Metabolomics and systems biology approaches to study health and disease

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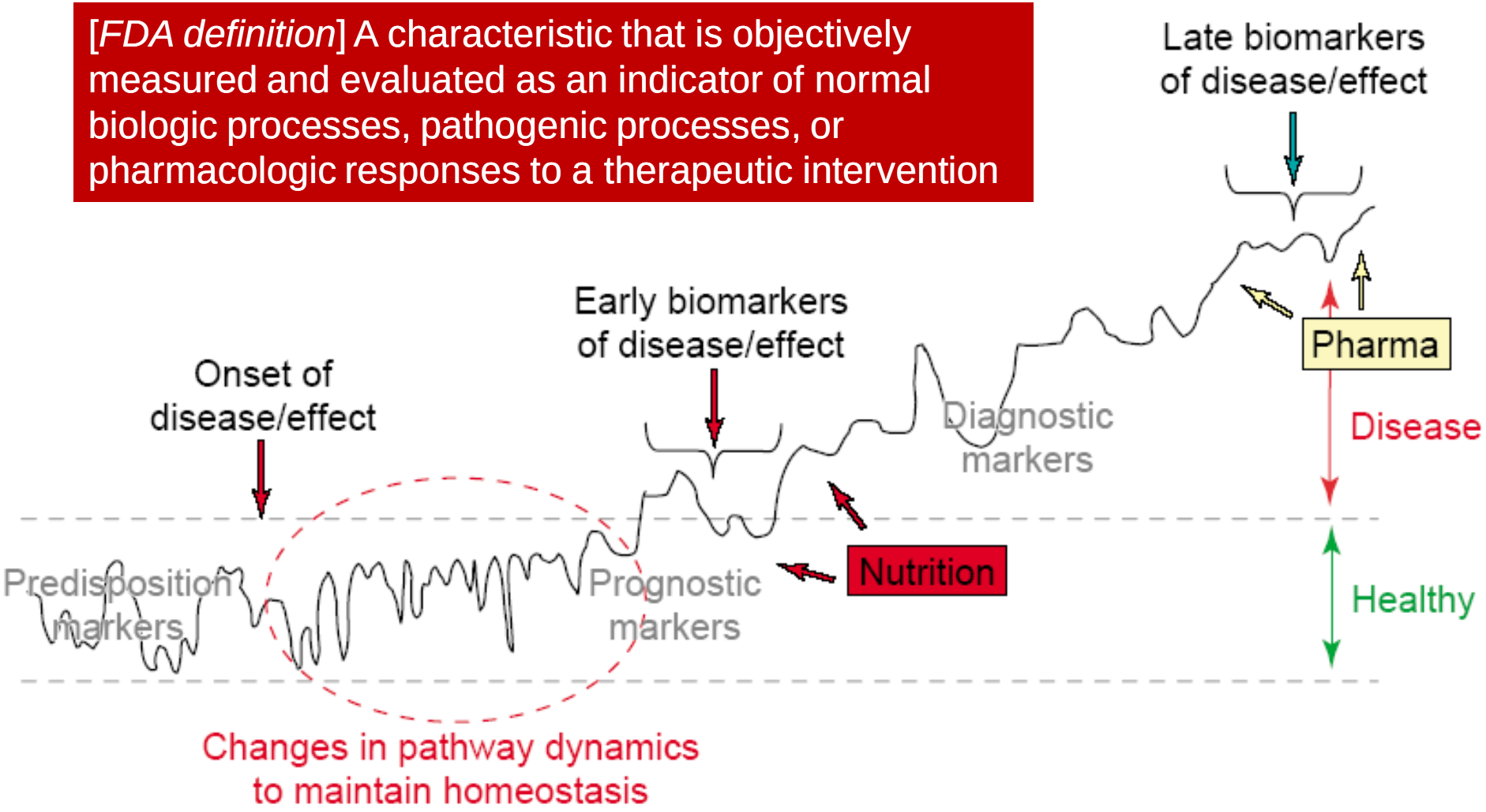
Biomarker concept in domain of human health

[*Wikipedia definition*] A substance used as an indicator of a biological state

[*FDA definition*] A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

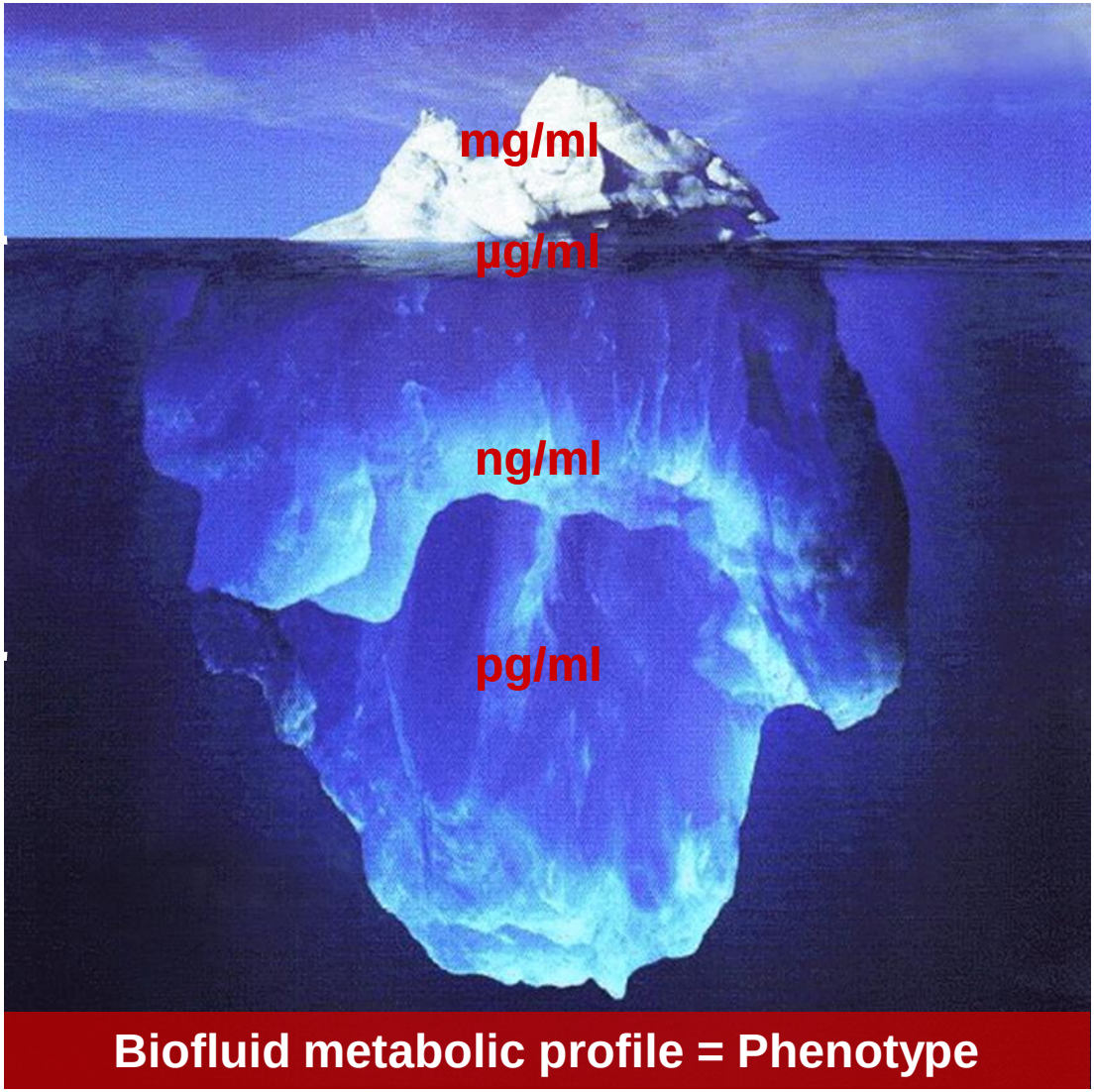


Metabolome

NMR

Mass Spectrometry

CUSTOM



Homeostasis 'Housekeeping'

Organic Acids

Lipids

Amino Acids

Nucleotides

Steroids

Eicosanoids

Neurotransmitters

Peptides

Trace elements

Metabolomics in the clinic

Piloting in Imperial College London, Dept. of Surgery and Cancer: MS, NMR, online GC (”electronic nose”)

