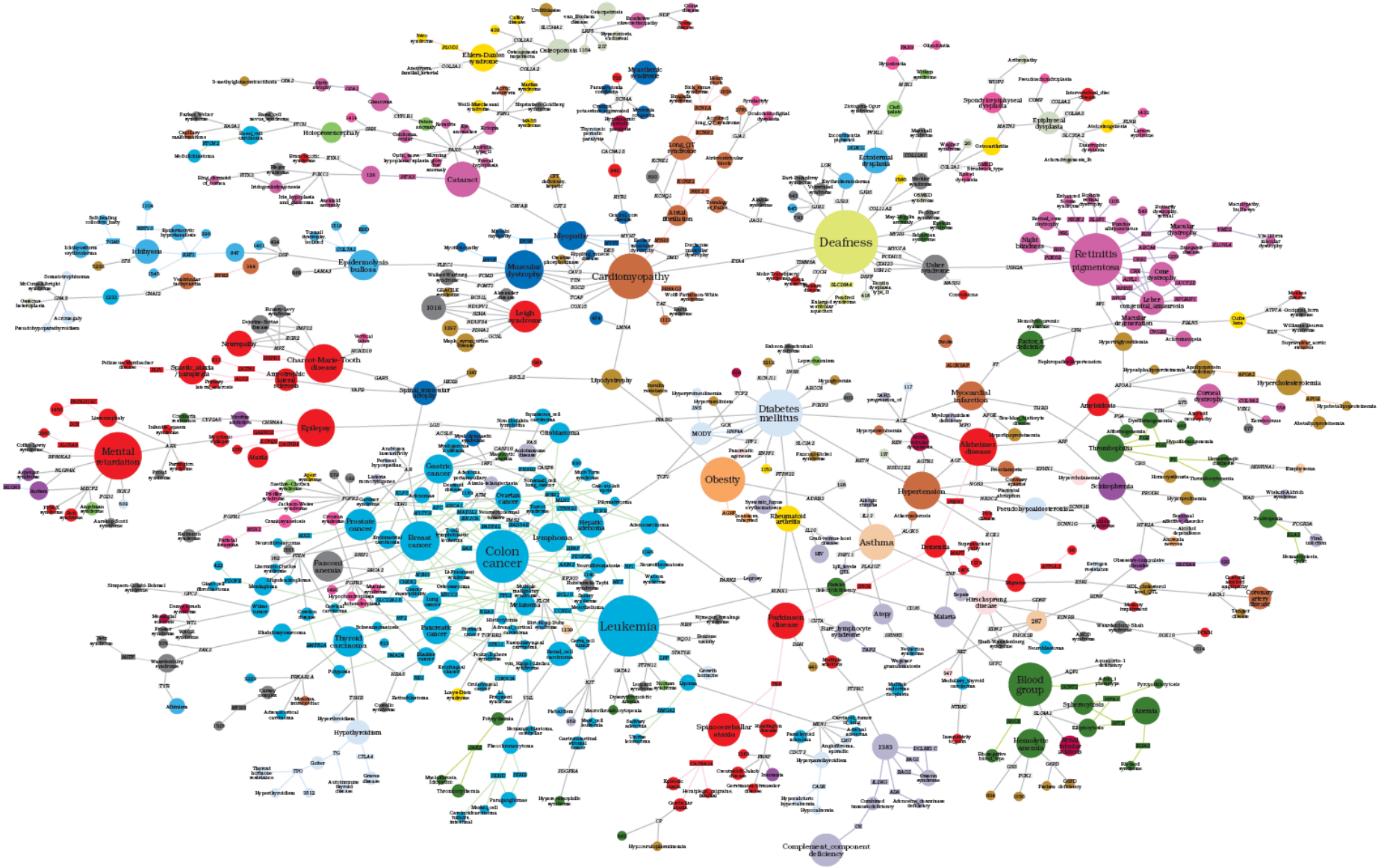
Metabolic homeostasis & syndrome





The human disease network

Goh K-I, Cusick ME, Valle D, Childs B, Vidal M, Barabási A-L (2007) *Proc Natl Acad Sci USA* 104:8685-8690



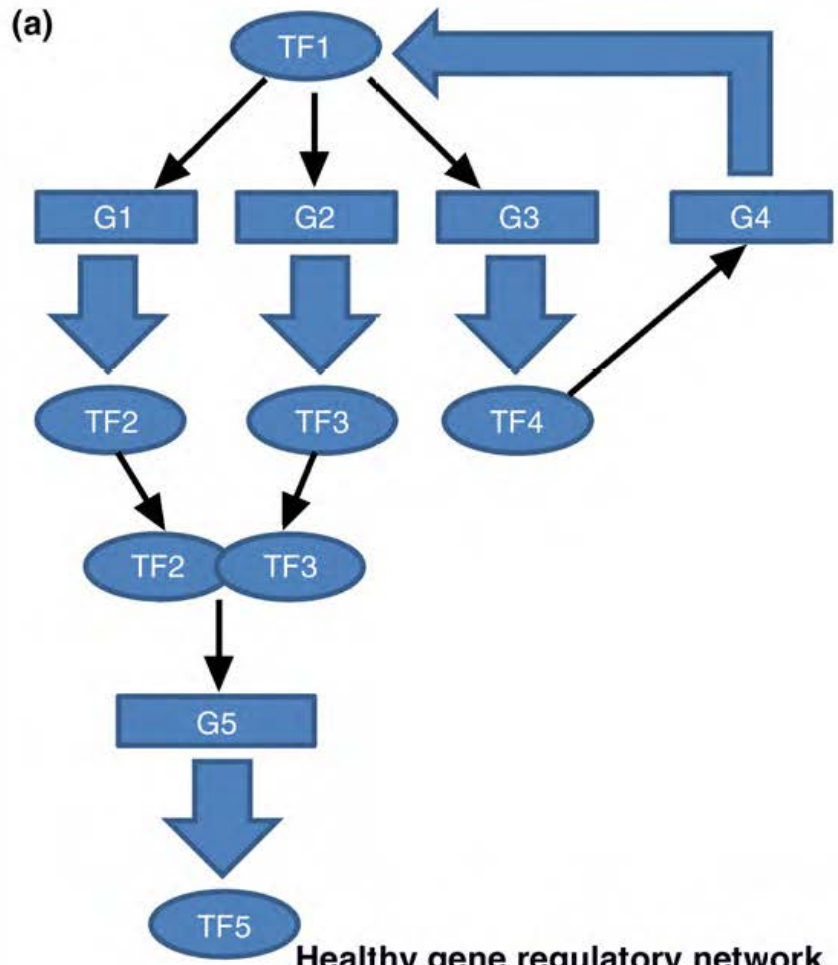
Controllability of complex networks

- 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”.

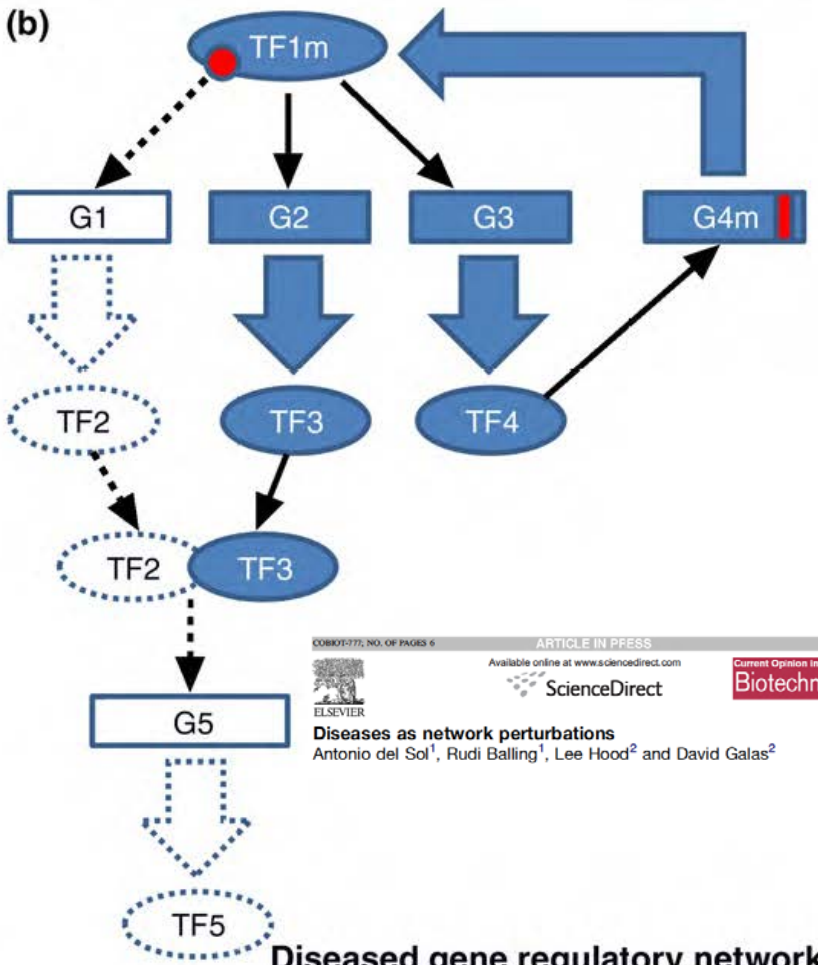
Yang-Yu Liu, Jean-Jacques Slotine & Albert-László Barabási

