ILSI Europe
Report Series

Emerging Technologies for Efficacy Demonstration

Summary Report of a Workshop held in February 2009

Organised by the ILSI Europe Emerging Technologies for Efficacy Demonstration Task Force

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EMERGING TECHNOLOGIES FOR EFFICACY DEMONSTRATION

By Laurent Fay & Peter Weber

SUMMARY REPORT OF A WORKSHOP HELD IN FEBRUARY 2009 IN BRUSSELS, BELGIUM
ORGANISED BY THE ILSI EUROPE EMERGING TECHNOLOGIES FOR EFFICACY DEMONSTRATION TASK FORCE

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For more information about ILSI Europe, please contact

ILSI Europe a.i.s.b.l.
Avenue E. Mounier 83, Box 6
B-1200 Brussels
Belgium
Phone: (+32) 2 771 00 14
Fax: (+32) 2 762 00 44
E-mail: info@ilsieurope.be
Website: http://www.ilsi.org/Europe

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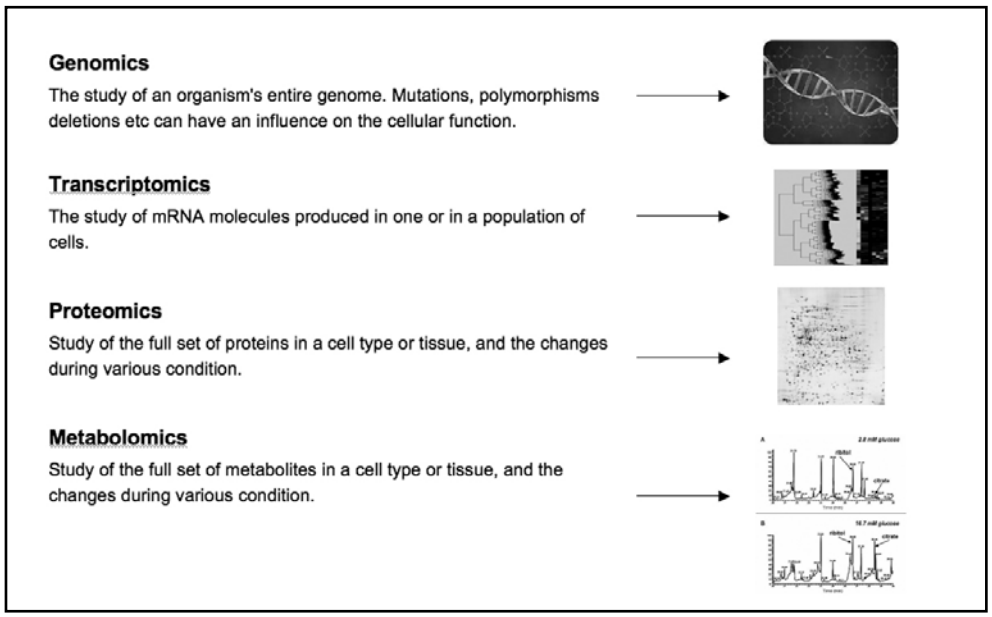
Authors: Laurent Fay, Nestlé (CH) and Peter Weber, DSM (CH)
Report Series Editor: Kevin Yates (UK)
Coordinator: Stéphane Vidry, ILSI Europe (BE)

INTRODUCTION

Nutrition sciences of the 20th century saw the identification of all the essential nutrients and the understanding of their biological importance in controlling metabolism and in maintaining health. Traditionally, nutrition research has dealt with providing nutrients to nourish populations. Nowadays, it focuses on understanding and improving health of individuals through diet. Modern molecular nutritional research is aiming at health promotion and disease prevention and at performance improvement.

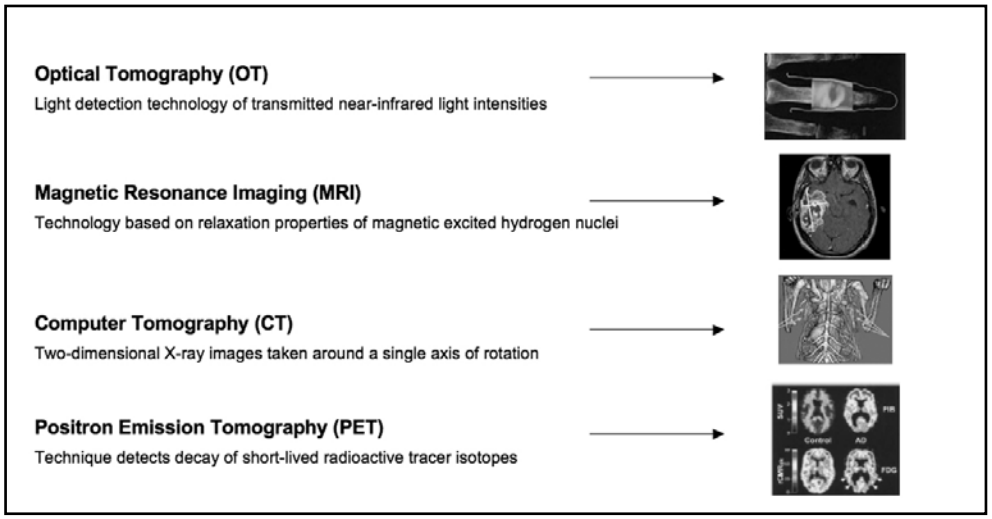
Many bioactive food ingredients are claimed to either reduce disease risk factors or to improve life quality by optimizing and maintaining body functions. These claims have to be based on a scientific substantiation. The project "Process for the Assessment of Scientific Support for Claims on Foods" (PASSCLAIM) developed a generic tool to assess the scientific support for health claims for foods. PASSCLAIM has become the gold-standard for scientific substantiation of health claims. However, due to its six years of development phase, PASSCLAIM is a static document which provides criteria to validate technologies and biomarkers which were state of the art at least six years ago.

