

Metabolomics and systems biology approaches to study health and disease

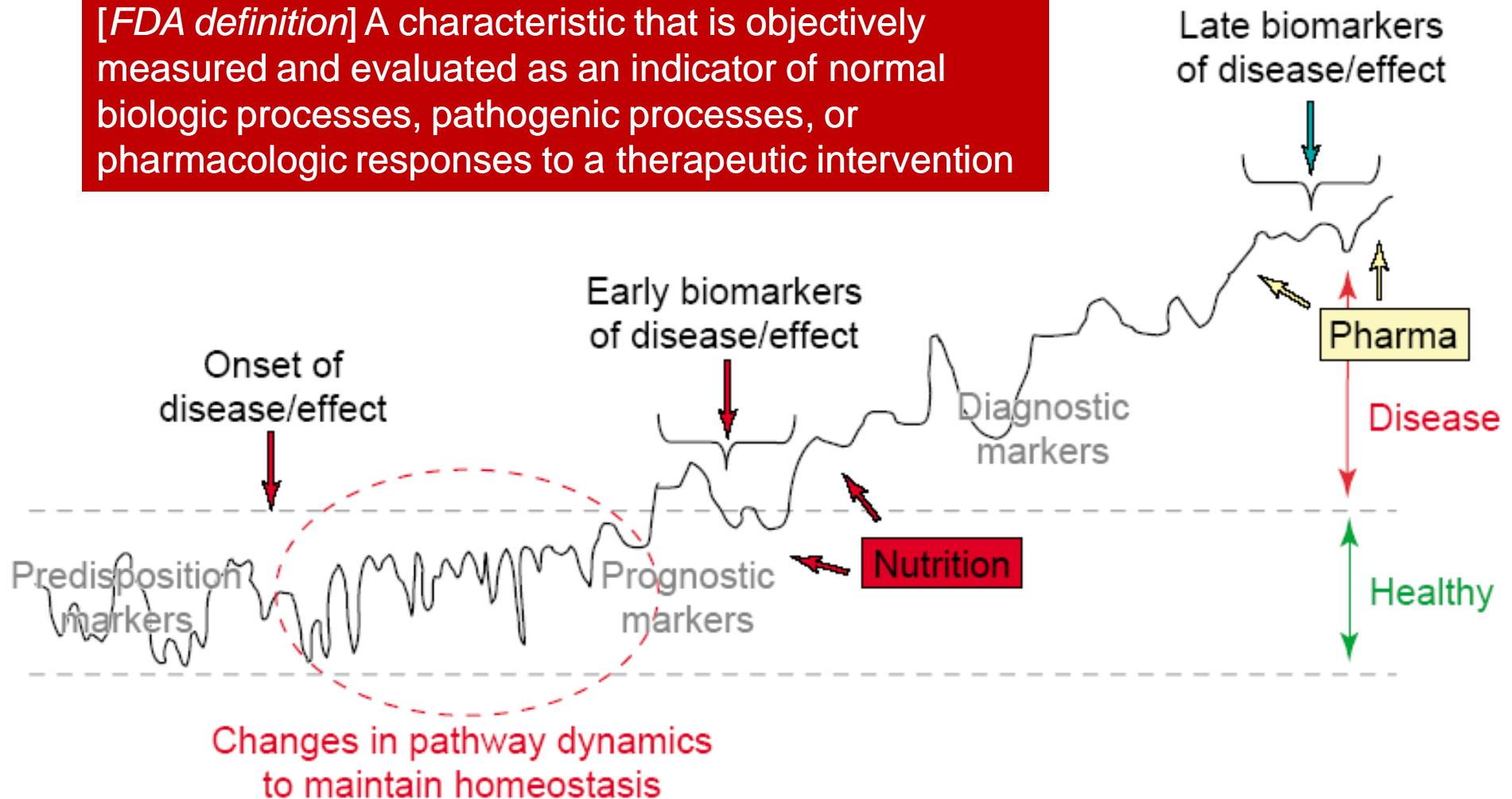
Matej Orešič

14.12.2011

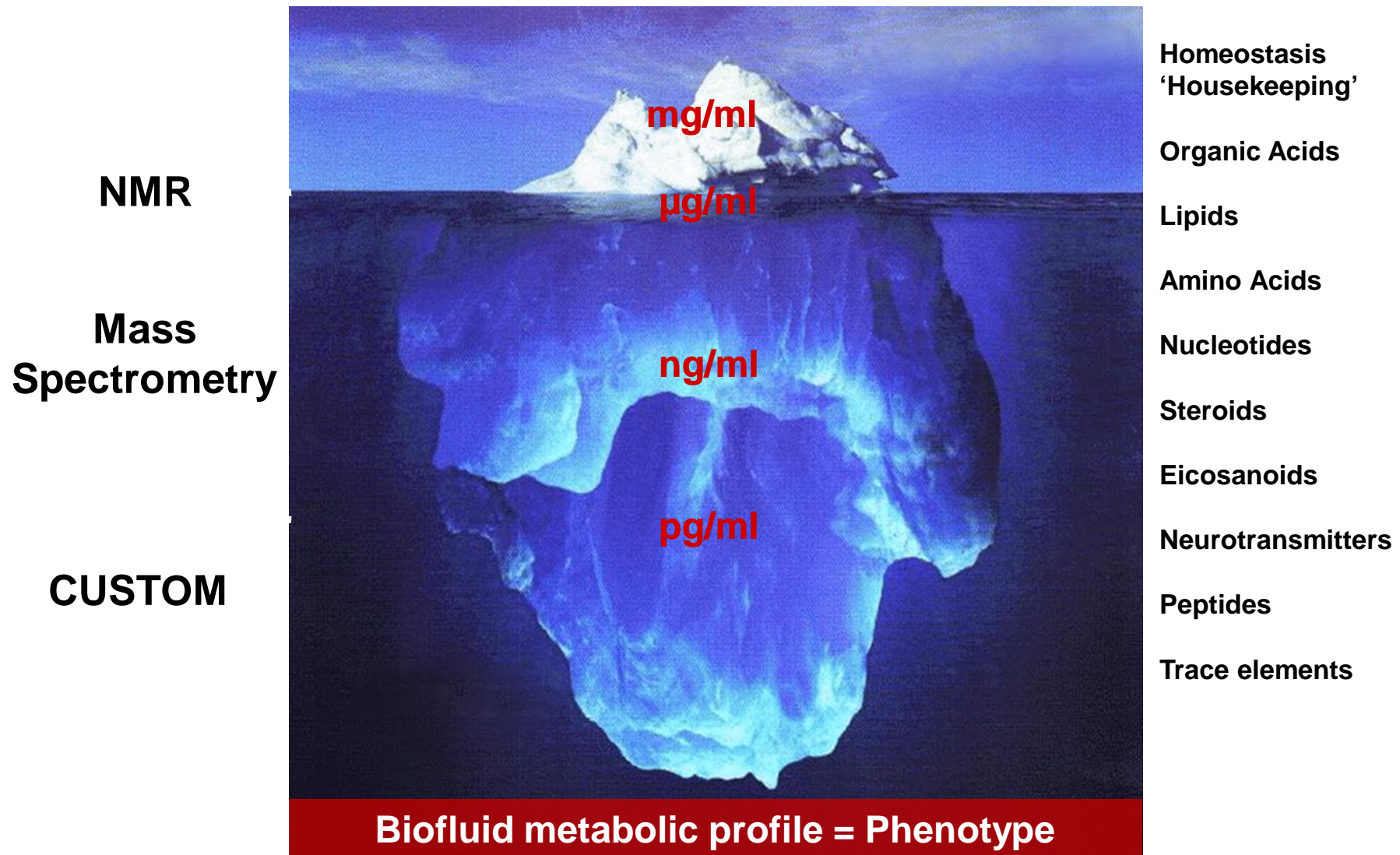
Biomarker concept in domain of human health

[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



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)

