Application of New Technologies and Methods in Nutrition Research
The Example of Phenotypic Flexibility

This large-scale integrating project is carried out with financial support from the European Commission, under the Seventh Framework Programme (FP7) for research, technological development and demonstration, Contract Number: FP7-KBBE-2011-5.
Nutrition and biomedical research are both looking at human health but from different perspectives. Whereas biomedical research primarily studies disease development and the effects of drugs on disease outcomes, nutrition research attempts to define diets or dietary factors that can improve health and/or prevent diseases. Although goals and pathways differ, nutrition and biomedical research share concepts and use common life science based technologies.

For historical reasons, nutrition research has been mainly observational and has only recently performed more mechanistic studies by assessing the effects of nutrients and non-nutrient components of foods on gene and protein expression and metabolic outcomes. By adopting these new methodologies, nutrition research has moved into the core of the life sciences by studying the effects of the most important environmental factor – the diet – on mammalian organisms and their health status.

However, approaches in nutrition research are not yet sufficiently standardised – neither within the European research arena nor when worldwide research efforts are taken into account. A growing number of studies are being performed using similar, rather than identical technologies and procedures, making it difficult or impossible to compare results.

It is therefore one of the goals of the NutriTech project to provide within the framework of a proof of concept study with partners from Europe, North America and the Pacific region, the highest level of standardisation with harmonised technologies and procedures in state-of-the-art nutrition research.

NutriTech exploits the concept that continuous optimal adaptation to changing (metabolic) environments is a prerequisite for maintaining optimal health, and that quantification of these adaptive processes (i.e. of phenotypic flexibility) may lead to a new generation of useful biomarkers in the nutrition and health research, as well as for food product development. Apart from the technological aspects, NutriTech will achieve a scientific breakthrough in nutrition research by developing a series of biomarkers quantifying processes important for diet-related health.

In order to enable the validation and standardisation of the new technologies as described above, NutriTech is currently studying “phenotypic flexibility” in relation to nutrition. Within the project, phenotypic flexibility is defined as (the interplay of) all relevant processes underlying metabolic adaptations (e.g. response to changes in diet or physical activity). Phenotypic flexibility can thus be used to study, validate and develop available methods and technologies.

NutriTech will combine classical approaches of human nutrition research with new analytical technologies and methodologies to comprehensively assess the diet-health relationship and critically assess their usefulness and value for the future of nutrition research.

Specifically, NutriTech will employ technologies and methodologies on a gene, cell, organ and whole body level with the goal to capture multiple, physiological changes in response to standardised nutritional challenges on the background of a diet and lifestyle intervention. Technologies will include genomics, epigenomics, transcriptomics, proteomics, lipidomics and metabolomics (including flux analysis), laser scanning cytometry, Nuclear Magnetic Resonance (NMR) lipoprotein profiling and advanced imaging by MRI/MRS.

Standardised methodologies for monitoring subtle phenotypic changes in relation to dietary challenges will be developed and validated.

All information concerning the phenotypic changes in response to nutritional interventions will be made available through the NutriTech nutritional phenotype database, allowing for a comprehensive analysis of the links between diet and human phenotypic responses.
**Work Package 1: Metabolomics based food intake quantification**
A metabolomics based approach to identify a novel panel of biomarkers for assessment of macronutrient intake and their food sources will be used; in addition, a metabolomics based approach will be employed to cluster individuals into groups reflecting different dietary patterns.

**Work Package 2: Human intervention study**
A 12-week parallel design intervention study is performed where the intervention group will receive a 20% calorie restricted diet with optimal nutrition. Extensive sampling periods at the beginning and end of the study generated samples for technology evaluation.

**Work Package 3: Systemic biomarker analysis**

3a: Phenotyping the dynamics of metabolic changes
The prime goal of WP3a is to provide a comprehensive panel of metabolites and proteins in plasma that by their changes in the course of two dietary challenges as well the exercise test provide a measure of systemic phenotypic flexibility.

3b: Clinical (bio)chemistry
The WP also determines all classical clinical chemistry and biochemical data as well as those that cover the nutrition status. The WP3b also takes care of the standardization of biobanking and data storage for the classical and advanced analysis of samples from challenges in the human intervention study.

**Work Package 4: Imaging**
Accurate and reproducible phenotyping methods are critical in any program attempting to understand underlying mechanisms linking nutrition, health and disease development. Advances in preclinical and clinical in vivo imaging, especially magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), play a pivotal role in developing this field of translational research. The main objective of this work package is to determine the role of different fat depots, including ectopic fat (skeletal muscle, liver, pancreas) on metabolic flexibility following a dietary intervention.

**Work Package 5: Organ flexibility**

5a: Muscle and adipose flexibility
The goal is to measure the flux of nutrients as the earliest metabolic event during common challenges like diet exposure and physical activity and to unravel the relevant mechanisms (i.e. mitochondrial flexibility).

5b: Peripheral Blood Mononuclear Cells (PBMC) as biomarker
The aim of WP5b is to analyse whole genome gene expression changes in PBMCs in the human life style intervention study with the objective to establish its function as an early and sensitive marker for diet-related health.

**Work Package 6: Genome analyses**

6a: Genome integrity
The goal of WP6a is to develop high content analysis assays for simultaneous measurement of multiple biomarkers of genome integrity and DNA damage response using Laser Scanning Cytometry (LSC) and to identify which of these markers are most sensitive to nutritional challenge.

6b: Genomic variation
The objective of WP6b is to integrate the (whole) genome analysis in nutrition studies by establishing a harmonised platform that allows evaluation of genomics data together with all phenotypic data and results in the context of nutritional intervention studies.

**Work Package 7: Integration**
This work package is responsible for absorbing the data, ensuring availability of the data to all beneficiaries in a standardized and structured way and making it possible to query the data (through the nutritional phenotype database dbNP). Integrated analysis of all data generated in the NutriTech study is the key activity towards understanding the power of emerging technologies for use in combination with established methods. Furthermore, the evaluation of the NutriTech data will be embedded in relevant publicly available data. This WP will derive practical and integrated methods from the extensive phenotyping technologies for use in cohort studies.

**Work Package 8: Cohort validation**
WP8 validates a number of deliverables, derived from application of extensive analytical procedures and methods in a setting of controlled human intervention as well as well-characterised observational studies, in a setting where both larger numbers of study subjects and (therefore) less expensive analytical methods must be applied.

**Work Package 9: Harmonisation and dissemination**
In WP9 a sustainable global network should be created in order to promote, disseminate and harmonise emerging technologies in state-of-the-art nutrition and health research. This network will then be used for the dissemination of the NutriTech project’s approach and its results to academic, governmental and industry stakeholders. The primarily focus of this dissemination activities will be Europe, however, a global scope is envisaged.

**Work Package 10: Coordination**
The overall objective of the Coordination and Management WP is that of ensuring the smooth realization of NutriTech, optimizing the organization and timing of activities and resources, so that both scientific and strategic project goals can be fully attained.
The project started on 1 January 2012 and is intended to run for 54 months until June 2016. This is realistically the minimum timeframe for a project of this magnitude. The work plan was designed so that most of the work began immediately, but some of the tasks require input from other work packages before they can begin their activities.
Kick-off Meeting, 12-14 March 2012, Volendam, the Netherlands

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