Nature 473, 167–173, 2011

Diseases as network perturbations
Mutation leading to the gene regulatory network malfunctioning



Healthy gene regulatory network



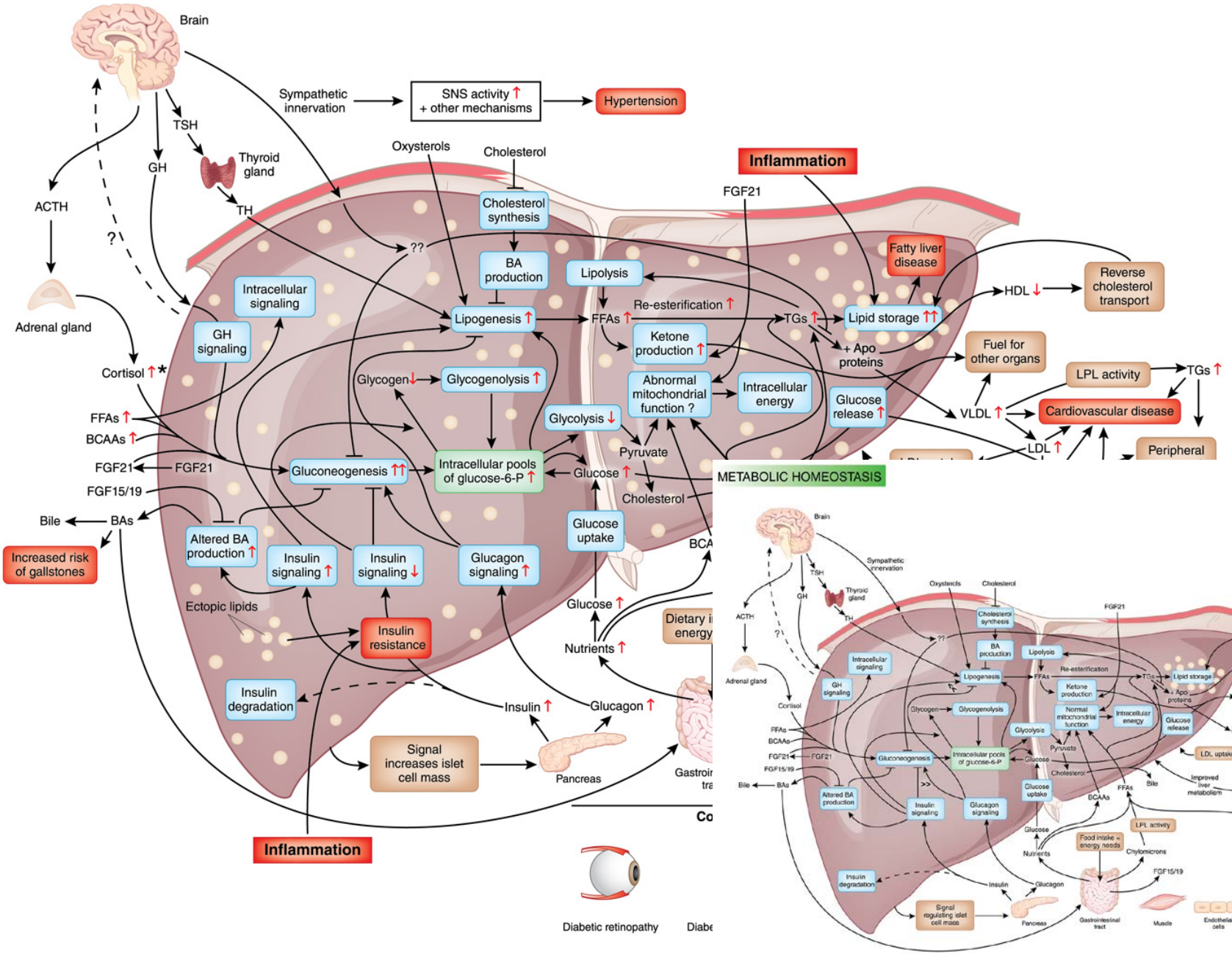
Diseased gene regulatory network

Current Opinion in Biotechnology

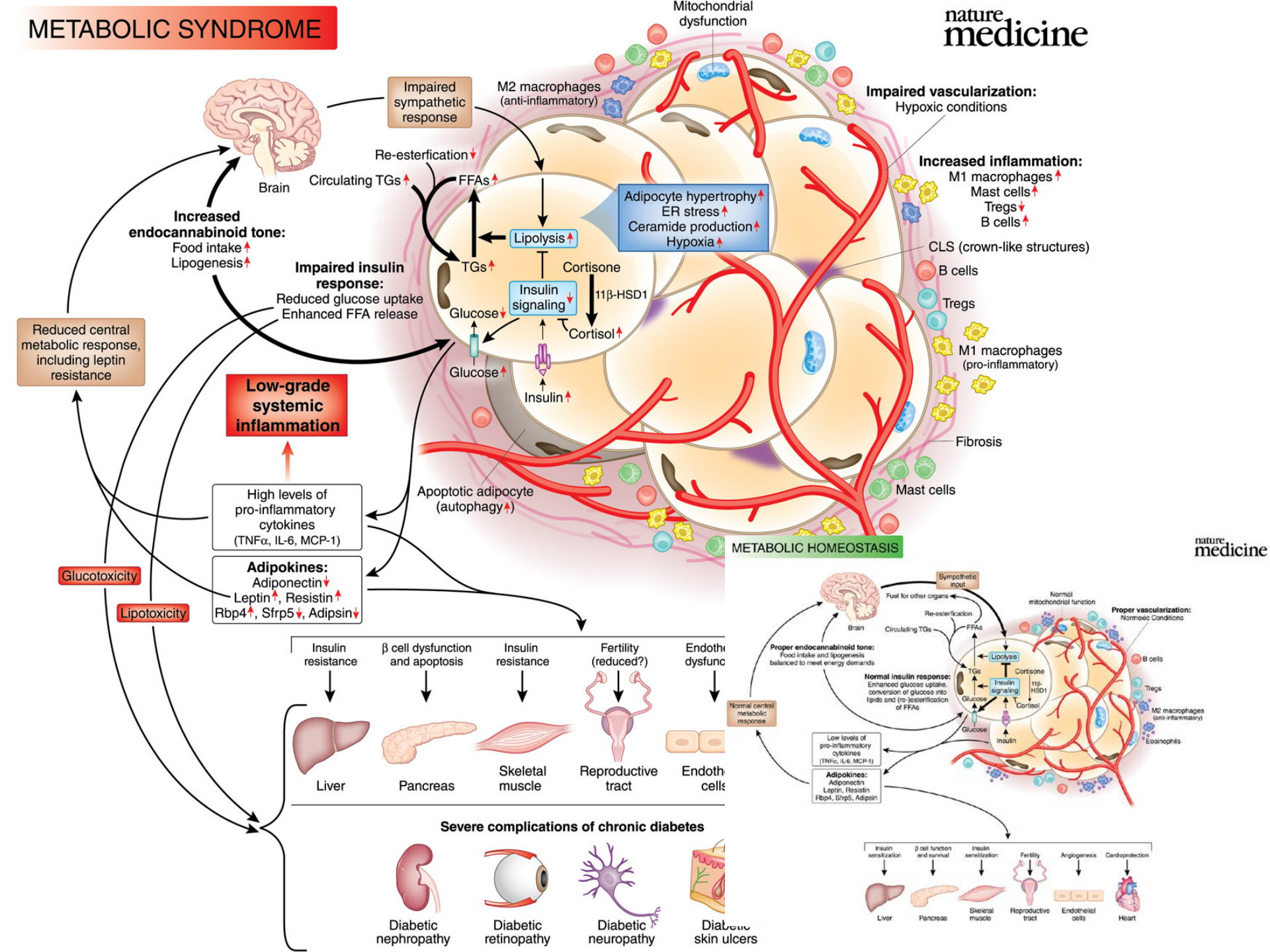
Network-based disease classification

- 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.