Figure 1: 'Omics' Technologies



Nowadays, new technologies are used in nutrition research such as one giving access to holistic discovery of efficacy biomarkers namely genomics, transcriptomics, proteomics and metabolomics (Figure 1). Moreover, Imaging Technologies (e.g., Optical Tomography, Magnetic Resonance Imaging (MRI), Computer Tomography, and Positron Emission Tomography) are also routinely used for clinical diagnostics (Figure 2) and it is conceivable to use them to demonstrate efficacy of food ingredients.

Figure 2: Clinical Imaging Technologies



None of these new techniques was taken into consideration at the time of PASSCLAIM. Consequently, the ILSI Europe "Emerging Technologies for Efficacy Demonstration" Task Force organised a workshop to summarize the advancements of these new technologies and to discuss their roles in food product development and claim substantiation, addressing the following questions:

- How far have these emerging technologies been validated?
- How can they be applied and are they able to explore new mechanism of action or new functions?
- Is the technology mature enough for efficacy demonstration making former approaches outdated?
- What kind of claims can be obtained (function claims as opposed to disease risk reduction claims)?
- Are these technologies more suited to investigating homeostatic changes of the human body to nutrients rather than the established and accepted biomarkers that are often derived from diseases?

The following summarizes the discussion of these questions.

REGULATORY AND ETHICAL ASPECTS

Criteria for Imaging and for "Omics" Biomarkers

Prof. Andreu Palou, University of Balearic Islands, Palma de Majorca, Spain (member of EFSA's NDA Panel)

The European Food Safety Authority (EFSA) delivers independent scientific advice, information and scientific and technical support for the Community's legislation and policies in all fields that have a direct or indirect impact on food and feed safety including nutrition. The two key-aspects in a potential evaluation of food are safety and efficacy (and then conditions of use: populations, benefits etc).

A food can be regarded as "functional" if it is satisfactorily demonstrated that it affects beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an "improved state of health and well-being" and/or "reduction of disease risk". Imaging and -omics technologies are useful tools that may contribute to satisfactorily demonstrate health promoting effects of food/food components.

Today, EFSA does not have defined criteria for new imaging and -omics technologies regarding efficacy (health claims) of food products or ingredients. There has been an increase in consumption of functional foods lasting recent years and also an increase of confusing and false messages to consumers. The latter point is leading to consumers being misled. Therefore, the European Union developed a new regulation. The Regulation (EC) nº 1924/2006 of the European Parliament and of the Council of December 20, 2006 states that nutrition and health claims on food must be substantiated by scientific evidence. The Regulation covers two general types of claims used in the labelling, presentation and advertising of foods: the nutrition claims (content claims) and the health claims (efficacy claims) are subdivided into three categories:

- the generic or function claims;
- the reduction of disease risk claims;
- the claims on children's development and health

The real changes driven by Regulation 1924/2006 are summarized in five points:

1. harmonized communication of health benefits of foods to consumers;
2. only health claims which are scientifically substantiated will be allowed;
3. only food having an "appropriate nutrient profile" will be allowed to bear health claims and/or nutritional claims;
4. intellectual property drawn from research efforts will be protected (5 years);
5. R&D in the food sector is stimulated.

Applications for claims submitted to EFSA must contain information on the characteristics of the food/constituent such as the composition, the physical and chemical characteristics, manufacturing process, stability and bioavailability of the nutrients. The wording of the health claim and conditions of use should be specified with a rationale: the target population, the statements addressed to persons who should avoid using the food/constituent, the quantity of the food/constituent and pattern of consumption required whether this quantity could reasonably be consumed as part of a balanced diet, a warning for a food/constituent that is likely to present a health risk if consumed to excess, any other restrictions of use and directions for preparation and/or use.

The application must also contain all pertinent scientific data (published and unpublished, in favour and not in favour). A major focus will be the data from studies in humans which will be required for substantiation of a health claim, other data (e.g., from animal or cell experiments) will be considered only as supporting evidence.