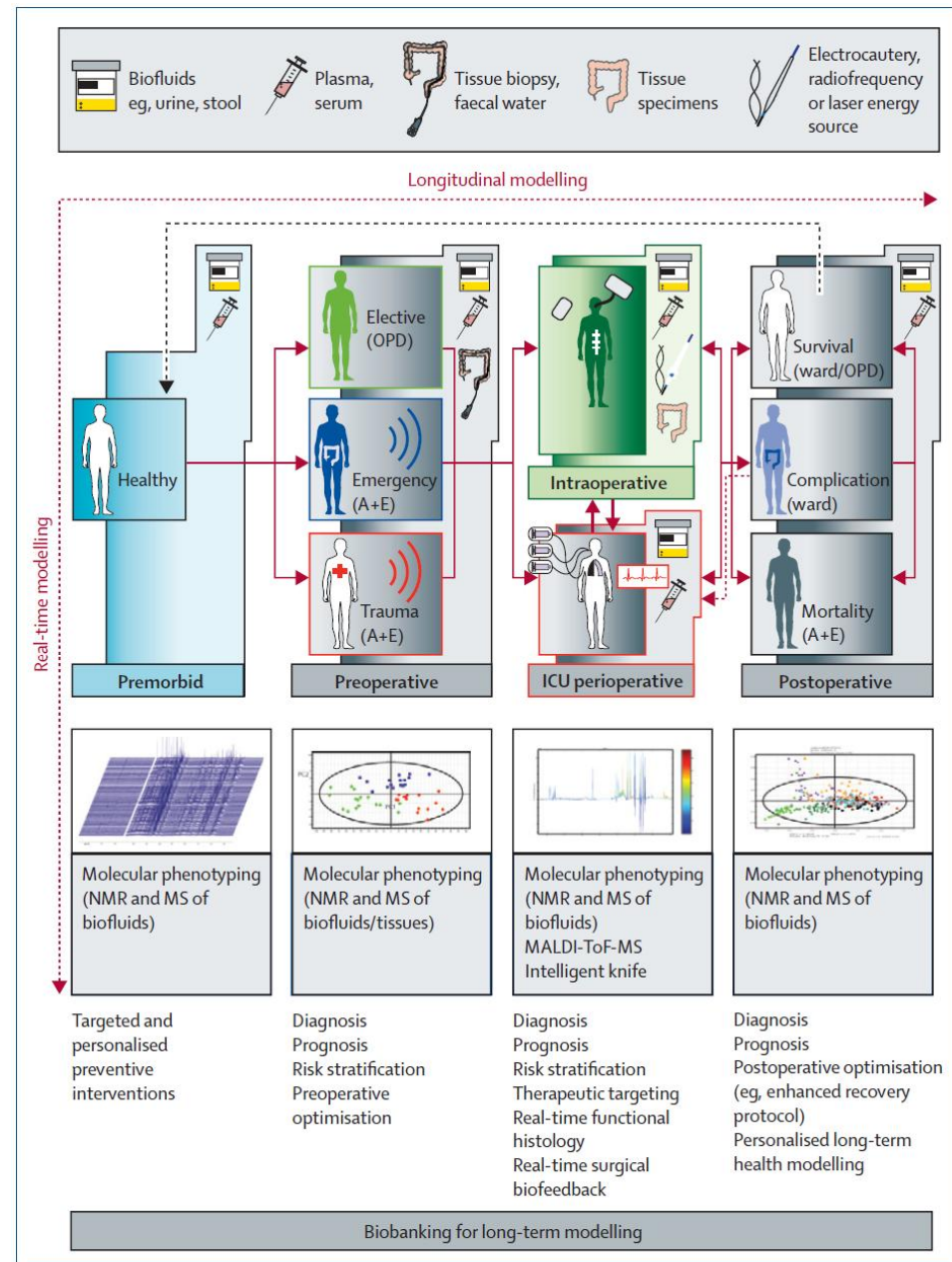


Figure: Global metabolic phenotyping pathway for the surgical journey

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/>



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Welcome

to the Quantitative Biology and Bioinformatics group page. We are an interdisciplinary team with competencies in bioinformatics, computational systems biology, and advanced analytical technologies. We are part of the Academy of Finland Centre of Excellence in Molecular Systems Immunology and Physiology Research (2012-2017), which is directed by Prof. Matej Orešič.

We are investigating

- how are the genetic and environmental factors imprinted in the metabolome;
- the mechanisms by which alterations of metabolome lead to (patho)physiological changes at the systems level;
- discovery and functional characterization of metabolic markers for multiple diseases or responses to interventions and environmental challenges.

We are relying on metabolomics techniques to characterize the metabolome, combined with systems biology strategies to investigate, e.g., how changes in gene expression, gut microbial composition or immune/inflammatory status alter the metabolic phenotypes. Current biomedical interests include metabolic and autoimmune diseases.

The emergence of systems biology and medicine is opening new opportunities to characterize and understand biological systems as well as to identify novel biomarkers and therapeutic avenues to benefit human health.

In spotlight

This sort of metabolomic approach to T1D natural history may be a pioneering example of environmental data-driven approaches. From commentary on our paper *Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes*, *J. Exp. Med.* **205**, 2975 (2008).

Finnish twin study yields new information on how cells cope with obesity [*Association of lipidome remodeling in the adipocyte membrane with acquired obesity in humans*, *PLoS Biol.* **9**, e1000623 (2011)].

Novel therapeutic opportunities offered by characterization of altered membrane lipid metabolism in breast cancer progression, *Cancer Res.* **71**, (2011).

Latest news

November 2011
PhD thesis by Erno Lindfors: Network Biology: Applications in medicine and biotechnology.

October 2011
New paper: M. Pflueger *et al.*, Age- and islet autoimmunity-associated differences in amino acid and lipid metabolites in children at risk for type 1 diabetes, *Diabetes* **60** (11), 2740-2747 (2011). (commentary)

October 2011
New paper: M. Sysi-Aho *et al.*, Metabolic regulation in progression to autoimmune diabetes, *PLoS Comp. Biol.* **7** (10), e1002257 (2011). (Press release)

October 2011
 Matej Orešič re-elected to the Board of Directors of the Metabolomics Society.



Diagnosis of psychosis

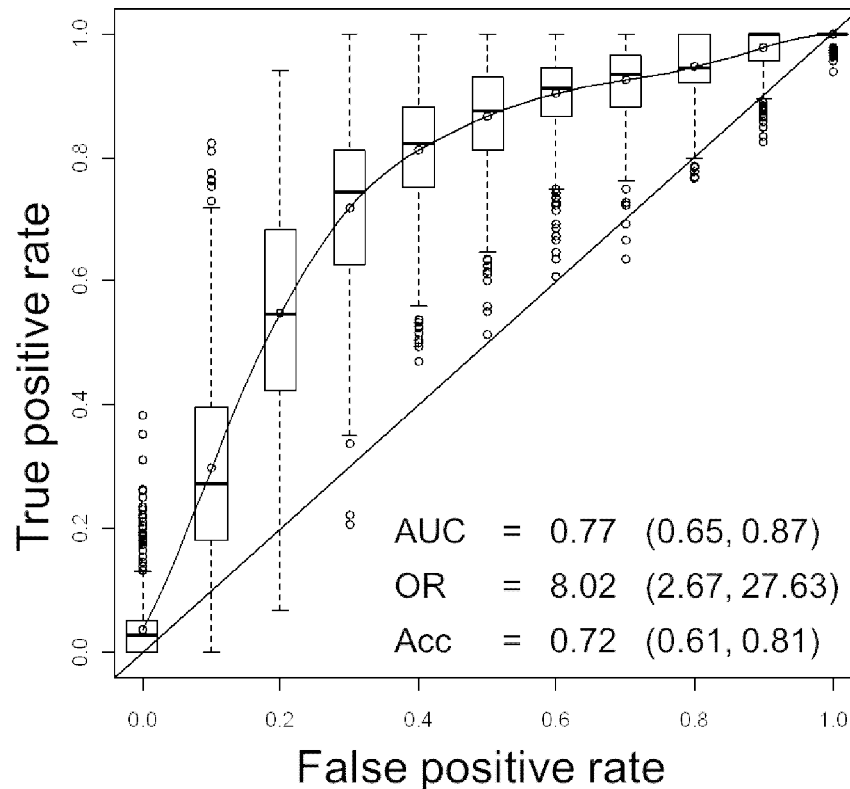
[Schizophrenia vs. Other psychoses (affective, non-affective)]

- 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.