Kinross et al, Lancet (2011)

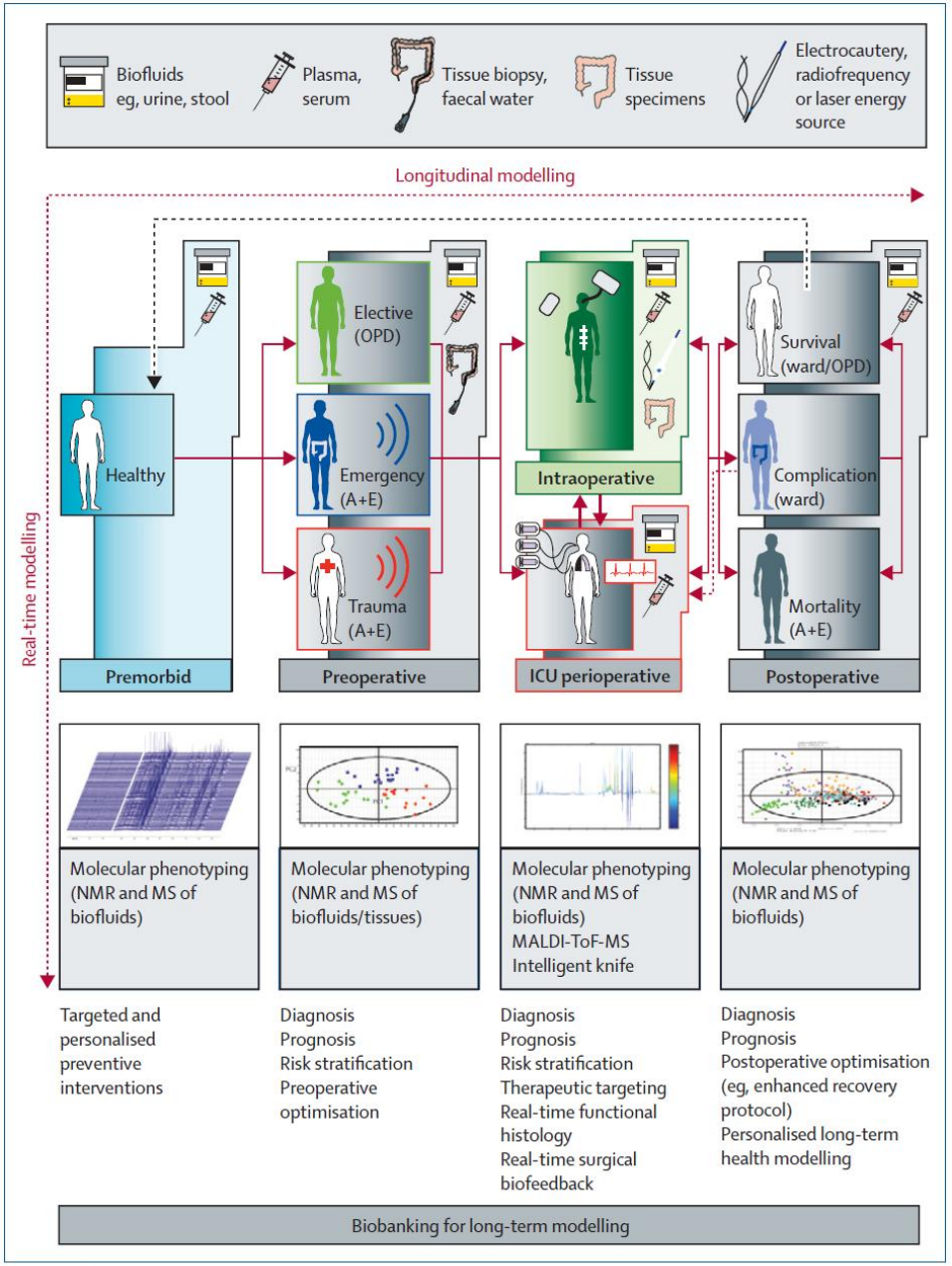


Figure: **Global metabolic phenotyping pathway for the surgical journey**

Metabolome as intermediate phenotype

- The metabolic phenotype is sensitive to subtle but pathogenically relevant factors such as age, lifestyle, nutrition and the microbe environment of the gut.

- Changes in the concentrations of metabolites may thus reflect both genetic and environmental factors influencing later susceptibility to chronic diseases.

Who we are
Personnel

- 30 persons
- Competences:
  - Metabolite analytics
  - Biochemistry
  - Microbiology (gut microbiota)
  - Computational biology
  - Bioinformatics
  - Statistics and data mining

http://sysbio.vtt.fi/

Diagnosis of psychosis
[Schizophrenia *vs*. Other psychoses (affective, non-affective)]

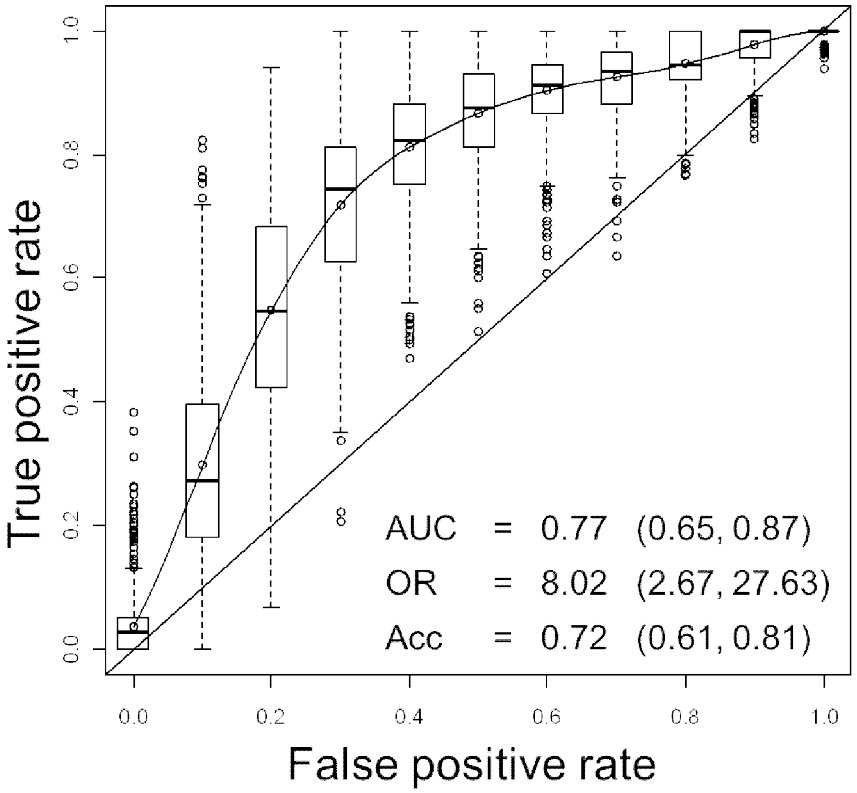
- Multivariate logistic regression applied, using random subset (67%/33%) cross validation without fixing the model.
- Proline and TG(18:1/18:0/18:1) selected as the best model.

Serum diagnostic test may help in diagnosis and treatment recommendation as part of psychiatric assesment.

Orešičet al, *Genome Med*. (2011)

Prediction of Alzheimer's disease (AD) based on concentrations of three metabolites in patients with mild cognitive impairment (MCI) at baseline (~5 year follow-up)

AD (n=52) vs Stable MCI (n=91) at follow-up



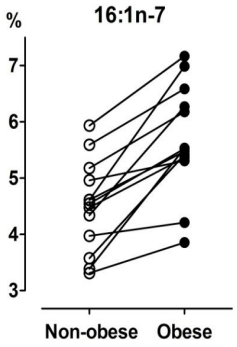
In a healthcare setting, the application of such an assay could complement the neurocognitive assessment by the medical doctor and could be applied to identify the at-risk patients in need of further comprehensive follow-up.

