

## References

L. Yetukuri et al., Bioinformatics strategies for lipidomics analysis: characterization of obesity related hepatic steatosis, *BMC Syst. Biol.* 1, e12 (2007).

Kotronen et al., Saturated fatty acids containing triacylglycerols are better markers of insulin resistance than total serum triacylglycerol concentrations, *Diabetologia* 52, 684-690 (2009).

Kotronen et al., Hepatic SCD1 activity and diacylglycerol but not ceramide concentrations are increased in the non-alcoholic human fatty liver, *Diabetes* 58, 203-208 (2009).

K. H. Pietiläinen et al., Global transcript profiles of fat in monozygotic twins discordant for BMI: pathways behind acquired obesity, *PLoS Med.* 5, e51 (2008).

M. Kolak et al., Adipose tissue inflammation and increased ceramide content characterize subjects with high liver fat content independent of obesity, *Diabetes* 56, 1960-1968 (2007).

G. Medina-Gomez et al., PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism, *PLoS Genet.* 3: e64 (2007).

J. Maukonen et al., PCR-DGGE and RT-PCR-DGGE show diversity and short-term temporal stability in the *Clostridium coccoides* - *Eubacterium rectale* group in the human intestinal microbiota. *FEMS Microbiol. Ecol.* 58, 517-528 (2006).

J. Maukonen et al., Intraindividual diversity and similarity of salivary and faecal microbiota, *J. Med. Microbiol.* 57, 1560-1568 (2008).

A.-M. Aura et al., Microbial metabolism of catechin stereoisomers by human faecal microbiota: Comparison of targeted analysis and a non-targeted metabolomics method. *Phytochem. Lett.* 1, 18-22 (2008).

R. Laaksonen et al., A systems biology strategy reveals biological pathways and plasma biomarker candidates for potentially toxic statin induced changes in muscle, *PLoS ONE* 1: e97 (2006).

P.V. Gopalacharyulu et al., Data integration and visualization system for enabling conceptual biology, *Bioinformatics* 21, i177-i185 (2005).

M. Orešič et al., Lipidomics: a new window to biomedical frontiers, *Trends Biotechnol.* 26(12), 647-652 (2008).

A.-M. Aura, Microbial metabolism of dietary phenolic compounds in the colon. *Phytochem. Rev.* 7, 407-429 (2008).

J. Tang et al., Integrating post-genomic approaches as a strategy to advance our understanding of health and disease, *Genome Med.* 1, e35 (2009).

## Contact

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## Do it the modern way!

VTT offers you cutting edge services in Systems biology

A substantial number of VTT's staff of close to 3000 persons is supporting the group of about 50 people who are dedicated to pursue VTT's research and related services for our customers in the area of Systems biology.

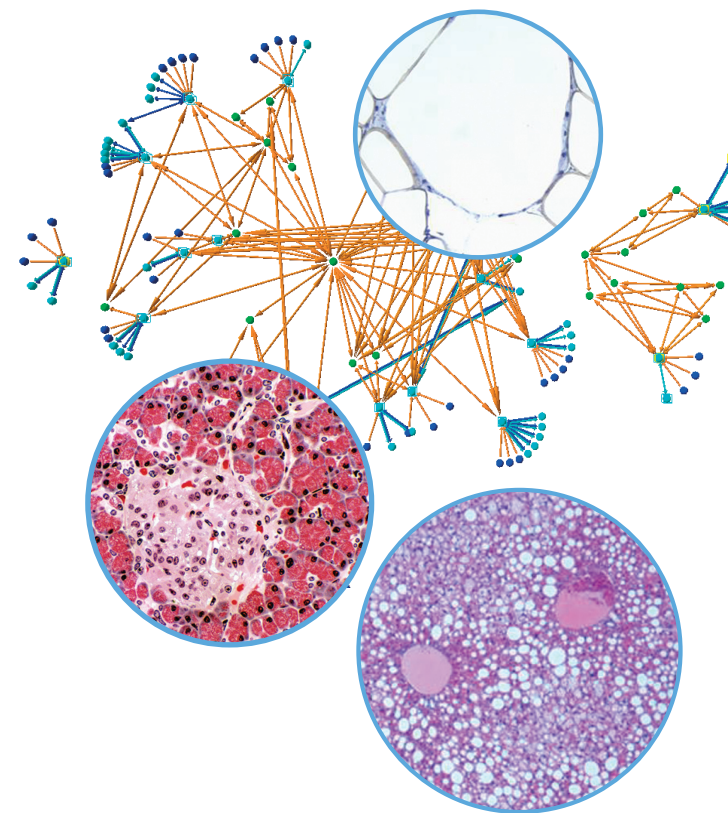
Based on several years expertise our team can with full confidentiality help companies in their search of biomarkers and new drug targets as well as pro-actively prevent failures in pre-clinical drug development. Zora Biosciences, a lipidomics specialist company located on the VTT campus, can be contracted to provide GLP validated throughput in lipid sample analytics.

