Title: ADIPOSE TISSUE EXPANDABILITY, LIPOTOXICITY AND THE METABOLIC SYNDROME

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Abstract: The link between obesity and type 2 diabetes is clear on an epidemiological level, however the mechanism linking these two common disorders is not well defined. One hypothesis linking obesity to type 2 diabetes is the adipose tissue expandability hypothesis. The adipose tissue expandability hypothesis states that a failure in the capacity for adipose tissue expansion, rather than obesity per se is the key factor linking positive energy balance and type 2 diabetes. All individuals possess a maximum capacity for adipose expansion which is determined by both genetic and environmental factors. Once the adipose tissue expansion limit is reached, adipose tissue ceases to store energy efficiently and lipids begin to accumulate in other tissues. Ectopic lipid accumulation in non-adipocyte cells causes lipotoxic insults including insulin resistance, apoptosis and inflammation. This article discusses the links between adipokines, inflammation, adipose tissue expandability and lipotoxicity. Finally, we will discuss how considering the concept of allostasis may enable a better understanding of how diabetes develops and allow the rational design of new anti diabetic treatments.
Title: DISCOVERY-BASED NUTRITIONAL SYSTEM BIOLOGY: POPULATION, GROUP, AND INDIVIDUAL LEVEL ANALYSES OF NUTRIGENOMIC DATA - THE DELTA VITAMIN STUDY

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Abstract: Although systems biology concepts and technologies are beginning to alter experimental design and analyses, research conducted in the 21st century continues to focus on physiological effects caused by providing an individual nutrient to groups of individuals with analysis of a small number of biomarkers. Similarly, geneticists focus on associating an individual polymorphism in a gene to a complex biological process, which typically is a disease. Genome wide association studies (GWAS) rely upon mathematical tools and criteria that analyze the association of multiple but independently-tested SNPs with some complex phenotype.

We are developing strategies for analyses of individual data (n-of-1) for identifying homeostatic groups and metabolic response groups. Our approach analyzes for patterns of metabolites that may be shared by others provided the same intervention. The data from n-of-1 studies are aggregated and used to analyze population level results: differences or similarities between sex, by age, by geographic location, or other dichotomous variables.

This n-of-1 experimental design was applied to a translational, community-based participatory research study. Children and teens (ages 6 to 14) were offered improved nutritious breakfast, lunch, and two healthy snacks during a 5-week summer day camp. Data aggregation (i.e., population level) results for nutrient intakes, healthy eating index scores, metabolite levels in plasma, and population genetic results were analyzed. The n-of-1 analyses identified metabolic two metabolic groups with different patterns of plasma and red blood cell metabolites. Two separate approaches were used to associate the metabolic patterns with genotype. One approach analyzed a global protein – protein interaction network by topological partitioning and enrichment analysis that grouped functionally related genes. Three modules within this global network contained SNPs that differed statistically between groups defined by patterns of metabolite levels. Two of these modules were involved in digestion and absorption functions and immune functions. A second approach used a novel middle-out (as opposed to top-down or bottom-up) procedure to analyze genotype data by defining and testing associations of single nucleotide polymorphisms of genes involved in micronutrient metabolism, related gene networks, and their protein-protein interactions. A subset of these genes was also enriched in the digestion/absorption module identified by the untargeted analysis using the protein-protein interaction partitioning approach. These data are now being integrated with proteomic data of over 1000 plasma proteins which will better define the physiological status of the study participants.

Our n-of-1 experimental design accounts for individual genetic, metabolomics, proteomic, and lifestyle (including dietary) differences and produces data that can be analyzed at the population level, metabolic group level, and individual level. It has not escaped our attention that this experimental design can be applied to a variety of biomedical research questions.

1This study was a collaboration between scientists at the

- USDA Obesity Research Prevention Research Unit (Little Rock, AR, USA),
- The Division of Personalized Nutrition and Medicine of the FDA/National Center for Toxicological Research (Jefferson, AR, USA),
- The Boys, Girls, Adults Community Development Center (Marvell, AR USA),
- The Department of Pediatrics, Faculty of Medicine of Ribeirão Preto, USP, Ribeirão Preto (SP, Brazil), Department of Mathematics, University of Trento, Italy and
- The Microsoft Research-University of Trento Centre for Computational and Systems Biology (Rovereto, Italy)
- Nestle Institute of Health Sciences (Lausanne, Switzerland)
Title: GENETIC/EPIGENETIC DIET INTERACTIONS AND CARDIOVASCULAR RISK FACTORS