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

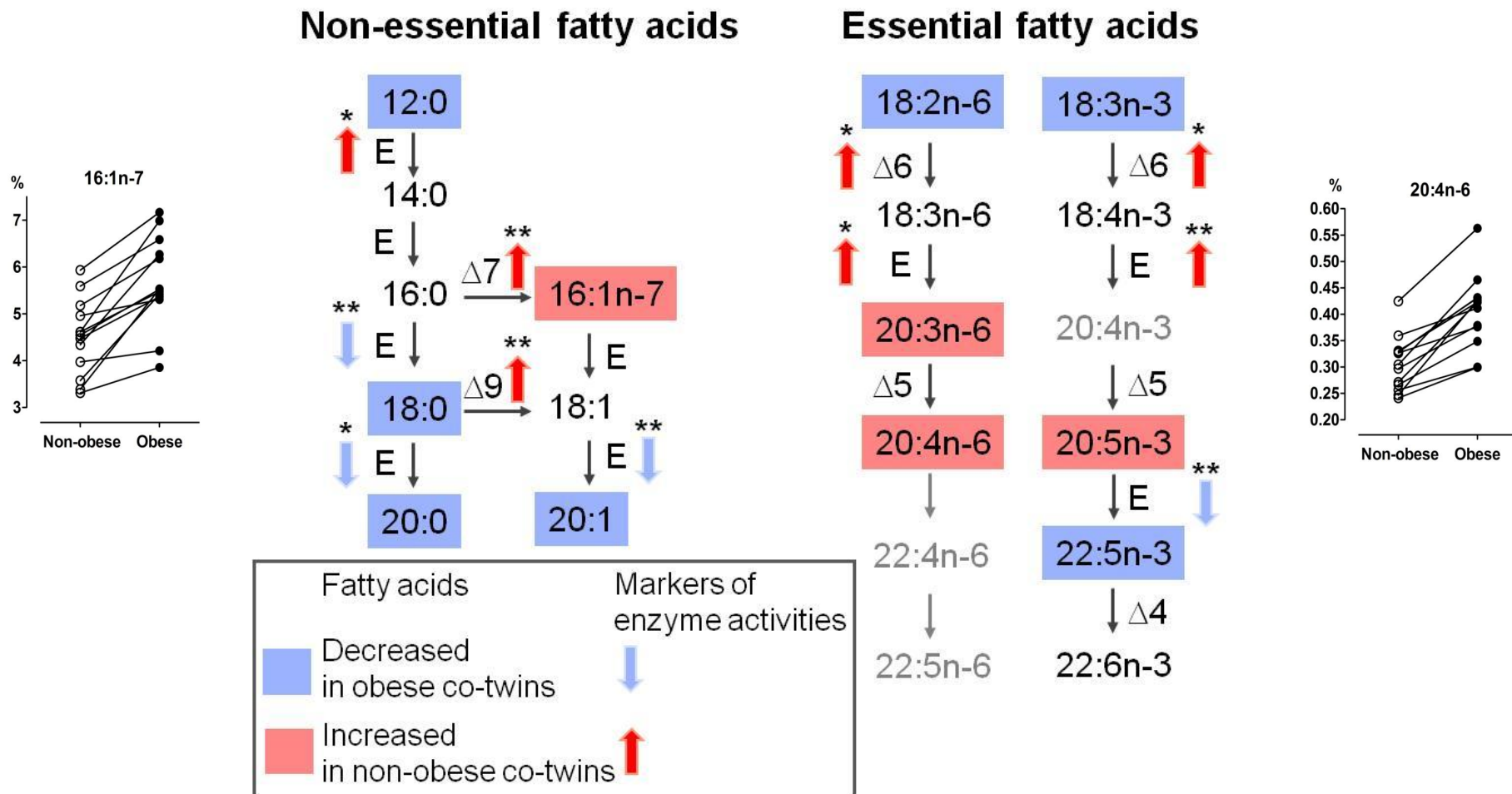


In a healthcare setting, the application of such an assay could complement the neurocognitive assessment by the medical doctor and could be applied to identify the at-risk patients in need of further comprehensive follow-up.

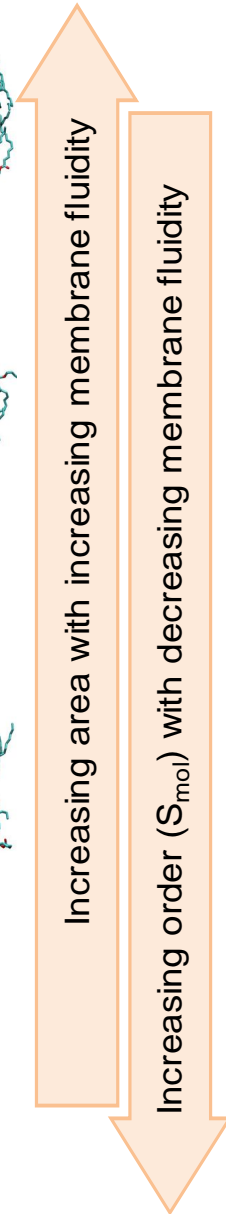
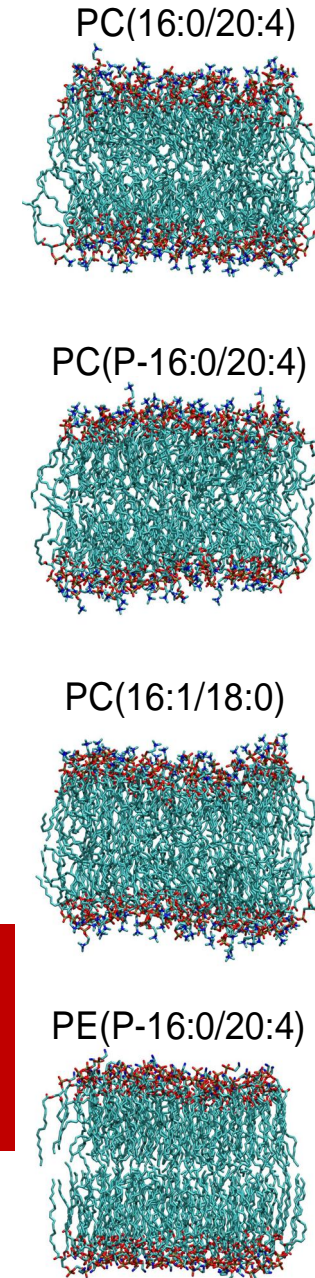
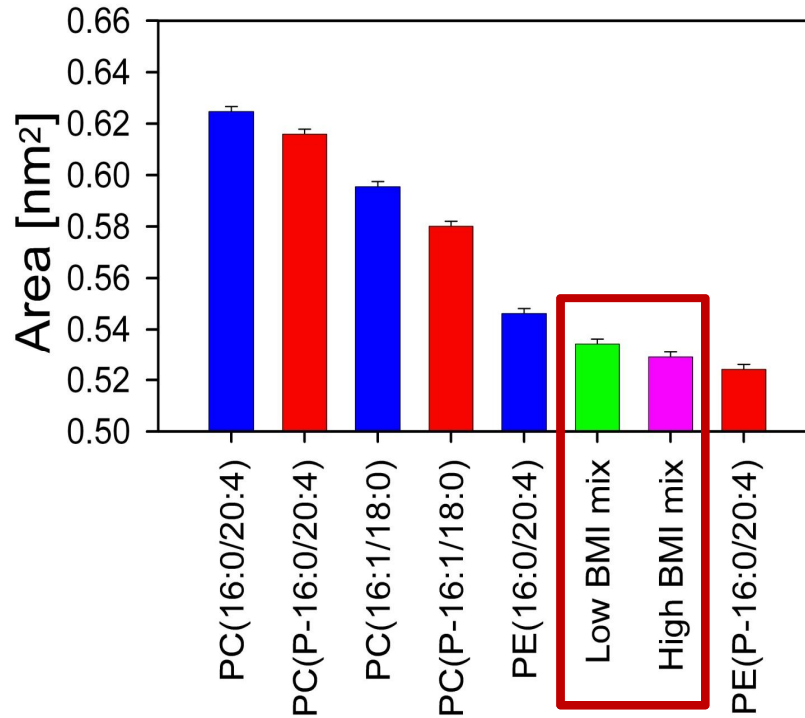
**Metabolic disease
as cost of
adipocyte adaptation to obesity**

