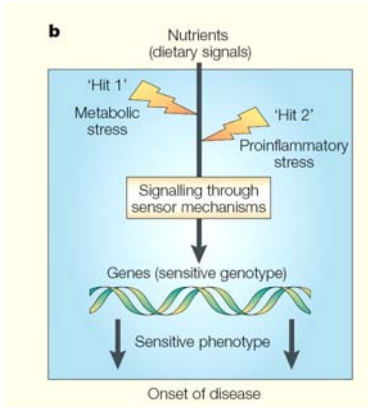
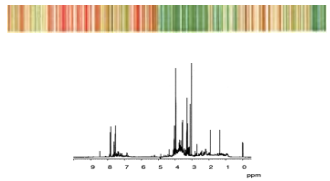
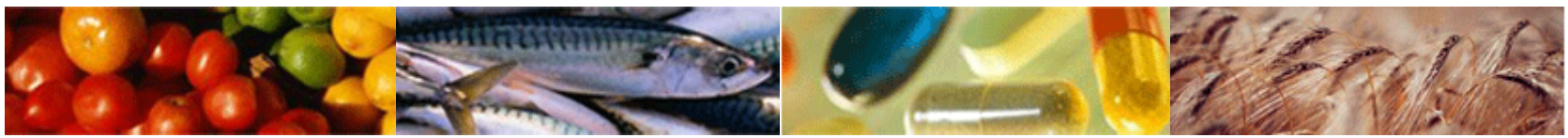


Michael Müller



Nutrigenomics: Providing Early Warning Molecular Biomarkers For Nutrient-Induced Changes to Homeostasis



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INNOVATIVE CLUSTER NUTRIGENOMICS

Outline

- Nutrigenomics: From complex problems to simple questions
- Free fatty acids as a “need for glucose” signal
- “Metabolic stress” and its signatures
- Human studies and the use of PBMCs
- Conclusions

Nutrigenomics

Target Genes
Mechanisms
Pathways

Foods
Nutrition

Signatures
Profiles
Biomarkers

Molecular Nutrition & Genomics

- Identification of dietary signals
- Identification of dietary sensors
- Identification of target genes
- Reconstruction of signaling pathways

Nutritional Systems Biology

- Measurement of stress signatures
- Identification of early biomarkers

Small research groups
Small budgets

Large research consortia
Big money

Complexity

Nutrigenomics

Complex Problems

Simple Questions

Transcription-factor pathways mediating nutrient-gene interaction

Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A Vitamin D Vitamin E	RAR, RXR VDR PXR
Minerals	Calcium Iron Zinc	Calcineurin/NF-ATs IRP1, IRP2 MTF1
Other food components		
	Flavonoids Xenobiotics	ER, NFκB, AP1 CAR, PXR

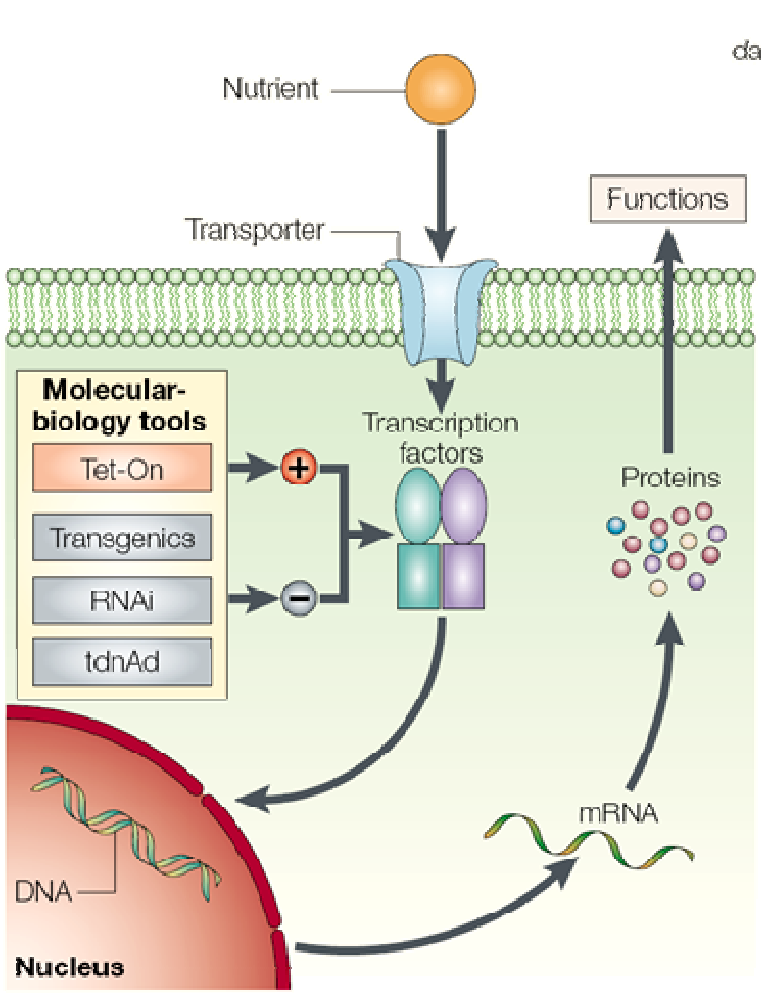
"Molecular Nutrition & Genomics"
The strategy of Nutrigenomics

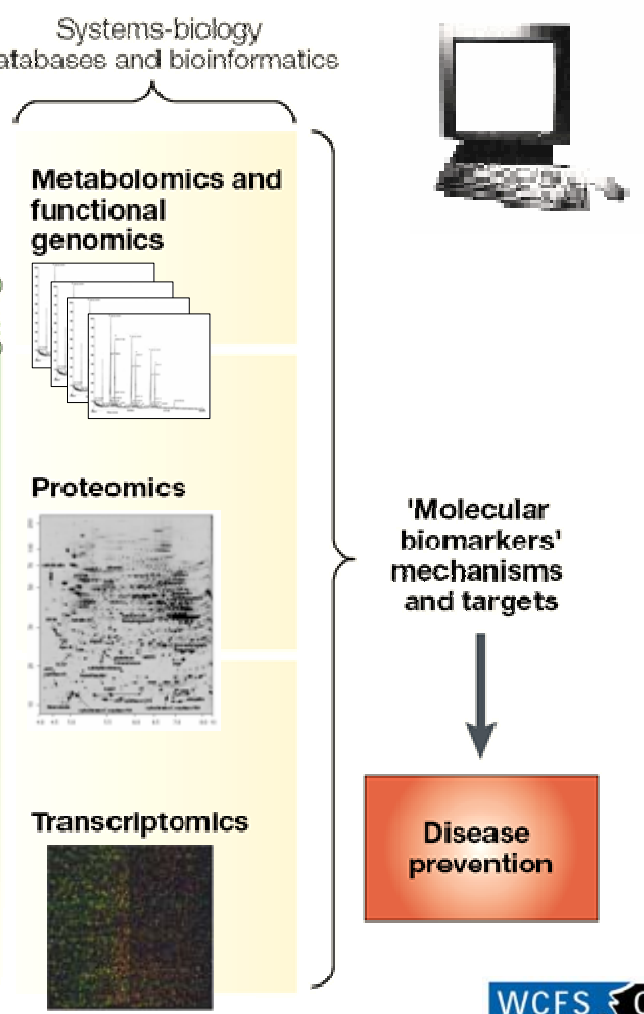
50000 (?) metabolites

80-100000 proteins

100000 transcripts

20-25000 genes





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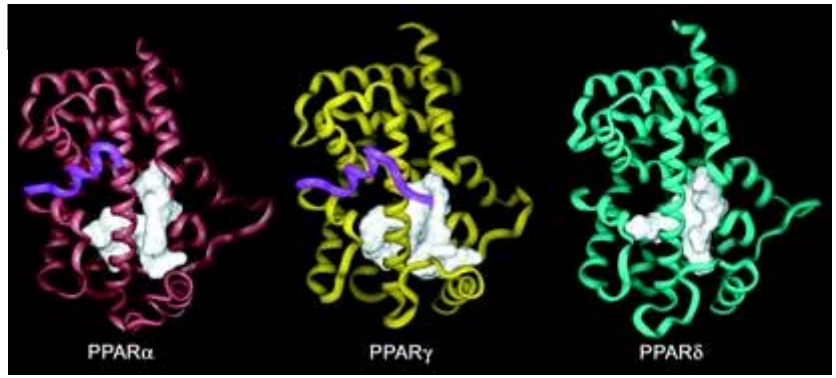
Functions of PPARs