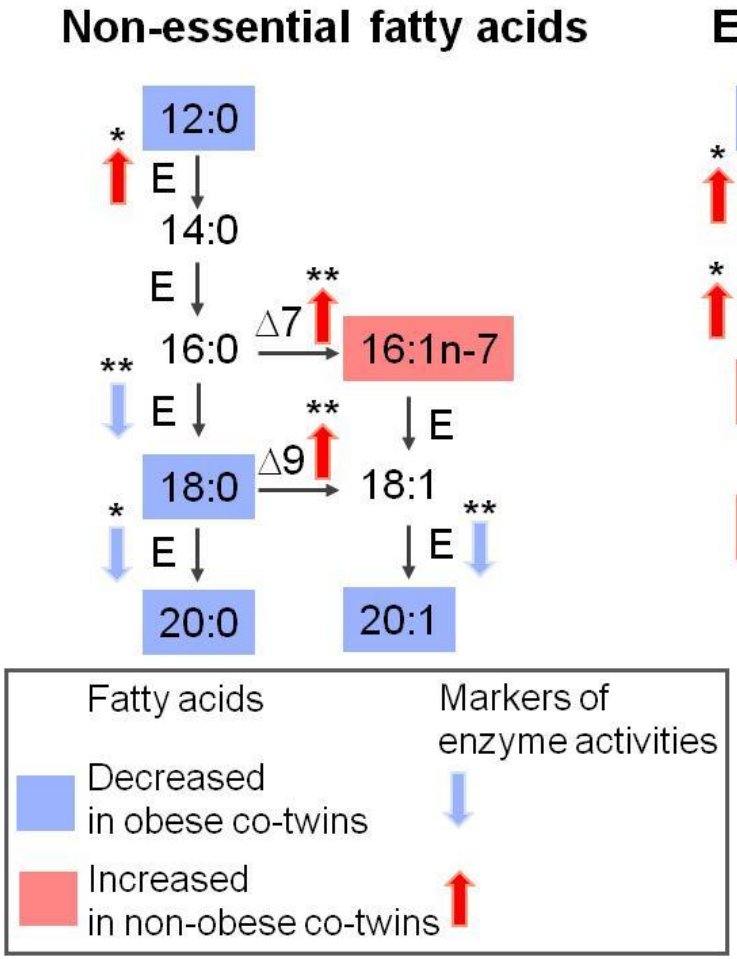
Orešičet al, *Transl. Psychiatry* (2011)

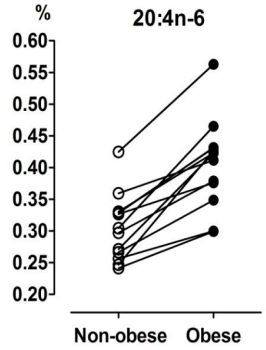
Metabolic disease *as cost of* adipocyte adaptation to obesity

Fatty acid composition in adipose tissue

- Remodeling of fatty acid composition in obesity, with unexpected elevation of PUFAs

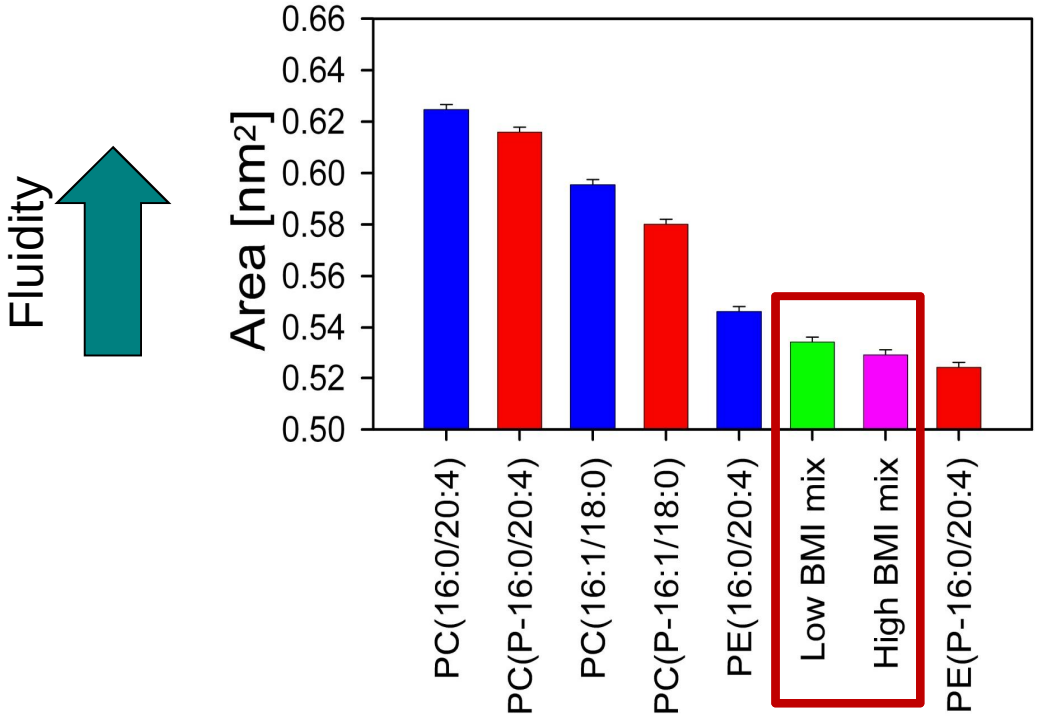


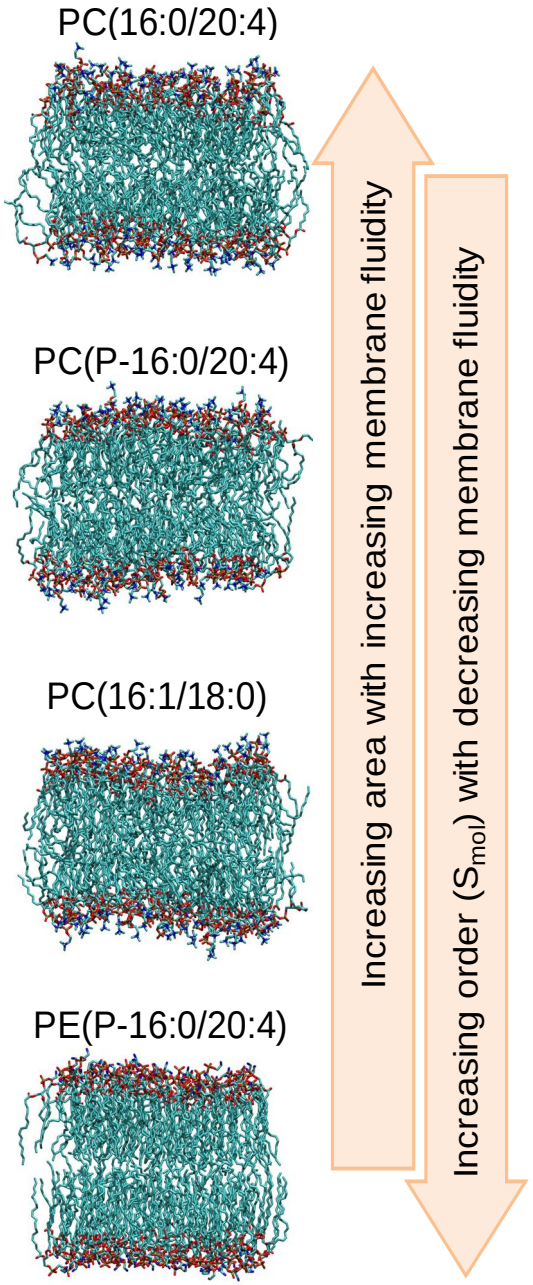




Pietiläinen et al, *PLoS Biol*. (2011)