Fatty acid composition in adipose tissue

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

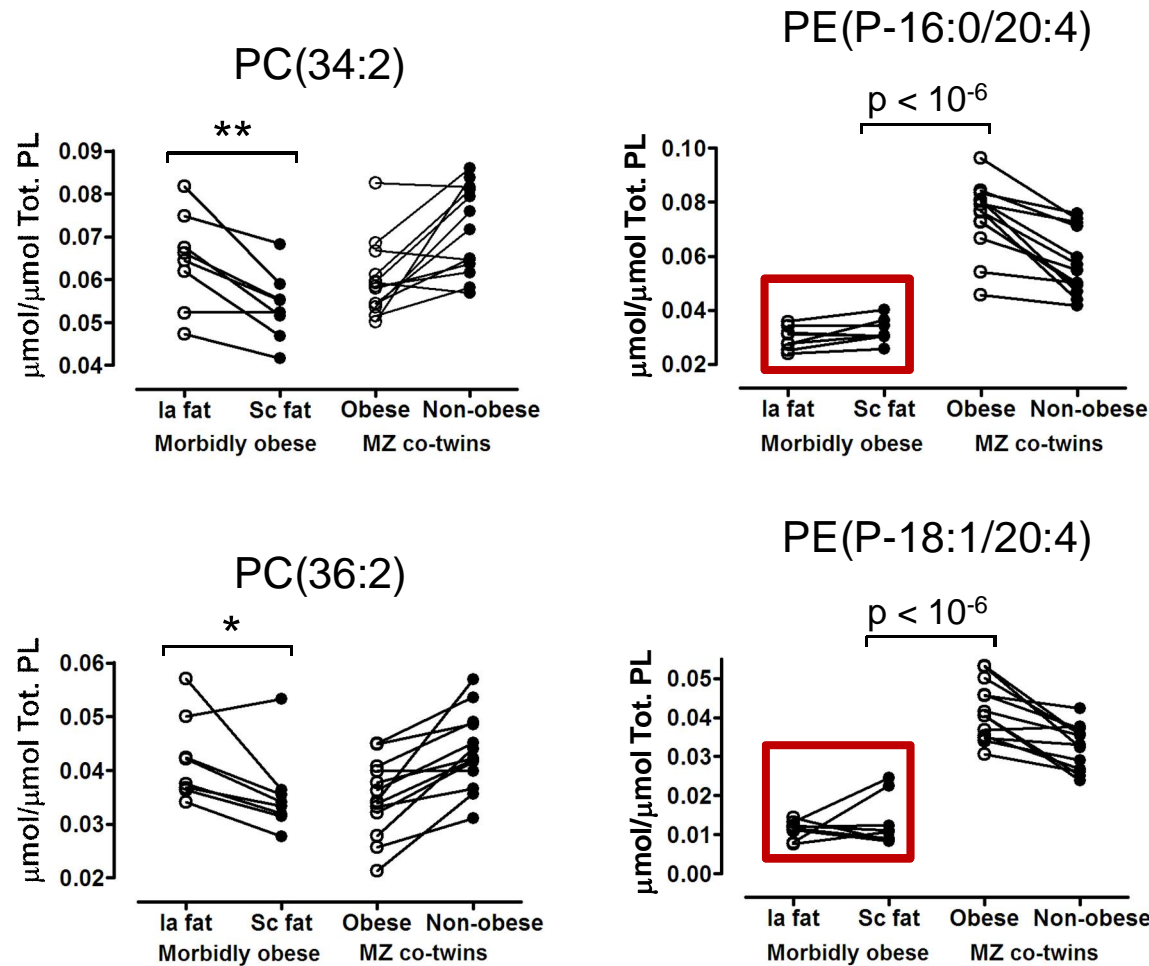


Lipid bilayer simulations

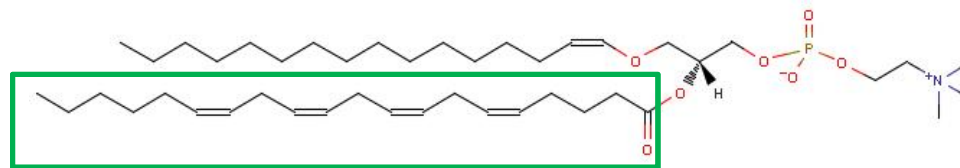


The observed membrane lipid changes in obese twins help maintain the membrane fluidity
 → an adaptive mechanism