"Fat sensors"

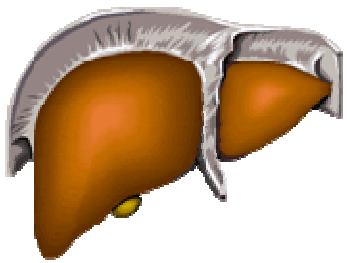


PPARα

-Nutrient metabolism (lipid, glucose, AAs)

- Proliferation

- Inflammation

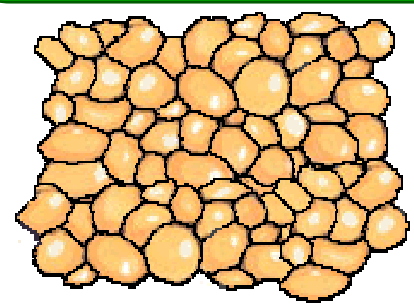


PPARγ

- Lipid and glucose metabolism

- Cell cycle control

- Inflammation



PPARβ

- Lipid metabolism

- Keratinocyte differentiation

- Inflammation

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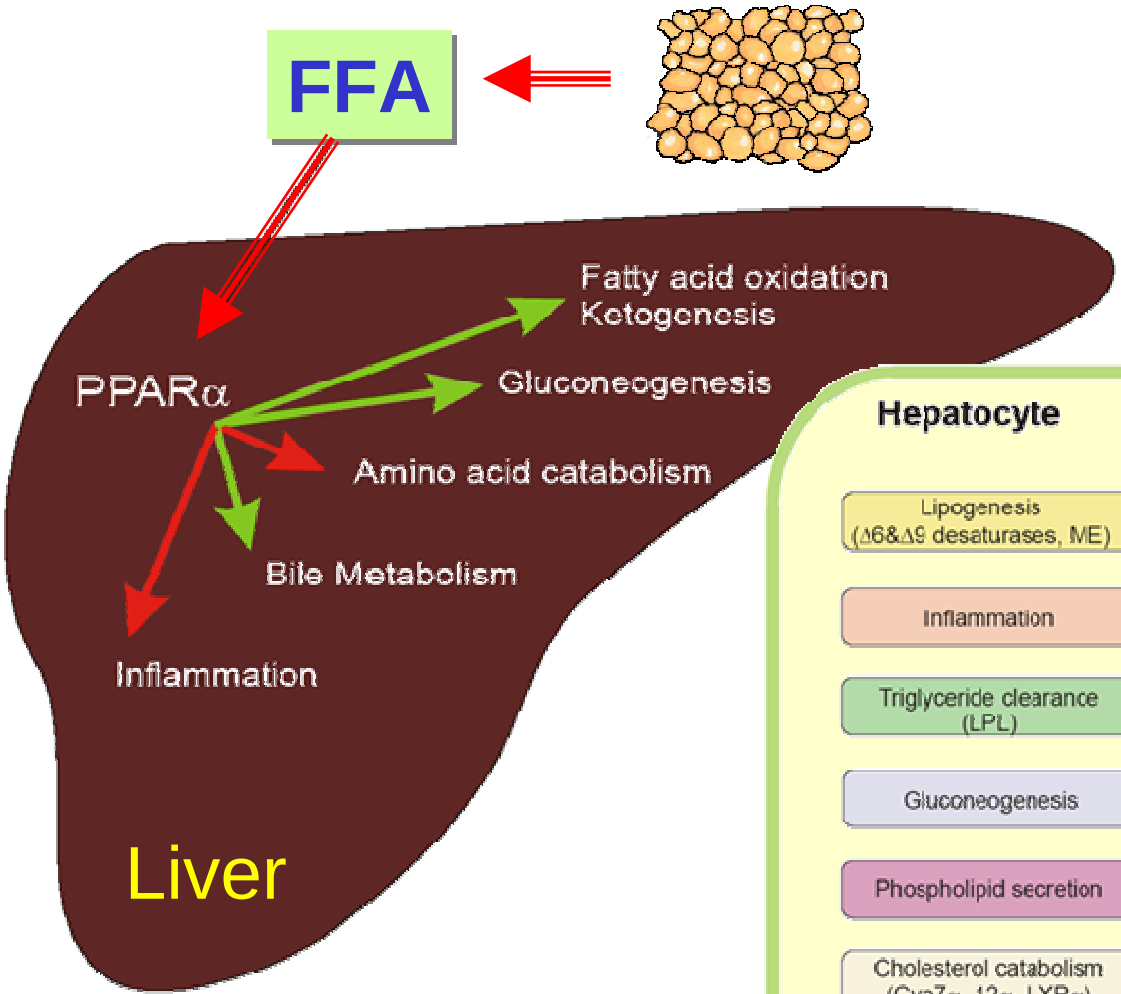
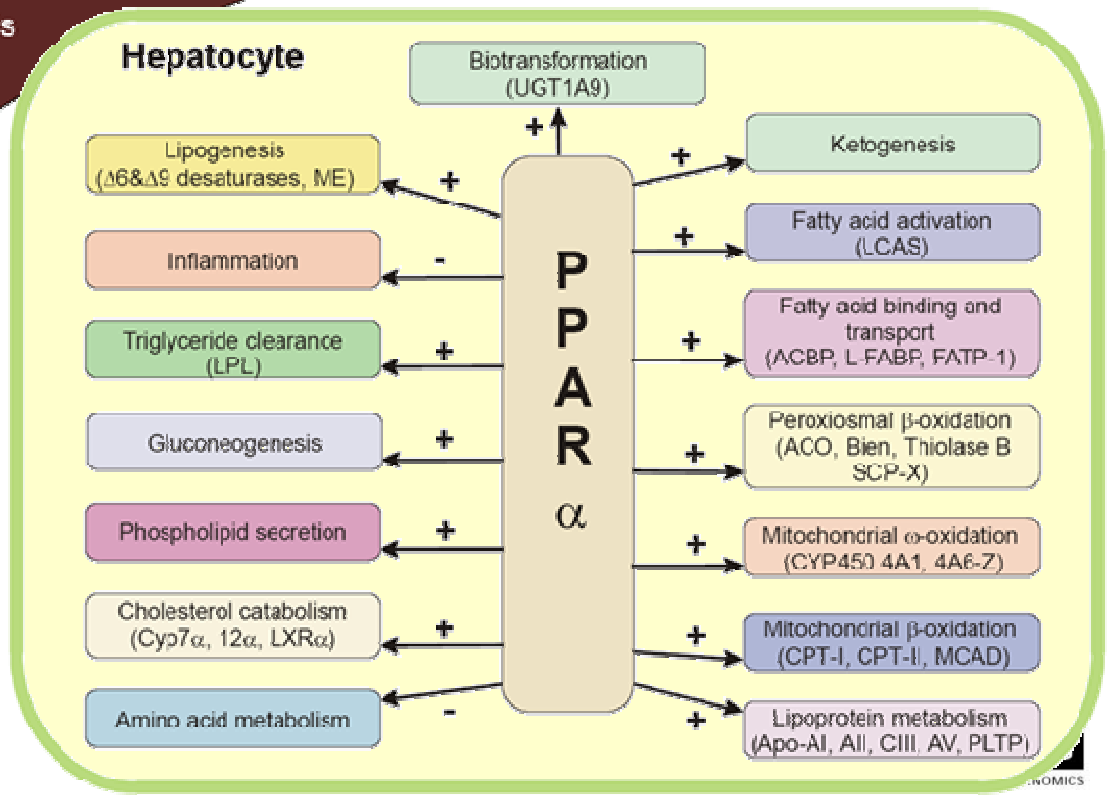
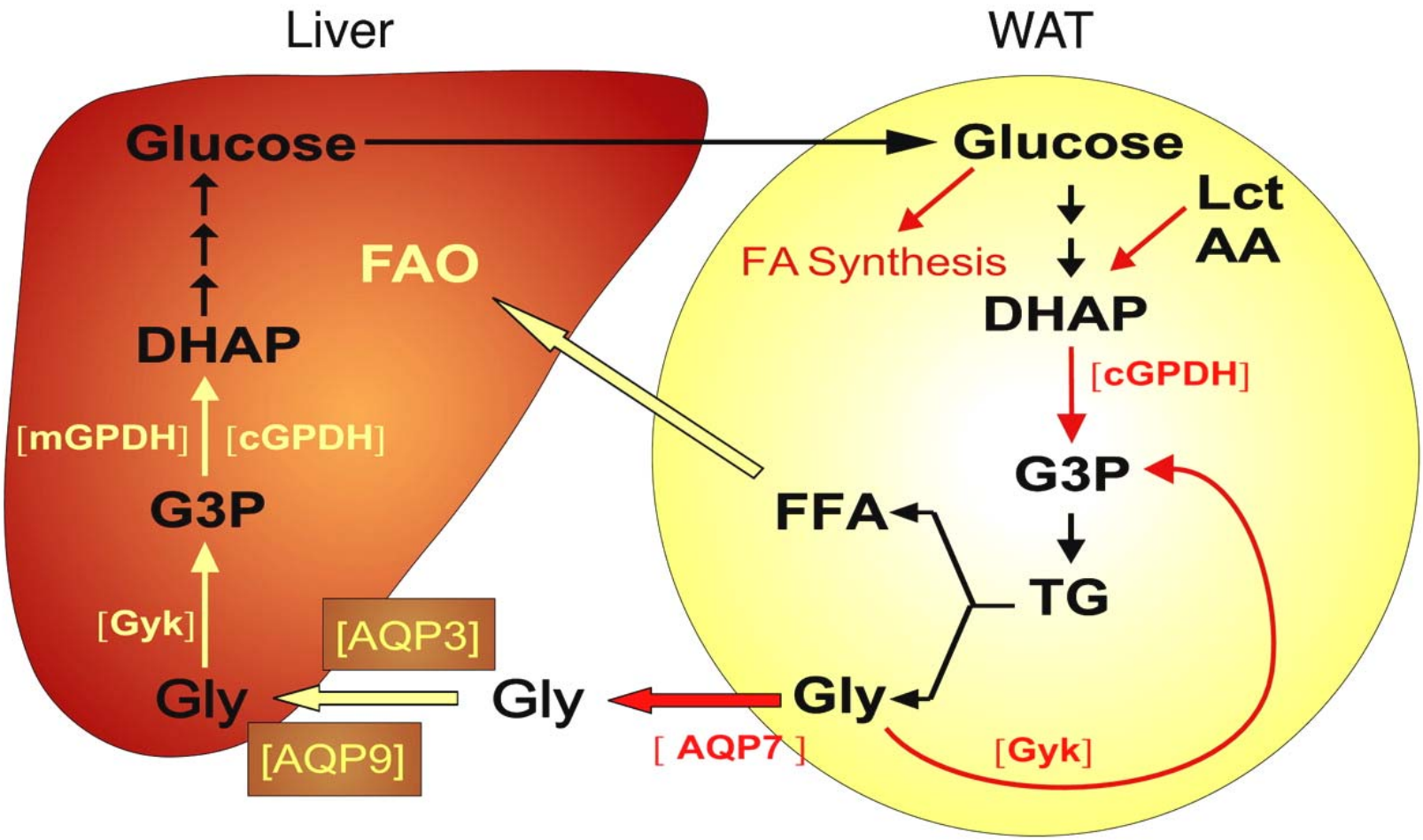
Role of PPARα in the hepatic response to fasting