Lipid bilayer simulations



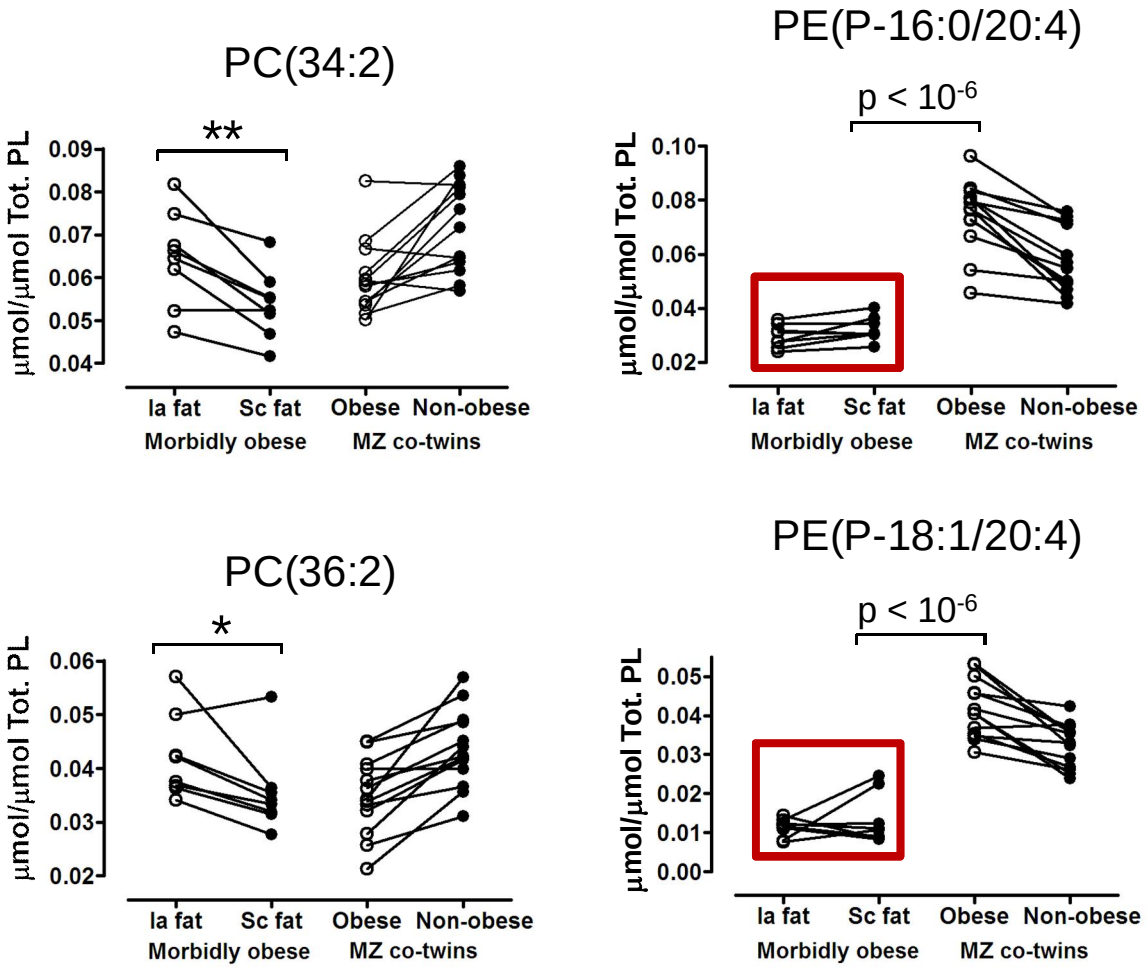


The observed membrane lipid changes in obese twins help maintain the membrane fluidity

→ **an adaptive mechanism**

Pietiläinen et al, *PLoS Biol*. (2011)

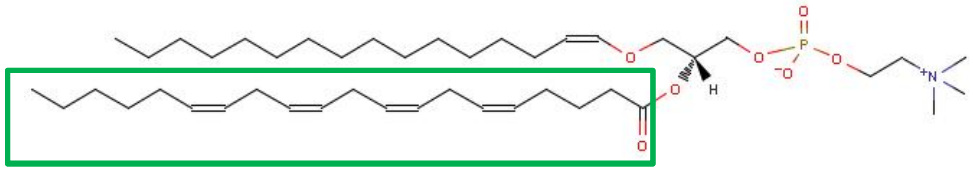
… in morbidly obese subjects the adaptive mechanism is broken down!



Data from morbidly obese subjects from Kotronen et al., *Obesity* (2009)

Pietiläinen et al, *PLoS Biol*. (2011

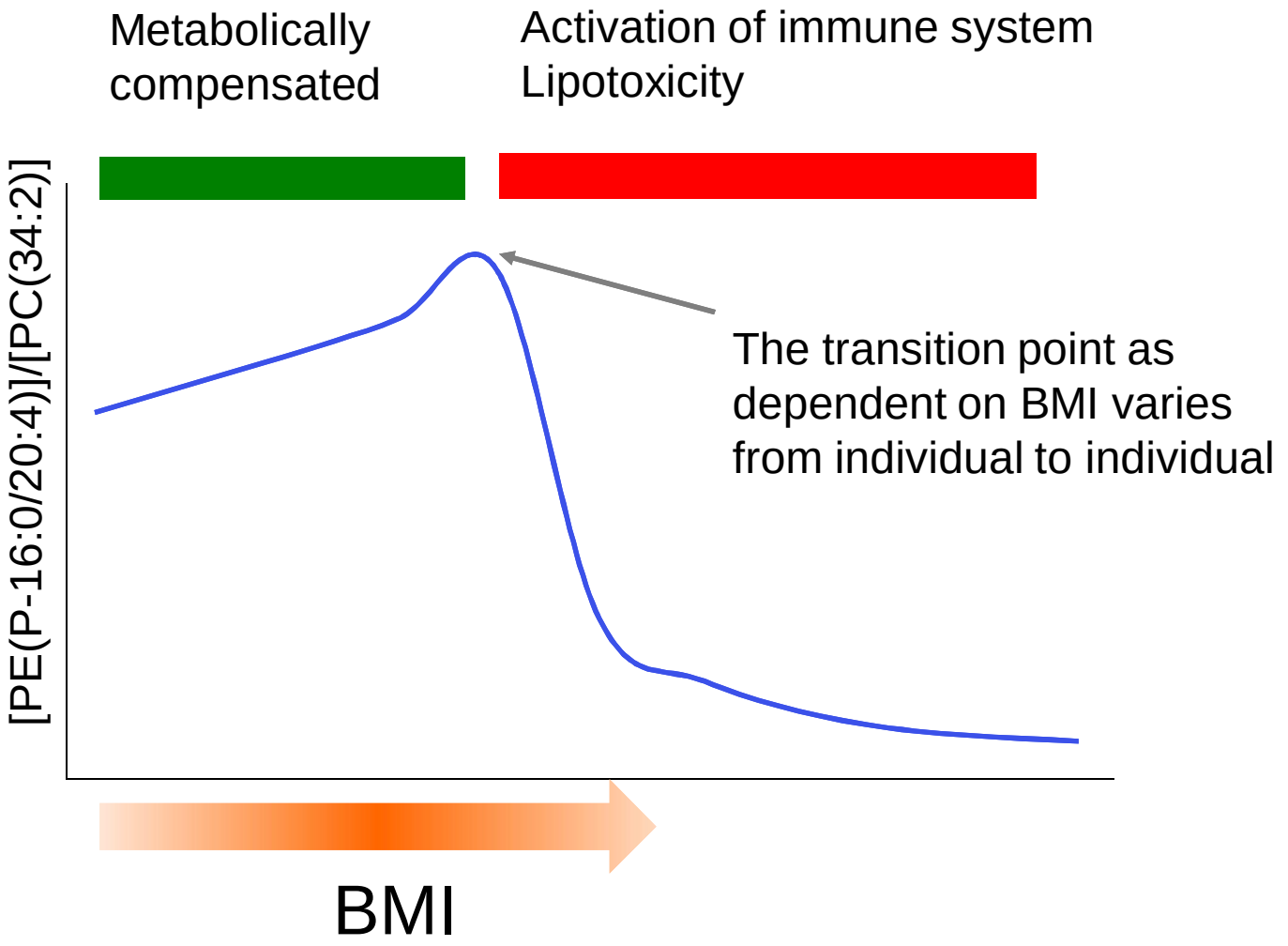
Alostatic load (or cost of adaptation) due to obesity



- Arachidonic-acid containing plasmalogens under oxidative stress become precursors of alipid mediators such as leukotrienes and hydroxyeicosatetraenoic acids
- These reactive lipids are important mediators of inflammatory response