The data from human studies will have to be comprehensively reviewed, addressing the specific relationship between the food and the claimed effect. This review should be performed in a systematic and transparent manner in order to demonstrate that the application reflects adequately the balance of all the evidence available. Finally, in cases there is a lack of data for a particular application, reasons and justification must be given for the absence of such data.

Three main factors are today strongly limiting the successful extension of health claims on foods:

- the lack of biomarkers for a number of physiologically relevant functions;
- the lack of early biomarkers;
- the lack of biomarkers on long term effects.

This lack of appropriate biomarkers is the main bottleneck for the consolidation and expansion of the health claim-based added values in the food sector. The identification and validation of robust biomarkers is crucial for assessing the potential effectiveness and benefits of health-promoting food compounds. New technologies may help to identify biomarkers in the relevant targeted population provided that a cause-effect relationship between the consumption of the concerned food and the claimed effect has been substantiated by generally recognized solid science.

Ethics Perception

Prof. Ulf Görman, Lund University, Sweden

Ethics is the systematic reflection on the moral aspects of life and its conflicts. Today we go first to non-maleficence (avoid harm) and then to beneficence (go for happiness). Products may be aimed at all or most consumers or consumers with identified needs, or risk groups identified by phenotypic means, or risk groups identified by genetic tests. The strongest audience for tailoring diet based on genetic information seems to be among a group already actively seeking health information (one third of the consumers).

Nutritional genomics has created hopes that gene-based nutrition planning can one day play a significant role in preventing chronic diseases. The food industry has an interest in using this knowledge for commercial purposes in developing a new generation of functional foods.

Among the general public there is an interest to adjust nutrition with expectations to improve health or prevent disease. According to a survey carried out recently in Sweden, consumers consider that health is important; most respondents consider their general health good or very good (77%). Most consumers would like to receive knowledge about future health and sickness (64%) but one third of the respondents report feelings of anxiety towards today's food habits. In the United States (US), 52% of consumers favour the idea of using individual genetic information to understand or optimize health and 72% are interested in using genomics to decrease the risk of specific diseases. However, 66% have concerns about privacy (insurance companies, government, employers), 25% have moral reservations and about one third express emotional uncertainty.

Today, 26 companies offer genetic analyses directly to the public, via Internet, or via a non-medical intermediary. According to US government, results of genetic testing are medically unproven and meaningless. Indeed, their dietary advices are simply common sense health recommendations, and they recommend costly supplements which may not be necessary.

The scientific evidence base for the role of interactions between specific genotypes and components of the diet in the development of polygenic diseases is fragmentary and not yet sufficiently robust to justify genetic testing as the basis for individual nutritional counselling. Until the scientific evidence concerning diet–gene interactions is much more robust, the provision of personalized dietary advice on the basis of specific genotype remains questionable. For the foreseeable future, the number of people who have received personalized nutritional advice based upon genetic tests is likely to be fairly small. In this situation the food industry may be interested in creating a larger market by developing products and marketing them in such a way that it is considered healthy not only for people with a specific genetic constitution, but also for others. This is an undesirable development because it may encourage the existing tendency to healthism (the unhealthy strive for health, Robert Crawford, 1980).

IMAGING TECHNOLOGIES

Imaging technologies refers to techniques that generate images of the human body or part of it (organs or tissues) for diagnostic purposes or anatomical investigations. These technologies are noninvasive and easily accessible in clinical diagnostic facilities. Moreover, they can be used in preclinical studies providing ways to translate data from the preclinical to the clinical phase of research.

Electrophysiological Neuroimaging in Diagnostics and Treatment of Dementia and Depression

Prof. Bernd Saletu, Medical University of Vienna, Austria

Today, imaging technologies are widely used as diagnostic tools in a medical environment and hardly for supporting mechanisms of action or for efficacy testing of food ingredients. Quantitative electro-encephalographic (EEG) analysis methods such as the 2-dimensional EEG mapping and the recently developed 3-dimensional EEG tomography such as low-resolution brain electromagnetic tomography (LORETA) have become important tools for diagnosis, differential diagnosis and treatment of mental disorders. EEG mapping is a powerful tool to diagnose both the degenerative and vascular subtypes of dementia. Utilizing EEG mapping in combination with neuronal network statistics of absolute delta/theta power, 90% of demented patients were correctly classified as compared with normally aging subjects. Correlation maps demonstrated significant relationships between computed tomography, clinical, psychometric and EEG variables. Anti-dementia/nootropic and cognition-enhancing drugs induce, as compared with placebo, opposite changes to the above described ones (key-lock principle). Event-related potentials (ERP) findings are mostly characterized by a lengthening of the P300 latency in dementia and a shortening with anti-dementia drugs, reflecting deficits and improvements in cognitive information processing.

