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Grow School for Oncology and Developmental Biology

Toxicogenomics in human studies and molecular epidemiology

Department of Toxicogenomics

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General background

Toxicological research aims to identify chemical hazards and assessing risks of human exposure. The introduction of molecular markers in human population studies aiming to establish associations between exposures and adverse health outcomes, often referred to as molecular epidemiology, has greatly improved the quality of exposure assessment and outcome measurements. It furthermore enables the investigation of specific gene-environment interactions. Particularly the application of genomics-based technologies in molecular epidemiology may improve our understanding of the pathogenesis of disease by identifying specific pathways, molecules and genes that influence the risk of developing disease.

In the department of Toxicogenomics, we have a multidisciplinary team of biologists, chemists, toxicologists and bioinformaticians that is working in close collaboration to establish the biological impact of exposures to potentially toxic compounds using samples from either clinical studies, large cohort studies or from well controlled dietary intervention studies. In addition to a number of projects that were initiated to establish a proof of principle focusing either on the impact of prenatal and early-life exposure to genotoxic chemicals in the development of childhood cancer and immune disorders (NewGeneris) [1] or the potentially beneficial health effects of the consumption of specific phytochemicals in blueberry juice (tUL project) [2] we present here a number of large scale EU funded projects in this domain.

[1] NewGeneris.org
[2] De Kok, T.M., *et al.* Curr. Pharmaceutical Biotechnol. 13, 255-264.

Reference www.toxicogenomics-um.nl

HeCaToS EU FP7 Project

HeCaToS aims at developing integrative *in silico* tools for predicting human liver and heart toxicity. The objective is to develop an integrated modeling framework, by combining advances in computational chemistry and systems toxicology, for modelling toxic perturbations in liver and heart across multiple scales.

Approach

The framework will include vertical integrations of representations from drug(metabolite)-target interactions, through macromolecules/proteins, to (sub-)cellular functionalities and organ physiologies, and even the human whole-body level. In view of the importance of mitochondrial deregulations and of immunological dysfunctions associated with hepatic and cardiac drug-induced injuries, focus will be on these particular Adverse Outcome Pathways. Models will be populated with data from innovative *in vitro* 3D liver and heart assays challenged with prototypical hepato- or cardiotoxicants; data will be generated by advanced molecular and functional analytical techniques retrieving information on key (sub-)cellular toxic evens. For validating perturbed AOPs *in vitro* in appropriate human investigations, case studies on patients with liver injuries or cardiomyopathies due to adverse drug effects, will be developed, and biopsies will be subjected to similar analyses. Existing ChEMBL and diXa data infrastructures will be advanced for data gathering, storing and integrated statistical analysis.

Outcome

Model performance in toxicity prediction will be assessed by comparing *in silico* predictions with experimental results across a multitude of read-out parameters, which in turn will suggest additional experiments for further validating predictions. HeCaToS, organized as a private-public partnership, will generate major socioeconomic impact because it will develop better chemical safety tests leading to safer drugs, but also industrial chemicals, and cosmetics, thereby improving patient and consumer health, and sustaining EU's industrial competitiveness.

Reference www.hecatos.eu

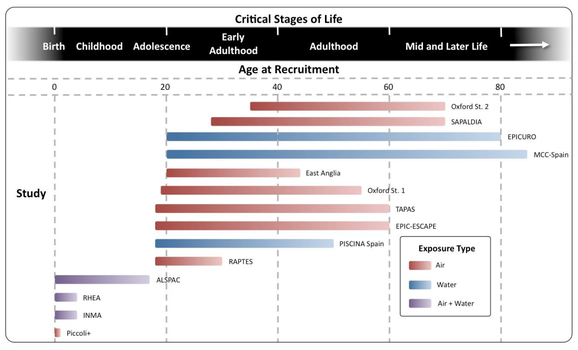
EXPOsOMICS EU FP7 Project

The exposomics project aims to develop a novel approach to the assessment of exposure to high priority environmental pollutants by characterizing the external and the internal components of the exposome, focusing on air and water contaminants during critical periods of life (see Figure). Within the project the focus is on exposure assessment at the personal and population level, development of personal exposure monitoring (PEM) and the integration of multiple "omics" technologies for the analysis of biological samples (internal markers of external exposures).

Approach

Building upon several EU-funded research projects with rich sets of health data, exposure data, biomarker measurements and publicly available data sources, this multidisciplinary project will:

- Pool and integrate information from short-term, experimental human studies and existing long-term epidemiological cohorts/consortia - including adults, children and newborns - to design focused investigations for the refinement of environmental exposure assessment based on the concept of *life-course epidemiology*
- Characterize the exposome, by (a) measuring the external component of the exposome at different critical life stages by developing high-technology tools, exploiting experience gained in existing EU initiatives (sensors, databases coupled with GIS, remote sensing), with a focus on air and water pollution; and (b) measuring internal biomarkers of the exposome (xenobiotics and metabolites, adductome, metabolome, transcriptome, epigenome, proteome) with up-to-date omic technologies.
- Use the above exposome measurements to model exposure to air pollution and water contamination in large population cohorts, through novel statistical Modeling.



Outcome

The outcome of this project will provide a new concept of integrated exposure assessment at the individual level, reducing uncertainty, and assessing how these refinements influence disease risk estimates for combined, multiple exposures and selected diseases.