Elucidation by employing:
1) k.o.-mice
2) specific ligands
3) transcriptome analysis
4) In vitro studies (Promoter studies, ChIP, etc)





CMLS, Cell. Mol. Life Sci. 61 (2004) 393–416



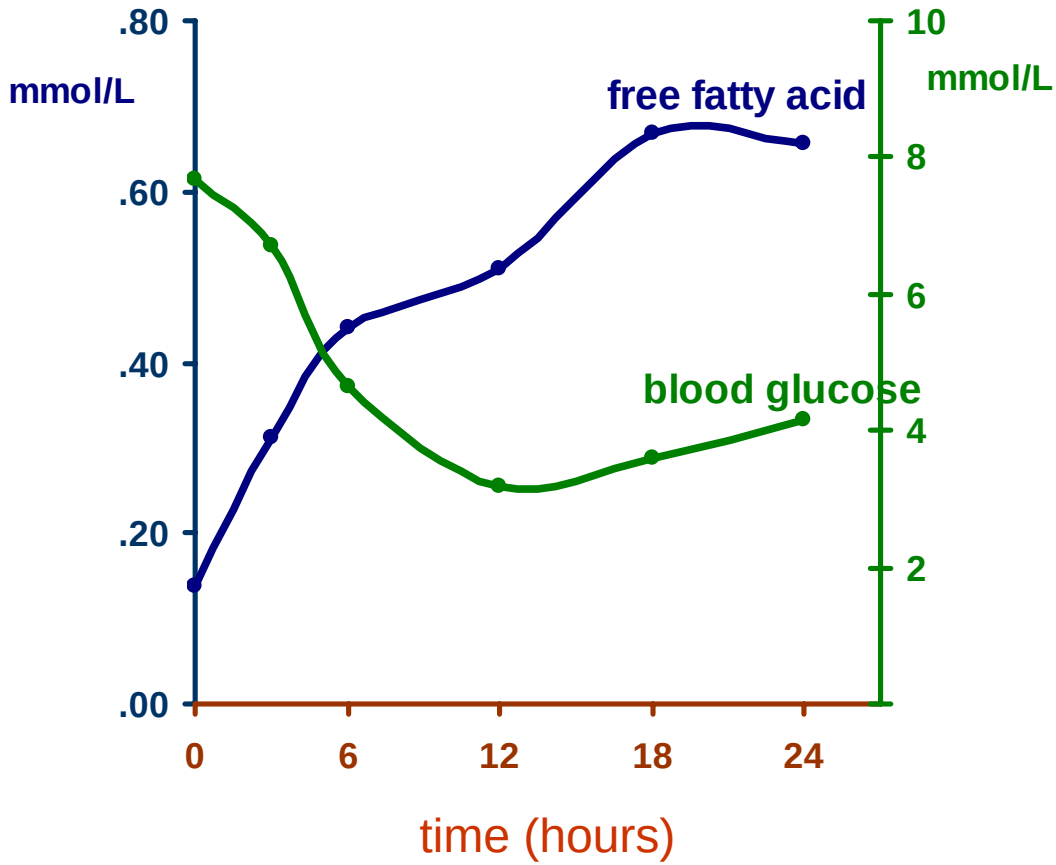
J. Clin. Invest. **114**:94–103 (2004).