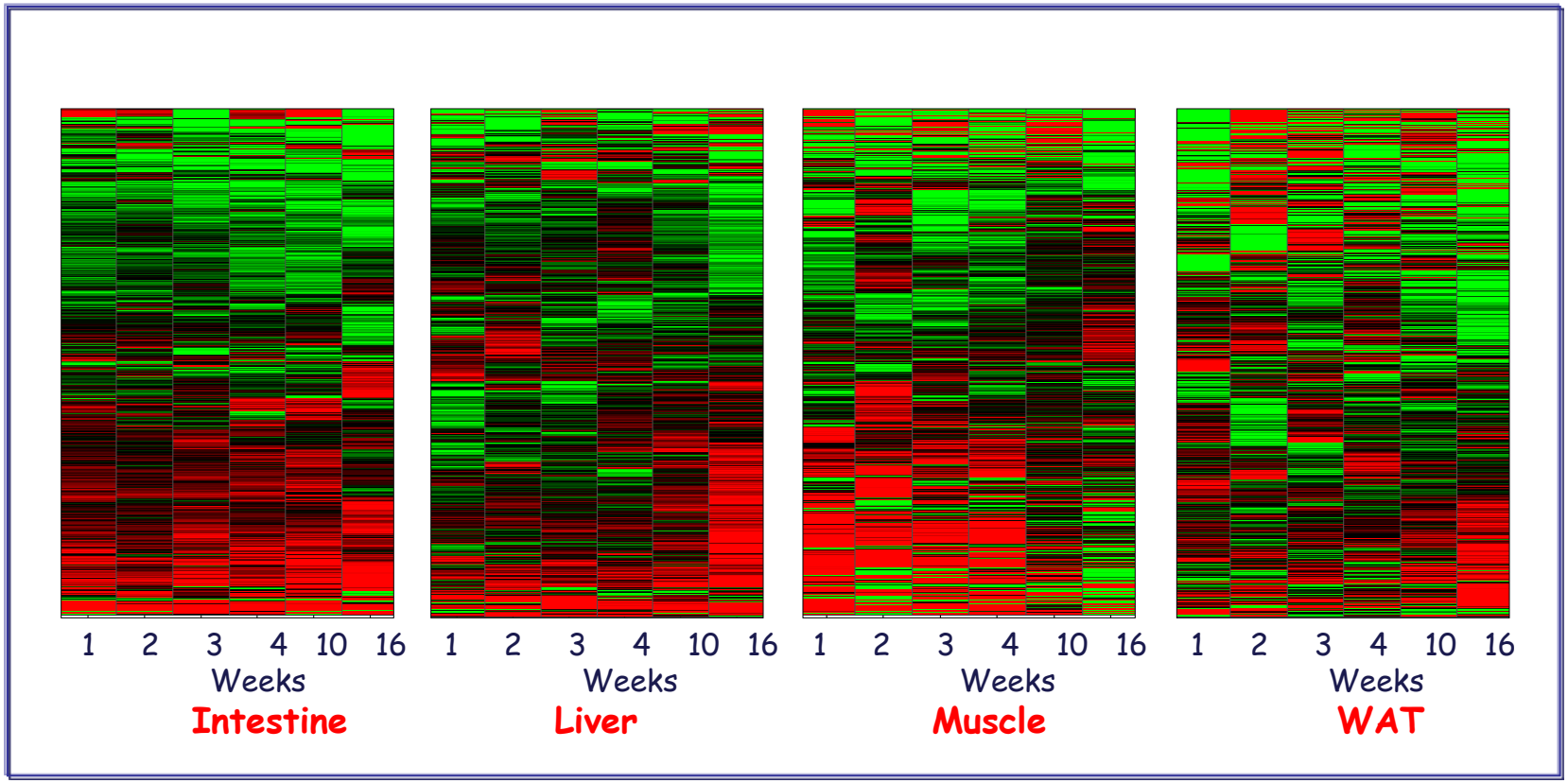
nature medicine



METABOLIC SYNDROME

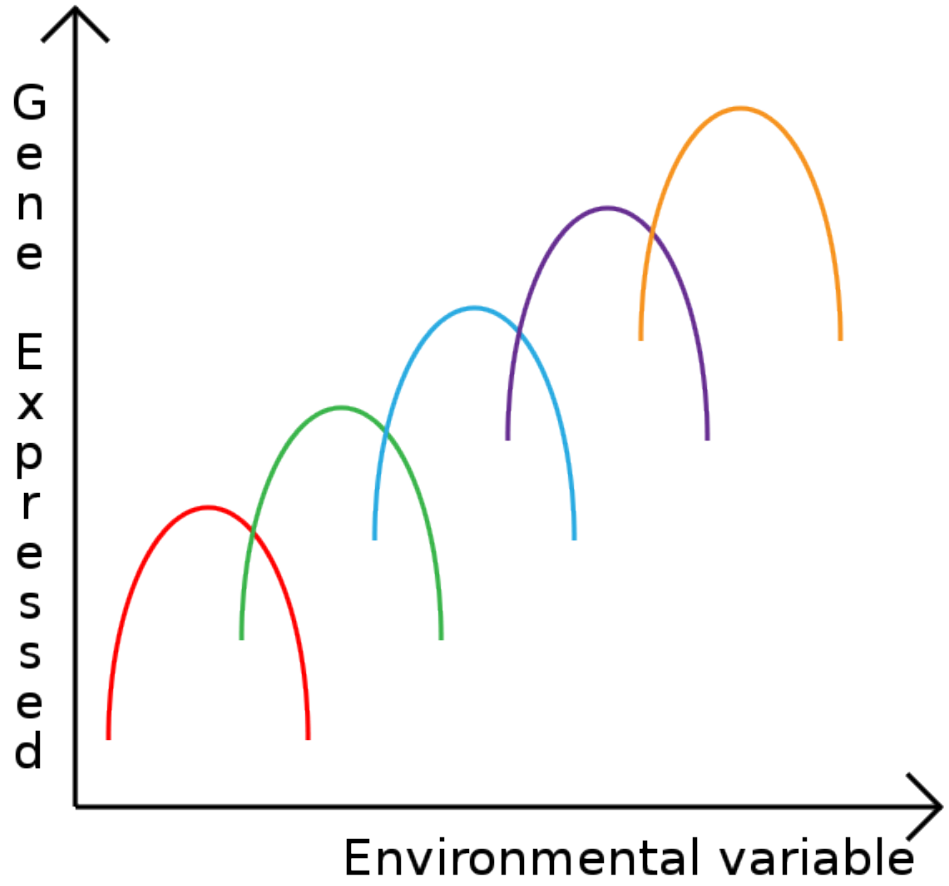


Organ-specific gene expression signatures of the early phase (metabolic stress) & the late phase of metabolic syndrome



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

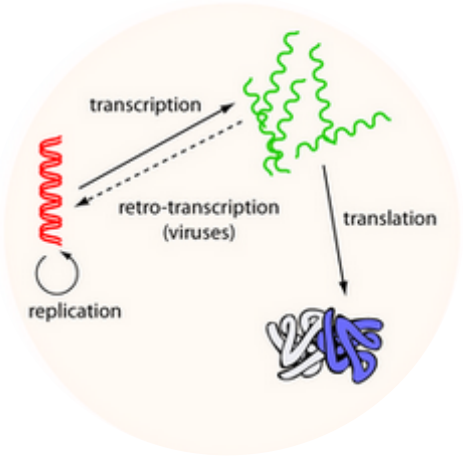
155 kg

76 kg

Genotype-phenotype plasticity

RNA

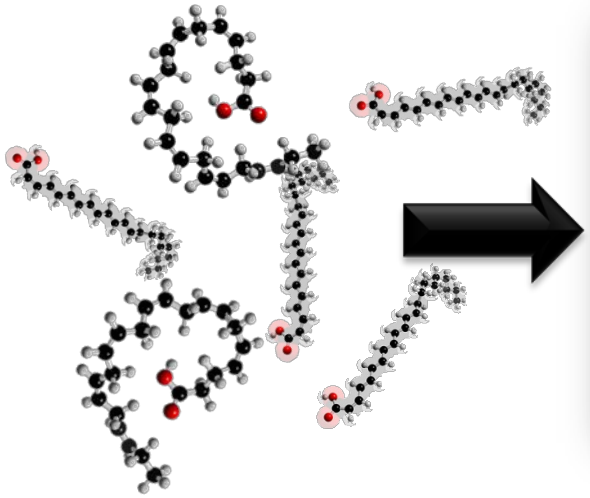
DNA

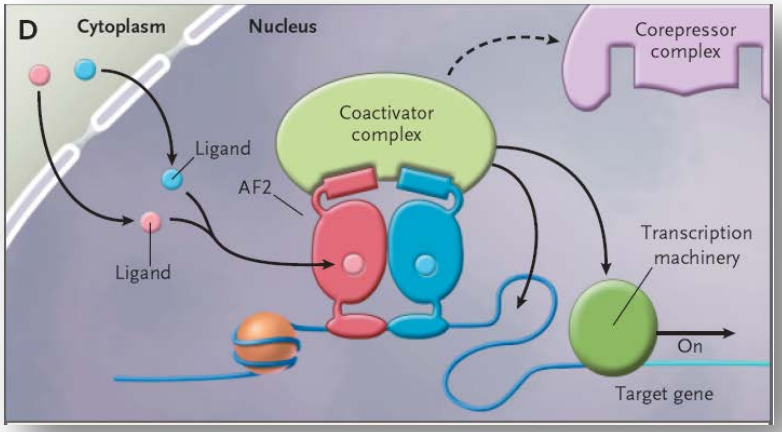


PROTEIN

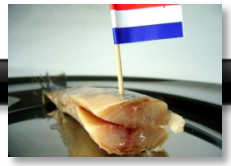
Understanding Nutrition

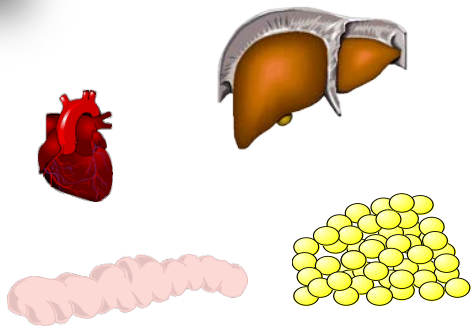
How nutrients regulate our genes: via sensing molecular switches