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

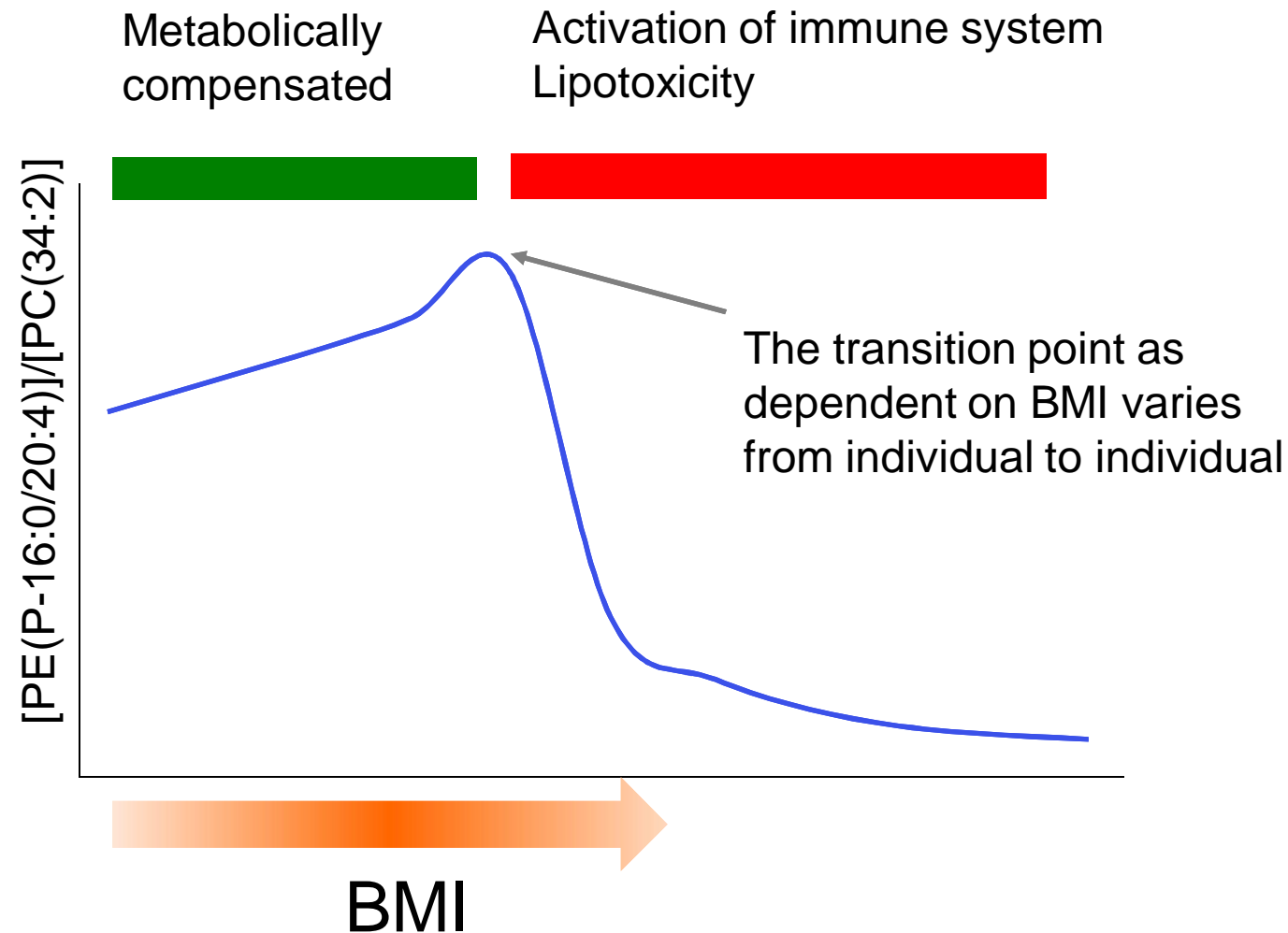


Allostatic load (or cost of adaptation) due to obesity



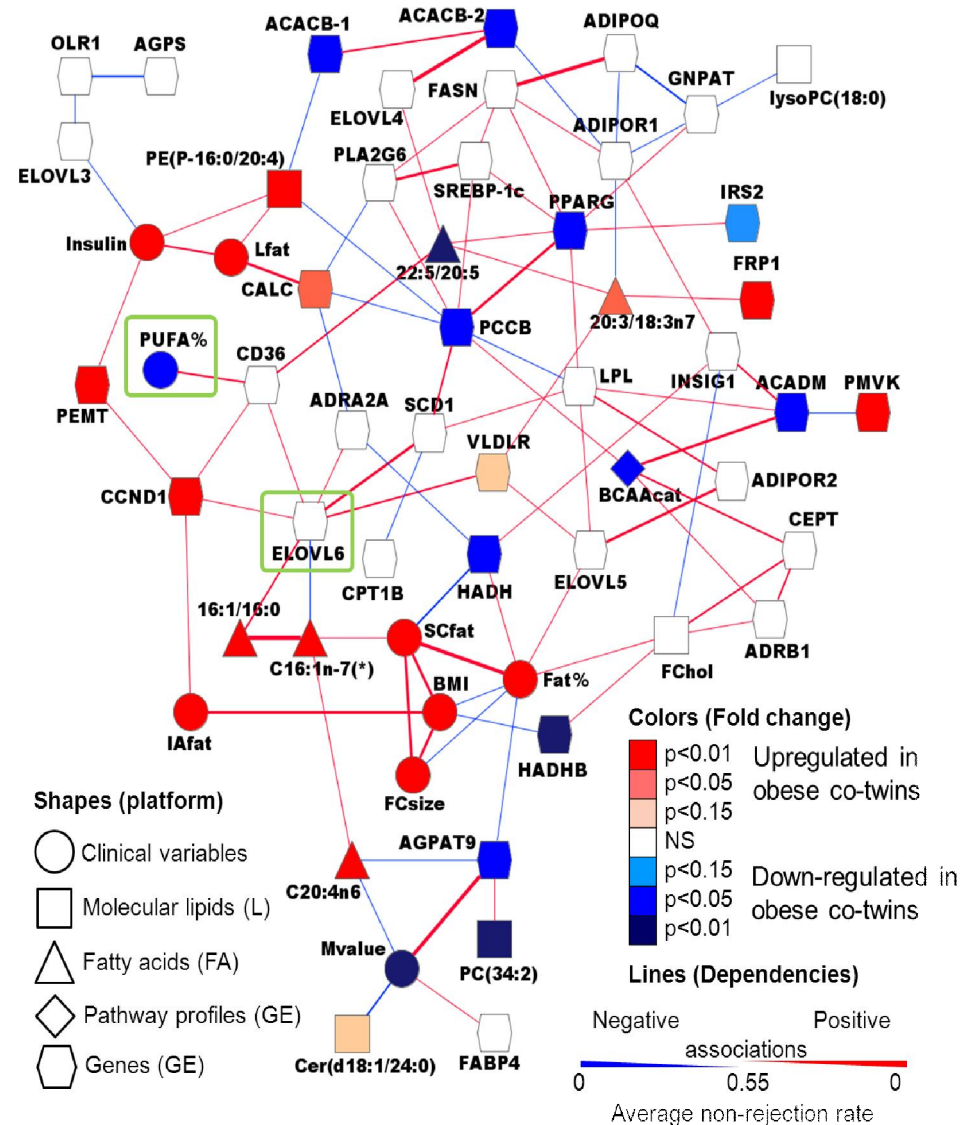
- Arachidonic-acid containing plasmalogens under oxidative stress become precursors of alipid mediators such as leukotrienes and hydroxyeicosatetraenoic acids
- These reactive lipids are important mediators of inflammatory response
- The lipid remodelling process occurring in the membranes may therefore make the adipocytes more **vulnerable** and prone to inflammatory responses and therefore to metabolic comorbidities of obesity

Progression of adipocyte membrane lipid remodeling



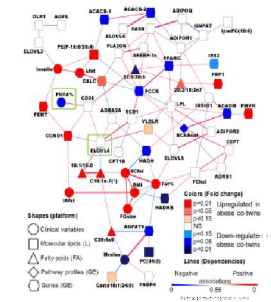
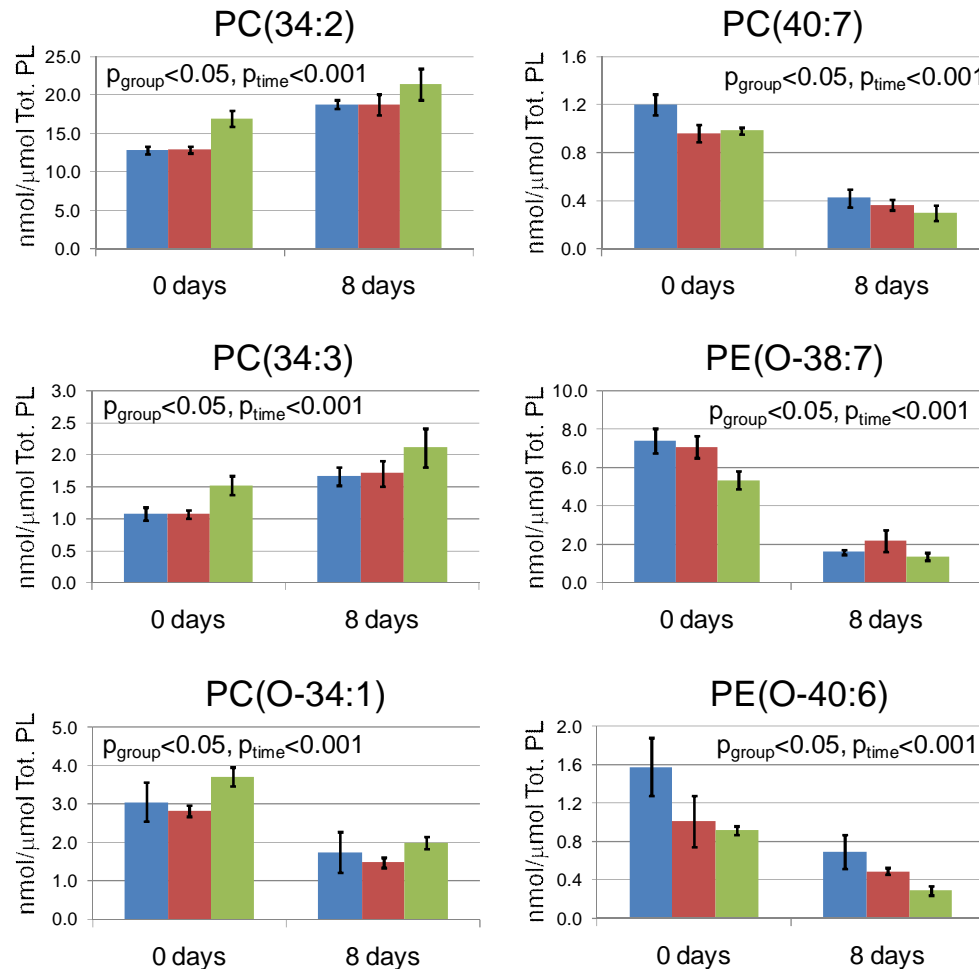
Can we modulate the membrane lipid remodeling?