PPARα governs glycerol metabolism

David Patsouris,[1] Stéphane Mandard,[1] Peter J. Voshol,[2] Pascal Escher,[3] Nguan Soon Tan,[4]
Louis M. Havekes,[2] Wolfgang Koenig,[5] Winfried März,[6] Sherrie Tafuri,[3] Walter Wahli,[4]
Michael Müller,[1] and Sander Kersten[1]

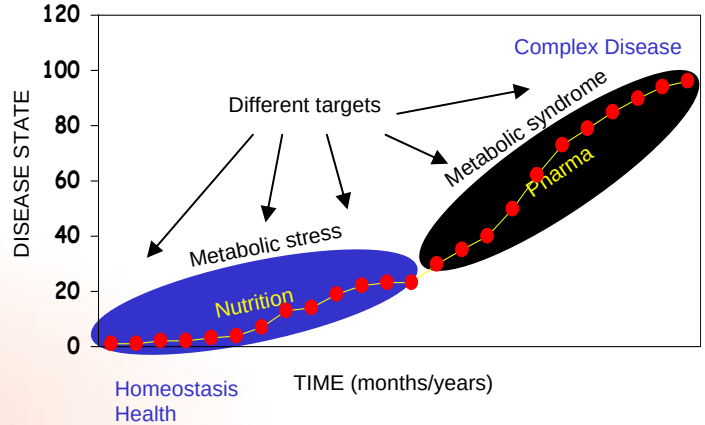
The role of free fatty acids

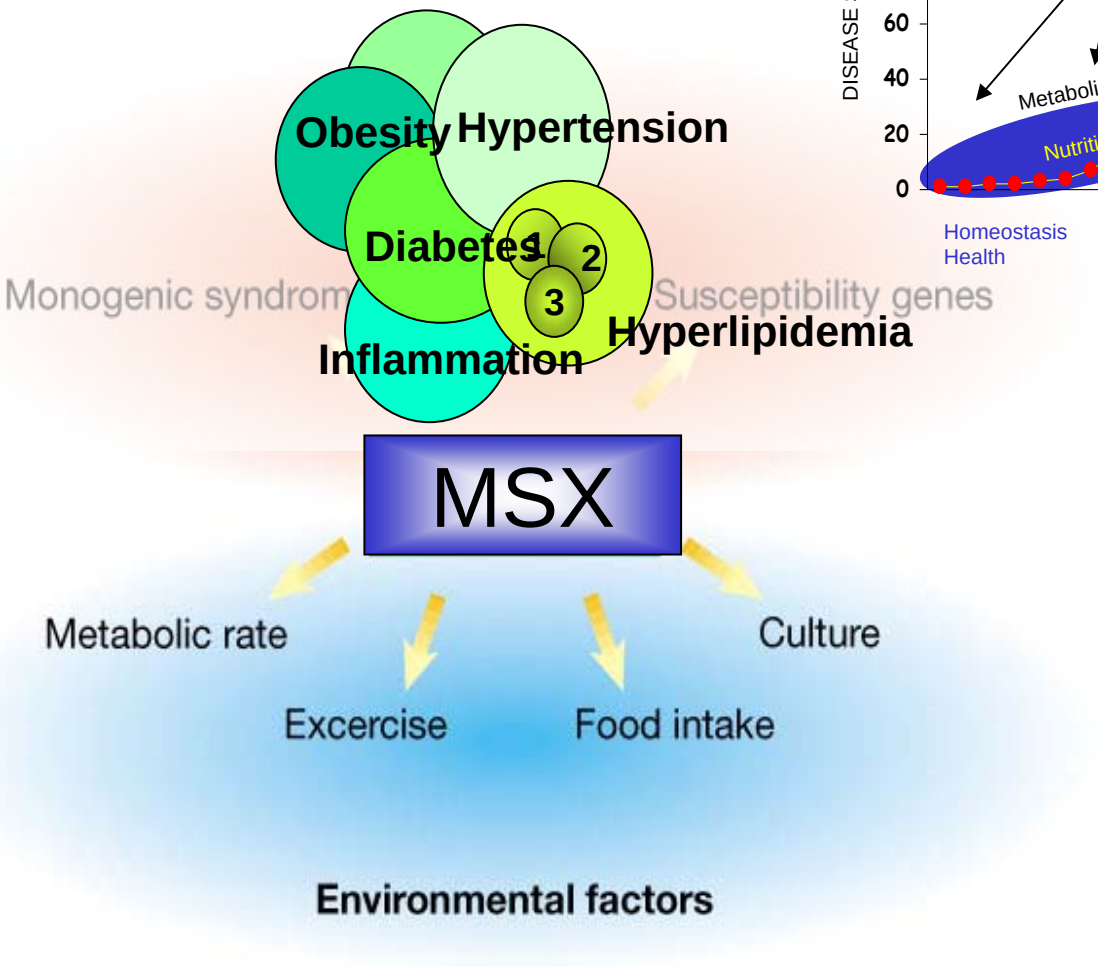
- During fasting
- During long endurance activity
- In obese people



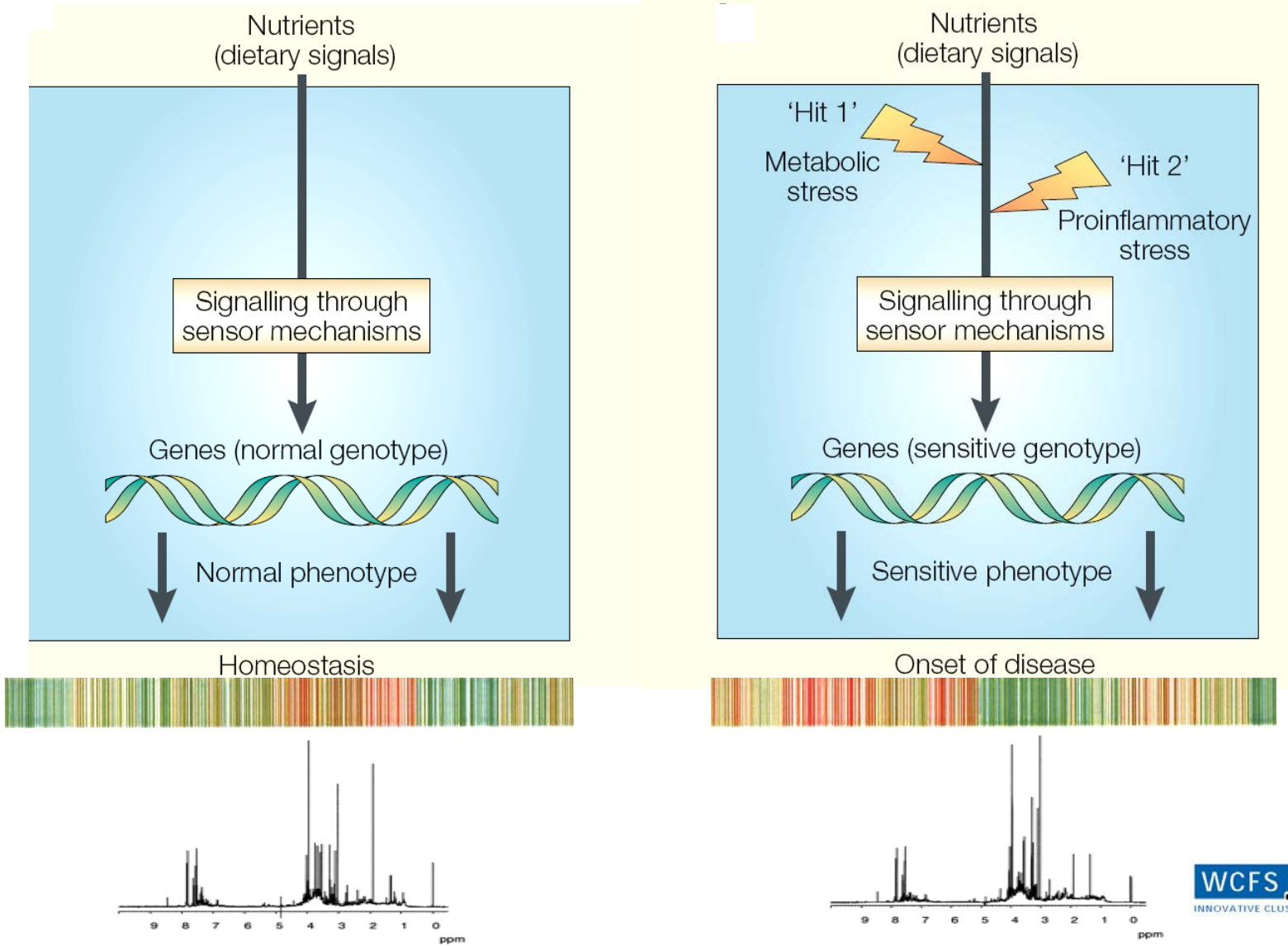
"Hunger" signal or
"Need for glucose" signal