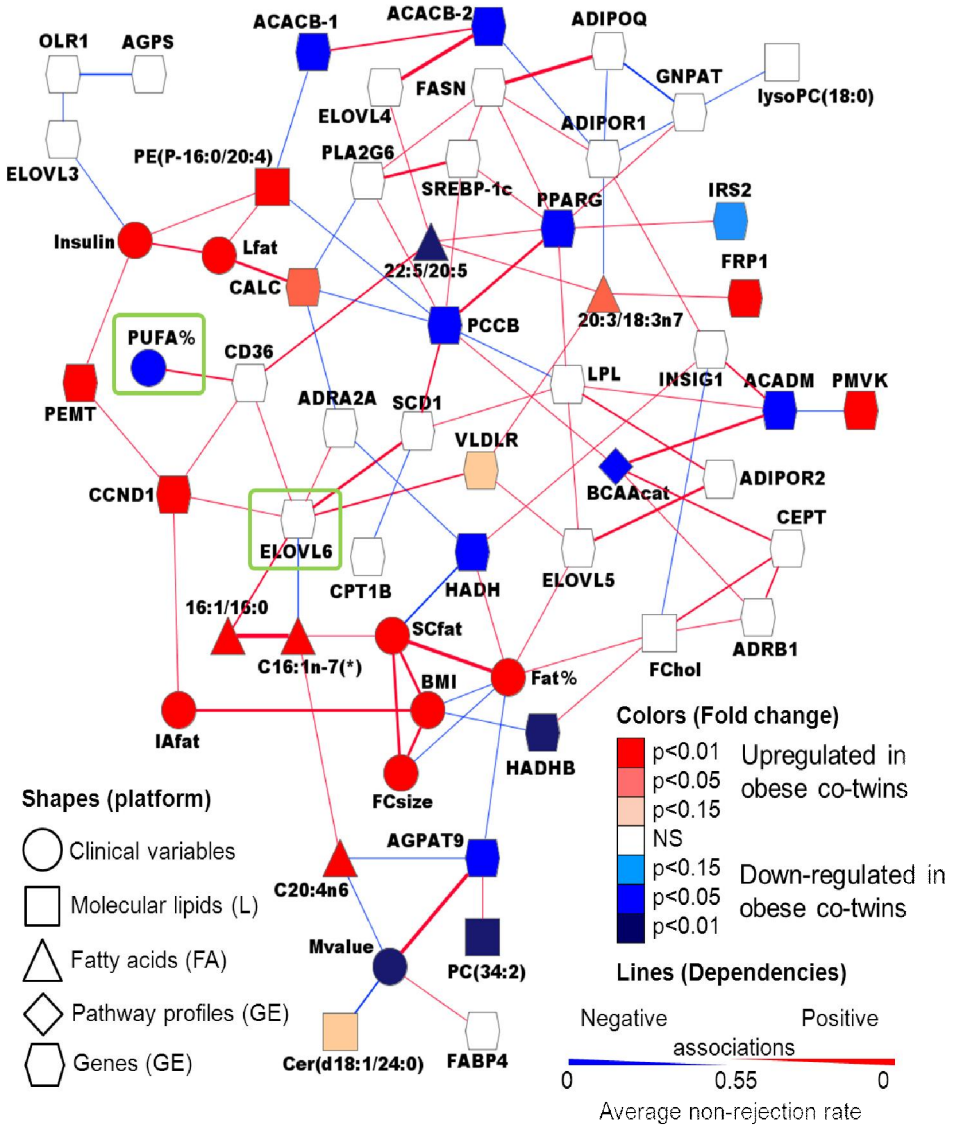
- The lipid remodelling process occurring in the membranes may therefore make the adipocytes more **vulnerable** and prone to inflammatory responses and therefore to metabolic comorbidities of obesity

Progression of adipocyte membrane lipid remodeling



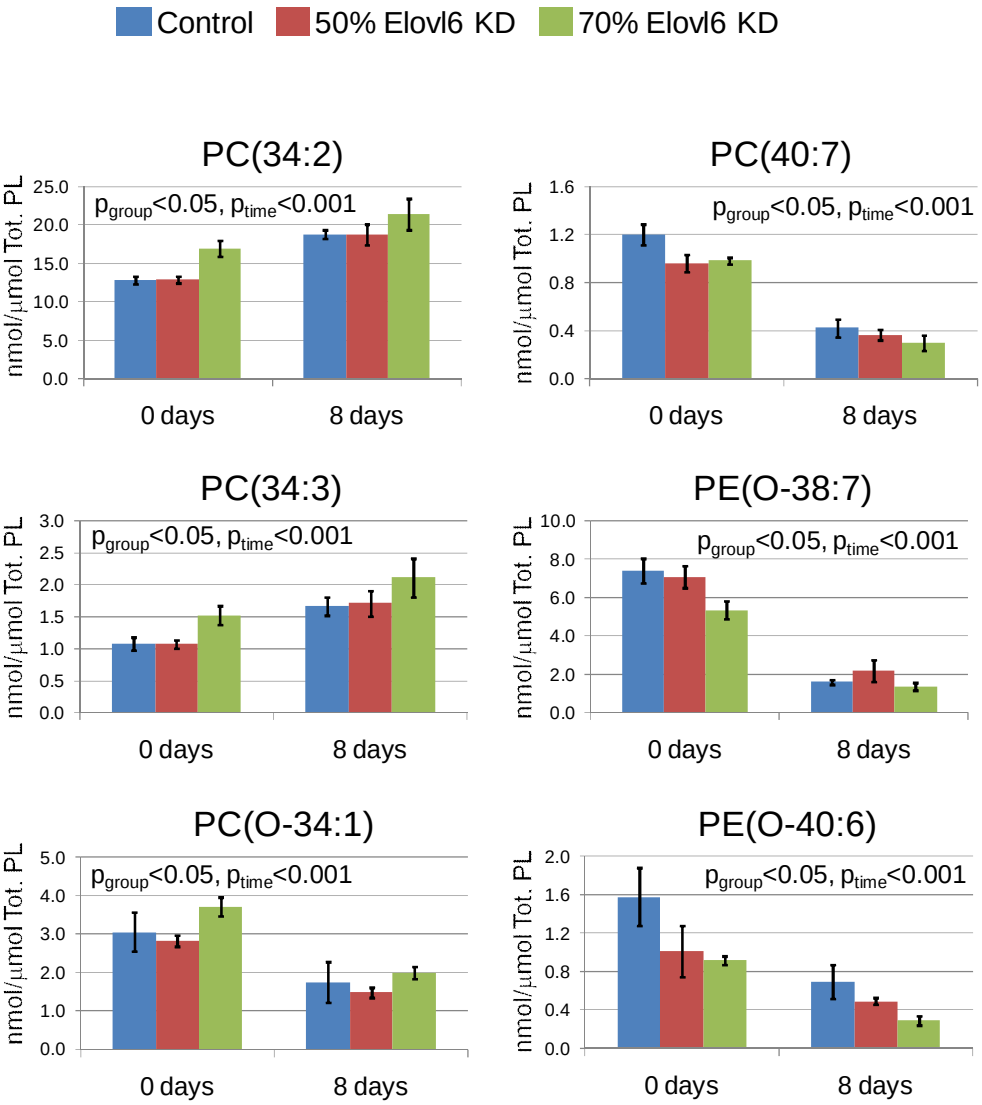
Can we modulate the membrane lipid remodeling?

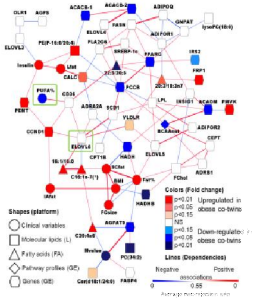
Regulation of adipose tissue remodeling: combining gene expression, lipidomics, and clinical data



Pietiläinen et al, *PLoS Biol*. (2011

Lipidomic changes in Elovl6 KD (adipocyte cell line) mirror the changes observed in acquired obesity