Improved organ capacity by PUFAs





J Clin Invest. 2004;114:94-103
J Biol Chem. 2006;28:934-44
Endocrinology. 2006;147:1508-16
Physiol Genomics. 2007;30:192-204
Endocrinology. 2007;148:2753-63
BMC Genomics 2007; 8:267
Arterioscler Thromb Vasc Biol. 2007;27:2420-7

Am J Clin Nutr. 2007;86(5):1515-23
PLOS ONE 2008;3(2):e1681
BMC Genomics 2008; 9:231
BMC Genomics 2008; 9:262
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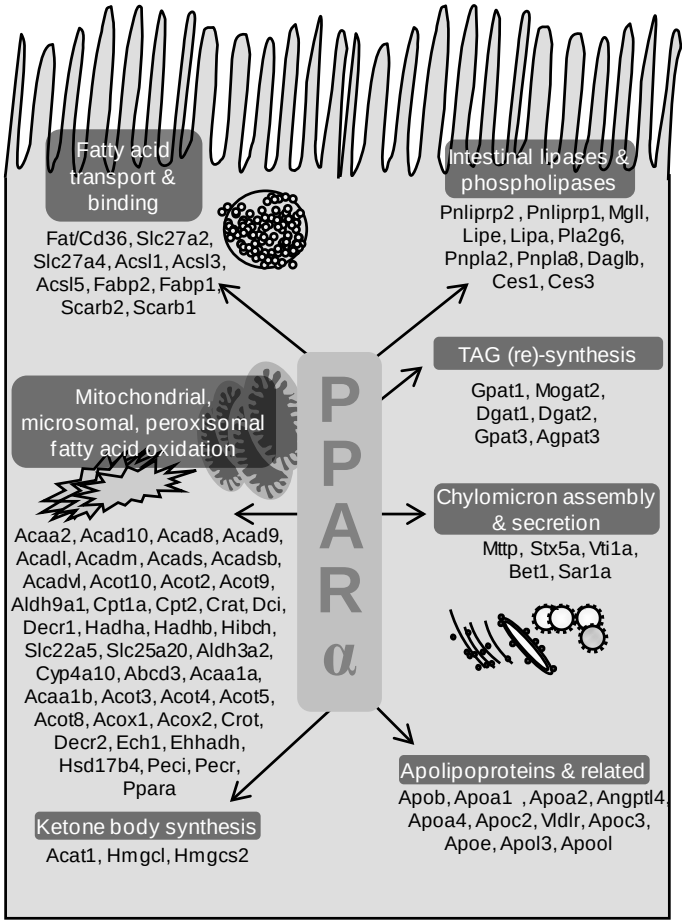
Arterioscler Thromb Vasc Biol. 2009;29:969-74.
Plos One 2009;4(8):e6796
HEPATOLOGY 2010;51:511-522

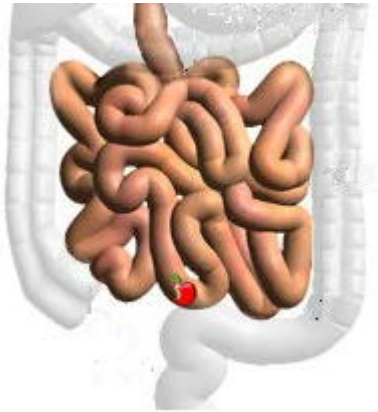
Am J Clin Nutr. 2009; 90:415-24
Am J Clin Nutr. 2009;90:1656-64
Mol Cell Biology 2009;29:6257-67
Am J Clin Nutr. 2010;91:208-17
BMC Genomics 2009
Physiol. Genomics 2009
Circulation 2010
Diabetes 2010
Cell Metabolism 2010

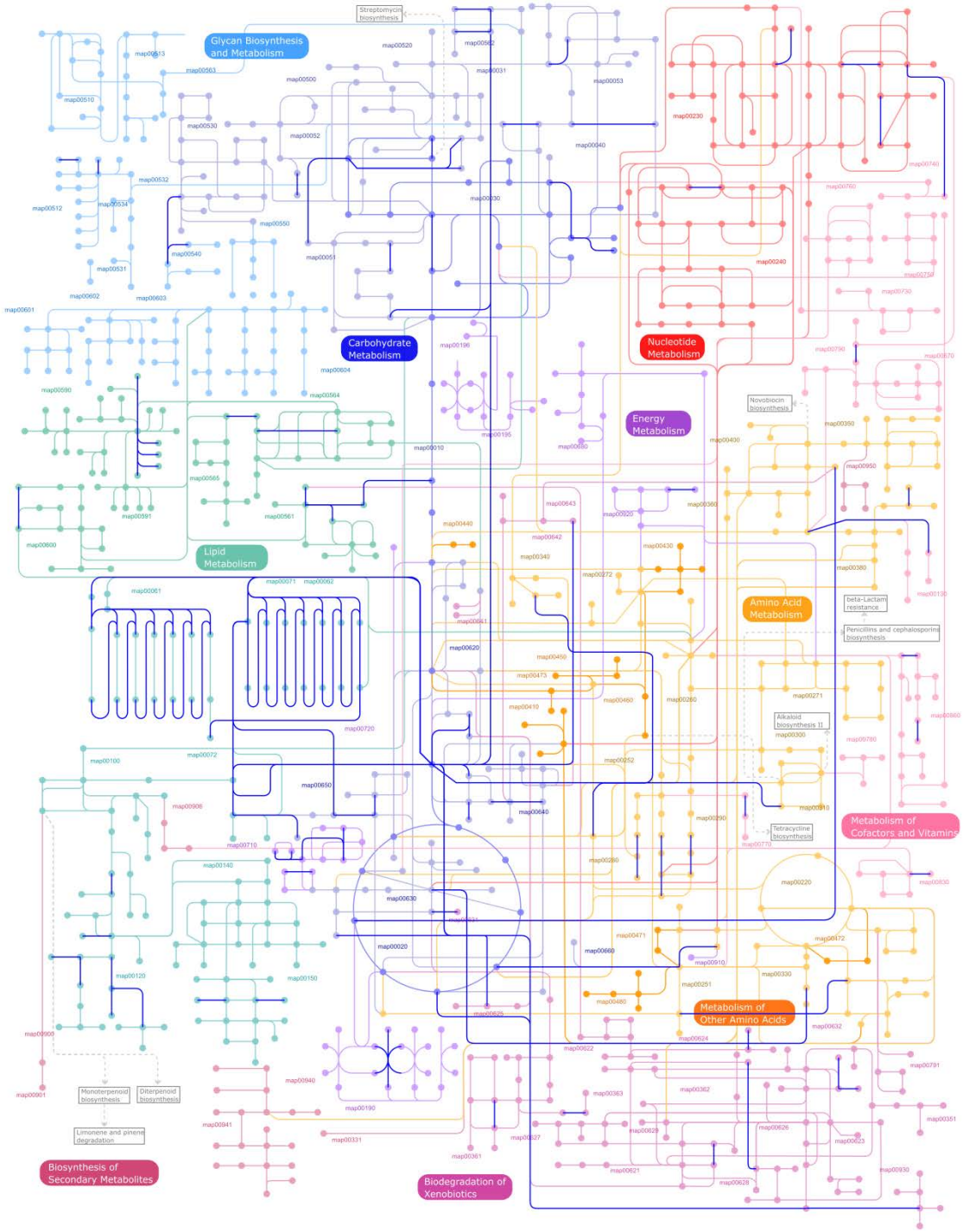
Intestinal PPAR target genes are largely regulated by dietary PUFAS/MUFAs