Factors influencing the development of metabolic syndrome





Signatures of health & stress -The "two hits": Metabolic and pro-inflammatory stress



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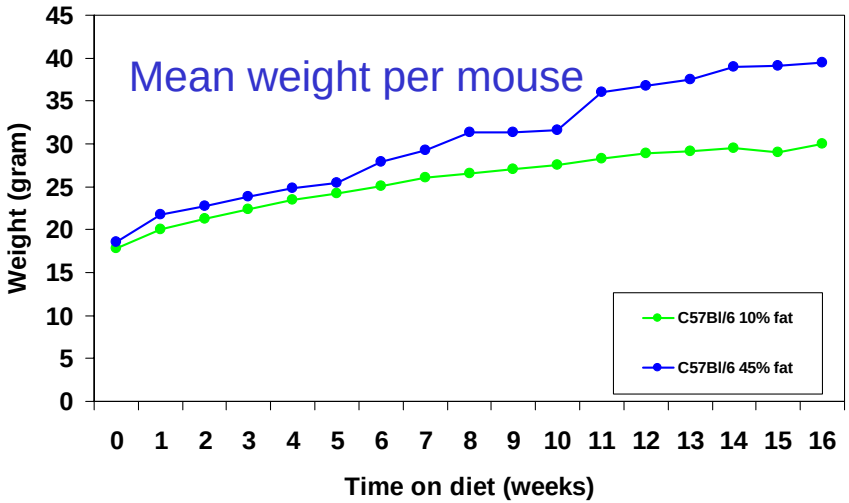
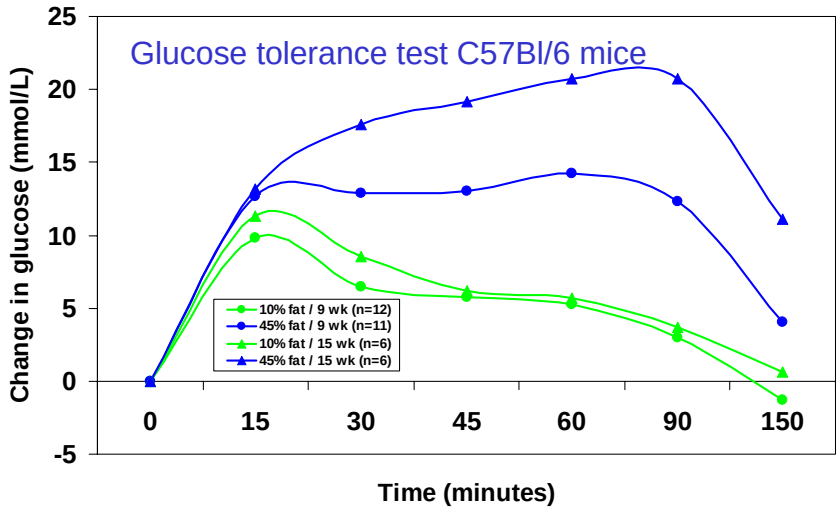
Mouse study: 45% High Fat versus 10% Low Fat



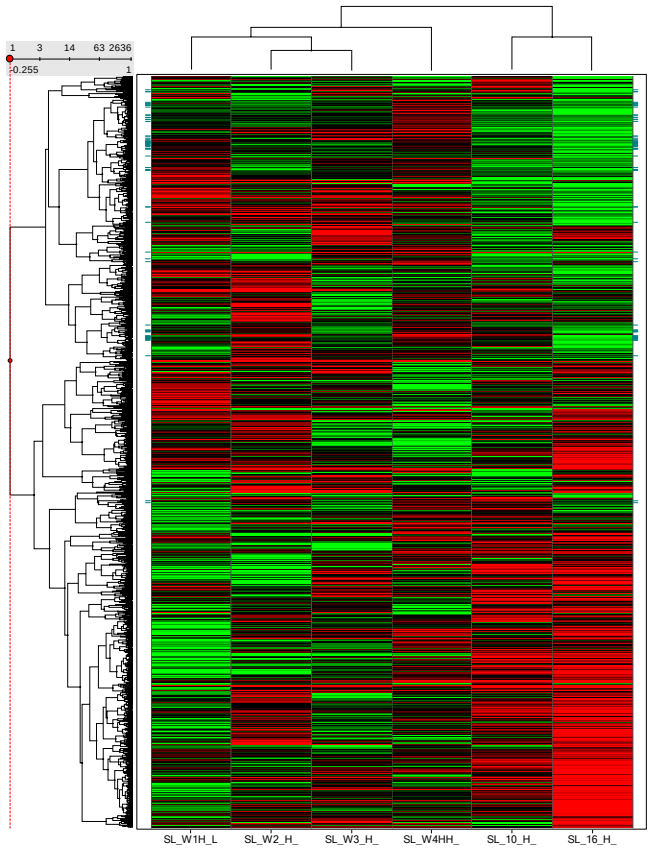


Intestine
Liver
Muscle
WAT

+ “omics” analysis

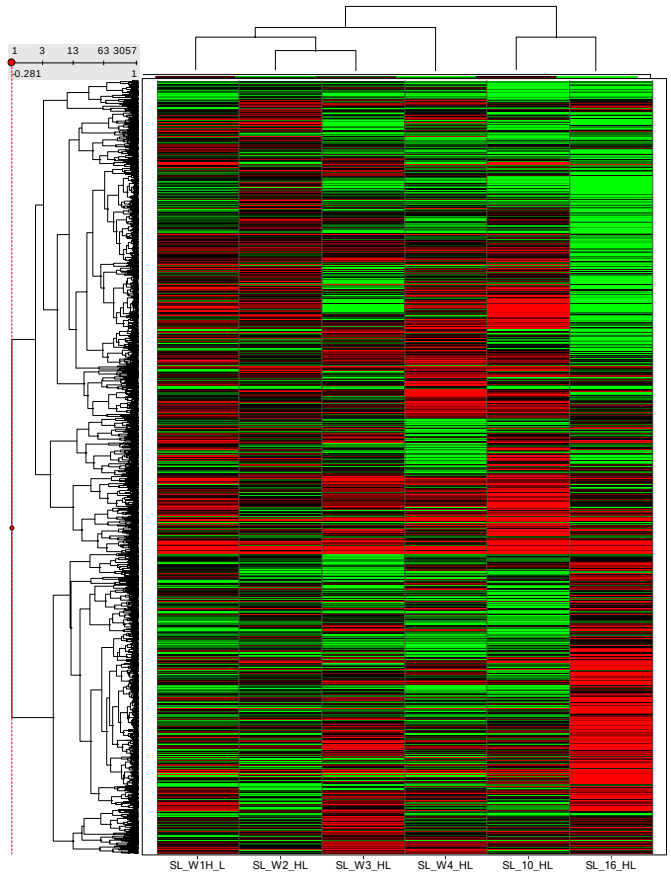
Hierarchical Clustering 'Liver and Intestine'