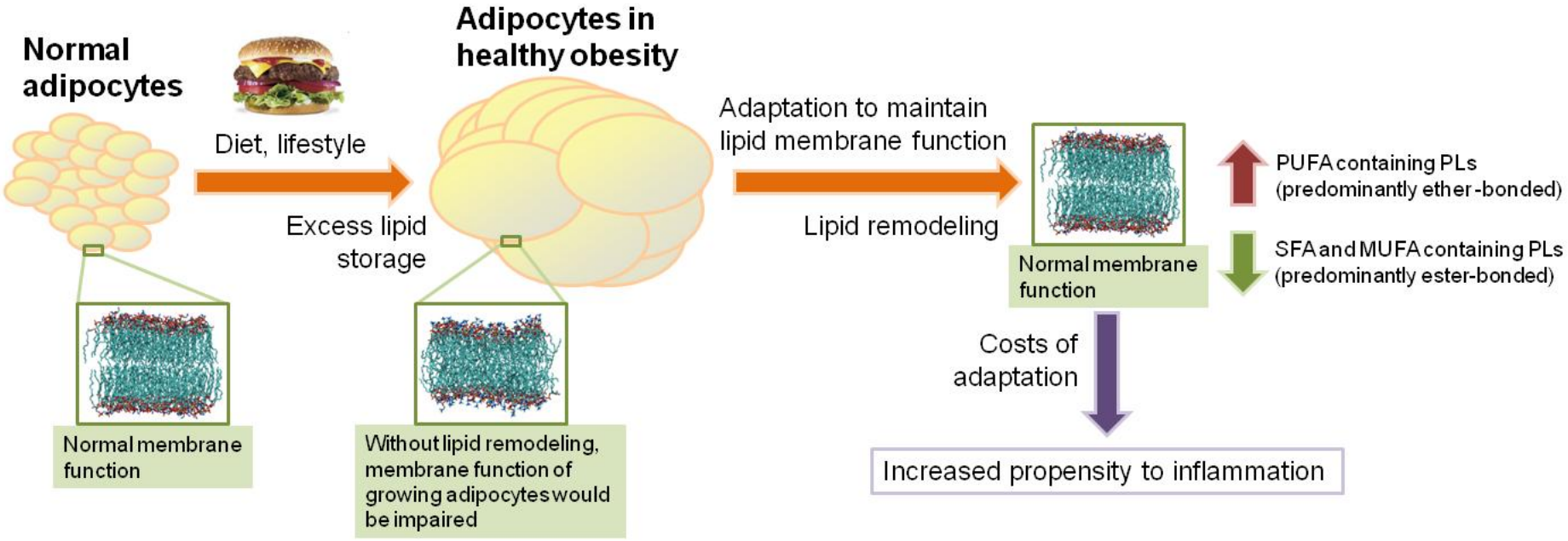


The identified adipose lipid network is amenable to genetic or therapeutic manipulation

→ New opportunity for prevention & treatment of obesity-associated metabolic comorbidities

Pietiläinen et al, *PLoS Biol*. (2011)

Adaptation in acquired obesity: benefits & costs

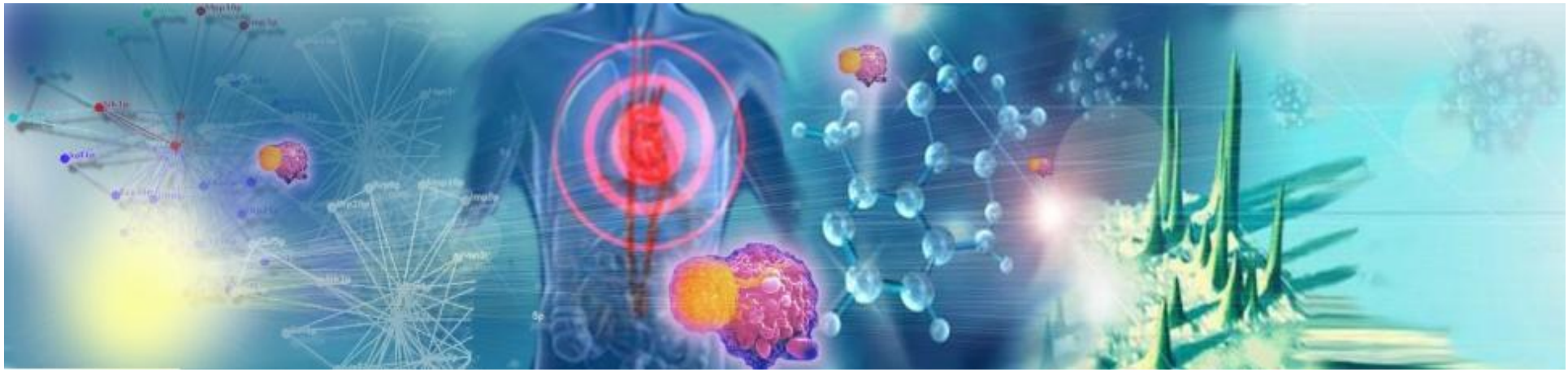


Pietiläinen et al, *PLoS Biol*. (2011)

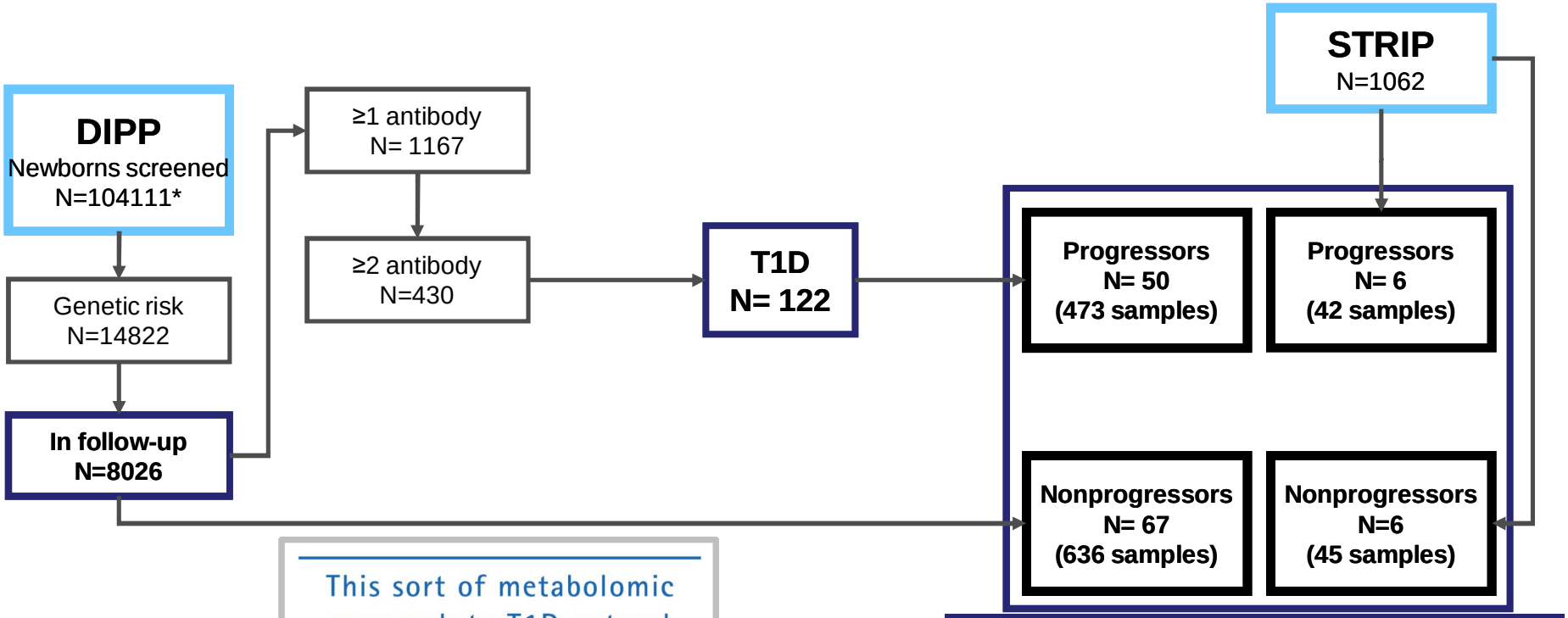
Autoimmune disease *as cost of* immune system response to host biochemical variation

SyMMyS

FINNISH CENTRE OF EXCELLENCE IN MOLECULAR SYSTEMS IMMUNOLOGY AND PHYSIOLOGY RESEARCH



Finnish Type 1 Diabetes Prediction and Prevention Study (DIPP)



This sort of metabolomic approach to T1D natural history may be a pioneering example of environmental data-driven approaches.