Here you can find few examples of VTT's capabilities developed in the extensive R&D-work over the past years in the area of obesity and related metabolic disorders.

Around the world, the proportion of people who are obese is increasing at an alarming rate. This obesity epidemic is being driven by lifestyle changes that encourage the over-consumption of energy-rich foods and discourage regular physical activity. The resultant energy imbalance leads to weight gain and also triggers numerous metabolic changes. These obesity-related metabolic changes increase a person's risk of developing adverse health conditions such as diabetes and metabolic syndrome. Although the genetic susceptibility has been established for obesity-related disorders, it is also evident that environment and gene-environment interactions play an important role in the development and progression of these diseases and conditions.

The new wave of "omics" tools offers an opportunity to tackle the complexity of metabolic disorders in a better way than ever before. **Systems biology** is a scientific which integrates high throughput experiments, data integration and mathematical modeling with the aim to understand organisms (phenotypes, control mechanisms) at a system level. **Metabolomics** is a discipline dedicated to the global study of metabolites (e.g. amino acids, bile acids, lipids), their dynamics, composition, interactions, and responses to interventions or to changes in their environment, in cells, tissues, and biofluids.

Metabolic phenotype is sensitive to pathogenically relevant factors such as genes, environment, lifestyle, diet and gut microbiota interactions. Metabolome is therefore studied as an **intermediate phenotype** linking the genetic and environmental determinants with the clinical phenotypes. Given the complexity of metabolic diseases such as diabetes and metabolic syndrome, metabolomics in combination with systems biology approaches offers an opportunity to discover novel disease-related and treatment-related biomarkers and mechanisms as well as provides a sensitive platform for characterizing the efficacy of existing therapies.



**Biomarker and target  
discovery in  
obesity, diabetes and  
metabolic syndrome**

Focus on metabolome  
and systems biology

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## VTT Research initiatives

VTT scientists use metabolomics and systems biology to study how are the genetic and environmental factors imprinted in the metabolome in the context of obesity, metabolic syndrome and related complications. The mechanisms are investigated by which alterations of metabolome lead to (patho)physiological changes at the systems level, with the final aim of discovery and functional characterization of metabolic markers and related mechanisms.

### Example: Adipose tissue in obesity and metabolic syndrome

VTT scientists have investigated metabolic pathways and lipid metabolism in adipose tissue in the context of obesity and metabolic syndrome in multiple human and experimental model studies. For example, in collaboration with Antonio Vidal-Puig from Cambridge University VTT scientists found that limited expandability of adipose tissue due to depletion of PPAR $\gamma$ 2 in ob/ob background leads to altered lipid profiles in the adipose tissue as well as to accumulation of lipotoxic ceramides in the peripheral tissues (pancreatic islets, muscle, liver). In another study, lipidomic analysis of human adipose tissue revealed that inflammation associated with elevated sphingolipids in subjects with elevated liver fat independent of obesity.

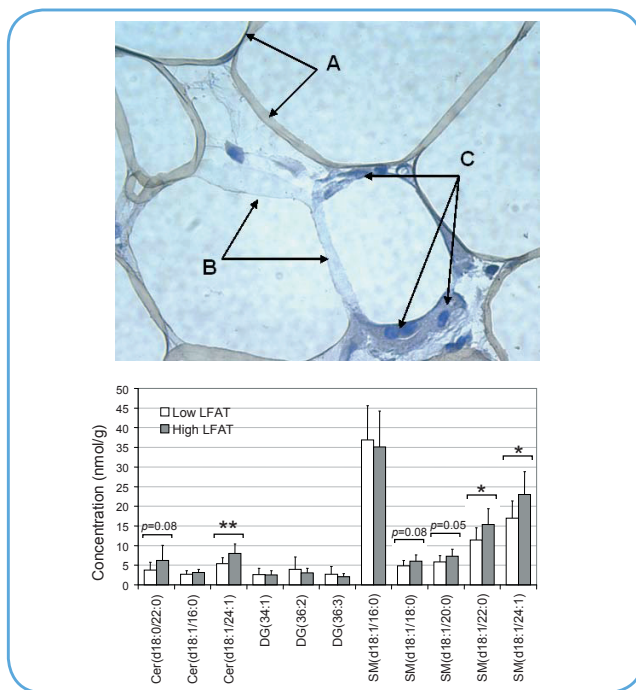


Figure 1. Inflamed adipose tissue and altered lipidomic profile in subjects with high liver fat independent of obesity. Adapted from M. Kolak et al., *Diabetes* 56, 1960-1968 (2007).