PHYTOME FP7 Project

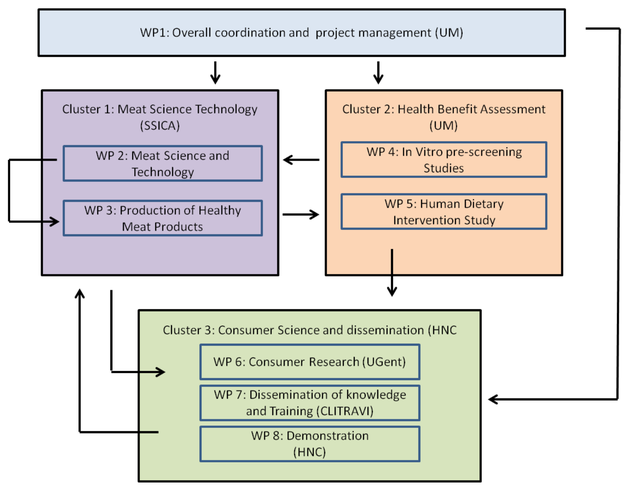
The consumption of red and processed meat has clearly been linked to the increased risk of colorectal cancer development. The underlying mechanism is hypothesized to involve the formation of carcinogenic N-nitrosocompounds in the gastrointestinal tract, from amine precursors and nitrite derived nitrosating agents. On the other hand, bioactive compounds found in fruits and vegetables, so called phytochemicals, are implicated in the defence against colon cancer, by means of antioxidant activities and the induction of protective cellular defence systems. The European PHYTOME project (Phytochemicals to reduce nitrite in meat products), aims to develop innovative meat products in which the food additive nitrite has been replaced by natural compounds originating from fruits and vegetables.

Approach

The PHYTOME project will develop new technologies to introduce the natural extracts during processing to different types of meat products. These techniques will guarantee good sensory quality of the product as well as microbiological safety. Once these techniques have been developed and optimized at laboratory scale, the health promoting effects of these products will be evaluated in a human dietary intervention study with healthy volunteers. After consumption of a fully controlled diet with either relatively high amounts of the traditional meat products or products produced following the new concept, faeces and colonic biopsies will be collected and investigated for markers of colorectal cancer risk. These markers include whole genome transcriptomics, DNA methylation changes and several markers of genetic damage, including specific types of DNA-adducts. Also the impact on the microbiome will be established. Also the effect on the endogenous formation of N-nitrosocompounds will be established and related to changes in colonic gene expression and epigenetic changes.

Outcome

The project will deliver new meat processing technologies, resulting in innovative meat products that have low or no nitrite and that have been shown to reduce the endogenous formation and exposure to potentially carcinogenic N-nitrosocompounds. The most promising combination of phytochemicals will be established as well as their impact on molecular pathways that are known to be relevant in colorectal cancer development. The interaction between the cluster on meat technology, health benefit assessment, and consumer sciences is presented on the right.



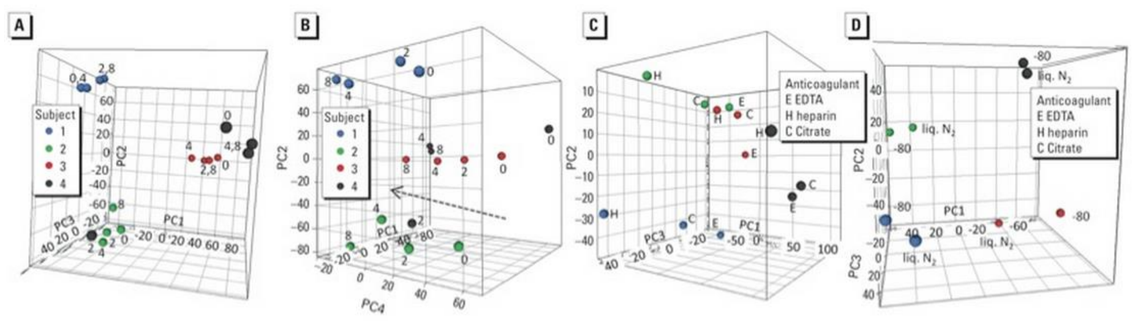
Reference www.phytome.eu

EnviroGenomarkers EU FP6 Project

This project is a large-scale application of the full range of 'omics technologies in a population study aiming at the discovery of novel biomarkers predictive of increased risks of a number of chronic diseases, the exploration of the association of such biomarkers with environmental exposures, and the discovery of biomarkers of exposure to high-priority environmental exposures. Cancer-related 'omics biomarkers are being developed using a case-control study nested within 2 cohorts, which contain biosamples collected prior to disease diagnosis, exposure and follow-up health information. Biomarkers will be compared in breast cancer and Non-Hodgkin's lymphoma (NHL) cases and equal numbers of matched controls, to evaluate their risk predictivity.

Approach

Biomarker search is based on state-of-the-art metabonomics, epigenomics, proteomics and transcriptomics, in combination with advanced bioinformatics and systems biology tools. To assess the suitability for omic analysis of biosamples collected in previous decades, we collected fresh blood samples without RNA preservative in heparin, EDTA, or citrate and held them at room temperature for ≤24 hr before fractionating them into buffy coat, erythrocytes, and plasma and freezing the fractions at -80 °C or in liquid nitrogen. We developed methodology for isolating RNA from the buffy coats and conducted omic analyses. Finally, we analyzed analogous samples from the EPIC-Italy and Northern Sweden Health and Disease Study biobanks.



Hebels *et al*, Environ Health Perspect. 2013 Apr;121(4):480-7.

Outcome

Microarray-quality RNA could be isolated from buffy coats (including most biobank samples) that had been frozen within 8 hr of blood collection by thawing the samples in RNA preservative. Different anticoagulants influenced the metabolomic, proteomic, and to a lesser extent transcriptomic profiles. Transcriptomic profiles were most affected by the delay (as little as 2 hr) before blood fractionation, whereas storage temperature had minimal impact. This indicates that most samples currently stored in biobanks are amenable to meaningful omics analysis, provided that they satisfy collection and storage criteria defined in this study.

Reference www.envirogenomarkers.net

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