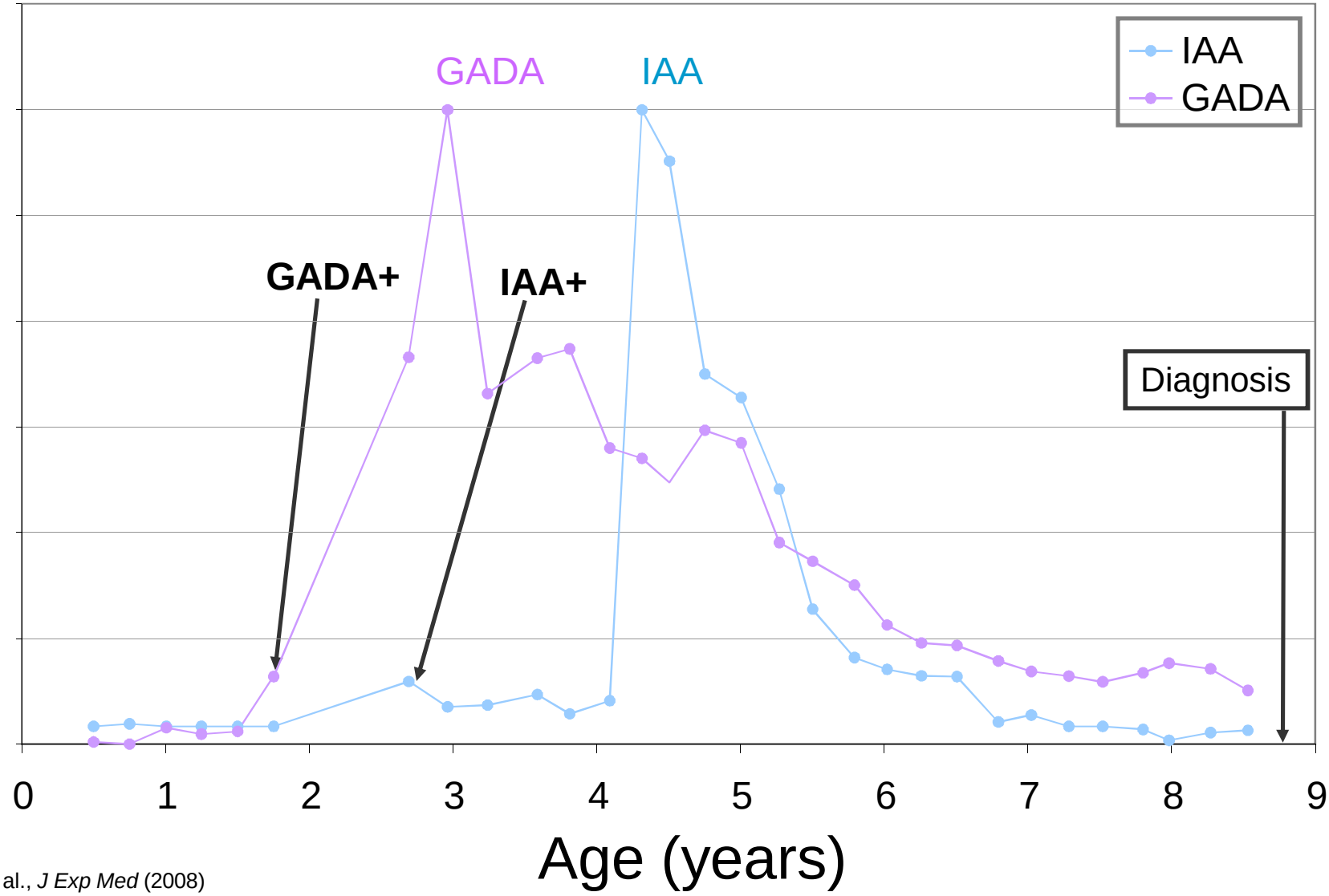
P. Bougnères & A.-J. Valleron
J. Exp. Med. (2008)

Cases and controls matched by gender, HLA genotype, city and period of birth.

M. Orešič et al., *J Exp Med* (2008)

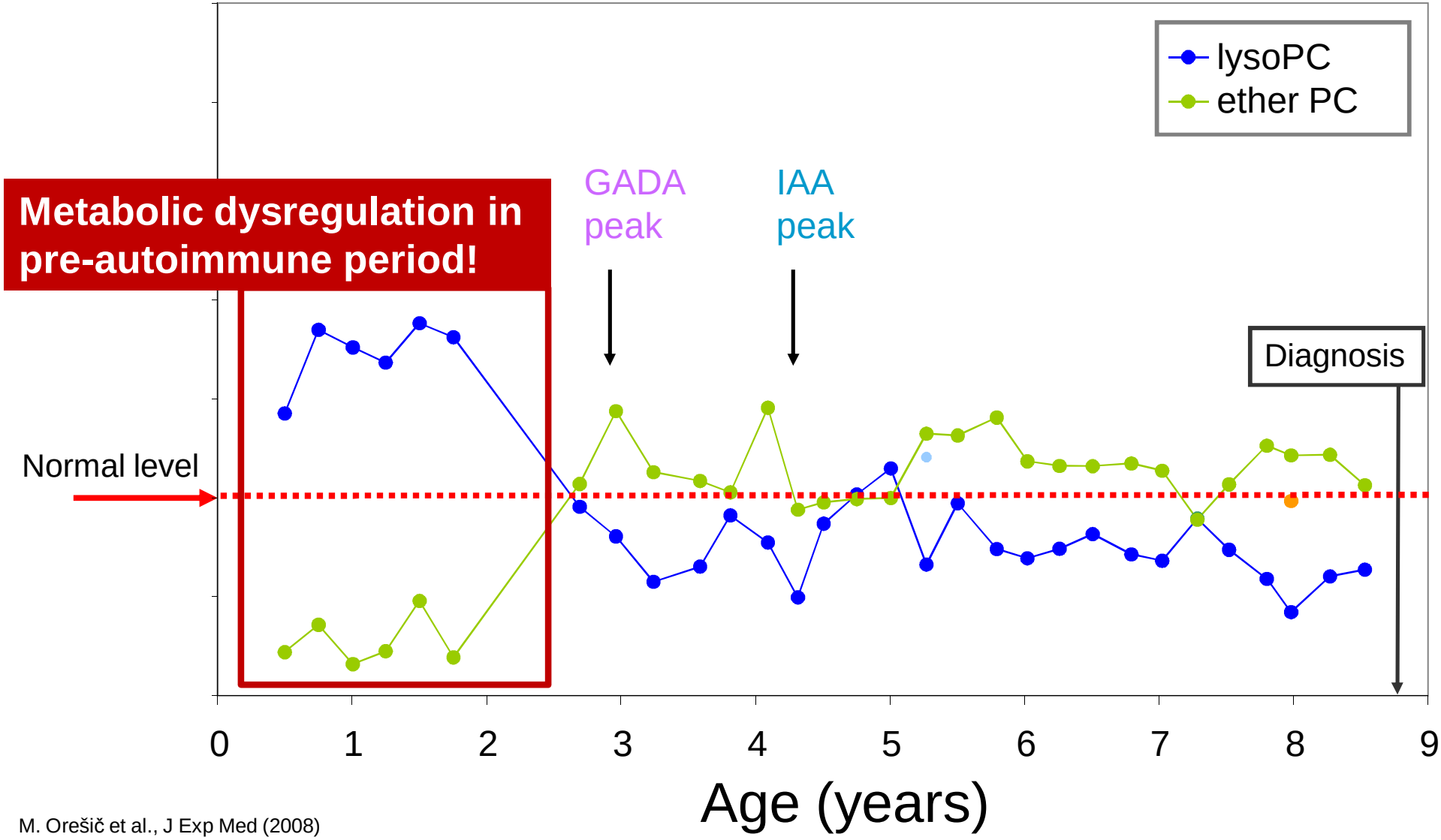
*as of June 2006

Case report: Girl who developed overt type 1 diabetes at age 9 years



M. Orešič et al., *J Exp Med* (2008)

Case report (cont)