EEG mapping in depression demonstrated a vigilance deterioration of a different (dissociative) type. Pharmaco-EEG maps of antidepressants may be subdivided into those of the sedative and non-sedative subtype. In ERPs an amplitude attenuation of P300 is the most consistent finding, mostly in the prefrontal areas. LORETA revealed a decrease in theta power which was negatively correlated with the Hamilton Depression Score, significantly in the ventromedial prefrontal cortex, the bilateral anterior cingulate gyrus as well as the left insular cortex. Alpha-1 LORETA power was negatively correlated with the Hamilton Depression Rating Scale (HAMD) in the right prefrontal cortex. Moreover, P300 source strength was reduced in the temporal, ventrolateral and orbitoprefrontal region as well as the rostral anterior cingulate cortex (ACC). Antidepressants, like citalopram and the nutraceutical and pharmaceutical ademetionine, induced, as compared with placebo, opposite changes in the aforementioned regions.

As a conclusion, EEG/ERP topography and tomography are valuable tools to access electrophysiological characteristics for dementia and depression. Thus, electrophysiological neuro-imaging can assist the clinician in the differential diagnosis of dementia and depression. Moreover, the methods may serve as prognostic instrument in choosing the optimal drug treatment for an individual patient. Nevertheless, it should also be pointed out that there is a discrepancy between the scientific community and the regulatory bodies. As an example, the US FDA does not recognize positron emission tomography (PET) as a validated technique for efficacy demonstration, despite the fact that the scientific community recognizes it as validated.

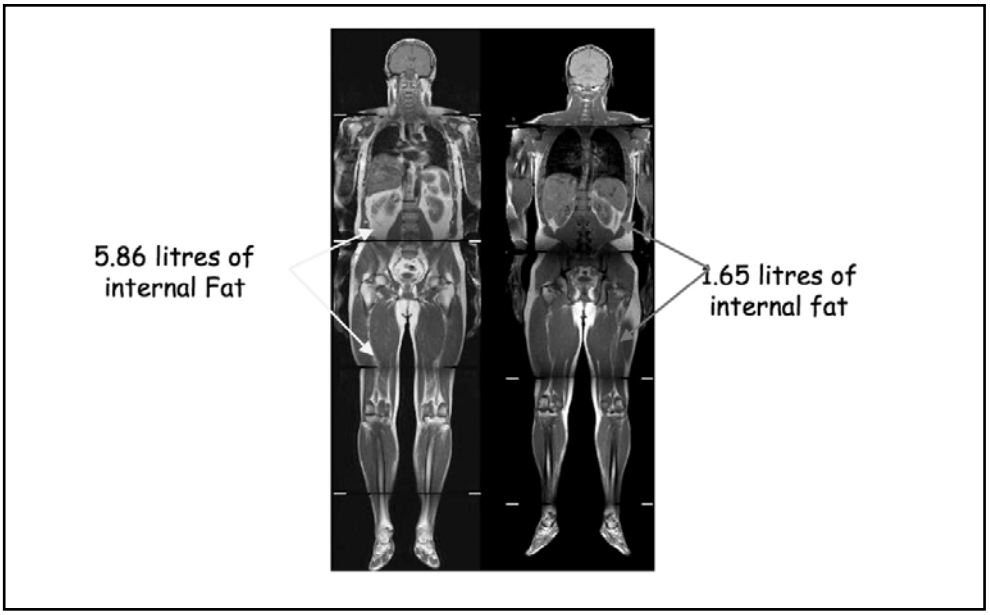
The Beauty of Body Fat

Prof. Jimmy Bell, Hammersmith Hospital, London, United Kingdom

One in five people in the United Kingdom (UK) are obese. Two thirds of men and half of women are obese/overweight. UK wakes up 25-30 tons heavier every morning. Forty percent of children in Europe will be overweight in 2010. Obesity correlates with type 2 diabetes and there is a strong correlation between the body mass index (BMI) and risk of type 2 diabetes. However, fat is not everything. For example, lipodystrophiIic patients who experience having not enough fat in their body are also predisposed to type 2 diabetes. People with Prader-Willi syndrome are extremely obese with normal insulin sensitivity. Last but not least, Sumo wrestling athletes with BMI over 45 have normal insulin sensitivity. Hence, the phenotype is more important than fat content and the location where fat is deposited is more important than the amount deposited. There are four different types of fat in the human body: the intra-muscular cellular lipids (IMCL), the intra-hepatocellular lipids (IHCL), the subcutaneous adipose tissue and the intra-abdominal adipose tissue.

There are different methods to measure human phenotypes. The doubly-indirect methods are estimates based on models developed from other techniques (weight/height, circumferences, skin folds, bioelectrical impedance). The indirect methods are based on models derived from direct methods assuming relationships between body compartments (densitometry, Dual Energy X-ray Absorptiometry (DEXA), dilution techniques, plethysmograph). The direct methods directly measure lean or fat tissue (dissection, Computed Tomography (CT), Magnetic Resonance Imaging (MRI)). The gold standard technique to measure these different fat regions is MRI which gives accurately regional fat distribution. MRI makes the different fat regions of an individual accessible to the investigation (Figure 3).