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Abstract: Nutrigenomics represents a suitable approach to cardiovascular medicine, potentially enabling both, better prevention and treatment of cardiovascular diseases (CVD) through optimization of individuals’ dietary intakes. However, nutrigenomics is still developing its research methodology and learning from its achievements and its shortcomings. Its foundations have been laid, allowing us to validate its theoretical basis and, from there, to pursue research aimed to obtain a higher level of scientific evidence needed for its effective translation to clinical practice. Despite their multifactorial complexity, CVD have been the group of diseases in which most progress has been made on the knowledge of their genetic risk factors, both in identifying candidate genes through the classic approach based on the protein function and through the recent genome-wide association studies. This has been possible due to the previous characterization of multiple intermediate phenotypes linked to those diseases, among which are plasma lipid concentrations, plasma glucose and related parameters, markers of inflammation and endothelial damage, oxidative stress, blood pressure, anthropometric measurements, and even phenotypes obtained by means of noninvasive imaging techniques such as measuring the intima-media thickness of artery walls. However, despite the spectacular advances made over recent decades in the discovery of genes and gene variants involved in the intermediate and final phenotypes of CVD, we still have a very incomplete knowledge of all genes and genetic variants that are providing such genetic susceptibility. Moreover, in that search for genetic susceptibility, the interaction with environmental factors must be taken into account. Therefore, a genetic variant will not always present a greater risk of disease, but its effects will be modified by the environmental factors (ie, tobacco smoking, physical activity, and dietary intake) that interact with it. Among the environmental factors, diet may be the most directly involved in the genetic modulation of the different intermediate and final phenotypes of CVD. Progress is being made on the elucidation of gene-nutrient interactions driven by the large consortia (i.e., CHARGE) that are able to bring together the sample sizes required to investigate simple gene-nutrient interactions. However, despite these large numbers most of the genetic variability for cardiovascular traits remains unexplained and more complex interactions cannot be analyzed with enough confidence. Therefore, new approaches need to be included to get a more complete picture, including epigenomics. Epigenomics has emerged as one of the most promising areas that will address some of the gaps in our current knowledge of the interaction between nature and nurture in the development of CVD. Epigenetic mechanisms include DNA methylation, histone modification, and microRNA alterations, which collectively enable the cell to respond quickly to environmental changes. A number of CVD risk factors, such as nutrition, smoking, pollution, stress, and the circadian rhythm, have been associated with modification of epigenetic marks. Further examination of these mechanisms may lead to earlier prevention and novel therapy for CVD.

This knowledge is not only crucial for contributing to better primary prevention of CVD but also for increasing the effectiveness of the treatment once the altered phenotypes have been diagnosed. Furthermore, from the Public Health point of view, the understanding of really important genetic-epigenetic-diet modulations could help to profile the general dietary recommendations for each population.
Title: **Metabolic Profiling in a Move Towards Personalised Nutrition**

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**Presenting author:** Lorraine Brennan

**Abstract:** The metabolic phenotype (metabotype) describes the metabolic state of an individual. There is an expectation that assigning individuals to a particular metabotype will provide valuable information in future nutrition research and in particular will play a role in personalised nutrition. We developed the concept of using the metabolic phenotype to identify responders to a nutritional intervention in the context of vitamin D and have developed it further to include response to challenge tests.

For the vitamin D study subjects were randomly assigned to receive 15 μg vitamin D₃ or placebo daily. Serum 25-hydroxyvitamin D (25(OH)D) and biomarkers of the metabolic syndrome were measured at baseline and after 4-weeks intervention. $k$-means clustering and $^1$H-NMR metabolomic analysis were used to explore responsive phenotypes. Using an unsupervised data mining technique on a set of targeted biomarkers we identified five unique phenotypes with distinct metabolomic profiles. When the effects of the intervention were examined in these phenotypes individually, a vitamin D responsive metabotype was identified. This cluster, characterised by lower serum 25(OH)D and higher levels of adipokines, showed significant responses in insulin, HOMA-score and CRP following supplementation. Metabolomic analysis revealed further metabolic changes in this group and the extent of change in 25(OH)D correlated negatively with changes in fasting glucose. Using a similar approach we investigated if metabolic phenotyping could predict the response to a dietary challenge: in this instance the phenotyping approach identified 3 metabotypes consisting of 3 different responses to an oral glucose tolerance test (OGTT). In conclusion, in both instances, metabolic phenotyping revealed a differential response to an intervention or a nutritional challenge. Further development of these concepts will be important for realisation of personalised nutrition.
Title: MODERN METABOLIC APPROACHES IN TRANSLATIONAL RESEARCH FOR DIABETES

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Abstract: This presentation will convey how a deep understanding of the underlying biology is needed to drive clinical success. Understanding of the systems underlying biology through a metabolic approach can provide essential insight for better target selection and biomarker identification in preclinical development. Further, studies that demonstrate the merits of this approach for translational science and clinical success will be detailed. Global metabolomics analysis, or metabolytics, has led to the discovery of biomarkers associated with the onset of insulin resistance.