Liver



Weeks 1 2 3 4 10 16

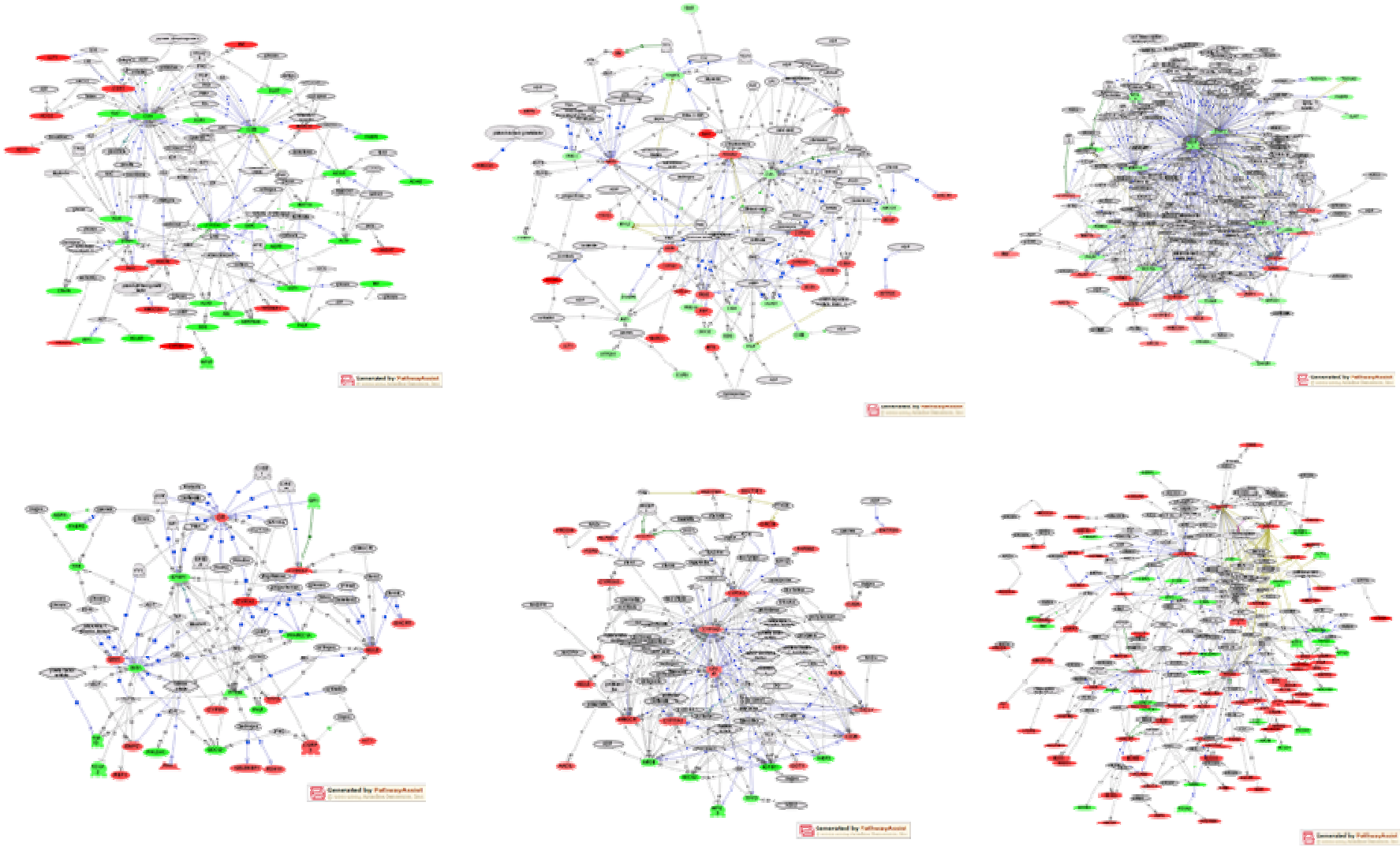
Intestine



Weeks 1 2 3 4 10 16

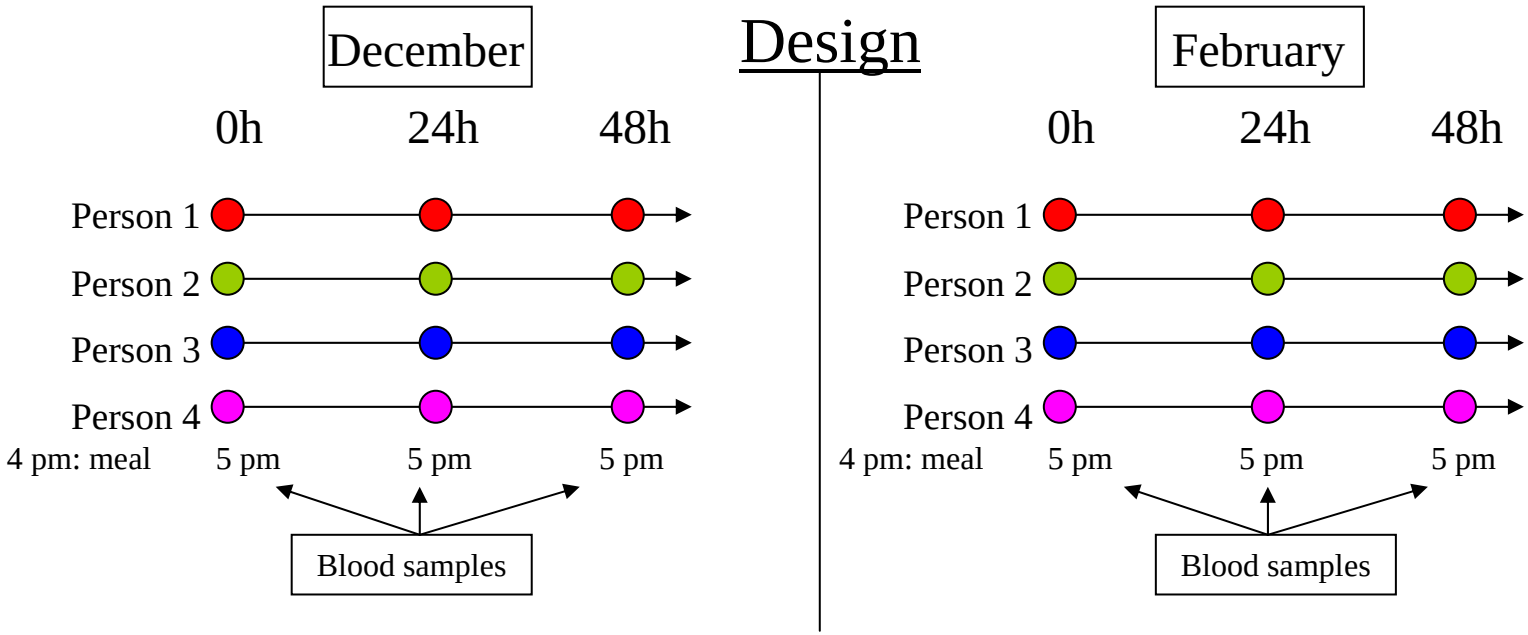
Clustering method: UPGMA (unweighted average)
Similarity measure: *Correlation*
Ordering function: Average value