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



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

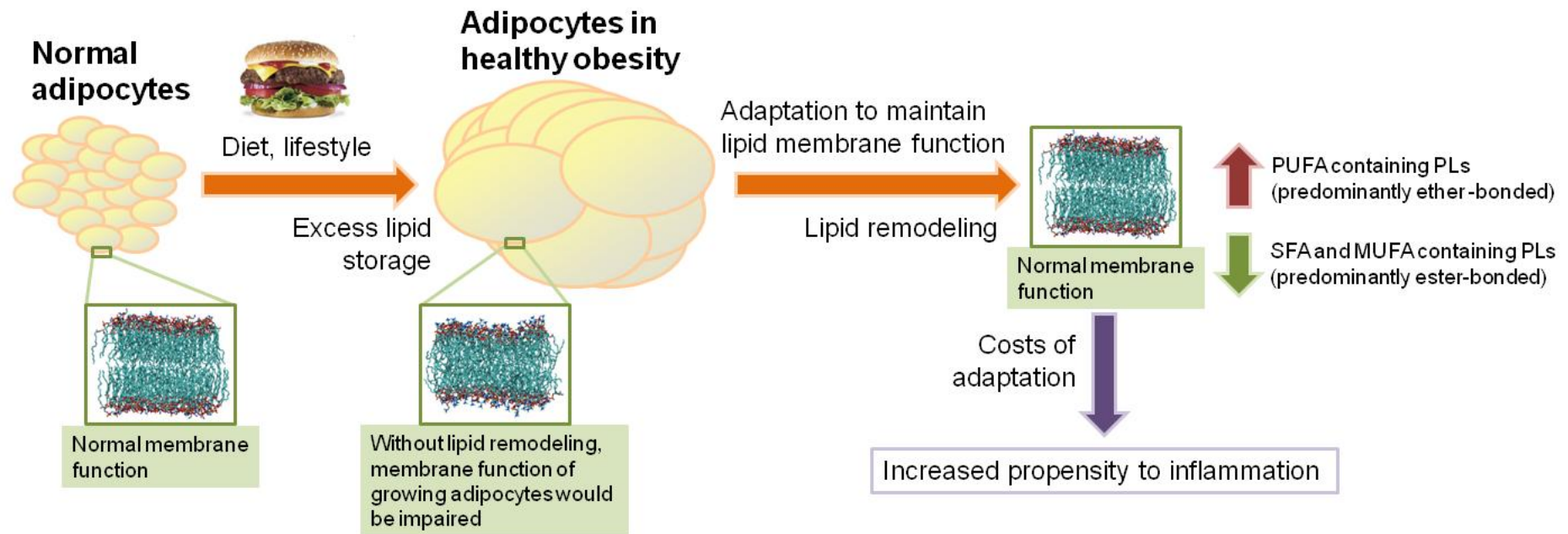
Control 50% Elovl6 KD 70% Elovl6 KD



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

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

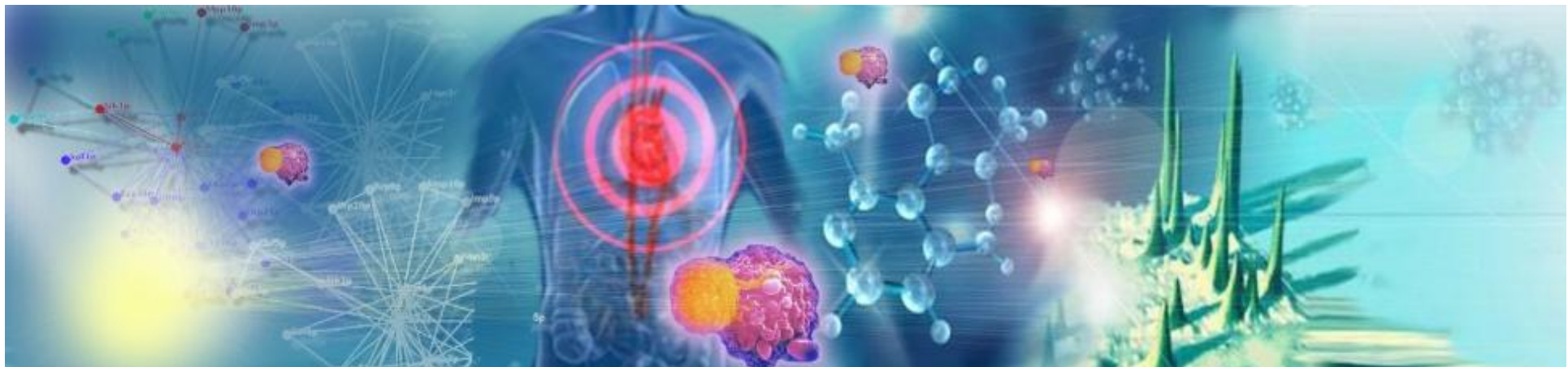
Adaptation in acquired obesity: benefits & costs



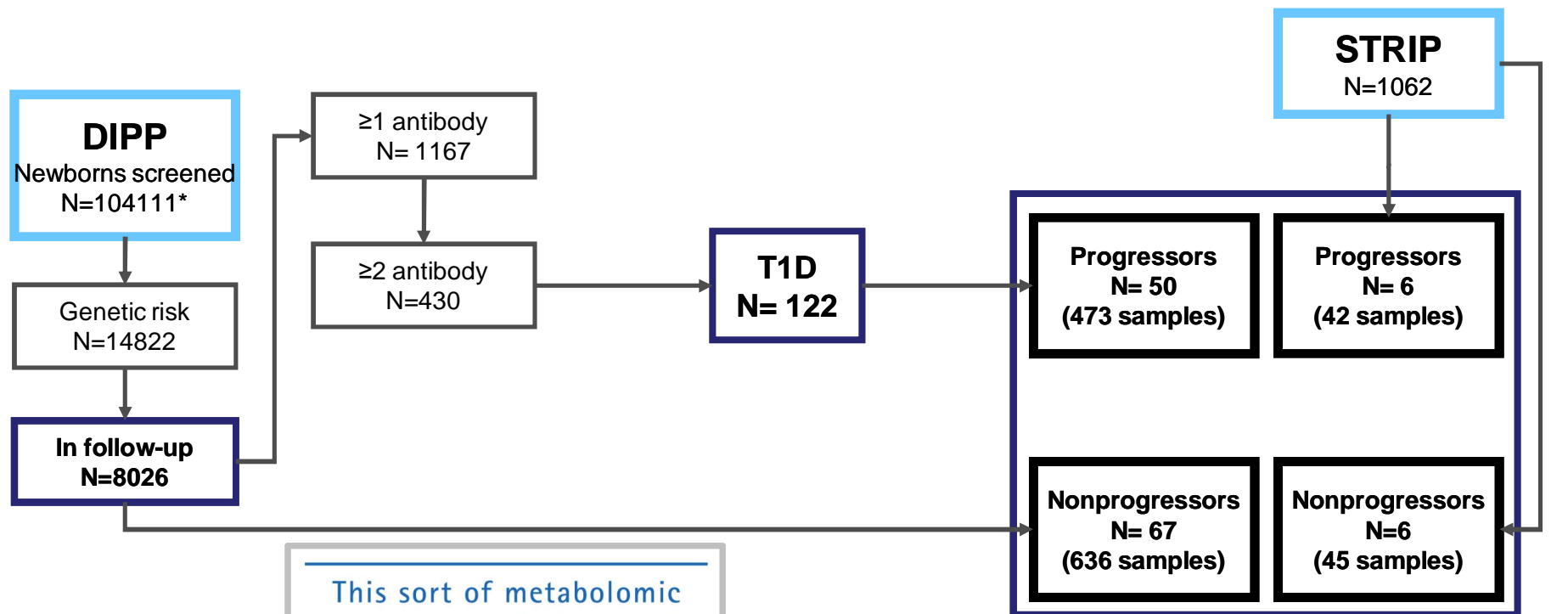
Autoimmune disease *as cost of immune system response* to host biochemical variation

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.