6h after oral gavage	OA 18:1	EPA 20:5	DHA 22:6	WY14643
Genes	508	874	894	1218

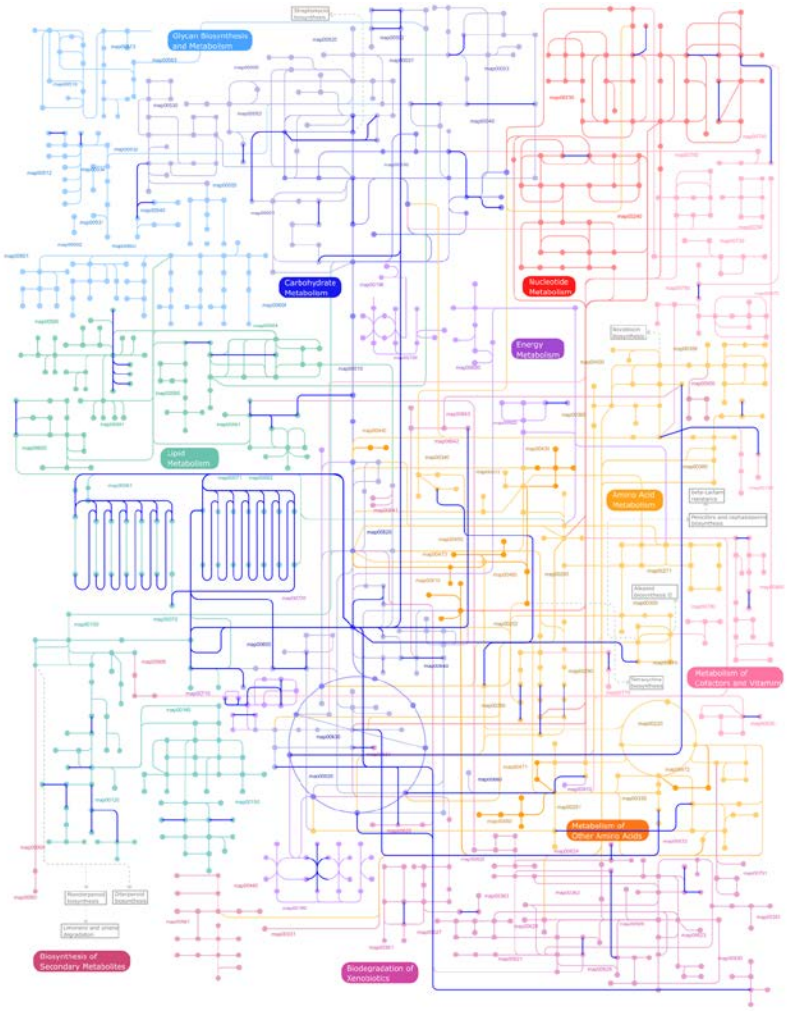


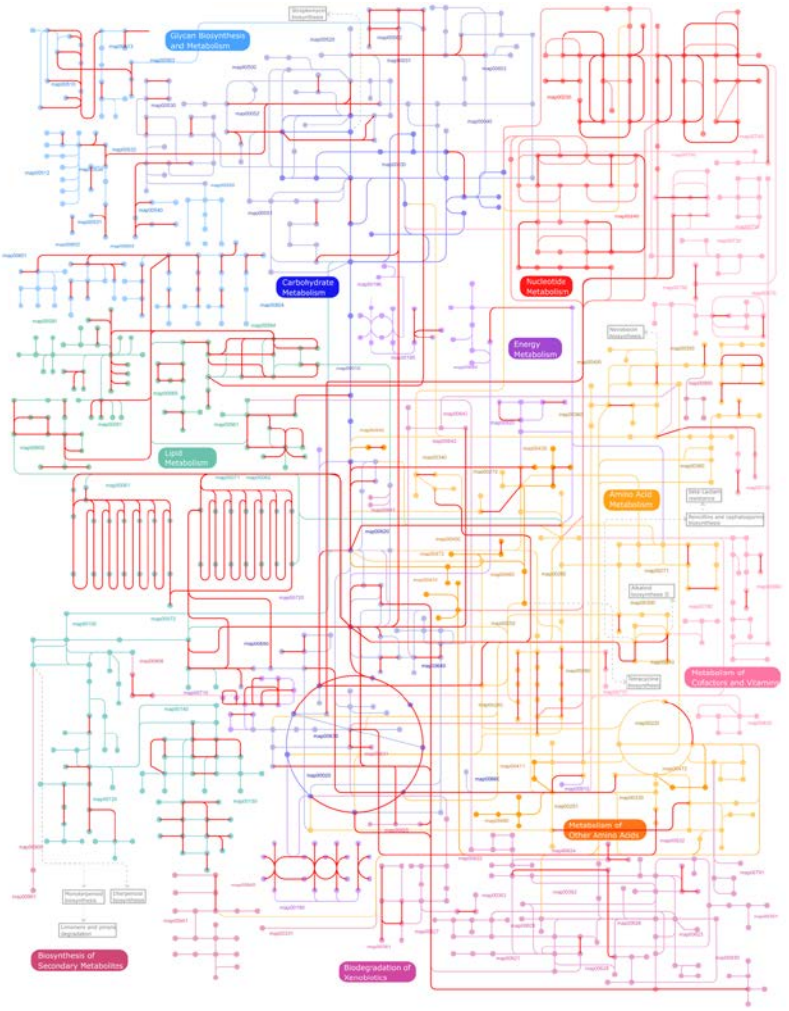
Intestine



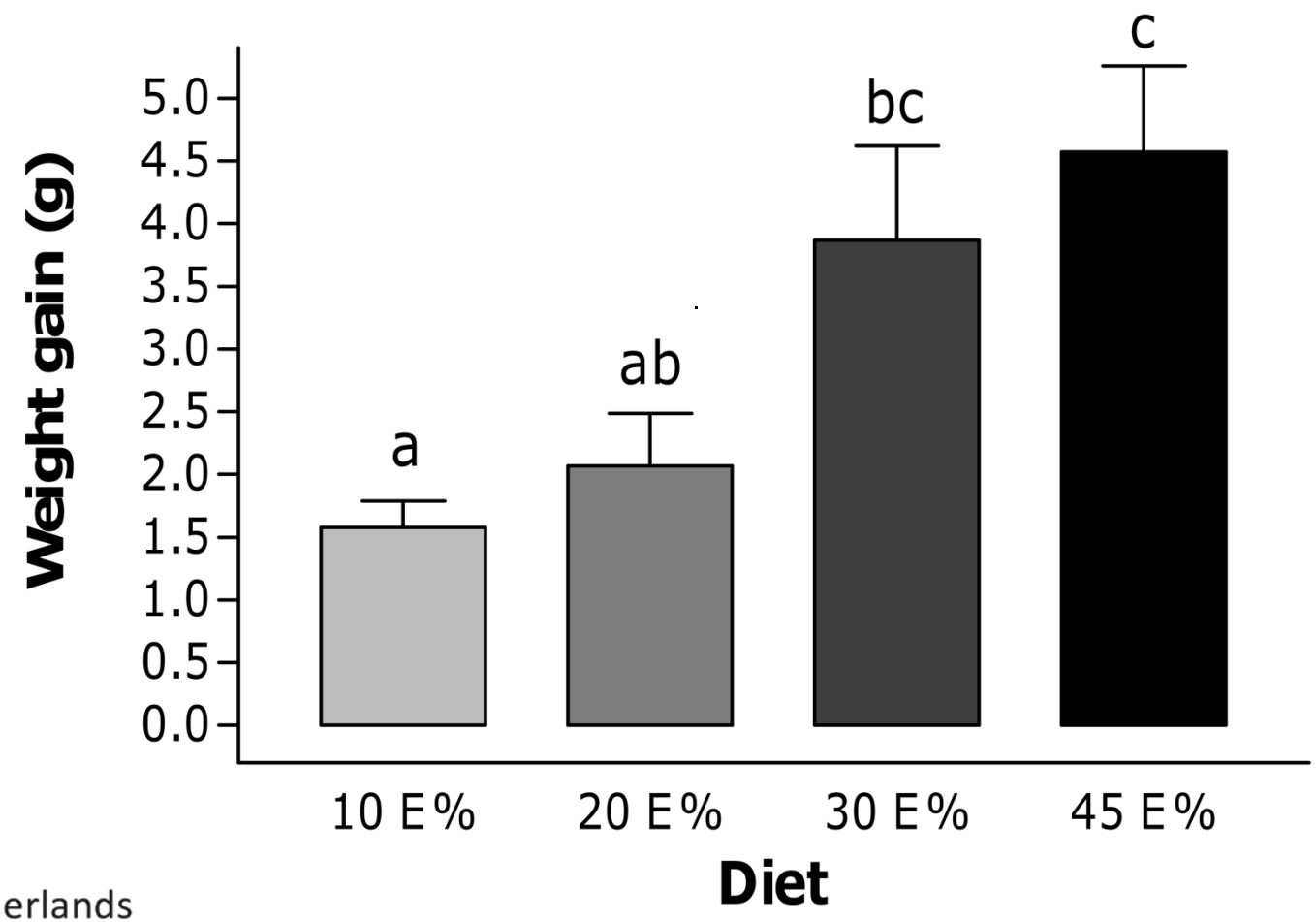

Glycan Biosynthesis and Metabolism
Carbohydrate Metabolism
Nucleotide Metabolism
Energy Metabolism
Lipid Metabolism
Amino Acid Metabolism
Metabolism of Cofactors and Vitamins
Metabolism of Other Amino Acids
Biosynthesis of Secondary Metabolites
Biodegradation of Xenobiotics
Streptomycin biosynthesis
Novobiocin biosynthesis
beta-Lactam resistance
Penicillins and cephalosporins biosynthesis
Alkaloid biosynthesis II
Tetracycline biosynthesis
Monoterpenoid biosynthesis
Diterpenoid biosynthesis
Limonene and pinene degradation