Figure 3: MRI scans from subjects of similar age, gender, BMI and % body fat. The different levels of internal fat correlate with different disease risks for the subjects. (courtesy Thomas and Bell, 2008)



For every weight, females carry more fat (30% for healthy) than males (20%) but in terms of internal fat, the situation is reversed. About 40% of the population shows mild/severe fatty infiltration which is strongly correlated with the risk of type 2 diabetes. Lean subjects have a large range of intra abdominal fat. The whole concept of being fat needs to be redefined based on the fact that people who are "thin outside" may be "fatty inside". MRI technology also demonstrated that people who maintain a normal BMI through diet rather than exercise are likely to have major deposits of internal fat, even if they are otherwise slim. On the contrary, when people exercise, they tend to burn internal fat. Lifestyle changes have to include physical activity. It is just not enough to diet.

As a general comment about technologies capable to assess healthy people, Prof. Bell concluded that normality is easy to define, whereas defining health is more challenging.

Emerging Technologies for Efficacy Demonstration of Hydration

Prof. Ron Maughan, Loughborough University, United Kingdom

Hypohydration, if sufficiently severe and prolonged, has adverse effects on subjective feelings of well-being and on both cognitive and physical performance. In extreme cases, it can be fatal. Acute diarrhoea induces dehydration leading to death (2 million children per year). There is no single ideal measure of hydration because euhydration (normal state of body water content; absence of absolute or relative hydration or dehydration) is not a constant. Body water content is in a state of constant flux. Specific tissue water content may be more relevant than the whole hydration status. Moreover, there is little evidence that skin hydration reflects total body hydration.

Body water is distributed in two compartments: intra-cellular and extra-cellular compartment. Dilution of tracers, whether isotopic or chemical, gives information on total body water or on the volume of specific compartments, and is likely to remain the method of choice. Bio-electrical impedance methodologies are in widespread use, but precision of these instruments is poor and they do not respond reliably to acute changes in body water content. For practical purposes, hydration status is best assessed by simple measures of urine parameters such as frequency and volume, colour, specific gravity, conductivity and osmolarity.

Imaging techniques are particularly useful in assessing volume changes in specific tissues such as muscle and brain: because the brain is enclosed within a rigid skeletal structure, volume changes result in pressure changes that may have functional consequences. MRI data, however, show that brain and CerebroSpinal Fluid volume may be protected during moderate dehydration. Functional outcomes may be the most relevant in the assessment of nutritional interventions. Computer-based test batteries for assessment of cognitive function allow greater precision and sensitivity than before, but they lack specificity at their current stage of development.

NUTRIGENOMICS TECHNOLOGIES

Nutritional genomics (nutrigenomics and nutrigenetics) refers to the interaction between nutrition and the human genetic make up. Nutritional genomics can be defined as the application of high throughput genomics (transcriptomics, proteomics, metabolomics/metabonomics) and functional genomic technologies to the study of nutritional sciences. These high throughput genomics technologies allow the determination of the concentrations of the complete set of a specific type of biomolecule (mRNA, protein, or metabolite, respectively) in a certain situation and are used to compare different environmental conditions. Nutrigenomics technologies are nontargeted and holistic. In nutrition research, they make it possible to decipher the mechanism underlying the biological effects of nutrients and the relationship between these nutrients on human health.

Transcriptomics

Dr. Ruan Elliott, Institute of Food Research, Norwich, United Kingdom

Transcriptomic technologies have arguably achieved the highest level of technical maturity of any of the functional genomics. Production of very high quality, genome-wide expression profiling data is now a routine matter and concerns about meaningful cross-platform comparisons have been largely dispelled. Moreover, universal standards have been adopted for transcriptomic data handling and infrastructures, such as public repositories, a development that ensures secure long-term data storage and access to legacy data.

Transcriptomics provides new avenues for biomarker development and insights into beneficial and detrimental biological effects (both predicted and unexpected) and the mechanisms underlying them. As such, transcriptomics has great potential for application in risk-benefit analyses. However, to translate this potential, more work is required to (1) confirm relationships between changes in gene expression profiles and biological processes/endpoints and (2) further evaluate applicability in human studies, in particular validating responses observed in accessible tissues as indicators of responses in target tissues. Substantial reductions in the cost of transcriptomic analysis, driven by a highly competitive commercial market, mean that it is increasingly feasible to undertake the types and scale of studies necessary to achieve these goals.