### Example: Liver fat in the metabolic syndrome

Fatty liver overproduces components of the metabolic syndrome such as glucose and lipids. VTT scientists have been investigating lipid pathways involved in hepatic steatosis, as well lipidomic profiles of human liver tissues in the context of metabolic syndrome (Figure 2). As part of the European FP6 project HEPADIP ([www.hepadip.org](http://www.hepadip.org)), VTT is involved in a large scale profiling of plasma and liver biopsy samples from subjects with quantified liver fat, aiming to derive new plasma markers of liver fat content.

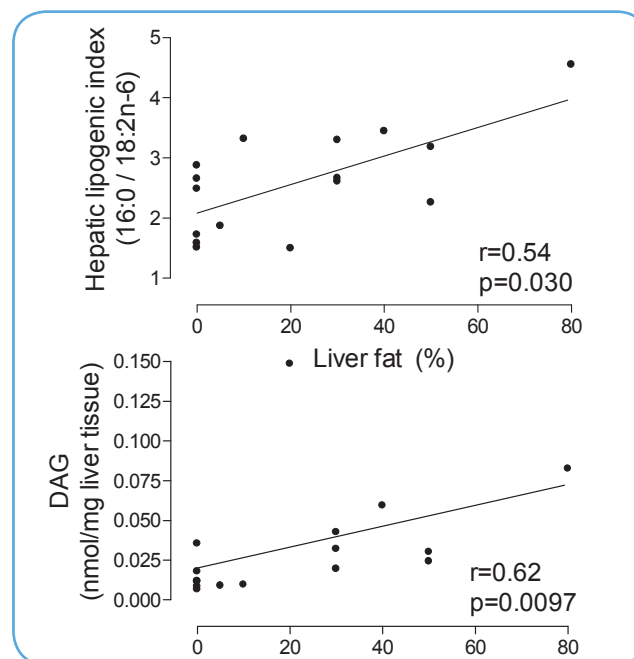


Figure 2. Liver lipogenic index (ratio of C16:0 and C18:2n-6 fatty acids) and diacylglycerol (DAG) concentrations as dependent on liver fat content; based on lipidomic analyses of human liver biopsy samples. Adapted from Kotronen et al., *Diabetes* 58, 203-208 (2009).

## Summary of analytical platforms and research methods offered

- Metabolomics
- Lysate arrays
- Gene expression (microarrays, quantitative methods)
- microRNA profiling
- Characterization of gut microbiota and colonic metabolites
- Systems biology strategies to integrate and model multiple types of data in clinical and biological context

## Description of specific platforms

### Metabolomic analysis and bioinformatics

Metabolomic analysis of samples in clinical and nonclinical studies (biofluids, tissue biopsies, cells)

- Global lipidomic and metabolomic analysis (UPLC/MS and GCxGC-TOF/MS, high resolution MSn).
- Targeted quantitative methods (GC, UPLC, UPLC/MS/MS, GC/MS, GCxGC-TOF/MS) for specific classes of metabolites, e.g. bile acids, fatty acids and eicosanoids, endocannabinoids, amino acids and related metabolites, metabolites of central carbon metabolism, ketone bodies.
- Development of customized platforms for specific customer needs.
- Data processing, including ability to deal with stable isotope tracer data, quantification, metabolite identification, metabolic pathway mapping, statistical analysis (univariate, multivariate).

### Characterisation of intestinal microbiota in health and disease

Analysis of the human and animal model samples (both oral and faecal)

- culture-based techniques - focusing on anaerobic bacteria such as clostridia, bifidobacteria and lactobacilli
- molecular techniques for population, group, genus, species or strain level identification (DGGE, DHPLC, specific PCR / RT-PCR / hybridisation including VTT-TRAC) qPCR, fingerprinting methods such as PFGE, RAPD, ribotyping)
- heterogeneity of colonisation within and between individuals, strain-similarity between individuals, especially regarding lactobacilli and bifidobacteria
- in vitro digestion model for release, degradation and conversion of dietary components for identification of food related intestinal metabolome and studying of their effects.

### Systems biology: phenotype characterization, biomarkers, pathways

Combining metabolomic data with other levels, including gene expression, microRNA, proteomics, genome-wide association studies, gut microbiota. Advanced computational modelling approaches include:

- Mapping of human and experimental model (mouse) metabolic profiles to provide translational biomarkers.
- Dependency and causal models derived from e.g. combined genetic, gene expression, metabolomics and clinical data.
- Pathway reconstruction in the phenotype context, derived from multiple omics datasets and pathway/interaction databases.
- Tissue sensitive markers derived from biofluid metabolite profiles.