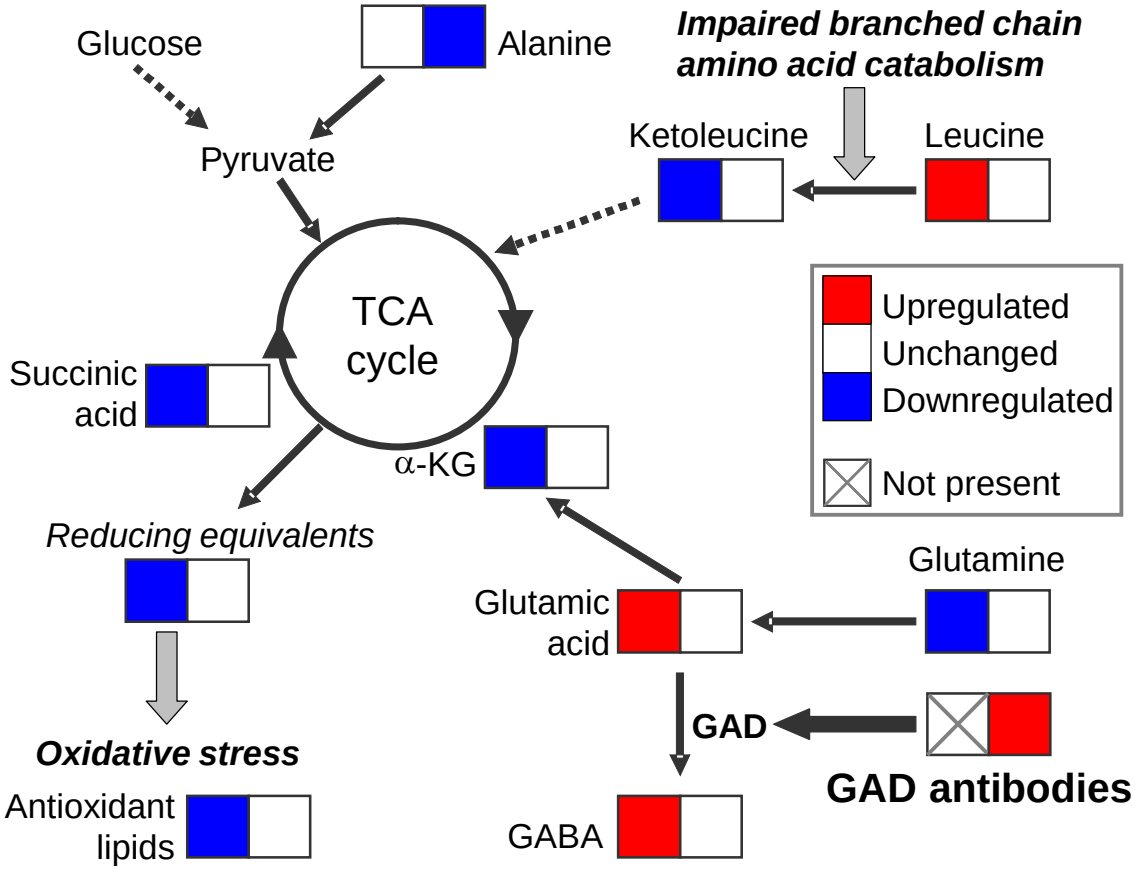
M. Orešič et al., J Exp Med (2008)

Metabolic profile prior to autoimmune (GADA) response (Progressors *vs*. Nonprogressors)

Elevated glutamate & GABA

Diminished TCA cycle metabolites

M. Orešič et al., J Exp Med (2008)



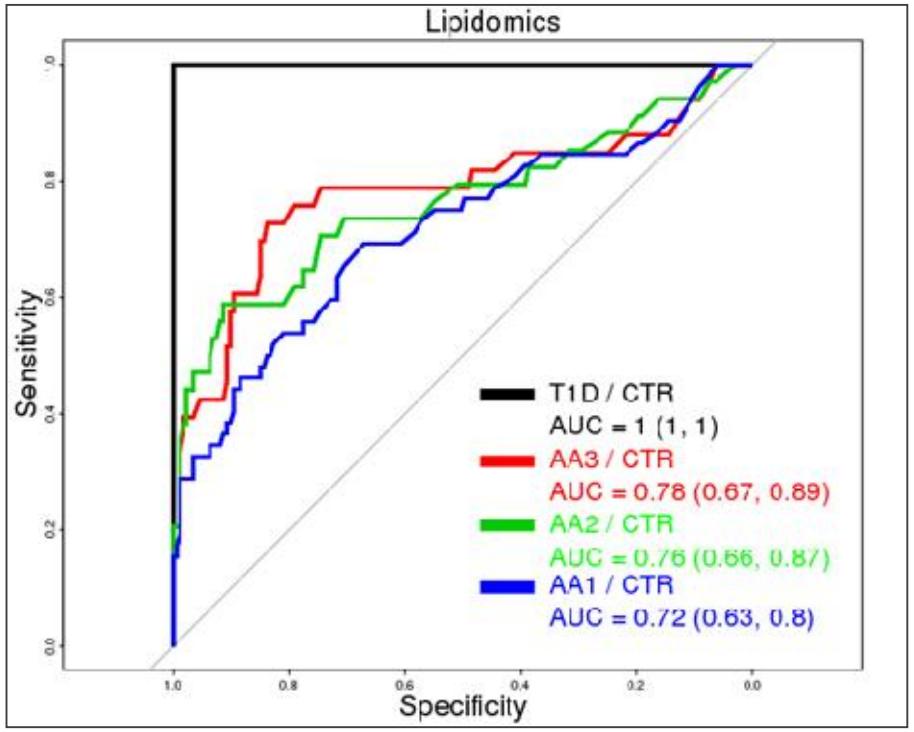
From “metabolic stress” to restoration of metabolic homeostasis by autoantibodies targeting the dysregulated pathways

Can we predict T1D at birth?

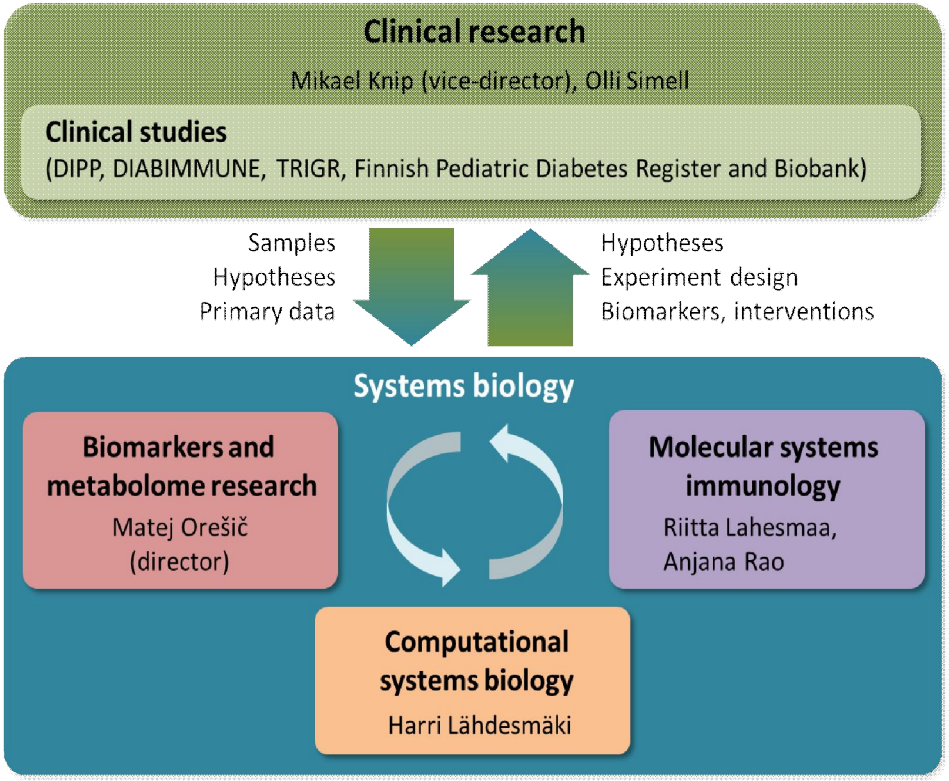
- cord serum metabolome in progressors to T1D (*N*=33), newborns who developed 3 or 4 (*N*=32), two (*N*=34), or one (*N*=50) islet autoantibody (Aab) during the follow-up, and controls (*N*=160) matched for gender, HLA genotype, city and period of birth.
- Metabolomics platforms: (1) global lipidomics using UPLC-MS, (2) global metabolomics using GCxGC-TOFMS, and (3) bile acid platform using UPLC-MS/MS.

Main findings

- T1D and 3-4Ab groups are most similar and characterized by diminished phospholipids (ether phosphatidylcholines and sphingomyelins), confirming earlier data.
- A lipid signature of 3 lipids was derived based on T1D progressor cord blood profile and independently tested on other subgroups.
- The signature predicts T1D in the 3-4Ab group with **odds ratio of 18**!
- The metabolic signature is **independent of HLA associated T1D risk.**



Finnish Centre of Excellence in Molecular Systems Immunology and Physiology Research (*SyMMyS*) 2012-2017



- to understand the molecular mechanisms that control the immune system as well as the interactions between the immune system and other physiological systems in health and disease
- to translate this knowledge into novel treatment and prevention strategies of inflammatory/ immune-mediated disorders, with specific focus on type 1 diabetes