We have developed assays to quantify the blood levels of many important dietary nutrients including fatty acids, sterols, amino acids, and other markers of nutrient status including acylcarnitines and bile acids. We have used these assays to identify the relationship of blood measures of nutrients with metabolic outcomes including conversion to diabetes. Here we present the results of this approach using baseline samples from the Insulin Resistance Atherosclerosis Study, where we determined the association of baseline nutrient levels with risk for diabetes within five years. We found strong positive associations of blood saturated fats and cholesterol synthesis intermediates, and strong negative associations between plant based fatty acids and sterols with diabetes risk. These observations are consistent with the nutrition guidance for diabetes prevention based on major clinical prevention trials. Additionally, weak positive associations between branched chain amino acids and odd-chain acylcarnitines and diabetes risk were observed.
Abstract: Personalized nutrition refers to providing foods and diets according to individual needs. Most often the needs are considered to be based on a person’s genetic and metabolic fingerprint, and the aim is to provide nutrients and foods which would help to reduce the personal risk of disease. Eating behaviour, diet and thus nutrition are determined by complex interactions between the individual and environment. With increasing welfare in the society, in abundance of food variation and availability, taste and hedonic values are emphasized as food selection criteria. Non-hunger eating has also become one way of comfort especially in stressful circumstances. Many of the genes associated with overweight in GWAS studies are related to control of eating behaviour. To assist consumers in improving their nutrition, it is thus be important to also consider those physiological control systems defining different eating patterns. Developing (generally) healthy foods aligned to personalized triggering of taste and hedonic reward system would provide large assets for public health. Translational nutrition should also consider the biological variation underlying food choice and satisfaction, which to a large extent define the adherence to healthy diets, consistently shown to reduce the risk of chronic diseases.
Title: REDOX REGULATION OF METABOLIC FUNCTION IN LIVER, FAT AND β-CELLS AFFECTS GLUCOSE HOMEOSTASIS, LIPID HANDLING AND INSULIN SECRETION.

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Presenting author: Barbara E. Corkey

Abstract: Many environmental changes have accompanied the rising onset of obesity and diabetes. Much has changed that might explain this increasing incidence of obesity and diabetes, however, many of those changes have not been carefully studied. Our foods have changed, living conditions, activity levels, the air we breathe have all changed. I will present evidence that redox changes in response to nutrients and some food additives and may serve to communicate the metabolic status to all tissues. These redox changes may influence tissue specific liver, fat and β-cell functions through generation of reactive oxygen species (ROS). Previous studies have explored the role of intracellular redox in regulating metabolism. The capacity of extracellular redox to communicate to the inside of the cell, is potentially an important form of inter-organ communication that may prove exciting for further investigation and possible intervention. If the concept that redox-driven ROS generation is validated, particularly in humans, it may be possible to use this knowledge in food selection and to prevent a cascade from β-cell hypersecretion of insulin leading to insulin resistance, fatty liver, obesity, metabolic syndrome and diabetes.

Our data document an increased redox state in response to fatty acids, lactate and certain amino acids. In addition we have found redox-dependent ROS generation in primary hepatocytes, cultured human adipocytes and rat pancreatic β-cells and islets. Increased ROS in these tissues is accompanied by decreased hepatic gluconeogenesis and glycogen storage, altered lipid storage and adipogenesis in fat cells and increased basal with diminished glucose-stimulated insulin secretion. Our data also suggest that several environmental factors that have arisen in recent decades such as emulsifiers and artificial sweeteners are also modifiers of redox or ROS and thus metabolic function. Our model presents the novel concept of redox as a master regulator of metabolism that generates signals to alter metabolic function in many tissues thus regulating anabolic and catabolic function appropriately. This is perhaps analogous to the generally accepted concept of transcriptional master switches that regulate families of anabolic and catabolic genes.

If the concept that redox-driven ROS generation is validated, particularly in humans, it may be possible to use this knowledge in food selection and to prevent or reverse the development of metabolic syndrome and diabetes.
Title: SYSTEMS MEDICINE OF RESPIRATORY DISEASES: INTERPLAY OF ENERGY METABOLISM, NUTRITION AND EXERCISE

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Presenting author: Charles Auffray

Abstract: From functional genomics to systems biology and systems medicine

Systems approaches are being used to tackle the complexity and emerging properties of biological systems through exploratory and targeted investigations in iterative combinations of experiments with computational and mathematical modelling. This research strategy, applied to clearly formulated and formalized biomedical questions, enables understanding the dynamic behaviour of biological systems in normal and perturbed conditions. Evolution, development, physiology and disease are viewed as dynamic processes that operate on widely different scales in space and time between biological states that are constrained by interrelationships among network components and environmental influences. In this context, detecting, understanding and treating disease translates into identifying and manipulating global perturbed networks, e.g. through exercise and nutrition to influence control of metabolism and immunity, rather than focusing only on unique failing components. Application of systems biology approaches to biomedical questions is opening the way to the development of systems medicine.