The scope for transcriptomic studies in humans encompasses mechanistic investigations through the sampling of biopsies and biomarker development through routine analysis of RNA from leukocytes. However, we need to know the extent of the normal biological noise (intra-individual, day-to-day variation, inter-individual variations) and the range of (and variation in) responses to nutritional interventions. Transcript levels for about 40% of genes differ significantly between individuals. Therefore, for nutritional intervention, the best approach is to employ study designs that use each individual as their own control. In the search for biomarkers of health the established biomarkers of disease (risk) are of limited use. Indeed, health is more than absence of disease. More appropriate (and more sensitive) indicators of health may be obtained through the examination of the robustness of homeostatic responses. We need to use omics to move from univariate measure of robustness (glucose/insulin response to oral glucose tolerance test) to multivariate analysis of homeostasis.

Proteomics

Dr. Baukje de Roos, University of Aberdeen, Aberdeen, United Kingdom

Proteomics is emerging as a valuable tool in nutritional research. Still, the amount of research papers in proteomics remains below the number of reviews. It is because proteomics faces several challenges such as a high variability in sample preparation, it only detects abundant proteins, a high level of analytical and biological variability leading to errors in Mass Spectrometry based analysis, a misuse of statistical tools and a high rate of false positives. However, proteomics is claimed to be able to identify thousands of proteins that can potentially provide valuable new human plasma, platelet or peripheral blood mononuclear cell (PBMC) biomarkers for health or disease, assist in identifying dietary responders from nonresponders and enable discovery of mechanisms of effects of beneficial food components. Biomarkers can also be obtained indirectly from the use of animal models, where proteomics of target organ tissues has already provided valuable insights in the effects of several dietary interventions on proteins involved in the regulation of glucose and fatty acid metabolism, oxidative stress and the redox system. Often, such changes are reflected in the regulation of specific plasma, platelet or PBMC proteins in humans.

Although different proteomics approaches have so far been successful in elucidating changes in mechanistic pathways that relate to glucose and fatty acid metabolism, oxidative stress and inflammation, only very few new biomarkers have been emerging and validated to date, as candidate biomarkers first must be validated through large scale clinical trials.

Will proteomics biomarkers take off at last? Indeed it is difficult to find those proteins that are biomarkers. Blood is challenging to work with because the huge variability in protein abundance and also because mass spectrometry has not been sensitive enough to spot clinically relevant biomarkers in the ng/ml range. The success of plasma, platelet and PBMC proteomics, or indeed proteomics of organ tissues, in biomarker discovery will eventually depend on the parallel introduction and adaptation of selective, quantitative and sensitive methods, like multiplex immunoassays and the quantitative analysis of specific peptides (including those that are post-translationally modified) in complex biological mixtures such as human plasma in the multiple reaction monitoring (MRM) mode. Such methods will enable the development of assays to evaluate and validate newly discovered candidate biomarkers in human plasma and blood cells.

Metabolomics

Prof. Michael J. Gibney, University College Dublin, Ireland

Metabolomics is the study of the metabolic profiles of individuals where the profiles or signatures represent the totality of a pattern of occurrence of small molecules measured either using Nuclear Magnetic Resonance (NMR) or Mass Spectroscopy (MS) technologies. Individuals or groups of individuals, who share common profiles, cluster together in 2 dimensional pattern recognition methods. Individuals or groups who cluster apart from one another have significantly different metabolic signatures. In the event that two groups cluster separately, it is then possible to examine the average NMR or MS spectra to ascertain which areas of the spectra are different and therefore responsible for the separation of the two clusters. That then leads to an analysis of the metabolic pathways involving the identified metabolites to seek a biological explanation for the differential occurrence of the metabolite in the biofluids of the two groups.

Most of the work carried out to-date with metabolomics has been in the area of clinical medicine, pharmacology and in toxicology. In these instances, the factor which distinguishes two groups is the presence or absence of a disease, a drug or a toxic compound. Thus very strong signals arise from these factors leading to marked differences in metabolism, reflected in clear separation of clusters in the pattern recognition of metabolomics. In human nutrition, the metabolic effects of nutritional modifications are far more subtle and are also far more likely to be general in their effect rather than specific. In most of the cases, the subtle differences in the metabolomic profiling lie in the parallel effects of the non-nutrient components of foods, the phytochemicals, particularly in urinary metabolomic profiles, and particularly in plasma the role of endogenous metabolism is reflecting genotype-phenotype interactions. However, to perform studies with metabolomics we need more basic studies to set-up the foundations of metabolomics and to thus understand the drivers of its variations (gender, locations, age, lifestyle, etc.). Thus, while metabolomics offers great potential in human nutrition, its full potential requires careful studies to help underpin our interpretation of results.