Comparison intestine / liver





Dose-dependent effects of dietary fat on development of obesity in relation to intestinal differential gene expression in C57BL/6J mice

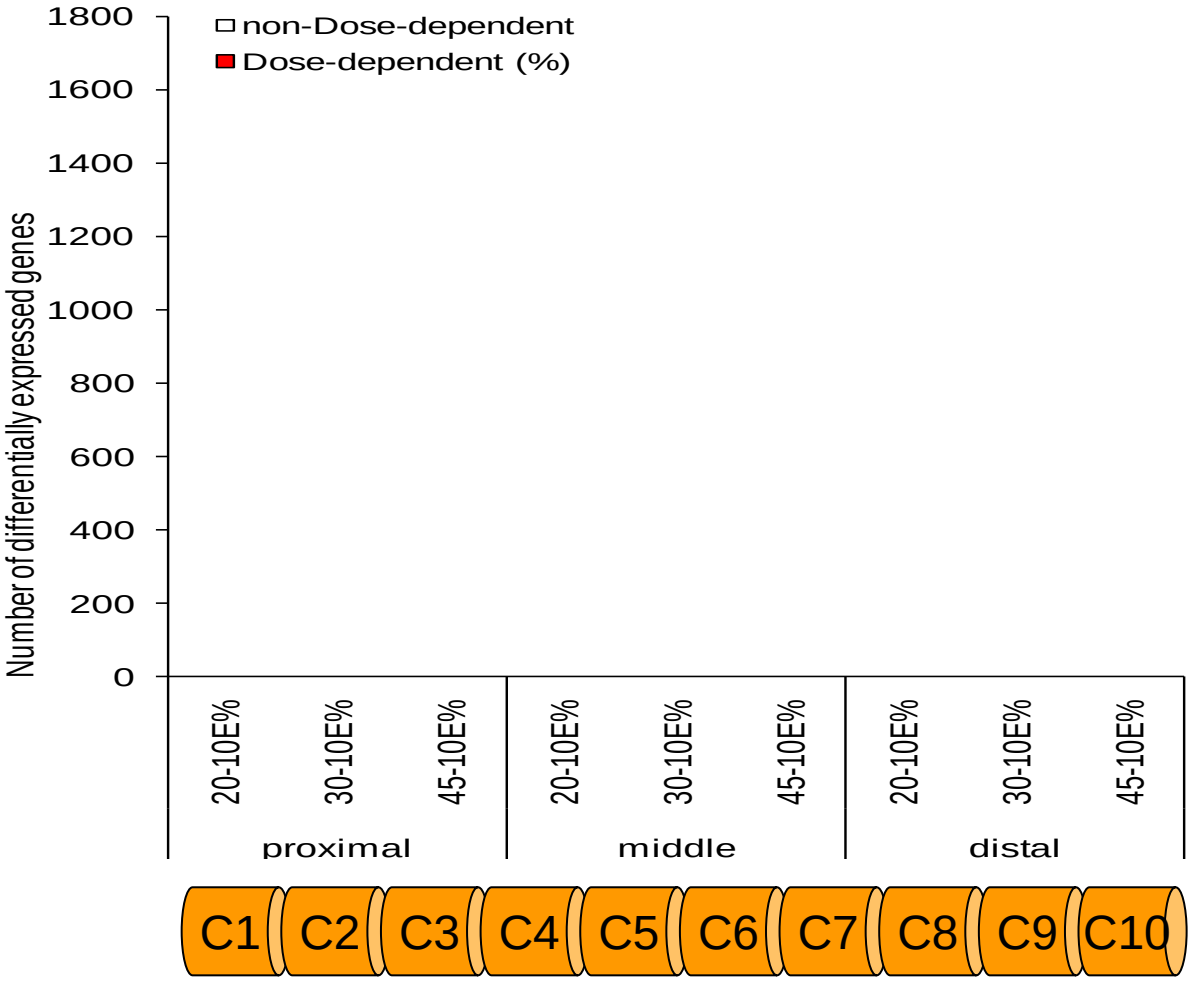


PLOS one 2011

Netherlands Nutrigenomics Centre

NuGO the european nutrigenomics organisation

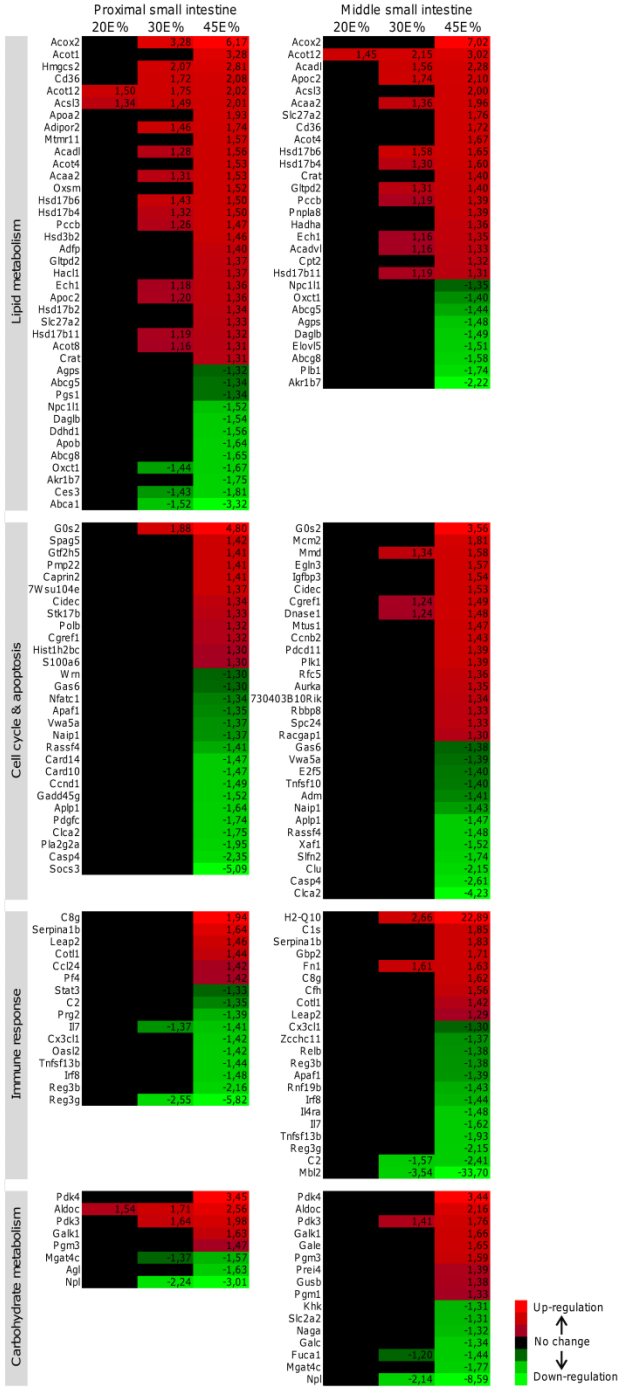
Robust & concentration dependent effects in small intestine
Differentially regulated intestinal genes by high fat diet



Netherlands Nutrigenomics Centre

PLOS one 2011

NuGO the european nutrigenomics organisation



Heat map diagrams of fat-dose dependently regulated genes, categorized according to their biological function