Pathway analysis supports searches for common regulators



Liver data weeks 1,2,3,4,10 + 16 HF vs LF –0.5<SLR> 0.5

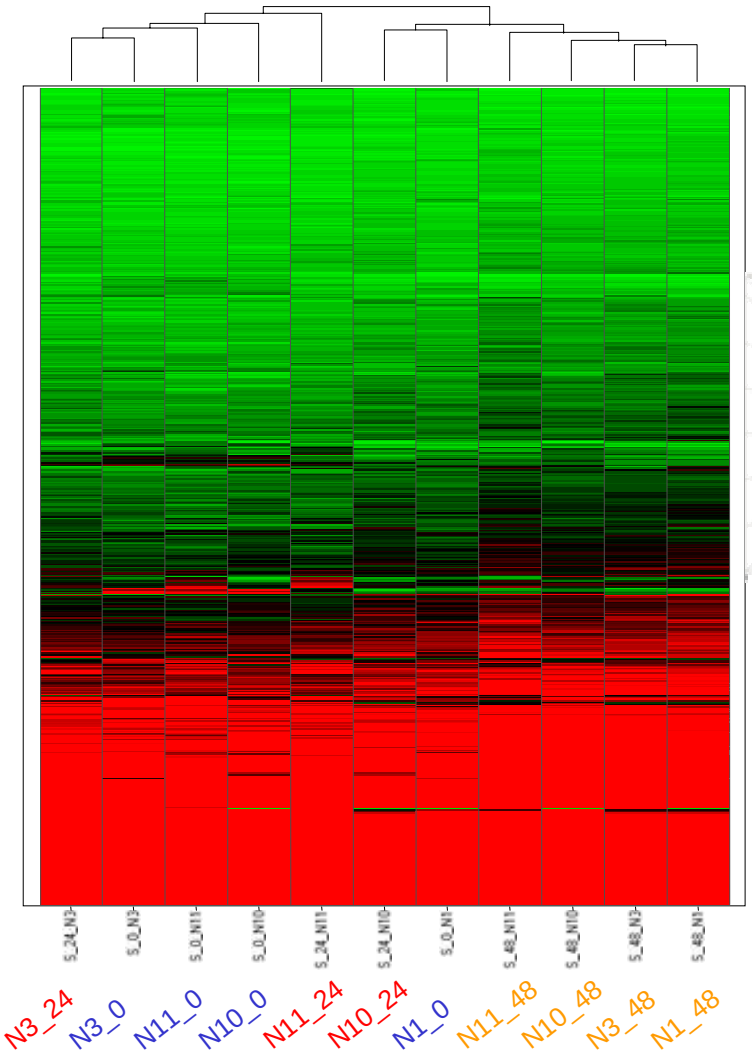
Human Studies "Fasting signatures"

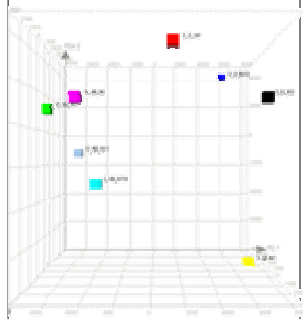


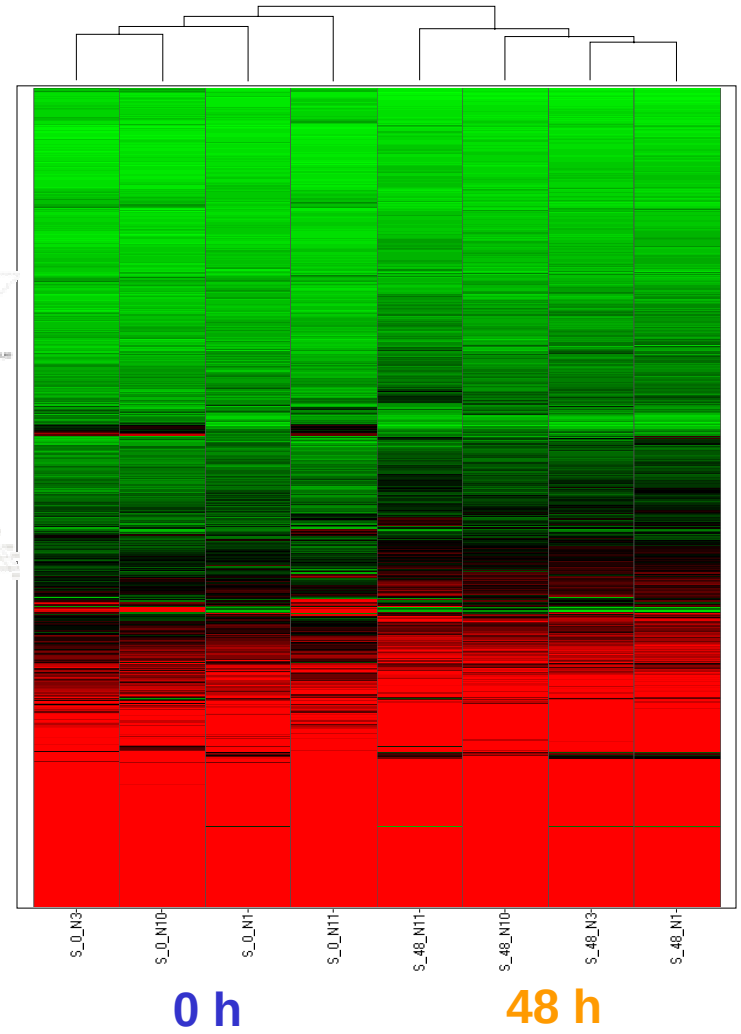
- Get insight in basic gene expression of human PBMCs (inter- and intra-individual variation)
- Explore the possibilities of using PBMCs as markers for nutritional status
- Focus on fatty acid dependent gene expression signatures