PERSONALISED NUTRITION AND CONSUMER PERCEPTION

Nutrigenomics: Towards Personalisation of Dietary Recommendations

Prof. J.M. Ordovas, Tufts University, Boston, MA., USA

A well-known phenomenon in nutrition research and practice is the dramatic variability in inter-individual response to any type of dietary intervention. There are many factors influencing response, and they include, among others, age, sex, physical activity, alcohol and smoking, as well as genetic factors that will help to identify vulnerable populations/individuals that will benefit from more personalized and mechanistic based dietary recommendations. This potential could and needs to be developed within the context of nutritional genomics that in conjunction with systems biology may provide the tools to achieve the holy grail of dietary prevention and therapy of common diseases. This approach will break with the traditional public health approach of "one size fits all." The current nutrigenomic evidence comes primarily from the cardiovascular diseases (CVD) field and it has begun to identify subgroups of individuals who benefit more from a low fat diet, whereas others appear to benefit more from high monounsaturated or polyunsaturated fatty acid (PUFA) diets. Of interest is the increasing evidence showing that when it comes to cardiovascular health, n-6 and n-3 families of PUFAs interact very differently with genetic variants to modulate CVD risk factors. Thus, while some subgroups of individuals may be at higher risk from high consumption of PUFA n-6 (i.e., carriers of the minor allele at the APOA5-1131T>C single nucleotide polymorphism), others may greatly benefit from increased consumption of PUFA n-3 (i.e., carriers of the APOA5-1131C or the A allele at the IL1beta 6054G > A SNP).

The continuous progress in nutrigenomics will allow us to identify those individuals for whom diet plays no major role in their CVD risk as well as those who may benefit from specific gene-based dietary advice. However, in order to gain knowledge in this area, the overwhelming amount of genetic data being generated needs to be balanced with reliable and comprehensive phenotypic information gathered over time in very large numbers of subjects. Unfortunately, the existing longitudinal studies lack, individually, the size needed to deal with the complexity of the gene-environment interactions modulating human health and disease, nor are the statistical tools ready to deal with these complex interactions. Moreover, the evidence needs to be supported by properly designed intervention studies. Therefore, whereas it is accepted that our responses to the environment (i.e., diet) are largely determined by our genetic make up, our current knowledge is insufficient to successfully implement the practical use of genetics to predict disease or to personalize dietary advice for the prevention of common diseases, such as diabetes and cardiovascular diseases. However, personalized nutrition is a valid concept with potentially enormous benefits for disease prevention and it is essential to dedicate effort and resources towards a better understanding of this complex field.

Investigating the Consumer Perception System on Emerging Technologies in the Food Area

Dr. Andreas Varlamos, Food Allergens Laboratory, Rethymno, Greece

Emerging/new technologies could only be in favour in consumer's perception if they can prove that they benefit and do not harm the food quality characteristics and/or the confidence on the technology and/or food prices. Consumers are indifferent to technologies that do not benefit their needs, and they are against them if the technologies deliver risks (unacceptable or not clearly outweighed by benefits) in health, in environment etc. In this framework it seems bad business practice to insist in technologies, which are perceived by consumers as not beneficial and/or risky (or if risks outweigh the benefits), and as such this should be avoided.

To improve consumer's perception of new technologies, R&D should focus on food products as the main tool for human body development – positive evolution. The challenge is in the prudent/wise use of science and technology for the best serving/benefit of human biology. Also, one should make use of "customer focus" concepts, which are free of the manipulation of individual's opinion on their health and needs. To overcome possible barriers in the "customer focus" concept applications, it is necessary to be confronted with any established human thinking-learning disabilities and furthermore it is a must to cooperate (under a framework of principles) with customer organizations. The interest of "right" business activity is in harmonization with consumer association interests.

It is important to keep in mind that the market acceptance of a new technology may be more costly and difficult than its design and development. There should be consultation with the public on their views on new technologies and these views should be meaningfully integrated into research and where appropriate, policy making. Market acceptance could be facilitated, if consumer associations and/or federations (like the European Consumers' Organisation (BEUC) and its national members) positions are taken into account and if food researchers and businesses are open and transparent during the whole R&D cycle (i.e. R&D decision/initiation, execution and application).

Quality management concepts are both the motivator to insist on the points mentioned above and the tool to work towards this direction. The food business should provide consumers with the information they need to make the right food choices (including risks, benefits and their uncertainties). Especially in case of food quality information (including nutritional claims), these should be objectively demonstrated without doubts and easy to understand and accepted by consumers. Food operators should take continuously under consideration that lay consumers are able to recognize "trusty" products and producers, and that they will choose these products/producers based on their perception about the advanced quality characteristics and confidence delivered.

DISCUSSION AND CONCLUSION

Nutrition research is today facing the challenge of elucidating the relationship between health, disease and metabolism and the effects of nutrition, pharmaceuticals or environmental factors. Global profiling tools such as imaging and nutrigenomics technologies are required to fully understand the impact of genetic modifications, toxicological interventions and exposure to stimuli (e.g., noxious agents, stressors, nutrients, genetic modification, patho-physiologic or environmental conditions) on the network of transcripts, proteins and metabolites found within a cell, tissue or organism. The major difficulties that these new technologies are facing still lie ahead of us. For example, the integration of gene and protein expression profiles with metabolic fingerprints is still in its infancy as we need to understand how to (1) select relevant sub-sets of information to be merged and (2) resolve the issue of the different time scales, at which transcripts, proteins and metabolites appear and act. Furthermore, the definition of health is a less clear-cut issue than the one of disease. Moreover, holistic and imaging technologies in nutrition must be particularly sensitive, as they have to reveal many weak rather than a few abundant signals to detect early changes. Last but not least, in the food context, health cannot be uncoupled from pleasure, that is, food preference and nutritional status are interconnected and the benefit delivered should be science-based to fit with the regulatory environment, and properly communicated to meet the expectations of consumers.