Understanding severe asthma through systems biology

The pre-competitive IMI U-BIOPRED Consortium is using a systems approach to develop unbiased phenotype handprint biomarkers for the prediction of respiratory disease outcomes, focusing on understanding severe asthma. The aim is to overcome the hurdles encountered in the development of drugs to efficiently control the clinical course of severe asthma through better definition of clinical phenotypes, the development of predictive fingerprint and phenotype handprint biomarkers. These will be derived from a cohort of paediatric and adult severe asthmatics followed up for disease progression and exacerbations to refine diagnostic criteria and phenotype definitions, by combining molecular, histological and patient-reported data. It relies on the open-source knowledge management platform tranSMART to store, analyze and model a wide variety of biological, clinical and high-throughput functional genomics data. Work by a coalition of biologists, clinicians, engineers and computer scientists at academic and industrial laboratories are conducted in close interaction with patient organizations and a regulatory agency, and extended to other respiratory and allergic diseases.

Emergence of P4 medicine and its future impact on healthcare

U-BIOPRED and its companion EU-FP7 projects IMI-eTRIKS, ICT-AirPROM and Health-MeDALL and SysCLAD are examples of the move from the traditional reactive medicine based on the same treatment for all patients towards a predictive and preventive medicine that will increasingly be personalized to the needs of individual patient with their active participation. Systems approaches are catalyzing the emergence of Predictive, Preventive, Personalized, Participatory (P4) Medicine, revolutionizing medical practice and healthcare in the 21st century. It is expected that P4 medicine will be able to overcome the current limitations of disease complexity (through stratification of patients and diseases by molecular diagnostics) and drug discovery (through the analysis and targeting of disease-perturbed networks). The roadmap for implementation of Systems P4 medicine in Horizon 2020 is being defined through the CASyM coordinated action, toward the development of an international network of systems biology and medicine centers dedicated to inter-disciplinary training and education. The goal is to reverse the trend in non-sustainable escalating costs in drug and diagnostics development, in healthcare management, thus also reducing the gap between developed and developing countries.

References

**Title:** TARGETED AND UNTARGETED LIPIDOMICS REVEAL UNIQUE LIPID PROFILE IN “OMEGA-3” TRANSGENIC MICE

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**Abstract:**
Essential fats, such as omega-3 and omega-6 fatty acids, must be obtained through the diet and cannot be synthesized de novo in mammals. In 2004, the fat-1 transgenic mouse model was developed, enabling the mouse to endogenously convert omega-6 to omega-3 fatty acids. Research has demonstrated that the fat-1 mouse is protected against a wide variety of diseases and conditions related to inflammation including colitis, pancreatitis, asthma, hepatitis, liver disease, atherosclerosis, insulin resistance, and several types of cancer (breast, colon, pancreatic, liver).

Although a large number of studies have demonstrated reduced disease risk and health benefits in fat-1 mice, a comprehensive comparison of lipids profiles in fat-1 and wild-type mice has not been previously feasible due to lack of a sensitive and comprehensive analytical technique capable of simultaneously quantifying high-abundance (e.g., phospholipids) and low abundance lipids (e.g., oxylipins).

In this study, we used a state-of-the-art, high-throughput assays for the analysis of bioactive lipid species in plasma and liver samples from fat-1 and wild-type mice, providing new clues to the pathways and mechanisms that may be involved in the health benefits associated with alterations of the omega-6/omega-3 fatty acids ratio.
Abstract: Personal genetic information has become increasingly accessible to the public as a result of direct-to-consumer (DTC) genetic tests, however, concerns have been raised over their value and potential risks. Current genetic tests are largely unregulated, though some measures are being taken to regulate this emerging market in certain jurisdictions. Proponents of DTC genetic testing assert that providing consumers with personalized genetic information will motivate them to adopt healthier lifestyle and dietary habits aimed at reducing risk of disease. However, the effects of providing personalized genetic information on behavioural change remain unknown. We have recently initiated the first randomized controlled trial of genetic information to determine whether providing individuals with genetic information results in improved dietary habits more than general dietary advice. The genetic information provided is based on recent advances that will be presented, which suggest that individuals with certain genetic variants could benefit more from targeted nutritional advice that is more stringent than general dietary recommendations. As the science of nutrigenomics develops with clear examples of benefits for personalized nutritional advice, there will be a growing need for healthcare professionals such as dietitians to have access to credible genetic test kits to enable them to provide the necessary information and advice for those seeking to improve their health by optimizing their nutritional status based on their DNA.