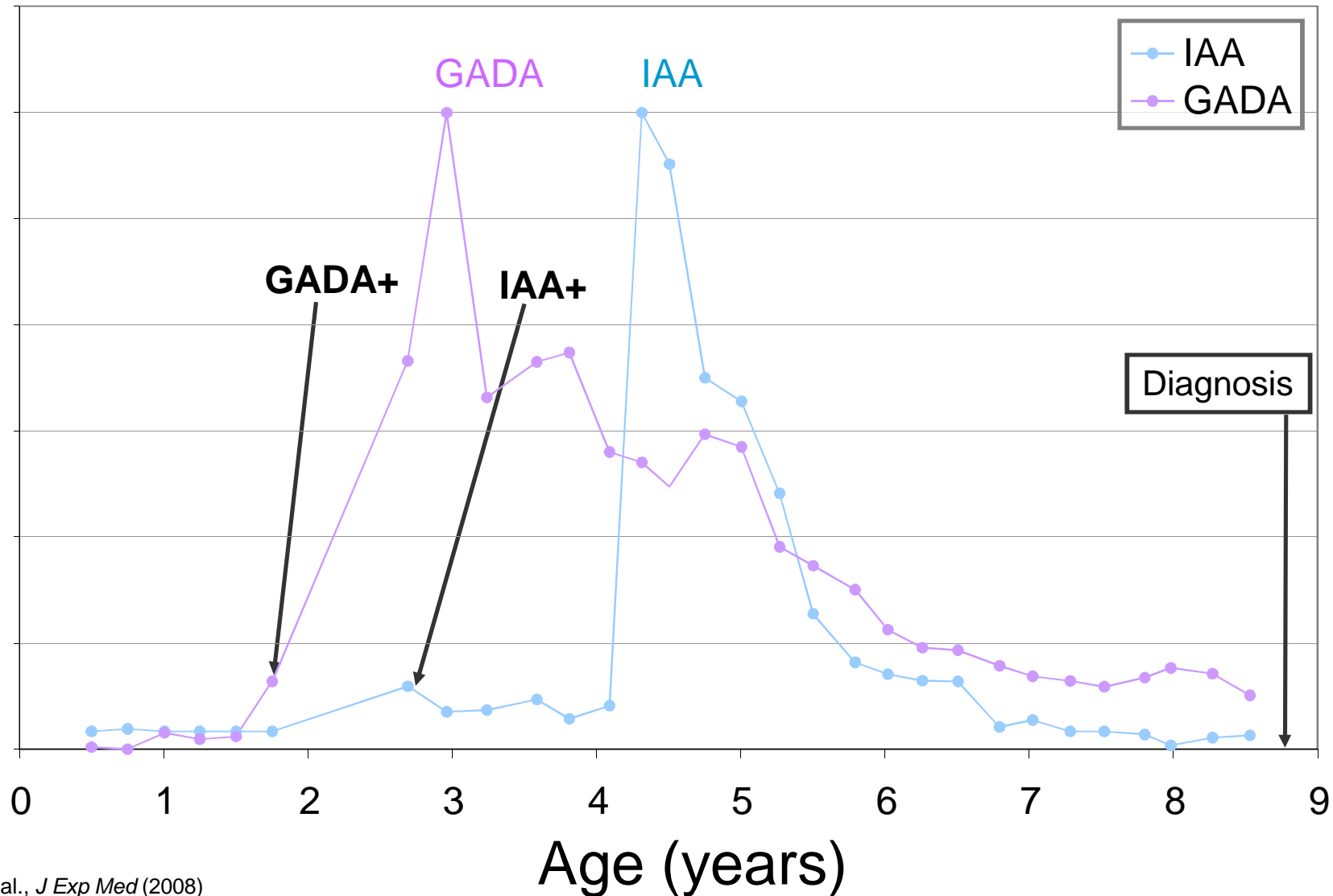
P. Bougnères & A.-J. Valleron
J. Exp. Med. (2008)

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

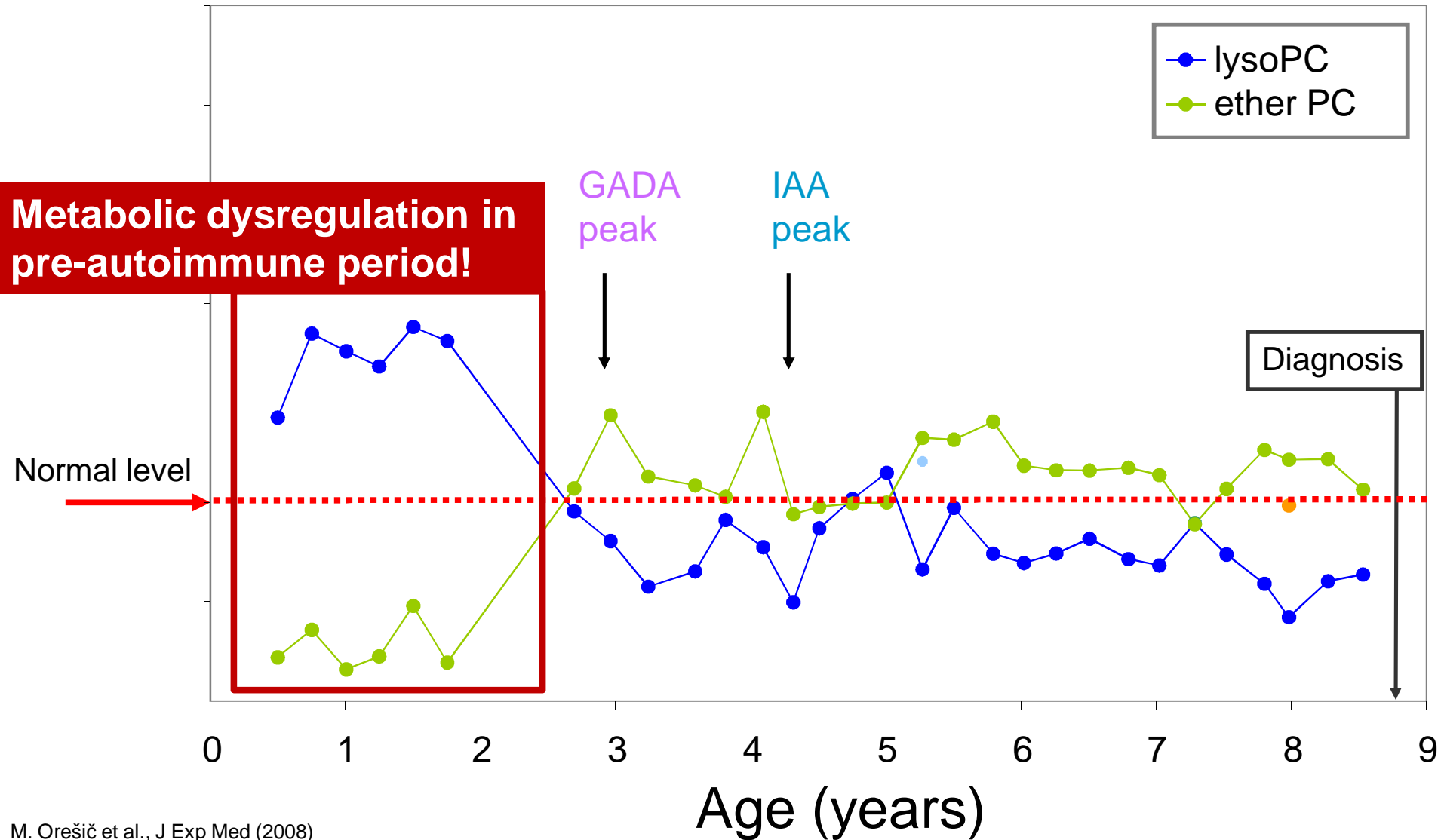
M. Orešič et al., *J Exp Med* (2008)