In current practice of health claim substantiation mainly traditional methods are taken into account. Indeed, even if imaging and nutrigenomics are validated from an analytical viewpoint they do not necessarily reflect suitable biological phenomena and the identification of biomarkers to demonstrate efficacy is still an open field especially in nutrition research. Collaborative R&D projects (e.g. EC funded BIOCLAIMS) have been proposed. Nevertheless, we should use new technologies to open new potential health claims on food, to minimize animal investigations and to accelerate the translation to human studies. We should not encourage the development of animal models but promote a larger use of in silico and in vitro studies to move more quickly to human intervention studies.

Today, not all of these technologies are at the same level. Functional imaging and morphological imaging are extremely advanced. They are windows to the brain to understand how the normal/pathological brain is functioning. There is ample evidence that some functions correlate with disease and some registered drugs and it has been demonstrated that nutraceutical substances may have beneficial effects on vigilance and cognitive function. However, imaging technologies are not well enough known by the nutritional community.

The nutritional community needs a dictionary of validated markers. Such a catalogue could be structured along the criteria that EFSA is applying on the article 13 health claims. Those criteria are not going to change because of the new technologies. Most evidence will be mechanistic or at the functional level. Imaging and nutrigenomics technologies will not necessarily deliver surrogate endpoints. Therefore, and overall, we need to make proof-of-principle studies (e.g. can these technologies demonstrate efficacy of plant sterols?). To improve the rate of success, we should take into account genetic predisposition to better master the questions posed by inter-individual variability. These proofs-of-principle are needed before taking any decision on the use of imaging and nutrigenomics technologies for health claim substantiation and the involvement of regulatory bodies is of paramount importance.

LIST OF ACRONYMS

ACC	Anterior cingulate cortex
APO	Apolipoprotein
BMI	Body mass index
CT	Computed tomography
CVD	Cardiovascular diseases
DEXA	Dual energy X-ray Absorptiometry
EC	European Commission
EEG	Electro-encephalographic
EFSA	European Food Safety Authority
ERP	Event-related potentials
FDA	Food and Drug Administration
HAMD	Hamilton depression rating scale
IHCL	Intra-hepatocellular lipids
IL	Interleukin
IMCL	Intra-muscular cellular lipids
LORETA	Low-resolution brain electromagnetic tomography
MRI	Magnetic resonance imaging
MRM	Multiple reaction monitoring
mRNA	Messenger ribonucleic acid
MS	Mass spectroscopy
NDA	Dietetic products, nutrition and allergies
NMR	Nuclear magnetic resonance
PASSCLAIM	Process for the Assessment of Scientific Support for Claims on Foods
PET	Positron emission tomography
PBMC	Peripheral blood mononuclear cell
PUFA	Polyunsaturated fatty acid
R&D	Research and Development
SNP	Single nucleotide polymorphisms
UK	United Kingdom
US	United States of America

WORKSHOP PARTICIPANTS

Dr. Jean-Michel Antoine	Danone	FR
Prof. Jimmy Bell	Imperial College London	UK
Dr. Julio Boza Puerta	Coca-Cola Europe	BE
Dr. Baukje de Roos	University of Aberdeen	UK
Mr. Kees de Winter	The European Consumers' Organisation (BEUC)	BE
Dr. Ruan Elliott	Institute of Food Research	UK
Dr. Laurent Fay	Nestlé	CH
Prof. Michael Gibney	University College Dublin	IE
Prof. Ulf Görman	Lund University	SE
Dr. Michele Kellerhals	Coca-Cola Europe	UK
Dr. Kerstin Kramer	Monsanto	BE
Prof. Ronald Maughan	Loughborough University	UK
Prof. José Ordovas	Tufts University	US
Prof. Andreu Palou	University of the Balearic Islands	ES
Ms. Valérie Rolland	European Commission – DG Research	BE
Prof. Bernd Saletu	Medical University of Vienna	AT
Dr. Özgür Sancak	DSM	CH
Dr. Nico van Belzen	ILSI Europe	BE
Dr. Andreas Varlamos	Food Allergens Laboratory	GR
Dr. Stéphane Vidry	ILSI Europe	BE
Dr. Peter Weber	DSM	CH
Dr. Josephine Wills	European Food Information Council – EUFIC	BE
Dr. Jonas Wittwer	DSM	CH

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