PLOS one 2011

Netherlands Nutrigenomics Centre

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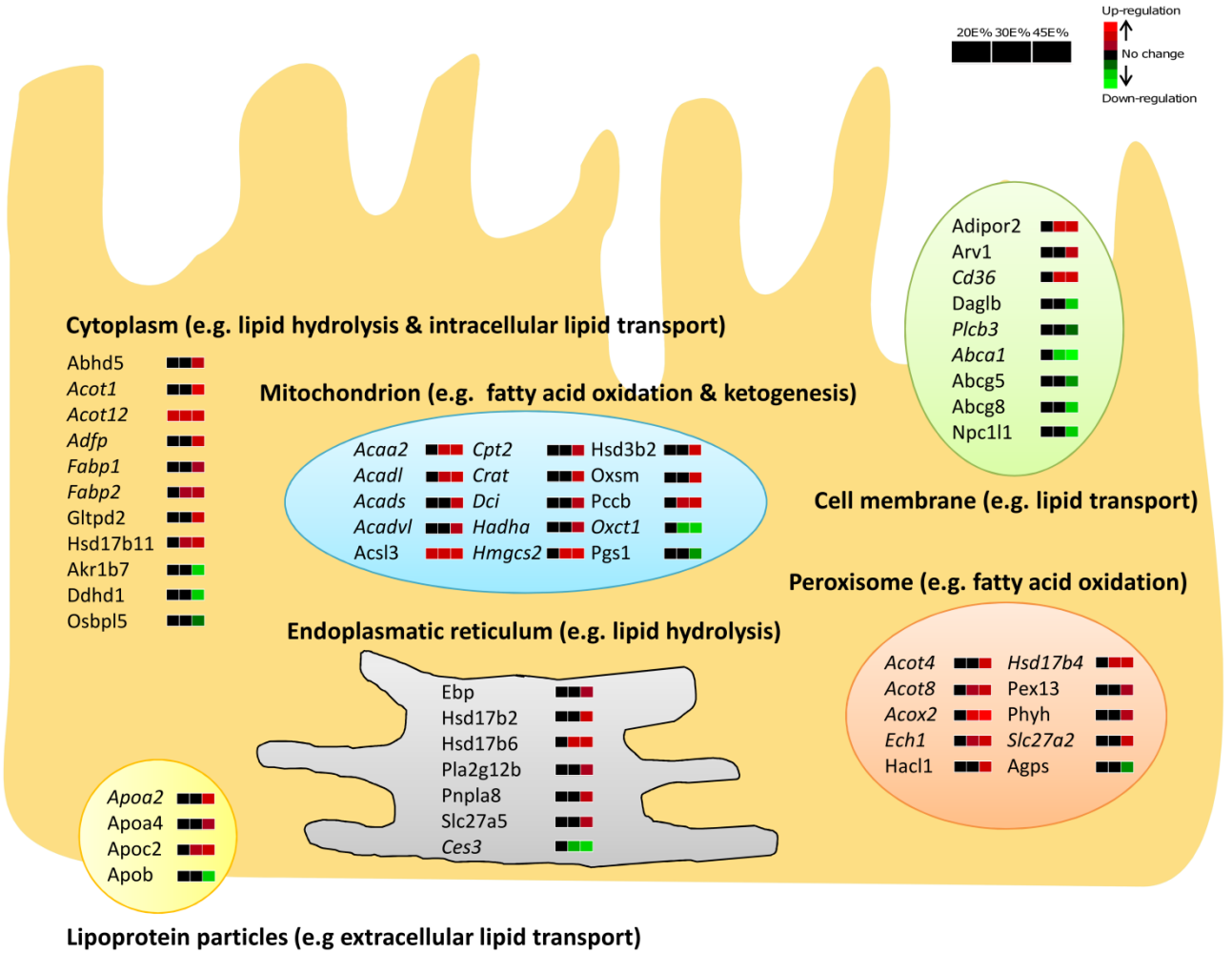
Cellular localization and specific lipid metabolism-related function of fat-dose dependently regulated genes



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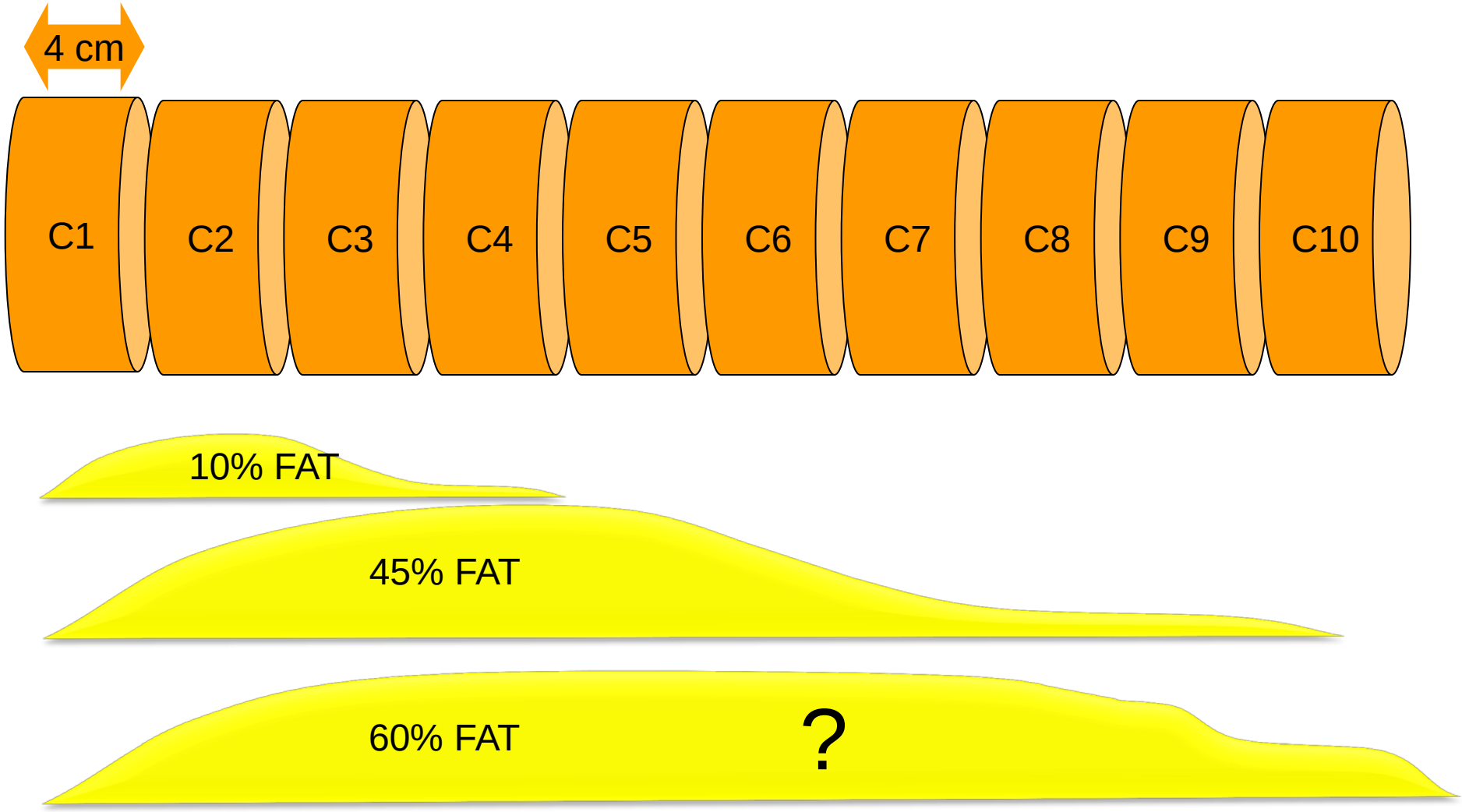
The intestinal tube model for lipid absorption



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.

Human nutrigenomics study
"Old" & "new" biomarkers

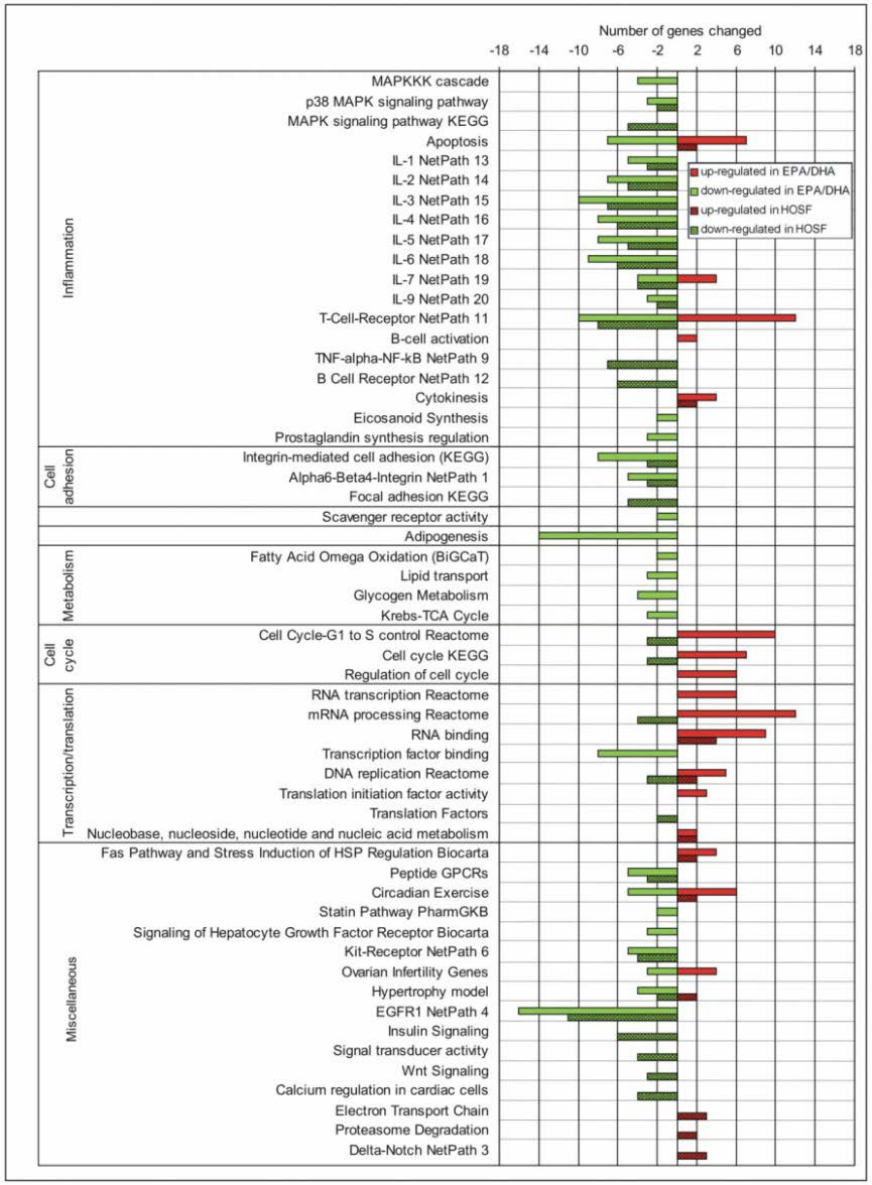
CONCLUSION: Supplementation with high or low doses of fish oil for 26 weeks did not influence the QOL of healthy older individuals. J Am Geriatr Soc 57:1481–1486, 2009.

Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial[1–3]

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.

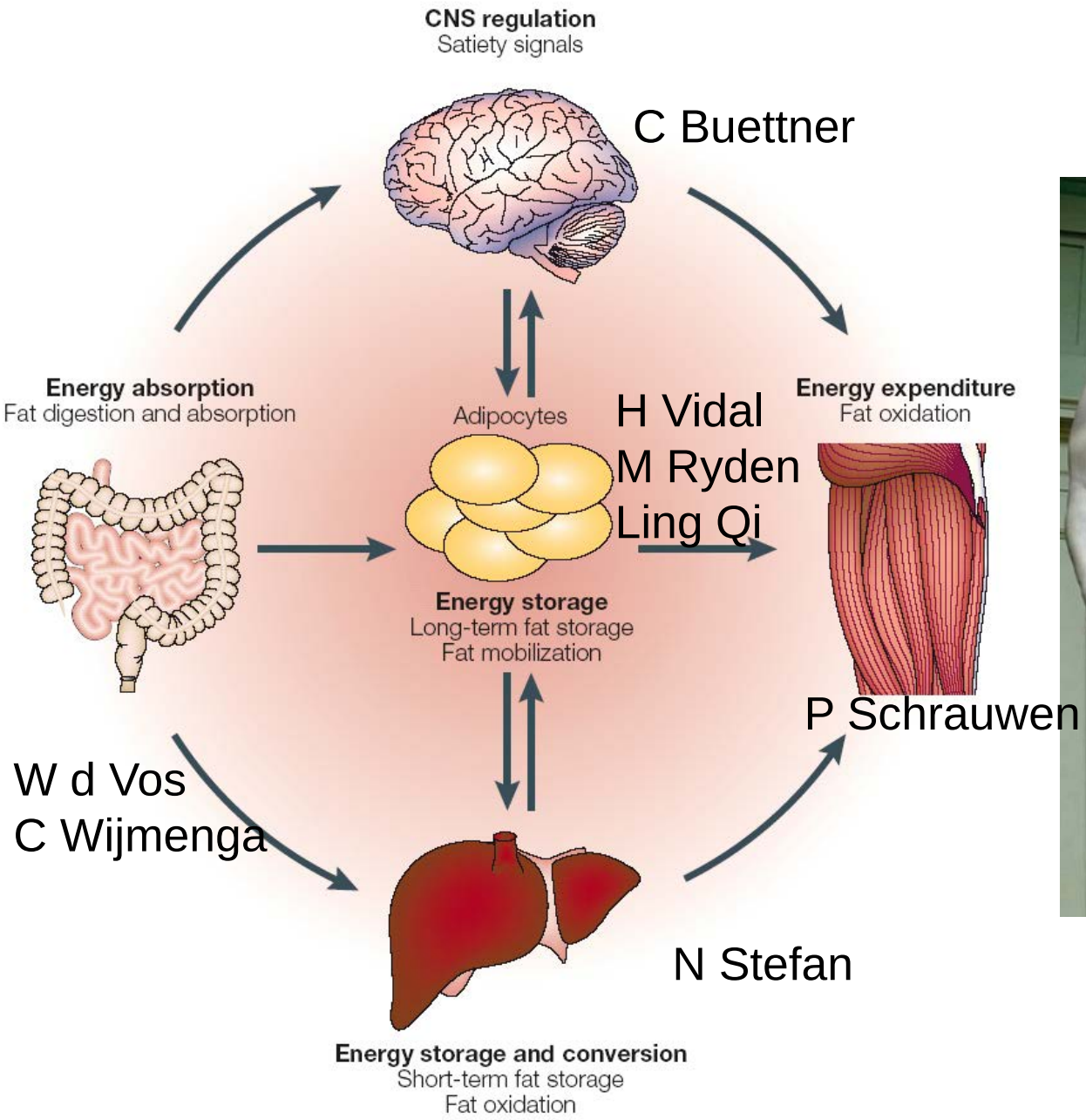
Fish-oil supplementation induces anti-inflammatory gene expression profiles in human blood mononuclear cells



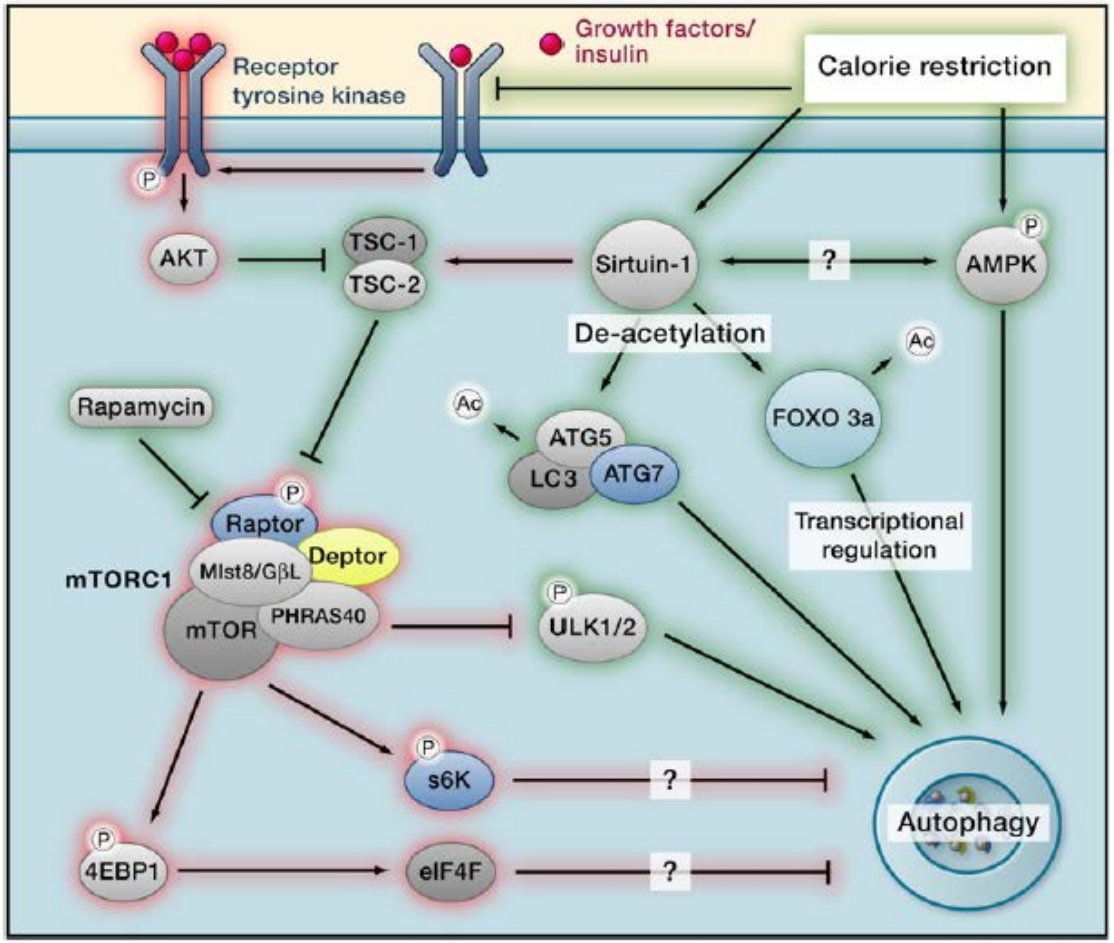
Less inflammation & decreased pro-arteriosclerosis markers
= Anti-immuno-senescence

Bouwens et al. Am J Clin Nutr. 2009

NUGO week 2011



NUGO week 2011



L Fontana

R Singh

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

Netherlands Genomics Initiative
nutrigenomics consortium
Diabetes Fonds
NWO
Nederlandse Organisatie voor Wetenschappelijk Onderzoek
nzo
TI FOOD NUTRITION
MARIE CURIE ACTIONS
NuGO the european nutrigenomics organisation

WAGENINGEN UNIVERSITEIT
WAGENINGEN UR

THANKS

Netherlands Nutrigenomics Centre