*as of June 2006

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



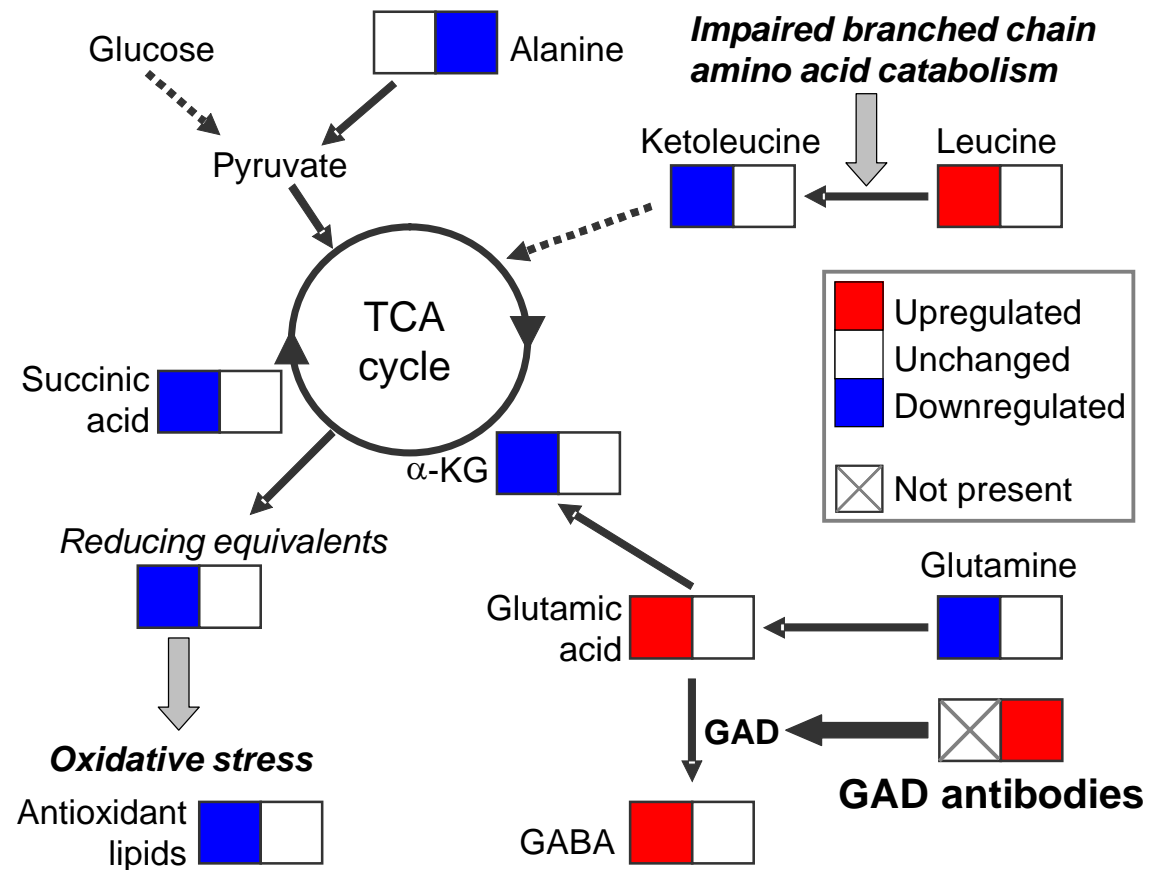
Case report (cont)



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)



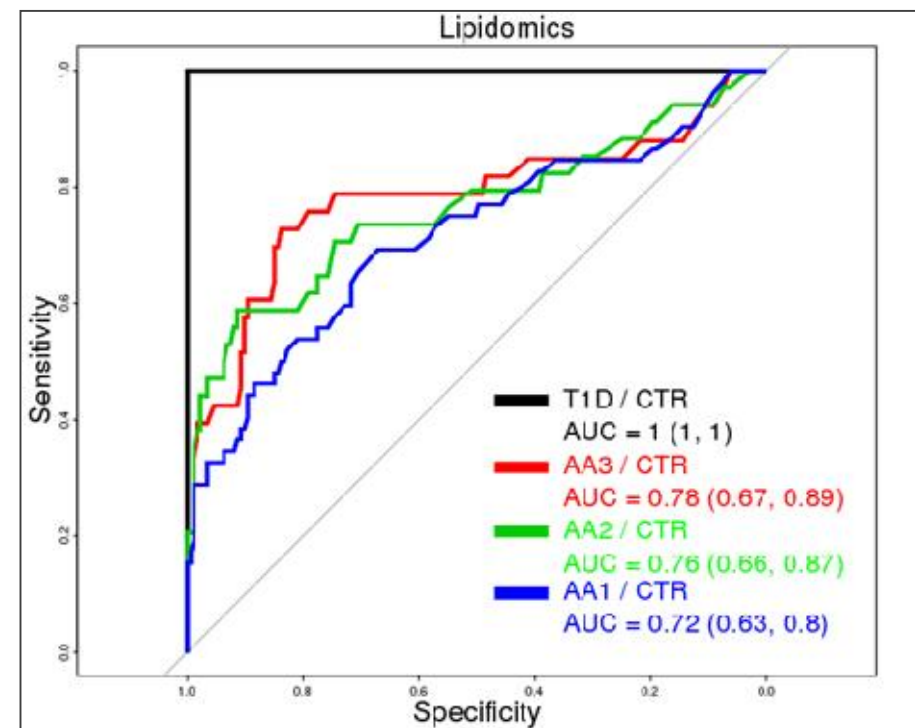
From “metabolic stress” to restoration of metabolic homeostasis by autoantibodies targeting the dysregulated pathways

Can we predict T1D at birth?

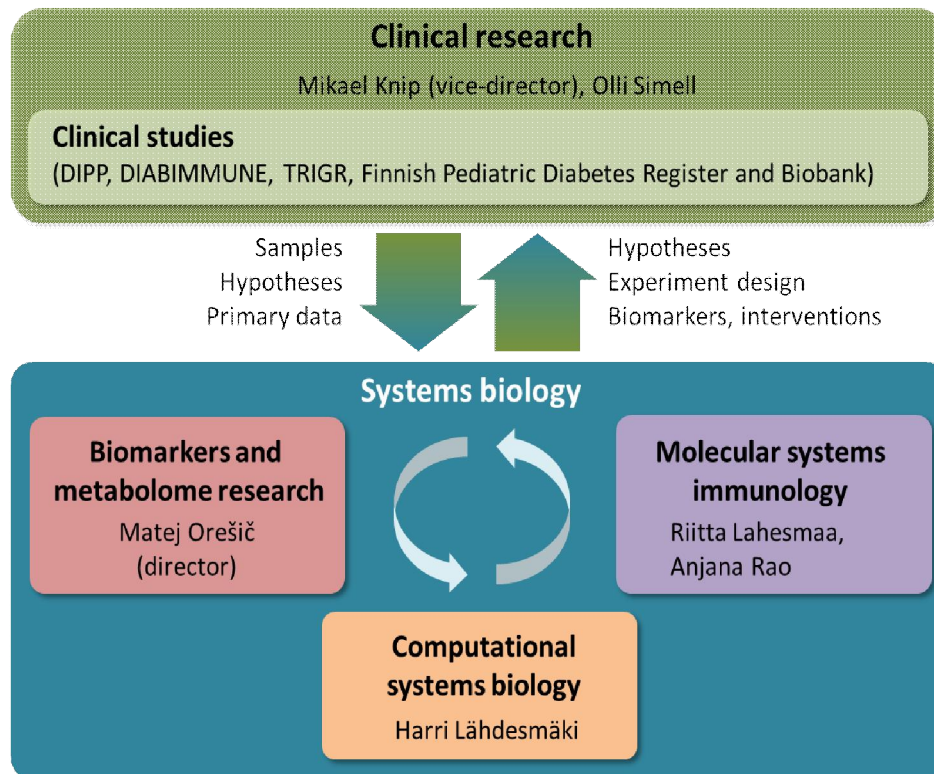
- cord serum metabolome in progressors to T1D ($N=33$), newborns who developed 3 or 4 ($N=32$), two ($N=34$), or one ($N=50$) islet autoantibody (Aab) during the follow-up, and controls ($N=160$) matched for gender, HLA genotype, city and period of birth.
- Metabolomics platforms: (1) global lipidomics 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