Hierarchical Clustering

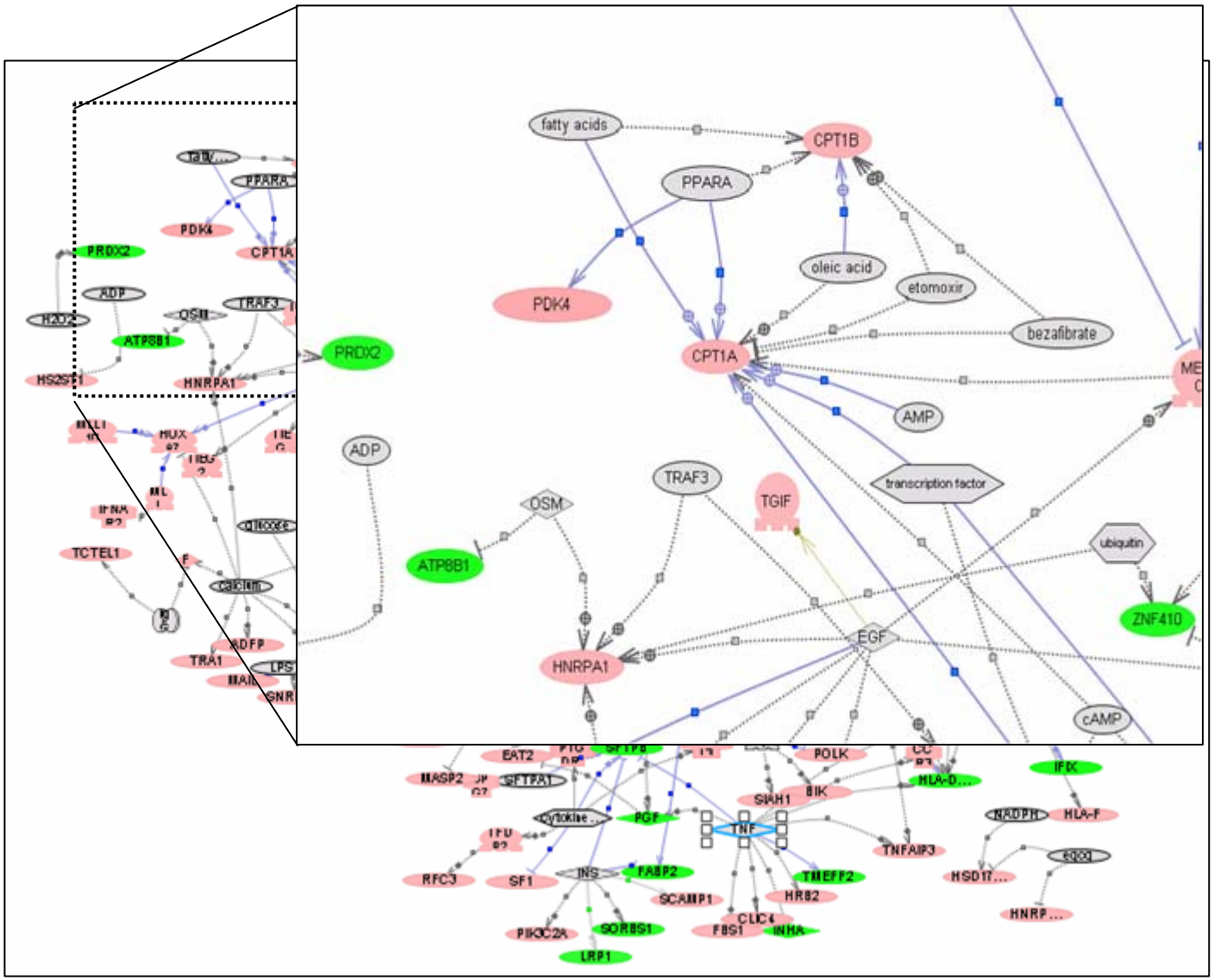
Clustering method: UPGMA (unweighted average)
Similarity measure: Euclidean distance
Ordering function: Average value







"Zoom-in": Common regulators (slr>0.5 or <-0.5)



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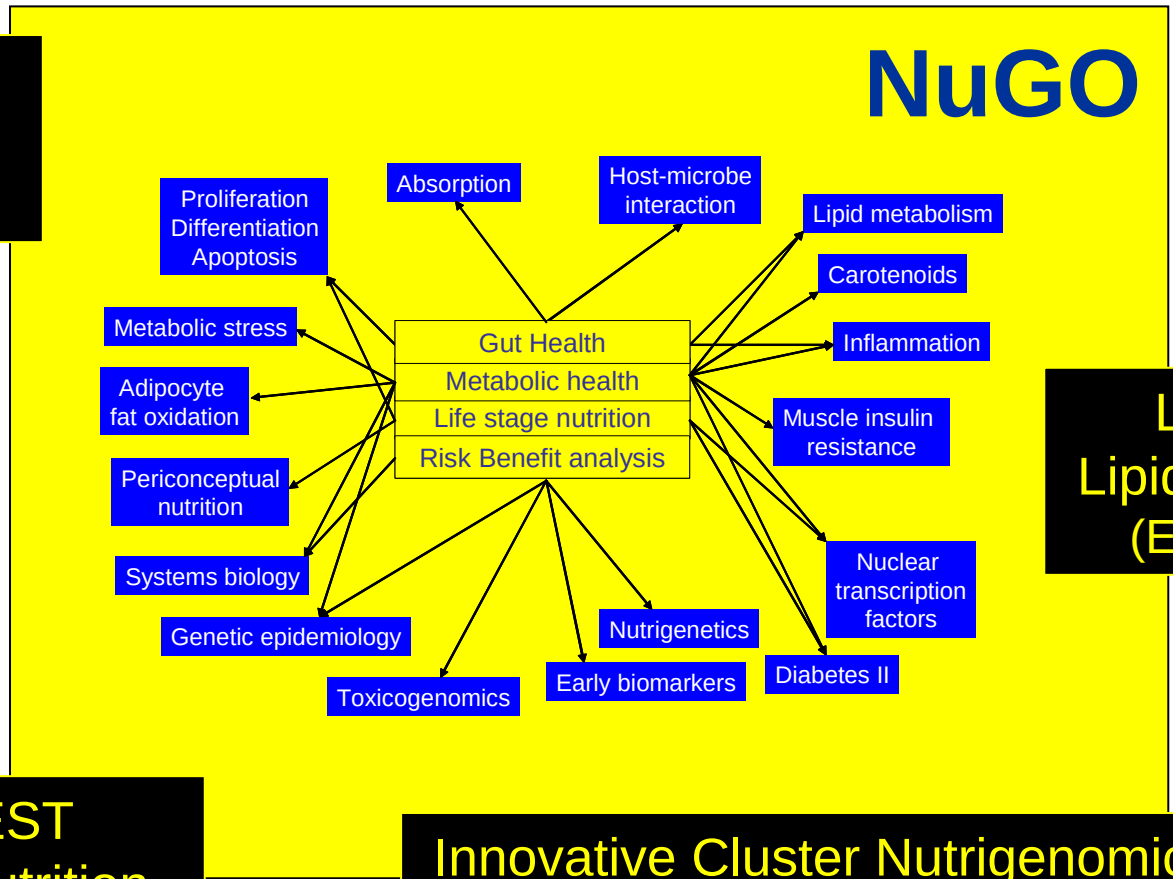
Conclusions

- Nutrigenomics is the application of high-throughput genomics tools in nutrition research.
- Applied wisely, it will promote an increased understanding of how nutrition influences metabolic pathways and homeostatic control, how this regulation is disturbed in the early phase of a diet-related disease and to what extent individual sensitizing genotypes contribute to such diseases.
- Ultimately, nutrigenomics will allow effective dietary-intervention strategies to recover normal homeostasis and to prevent diet-related diseases.
- However, huge efforts (money + smart ideas) are needed to solve already identified and future problems:
  - Extract biological relevant data from nutrigenomics datasets (“signal versus noise”)
  - Translate animal data to the human situation (in particular for complex diseases)
  - Is nutritional “systems biology” the method to identify biomarkers?
  - How tailored-made can nutrition be in the future?

Collaboration - Linking to EU programs

DIOGENES
obesity
(EU, 12M€)



LIPGEN
Lipids & genes
(EU, 14M€)

EARNEST
early life nutrition
(EU, 14M€)

Innovative Cluster Nutrigenomics
Chronic metabolic stress
(Dutch, 21M€)

Thanks to:

Ben van Ommen

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Division of Human Nutrition
Wageningen University

Members of the
IOP Genomics "Gut Health"
Centre for Human Nutrigenomics
Nutrigenomics Consortium/WCFS

NWO

Diabetes-fonds

IOP-Genomics

WAGENINGEN UNIVERSITY
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